KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, KUMASI

COLLEGE OF SCIENCE

DEPARTMENT OF MATHEMATICS

SOLVING THE FITZHUGH-NAGUMO MODEL WITH PYTHON



BY:

SARPONG, JULIET ASANTEWAAH

DEBRAH,JENNIFER OWUSUA

AMOAKOHENE, FRITZ EFFAH

KORSAH, EMMANUEL-

A PROJECT THESIS SUBMITTED TO THE DEPARTMENT OF MATHEMATICS, KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, AS A PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF

***BACHELOR OF SCIENCE (BSc.)* in MATHEMATICS**

MAY 2020

Abstract

Factual investigations of the World Health Organization(WHO) show that, the primary cause of sudden demise globally is cardiovascular disease. Specifically, abrupt heart death because of ventricular fibrillation arrhythmia is the most common and regularly, the principal indication of a coronary infection. Because of the significant stretches of clinical approval and frequently the prohibitive cost of creating dependable treatment for heart neurotic conditions, the pace of cardiovascular research is not in its dynamic form. One of the most significant tasks is to assemble a total and steady model of the heart as an auto-wave medium constrained by a neural system.

With the flexibility of data on the development and transmission of cardiac impulse, the reasonable use of cardiovascular scientific display is expanding in its utilization in current medication. These models help scientists study the intricacy of heart conditions and help clarify the hidden components of heart arrhythmia. The most popular numerical model portraying a transmission of electro-magnetic excitation in the heart tissue or the nerve framework is the FitzHugh-Nagumo(FHN) model. There are a few models that give a refreshed depiction of the impulses that are transmitted in the heart, for instance the Aliev - Panfilov model.

In this research, we pose a numerical solution to the FHN model using the Python programming language.This study is intended to look at numerical answers for the FitzHugh-Nagumo(FHN) model, to help rearrange the multifaceted nature of the structure and electrical impulses in the heart. Since the FitzHugh-Nagumo model is straight, it allows its solution to be viewed as a whole. This permits a geometrical clarification of significant natural wonders identified with neuronal volatility and spike-creating mechanism. Therefore,this study will help in introducing a practical use of cardiovascular numerical solutions display for its utilization in modern medicine,which in tend assists and clarifies the basic mechanism of heart arrhythmia.

Acknowledgement

We thank God Almighty for his abundant grace, guidance and favor upon us throughout the academic year and most importantly this study.
We wish to express our gratitude to our supervisor, Dr. Gaston E. Awashie, for his guidance,patience,encouragement and support provided throughout this thesis.

Contents

1 INTRODUCTION **7**

1.1 Background of Study 7

1.2 Problem Statement 10

1.3 Objectives 10

1.4 Organization of the Study 11

2 LITERATURE REVIEW **12**

2.1 Introduction 12

2.2 Cardiac Myocyte 12

2.3 Construction of Cardiac Action Potential Based on Mathematical Formalism 14

2.3.1 The Nerve Axon Action Potential (AP) Model 14

2.4 Electrical Activity of the Heart 16

2.4.1 Electrical System of Heart 17

2.5 Cardiac Cell Model 19

2.6 Cardiac Tissue Excitation and Spiral Waves 20

2.6.1 Ionic Models 20

2.6.2 Hodgkin-Huxley 21

2.6.3 Luo-Rudy I 22

2.6.4 Fox Model 24

2.6.5 Non-Ionic Models 25

2.6.6 FitzHugh-Nagumo (FHN) model 25

2.6.7 Aliev-Panfilov Model 26

2.7 FitzHugh-Nagumo Model 27

2.8 Python (programming language) 29

2.8.1 Numpy 30

2.8.2 Scipy 30

2.8.3 Matplotlib 31

3 NUMERICAL METHODS **32**

3.1 Euler Method 32

3.2 Runge-Kutta Method 34

3.3 Finite Difference Method 35

3.4 Newton-Raphson Method 36

3.5 ODEINT from the Scipy Module 37

4 SOLVING THE FITZHUGH-NAGUMO MODEL **40**

4.1 Introduction 40

4.1.1 ODEINT from the Scipy Module in Python 41

5 CONCLUSION **47**

6 REFERENCES **49**

Chapter 1

INTRODUCTION

1.1 Background of Study

According to the World Health Organization, cardiovascular diseases are the No.1 reason for death internationally; taking an estimate of 17.9 million lives year after year. Some types of heart diseases such as high blood pressure,are risk factors for atrial fibrillation(AFib), which is a type of arrhythmia. Cardiac arrhythmia is very common and nearly everyone will experience an abnormal heart rhythm sometime during their lives.

Arrhythmia, otherwise called heart arrhythmia or cardiac arrhythmia , is a collection of conditions wherein the heartbeat is unpredictable, excessively quick, or extremely slow. The pulse that is excessively quick ,over 100 beats per minute in adults is called **tachycardia**, and a pulse that is excessively slow – underneath 60 beats per minute in adults is called **bradycardia**. A few sorts of arrhythmias have no manifestations. Side effects when present may include palpitations or feeling a delay between pulses. In increasingly genuine cases, there might be discombobulation, dropping, brevity of breath or chest pains. While most sorts of arrhythmia are not unique or seroius,some such as the ventricular fibrillation and the initially mentioned atrial fibrillation(AFib) put at risk a person to complications such as stroke or heart failure. Others may bring about unexpected death.

Specifically, abrupt heart death because of ventricular fibrillation arrhythmia is the most widely recognized and frequently the main indication of a coronary disease.

Ventricular fibrillation is a pulse rate issue that happens when the heart beats with quick, inconsistent electric impulses. This causes flowing chambers in your heart (the ventricles) to plummet, rather than pump blood. In some cases caused by a heart attack, ventricular fibrillation causes your blood pressure to drop, blocking blood supply to your essential organs.
Ventricular fibrillation, a crisis that requires quick clinical attention, cause the individual to collapse in seconds. It is the most common reason for unexpected heart deaths. Emergency treatment includes Cardiopulmonary Resuscitation (CPR) and shock treatments to the heart with a device called an Automated External Defibrillator (AED). Loss of consciousness is the most widely recognized indication of ventricular fibrillation.

How about we consider an ordinary heartbeat to help us understand ventricular fibrillation. At the point when your heart pulsates, the electrical driving forces that cause it to contract finish an exact pathway your heart. Break in these driving forces can cause an unpredictable heartbeat (arrhythmia).
The heart is separated into four chambers. The chambers on each half of your heart structure form two abutting pumps, with an upper chamber(atrium) and a lower chamber (ventricle). When the heart beats, the smaller, less muscular atria contracts and fill the ventricles with blood. This constriction begins after the sinus node a small group of cells in your right atrium sends an electrical pulse making your right and left atria to contract.
The impulse at that point goes straight to the center of your heart, to the atrioventricular node, which lies on the pathway between your atria and your ventricles. From here, the electrical impulse leaves the atrioventricular node and goes through your ventricles, causing them contract and pump blood throughout your body.

Treatments to forestall abrupt heart deaths, for those in high risk of ventricular fibrillation, include medication and implantable devices that can reinstate a normal heart rhythm. A basic cause for ventricular fibrillation is the formation and subsequent breakup of spiral waves. Spiral waves, are self-sufficient waves of excitation that rotate freely or around an obstacle, reactivating at the same area of tissue at a much higher frequency than the normal sinoatrial(SA) node would do, increasing the normal rate at which the heart beats. In a worst case scenario, a spiral wave might break up into smaller spiral waves giving uncoordinated contractions of the heart in a phenomenon known

as fibrillation that can lead to cardiac arrest and sudden heart death.

