RESEARCH ARTICLE

Modeling Ventricular Muscle Cell by the Least Parameters

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ABSTRACT

Modeling the dynamics of ventricular muscle cell require models that reproduce realistic characteristics in cell. In this paper, we present a minimal model for ventricular muscle cell that is designed to reproduce important characteristics of cardiac cell, including action potential (AP) amplitudes and morphologies, excitability and all or none criteria. To generate the minimal model, first, we presented a general form of a nonlinear model with two-state variables for the cell, and then parameters of the model have been fitted by using the theories and experiments that has done on COR software. Findings show the proposed minimal model has important features for example; it is simple and is computationally efficient.

KEYWORDS: *Ventricular action potential (AP), Minimal model, Computer simulation*

INTRODUCTION

Computational models of heart cells have a long history of development during which they have become perhaps the most detailed cell models available today. Over 100 such models are listed on the CellML website (www.cellml.org), which means that they can be down-loaded and used immediately with software that is CellML compatible [1] The first models using equations for the kinetics of ion channels were created in 1960 [2,3] and they were based on early experimental work on the potassium channels in heart muscle [4–6] and on the ground-breaking work of Hodgkin and Huxley who created the first nerve axon model [6].In next years, other models were presented. Surveying of these models shows that they contain a large number of the ion currents, gating coefficient and state variables, so they are very complicated. For example, Ten Tusscher2004 model [7] has 12 currents, 14 gating coefficients and 17 state variables. The weakness of the model is apparent when we want to simulate the interaction of many cells; for example, to simulate heart tissue and propagation of action potential in cells. Large family of the cellular electrophysiological models is conductance-based or Hodgkin-Huxley (HH) model [8]
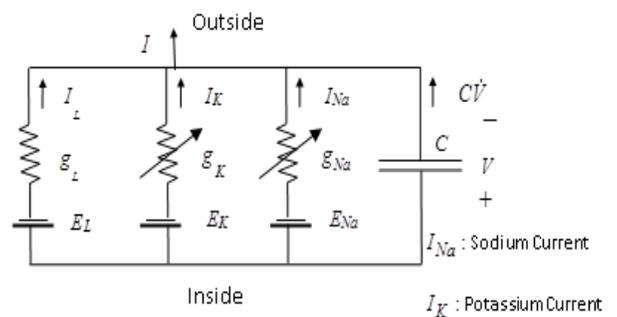

Figure No. 1. Equivalent circuit representation of a patch of cell membrane

I_{Na} : Sodium Current
I_K : Potassium Current
I_L :

Figure 1 shows an example of a cell model based HH. In this model, the cell membrane has been equaled with a capacitor (C), a few nonlinear conductances (g) that are dependent to voltage and a few voltage sources (E). Capacitor (C) is the representation of the membrane

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capacitance, Conductance (g) demonstrates voltage-gated[1] and voltage source (E) is the Nernst equilibrium potential. In Figure 1 is considered three currents for a cell. Today, the numbers of the circuit branches are increasing and elements are complicated by discovery of various ionic currents and phenomena in the cell membrane. Minimal electrophysiology model has a minimum numbers of state variables and it enables us to simulate   behavior and performance of cell electrophysiology. Figure 1 shows an example of a minimal model with the lowest numbers of branches and the simplest elements.

2-Methods

2-1- Introduce $I_{na,p} + I_K$ minimal model

Although the number and complexity of ionic currents in cardiac cells are high, currents can be classified to two general categories that are inward and outward currents. In addition to, voltage-gated that produce ionic currents are divided two categories amplifying and resonant gating. The amplifying gating amplifies voltage changes via a positive feedback loop. It means that increasing it raises the voltage and raise the voltage increase it. Resonant gating opposes voltage changes via negative feedback loop.

Opening a gate because of increasing the voltage has two different effects. If the gate is correlated to inward current to open it increases the voltage (positive feedback) and if a gate is related to outward current to open it decreases the voltage (negative voltage).

