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MATHEMATICAL ANALYSIS OF ELECTROPHYSIOLOGICAL CARDIAC TISSUE MEMBRANE MODELS

[1]Ojimadu U. H, [2]Oluwole, A. O., *[1]Olasupo A. O., [1]Usman M. A., [1]Odule T. J., [1]Olubanwo O. O., [3]Oyewole O., [4]Ayodele M. A.

[1]Department of Mathematical Sciences, Olabisi Onabanjo University, Ago-Iwoye, Nigeria.
[2]Department of Internal Medicine, Ben Carson (Snr) School of Medicine, Babcock University.
[3]Physical Sciences Department, Bells University of Technology, Ota, Nigeria.
[4]Open and Distance Learning Centre, Olabisi Onabanjo University, Ago Iwoye, Ogun State, Nigeria.

*Corresponding authors' email: ahmed.olasupo@oouagoiwoye.edu.ng

ABSTRACT
This paper presents some cardiac electrophysiological models. Proper mathematical analysis was done on the proposed models. In the cause of the analysis, several assumptions were made which helped in providing a parallel platform for making qualitative solutions so as to reduce any form of bias. Graphical analysis was adopted in solving the cardiac electrophysiological models using conservation and dispersions equations. The results obtained were derived from computer simulation by observing ring lengths on a valid restitution curve. The restitution curves helps us to subject three different turns of ring lengths and certain observations were made on the behavior of the three ring lengths. An increase in ring length will cause a corresponding increase in blood circulation and vice versa. It was suggested that 2D or 3D computer simulation should be adopted for better performance and yield of the models.

Keywords: Cardiac electrophysiological models, Restitution curve, Computer simulation, Graphical analysis, Ring length

INTRODUCTION

The heart is a muscular pump responsible for the transportation of blood and nutrients through blood vessels and arteries. This function of the heart makes it a very vital organ in the human body system. Once the heart stops working, it results in cardiac arrest. A great number of sudden deaths that occur in recent times is traceable to cardiac arrest, which is due to the cardiac electrical abnormalities preventing blood circulation to various compartments of the body. In view of this, we shall take a look at a thorough analysis of the electrical activities of the heart and deduce a mathematical analysis for the electrophysiological cardiac tissue membrane model.

Cardiac electrophysiology is the study of the mechanisms, functions and performance of the electrical activities of the heart (Adebisi et al., 2012). The mechanical contraction of the heart muscles is activated by electrical depolarization of the cell membrane and coordinated by the distribution of depolarization through the tissue from the Sino Atrial Node (SA Node) to other regions of the heart.

Researchers have studied the sequence of activities which cause depolarization and repolarization of the heart, which can be measured through electrodes and other many techniques like optical imaging (Efimov *et., al* 2004). It is in view of this that electrophysiological models were adopted, inspired by the pioneer work of (Hodgkin and Huxley 1952), which gave rise to many mathematical models (Fenton and Cherry 2008). (Nash and Panfilov 2004) presented a computational framework to couple a three-variable. Excitation-tension model to governing equations of nonlinear, stress equilibrium employing the electromechanical and mechano-electric feedback (FitzHugh 1955).

Unlike other cells in the human body, the cardiomyocytes responsible for the excitability of the heart cells obeys the "all-or-none" law, meaning that if the stimulus is above a suitable threshold, a complete action potential with peak value independent of the stimulus generated, otherwise no response is provided by the cell. Therefore, the cardiac muscles of the heart are arranged in inter-connected manner such that if one of the muscle cell is excited, the action potential will spread from cell to cell through its interconnection. The interconnected nature of the cardiac muscle fibres is called syncytium (Praveen *et., al* 2016). This paper seeks to identify some cardiac electro-physiological models in (Henriquez, C.S and Papazogou, AA 1996), Arrhythmogenesis, (Clayton, R.H. and Panfilov, A.V. 2008), (Nash et., al 2006), (Niederer, S.A and Smith, N.P 2007) and provide a mathematical analysis for cardiac electrophysiological models. The mathematical analysis of this model will be useful to determine the diagnostic information about the heart.

