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RESEARCH ARTICLE

A model for simulating restitution phenomenon in a single cardiac cell

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ABSTRACT

Up to now, a large number of electrophysiological models have been introduced for simulating the cells. These models are very complicated and they use much time to run. One of most important goals for researchers is to offer a model which has less computational complexity, in the other word, has the minimum number of state variables.

In this paper, is introduced a minimal model for cardiac cell which has a minimum number of state variables and It is enable to simulate different features of Action potential, restitution curve for action potential duration (APD) and least Diastolic interval (DI).

For validation this model, it is compared to reliable electrophysiological model. At the result, this minimal model (MM) is very simple to simulate restitution, so it is proper to simulate tissue level.

1. INTRODUCTION

About fifty years ago, the first cardiac cell model is presented by Hodgkin and Huxley [1]. After that, different cardiac cell models are presented. These models are categories in 3 set: 1) first generation are ionic models which are enable to produce basic ionic currents such as Beeler-Ruter [2] and Luo-Rudy [3] 2) second generation of models which are contained more currents and dynamic ionic concentration exchangers and pumps, for example, D.Francisco noble [4]. 3) Models which are simple and they are composed of necessary currents for simulating mesoescopic features, e.g., conduction velocity (CV) restitution and action potential (AP) restitution.

Simulating based on first and second foster are very complicated from computational point, so It is better to nominate smallest and main feature for the special phenomenon and then simulating it by simple models.

The aim of this study is to design a computer model of action potential which has a less computational complexity. In addition to, It is enable to simulate the restitution feature and comparing It with two another electrophysiological models.

2. Method

2.1. Producing the minimal model

Using a model which is presented for Thalamocortical neuron [7], we introduce a minimal model for cardiac cell. This model has two inward currents which are a fast inward current with an activation gating variable and a slow inward current with inactivation gating variable. In addition to, this model has an outward current. Equations (1) to (8) describe the proposed minimal model.

In figure 1 is shown action potential for Thalamocortical neuron. According this figure, this AP does not have features of cardiac cell.

$$C\dot{V} = I - (I_L + I_{Na} + I_h) \quad (1)$$

$$I_{Na} = g_{Na} m_\infty(V)(V - E_{Na}) \quad (2)$$

$$m_\infty(V) = \frac{1}{\exp((V_{halfNa} - V)/K_{Na}) + 1} \quad (3)$$

$$I_h = g_h h(V - E_h) \quad (4)$$

$$\dot{h} = (h_\infty(V) - h)/\tau_h(V) \quad (5)$$

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$$\tau_h(V) = c_{base} + c_{amp} \exp\frac{-(V_{\max} - V)^2}{\sigma^2} \quad (6)$$

$$h_\infty(V) = \frac{1}{\exp((V_{halfh} - V)/K_h) + 1} \quad (7)$$

$$I_L = g_L(V - E_L) \quad (8)$$

Parameter	Before	After	Parameter	Before	After
K_h	-5/5	0.05	g_{Na}	0/9	20
c_{base}	100	20	E_{Na}	20	60
c_{amp}	1000	360	V_{halfNa}	-20	-18
$V_{\max}$	-75	12	K_{Na}	15	14.5
σ	15	18	g_h	3	10.67
g_L	1/3	4.5	E_h	-43	-84
E_L	-80	-90	V_{halfh}	-75	-80

Table 1. The value of different parameters in minimal model befor and after modifying AP of Thalamocortical neuron.