If the gate is closed in rest state, and it opens by increasing the voltage is called activation gate. Also, if the gate is open in rest state, and it closes by increasing the voltage is called an inactivation gate. A current (inward or outward) has one or two types of gating variables (activation or inactivation).

So, an amplifying current is an inward current with activation gating or an outward current with inactivation gating. Similarly, a resonant current is an inward current with inactivation gating or an outward current with activation gating. We need both positive and negative feedbacks to produce a model from a dynamical system.

In this paper, to produce a minimal model, we choose an inward and outward current. Inward current is $I_{Na,p}$; its voltage-gated is activation gate (m) so $I_{Na,p}$ is an amplifying current. Outward current is I_k, its voltage-gated is activation gate (n) I_k so is a resonant current.

In addition to in the proposed minimal model such as models based Hodgkin-Huxley introduce a leakage current (I_L). Equivalent circuit for this model has shown in Figure1.

Considering the Figure **1** equations of the proposed model is:

$$C\dot{V} = I - \overbrace{g_L(V - E_L)}^{I_{Leak=I_L}} - \overbrace{g_k n(v)(V - E_k)}^{I_k} \qquad (1)$$
$$- \underbrace{g_{Na} m_\infty(v)(V - E_{Na})}_{I_{Na,p}}$$

$$\dot{n} = \frac{n_\infty(v) - n}{\tau_n(v)} \qquad (2)$$

$$n_\infty(v) = \frac{1}{1 + \exp(\dfrac{V_{1/2(K)} - V}{k_k})} \qquad (3)$$

$$\tau_n(v) = C_{base} + C_{amp} \exp\frac{-(V_{max} - V)^2}{\sigma^2} \qquad (4)$$

$$m_\infty(v) = \frac{1}{1 + \exp(\dfrac{V_{1/2(Na)} - V}{k_{Na}})} \qquad (5)$$

Equations (1) to (5) show the proposed model has some parameters which have to fit. Each of parameter has an especial electrophysiological equivalent and it has to fit in the acceptable range for ventricular AP.

2-2- Parameter fitting

Figure 2 shows action potentials (APs) for some of the cells. In Accordance with Figure 2 ventricular AP has particular features and it is different to other cells: action potential duration (APD) 200-300 milliseconds (ms), resting potential -90 millivolt (mV) and notch potential are some of these features.

First, we have to fit parameters of the $I_{Na,p} + I_K$ minimal model to simulate ventricular AP. In this paper, Rat's brainstem neuron parameters [9, 10] are as starting point and then in three stages, they are fitted to produce ventricular AP. Three stages contain: 1- production resting potential -90 (mV) 2- production APD 200-300 (ms) 3- production notch potential.

We used Cellular Open Resource (COR) software [1] to accomplish experiments. COR is software which   contains cellular electrophysiological models. It has produced by researcher of Oxford University.
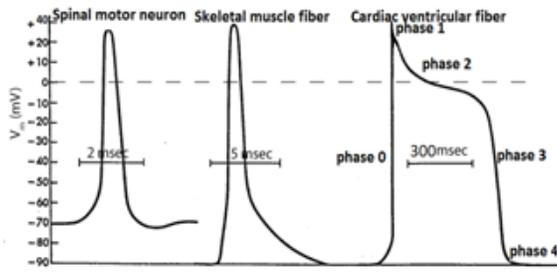
Figure 2. morphology of the AP in three cells: Spinal motor neuron, skeletal muscle fiber, cardiac ventricular fiber.