MODELS OF CARDIAC ELECTROPHYSIOLOGY

A model helps us to understand relationships between physical phenomena. It helps us to represent real situations using symbols and relationships. We shall be looking at some cardiac electrophysiological models to help us better describe relationship between variables in cardiac electrophysiology. The heart is enhanced by a special system for generating rhythmical electrical impulses to cause rhythmical contraction of the heart muscles and conducting these impulses rapidly through the heart is the Sino Atrial Node (SA), the Atrio-Ventricular Node (AV), AV Bundle, Right and Left Bundle Branches. Purkinje Fibres are the main components of the conducting system in the heart (Guyton and Hall 1996). The electrical impulses induce intracellular calcium cycling which in turn causes heart muscles to contract which is known as the excitation-contraction coupling (ECC)

Hodgkin Huxley Model

This model is the basis for the cardiac electrophysiological models. In this work of (Hodgkin and Huxley 1952), the Beeler-Reuter (BR) model describes the trans membrane voltage in a single cell as follows

$\frac{\partial v_m}{\partial t} = -\frac{I_{ion}}{C_m}$ (1)

Where, v_m represents transmembrane voltage, C_m represents membrane capacity and the total current is described as:

$I_m = C_m \frac{\partial v_m}{\partial t} + I_{Na} + I_K + I_L - I_{app}$ (2)

Where I_{Na} = Voltage-gated Na current

I_K = Voltage-gated K current

I_L = Voltage-gated Leaked current

I_{app} = Applied stimulus current

The electrical characteristics of excitable cell such as cardiac myocytes and hence, it is a continuous time model

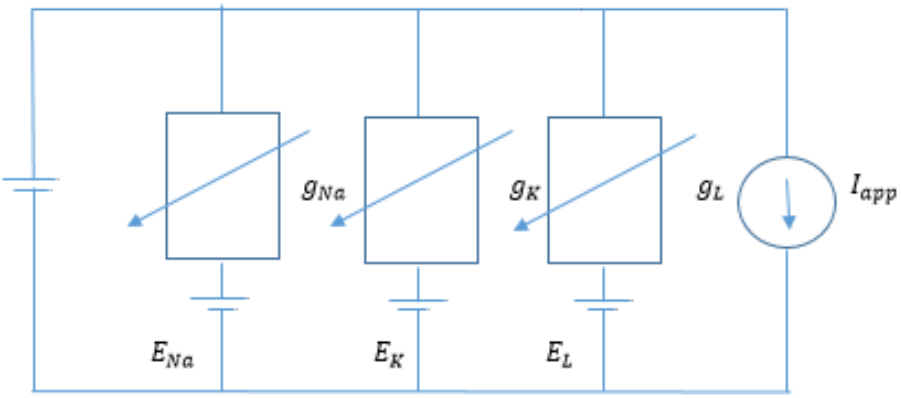


Figure 1: Intracellular Medium

Hodgkin – Huxley Model of Action Potential

The movement of each of these currents (Sodium (Na), Potassium (K), and Leaked (L) current) is proportional to the conductance times the driving force [3]. Hence

$I_{Na} = g_{Na}(V_m - V_{Na})$ (3)

$I_K = g_K(V_m - V_K)$ (4)

$I_L = g_L(V_m - V_L)$ (5)

From equation (1), if I_{ext} is the externally applied current, then

$I_{ext} = C_m \frac{\partial v_m}{\partial t} + I_{ion}$ (6)

Therefore, combining equations (3), (4) and (5) into equation (2), we obtain

$I_m = C_m \frac{\partial v_m}{\partial t} + g_{Na}(V_m - V_{Na}) + g_K(V_m - V_K) + g_L(V_m - V_L) - I_{app}$ (7)

This is the Hodgin-Huxley Method of the action potential.

The Cable Model

One dimensional fibre is considered as an extended cylindrical cell membrane. The relationship will be considered as valid if the gap junction resistance is negligible. In this model, charge carriers are assumed to move in only one dimension inside and outside of the cell. To better visualize the behavior of ionic current across the cell membrane, we need a model of electrical behavior of the cells in terms of action potential. Lord Kelvin developed the cable model to demonstrate the cardiac cell which is considered as a cylindrical membrane which separates internal conducting medium from extracellular conduction medium from extracellular conduction medium as shown in Figure 2 below:

