IOSR Journal of Biotechnology and Biochemistry (IOSR-JBB)
ISSN: 2455-264X, Volume 1, Issue 2 (Jan. – Feb. 2015), PP 01-11
www.iosrjournals.org

Modeling of generation and propagation of cardiac action potential using fractional capacitance

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Abstract: *This paper proposes modeling of canine cardiac action potential using fractional differential equations (FDE). The movement of ions across cardiac myocytes (heart muscle) generates a voltage signal which propagates along the body of the cell as action potential. The complex behavior of such physiological events can be understood by developing mathematical models that describe the biological phenomena. Typically, ordinary linear differential equations are used for constructing these mathematical models. In this paper we have shown that a non-integer order differential equation model can capture these events more precisely. Using FDE we are able to model cardiac action potential with a higher degree of accuracy compared to ordinary differential equations (ODE).*

Keywords: *Action potential (AP), Cardiac arrhythmia, Cardiac myocytes, Electrical model, Fractional differential equations (FDE), Ion exchange mechanism*

I. Introduction

Heart beat is triggered by a series of electrical events taking place in the tissues of the heart. These electrical events are characterized by changes in electric potential between the interior and exterior of the cells of the cardiac tissue, leading to the generation of cardiac action potential. This action potential is a spike generated by the difference of potential between the interior and the exterior of each cardiac cell and follows a consistent trajectory [1]. Such spikes are generated due to the movement of ions through the transmembrane ion channels in the cardiac cells [2]. The period during which the action potential spike lasts is called the absolute refractory period. No other action potential can be fired during this period [3]. The absolute refractory period is followed by the relative refractory period. During this period a stronger than usual stimulus is required to fire another spike [3].

The abnormal conduction or irregular formation of an action potential can disrupt the normal rhythm of the heart and may lead to conditions such as cardiac arrhythmia, tachycardia or bradycardia [7, 8]. Such alterations in the normal rhythm of the heart, if not diagnosed properly, can prove to be fatal in many cases [8, 9]. A cardiac myocyte model captures the ionic phenomenon at the cellular level with a mathematical description and describes the generation and propagation of the action potential [1]. This modeling of the cardiac action potential can be extremely helpful in analyzing the rhythmicity of heart. Hodgkin and Huxley, in 1952, proposed an electrical model of the giant squid axon (nerve cell) [10]. Much of the mathematics of cardiac cell modeling is inspired by the Hodgkin-Huxley (HH) model [11,12]. This analogy has been drawn because of the fact that neural and cardiac cells have similar ion exchange mechanisms [1].

The complexity of mathematical models capturing the dynamics of cardiac myocytes has increased over the past few decades [13, 14]. The discovery of new ion channels and ionic phenomena in addition to the advancement in voltage-clamp techniques has contributed towards increasing this complexity [14-22].

In the resting phase, also known as the polarized state, the interior of the cardiac myocyte has higher concentration of K^+ ions as compared to the exterior [23]. Phosphate and the conjugate bases of organic acids are the major anions inside the cell [23]. Outside the cell, Na^+ ions and Cl^- ions have higher concentration [23]. In cardiac myocytes, at the beginning of the depolarization phase, the influx of Ca^{2+} ions through voltage-gated calcium channels on the sarcolemma induces release of Ca^{2+} ions from the sarcoplasmic reticulum. This phenomenon is called calcium-induced calcium release [4] and increases the free Ca^{2+} ions concentration in the myoplasm causing muscular contraction. At the same time Na^+ ions enter the cell, further depolarizing the cell. As the cell potential reaches a threshold, fast Na^+ ion channels open on the sarcolemma and an action potential (AP) is fired. As the cell is depolarized and reaches a positive potential with respect to the exterior of the cell, K^+ ion channels open. The K^+ ions leave the cell while Ca^{2+} ions are still entering the cell. No new AP spike can be fired during this period. This period is known as the absolute refractory period. When the absolute refractory period subsides, Ca^{2+} ion channels close while flow of K^+ ions out of the cell continues, causing repolarization of the cell. The cardiac muscle cells are tightly bound such that when one of these cells is excited the action potential propagates to all of them [2, 4, 5]. The selective permeability of these ion channels leads to the generation and propagation of the action potential [6]. Mutations in cardiac ion channels may lead to

deformation in the action potential [6].

Models of cardiac cell can provide useful insights into the underlying ion exchange mechanism [73]. Several models of cardiac myocytes have been proposed over the past few decades [73]. The Beeler-Reuter, Luo-Rudy, Jafri et al., Winslow et al., Fox et al., Greenstein-Winslow, Cabo-Boyden, Hund-Rudy and Flaim et al. models are some of the most significant ones [69,14-22].

