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Identification of Ionic Conductances in a Reentry Model of Ventricular Myocardium Cells

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Abstract: In this study, a new method will be introduced to find ionic conductance parameters of ventricular cell channels that are part of a reentry loop. These parameters play a significant role in generation and dispersion of a normal action potential and hence ECG signal and formation of a reentry. The dangerous phenomenon reentry, occur when an electrical impulse travels in a circle within the heart, rather than moving outward and then stopping. Depending on the timing, this can produce a sustained abnormal rhythm, a self-limiting burst of supraventricular tachycardia, or a dangerous ventricular tachycardia. Here, a detailed Luo-Rudy model has been used for modeling ventricular myocardium cells and construction of a one-dimensional ring for reentry simulations. The proposed method is based on using Genetic Algorithms to identify the unknown parameters. The advantage of the proposed method over Least Squares parameter estimation approach is provided.

Key words: Identification, ionic models, least squares, genetic algorithm, reentry

INTRODUCTION

In the debate of heart disease, it can be said that many arrhythmias are caused by the lack of normal function of ionic channels in the plasma membrane of heart cells. This problem has an important effect on the conductive features of those channels and results of arrhythmia in a particular area of heart tissue which was informed by Klabunde (2005), Nagata *et al.* (2004), Chay and Chay (1994), Chay (1996), Guyton and Hall (1996).

For heart patients, often medicines are prescribed which first could remove the respective illness. The selection of type the and dose of medicines prescribed, are mostly based on the symptoms that the physician obtains from different tests, such as the study of ECG signals, blood sugar and fat tests (TG, FBS, CBC) along with the patient's statements. Since none of the symptoms are accurate or precise enough in specifying the increase or decrease or degree of particular ions in the heart tissues (which causes disease), sometimes the medicine that is prescribed as a remedy, can lead to arrhythmia reinforcement or even patient death confirmed by Chay and Chay (1994) and Klabunde (2005). So, it is necessary to study more specifically and to measure the special factors of an arrhythmia to recognize the type and dose of drugs.

Two types of dangerous arrhythmias that are initiated in the heart ventricle are ventricular tachycardia and ventricular fibrillation, where, if there is not a quick assistance, they can result in a patient's death. The source of both arrhythmias should be researched by a special phenomenon, called reentry, which occurs in the cells of the heart tissue. Theoretical and experimental studies have shown that the region of the heart tissue, which is involved in reentry, has cells that are not in a normal state; dead or have low activity. One reason for low activity of these cells is the lack of normal function of ionic channels in them. Indeed, the channels are responsible for the crossing of different ions, which play a pivotal role in the transferring stimulation and action potential from one cell to another cell declared by Guyton (1996) and Klabunde (2005). It is clear that by identifying the exact rate of conducting ionic channels, this could play an important role in the medicine prescription and the remedy process of Reentry and prevention of serious tachycardia and ventricular fibrillation arrhythmias.

In this study, it is attempted to simulate a one-dimensional reentry wave using Luo-Rudy (L-R) ionic model Luo and Rudy (1991) of myocardium cells. Then, ionic conductance parameters related to intra tissue cells were identified, to obtain a better view of how ionic channels are obstructed, which eventually can result in the type and dose of a more proper medication. Known parameters of a healthy cardiac cell in the L-R model are referred to as normal cell parameter, or normal tissue parameters.

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EXPLANATION OF L-R MODEL EQUATIONS IN PRODUCING REENTRY PHENOMENON

Research has shown that reentry takes place in conductive paths from the heart that for some reason, at least one path has been stricken with slow conduction which was proved and shown by Chay and Chay (1994), Gayton (1996) and Klabunde (2005). The slow conduction is caused by, the decreasing conduction rate of sodium, calcium, potassium and other ions in ionic channels. In this case, stimulus wave in addition to its normal movement from atria to ventricles and at last to the whole heart, is captured in a small closed path (which includes a path with slow conduction) and stimulates the cells within the path. Since the length of the path where reentry occurs, is generally short, the stimulus wave quickly revolves the formed circle. So, the beat frequency in the path is increased so high that it practically takes over the stimulus control. Subsequently, heart beats are controlled with a frequency higher than a healthy heart and this causes the blood not to reach the organs and causes excessive exhaustion of the heart. What is necessary in this case is to study more accurately the area including reentry wave from the viewpoint of the slowness rate of ionic channel conduction, along with the determination of role degree of each channel in the formation of reentry.