2-2-1- Production resting potential -90 (mV)

Resting potential of the ventricular cell is about -90 (mV), but it is about -60 (mV) in Rat's brainstem neuron. In resting potential all inward and outward currents balance each other so the net current is zero corresponds to the resting membrane potential, if the stimulus current be zero, then by replacement $I = 0$, $\dot{V} = 0$ and $V = V_{rest}$ in relation (1) :

$$V_{rest} = \frac{g_{Na} m_\infty E_{Na} + g_k n E_k + g_l E_l}{g_{Na} m_\infty + g_k n + g_l} \quad (6)$$

Relation (6) shows that many parameters effect on V_{rest} such as sodium and potassium and leakage Nernst equilibrium potential and, etc. for determination parameter what has the most influence on the resting potential we use from the sensitivity analysis. In this method, sensitivity resting potential to changes each parameter is found by differentiating (6) :

$$K = \frac{\Delta V_{rest}}{\Delta x} \qquad x\ can\ be\ each\ of\ parameters \quad (7)$$

The following has calculated K respect to some parameters:

$$\frac{\partial V_{rest}}{\partial g_l} = \frac{g_{Na} m_\infty (E_l - E_{Na}) + g_k n (E_l - E_k)}{(n g_k + m_\infty g_{Na} + g_l)^2} \quad (8)$$

$$\frac{\partial V_{rest}}{\partial V_{halfk}} = \frac{g_k g_{Na} m_\infty (E_k - E_{Na}) + g_k g_l (E_k - E_l)}{(n g_k + m_\infty g_{Na} + g_l)^2}$$

$$\times \frac{-e^{(V_{halfk} - V)/k_k}}{\tau_k k_k} n_\infty^2 \quad (9)$$

$$\frac{\partial V_{rest}}{\partial E_{Na}} = \frac{m_\infty g_{Na}}{n g_k + m_\infty g_{Na} + g_l} \quad (10)$$

$$\frac{\partial V_{rest}}{\partial E_l} = \frac{g_l}{n g_k + m_\infty g_{Na} + g_l} \quad (11)$$

$$\frac{\partial V_{rest}}{\partial E_k} = \frac{n g_k}{n g_k + m_\infty g_{Na} + g_l} \quad (12)$$

By comparison equations (8) to (12), V_{halfk} and E_l are known as the most important parameters to fit the resting potential (experiments have done on COR software satisfy this idea). So, to production desirable resting potential decrease V_{halfk} and E_l.

2-2-2- Production APD 200-300 (ms)

Phase 1 in the proposed minimal model is induced by potassium current; Furthermore, Phase 2 (plateau) is dependent to potassium current too, so it seems to increase APD we have to debilitate potassium current. We can perceive from part of relation (1), there are many ways to debilitate it: decreasing g_k, increasing E_k and decreasing n. To decreasing n, we increase τ_k, V_{halfK} or k_k. We do some experiments to determination important parameters on APD (by using COR software). In these experiments, in each level we only change a parameter and fix other parameters. Figure 3.A and figure 3.B show effect of g_k and E_k on APD. It can be observed by decreasing g_k or increasing E_k, APD raises. Figure 4 illustrates effect of parameters n $(V_{halfK}$, k_k and $\tau_k)$ on APD. Finally τ_k **is** determined as the most important parameter on APD.
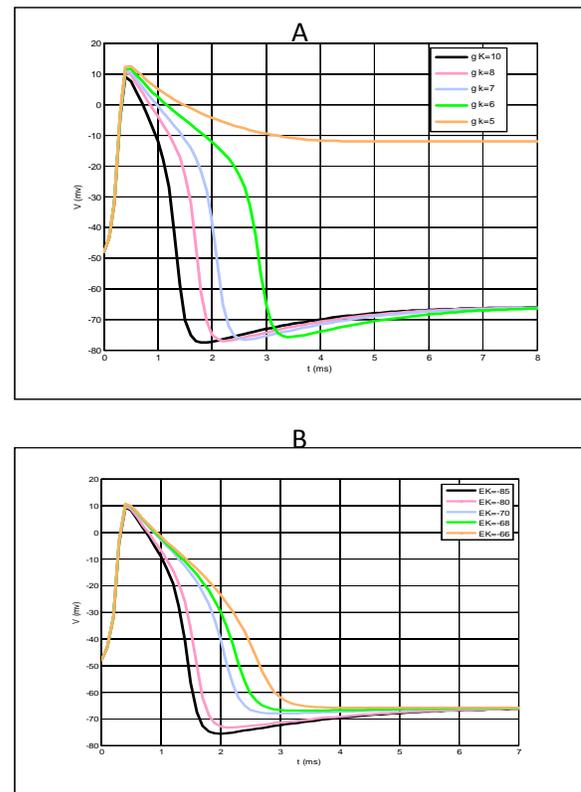