Luo and Rudy, in 1991, proposed a mathematical model of the electrical activity of mammalian ventricular myocyte [68] based on the Beeler and Reuter model [69]. Their aim was to improve the Beeler and Reuter model by incorporating advanced empirical data available with the improvement in experimental techniques in subsequent years. The Luo-Rudy model focuses on the phenomena of depolarization and repolarization in cardiac action potential. This model was limited to modeling the phenomena related with the fast inward Na^+ current and the outward K^+ currents. Later they improved the model by incorporating electrophysiological phenomena that regulate intracellular Ca^{2+} ion handling. This model is known as the Luo-Rudy 2 (LR2) model (1994) [18]. Jafri et al. (1998) improved upon the Luo-Rudy model by adding more detailed descriptions of the Ca^{2+} ions. They incorporated calcium-induced calcium release from Sarcoplasmic Reticulum (SR) in their model. Based on the guinea pig ventricular model proposed by Jafri et al. [15], Winslow et al. (1999) developed the first canine ventricular myocyte model for normal and infarcted cells [16]. In this model the data was taken from O'Rourke et al [70]. The Winslow et al. model predicts the mechanism of increase in action potential duration during heart failure. This phenomenon is related to the change in the release of Ca^{2+} ions from the SR.

The models discussed above, do not model the alternans of canine ventricular action potential duration completely. To overcome this limitation, Fox et. al (2002) [13] developed a model incorporating ionic currents from the Luo-Rudy [18], Winslow et al. [16] and Chudin et al. [17] models to describe the alternans occurring at fast pacing rates.

The ionic currents in the infarcted cardiac myocytes are significantly different from those in the non-infarcted cells. Cabo and Boyden (2003) developed a model to study the change in ionic currents in the infarcted and normal cells and the response of the action potential of infarcted cells to antiarrhythmic agents [19]. This model is based on the LR2 model.

Hund and Rudy [14], in 2004, developed an elaborate model of the canine ventricular epicardial cells to study the relationship between pacing rate, action potential properties, and Ca^{2+} ion channels. This model was based on the hypothesis that the action potential duration and Ca^{2+} transient current depend on the pacing rate of cardiac myocytes. Change in the pacing rate could lead to cardiac arrhythmias that may even result in death. This model incorporates more detailed description of calcium channels than many previous models.

Greenstein and Winslow (2002) [20] improved upon the Winslow et al. canine ventricular model adding more details about the intracellular Ca^{2+} ion handling. The model captures the calcium induced calcium release in the SR by using multiple calcium release subunits. This results in a very complex model with several thousand variables in each simulation making it computationally very intense. Greenstein et. al [21], in 2006, published a simplified version of the above model by using the method described by Hinch et. al [71].

Based on the simplified Greenstein et al. model, Flaim et al. (2007) [22] published a model to investigate the contribution of sustained components of I_{Na} and I_{Kv43} in shaping the canine ventricular action potential and to study their impact towards increasing the risk of cardiac arrhythmia.

In the present work the Hund-Rudy dynamic (HRd) model has been considered based on canine ventricular cell [14]. This model has been chosen for the following two reasons. Firstly, it incorporates the dynamic Ca^{2+}/calmodulin-dependent protein kinase II [24] (CAMKII) activity, which helps in regulating ion exchange in myocytes [25]. By autophosphorylation CAMKII enables detection of Ca^{2+} ion spike frequency and determines the AP duration [26]. Secondly, the HRd model has low computational complexity and is mathematically tractable. It has been empirically proven that the CAMKII regulatory pathway plays a role in the force-frequency relation and rate-dependent CaT abbreviation [27-29]. Through the inclusion of the CaMKII regulatory pathway this model represents an important advance in the physiologic representation of rate dependent cell processes. It is one of the most appropriate cardiac cell models as it incorporates dynamic CaMKII activity and regulation of intracellular calcium ions handling [13].

Hawkins et al. (1994) [30] have included "local control" Ca^{2+} ion release, in their rabbit AP model, as proposed by Toyofuku et al. (1994) [31] which involves statistical activation of individual Ca^{2+} ion release units in the Sarcoplasmic Reticulum. But, computational demands discourage the use of this model in modeling cardiac arrhythmias. The HRd model, on the other hand, reproduces the local-control features by using a macroscopic approach. This approach while reducing the computational demands, maintains the accuracy of the Hawkins et al. model. It also incorporates late sodium ion current, dynamic chlorine ion concentration changes, and calcium ion dependent outward transient current and novel I_{rel} formulation. Ca^{2+} ion release from the junction sarcoplasmic reticulum (JSR) constitutes the I_{rel} current. Junction Sarcoplasmic Reticulum (JSR) is the part of the SR that contains calcium release channels. These features of the model distinguish it from other

models where electrophysiological remodeling is done after heart failure [16] and cardiac infarction [19]. Since the model has only 29 variables, it is computationally more tractable compared to the Greenstein et al. and Flaim et al. models.

