

Real-Time Simulation and Control of Spatio-Temporal
Cardiac Excitation using an Analog-Digital Hybrid Circuit Model

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Summary

Action potential of a cardiac cell membrane and its conduction in the cardiac tissue provide a basis of the electrophysiological function of the heart through the cardiac excitation-contraction coupling mechanism. Towards a better and a quantitative understanding of electrophysiological mechanisms of the reentrant cardiac arrhythmias at cellular, tissue, and organ levels, mathematical models of cardiac cells, tissues, and the heart have been developed and analyzed by simulating conduction of action potentials in a variety of conditions. However it is inevitable for those models to become large scale in the number of dynamical variables, requiring immense amount of computational time for their dynamic simulations. In this study, an analog-digital hybrid circuit model of electrical excitation of a cardiac cell based on Luo-Rudy phase I (LR-I) model, a typical mathematical model of a cardiac cell was developed. Through its hardware implementation, real-time simulations of the cellular excitations as well as their propagation in a cardiac tissue model have been performed with the hybrid circuit model.

This thesis is organized as follows. It is started with a general introduction in Chapter 1. The research background is discussed in Chapter 2, where physiology of the heart and the mechanism of electrical system which controls the cardiac contraction are elaborated. These are then followed by explaining the basis of knowledge on electrical potentials that exist across cell membranes and describing how they are modeled. Computational techniques of mathematical modeling and hardware-implemented circuits that have been developed over past few decades in understanding the dynamics of cells and excitation-conduction are also reviewed especially in cardiac cell modeling.

Chapter 3 is focusing on the work presented in a single cell model, where a design method of the analog-digital hybrid circuit cell is overviewed, followed by details of the analog-digital hybrid active circuit. The design method of current-voltage (I - V) relationships between ion currents and the membrane potential reproduced by analog and digital circuits is also explained. Furthermore, action potential of the hybrid circuit model is initiated by an external stimulus and the result is compared to the result of the LR-I model. Action potential generation of the hybrid circuit model in response to periodic current impulse trains with different interval (period) T are carried out and comparisons to the result from the LR-I model are presented. Classification of excitation response patterns on the parameter plane spanned by the period T and the intensity A of the impulse trains

in the hybrid model and LR-I model are analyzed, and the results between the two models are also compared. According to the simulations results, the action potential characteristics of the hybrid cell model and the LR-I cell model are comparable as the hybrid cell model generally well reproduces the I - V relationships of ion currents described in the LR-I model, as well as the action potential waveform, and the excitation dynamics in response to periodic current impulse trains with various intervals and intensity levels.

In Chapter 4, the work on investigating the spatio-temporal dynamics and control of reentrant action potential conduction in active cable models is being reviewed. Manner and underlying mechanisms in the initiation of the reentrant action potential conduction in a one dimensional ring-topology-network of the hybrid active circuit cable model are constructed as a model of anatomical reentrant tachycardia. Dynamics of the hybrid active circuit cable model are then compared with those in the numerical simulation of the LR-I cable model. Resetting and annihilation of the reentrant wave under the influence of single and sequence of stimulations are investigated by using the hybrid cable model and comparisons to the result from the LR-I cable model are carried out. Resetting and annihilation of the reentrant wave are of crucial importance in clinical situations where the reentrant cardiac arrhythmias are often controlled and terminated by delivering electrical stimulations to the heart through catheters. Phase resetting curves (PRCs) of both models are presented to show the relationship between the phase reset of the reentry and the phase of single stimulation. According to the PRCs, sequential phase resetting by periodic stimulation that leads to annihilations of the reentry are predicted and illustrated with one-dimensional discrete Poincare mappings. As the results in the simulations of the reentrant action potential conduction, quantitative correspondence between the hybrid cable model and the LR-I cable model was demonstrated using a one dimensional active cable as a model of the anatomical reentry in a cardiac tissue with various conditions. Those include (1) unidirectional block to initiate reentry, (2) phase resetting by single impulsive stimulations, (3) annihilations of the reentry by appropriately timed single stimulations, (4) phase resetting curves (PRCs) that can characterize the reentry dynamics in response to single stimulations at various timings, and (5) sequential phase resetting that leads to annihilation of the reentry as predicted by the one dimensional discrete Poincare mappings.

Finally, general discussion and conclusions are being reviewed in Chapter 5. The overall results of the hybrid circuit model are satisfied with those of the LR-I model, corresponding to the subjects examined in the study. Therefore, by taking into account the satisfactory results and the real-time simulation capability of the hybrid model, these can be concluded that the hybrid model might be a useful tool for large scale simulations of cardiac tissue dynamics, as an alternative to numerical simulations, toward further understanding of the reentrant mechanisms. As a matter of fact, minimizing power consumption and physical size of the circuits need to put into consideration regarding to large-scale development of the hybrid model.

Chapter 1

Introduction

Electrical excitations of cardiac cell membranes and their propagation in the heart tissue control the mechanical contractions of the cells through the cardiac excitation-contraction coupling mechanism, leading to coordinated contractions of the heart to pump blood. The excitation event is finely controlled by influx and efflux of transmembrane currents through various types of ion channels permeable to specific kinds of ions[1].

The cardiac excitation can be characterized by an action potential, where the action potential is generally has 5 phases. Figure 1.1 shown here represents the ventricular cardiac action potential waveform with the phase classification. The cardiac action potential is often generated in response to a supra-threshold current stimulation applied to a cell, in which fast inward Na^+ current causes a rapid increase in the membrane potential (phase 0), followed first by transient outward K^+ current causing the small downward deflection of the action potential (phase 1), and then by slow inward Ca^{2+} current that almost counterbalances slow delayed rectifier K^+ current for producing the action potential plateau (phase 2). A rapid repolarization then takes place, where the slow inward current is terminated, while the slow delayed rectifier K^+ outward current as well as other types of outward and inward K^+ currents are maintained (phase 3). Finally, the membrane potential resettles at the resting potential (phase 4).