Different ionic models have been proposed on heart cells most significantly by Hodgkin and Huxley (1952), Luo and Rudy, (1991) and Beeler and Reuter (1977). All of the equations related to these models are drawn from equations of a basic model, called Hodgkin-Huxley model (1952). In this model, behavior of a neural cell of a giant fish has been studied. The studies were based on experiments done via space clamp method. Indeed model L-R is one of the models that studies behavior of a cell of myocardial tissue of ventricle (in more details) in the view of ionic currents and channels extensively discussed by Luo and Rudy (1991).

In this study, by formation of a continuous one dimensional circle of myocardial tissue cells of ventricle (which L-R model shows their features and explanation) and in the following, by stimulating only one of the circle cells (for example first cell) in arbitrary time, a reentry phenomenon is produced.

Equations of stimulus wave in circle formed based on action potential of myocardial tissue cells of ventricle are as follow:

$$\partial V / \partial t = -I_{ion} / C_m + D(\partial^2 V / \partial x^2) \quad (1)$$

where, V(mV) is potential of cells membrane (action potential of cells), C_m = 1 ($\mu F\ cm^{-2}$) is condenser capacity of membrane, D ($cm^2\ m\ sec^{-1}$) is intercellular infiltration coefficient (which in healthy tissue is 0.001), x (cm) is distance between centers of two cells, t (msec) is time and I_{ion} ($\mu A/cm^2$) is intramembranous ionic current density for cells which by explanation in model L-R is formed of seven different and independent currents as follows:

$$I_{ion} = I_{stim} + I_{Na} + I_{Ca} + I_K + I_{K1} + I_{Kp} + I_b \quad (2)$$

$$I_{Na} = G_{Na} m^3 hj(V - E_{Na}) \quad (3)$$

$$I_{Ca} = G_{Ca} df(V - E_{Ca}) \quad (4)$$

$$I_K = G_K x x_i (V - E_K) \quad (5)$$

$$I_{K1} = G_{K1} K1_\infty (V - E_{K1}) \quad (6)$$

$$I_{Kp} = G_{Kp} K_p (V - E_{Kp}) \quad (7)$$

$$I_b = G_b (V - E_b) \quad (8)$$

where, I_{Na} is inward fast sodium current, I_{Ca} is incoming slow current, I_{K1} is time-dependent potassium outward current, I_K is time-independent potassium outward current, I_{Kp} is potassium current related to action potential activating pan with calcium, I_b is the background leakage current, and I_{stim} is the stimulation current for producing reentry wave in the circle. It is worth mentioning that the parameters m, h, j, d, f and x are unit less valve variables obtained as solutions to Eq. 9 and with appropriate rate constants.

$$dy / dt = (y_\infty - y) / \tau_y \quad (9)$$

Where:

$$\tau_y = 1 / (\alpha_y + \beta_y) \quad (10)$$

y_∞ and τ_y correspond to steady state value of y and its time constant reported by Luo (1991). x_i Is trapdoor variable, which is calculated based on an equation dependent on cell voltage and $K1_\infty$ is equal to value of infinite state of trapdoor variable for current I_{K1} in (6). Note that values of G_{na}, G_{ca}, G_K, G_{K1}, G_{Kp} and G_b ($mS\ cm^{-2}$) are conductances or ionic conductions of cell membrane of heart in this model and E (mV)in any of Eq. 2-8 is Nernst potential for current in equation. Complete detail on model L-R can be found in the study of Luo (1991).