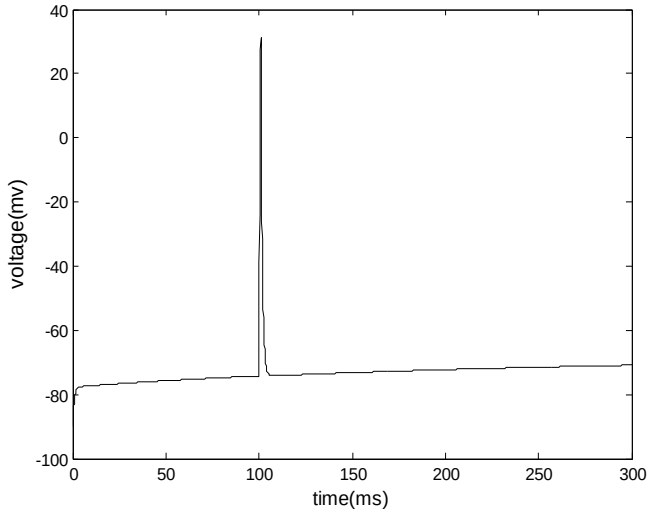


Figure 1.Generated AP from Thalamocortical neuron.

2.2. Fitting the parameters

Each parameter is adjusted using the electrophysiological experiments and hypothesis. Each parameter has been decreased or increased Based on its behavior on the cell. Changing the parameters have to accomplish parallel because it may effect on action potential morphology. Moreover, each parameter has a bound range which It means you have to change It in this bound.

Figure 2 shows the produced action potential based on parameters on Table 1.

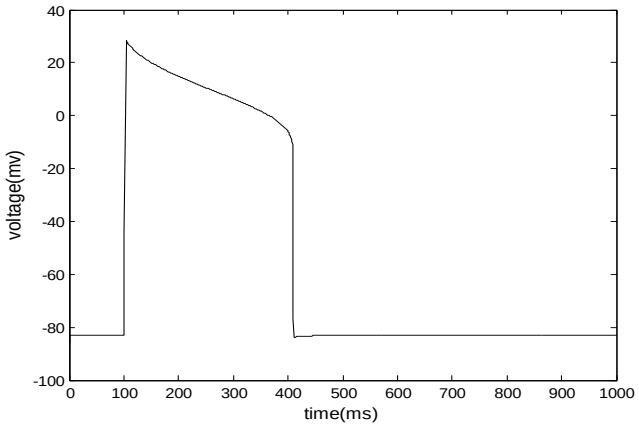


Figure 2.Generated AP from minimal model. Stimulus current is 50 $uA/cm2$

3. Result

For validation of this model, there criterions is probed: 1) excitability 2) All or none 3) action potential morphology.

3.1. Excitability which It means that the cell is in the rest state until any stimulation is not applied to It, but by using an efficient stimulus It produces AP. As shown in figure 3 before time 700 ms, there is not any stimulation, so there is not AP, but in time 700 ms action potential is generated.

3.2. All or none criterion means if external stimulus current is equivalent to threshold mount, action potential generates, but if It is smaller than threshold mount, AP does not generate. Moreover, by using a stimulus current which is larger than threshold mount does not change AP morphology.

Threshold mount in this model is 50 microA. Figure 4 shows using a stimulus current which is larger than 50 uA APs are same (figure 4.a) and otherwise AP does not generate (figure 4.b).

3.3. Based on AP morphology, this model has features of cardiac cell for example, action potential duration (APD) is 300-400 ms and resting potential is about -86ms.