The resting membrane potential of normal cardiac cell is approximately -80 to -85 mV and it rises from its normally negative value to a positive value up to 60 mV to 80mV during the excitation. The action potential lasts for about 200 ms. The excitability of the cell is determined by how much the Na^+ and Ca^{2+} channels regain their capability to inflow the currents after prior excitations, causing the refractoriness of the cell. Refractoriness here means the condition during which time the cells cannot fully respond to the stimulus. Thus if another stimulation is applied before the cell regains its excitability enough, it

cannot induce the action potential fully or even partially, leading to complex phase-locked, sometimes chaotic, responses when the membrane is stimulated by a periodic sequence of current injections[2, 3].

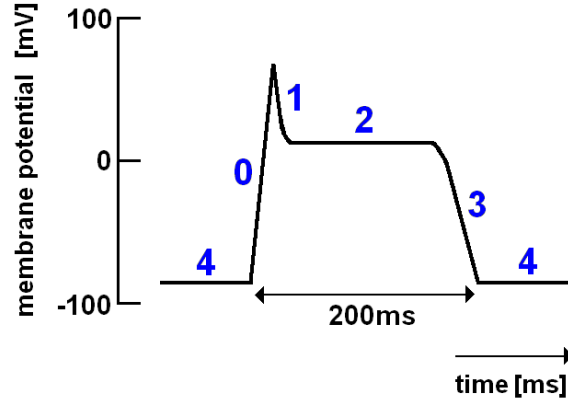


Figure 1.1: Phases of the cardiac action potential

The excitability and refractoriness of cardiac cells are features commonly shared by a class of nonlinear dynamical systems called excitable systems[4]. The heart consists of a huge number of such excitable cells connected locally via electrical synapses, referred to as the gap junctions, that allow spatial conductions of the action potentials through the heart tissue, leading to the coordinated contraction of the heart for every single beat. In a normal heart, the action potential wave dies when it reaches a complete activation of myocardium because of a refractoriness effect of the cardiac tissue that has excited before. Under uncommon conditions, the propagating wave does not die out completely but re-excite the myocardium that has recovered from the refractoriness. In this case, excitation would rotate around an area of conduction block. Most evident is reentry of cardiac excitation, which occurs when previously activated tissue is repeatedly activated by the propagating excitation wave as it reenters the same region and reactivates it at a high frequency.

Apropos of the heart is a typical dynamical system of excitable media, among other systems in physics, chemistry, and biology, in which all of them share phenomenologically common behaviors associated with the excitability and refractoriness of the media, such as reentry excitations including spiral and scroll waves of excitations[5, 6, 7, 8]. The most common type of reentry is circus movement reentry. As for the heart dynamics, some cardiac arrhythmias are perpetuated by reentrant mechanisms, in which a local excitation

conducts through a part of the heart to recirculate back to the original site, causing a rapid heart beat referred to as the reentrant tachycardia[9].

Methodologies that have been employed so far to theoretically understand the non-linear dynamics of excitable media include mathematical modelings and their computer simulations as well as electronic experiments that utilize hardware-implemented nonlinear circuits, by which experimentally observed dynamics of real-world chemical, physical, and physiological excitable media could be reproduced and analyzed qualitatively and/or quantitatively. The use of mathematical models with their computer simulations is favorable because of their large capability of describing physical and/or physiological mechanisms in detail, allowing practically one-to-one correspondence between parameters in the models and physical quantities.

The mathematical modelling in excitable media is pioneered by Hodgkin and Huxley, who formulated a mathematical description of action potential generation in the giant squid axon in 1952[10]. Indeed, mathematical models of the cardiac action potential in single cells continue their remarkable development and improvement after the Hodgkin-Huxley model. As for, much of the mathematics of cardiac cell modeling is drawn from the Hodgkin-Huxley formulation. Progress in mathematical modeling and computational techniques has facilitated using simulations as a tool for investigating cardiac dynamics. In which, models of cardiac cells are defined by mathematical descriptions of electrical events at the cellular level that give rise to cardiac action potentials. Starting from the simplified cardiac model, the FitzHugh-Nagumo model[11] that described a generic excitable media of the cardiac cells, the Noble Purkinje model[12], the Beeler and Reuter[13], the Luo-Rudy ventricular model[3, 14, 15] have been developed to represent different regions of the heart. Until today, the models become more advance but complicated from year to year as variables parameters in the mathematical descriptions are increased in order to represent the cellular processes in more detail. Thus, tissue models consisting of a large number of single cell models cause a new problem in the amount of computations required to obtain meaningful results from their simulations[16]. Due to this drawback, most research articles dealing with cardiac tissue models give their excuses for not to use the latest detailed single cell models as their compartmental nodes, but use rather simple models instead.

Meantime, hardware-implemented excitable media have their own long history of in-

vestigation, comparable to that for the mathematical models, as traced back to circuits of excitable systems proposed in 1960's[17, 18, 19]. To this day, the hardware models provide valuable tools for real-time simulations whose computational speeds are independent of the number of cells connected if one tries to perform action potential conduction on a multiple coupled analog circuits as a model of a cardiac tissue. However, they are less suited in modeling biophysically-detailed and complicated mechanisms of the ion currents. Only a few studies have succeeded to design analog circuits that are biophysically detailed and have quantitative correspondence to a real cell[20].

One of main issues for studying excitation conduction in the field of cardiac physiology and pathology is to understand how the action potential conduction and reentry dynamics at the tissue level are influenced by a cellular level dysfunction of specific ion channels[21, 22] that cause abnormal cellular excitation such as in the long QT syndrome[23]. In order to provide comprehensive answers to this sort of question using a mathematical or hardware circuit model of cardiac tissue, it is required for every cellular model (compartmental node) used in the tissue model to include physiologically and quantitatively plausible models of ion channel currents rather than simple and qualitative models.