Figure 3. The value of the APD in the $I_{Na,p} + I_K$ model depends on the value g_k (figure 3.A) and E_k (figure 3.B)

2-2-3- Production notch potential

Notch potential is one of the most important features of cardiac cells what is about 10 to 30 (mV) and other cells may not have it. We know from section 2-2-2 plateau phase is fitted by τ_k so, it can adjust notch voltage. Voltage-sensitive time constant τ_k can be approximated by the below Gaussian function:

$$\tau_k(v) = c_{base} + c_{amp} \exp \frac{-(V_{max} - v)^2}{\sigma^2} \qquad (13)$$
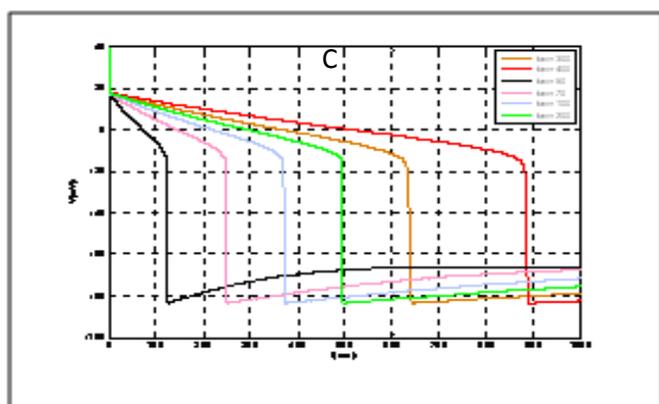
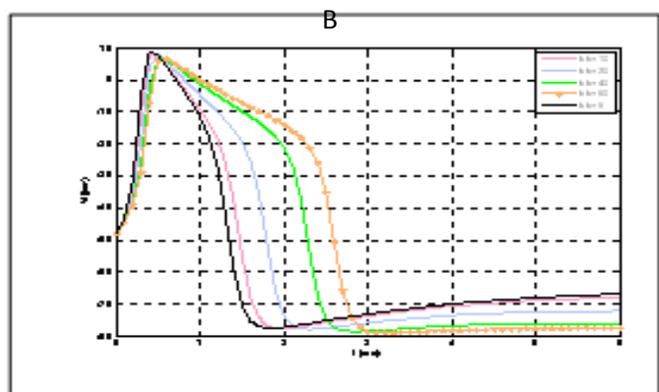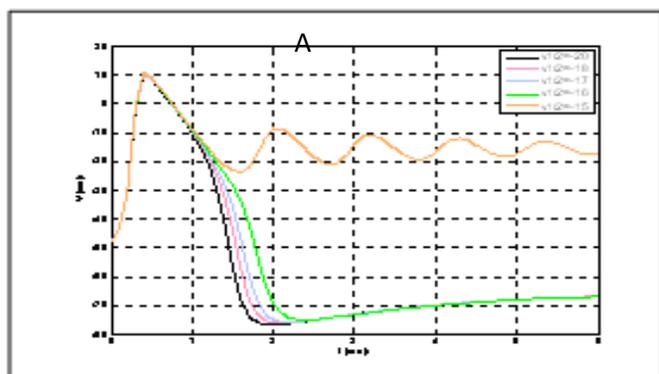Each of parameters in equation (13) **is** described in figure **5.**