Due to the long run of clinical validation and most often the restrictive cost of developing reliable treatment for coronary conditions, the pace of cardiac research is not progressive as expected.
With the availability of precise information on the formation and transmission of cardiac impulses due to cardiac excitation, the realistic application of cardiac mathematical modeling is increasing in its use in modern medicine. These models help researchers study the complexity of heart conditions and help elucidate the underlying mechanism of cardiac arrhythmia
One of the most significant task is to create a complete and predictable model of the heart as an autowave medium constrained by a neural network.
Historically, the first model that adequately portrays the elements of a neuron as far as its physical and chemical makeup was the Hodgkin-Huxley (HH) model. The HH-model contains 4 differential conditions setting up the relationship between the membrane potential of the neuron and the variables of its ion channels. The numerical recreation indicated an acceptable concurrence with the experimental dta, however the HH-model ended up being unreasonably complex for the analytical study.
The investigation of the asymptotic simplification of the HH-model revealed the similarity of its phase portrait with the Van der Pol equation which is the 2nd order equation for the oscillator with nonlinear attenuation. This allowed to reduce the number of equations to two in the FitzHugh-Nagumo (FHN) model, the dynamic methods of which have been studied exhaustively to date.
The most popular numerical model depicting a transmission of electromagnetic excitation in the heart tissue or the nerve framework is the FitzHugh - Nagumo(FHN) model. There are several models that provide an updated description of the impulses that are transmitted in the heart, for example the Aliev - Panfilov model.
In this research, we pose a numerical solution to the FHN model. The problem involves a system of ordinary differential equations dependent on a time variable. The numerical solution is evaluated using the Scipy Python package.

1.2 Problem Statement

This study is designed to examine numerical solutions to the FitzHugh-Nagumo(FHN) model, to help simplify the complexity of the structure and electrical activities in the heart.Since the simplicity of the FitzHugh-Nagumo model allows its solution to be viewed at once. This allows a geometrical clarifition of significant biological phenomena related to neuronal excitability and spike-generating mechanism.Therefore,this study will aid in presenting a realistic application of cardiac mathematical modeling for its use in modern medicine,which in tend help elucidate the underlying mechanism of cardiac arrhythmia

1.3 Objectives

- Use appropriate software program to create a simulation of the FitzHugh-Nagumo mathematical model.
- To present numerical methods that can be used to solve the systems of ODEs of the FHN model.
- To determine the numerical solution of the FHN model
- To make an input to the general stock of knowledge available on cardiac mathematical modelling

1.4 Organization of the Study

This study is organized into five chapters. Chapter one gives a general introduction of the study, which consists of the background of the study,the problem statement, objectives and the organization of the study.

In chapter two, basic concepts were introduced related to cardiac myocite,cardiac cell modelling, cardiac excitation and cardiac mathematical models. Also,the chapter presents an overview of the modeling techniques for cardiac excitation on action potential which includes the cellular domain of the heart and an introduction of the Python Programming language. The FitzHugh-Nagumo model being the main focus of the study is explained in details.

Chapter three being the methodology, contains the numerical methods chosen to solve the equations that arise out of cardiac mathematical models. In chapter four, the system of ODEs of the FHN model was solved using the ODEINTs package in the Python Scipy Module from chapter three. Finally, chapter five offers the conclusion and the chapter six containing the reference.

Chapter 2

LITERATURE REVIEW

2.1 Introduction

In this chapter, we will view the electrical activity of the heart and introduce the fundamentals of cardiac cell modeling. An overview of most ionic and simplified models which will be used further in this research will also be presented. A simple introduction to Python and its packages that were useful later in this report will be given.

2.2 Cardiac Myocyte

The cardiac myocyte is unique in that, it is responsible for the coupling of electrical impulse to mechanical function, a process with so-called “excitation-contraction coupling" (Bers 2005). In addition to the ions included in the complex processes of the cardiac myocyte, Ca^{2+} may be the most important ($source$). This is because it is closely related to both electric and mechanic processes and activities in the heart. In the cardiac myocyte, the active change in ionic concentrations (Na^{+}, K^{+} Ca^{2+} and CL^{-}), membrane voltage, time sequence and various regulatory pathways determine the ion channel kinetics, which can be expressed as mathematical formalisms ($source$).

There are many ion channels put together in a single cell, and their interactions are complicated nonlinear processes, making the single cardiac cell an interconnected system with high synergism

and integration. These characteristics and properties make it possible to use the computational approach to analyze as well as clarify the underlying mechanisms of the whole cardiac cell. Over the previous decades, there have been a few endeavors to build cardiac cell models in light of this approach. Among them, the Luo-Rudy dynamic (LRd) model, which has been one of the most famous models since it was first published by (Luo and Rudy, 1991). The LRd model was used as a mathematical model of guinea pig ventricular myocyte, which is derived from individual channel-based approach by using Hodgkin-Huxley type formalism initially (Luo and Rudy, 1991). The LRd model contains many nonlinear ordinary differential equations (ODEs) regarding the dynamic change of intracellular ion concentrations and kinetic changes of the ion channels. Also, they are used to derive macroscopic ionic currents through the channels and to construct the cell membrane action potential(AP). The model has become popular due to its refined and feasible design of formalism, and most important of all, its realistic simulation of the electrophysiological or pathological behaviors of cardiac cell in the real world. Specifically, the LRd model has kept progressing with improved knowledge about the detailed molecular function and structure, its kinetic properties, and the modifications caused by genetic mutations of the cardiac ion channels (Silva and Rudy, 2005; Rudy and Silva, 2006; Faber et al., 2007; Silva et al., 2009). Considering the progress in the action potential (AP) models over the years, the Hodgkin-Huxley AP model of nerve axon was the first model, which served as the reference point for all other modern cardiac and nerve AP models. The AP model formation followed, by incorporating detailed ion (Na^+, K^+ Ca^{2+}) channel models into the LRd cell based on Markov chain formalism (Silva and Rudy, 2005; Rudy and Silva, 2006). Finally, was the conjunction with two important intracellular regulatory pathways including the CaMKII (Hund and Rudy, 2004) and the β-adrenergic signaling cascades (Faber and Rudy, 2004).

2.3 Construction of Cardiac Action Potential Based on Mathematical Formalism

2.3.1 The Nerve Axon Action Potential (AP) Model

The Hodgkin-Huxley (HH) model describes the electrical functions of excitable cells like neutons and/or cardiac cells based on a mathematical approach. Initially, Hodgkin and Huxley used the voltage-clamp technique to study the changes of voltage-dependent conductance in excitable cells of the squid nerve axon (Hodgkin and Huxley, 1952). The intracellular recording of the axon membrane potential (Vm) revealed that inward movement of Na+ contributed to the initial rising phase, termed as depolarization, while outward flow of K^+ resulted in a falling phase, termed as repolarization (Hodgkin, Huxley & Katz, 1952b). A mathematical model was then developed to interpret the axon AP morphology that they had recorded (Hodgkin, Huxley & Katz, 1952). According to Hodgkin and Huxley (1952), considering a single axonal cell, the relation of Vm and the total transmembrane ionic current (I ion) can be formulated as the following differential equations:

$$\frac{dV_m}{dt} = -\frac{1}{C_m}.I_{ion}$$

$$I_{ion} = I_{Na} + I_K + I_L$$

where C_m is the membrane capacitance ($\mu F/cm^2$) provided by charge separation of the lipid bilayer. I_{ion} is the sum of three currents: I_{Na}, which represents the depolarizing Na^+ current, I_K, which accounts for the repolarizing K^+ current and I_L, a small leakage current that is primarily carried by Cl- ion. The driving force for each ion current is generated by transmembrane ion concentration gradient, which is the difference between membrane potential V_m and the equilibrium potential E for each ion ($V_m - E$). Hodgkin and Huxley used several hypothetical “gates" to modulate the flow of ions through the channel. The conductance of the N^+ channel is modeled by three identical fast gates m and one slow gate h, while the conductance of K^+ channel is modeled by four identical fast gates n during the AP. In voltage-gated ion channels, the channel gate is a function of both time and Vm, and each gate can transition with first-order voltage-dependent kinetics between the opening and closed status, which is independent of the status of all other gates. The N^+ and K^+ can only pass through the channel when all gates are open. The conductance of leakage ion I_L is assumed constant and does not vary with time or V_m It is intriguing that Hodgkin

and Huxley developed such a relatively simple and precise matematical model of the axonal AP, even with the underlying mechanisms of time- and voltage-dependent gating in the ion channel are still unknown at the time ($source$). It was decades later that people were able to identify and even record single-ion chnnels and elucidate the detailed three-dimensional conformation and structure of channels. Hodgkin and Huxley's foresight and originality of the ion channel model has remained as the basis for modern neuronal and cardiac AP models.

2.4 Electrical Activity of the Heart

The electrical conduction system of the heart transmits signals generated usually by the sinoatrial node to cause contraction of the heart muscle (*source*). According to (*source*), the signal generated in the sinoatrial node travels through the right atrium to the atrioventricular node, along the bundle of his and through bundle branches to cause contraction of the heart muscle. This signal stimulates contraction of the heart muscle. This signal stimulates contraction first of the right and left and left ventricles. This process allows blood to be pumped throughout the body.