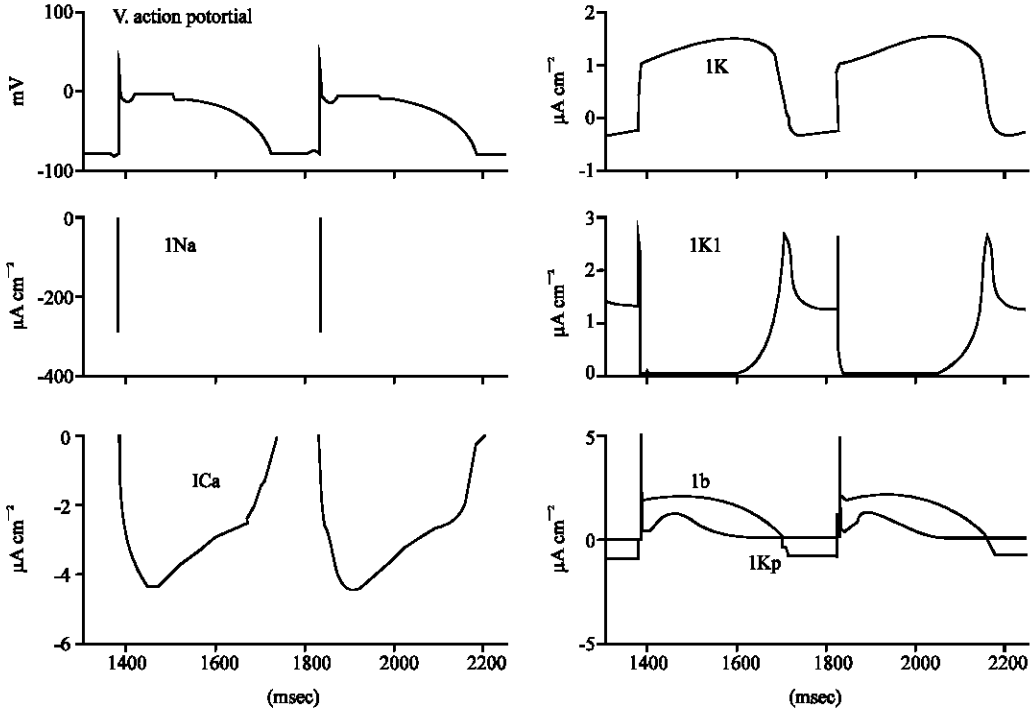

Fig. 1: Representation of action potential wave of first cell in reentry circle

For simulation of the reentry wave, the equations are solved through Euler Implicit Disconnection Approach described by Kamont and Newlin-ukowicz (2003). For the simulation, the number of cells within circle was considered N = 400 and distance between them was planned $\Delta x = 0.05$ (cm) (close to real distance between ventricular cells). Moreover, for acquiring more complete information and achieving a stable state of action potential of cells, a time range of disconnection, as small as possible equal to $\Delta t = 1$ (msec) was chosen. The primary conditions for producing reentry are considered a stimulation current (which only one of the cells arrives) with current density 70 ($\mu A\ cm^{-2}$) and width of 2 (msec). In order for a stimulation wave to scatter in only one direction, the circle was blocked on one side. Figure 1 shows action potential wave and ionic currents for the first cell in the circle. In this case, the conduction rate for ionic channels of each cell corresponds to its normal value. An abnormal action potential signal can be obtained by changing these condition values for the cells in the circle.

The aim of this study is to identify ionic conductions of sodium, calcium and potassium channels; that is to find G_{na}, G_{ca}, G_K, G_{K1}, G_{Kp} and G_b values, which is achieved by using the data signal of action potential of a cell and its adjacent cells.

IDENTIFICATION THROUGH LEAST SQUARES ERROR

Least squares error method can be used for identifying the six parameters of ionic conductions of channels (G_{na}, G_{ca}, G_K, G_{K1}, G_{Kp} and G_b) described by Dokos and Lovell (2004), Audoly *et al.* (2001) and Mendel (1986).

This method was used on acquired data from action potential wave, for a cell within a circle when all of the cells are normal. In identifying the parameters for a cell by action potential of the same cell through Least squares error method, equations in reentry model were considered. In this case and based on applied disconnection type (central disconnection), action potential wave of the first cell was considered as outgoing and action potential wave of adjacent cells, second and last cells, as incoming. Table 1 shows the results of identifying parameters by Least Squares Error method and comparing them with the normal values of parameters in model L-R.