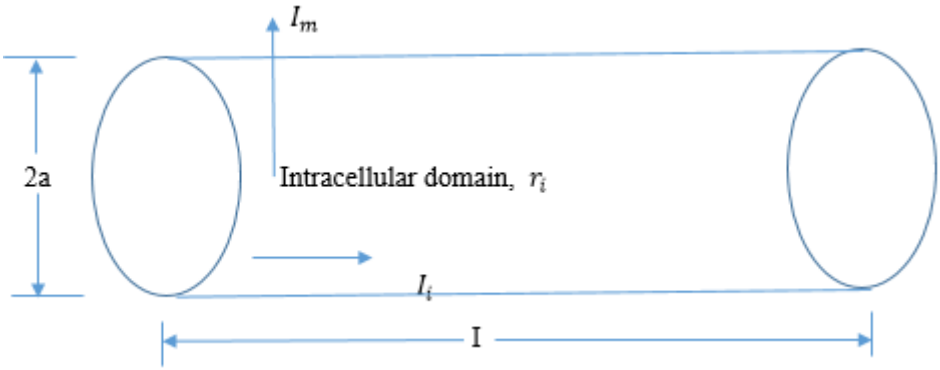


Figure 2: Schematic representation of an extended excitable cell

The cell membrane act as a relative insulator with properties described in (Boyett et., al 1997) and the potential depends only on the length variable and on time as shown in figure 3

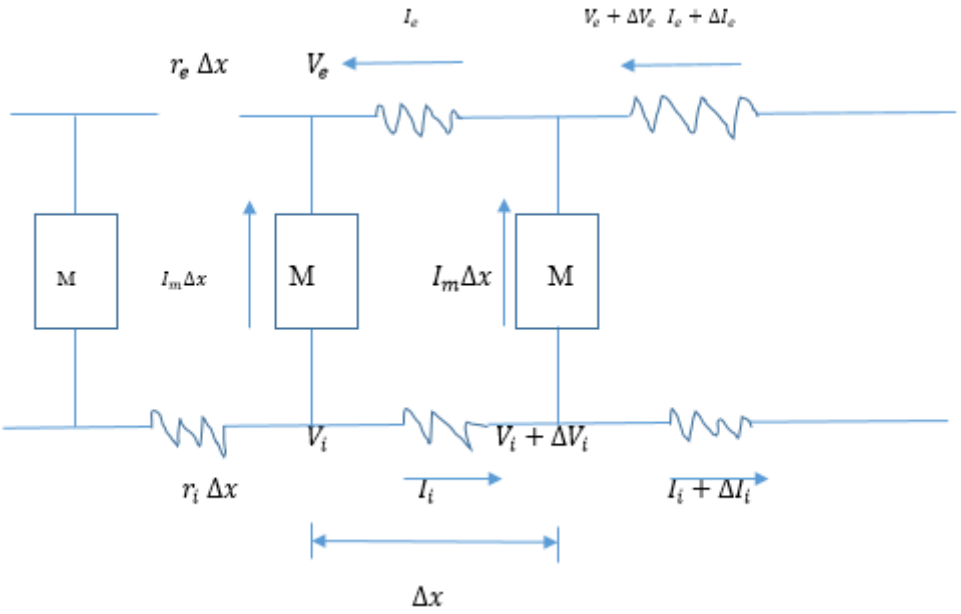


Figure 3: Schematic representation of cell membrane

M = Lumped properties of the membrane over a length Δx
r_i = intracellular conductors resistance per unit length
r_e = extracellular conductors resistance per unit length
I_m = membrane current
V_m = membrane potential
$V_m = V_i - V_e$
V_i= intracellular potential
V_e= Extracellular potential
I_i= Current flowing inside the call
I_e = Current flowing outside the cell

According to Newton's law, action and reaction are equal and opposite. Thus, applying the Ohm's law at inner conductor.

$$I_i r_i \Delta x = -V_i \quad (8)$$

In the limit Δx tends to zero, this becomes;

$$\frac{\partial V_i}{\partial x} = -I_i r_i \quad (9)$$

$$\frac{\partial V_e}{\partial x} = -I_e r_e = I_i r_e \quad (10)$$

Applying the cardiac computational limit at any node, we obtain

$\Delta I_i = -I_m \Delta x$; that is

$$\frac{\partial I_i}{\partial x} = -I_m \quad (11)$$

According to the definition of V_m

$$\frac{\partial V_m}{\partial x} = -I_i(r_i + r_e) \quad (12)$$

Differentiating equation (12) and substitute in (11), we obtain

$$\frac{\partial^2 V_m}{\partial x^2} = I_m(r_i + r_e) \quad (13)$$

Making I_m, the subject of (13), we get

$$I_m = \frac{1}{(r_i + r_e)} \frac{\partial^2 V_m}{\partial x^2} \quad (14)$$

The membrane current per unit length is

$$I_m = C_m \frac{\partial V_m}{\partial t} + \frac{V_m}{r_m} \quad (15)$$

Where C_m = membrane capacitance per unit length
r_m = membrane resistance per unit length substituting equation (15) into (14), we have

$$\frac{\partial^2 V_m}{\partial x^2}(x,t) = (r_i + r_e)\left(C_m \frac{\partial V_m}{\partial t} + \frac{V_m}{r_m}\right) \quad (16)$$

The equation (16) represents the one dimensional cable equation.