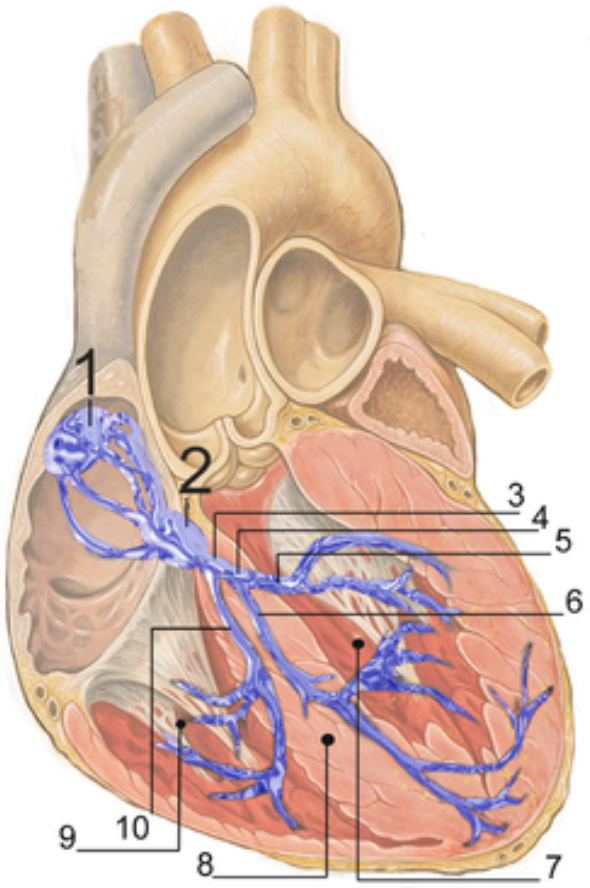


Figure 2.1: **Electrical conduction system of the heart**Source: wikipedia.org

1= S-A Node, 2= A-V Node, 3=. Bundle of His, 8= Septum

Modeling of Cardiac Electrical Activity through Cellular Automata concepts provides an efficient and effective stimulation in comparison to other reaction diffusion models. These reaction difusion models require huge burden of computational steps with complexities, whiles other Cellu-

lar Automata (CA) gives a face-paced time duration with oderate number of neighbouring cells. The CA Neural Network Model also solves the the big and obvious problems in Cardiac diagrams, that is, ELECTROGRAMS pattern recognition and classification (*source*). Cellular Automata implies on propagation of electrical wave AP (Action Potential) by computation of its prototypical property which gives Virtual Bi-polar and Mono-polar cardiac diagrams (*source*). It can simulate through this model at any instance in space with efficient manner. The purpose of this study is to plot a model for the implementation of Cardiac Electrical Activity which is capable to compute in, any complex phenomena without doing any complex calculatons. The heart has its own pacemaker which controls the rhythmic physiological and electrical activity. Heart muscles are myogenic because their contraction rhthimically originate from muscle tissues without any externa simulation. The Contraction of the heart chambers is initiated by S-A Node, thus, the S-A Node is known as Pacemaker (*source*). The Pacemaker lies within the upper segment of the right Atrium. It is made from a combination of specialized cellswhich are the electrical stimulus for every wave of excitation of the contraction of the Atria. The S-A node is a stimulus for contraction of heart in the form of signals which are generated when Vena cave pumps the blood and fill the right Atrium from other parts of body (*source*). Those signals are what causes the contraction of the Atria and circulate blood through valves into both of the ventricles.

2.4.1 Electrical System of Heart

The "Electrical System" of the heart is also known as the "Cardiac Conduction System". This cardiac electrical system manages all the activity that happens during the blood circulation. The Electrical Activity System mainly consists upon three major portions:

- Sinus or S-A Node (Located in specific region of right Atrium close to the point of entry of Superior vane cava)
- Atrio-Ventricular or A-V Node (Present on Interventricular Septum close to Tricuspid Valve)
- His-Purkinje System (lies in along the walls of Ventricles)

The Electrical Conduction System is normally examined with Electrocardiogram (ECG or EKG), which gives a graphical representation of the heart's condition and activities (*source*). When the

heart pumps blood through the entire body, the muscles of the heart contract in the atria which is triggered by an instataneous change in electrical impulse thereby propagating a fast rhythm called the action potential (AP).

Electrical activities of the heart can also be monitored by the artificial pacemaker. The electrodes in the device detects the electrical spikes or activitis and send that data through wires to the computer in the generator. If it detects that there is an abnormal rhythm in your heart, the computer will direct the generator to send electrical pulses to your heart to restore its normal rhythm (Gharpure, 1995).

2.5 Cardiac Cell Model

The current generation of cardiac cell models are mainly based on the Hodgkin-Huxley model of the squid giant axon (Hodgkin and Huxley & Katz, 1952). This was first adapted for the cardiac Purkinje cells by Noble (Noble, 1962). The background of the development of these models has been reviewed by Clayton and Panfilov (2008), in addition to what is known about the structure and function of cardiac ion channels, pumps and exchangers (Carmeliet, 1999; Roden et al.,2002), and the details of intracelullar Ca^{2+} handling (Bers and Guo, 2005). A more recent development has been the use of Markov state-based models for describing ion channel behaviour (Clancy and Ruddy, 2001).

One significant step involved in modeling the electrical activity in the heart is simulating the potential difference change across the membrane at the level of the cells. Various mathematical models exist, which differ by complexity, accuracy and type of tissue ($source$). This study tends to describe these different cell models and simplified models: Hodgkin-Huxley, Fox, Luo-Rudy, FitzHugh-Nagumo and Aliev-Panfilov. The sections presented below give a more complete description of the models.

2.6 Cardiac Tissue Excitation and Spiral Waves

Cardiac Tissue Excitation(CTE): impulse from the nodes to heart tissues to cause heartbeat the behaviour of CTE is self-sustaining likened to Spiral Waves. When there is a break in the Spiral Waves, Ventricular Tachycardia occurs.

There are two main kinds of models for Cardiac Arrhythmia.

- Ionic Models
- Non-Ionic Models

2.6.1 Ionic Models

Ionic membrane models describe the mean behavior of the ionic channels in a small membrane patch containing a number of the latter large enough to observe their statistical evolution through time (Henriquez, 1993). The first membrane model for ionic currents appearing in both the monodomain and the bidomain model relies on the choice of the membrane model for the cell conductivity.

Ionic models precisely develops most of the basic characteristics of cardiac tissues (Depolarization and Repolarization phases of the action potential) examples;Panfilov Model(2 variables) and Luo-Rudy I Model(8 variables). The ionic models are not suitable for modeling problems such as the problem of Re-entrant Cardiac Arrhythmia.

2.6.2 Hodgkin-Huxley

In 1963, Alan Hodgkin and Andrew Huxley were honoured for their discoveries concerning the "ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"(Hodgkin & Huxley, 1952). Using the axon of a giant squid, they devised a method for modelling the potential difference across a cell membrane which has become the basis for all subsequent modern cardiac cell models. In Hodgkin-Huxley model, the total current density I_{tot} is equal to

$$I_{tot} = C_m \frac{\partial E}{\partial t} + I_{ion}$$

where

$$I_{ion} = I_{Na} + I_K + I_{KI}$$

of which I_{Na} corresponds to the sodium current, I_{KI} to the potassium current and I_L to a leftover leak current. E represents the potential difference across the membrane which, in order to retain consistency with other notations, we will name V for the remainder of the derivation. According to Hodgkin and Huxley (1952) after 200μ the I_{tot} becomes negligible and therefore equation the equation above can be simplified as:

$$\frac{\partial V}{\partial t} = -\frac{I_{ion} + I_{stim}}{C_m}$$

where I_{stim} is some initial stimulus current.