In the past two decades, fractional differential equations (FDE) are being used to model the dynamics underlying complex biophysiological phenomena [32-37]. For example, in [32] it has been shown that the dynamics of biological systems can be represented by FDE [39,40]. However, the ventricular cardiac cell models, including the HRd model utilize ODE to model the bio-physiological dynamic phenomena. It has been shown that FDE models the step response of a capacitor more accurately than ODE [41]. Thus the AP trajectory generated by the HRd model does not model the refractory period accurately. In the current paper, a modified HRd model has been proposed using FDE and compared the results with actual recorded canine ventricular cardiac action potential data. In this paper it has been shown that the FDE model gives a more accurate cardiac action potential compared to the conventional ODE model. An electrical circuit based on our fractional FDE model has also been designed that gives an electrical abstraction of the transmembrane ion exchange mechanism.

II. Theory

Ion exchange mechanism

There are essentially four phases of the cardiac action potential as shown in figure 1 [72]. The first phase, phase 4 in figure 1, is the polarized or resting membrane potential. In this phase the cell is not being stimulated [2]. The resting membrane potential in the ventricular epicardium is normally about -85 to -95 mV [2]. In this phase there is a higher concentration of Na^+ ions on the exterior of the cell membrane compared to the interior. The concentration of K^+ is higher on the interior of the membrane compared to the exterior. But the net concentration of positively charged ions on the exterior of the cell is higher than the interior. This leads to a negative potential inside the cell relative to the outside. This inequality in the distribution of ions is maintained by the selectively permeable cell membrane. During the initial phase the membrane is highly permeable to K^+ ions and relatively less impermeable to other ions. Thus K^+ ions are instrumental in determining the resting membrane potential. This resting state is disturbed when an adjacent cell stimulates the cell with an electric current. As soon as the cell is stimulated, its permeability towards Na^+ ions increases. This leads to a fast inward movement of Na^+ ions, as shown in figure 1, thus depolarizing the cell. This rapid depolarization triggers an action potential [37, 38]. This phase is called phase 0. Once the interior of the cell reaches a peak positive potential, the voltage-gated Na^+ channels are closed. This is the phase 1 of the myocyte action potential (See figure 1). In phase 2 of the cardiac action potential, the slow outward movement of K^+ ions continues. A small outward current is also contributed by the inward movement of the negatively charged Cl^- ions. This results in a drop in potential inside the cell (Refer to figure 1). But at the same time voltage-gated Ca^{2+} ion channels open and positively charged Ca^{2+} ions enter the cell. This leads to an equilibrium being formed between inward and outward currents for about 150 ms leading to the formation of a "plateau" [2]. During this phase the potassium ion permeability is reduced. This phase is followed by rapid repolarization. The voltage-gated Ca^{2+} ion channels close, while the slow outward movement of K^+ ions is maintained. This phenomenon maintains a net outward current, and facilitates opening of more types of K^+ ion channels. This phase is known as phase 3, as shown in figure 1. This process continues till the interior of the cell reaches a potential of about -85 mV [43].

The duration between the firing of the action potential, phase 0, till the end of the plateau phase, phase 2, is known as the absolute refractory period. It is impossible to fire another action potential during this period. The duration between the plateau phase, phase 2, till the end of the action potential, phase 4, is called the relative refractory period. During this period a stronger-than usual stimulus is required to evoke another action potential [3].

Hund-Rudy dynamic (HRd) model

The Hund Rudy Dynamic is a mathematical model of canine ventricular epicardial cells. This model comprises several transmembrane currents, like fast Na^+ ion current, fast and slow components of the delayed rectifier K^+ ion current, transient outward K^+ ion current, inward rectifier K^+ ion current, plateau K^+ ion current, L-type Ca^{2+} ion current, Na^+- Ca^{2+} exchanger ion current, Na^+-K^+ ion pump current, Ca^{2+} ion current in sarcolemma, late Na^+ ion current, Ca^{2+}-activated Cl^- ion current, and background Ca^{2+} and Cl^- ion currents [14]. A salient feature of this model is that it includes the Ca^{2+}/calmodulin-dependent protein kinase (CaMKII). CaMKII is an important chemical for regulating action potential and calcium ion transient (CaT) rate dependence. This feature was not included in the previous models.