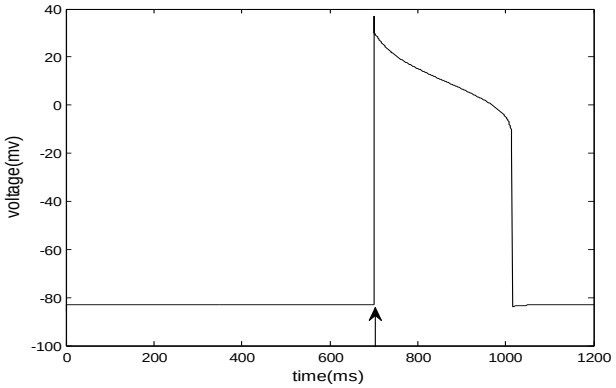
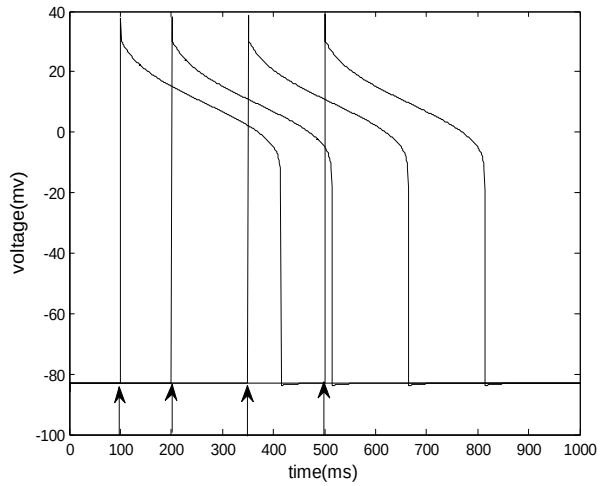
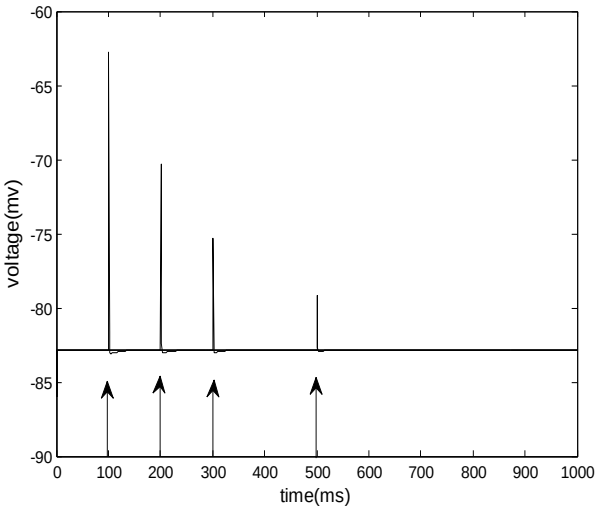


Figure 3. Generated AP by stimulus current in 700 msec (arrow). before time 700 ms, there is not any stimulation



a



b

Figure 4. Generated AP for different stimulus current. a.The same APs for different stimulus current that are more than threshold mount. Stimulus currents are sequentially from left: 70,80,90,100 uA in time 100,200,350.500 msec. b. if the stimulus current is smaller than threshold mount, AP does not generate. Stimulus currents are sequentially from left: 10,20,30,40 uA in time 100,200,300.500 msec.

3.4. Investigating Restitution phenomenon

In figure 5, Using dynamic protocol and equation in [8] restitution curves of minimal model is shown. Regarding this figure represents cell answers as same to whole of stimulus for a lot of periods. In fact, the response is 1:1 and restitution is flat. In this state, changing DI does not modify APD and cell has a fixed APD regardless to preceding diastolic interval. (the right of curve) but for BCL which is smaller than 350 ms, cell does not answer to whole of stimulus as same, APD does not change and alternans is occurred. In this case, the curve is not flat and the slope of curve is gradually increasing. For slopes that are larger than one, the answer is 2:2 instead of 1:1 and period of oscillation is twice. Figure 6 shows bifurcation curve (APD respect to BCL) which represents in small periods, bifurcation has occurred, so APDs are long and little.

As shown in figure 7, models are sensitive to frequency changes. Slope of restitution curve for minimal model is larger than 1, DI is between 11 to 110 for this slope. Slope is smaller than 1 for LR-I model and is 1 in smaller DI. . Restitution curve for Ten Tusscher model (TNNP) is flat even for smaller DI

Comparing these models have brought in table2. The least DI (DI_{min}) is different between models. Minimal model has the least DI_{min} between models.