2.6.3 Luo-Rudy I

The first cardiac AP models were the Purkinje fiber, which formulated by McAllister et al., (1975), and the mammalian ventricular myocyte (B-R model) formulated by (Beeler and Reuter, 1977). These two models both describe the ion currents based on the Hodgkin Huxley formalism. In 1991, Luo and Rudy had published the first Luo-Rudy model (LR-I) of the mammalian (Guinea pig) ventricular AP2, which included the update experimental information that have been accumulated since the formulation of the B-R model in 1977. In this model, the rate change of cardiac membrane potential Vm with time is described by:

$$\frac{dV_m}{dt} = -\frac{1}{C_m}.(I_i + I_{st})$$

$$I_i = I_{Na} + I_K + I_{KI} + I_{KP} + I_b + I_{Si}$$

where C_m is the membrane capacitance ($\mu F/cm^2$), I_{st} is the stimulus current, Ii is the sum of total transmembrane ionic current ($\mu A/cm^2$) including: I_{Na}, the fast inward Na^+; I_K, the time-dependent K^+ current; I_{K1}, the time-independentK^+ current; I_{KP}, the plateau K^+ current; I_b, the background current; and I_{si}, the slow inward current carried by Ca^+.

In this model, six ion currents were incorporated to construct the cardiac AP. The I_{Na}, I_K, I_{K1}, and I_{KP} currents were reformulated based on the Hodgkin-Huxley formalism. The I_{si} current was retained from the original B-R model to maintain the AP plateau. The LR-I model had gained its success in simulating the depolarization and repolarization phases of the AP and several electrophysiological phenomena like supernormal excitability, Wenckebach periodicity, and aperiodic patterns of the cardiac cell to periodic stimulation (Luo and Rudy, 1994) The LR-I cell did not account for dynamic changes of intracellular ion concentrations (Na^+, K^+ Ca^{2+}) during the AP, especially the intracellular Ca^{2+} $[Ca^{2+}]_i$ transients (CaT), which is the essential component of living cardiac myocyte expressing their contractile function. In 1994, Luo and Rudy had modified their LR-I to the Luo-Rudy dynamic model (LR-II), where dynamic changes of ion concentrations during the AP were accounted for and formulated. Also, the L-type Ca^{2+} channel current($I_{Ca(L)}$) was reformulated based on the most advanced results from single-channel and single-cell experiments at that time. Several intracellular pumps and exchangers such the Na^+/Ca^{2+} exchanger (I_{NaCa}), theNa^+/K^+ pump (I_{NaK}), the sarcolemma Ca2+ pump (Ip(Ca)) and the nonspecific Ca^{2+}-activated current ($I_{ns(Ca)}$) were incorporated to maintain and regulate the intracellular ion balance in the

cardiac cell. The SR system was also reformulated to construct the detailed kinetics of intracellular Ca^{2+} fluxes, including the following: separation of SR compartment into the network SR (NSR) and the junctional SR (JSR), calsequestrin (CASQ2) as the Ca^{2+} buffer in the JSR, uptake of Ca^{2+} (I_{up}) through the SR Ca^{2+} ATPase (SERCA) by the NSR, leakage of Ca^{2+} (I_{leak}) from the NSR into intracellular space, translocation of Ca^{2+}(I_{tr}) from the NSR to the JSR, and release of Ca^{2+} fluxes (I_{rel}) via the ryanodine receptor 2 (RyR2) by the JSR. In addition, Ca^{2+} buffers like calmodulin (CMDN) and troponin (TRPN) in the myoplasma were also included in the model.

This model provides an accurate simulation of dynamic changes in ion concentrations and, in particular, intracellular CaT and fluxes during the AP. The properties of the model provided the basis of the excitation-contraction coupling process in cardiac cells. In addition, arrhythmogenic behaviors of the single cell including early afterdepolarization (EAD), delayed afterdepolarization (DAD), and triggered activity were also investigated in this model Luo and Rudy, 1994). The LRd model provides a useful tool for basic and clinical investigation of electrophysiological processes and helps explain the underlying mechanisms that are not easily demonstrated in the experiments. Over the past decades, the LRd model has been updated to keep up with the accumulating information about ion channels and intracellular signaling pathway in cardiac cells, including the replacement of the time-dependent K^+ current I_K with the rapid and slow components of the delayed rectifier K^+ K+ current, I_{Kr} and I_{Ks} (LRd95), Zeng et al., (1995) formulation of I_{Ks} for different cell types with endocardial, midmyocardial and epicardial cells (LRd99), Viswanathan and Rudy, (2000) development of a novel theoretical model of the canine ventricular myocyte (Hund-Rudy dynamic (HRd) model),Decker et al., (2002) formulation of the β-adrenergic signaling cascade Faber and Rudy, (2007) and the Ca^{2+}/calmodulindependent protein kinase (CaMKII) regulatory pathway, Hund and Rudy, (2007) and most important of all, reformulation of I_{Na}, I_{Ks}, $I_{Ca(L)}$ and I_{rel} based on a detailed Markov chain formalism (LRd00) Clancy and Rudy 2001; Faber and Rudy, 2007).

2.6.4 Fox Model

In 2001, Jeffrey Fox, Jennifer McHarg and Robert Gilmour presented the Fox model of canine myocyte. Built upon previous canine models, the Fox model specifically addresses the inability of previous models in simulating stable electrical alternans. Alternans describe a phenomenon where the duration of the action potential alternates between cycles. This is an especially interesting abnormality for cardiac modelers as there is evidence that alternans are a precursor to ventricular arrhythmia and therefore ventricular fibrillation (Fox, McHarg & Gilmour, 2002). This model uses 13 currents to describe the movement of ions across the membrane:

$$I_{ion} = I_{Na} + I_{Kl} + I_{Kr} + I_{Ks} + I_{to} + I_{Kp} + I_{NaK} + I_{NaCa} + I_{Nab} + I_{Cab} + I_{pCa} + I_{Ca} + I_{CaK}$$

where I_{Na} and I_{Nb} describe the sodium current, $I_{Kl}, I_{Kr}, I_{Ks}, I_{to}$ and I_{Kp} describe the potassium current and I_{Ca}, I_{pCa}, and I_{Cab} describe the calcium current. Furthermore, $I_{CaK}$is the potassium current through the calcium channel, I_{NaCa} is the sodium and calcium exchange current and I_{NaK} is the sodium and potassium pump current. The model consists of a system of 13 ODEs.

2.6.5 Non-Ionic Models

Some of the non-ionic models can describe adequately the dynamics of pulse propagation in the myocardium. examples; FitzHugh-Nagumo(FHN) model and Aliev-Panfilov model.

2.6.6 FitzHugh-Nagumo (FHN) model

The FHN Model is an example of a relaxation oscillator since, if the external stimulus I(ext) reaches a certain threshold value, the device will display a characteristic excursion in phase space until the variables v and w relax back to the rest (FitzHugh,1961; Nagumu, Arimoto & Yoshizawa, 1962). This behavior is a characteristic of spike generations (a fast, nonlinear elevation of v membrane voltage, diminished over time by a slower, linear recovery variable w) in a neuron after stimulation by an external input current FitzHugh,1961; Nagumu, Arimoto & Yoshizawa, 1962. The equations for this dynamic system is:

$$\frac{dv}{dt} = v - \frac{1}{3}v^3 - w \tag{2.1}$$

$$\frac{dw}{dt} = c(v + a - bw) \tag{2.2}$$

Where the parameters $a = 0.7$, $b = 0.8$, $c = 0.08$ (FitzHugh,1961)

The FitzHugh-Nagumo model is a simplified version of the Hodgkin-Huxley model which designs a detailed manner activation and deactivation dynamics of a spiking neuron. In the original papers of FitzHugh, this model was called Bonhoeffer van der Pol oscillator (named after Karl-Friedrich Bonhoeffer and Balthasar van der Pol) because it contains the van der Pol oscillator as a special case for a=b=0 (FitzHugh,1961). The equivalent circuit was suggested by Jin-ichi Nagumo, Suguru Arimoto, and Shuji Yoshizawa (Nagumu, Arimoto & Yoshizawa, 1962). Although the form of the equations has remained quite consistent, the values of the constants have been modified multiple times in order to increase the accuracy of the waveform.