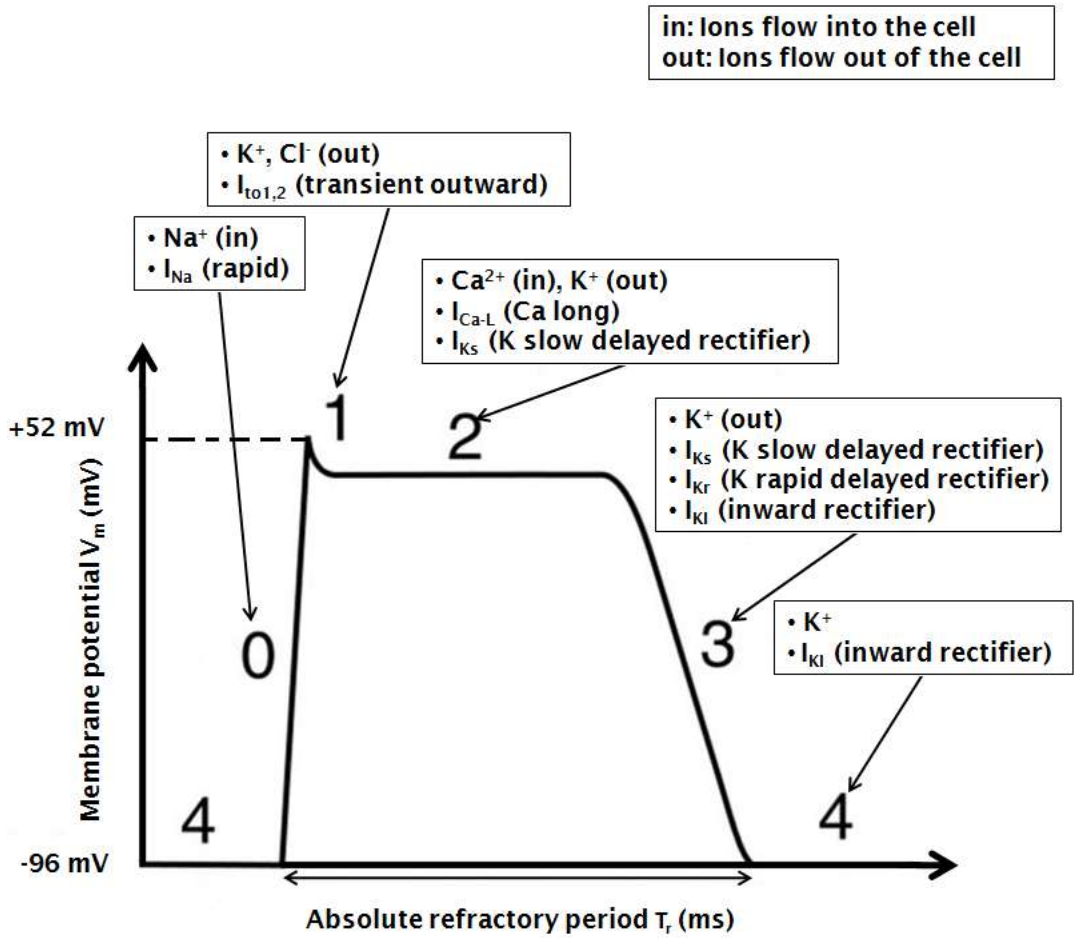

Figure 1: Ventricular action potential. In phase 0 there is rapid inflow of Na^+ ions (I_{Na}) which leads to depolarization of the cardiac myocyte. In phase 1, K^+ and Cl^- ions start flowing out generating the transient outward current, $I_{to1,2}$ and the fast Na^+ ion channels are inactivated. A balance between outward movement of K^+ ions through slow delayed rectifier potassium channels, I_{Ks}, and inward movement of Ca^{2+} ions (I_{Ca}) through L-type calcium channels is maintained in phase 2. In phase 3 the slow delayed rectifier (I_{Ks}) K^+ ion channels are still open, while the L-type Ca^{2+} ion channels close. This net outward current facilitates the opening of other types of K^+ ion channels like rapid delayed rectifier K^+ ion channels (I_{Kr}) and the inwardly rectifying K^+ ion current, I_{K1}. This causes rapid repolarization of the cell. The delayed rectifier K^+ ion channels close when the membrane potential reaches about -85 mV, while I_{K1} remains conducting throughout phase 4, contributing to set the resting membrane potential [72].

Even though the HRd model has improved upon the previous models, the absolute refractory period of the cardiac action potential generated by this model is slightly less than the recorded action potential. The reason for this is that the HRd model uses ordinary differential equations to describe the ionic processes that fail to account for the dielectric losses in the membrane [44, 32]. Whereas, fractional differential equations, as already discussed, model the step response of the capacitor more accurately [41].

Fractional differential equations (FDE)

The notion of fractional calculus comes from the idea that the order of differentiation can be generalized to a real number [74]. Hence, in equation (1), q can be any real number [75]. And, when q takes an integer value, D^q acts as an ordinary integer order differential operator [45].

$$D^q y = \frac{d^q y}{dx^q} \qquad (1)$$

It is to be noted that for integer values of q, fractional derivative of a function at a given point depends on the values of the function in the neighborhood of that point. Whereas, for integer values of q the derivative of the function does not depend entirely on the neighborhood of that point [75]. In fact, the derivative shows long

range memory behavior [32, 52].

The idea of fractional derivative can be extended to the current voltage relationship of a capacitor. It has been shown that all dielectrics are lossy in nature [46-48]. Hence, there can be no ideal capacitor. In fact, it has been observed that, in general, dielectric materials encounter losses that can be best captured by a fractional capacitor [49]. The theory of fractional capacitor model emerges from Curie's empirical law [49]. This law can be generalized to

$$i(t) = C_f \frac{d^q u(t)}{dt^q} \qquad (2)$$

where i(t) is the current across capacitor, C_f is the fractional capacitance, q is the order of derivative, and u(t) is the excitation voltage.