The simulation results, based on the Least squares error method, for identifying ionic conductions of a cell in a reentry circle, produced by using parameters of a normal cell, were not close to its (normal) values in the L-R model. It should be mentioned that the estimated parameters, although far from their expected values, were able to produce an action potential that was fairly close to the

Table 1: Values of the identified parameters from LS method and their comparison with normal values for healthy cells

Parameters (Conductances) (mS cm^{-2})	Normal value	Estimated parameters with LS
G_{Na}	16.00000	272340.650
G_{Ca}	0.09000	-6720.200
G_K	0.28200	-138.240
G_{K1}	0.60470	0.001
G_{Kp}	0.01830	-0.066
G_b	0.03921	41.930

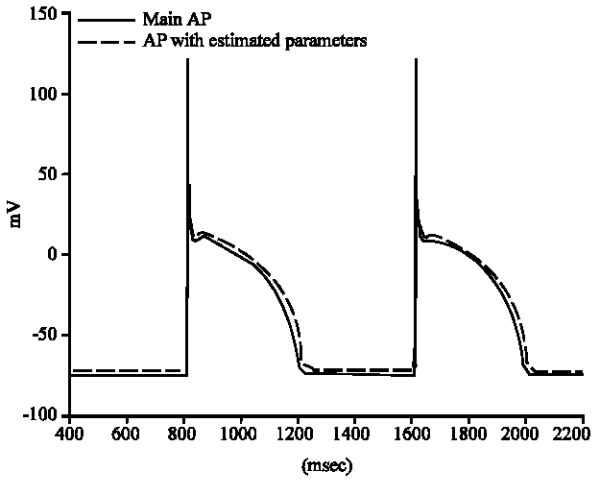

Fig. 2: Action potential curves produced from LS method compared to normal action potential curve for the first cell

real normal action potential, based on assumed normal values (Fig. 2). This indicates the existence of local solutions in the identification problem, which has been confirmed by the researchers who have worked in reconstruction of the action potential of a ventricular cell outside the reentry circle according to Dokos and Lovell (2004). Local solutions could be associated with existence of linear and/or nonlinear relationships between ionic conductions of a cell or unaccounted conduction parameters in the L-R model.

Finally, the LS method was unable to obtain estimation results that would give a small prediction error and good action potential tracking in a reentry cell. Next, in order to improve the results, a general optimization method was employed. It should mention that using Weighted Least Squares (WLS) method was also considered, but this required defining a suitability function that would be used to produce the weighted matrix at each iteration and due to the size of the simulation data this approach was not practical. WLS method can be effectively used for the case that there are limited cells or when using a simpler model is considered as shown by Dokos and Lovell (2004).

Table 2: GA parameters for identification

GA parameters	Identification
Population size	70
Generation	10
Selection fcn	Selection roulette
Elite count	1
Crossover fcn	Crossover two point
Crossover fraction	0.9
Mutation fen	mutation uniform
Mutation rate	1

IDENTIFICATION THROUGH GENETIC ALGORITHM

Genetic Algorithm (GA) is an optimization method based on research (Holland, 1975) used in and imparted on two selection elements and reproduction in nature according to Whitley (1994). Genetic algorithm is used in different applications such as functions optimization, identifying systems, processing picture and so on. Although the application range of this algorithm is very wide, it is seen often as functions optimization declared by Whitley (1994).

Since GA research is based on a population of points not a point, by choosing proper actors such as determination of incision possibility, mutation and elitism, it is more likely to attain the optimum answer. Table 2 presents the parameters and functions used for simulations.

Here, similar to the Least squares error method, certain information were used including an outgoing signal related to action potential wave of the first cell and two incoming signals related to the action potential wave of the second and last cells. Mean square error was chosen as the suitability function.

In order to improve the accuracy of the identification process, especially for the points where, the action potential slope is high (like the first phase of an action potential described by Luo and Rudy (1991) and Beeler and Reuter (1977), before performing GA operation, using extrapolation, a maximum of additional 1400 data points, between two available data points were added. This number has no significance and it is related of our computational capability. The initial values of the ionic conductances for simulations were selected to have a ±20% variation from their values in a normal tissue. Table 3 shows results of identification by genetic algorithm method and its comparison with normal conductance parameters in the L-R model with the aforementioned deviation from the normal values.