2.6.7 Aliev-Panfilov Model

Built on the FitzHugh-Nagumo model, Rubin Aliev and Alexander Panfilov in 1996 created the simplified Aliev-Panfilov model to improve Potential form of action and discuss the recovery properties of cardiac tissue. Therefore, the model addresses the cycle length relation. This is critical once more when trying to simulate arrhythmia in heart tissues (Aleiv & Panfilov,1996).

$$\frac{\partial u}{\partial t} = D\Delta u - ku(u-\alpha)(u-1) - uw, \tag{2.3}$$

$$\frac{\partial w}{\partial t} = -\left(\epsilon_0 + \frac{\mu_1 w}{u+\mu_2}\right)(w + ku(u-\alpha-1)) \tag{2.4}$$

where $D = 1, \alpha = 0.15, k = 8, \epsilon_0 = 0.002, \mu_1 = 0.2, \mu_2 = 0.3$(Aleiv & Panfilov,1996)

Aleiv and Panfilov (1996), modified the FitzHugh-Nagumo model of an excitable medium so that it describes adequately the dynamics of pulse propagation in the canine myocardium. The modified model is simple enough to be used for intensive 3-dimensional (3D) computations of the whole heart. It simulates the pulse shape and the restitution property of the canine myocardium with good precision. The Aliev-Panfilov model is a simple model for signal propagation in cardiac tissue, and accounts for complex behavior such as how spiral waves break up and form elaborate patterns. Spiral waves can lead to life-threatening situations such as ventricular fibrillation.
The model comprises two parts: a system of two ordinary differential equations (ODEs) and a partial differential equation (PDE). The ODE parts describes the kinetics of reactions occurring at every point in space, and the PDE part describes the spatial diffusion of reactants.
In their models, the reactions are the cellular exchanges of various ions across the cell membrane during the cellular electrical impulse. Our simulation has two state variables. The first corresponds to the transmembrane potential while the second represents the recovery of the tissue.

2.7 FitzHugh-Nagumo Model

This being the model of focus for this study. The FitzHugh-Nagumo(FHN) model was published in 1961 by J Richard FitzHugh who proposed the design and Nagumu, Arimoto and Yoshizawa in 1962 developed the analogous circuit, which described an excitable device prototype (e.g., a neuron). The FHN Model is an example of a relaxation oscillator since, if the external stimulus I(ext) reaches a certain threshold value, the device will display a characteristic excursion in phase space until the variables v and w relax back to the rest. This behavior is a characteristic of spike generations (a fast, nonlinear elevation of v membrane voltage, diminished over time by a slower, linear recovery variable w) in a neuron after stimulation by an external input current. The equations for this dynamic system is:

$$\frac{dv}{dt} = v - \frac{1}{3}v^3 - w \tag{2.5}$$

$$\frac{dw}{dt} = c(v + a - bw) \tag{2.6}$$

Where the parameters $a = 0.7, \quad b = 0.8, \quad c = 0.08$ (FitzHugh & Nagumo,1961)

Zapping between the left and right branches of the cubic nullcline will nicely define the dynamics of this mechanism. This model is relatively simple, consisting of fewer parameters and only two equations. One is for the quantity V, which mimics the action potential, and the other is for the variable W, which modulates V.

It hires an anticipation and a recovery component for modeling the polarization and repolarization of action potential. Mineral ions, such as sodium and potassium, and negatively charged protein ions, contained within the cell, maintain the resting potential. When the cell receives an external stimulus, its potential spikes toward a positive value, a process known as depolarization, before falling off again to the resting potential, called repolarization.

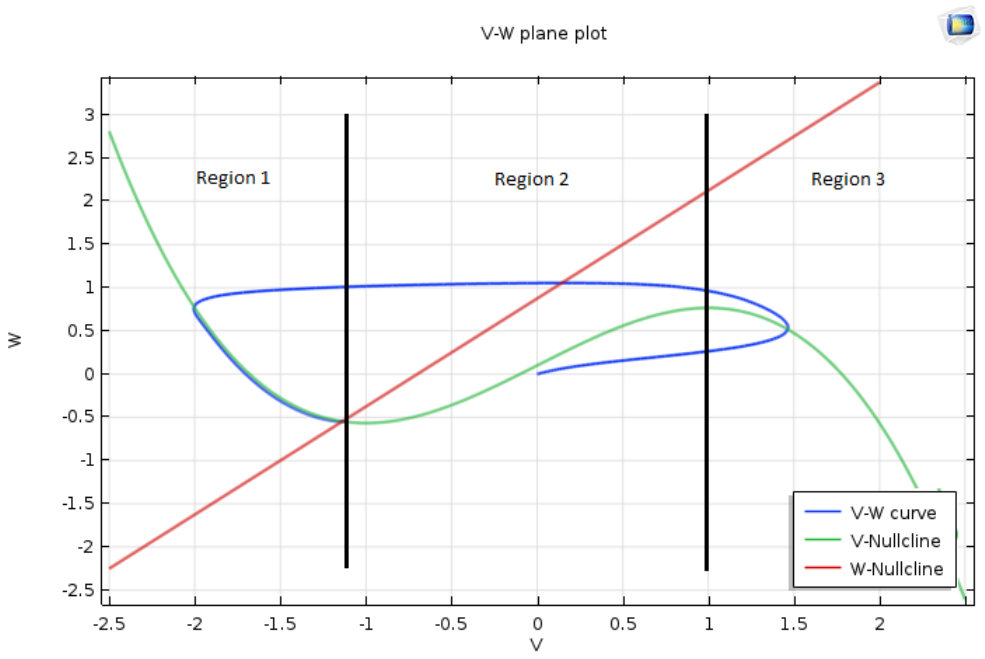


Figure 2.2: **Dynamics of the FitzHugh-Nagumo Model**

The FitzHugh-Nagumo model is a simplified version of the Hodgkin-Huxley model which models in a detailed manner activation and deactivation dynamics of a spiking neuron. In the original papers of FitzHugh, this model was called Bonhoeffer van der Pol oscillator (named after Karl-Friedrich Bonhoeffer and Balthasar van der Pol) because it contains the van der Pol oscillator as a special case for a=b=0. The equivalent circuit was suggested by Jin-ichi Nagumo, Suguru Arimoto, and Shuji Yoshizawa. Although the form of the equations has remained quite consistent, the values of the constants have been modified multiple times in order to increase the accuracy of the waveform.

2.8 Python (programming language)

Python is an interpreted, object-oriented, high-level programming language with dynamic semantics. Its significant level inherent data structures, joined with dynamic composing and dynamic mapping, make it extremely alluring for Rapid Application Development, just as for use as a scripting language to interface existing segments together. Python is straightforward, simple to learn , its syntax emphasizes readability and thus, diminishes the expense of program maintenance. Python supports modules and packages, which encourages program modularity and the reuse of code. The Python interpreter and the broad standard library are accessible in source or double structure without charge for every significant stage, and can be openly disseminated.
Example of python:
Program to calculate the factorial of a positive integer:

```
m = int(input('Please type any integer, and its factorial will be printed:
'))
if m < 0:
   raise ValueError('You must enter a positive integer')
factorial = 1
i = 2
while i <= m:
   factorial *= i
   i += 1
print(factorial)
```

What makes Python intriguing from a numerical and logical point of view is the broad measure of pertinent libraries that are accessible for this famous programming language (e.g., numpy, scipy, scikit-learn, Sage, etc).
Because of this rich ecosystem, you get a simple to learn, pleasant language that is extraordinary for scientific computing.

2.8.1 Numpy

NumPy is a python library utilized for working with arrays. It contains inbuilt function for working in linear algebra,fourier transform, and matrices domains. NumPy was created in 2005 by Travis Oliphant. It is an open source software and can used freely.
NumPy stands for Numerical Python.

In Python there are lists that serve the purpose of arrays, but they are quite slow to process. NumPy aims to provide an array object that is up to 50x faster than the traditional Python lists. The array object in NumPy is called ***ndarray***, it provides a lot of supporting functions that make working with ***ndarray*** very easy.
Arrays are frequently used in data science and scientific computing, where speed,accuracy and resources are very important.

2.8.2 Scipy

Mathematics deals with a huge number of concepts that are significant and yet, complex and tedious. Notwithstanding, Python gives the full-fledged SciPy library that settle this issue for us.
What is SciPy?
SciPy is an open-source Python library which is used to solve scientific and mathematical problems.. It is based on the NumPy expansion and permits the user to control and visualize data with a wide scope of high-level commands. As referenced before, SciPy expands on NumPy and hence if you import SciPy, there is no reason to import NumPy. But importing both libraries would not afffect your program.

NumPy vs SciPy
Both NumPy and SciPy are Python libraries utilized for scientific and numerical analysis. NumPy contains array data and basic operations such as sorting, indexing, etc whereas, SciPy comprises of all the numerical code. Despite the fact that NumPy provides a number of functions that can help resolve linear algebra, Fourier transforms, and so on, SciPy is the library that really contains fully-featured versions of these functions along with many others. In any case, on the off chance that you are doing scientific computing with Python, you should introduce both NumPy and SciPy

since SciPy expands on NumPy.