III. Materials and methods

Fractional calculus (FC) implies integration and differentiation to an arbitrary order [51]. The order of the differential or integral operator, for example q in equation (1), can take any real or complex value [50, 51].

FC has been successfully applied in various fields such as modeling of dynamical systems in control theory, electrical circuits, transmission lines, and viscolelasticicy [53,54]. Recent studies have shown that FC, when applied to problems in physics and engineering, provides significant advantage over conventional integer order calculus in the modeling and control of systems [53-57]. The importance of fractional order models is that they yield a more accurate description and give a deeper insight into the physical processes underlying a long range memory behavior [44].

Capacitors are one of the most indispensable elements in integrated circuits and are used extensively in many analog and digital electronic systems [58]. As capacitors occupy significant amount of die area, it is essential that they are area-efficient [58]. However, various studies have demonstrated that the ideal capacitor cannot exist in nature [46-48]. Westerlund and Ekstam have shown that the dielectric materials exhibit a fractional behavior yielding electrical impedances of the form $1/(j\omega CF)^q$, with $q \in R^+$ [49].

Proposed fractional HRd model

The HRd model has been formulated using ODE. This model fails to capture the accurate refractory period of the canine ventricular action potential. In fact, even in the steady state, ion exchange continues across the membrane. This phenomenon cannot be modeled accurately through a static (or ideal) capacitor. Intuitively, it should be possible to better capture the dynamic ion-exchange mechanism across the membrane of cardiac myocyte through a leaky (or fractional) capacitor. Hence, we propose a modified form of the HRd model that utilizes fractional capacitor. Later in this section, it will be shown that our proposed modification leads to accurate modeling of absolute refractory period of canine ventricular cardiac action potential. Use of fractional capacitor facilitates the modeling of the ion exchange mechanism of cardiac myocytes using FDE. The order of an FDE, however, cannot exceed the number of available initial conditions [59]. Hence, the minimum number of initial conditions required is the smallest integer greater than the order of the FDE. The HRd model has only one set of initial conditions. This implies that the order of the FDE cannot exceed 1. The modified HRd model is given by

$$\frac{d^q V_m}{dt^q} = \frac{-I_{tot}}{C_f} \qquad (3)$$

where,

q Order of fractional derivative,

V_m Voltage difference across membrane,

C_f Fractional capacitance,

I_{tot} Total transmembrane current,

$$I_{tot} = I_{Ca,t} + I_{Na,t} + I_{K,t} + I_{Cl,t} + I_{stim} \qquad (4)$$

$I_{Ca,t}$ Total transmembrane Ca^{2+} current,

$$I_{Ca,t} = I_{Ca(L)} + I_{Ca,b} + I_{p,Ca} - 2I_{NaCa} \qquad (5)$$

$I_{Na,t}$ Total transmembrane Na^+ current,

$$I_{Na,t} = I_{Na} + 3I_{NaK} + I_{Ca,Na} + 3I_{NaCa} + I_{Na,L} \qquad (6)$$

$I_{K,t}$ Total transmembrane K^+ current,

$$I_{K,t} = I_{Ks} + I_{Kr} + I_{K1} + I_{Ca,K} + I_{to1} + I_{Kp} - 2I_{NaK} \qquad (7)$$

$I_{Cl,t}$ Total transmembrane Cl^- current,

$$I_{Cl,t} = I_{to2} + I_{Cl,b} \qquad (8)$$

I_{stim} Stimulus current, μA/μF

The initial value of the membrane potential V_m was -84.4 mV and the current stimulus I_{tot} was 1 μA. The current stimulus is applied for a period of 0.01 ms. Once the spike reaches a threshold value of -70 mV, action potential is fired. The value of the fractional capacitance was 0.0015903 μF/cm^2. The detailed list of ion concentrations and other parameters used in the model is described in table 1 [14].

Table 1: Ionic concentrations at rest*

$[Ca^{2+}]_i$	0.0822×10^{-3} mmol/L
$[Cl^-]_i$	19.53 mmol/L
$[K^+]_i$	142.82 mmol/L
$[Na^+]_i$	9.71 mmol/L
$[Ca^{2+}]_{JSR}$	1.25 mmol/L
$[Ca^{2+}]_{NSR}$	1.25 mmol/L
$[Ca^{2+}]_o$	1.8 mmol/L
$[Cl^-]_o$	100 mmol/L
$[K^+]_o$	5.4 mmol/L
$[Na^+]_o$	140 mmol/L

*After model is undisturbed for 1000 s.