Figure 4. The value of the APD in the $I_{Na,p} + I_K$ model depends on the value of the state variable n (V_{halfK} (figure 4.A), k_k (figure 4.B) and τ_k (figure 4.C))

The graph of the function is above C_{base} with amplitude C_{amp}. The maximal value is achieved at V_{max}. The parameter σ measures characteristic width of the graph,

$$\tau_k(V_{max} \pm \sigma) = c_{base} + c_{amp} / e$$

For this purpose, we select $V_{max} = 18$ and $\sigma = 11$, with these selections in bound of 7 to 29 (mV) ((18-11=7) to (18+11=29)) voltage changes quickly.
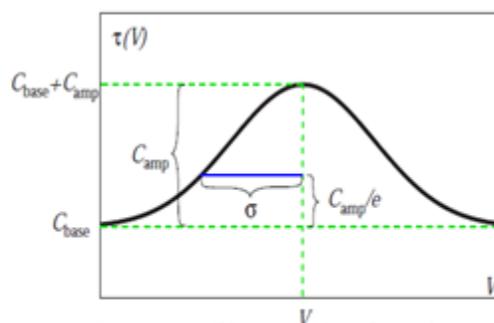
Figure 5. $\tau(V)$ Gaussian function, effect of each parameter on $\tau(V)$ is shown.

3-Results

In this section using the described theories from 1 to 3 will produce a ventricular action potential.

A) Resting potential: As it was stated E_l and V_{halfk} are the most effective parameters on the resting potential so, by using relation (6) we decrease them to fit resting potential. For this purpose, we decrease $V_{halfk} = -92$ and then change E_l and E_K until to produce -90 (mV) resting potential. Doing some experiments on COR software shows by using -98 and -100 for E_l and E_K resting potential will fit.

B & C) APD and notch potential: as is found from the experiments, APD will be adjusted by τ_k. This parameter effects on notch potential, too. So, by using proper quantity for c_{base} and c_{amp} and σ produce notch potential:

$$I = 60 \qquad (14)$$

$$g_{Na} = 18, \quad E_{Na} = 100, \quad V_{halfNa} = -20, \quad K_{Na} = 15$$

$$g_k = 11, \quad E_k = -100, \quad V_{halfk} = -92, \quad K_k = 5$$

$$For \quad \tau_k : V_{max} = 18, \quad C_{base} = 50, \quad C_{amp} = 190, \quad \sigma = 11$$

$$g_l = 5, \quad E_l = -98$$

Figure 6 shows AP of $I_{Na,p} + I_k$ minimal model

4-Discussion

We prove that the model is really a model of ventricular cell, and it can be able to simulate its behavior. For assessing the Model accuracy, three criteria: AP morphology, excitability and all or none is used.

Comparing figure 6 with AP morphology such ten tusscher2004 or noble2000 represents that the most features are same, for example, notch potential, resting potential and APD. So action potential morphology is heeded.
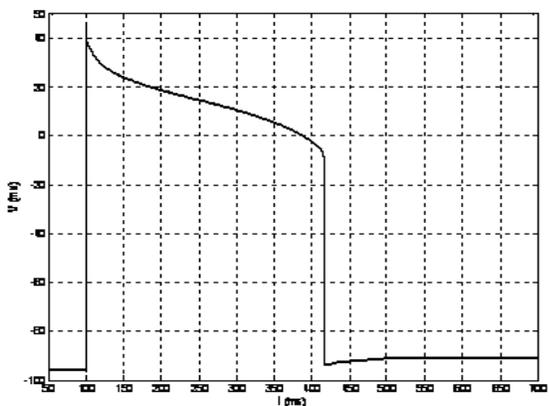

Figure 6. Action potential that is generated from $I_{Na,p} + I_K$ model.