Thus, throughout the study, an analog-digital hybrid circuit model of an excitable cell that can quantitatively reproduce the action potential generation and phase-locked and chaotic responses to periodic current pulse stimulations observed in Luo-Rudy phase I (LR-I) model[3] for a mammalian cardiac ventricular cell is proposed. Firstly here, the circuit model is reported briefly. Then a model of spatially distributed extension of a one-dimensional cardiac tissue with its hardware implementation is proposed. The circuit model allows us to perform real-time simulations of spatially conducting cardiac action potentials. In particular, simulation results show that the circuit tissue model can exhibit real-time dynamics for initiation of the reentry induced by unidirectional block and for phase resetting that leads to annihilation of the reentry in response to impulsive current stimulations at appropriate locations and timings. The dynamics of the hybrid model are compared to those obtained numerically in LR-I model in order to demonstrate that the circuit model can be utilized for simulating large scale cellular network in real-time as an alternative to numerical simulations.

Chapter 2

Background

2.1 Electrical System of the Heart

The heart is composed of two atria and two ventricles with four chambers to operate as a pump in supplying blood through the circulatory system. It is composed of three major types of cardiac muscle: atrial muscle, ventricular muscle, and specialized excitatory and conductive muscle fiber. As shown in Figure 2.1, the specialized excitatory and conductive fibers are mainly consist of sinoatrial (SA) node in which the normal rhythmic self-excitatory impulse is generated, atrioventricular (AV) node in which the impulse from the atria is delayed before passing into the ventricles, AV bundle, which conducts the impulse from the atria into the ventricles, and left and right bundles of Purkinje fibers, which conduct the cardiac impulse to all parts of the ventricles. They provide an excitatory system for the heart and a transmission system for rapid conduction of electrical signal, called action potential, through the heart. This mechanism will be explained later in this section.

Figure 2.2 illustrates a typical anatomy section of cardiac muscle showing arrangement of the cardiac muscle fibers in a latticework. Cardiac muscle has myofibrils that contain actin and myosin filaments interdigitate and slide along each other during the process of contraction. The angulated dark areas crossing the cardiac muscle fibers in Figure 2.2 are called intercalated discs, referred to as gap junctions. They are cell membranes that separate individual cardiac cells from each other. Electrical resistance through the in-

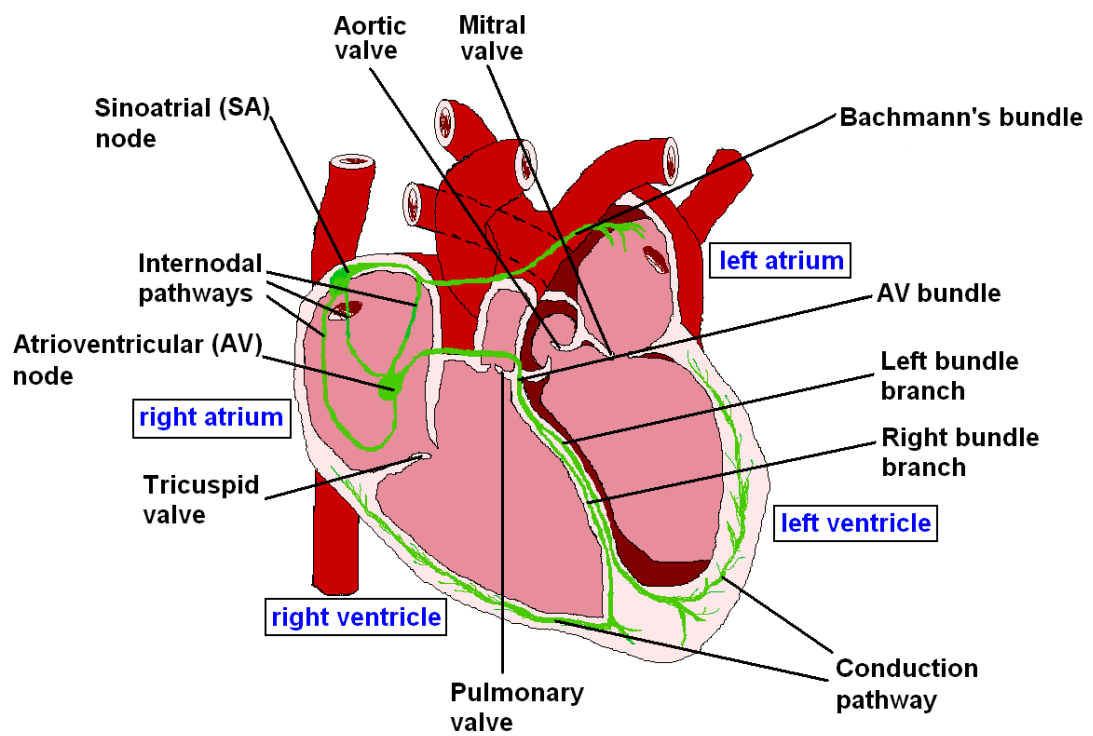


Figure 2.1: The heart

tercalated disc is only 1/400 the resistance through the outside membrane of the cardiac muscle fibers[24]. Therefore, ions flow with relative ease along the axes of the cardiac muscle fibers so that the action potential travel from one cardiac muscle cell to another, past the intercalated discs, without significant obstruction. In other words, the cardiac muscle cells are so tightly bound that when one of these cells becomes excited, the action potential spreads to the entire of heart from cell to cell throughout the latticework interconnection.