Bidomain Model

The bidomain model is a mathematical model for the electrical propagation of the cardiac muscle that takes into account the anisotropy of both intracellular and extracellular spaces (Praveen et., al 2016). The model is the generalization of one dimensional cable theory (Boyett et., al 1997) and it is also known as continuum models. Every muscles of the myocardium lies in the intracellular and the extracellular domains (Belhamadia 2010) and (Keener and Sneydb 1998). This model takes into consideration the different electrical conductivities of the Intracellular and Extracellular spaces using the myocardial fibre as a reference point, their conductivities in the direction parallel to this fibre are always in the perpendicular direction to the myocardial fibres. The variation in anisotropy ratios of the intracellular and extracellular cells accounts for the assumptions of the bidomain models. This model has two nonlinear partial differential equations coupled to a system of ordinary differential equations.

Considering the generality that conductivities of extra and intra-cellular fluid show anisotropy along the fibre axis x. Then $g_e(x)$ and $g_i(x)$ are given functions of x.

By definition $V_m = V + V_e$. According to ohm's law;

$$\frac{\partial V_i}{\partial x} = -r_i I_i, \frac{\partial V_e}{\partial x} = -r_e I_e$$

As defined in equations (9) and (10). According to Kirchoff's law the loss of longitudinal current (per unit length) must precisely equal the transmembrane current.

$$\frac{\partial I_m}{\partial x} = -I_m, \frac{\partial I_e}{\partial x} = -I_m + I_a \quad (17)$$

Where I_a= externally current applied to external domain and resembling defibrillation shock applied to tissues of higher dimensions.

And $I_m = C_m \frac{\partial V_m}{\partial t} + \frac{V_m}{r_m}$ as in equation (15)

Using equations (9), (10) and (17), we obtain two basic equations for bidomain one-dimensional tissue representation

$$\frac{\partial V_m}{\partial t} = \frac{1}{C_m}\left[\frac{\partial}{\partial x}\left(\frac{1}{r_i(x)}\frac{\partial V_m}{\partial x}\right) + \frac{\partial}{\partial x}\left(\frac{1}{r_i(x)}\frac{\partial V_e}{\partial x}\right)\right] - \frac{1}{C_m}(I_{ion} + I_{app}) \quad (18)$$

And $\frac{\partial}{\partial x}\left[\left(\frac{1}{r_i(x)} + \frac{1}{r_e(x)}\right)\frac{\partial V_e}{\partial t}\right] = -\frac{\partial}{\partial x}\left[\frac{1}{r_i(x)}\frac{\partial V_m}{\partial x}\right] - I_a \quad (19)$

If r_i and r_e do not change along the fibre axis x, equations (18) and (19) may be simplified

$$\frac{\partial V_m}{\partial t} = \frac{1}{C_m r_i}\left[\frac{\partial^2 V_m}{\partial x^2} + \frac{\partial^2 V_e}{\partial x^2}\right] - \frac{1}{C_m}(\sum I_s + I_{st}) \quad (20)$$

And $\left(\frac{1}{r_i} + \frac{1}{r_e}\right)\frac{\partial^2 V_e}{\partial x^2} = \frac{-1}{r_i}\frac{\partial^2 V_m}{\partial x^2} - I_a \quad (21)$

Where I_{st} = stimulated current
And I_s = excited current
These two equations (20) and (21) can be reduced to one if we substitute the expression for $\frac{\partial^2 V_e}{\partial x^2}$ obtained from equation (21) into (20), we obtain

$$\frac{\partial V_m}{\partial t} = \frac{1}{C_m r_i}\frac{\partial^2 V_m}{\partial x^2}\left[\frac{1}{\frac{r_e}{r_i}+1}\right] - \frac{1}{C_m}\left[\sum I_s + I_{st} + I_a\frac{1}{1+\frac{r_i}{r_e}}\right] \quad (22)$$

Monodomain Model

The monodomain model is a reduction of the bidomain model of the electrical propagation in the myocardial tissue. The assumption is that the Intra and extra-cellular domain have equal anisotropy ratios. It implies that the conductivities in the intracellular space is directly proportional to the extracellular space.