IV. Results

Determination of fractional order

The modified HRd model with fractional capacitance was simulated for different values of order of derivative q, and corresponding values of absolute refractory period T_r, were obtained. A mathematical relation was found between q and T_r using curve fitting method. A polynomial equation of third order was obtained as given by Eq. 9.

$$q = p_1 T_r^3 + p_2 T_r^2 + p_3 T_r + p_4 \qquad (9)$$

where,
q = fractional order
T_r = absolute refractory period
$p_1 = -7.476 * 10^{-6}$
$p_2 = 0.004595$
$p_3 = -0.9419$
$p_4 = 65.377$

Fig. 2 shows the plot of fractional order corresponding to the given refractory period. Along the x-axis is the value of the absolute refractory period in milliseconds (ms) and the y-axis shows the corresponding order of fractional derivative (q). Thus, given a refractory period value, its corresponding order of derivative can be found from the graph. The scatter plot in Fig. 2 shows the values obtained through simulations of the modified HRd model for various values of q. The solid line in the same figure shows the values obtained from Eq. 9. The graph shows the absolute refractory period corresponding to fractional order from 0.982 to 1. It is well known that D^q has an m-dimensional kernel, and therefore we certainly need to specify m initial conditions in order to obtain a unique solution of the straightforward form of a fractional differential equation, viz.

$$D^q y(x) = f(x, y(x)) \qquad (10)$$

with some given function f. But, using Eq. 9 the graph can be extrapolated in both directions. This overcomes the limitation imposed by the availability of a single initial condition which restricts the maximum value of order of derivative to 1.

The order of fractional derivative for a given absolute refractory period can be obtained from the above equation. The error between the data obtained from simulation and that from the equation was calculated. The accuracy turned out to be 99.8 percent.

The value of absolute refractory period obtained from the simulation of the HRd model was 186.4 ms, whereas the actual recorded value is 200.45 ms [60]. It can be noted that there is significant difference between the refractory period obtained from the HRd model and that from the actual data. We obtained the exact value of

the refractory period, 200.45 ms [60] (refer to figure 5), for order of FDE taken as 0.985, the set of parameters and initial conditions being the same. Fig. 3 shows the change in refractory period as the order of differentiation is changed from 1 to 0.985. Fig. 4 shows the comparison of the proposed model with HRd model and experimental data. The experimental data was obtained from the paper by Sicouri and Antzelevitch [60].

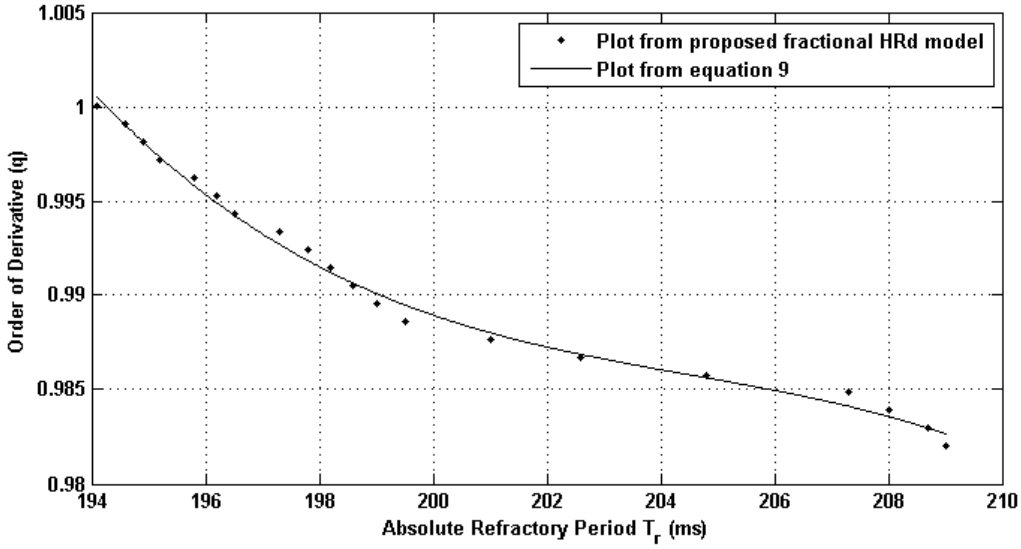

Figure 2: Fractional order corresponding to given refractory period. The solid line shows the plot obtained from curve fitted eq. 9 and the dotted line shows the plot obtained from the simulations of the modified HRd model for different values of order of derivative versus absolute refractory period.