2.8.3 Matplotlib

Matplotlib is a great visualization library in Python for 2D plots of arrays. Matplotlib is a multi-platform data visualization library based onNumPy arrays and intended to work with the elaborate SciPy stack. It was introduced by John Hunter in the year 2002.
One best advantage of visualization is that it helps us visual access to enormous measures of data in effectively comprehensible visuals. Matplotlib has a few plots like line, bar, scatter, histogram and so on.

Chapter 3

NUMERICAL METHODS

In this chapter, we would discuss some of the numerical methods for solving ordinary differential equations(ODEs). Cardiac related models consist of a system of nonlinear ODEs and PDEs which can not be solved analytically. Therefore powerful numerical methods should be used to solve them. Some of these methods are Newton-Raphson method combined with other methods(since it alone, can not be used to solve these types of equations), Euler method, Runge-Kutta method, Finite Difference Method and the Python ODE solver(ODEINT).

3.1 Euler Method

The euler method is the simpliest and most common numerical method for solving ODEs. It is used to solve initial value problems and approximates the derivative of a function to its gradient at a point.

$$\frac{dx}{dt} = f(x,t) \approx \frac{\Delta x}{\Delta t} \qquad (3.1)$$

$$f(x_n, t_n) \approx \frac{x_{n+1} - x_n}{t_{n+1} - t_n} \qquad (3.2)$$

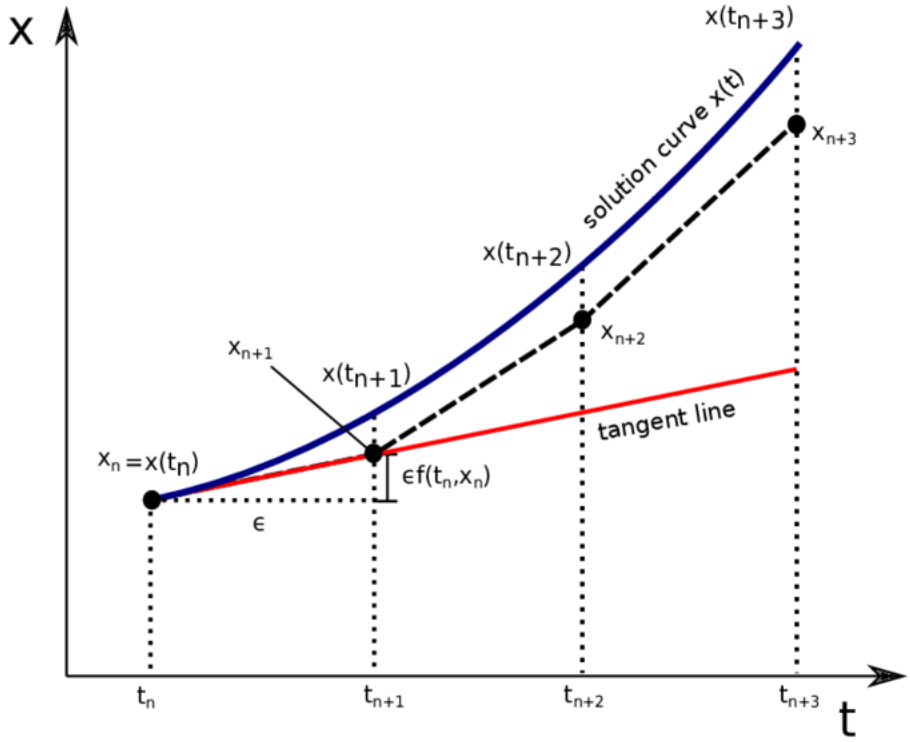


Fig 3.1

Let $t_{n+1} - t_n$ be h, normally called the step size. Rearranging the above equation;

$$x_{n+1} = hf(x_n, t_n) + x_n \qquad (3.3)$$

With an initial condition, the approximate value for x can be found. The smaller the step size, the more accurate the approximation is. It is therefore inconvinient when the interval is really wide or large, hence more points would be needed, which is time consuming.

3.2 Runge-Kutta Method

This is like the higher order Euler method. It has a general formular;

$$x_{n+1} = x_n + \Sigma_{i=1}^{m} b_i k_i \qquad (3.4)$$

where $k_i = hf(x_i + c_i h, x_n + h\Sigma_{i=1}^{m} a_{ij} k_j)$ (3.5)

To be able to solve ODEs with this method, one must know the Butcher tableau:

$$\begin{array}{c|ccccc} c_1 & & & & & \\ c_2 & a_{2,1} & & & & \\ c_3 & a_{3,1} & a_{3,2} & & & \\ \vdots & \vdots & & \ddots & & \\ c_s & a_{s,1} & a_{s,2} & \cdots & a_{s,s-1} & \\ \hline & b_1 & b_2 & \cdots & b_{s-1} & b_s \end{array}$$

Fig 3.2

The entries of the Butcher tableau are to be inserted in the equation above. Both the Euler and Runge-Kutta were all derived from the Taylor Series expansion and they are explicit methods.In cardiac cell models, the numerical solutions may be unstable and very small step sizes are needed. For this reason,the limited stability explicit methods may not be sufficient. These types of ODEs are called Stiff ODEs.

3.3 Finite Difference Method

This method is also derived from the Taylor series expansion. There is a forward difference, central difference and a backward difference. The order of the method depends on where one wishes to truncate the Taylor series expansion. Since the FHN model is consists of only first order differential equations, we will be talking only of the first order finite difference methods, although the higher the order of the FDM, the more accurate the approximation is.
First order forward difference is given by;

$$y'(x_i) = \frac{y_{x_{i+1}} - y_{x_i}}{h} \qquad (3.6)$$

The first order backward difference formular is also given by;

$$y'(x_i) = \frac{y_{x_i} - y_{x_{i-1}}}{h} \qquad (3.7)$$

Lastly, the central difference formular;

$$y'(x_i) = \frac{y_{x_{i+1}} - y_{x_{i-1}}}{2h} \qquad (3.8)$$

h is the step size and i is the number of iterations.Each of these formulae can be inserted into a first order ODE, giving an IVP or BVP, series of iterations are generated depending on the number of points needed. An approximation for that ODE is then solved for.

3.4 Newton-Raphson Method

This method is another iterative method can be used alone or can be combined with other methods depending on how the problem is. It is used to solve both linear and nonlinear equations, whether they are systems of equations or not, when given an initial guess. It is used to find the approximate value for the equation $F(X) = 0$. For a single equation, the Newton's method formular is giving by

$$X_{k+1} = X_k - \frac{F(X_k)}{F'(X_k)} \qquad (3.9)$$

.

Yet, the FHN model is a system of ODEs and equation (3.9) can not be used.For such situations, the Newton's method above, is modified to get;

$$X_{k+1} = X_k - J^{-1}(X_k)\, F(X_k) \qquad (3.10)$$

$F(X_k)$ contains an array of functions, $J(X_k)$ is the jacobian containing the partial derivatives of the functions with respect to the variables and X_k is the array of variables as shown below.

$$\begin{bmatrix} X_{k+1}^0 \\ . \\ . \\ . \\ X_{k+1}^m \end{bmatrix} = \begin{bmatrix} X_k^0 \\ . \\ . \\ . \\ X_k^m \end{bmatrix} - \begin{bmatrix} \frac{\delta F_1(X_k^0)}{\delta X_k^0} & . & . & . & \frac{\delta F_1(X_k^m)}{\delta X_k^m} \\ & . & & & \\ & . & & & \\ & . & & & \\ \frac{\delta F_m(X_k^0)}{\delta X_k^0} & . & . & . & \frac{\delta F_m(X_k^m)}{\delta X_k^m} \end{bmatrix}^{-1} \begin{bmatrix} F_1(X_k^0) \\ . \\ . \\ . \\ F_m(X_k^m) \end{bmatrix}$$

$$X_k = X_{k-1} + X_{k+1} \qquad (3.11)$$

When the initial condition is given, it is inserted in the function, and inserted in the Jacobian after finding the partial derivatives, these are then inserted into the whole equation to solve for the first iteration. The next X is generated by equation (3.11) and we continue for the desired number of iterations.