From equation (22), we observe the presence of additional stimulus

$I_a\frac{1}{1+\frac{r_i}{r_e}}$ originally applied to extra-cellular domain

If we denote $\frac{r_i}{r_e} = \delta$. Then if the diffusion co-efficient for bidomain case is D' and $D = I_a$ then we can re-write $I_a \cdot \frac{1}{1+\frac{r_i}{r_e}}$ as D' so that

$D' = \frac{D}{1+\delta}$ because $\delta > 0$,

$D' < D$ and when $\delta \to 0$ in equation (22), then we arrive at the monodomain models, given below

$$\frac{1}{r_i C_m}\frac{\partial^2 V_m}{\partial x^2} = \frac{\partial V_m}{\partial t} + \frac{1}{C_m}\sum I_s + \frac{1}{C_m} I_{st} \quad (23)$$

Equations (23) is the monodomain model.

RESULTS AND DISCUSSION

To graphically analyse the electrophysiological models, we have to study the excitation wave propagation in a ring of cardiac tissue, which is subjected to significant practical and theoretical importance (Karma *et., al* 1994), (Chialvo 1990) and (Ito and Glass 1992). Circulation of a pulse around a ring-shaped excitable tissue can be started by applying two stimuli at two approximately chosen points on a ring with a time delay. The circulation of the excitation in a ring is governed by two relationships. The first is conservation equation.

$$T_{CK} = APD_K(DI_{k-1}) + DI_k;\ T_{CK} = \frac{L}{\theta_K} \quad (24)$$

The second is the dispersion equation

$$\theta_K = f(DI_{k-1}) \quad (25)$$

K = Subscript indicating the number of pulse turn in a ring.
T_{CK}= time required for circulation of the pulse around the ring
APD_K= action potential duration
DI_k= diastolic interval
θ_K = velocity of pulse propagation

For us to plot this graph, the following assumptions are necessary

i. APD restitution curves measured on an isolated cell and on a cell in a ring are the same
ii. The velocity of a pulse propagation in a ring is constant for the duration of a turn in circulation

Equation (24) represents a straight line in the coordinates (APD, DI). The distance of this line from the centre of coordinates is proportional to the ring length L. the dependent variable in equation (25) is plotted under ADP restitution curve. Both curves in equation (24) and (25) are obtained by computer simulation of the simplified model (Kogan et., al 1995). The first turn of pulse propagation in a ring is clarified in figure 3A and the other three in figure 3B are three cases with ring lengths $L_1 > L_2 > L_3$ which corresponds to stable circulation of the border of instability and unstable circulation respectively for the main tissue formed with cell models without developed Ca dynamics.

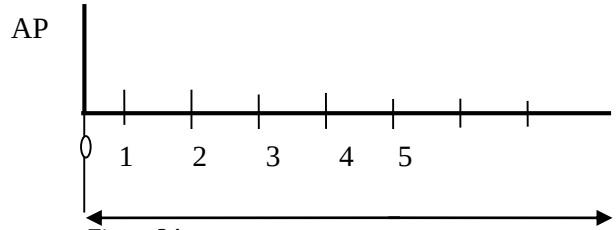
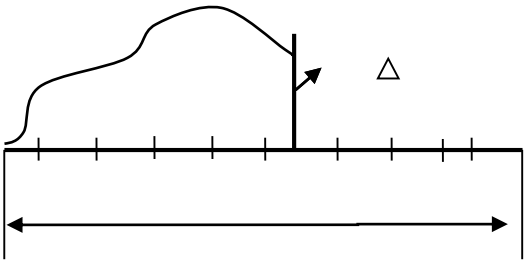