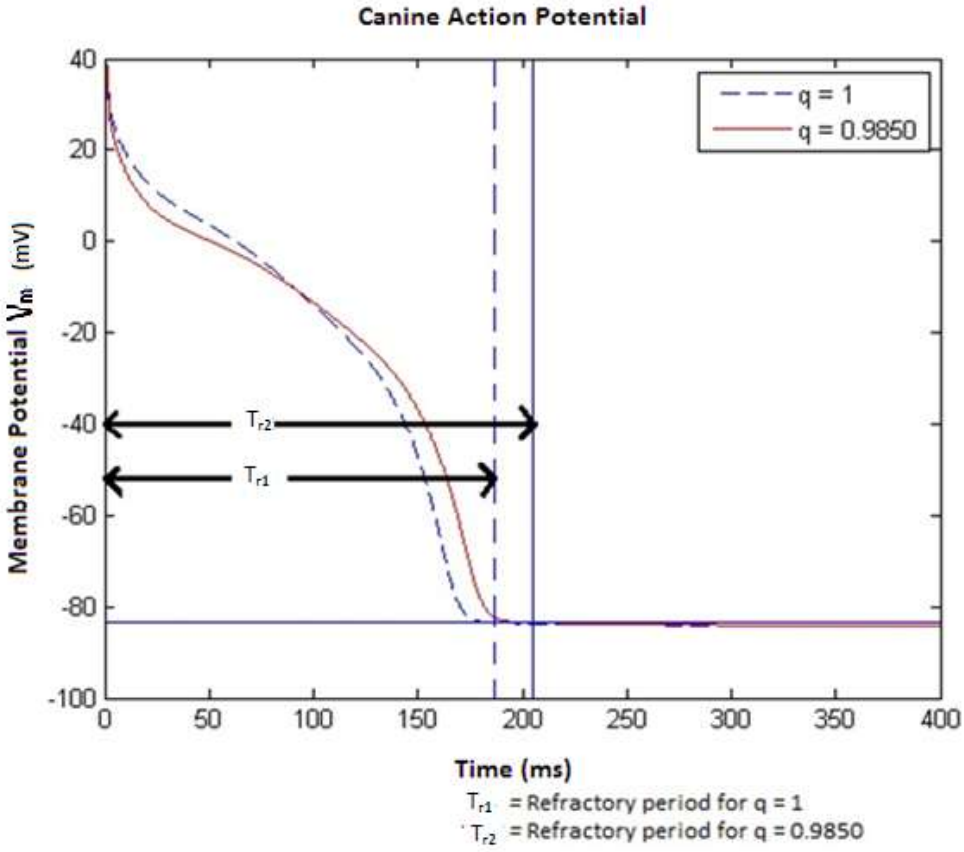

Figure 3: Action potential for order of derivative q = 1 and q = 0.985.

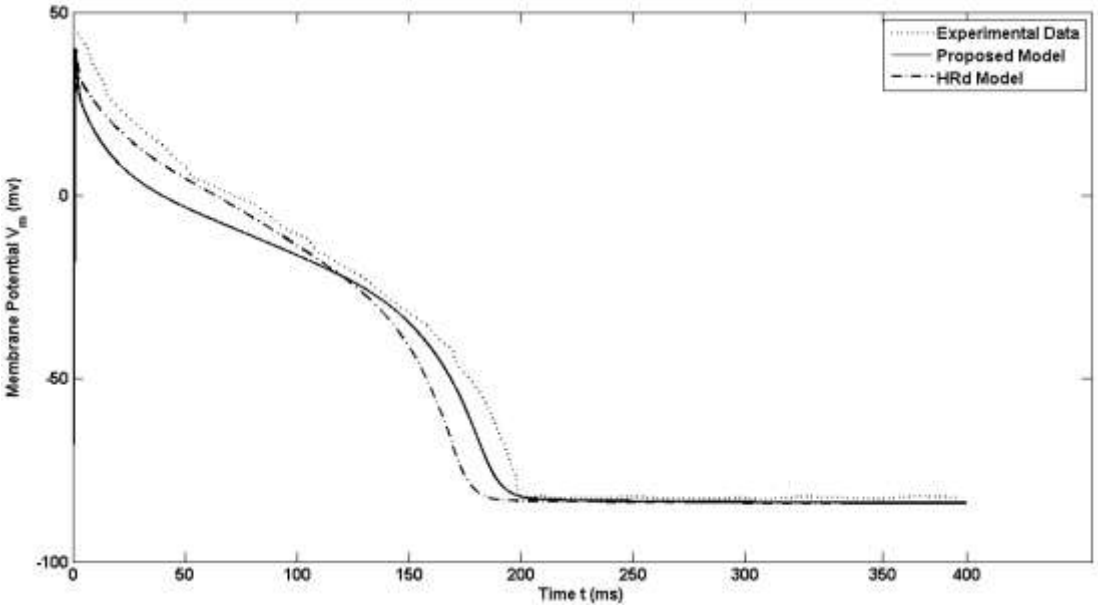

Figure 4: Comparison of the proposed model with HRd model and experimental data.