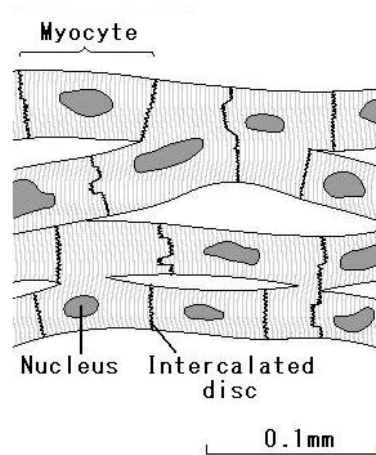


Figure 2.2: The cardiac muscle

The period from the end of one heart contraction to the end of the next is called the cardiac cycle. The cardiac cycle consists of a period of relaxation called diastole followed by a period of contraction called systole. The electrical activity events during the cardiac cycle can be recorded by an electrocardiogram, known as an ECG. Figure 2.3 illustrates the ECG wave during the cardiac cycle. The relationship of the ECG wave to the cardiac cycle may be explained as follows. Each cycle is initiated by spontaneous generation of the action potential in the SA node. The SA node is located in the right atrium. When the right atrium is full with blood, the electrical signal spreads across the cells of the right

and left atria through atrial muscle fibers, such as Bachmann's bundle. This signal causes the atria to contract. This pumps blood through the open valves (tricuspid valve and mitral valve at the right and left side of the heart, respectively) from the atria into both ventricles. The *P* wave on the ECG in Figure 2.3(a), marks the contraction of the atria as shown in 1 of (b) in the Figure 2.3. Here, in the Figure 2.3(b), the dark green dots correspond to the conduction of the action potential signal, and the disc-shaped symbols in red and blue are respectively subjected to oxygen-rich blood and oxygen-poor blood.

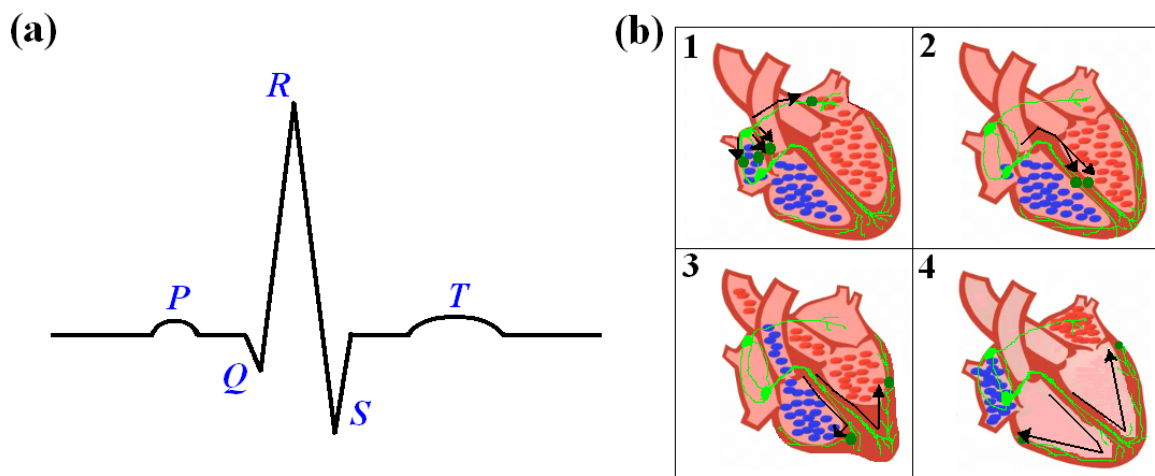


Figure 2.3: The electrocardiogram wave and the cardiac cycle

Then, the signal arrives at the AV node near the ventricles and it is slowed for an instant to allow the right and left ventricles to fill with blood. On the ECG wave, this interval is presented by the start of the line segment between the *P* and *Q* wave. The signal is released and moves next to AV bundle located in the ventricles. From the AV bundle, the signal fibers divide into left and right bundle branches through the Purkinje fibers that connect directly to the cells in the walls of the ventricles, which run through the septum as shown in 2 of (b) in Figure 2.3. On the ECG, this represented by the *Q* wave. The signal spreads quickly across the ventricles (3 of (b) in Figure 2.3). As the signal spreads across the cells of the ventricle walls, both ventricles contract, but not at exactly the same moment. The left contracts an instant before the right ventricle. As for,

the contraction of the left ventricle pushes blood through the aortic valve to the rest of the body and the contraction of the right ventricle pushes blood through the pulmonary valve to the lungs. On the ECG, the *R* wave marks the contraction of the left ventricle and the *S* wave marks the contraction of the right ventricle. As the signal passes, the walls of the ventricles relax and await the next signal, where according to the ECG, the *T* wave marks the point at which the ventricles are relaxing, that is, the *T* wave occurs slightly prior to the end of ventricular contraction (4 of (b) in Figure 2.3).

This contraction process continues over and over in a normal rhythmic rate of approximately 70 beats per minute. The rhythmical contraction of the heart works continuously, much like a pump, in order to provide a major source of power for moving blood through the vascular system. It is said that the SA node is the normal pacemaker of the heart as it controls the heart's rhythmicity. This is because of its rate of rhythmic discharge is greater than either the AV node or the Purkinje fibers, and that of any other part of the heart.

However, under abnormal conditions, where some other part of the heart develops a rhythmic discharge rate that is more rapid than that of the SA node, the pacemaker of the heart shifts from the SA node to the other part of the heart. A pacemaker elsewhere than the SA node is called ectopic pacemaker and this will cause abnormal impulse generation of the heart which that might induce abnormal sequence of contraction. Moreover, it is known that the relationship of a refractory period to the rapidity of transmission of the cardiac impulse throughout the ventricles plays an important role in causing synchronous contraction of the heart. Here, the refractory period, also known as the duration of the muscle contraction is generally about 150 ms in atrial muscle and 200 ms in ventricular muscle. That is any serious delay in transmission of the impulse through the ventricle can make it possible for the impulse from the last excited ventricular muscle to reenter the first muscle. This, in turn, sets up a reentrant circuit which causes abnormal impulse conduction in the heart. These phenomena of abnormal impulse generation and conduction

are thought to be able to create conditions that cause serious cardiac arrhythmias, the abnormal rhythmicity of the heart. Therefore, to prevent or to treat this problem, better understanding of underlying mechanisms to these phenomena will be necessary.