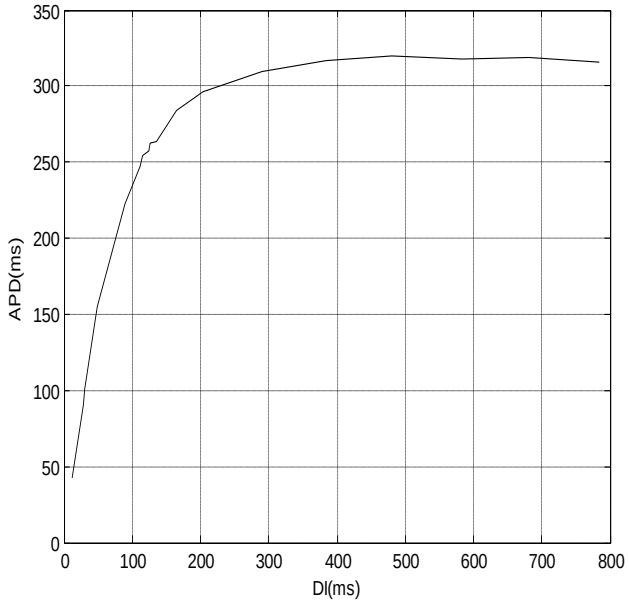


Figure 5. Generated restitution curve of minimal model using dynamic protocol.

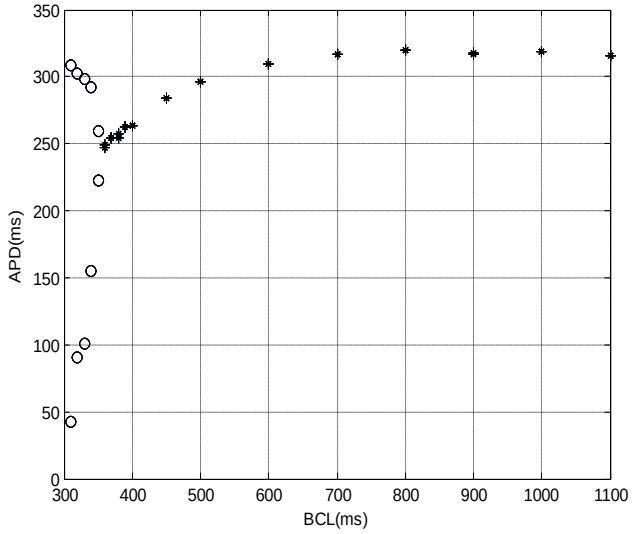


Figure 6. Bifurcation diagram of minimal model. for BCL smaller than 350 ms, alternans is occurred and there are 2 APDs for each BCL.

TNNP	LR-I	MM	
17	8	2	The number of state variables in one cell
1.027s	0.578s	0.399s	10second simulation
-86.2	-3.853	-82.86	Resting potential
123.85	124.1	120.52	Phase 0 amplitude
63.73	49	13	$DI_{\min}$

Table 2. Summary of properties of different models.

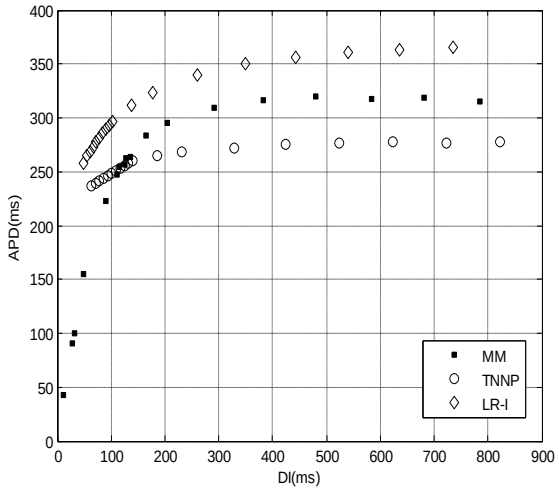


Figure 7. APD restitution curves for TNNP , LR-I and MM (minimal model that proposed in this paper).

4. Conclusion

As stated in table 2, minimal model has a least parameters respect to another models so, It is very fast e.g., this table shows running time for models which are simulated in 10 seconds, findings represent minimal model use half time which LR-I is used and a quarter time TTNP. So, this model is very proper to simulate in tissue level.

As the result, this proposed minimal model is efficient for treatment of cardiac fibrillation because of simulating restitution phenomenon.

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Conflict of Interest: None Declared