The values of parameters are in (14)

In system excitability, criterion is established in it, when the system is at rest and stable conditions, applying a little pulse of stimulation produces a small positive potential of membrane and indeed occurs depolarization.

This small amount of potential which produces a little flow back to the resting membrane potential is, in fact, it does not simulate with little stimulation and doesn't produce AP. However, if amplitude of stimulation be sufficient, system will stimulate absolutely and will produce AP.

In figure 7, we see that applying a small current of a stimulation system doesn't stimulate but with 200 micro amperes excitation system stimulates and generates AP. So, model $I_{Na,p} + I_k$ has excitability criterion.
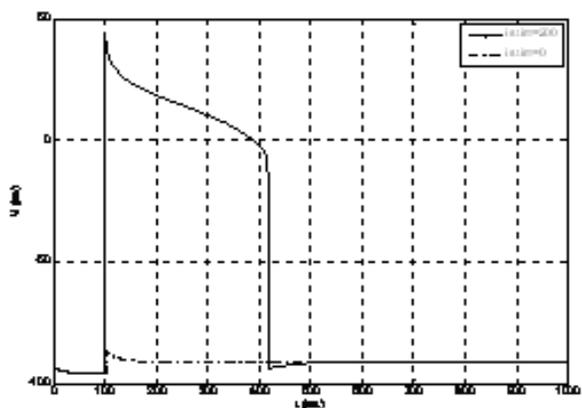

Figure 7. Researching excitability criterion. With stimulus less than threshold does not generate AP.

A common criterion in the cardiac cells is they always generate all-or-none action potentials. So, for validation a model, it must have the same property. According to this criterion with applying stimulation large enough, cell stimulates, and it generates AP.

However, if amplitude of stimulation be in the range a little more than the minimum required, its morphology and amplitude of AP do not change. Now we research this criterion in our proposed model.

In figure 8 AP hasn't been generated by a pulse of current with amplitude less than 200 micro amperes. However, if amplitude of stimulation be more than 200 micro amperes it will generate same APs. It means amplitude of stimulation more than 200 micro amperes does not change AP morphology. So, $I_{Na,p} + I_k$ model has all or none criterion.
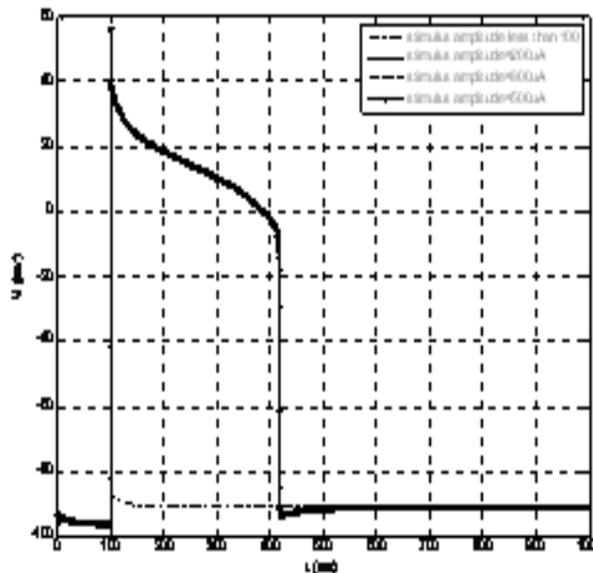

Figure 8. Researching all or none criterion. Rising of the stimulus more than threshold does not change AP morphology

The proposed model is very proper due to the low number of state variables (two variables) and thus low complexity computational for simulation of cardiac arrhythmias such as atrial fibrillation action potential. So, its importance and efficiency in tissue level are predicted. One of the criteria for researching accuracy of the proposed model from cardiac AP is compatible with morphology of AP from the electrophysiological model. In this paper, it has been only attended to morphology AP, and we did not attend to other features such as precise slopes of cardiac AP from the electrophysiological model. It seems it better do more research in this field.

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