2.2 The Membrane Potential

Electrical potentials exist across the membranes of all cells of the body and some cells, such as nerve, skeletal muscle and cardiac cells, are excitable, that is capable of producing and transmitting action potentials along their membrane in response to electrochemical impulses. Generally, an excess of negative ions (anions) accumulates immediately inside the cell membrane along its inner surface, and an equal number of positive ions (cations) accumulates immediately outside the membrane. The effect of this is the development of a membrane potential during a polarized state at a resting membrane potential with the cell more negatively charged inside than outside the membrane. As illustrated in Figure 2.4, basically, the cell membrane is endowed with a sodium and potassium pump, where sodium being pumped to the exterior and potassium to the interior, however, because about three sodium ions are pumped out of the cell for about two potassium ion that is pumped in, more positive ions are pumped out of the cell than into it. Moreover, the resting membrane is normally more permeable to potassium as to sodium and since most of the anions inside the cell are nondiffusible, the negative charges remain inside of the cell so that the cell becomes electronegative, while the outside becomes electropositive. This causes the membrane potential inside the cell falls to approximately -85 mV, that is the resting membrane potential of the membrane.

A sequence of changes in the membrane permeability mainly for sodium ions and potassium ions could cause changes in the membrane potential. Where the first stage, which is called a depolarization, is a sudden increase in the permeability of the membrane to sodium ions causes the cell positively charged on the inside and the rapid raise of the membrane potential and the second stage, which is called a repolarization, is an increase

in potassium ions permeability causes the membrane potential to reestablish and back to normal. This short-lasting event in which the electrical membrane potential of a cell rapidly rises and falls is called an action potential.

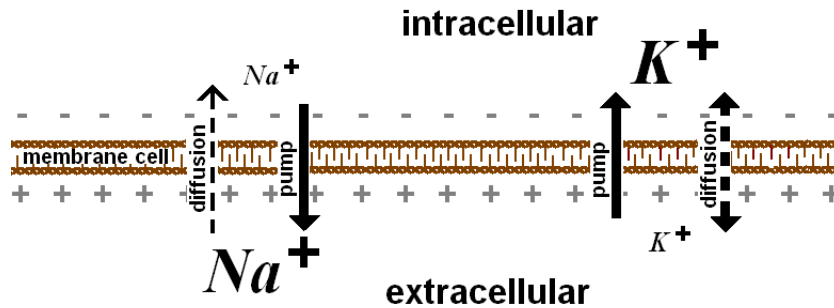


Figure 2.4: Establishment of a membrane potential in the resting membrane

History in the research of the membrane potential began with the idea that cardiac cells could produce action potentials in response to an electrical stimulus, which proposed by Henry Bowditch in 1871, based on his studies on contraction of heart muscle by stating that tissues respond to stimuli in an all-or-none manner[25]. He established the two properties that define excitable tissues which are related to the concept of threshold for stimulation and the response of excitable tissues to stimuli above threshold that is not depend on the intensity of the stimuli. The threshold is the starting point of the excitability in the cell according to a refractory state, the condition of the cell which it cannot supporting the passing of the action potential wave at a certain amount of time. However, the first action potentials were not measured in cardiac cells but in a nerve cell of the the giant axon of the squid, because of its large size. Hodgkin and Huxley[26, 27] and Curtis and Cole[28, 29] were the first to measure an action potential in the squid axon using the intracellular micropipette for measuring voltage and current across the membrane of a cell by inserting the micropipette inside the cell. Then, with advances in microelectrode to measure in much smaller cells, Ling and Gerard[30], and Nastuk and Hodgkin[31] were able to record the resting and the action potential in skeletal muscle cells. Caroboeuf and Weidman[32] and Draper and Weidmann[33] were the first to measure the resting membrane potential

and the action potential in mammalian cardiac muscle. Woodbury et al.[34] were the first to measure it in frog heart. The characteristics of the cardiac action potential, such as resting membrane potential and rapid upstroke, are similar to that in nerve and skeletal muscle cells. Nevertheless, the cardiac action potential has a duration of 100-500 ms, different to nerve and skeletal cell potentials that have duration of less than 5 ms.

The membrane potential can be developed by specialized membrane-spanning protein that control the movement of ions either by passive electrodiffusion through transmembrane pores (channels) or translocation across the membrane by carrier proteins (pumps, exchangers and transporters). When a concentration difference of ions across a membrane causes diffusion of ions through the membrane, thus creating a membrane potential, the magnitude of the potential is determined by the ratio of tendency for the ions to diffuse in one direction. If a permeable membrane separates two solutions, A and B , and if ion X is present on either side of the membrane, the relative probability of finding a particle in either solution A or solution B is given by the Boltzmann equation:

$$\frac{P_B}{P_A} = \exp\left(-\frac{u_B - u_A}{kT}\right) \quad (2.1)$$

where,

u_A : the energy of the particle in solution A

u_B : the energy of the particle in solution B

P_A : the probability of a particle being in state A

P_B : the probability of a particle being in state B

k : Boltzmann's constant

T : absolute temperature

Equation (2.1) can be constructed in terms of molar energies and concentrations, to

take account of the properties of the bulk solutions rather than individual components:

$$\frac{[X]_B}{[X]_A} = \exp\left(-\frac{U_B - U_A}{RT}\right) \quad (2.2)$$

where,

$[X]_A$: concentration of ion X in state A

$[X]_B$: concentration of ion X in state B

U_A : molar energy of state A

U_B : molar energy of state B

R : gas constant

Rearranging Eq. (2.2) and taking logs gives the following equation:

$$U_B - U_A = -RT \ln\left(\frac{[X]_B}{[X]_A}\right) \quad (2.3)$$

This shows the molar energy difference in state A and B due to the concentration gradient.