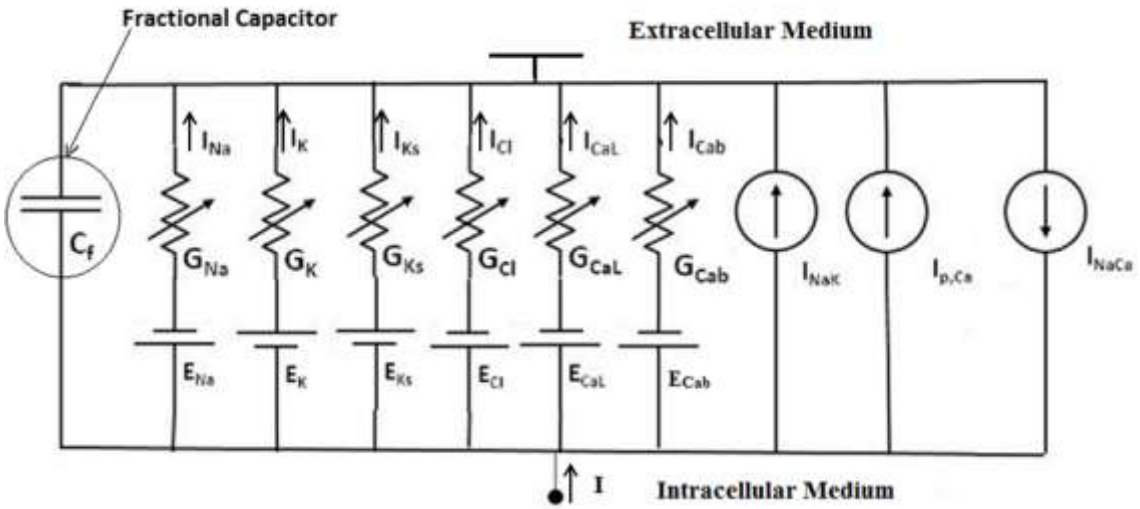

Figure 5: Electrical abstraction of the cardiac cell membrane. C_f is the fractional capacitor. G_{Na}, G_K, G_{Ks}, G_{Cl}, G_{CaL}, and G_{Cab} are conductances of Na^+ ions, K^+ ions, slow delayed rectifier K^+ ion channels, Cl^- ions, L-type Ca^{2+} ion channels, and background Ca^{2+} ion channels, respectively. I_{Na}, I_K, I_{Ks}, I_{Cl}, I_{CaL}, and I_{Cab} are the corresponding currents through these channels.

Circuit model

The modified HRd model was translated into an electrical network comprising fractional capacitor, resistors, and voltage and current sources as shown in Fig. 5. This circuit describes the changes in Na^+, K^+, and Ca^{2+} ions in the myoplasm, and the Ca^{2+} ions in the sarcoplasmic reticulum. The semipermeable membrane of the myocyte acts as a fractional capacitor by creating a charge separation between the interior of the cell and the extracellular environment. The fractional capacitor accounts for the dielectric losses in the membrane. The Nernst potential is created by the difference of ion concentrations across the cell membrane in resting phase, and is represented by a battery. Conductances of the voltage dependent ion channels are represented by variable resistors. Ion channels which do not depend on voltage are represented as current sources.

V. Discussion

The current across a capacitor is proportional to the first order derivative of the potential difference between two points. Whereas, the current across a resistor is linearly proportional to the potential difference between the two points. A leaky capacitor exhibits a behavior similar to a resistor, to a certain degree. The order of the fractional derivative 'q' is determined by this behavior. Thus, the fractional capacitance implies that the property of the capacitor lies between an ideal capacitor and an ideal resistor. The closer the order 'q' lies to 1,

the more it resembles a capacitor. As the order decreases, the behavior of the capacitor tends to resemble a resistor. Hence, Equation (2) models the behavior of a capacitor more accurately. Equation (3) shows the HRd model generalized for fractional order.

In order to verify graphically whether the proposed methodology leads to high accuracy, we evaluate the modified HRd model and compare the results with both the actual recorded signal and the HRd model graph. Figure 4 shows the results of the comparison. It can be observed that the value of the absolute refractory period obtained from the fractional HRd model is closer to actual recorded data as compared to that of the original HRd model. This validates our proposed modification. The results obtained for canine action potential can be extended to the human cardiac action potential as well.

Animal research has been instrumental in developing most of the medical treatments for humans [61-65]. Hence, the above model applied to canine cardiac action potential, can also be extended to the modeling of cardiac action potential in various regions of the heart and subsequently ECG signals in human beings. For example, the cardiac action potential can be mapped to the PR interval. Estimation of PR interval is critical to cardiac diagnosis [66, 67].

VI. Conclusions

In this paper we have proposed a modified form of the HRd model using fractional capacitance. This model captures the refractory period of the canine ventricular action potential precisely. Though several studies have been conducted for modeling the cardiac action potential, none of them were able to model the refractory period accurately. The refractory period is significant from the point of view of early detection of harmful cardiac arrhythmia which may, otherwise, lead to fatal conditions like myocardial infarction or heart attack.

We have also found a mathematical relation between refractory period and order of fractional derivative. This relation allows us to estimate the refractory period for order of derivative greater than 1 which was not possible otherwise.

An electrical circuit of the proposed model has also been designed.

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