The deviation is calculated as follows:

$$\left|\frac{p - p^*}{p^*}\right| \times 100 \qquad (11)$$

Table 3: Values of the identified parameters by GA method and their comparison to values in normal cells with ±20% deviations

Parameters (Conductances) (mS cm^{-2})	Normal value	Estimated parameters with GA	Deviations from normal value (%)
G_{Na}	16.00000	16. 4300	2.69
G_{ca}	0. 09000	0. 0960	6.67
G_K	0. 28200	0. 2580	8.51
G_{K1}	0. 60470	0. 6401	5.85
G_{Kp}	0. 01830	0. 0175	4.37
G_b	0. 03921	0. 0364	7.17

Table 4: Comparison of maximum and mean deviation of identified parameters from their normal values

Parameters	Maximum deviation in estimated parameters (%)	Mean deviation in estimated parameters (%)
Fitting with GA-1	8.51	5.8617
Fitting with WLS	35.60	10.5000

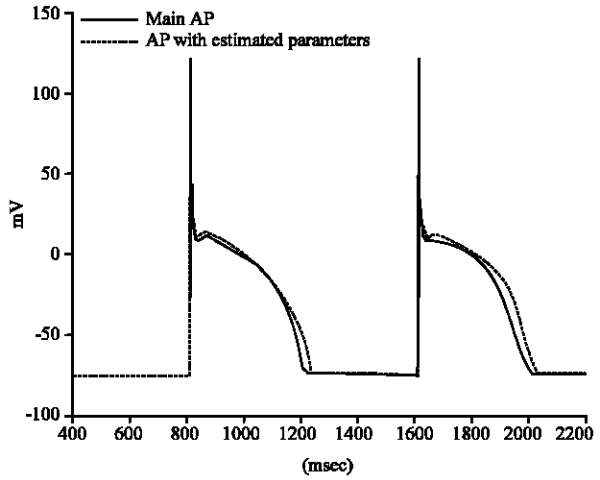

Fig. 3: Action potential curve from GA identification scheme and normal action potential curve of the first cell

where, p is the value of identified parameter and p* is the value of the parameter in healthy tissue

As the results in Table 3 indicates, genetic algorithm can effectively identify the unknown parameters. There were no published results for comparison purposes. The closest were the parameter identification results via Weighted Least squares method for 63 identified parameters in the Beeler-Reuter model, a simpler but very similar model, done just for one cell by Dokos and Lovell (2004). Table 4 shows a comparison of maximum and mean deviation of identified parameters from their normal values when identification is done through genetic algorithm with the identification results done by Dokos and Lovell (2004) through Weighted Least squares method.

According to Table 4, maximum and mean deviation of identified parameters from their normal values using genetic algorithm method for one cell in a reentry loop is less than the maximum and mean deviation of identified parameters using the WLS method. Please note that the identification scheme using WLS was done for 63 parameters, which include the 6 parameters considered in this study. Figure 3 shows the action potential curve constructed using GA and normal action potential curve of the first cell.

As seen in the Fig. 3, in this case the action potential generated from identified parameters closely follows the main action potential. The value of deviation in Genetic Algorithm method, especially for the mean value in Table 4, shows the ability of this algorithm in identification of ionic conductances when a deviation is more than 6% from its normal value. It should be mentioned that the GA algorithm even after several modifications could not identify the parameters precisely.

Since small changes in ionic conductions of heart cells can cause undesirable results, such as arrhythmia, more study is needed in this area to improve the parameter identification process of ionic conductions of cells in a reentry circle.

CONCLUSION

In this study, using genetic algorithms some internal features of heart cells in a reentry circle (like ionic conductances of cells) are reconstructed. In this matter of identification problem there were no recent published results except the parameter identification results via Weighted Least Squares Method for 63 identified parameters in the Beeler-Reuter model, done just for one cell by Dokos and Lovell (2004). This study inspired thoughts of identifying the exact rate of conducting ionic channels of a cell involved in a reentry circuit.

Here, by only considering the signal information of the action potential of cells within the reentry circle, ionic conductances were identified by assuming that they were from normal cells. Simulation results indicated the existence of other ionic conductance parameters or a relationship (linear and/or nonlinear) between the parameters that could play a role in identification process. Least Squares method was unable to handle the effect of these unaccounted parameters but with the help of GA, much better results were produced for the case that the circle cells were all healthy. It seems that by using more accurate ionic models, more efficient suitability function, empirical information of action potential signal, consideration of current and voltage signals of cells; it would be possible to identify the parameters more accurately.

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