Figure 3A



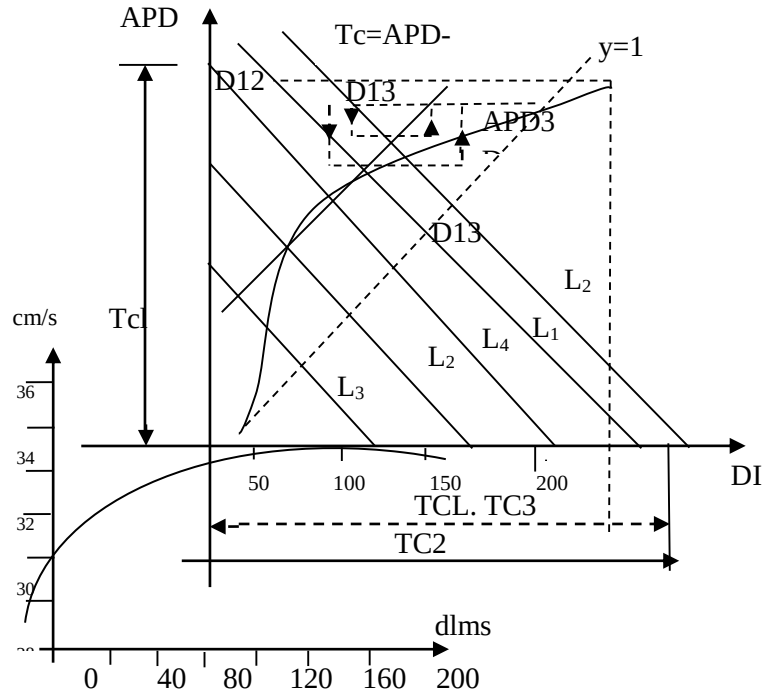


Figure 3B

RESULTS

To analyse the results obtained from the graph on fig 3A and fig 3B, we shall study the several turns of pulse circulations using this curves. In the conservation equation (24), we shall consider three cases:

First Turn

We initiate the excitation propagation in a ring when 1D fibre is at rest. Therefore, the APD_i=APD_{imax} and $\theta_1 = \theta_{1max}$

$$\lambda_1 = \theta_{1max} APD_{1max}$$

We assume that $L_1 > \lambda_1$, so $L_1 - \lambda_1 = \Delta I_1$ and $DI_1 = \frac{\Delta I_1}{\theta_{1max}}$

Second Turn

From APD restitution and dispersion curves (shown in fig 3B), we find APD_2 and θ_2. $\theta_2 < \theta_1$.

Assuming that θ_2 is a constant on the second pulse turn, we obtain $T_{c2} > T_{c1}$ and on the graph in figure 3B, the straight line L changes its position to L_1. Using the obtained values of APD_2 and θ_2, we determine the corresponding wavelength and DI_2 for the second turn;

$\lambda_2 = \theta_2 APD_2$ so $\lambda_2 < \lambda_1$

$L_1 - \lambda_2 = \Delta I_2$, so $\Delta I_2 > \Delta I_1$ and

$$DI_2 = \frac{\Delta I_2}{\theta_2};\ DI_2 > DI_1$$

Third Turn

Using APD restitution and dispersion curves, we find $APD_3(DI_2)$ and $\theta_3(DI_2)$; $\theta_3 = \theta_1$ but $\theta_3 > \theta_2$. The third cycle time $T_{c3} = \frac{L_1}{\theta_3} = T_{c1}$ and line L_1' return to the close vicinity of L_1. The wavelength $\lambda_3 = \theta_3 APD_3$. Since $APD_3 > APD_2$ and the diastolic interval on the third turn is

$DI_3 = \frac{\Delta I_3}{\theta_3}$, here $\Delta I_3 = L_1 - \lambda_3$

Because $\Delta I_3 < \Delta I_2 \ldots DI_3 < DI_2 \ldots$

The graphical analysis shows a corresponding relationship between the ring length L and the circulation of blood in the human cardiovascular system as modelled by cardiac electrophysiological model. For ring length L_1, the APD restitution curve shows a stable circulation, the ring length L_2 shows a border of stability in circulation while the ring length L_3 shows unstable circulation which leads to termination of circulation and could lead to sudden death since blood circulation ceases or paralysis of certain part of the human body system.

CONCLUSION

This paper reveals the mathematical analysis of electrophysiological models. It presents some of these models with a view of providing adequate information on the relationship between the cardiac functioning and its relevance to practical computer simulation. Some assumptions were made and the following conclusions were adopted for the advancement of knowledge in cardiac electrophysiological models. It was arrived at that as the ring length increases, there is an increase in blood circulation and a corresponding decrease in ring length will also result in reduction of blood circulation. It however suggested that other procedures such as 2D or 3D computer simulations should be adopted to produce a better result.

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