If the ion is charged, there will be not only a chemical force, but also an electromotive force. The electrical potential acting on anion of valence z in a potential field of Ψ is $zF\Psi$.

In the steady state, there will be no net flux of ions across the membrane. The potential across the membrane at which there is no net movement of ions is termed the equilibrium potential of that ion, and is calculated as follows:

$$0 = -RT \ln\left(\frac{[X]_B}{[X]_A}\right) + zFE_{eqm} \quad (2.4)$$

$$E_{eqm} = \left(\frac{RT}{zF}\right) \ln\left(\frac{[X]_B}{[X]_A}\right) \quad (2.5)$$

where,

E_{eqm} : the equilibrium potential

F : the Faraday constant

This is the Nernst equation. The equilibrium potential, E_{eqm} , also called the Nernst potential can be interpreted as the potential at which an ion is in equilibrium with its diffusional force. The uncoupled movement of a charged species through an open channel

can be described by the equation:

$$I_X = g_X(V_m - E_{eqm,X}) \quad (2.6)$$

where,

I_X : net current due to movement of ion X through the channel

g_X : conductance of the channel to ion

V_m : transmembrane voltage

$E_{eqm,X}$: equilibrium or Nernst potential for ion

This equation describes an ohmic conductor, as there is a linear relationship between current and voltage. Even though the Nernst equation can be used to calculate the correct reversal potential for an ion and the net driving force for an ion, the net flux is not always linearly related to the voltage difference, as implied by this equation.

As described before, in resting membrane potential, sodium ions are concentrated outside the cell and potassium ions are concentrated inside the cell, and cells are permeable to potassium ions because inward rectifier potassium channels are open at the resting membrane potential. This results in the diffusion of potassium ions from inside the cell to outside due to the gradient in potassium concentration and causes the accumulation of positive charge outside the cell, and negative charge inside the cell. Meanwhile, an electric field, which increases in magnitude as more potassium ions leave the cell, forces oppose diffusion forces and tend to move potassium ions from outside to inside the cell. The growing electric field will eventually prevent the efflux of more potassium ions until a situation of equilibrium will be reached. Therefore, if the cell membrane at rest were permeable only to potassium ions, the ion current flowing through the membrane at rest would be zero, and the resting membrane potential would be exactly the potassium equilibrium potential or Nernst potential. According to the Eq. (2.5), the potassium equilibrium potential can

be written as follows:

$$E_{eqm,K^+} = \left(\frac{RT}{F} \right) \ln \left(\frac{[K]_o}{[K]_i} \right) \quad (2.7)$$

where,

$[K]_o$: the potassium concentration outside the cell

$[K]_i$: the potassium concentration inside the cell

However, measured resting membrane potentials are not always identical to the potassium equilibrium potential. This indicates that the membrane is also permeable to ions other than potassium at negative membrane potentials. Thus, a more accurate estimation of the resting membrane potential can be obtained with the following formula, called the Goldman's equation, that takes into account other ions such as sodium, chloride.

$$E_{eqm} = \left(\frac{RT}{F} \right) \ln \left(\frac{P_K[K]_o + P_{Na}[Na]_o + P_{Cl}[Cl]_o}{P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_i} \right) \quad (2.8)$$

where,

P_K : the permeability of the cell membrane to potassium

P_{Na} : the permeability of the cell membrane to sodium

P_{Cl} : the permeability of the cell membrane to chloride

$[K]_o$: the potassium concentration outside the cell

$[Na]_o$: the sodium concentration outside the cell

$[Cl]_o$: the chloride concentration outside the cell

$[K]_i$: the potassium concentration inside the cell

$[Na]_i$: the sodium concentration inside the cell

$[Cl]_i$: the chloride concentration inside the cell

If a membrane at rest is permeable to several ions, the resting membrane potential represents a dynamic equilibrium in which the total ion current is zero but the individual ion currents through the different ion channels are not zero. But still, the Nernst potential

for potassium is a good approximation of the resting membrane potential of cardiac cells since the permeability of the membrane to potassium channels at rest is many orders of magnitude larger than the permeability to other ions.

According to experimental measurements of the transmembrane potentials, Hermann suggested that the cell membrane could be represented under subthreshold conditions by a resistance in parallel with a capacitance[35]. Curtis and Cole[36] measured cell membrane resistance and capacitance in nerve cells and showed that the electrical properties of the membrane are well represented by an RC circuit (Figure 2.5). Their experiments showed that cells have a high-conductance cytoplasm that is surrounded by a high-resistance membrane with an electrical capacitance of about $1 \mu\text{F}/\text{cm}^2$. The capacitor, C represents the capacitance of the lipid bilayer that forms the cell membrane, and the resistor, R represents the conductance of the ion channels that are open at the resting membrane potential.