3.5 ODEINT from the Scipy Module

The ODEINT is a function used to solve differential equations in Python with the Scipy.integrate package.

$$y = odeint(model, y0, t)$$

1. model: This is the function name that returns derivative values at requested y and t values as $\frac{dy}{dt} = model(y,t)$
2. y0: Initial conditions of the differential equation
3. t: Points in time at which the solution should be recorded. Additional points are often calculated to maintain accuracy of the solution but are not reported in the solution.

An example of using ODEINT is with the following differential equation with parameter k=0.3, the initial condition y0=5 and the following differential equation.

$$\frac{dy(t)}{dt} = -ky(t)$$

The Python code first imports the needed Numpy, Scipy, and Matplotlib packages. The model, initial conditions, and time points are defined as inputs to ODEINT to numerically calculate y(t).

```
import numpy as np
from scipy.integrate import odeint
import matplotlib.pyplot as plt

# function that returns dy/dt
def model(y,t):
   k = 0.3
   dydt = -k * y
   return dydt

# initial condition
y0 = 5

# time points
t = np.linspace(0,20)

# solve ODE
y = odeint(model,y0,t)

# plot results
plt.plot(t,y)
plt.xlabel('time')
plt.ylabel('y(t)')
plt.show()
```

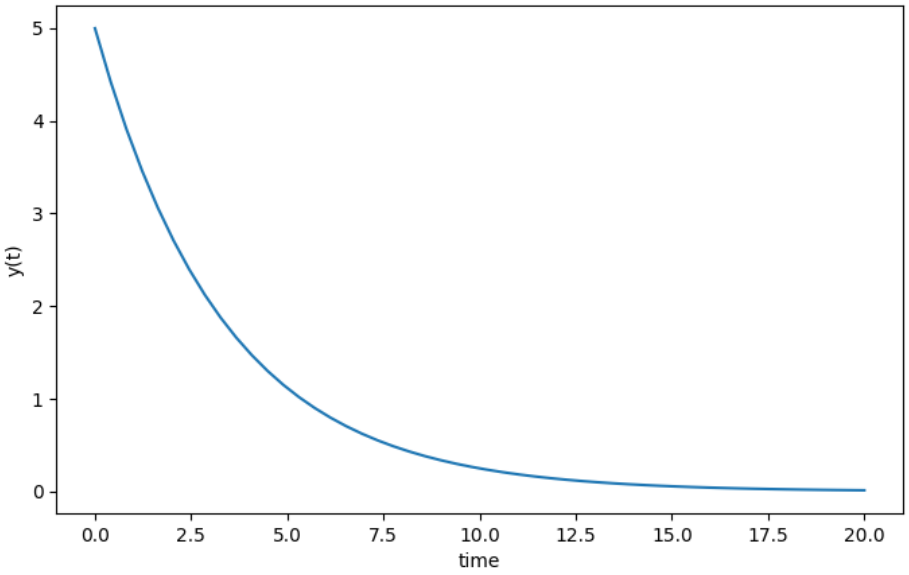


Figure 3.1: **Solution of the ODE**

Chapter 4

SOLVING THE FITZHUGH-NAGUMO MODEL

4.1 Introduction

In this chapter, we would apply the ODEINT python module to the FHN model. The exact solutions for cardiac cell models are generally not found. So using the ODEINT which consist of many numerical algorithms like the Euler and Runge-Kutta, the results are as follows;
FHN model;

$$\frac{dv}{dt} = v - \frac{1}{3}v^3 - w \qquad (4.1)$$

$$\frac{dw}{dt} = 0.8\,v + 0.0056 - 0.064\,w \qquad (4.2)$$

We would assume initial conditons of $v(0) = 1$ and $w(0) = 0$,a step size h or Δt will be computed by the Python code using the "np.linspace" function from Numpy and the range of values of the dependent variable,(t), $0 \leqslant t \leqslant 10$.
Since the model is a system of ODEs, we would solve it in a matrix form.

4.1.1 ODEINT from the Scipy Module in Python

Code:

```
import numpy as np
from scipy.integrate import odeint
import matplotlib.pyplot as plt

def model(z,t):
  v = z[0]
  w = z[1]
  dvdt = v - (1/3)*(v**3)-w
  dwdt = 0.8*v + 0.0056 - 0.064*w
  return [dvdt, dwdt]

z0 = [0,0]

t = np.linspace(0,10)

z = odeint(model, z0, t)
v = z[:,0]
w = z[:,1]

print(f"Values for v(t):\n v")
print("="*80)
print(f"Values for w(t):\n w")
plt.plot(t, v, 'r', label="v function")
```

```
plt.plot(t, w, 'b', label='w function')
plt.title("Numerical Solution of the FHN Model")
plt.xlabel("time(t)")
plt.ylabel("v(t) and w(t)")
plt.legend()
plt.show()
```

Results:

Values of t generated by the program:

[0.00000000, 0.20408163, 0.40816327, 0.6122449, 0.81632653, 1.02040816
1.2244898, 1.42857143, 1.63265306, 1.83673469, 2.04081633, 2.24489796
2.44897959, 2.65306122, 2.85714286, 3.06122449, 3.26530612, 3.46938776
3.67346939, 3.87755102, 4.08163265, 4.28571429, 4.48979592, 4.693877554.89795
6.12244898, 6.32653061, 6.53061224, 6.73469388, 6.93877551, 7.14285714
7.34693878, 7.55102041, 7.75510204, 7.95918367, 8.16326531, 8.36734694
8.57142857, 8.7755102, 8.97959184, 9.18367347, 9.3877551, 9.59183673
9.79591837, 10.00000000]

Values for v(t):

$[0.00000000e+00, \quad -1.24082729e-04, \quad -5.26453778e-04, \quad -1.25212349e-03,$

$-2.34469342e-03, \quad -3.84458017e-03, \quad -5.78698784e-03, \quad -8.19960612e-03,$

$-1.11000863e-02, \quad -1.44933532e-02, \quad -1.83687211e-02, \quad -2.26969561e-02,$

$-2.74273377e-02, \quad -3.24848253e-02, \quad -3.77674666e-02, \quad -4.31441718e-02,$

$-4.84530457e-02, \quad -5.35004205e-02, \quad -5.80608040e-02, \quad -6.18779274e-02,$

$-6.46670241e-02, \quad -6.61185448e-02, \quad -6.59033896e-02, \quad -6.36797648e-02,$

$-5.91017355e-02, \quad -5.18295441e-02, \quad -4.15418324e-02, \quad -2.79499135e-02,$

$-1.08144607e-02, \quad 1.00350424e-02, \quad 3.46775885e-02, \quad 6.30742368e-02,$

$9.50379672e-02, \quad 1.30200623e-01, \quad 1.67978557e-01, \quad 2.07540940e-01,$

$2.47786031e-01, \quad 2.87332466e-01, \quad 3.24532454e-01, \quad 3.57511146e-01,$

$3.84230801e-01, \quad 4.02570744e-01, \quad 4.10406808e-01, \quad 4.05670392e-01,$

$3.86370238e-01, \quad 3.50569830e-01, \quad 2.96329075e-01, \quad 2.21640970e-01,$

$1.24426078e-01, \quad 2.69892508e-03]$

Values for w(t):

$[0.00000000e+00, \quad 1.12879603e-03, \quad 2.20080323e-03, \quad 3.16797508e-03$

$3.97563615e-03, \quad 4.56300919e-03, \quad 4.86393633e-03, \quad 4.80798644e-03$

$4.32193748e-03, \quad 3.33164113e-03, \quad 1.76434800e-03, \quad -4.48547132e-04$

$-3.36832193e-03, \quad -7.04526887e-03, \quad -1.15147154e-02, \quad -1.67926506e-$

02

$-2.28711085e-02, \quad -2.97133901e-02, \quad -3.72492623e-02, \quad -4.53703129e-$

02

$-5.39256047e-02, \quad -6.27178977e-02, \quad -7.15006299e-02, \quad -7.99759235e-$

02

$-8.77938656e-02, \quad -9.45533007e-02, \quad -9.98045090e-02, \quad -1.03053923e-$

01

$-1.03771322e-01, \quad -1.01399857e-01, \quad -9.53693471e-02, \quad -8.51134007e-$

02

$-7.00909019e-02, \quad -4.98123486e-02, \quad -2.38713695e-02, \quad 8.01876975e-03$

$4.59845352e-02, \quad 8.99493040e-02, \quad 1.39591365e-01, \quad 1.94306766e-01$

$2.53181013e-01, \quad 3.14973098e-01, \quad 3.78112862e-01, \quad 4.40709910e-01$

$5.00569137e-01, \quad 5.55205971e-01, \quad 6.01854611e-01, \quad 6.37465688e-01$

$6.58697247e-01, \quad 6.61916938e-01]$

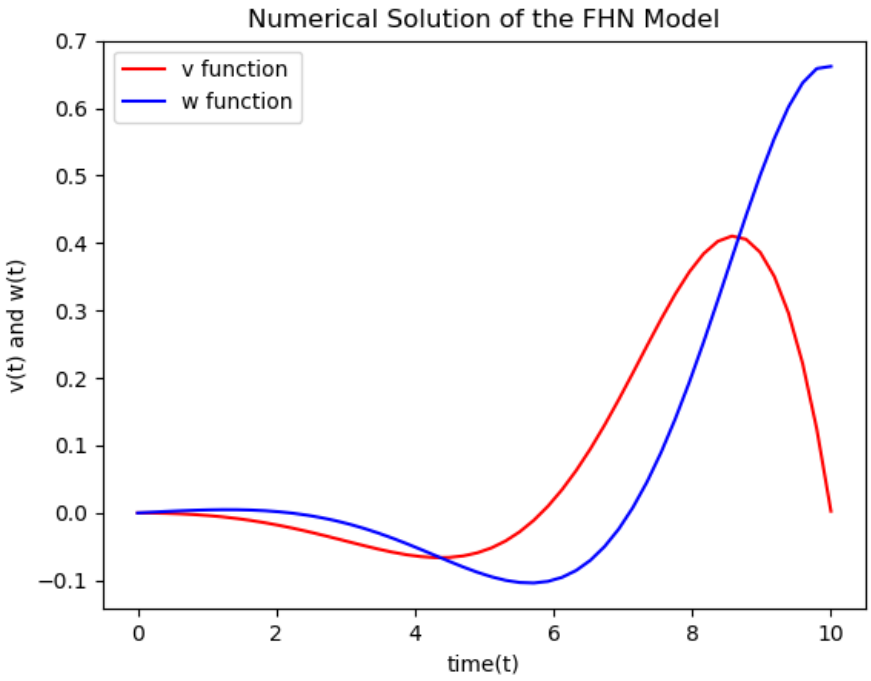


Figure 4.1: **Solution of the FHN Model**

Chapter 5

CONCLUSION

Various significant properties of cardiac tissue are often adequately modeled by the modern detailed ionic models. These quantitative cell models generally comprise of dozens of ODEs and do not make it easy to give their mathematical analysis;for a comprehensive introduction to the concept.

However, the FitzHugh-Nagumo model may be the simple phenomenological model suitable for analysis of nonlinear phenomena. This model captures the subjective attributes of electrical propagation inside the heart. In fact, phenomenological models like the FitzHugh-Nagumo have often successfully predicted the behavior of cardiac tissue.

Successfully, with the use of Python's ODEINT, the shape, amplitude, and time-dependence of this solution of the FHN Model as a function of was found.

Since the ODEINT consists of series of numerical algorithms, we did not have to use the Euler, Runge-Kutta or the Finite Difference Method on the FHN. It provides a more accurate answer and saves time.From the answers in chapter 4, the fast membrane voltage, v after some time decreases, while the slow recovery variable, w keeps increasing to a certain value and keeps steady. Hence after some time, v is diminished by w.

Chapter 6

REFERENCES

1. Aliev, R. R., & Panfilov, A. V. (1996). A Simple Two-Variable Model of Cardiac Excitation. Chaos Sol. Frac., 7(3), 293-301.

2. Beeler, G. W., & Reuter, H. (1977). Reconstruction of the Action Potential of Ventricular Myocardial Fibres. Journal of Physiological Review, 1977, 268, 177-210.

3. Bers, D. M., Guo, T. (2005). Calcium Signalling in Cardiac Ventricular Myocytes. Annals of New York Academy of Science 1047(1), 86-98.

4. Bressert, Eli (2012). Scipy and Numpy: An Overview for Developers. O'Reilly.

5. Carmeliet, E. (1999). Cardiac Ion Currents and Acute Ischaemia: From Channels to Arrhythmias. Physiological Review 79(3), 917-1017.

6. Clayton, R. H., & Panfilov, A. (2008). A Guide to Modelling Cardiac Electrical Activity in Anatomic Detailed Ventricles. Progress in Biophysics and Molecular Biology 96, 19-43.

7. Faber, G. M., Silva, J., Livshitz, L., & Rudy, Y. (2007). Kinetic Properties of the Cardiac L-Type Ca2+ Channel and its Role in Myocyte Electrophysiology: A

Theoretical Investigation. Journal of Biophysics, 92(5), 1522-1543.

8. Faber, G. M., Rudy, Y. (2007). Calsequestrin Mutation and Catecholaminergic Polymorphic Ventricular Tachycardia: A Simulation Study of Cellular Mechanism. Cardiovascular Research, 75, 79-88.

9. FitzHugh, R. (1955). Mathematical Model of Threshold Phenomena in the Nerve Membrane. Bulletin of Mathematical Biophysics 17(3), 257-278.

10. FitzHugh, R. (1961). Impulses and Physiological State in Theoretical Models of Nerve membrane. Biophysical Journal 1(6), 455-466

11. Fox, J. J., McHarg, J. L., & Gilmour, R. F. (2002). Ionic Mechanism of Electrical Alternans. American Journal of Physiology Heart Circulatory Physiology, 282(2), 516- 530.

12. Hanslien, M., Artebrant, R., Tveito, A., Lines, G. T., & Cai, X. (2011). Stability of Two Time-Integrators for the Aliev-Panfilov System. International Journal of Numerical Analysis and Modeling, 8(3), 427-442.

13. Henriquez, C. S. (1993). Simulating the Electrical Behaviour of Cardiac Tissue Using the Bidomain Model. Critical Reviews in Biomedical Engineering 21(1), 1-77.

14. Hodgkin, A. L. (1963). The Ionic Basis of Nervous Condition. Noble Lecture, University of Cambridge, United Kingdom.

15. Hodgkin, A. L., & Huxley, A. F. (1952). A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve. The Journal of Physiology, 117(4), 500-544.

16. Hodgkin, A. L., Huxley, A. F., & Katz, B. (1952). Measurement of Current Voltage Relations in the Membrane of the Giant Axon of Loligo. The Journal of Physiology,116(1), 424-448.

17. Hund, T. J., & Rudy, Y. (2004). Rate Dependence and Regulation of Action Potential and Calcium Transient in a Canine Cardiac Ventricular Cell Model. Circulation 110 (20), 3168-3174

18. Luo, C. H., Rudy, Y. (1994). A dynamic Model of the Cardiac Ventricular Action Potential. I. Simulations of ionic currents and concentration changes. Circulation Research, 74(9), 1071-96.

19. McAllister, R. E., Noble, D., & Tsien, R. W. (1975). Reconstruction of the Electrical Activity of Cardiac Purkinje Fibres. Journal of Physiology 251(1), 1-59.

20. McKinney, Wes (2017). Python for Data Analysis : Data Wrangling with Pandas, NumPy, and IPython (2nd ed.). Sebastopol: O'Reilly.

21. Nagumo, J., Arimoto, S., & Yoshizawa, S. (1962). An Active Pulse Transmission Line Simulating Nerve Axon. Washington Ireland Program, 50(10), 2061-2070

22. Noble, D. (1962). A Modification of the Hodgkin-Huxley Equations Applicable to Purkinje Fibre Action and Pacemaker Potentials. Journal of Physiology 160(2), 317-352.

23. Pastore, J. M., Girouard, S. D., Laurita, K. R., Akar, F. G., & Rosenbaum, D. S., (1999). Mechanism Linking T-Wave Alternans to the Genesis of Cardiac Fibrillation. Circulation Research, 99(10), 1385-1394.

24. Shajahan, T. K., Sinha, S., & Pandit, R. (2007). The Mathematical Modelling of Inhogenetics in Ventricular Tissue.

25. VanderPlas, Jake (2016). "Introduction to NumPy". Python Data Science Handbook: Essential Tools for Working with Data. O'Reilly, 33–96.