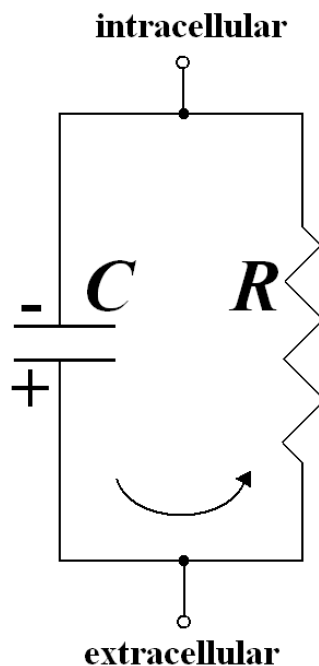


Figure 2.5: The Cole-Curtis model of passive membrane

As long as the membrane of the excitable cell in nerve, skeletal muscle or cardiac muscle remains completely undisturbed, the membrane potential remains at the resting

membrane potential, generally at -85 mV. However, any factor that suddenly increases the permeability of the membrane to sodium is likely to elicit a sequence of rapid changes in membrane potential lasting for several milliseconds, followed immediately thereafter by return of the membrane potential to its resting value. This sequence of potential changes is called the action potential. The action potential occurs mainly in two stage called depolarization and repolarization, and the action potential wave shows its various phases as it passes on a cell membrane. As describe in the introduction, the cardiac action potential consists of five different phases, which is more complex than that of skeletal or nerve cells. Depolarization is the earliest events in excitation, developing a positive state inside of the cell. This positive state inside the cell is called the reversal potential. Almost immediately after the depolarization phase of an action potential that has just previously changed the membrane potential to a positive value, the normal resting membrane potential returns. This is called repolarization.

Some of the factors that can evoke an action potential are electrical stimulation of the membrane, application of chemicals to the membrane to cause increased permeability to sodium, mechanical damage to the membrane, heat, cold or almost any other factor that momentarily disturbs the normal resting state of the membrane. Action potential generation is the result of ion current flowing through many ion channels that are embedded in the cell membrane. Those channels are permeable to different ions (sodium, potassium, calcium) and open and close at different voltage levels with different time constants. The ion current flowing through a channel is determined not only by the biophysical characteristics of the channel but also by the intracellular and extracellular environment that surrounds the cell membrane. For ion channels to perform their physiological function, there has to be a gradient in ion concentrations on both sides of the membrane. Sodium and calcium concentrations are higher outside that inside the cell; potassium concentration is higher on the inside. In maintaining those gradients, ion pumps transform metabolic energy into potential electrochemical energy that is used by the ion channels. Briefly,

ion channels can be thought of as mediating the dynamic portions of the action potential and in contrast, pumps and exchangers contribute to the overall behavior of the action potential, but they have slower effects than the rapidly opening and closing channels.

In having a quantitative understanding of action potential generation and propagation, the characterization of the individual currents which flow across the cell membrane, either by ion channels or pumps and exchangers, that contribute to the action potential has been required. Still, after all currents have been characterized, a quantitative understanding of the cell action potential is possible only when all ion currents are intergrated to reproduce the action potential. To intergrate the different ion currents to reconstruct the action potential, a parallel conductance model describe by an equivalent electrical circuit was proposed as shown in Figure 2.6, which was pioneered by Hodgkin and Huxley[10]. Since then, the research in area action potential generation and propagation has been active. The capacitor, C_m represents the membrane capacitance. The branches of the circuit represent the different ways in which ions move between the intracellular and extracellular spaces through the membrane and originate an ion current. Ions can move as a result of concentration gradients through channels whose conductance is time and voltage dependent, or through channels with constant conductance (background or leak). Ions can also be transported across cell membranes by pumps and exchangers that are necessary to restore concentration gradients, which also results in ion currents that contribute to the action potential. The battery on a particular branch represents the equilibrium (or Nernst) potential (E_i) for that ion, and the variable resistance represents that the resistance (R_i) (or conductance (G_i)) of the channel changes as a function of membrane voltage and time.

Furthermore, the total transmembrane current in the parallel conductance model can be expressed by the sum of membrane capacitive and ion currents as Eq. (2.9). Note that, the above equation is for computations of an action potential in a single cell where there are no spatial changes in transmembrane potential. The number of branches and the formulation of the currents depend on the type of tissue to model and they have

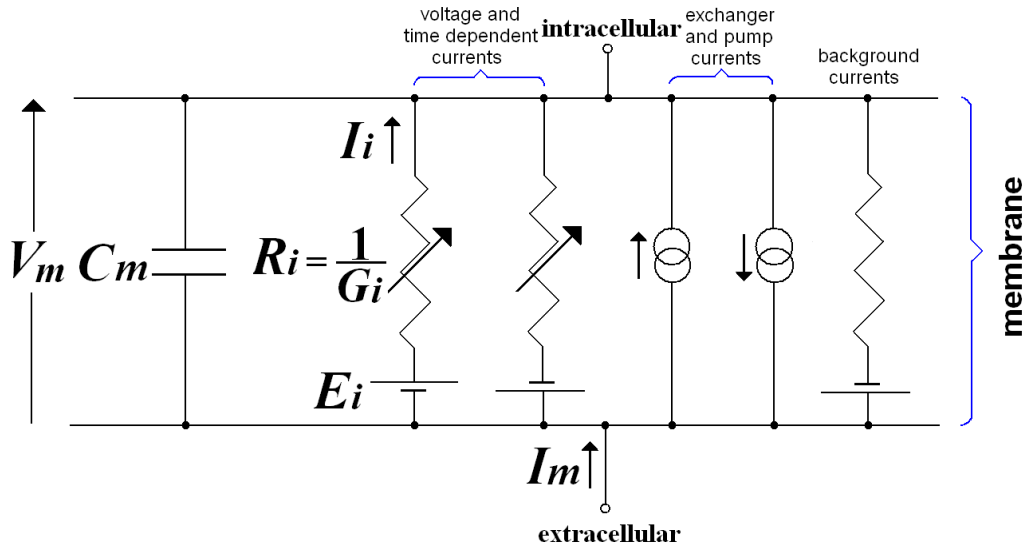


Figure 2.6: The parallel conductance model of active membrane

changed over time as the discovery of new currents or the reformulation of old currents. These action potential models and the mathematical description of the action potential, specifically in cardiac cell, will be described further in the next section.

$$I_m = C_m \frac{dV_m}{dt} + I_{ion} = C_m \frac{dV_m}{dt} + \sum I_i \quad (2.9)$$

where,

I_m : the total membrane current

C_m : the specific membrane capacitance to ion

V_m : the transmembrane voltage

I_{ion} : the total ion current

I_i : the ion current

2.3 Mathematical Models of Excitable Membrane

Since early twentieth century, experimental researches on the membrane potential and the action potential have made it possible to reveal the underlying mechanisms in the electrical state of the heart. Although the experimental studies are generally preferable, investigating the cardiac electrical behavior experimentally poses a number of challenges, such as a limitation on quantity of variables for monitoring or deprivation of high-resolution data in investigating larger preparations. On the other hand, modelling techniques for a computer simulation of cardiac electrical behavior are not associated with such complications. At the same time, it became clear that, a mathematical description used to simulate the cardiac action potential would be useful to interpret experimental data and also to generate hypotheses that could later be tested experimentally. Action potential models have been very useful in investigating different features of cardiac electrophysiology, from action potential generation in a single cell to action potential conduction in multidimensional structure of cardiac tissues.

It is known that the action potential is the result of the interaction of cellular components, including the dynamics of the different ion channels embedded in the cell membrane, changes in concentrations of ions inside and outside the cell, and how cells are connected. Hodgkin and Huxley[10] who are the first group that intend to formulate mathematically the cellular processes to lead the generation of the action potential. They proposed an ion model that is specified by 3 types ion channel currents that are involved in the generation of the action potential to represent the flow of sodium, potassium and chloride (leakage or background) through the membrane of squid axon. It is known that the formulation in ion models have always changed over time because of the revelation of new or more accurate currents. And, it also depends on a specific tissue or a cell that is needed to be modeled. Basically, in formulating an ion model of the action potential, the kinds of currents that should be part of the model have to be determined to model the individual ion channels. As for, the ion channels dominate depolarization and repolarization, and the process of

the repolarization is largely understood as the dynamic interaction of the membrane ion channels. Consequently, in many situations the action potential can be approximated well using a model containing only channels. Nonetheless, for the ion channels to perform their function, modelling the right changes in ion concentrations should be also put into consideration.

Once all ion currents and changes in ion concentrations have been formulated, the need to be intergrated in the equivalent electrical circuit of the parallel conductance model to produce an action potential. To compute the action potential, the intergration of the governing differential equation is as follows:

$$I_m = C_m \frac{dV_m}{dt} + I_{ion} \quad (2.10)$$

$$C_m \frac{dV_m}{dt} = I_m - I_{ion} \quad (2.11)$$

where,

I_m : the total membrane current [$\mu\text{A}/\text{cm}^2$]

C_m : the specific capacitance [$\mu\text{F}/\text{cm}^2$]

V_m : the transmembrane voltage [mV]

I_{ion} : the summation of all ion current [$\mu\text{A}/\text{cm}^2$]

The simplest way to intergrate the equation is to use the forward Euler method:

$$\frac{V_m^{t+\Delta t} - V_m^t}{\Delta t} = \frac{-I_{ion}^t}{C_m} + \frac{I_m^t}{C_m} \quad (2.12)$$

$$V_m^{t+\Delta t} = V_m^t - \Delta t \left(\frac{-I_{ion}^t + I_m^t}{C_m} \right) \quad (2.13)$$

From equation (2.13), the transmembrane potential at a later time ($V_m^{t+\Delta t}$) can be calculated from the transmembrane potential (V_m^t), the total ion current (I_{ion}^t) and the total membrane current (I_m^t) at a given time (t). In simulating the action potential, the total membrane current (I_m^t) stated here is the axial current, corresponding to such as external current stimulations. Δt is the time discretization step and the value of the time discretization step has to be small enough to calculate V_m accurately during rapid changes

in the transmembrane potential. Typically, a value of $\Delta t=1 \mu\text{s}$ is used.

Most of the modern electrophysiological concepts and methods were developed by the computational technique of the action potential models in nerve cells. Nevertheless, mathematical modeling in single cell that contributes to the action potential in cardiac cells also has been used extensively to increase the understanding of cardiac electrophysiology and has proven its usefulness. The typical parameters of the cardiac cell for reference in the cardiac cell modeling are shown in Table 2.1 [37]. Initiated in the first modeling attempt by

Table 2.1: The typical parameters of the cardiac cell

Symbol	Value	Definition
d_c	15 μm	Cell radius
l_c	15 μm	Cell length
σ_i	4 mS/cm	Intracellular conductivity
σ_e	20 mS/cm	Extracellular conductivity
C_m	1 $\mu\text{F}/\text{cm}^2$	Specific membrane capacitance
R_m	6 $\text{k}\Omega\text{cm}^2$	Specific membrane resistance
V_{rest}	-84 mV	Resting potential

FitzHugh[11] and Noble[12], continued by Beeler and Reuter[13], Luo and Rudy[3, 14, 15], and many others, until today[38] where a large number of detailed physical state variables has been introduced in the models, taking new experimental observations at cellular and sub-cellular levels into account[39, 40, 41]. Recent studies have started to use those detailed biophysical models to investigate excitation conduction in heart tissues[42, 43, 22, 44].

It is known that, the atria function principally as entry ways to the ventricles and the major function is in the ventricles, where the ventricles supply the main force that propels blood through the circulatory system of the body. Furthermore, the development of stray impulses in the heart or reentrants can cause ventricular fibrillation and the rapidity of transmission of the cardiac impulse throughout the ventricles plays an important role in preventing serious cardiac arrhythmias. As regards, in this study, we applied an ion channels-based model of the ventricular action potential, which is called the Luo-Rudy phase I (LR-I) model in developing the analog-digital circuit model. The detailed

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