Modeling and analyzing Ca 2+ channel dynamics during cardiac action potential

Conference Paper · March 2019

CITATIONS
0

READS
157

5 authors, including:

Sevgi Sengul Ayan
Antalya Bilim University
12 PUBLICATIONS **287** CITATIONS
SEE PROFILE

Ahmet Kursad Sircan
University of Hohenheim
2 PUBLICATIONS **1** CITATION
SEE PROFILE

Ahmet Kurt
Florida International University
13 PUBLICATIONS **6** CITATIONS
SEE PROFILE

Hasan Özdoğan
Antalya Bilim University
53 PUBLICATIONS **145** CITATIONS
SEE PROFILE

International Conference on Applied Analysis and Mathematical Modeling
ICAAMM19, **March 10-13, 2019, Istanbul-Turkey**

Modeling and analyzing Ca^{2+} channel dynamics during cardiac action potential

Sevgi ŞENGÜL AYAN[1], Ahmet Kürşad SIRCAN[2], Ahmet KURT[3], Hasan ÖZDOĞAN[5] and Nazmi YARAŞ[5]

[1]Antalya Bilim University, Dept. of Industrial Engineering,[2]Antalya Bilim University, Dept. of Electrical and Computer Engineering, [3]Antalya Bilim University, Dept. of Electrical and Electronics Engineering, [4]Akdeniz University, Biophysics Department, [5]Akdeniz University, Biophysics Department
E-mail: sevgi.sengul@antalya.edu.tr

Abstract: We have studied cardiac action potential model which consists 26 nonlinear first order differential equation in a detailed manner computationally. Later, it has been discussed what is the role of Ca^{2+} ion channel to the cardiac action potential by applying a mathematical measure called contribution analysis. Computational simulations are done to analyze the roles of Ca^{2+} gating variables and detailed analysis showed the changing dynamics of Ca^{2+} channel during cardiac action potential.

1) Introduction

Cardiomyocytes are electrically excitable cells and these electrical signals which is called cardiac action potentials play an important role in contraction of the heart [1,2]. The contraction activity of cardiomyocytes consists of three different steps: first, building of an action potential (AP); second, influx of extracellular calcium; and third, calcium-induced calcium release from the sarcoplasmic reticulum (SR). Cardiac action potentials are long APs due to the long plateau phase with a stable resting potential around -80 mV. The differences in shape and duration of APs occur due to the differences in the underlying ionic currents. Mainly, the negative resting potential is because of the inward rectifier K^+ current, I_{K1}, depolarization is caused by inward Na^+ current, I_{Na}, and the plateau phase by inward L-type Ca^{2+} current, I_{CaL} , which is also the main trigger for SR Ca^{2+} release. Repolarization, on the other hand is carried by inactivation of I_{Na} and activation of transient outward K^+ currents, I_t together with steady state K^+ current I_{ss}. Together with these main ionic currents, pumps and background currents are active during the action potential generation [1,2]. Moreover, different cardiac myocytes can generate different action potentials due to the different dynamics of these ion channels [3]. Therefore, understanding mechanisms of the electrical activity has been an important subject in both experimental and mathematical physiology of cardiac cells.

Mathematical models of the heart have been developed since 1960 based on experimental data and the early mathematical models were based on the extensions of the Hodgkin-Huxley model that is defined for nerve conduction [4,5,6]. The principle mechanisms of cardiac action potential revealed in the simple models were extended by formulating more complex cell models. Even though computational simulations using such detailed models have successfully reproduced realistic behaviors of cardiomyocytes, the complex model structures hinder our intuitive understanding. Analysis of membrane potential in cardiomyocytes is a difficult task. However, mathematical analysis of detailed models is crucial particularly to dissect the role of a specific component out of a complex network. Here we aimed firstly optimize a multi-compartment biophysical Hodgkin-Huxley type model according to the action potential we recorded from cardiomyocytes. Then show how mathematical techniques can be extended to apply this model and these mathematical techniques are useful in the analysis of real cardiac system. We will focus on the role of Ca^{2+} channel as an example and contribution analysis will be applied to achieve an improved understanding of the role of Ca^{2+} channel during an action potential generation of the cardiac cells.[7]

2) Methods

2.1 Model:

Here we optimized a detailed Hodgkin-Huxley type multi-compartment model by incorporating most

of ion channels and transporters we recorded experimentally from rat cardiomyocytes. This model contains 9 ion channels, 3 ion transporters and Ca^{2+} handling mechanism in sarcoplasmic reticulum (Eqn.1). All ion channels are modeled as Pandit, 2001 [8]. In our model, the potential difference across the plasma membrane varies according to:

$$\frac{dV_m}{dt}=(-I_{Na}-I_{CaL}-I_t-I_{ss}-I_f-I_B-I_{K1}-I_{NaK}-I_{CaP}-I_{NaCa}+I_{app})/C_m \quad (1)$$

where C_m is the membrane capacitance. There are 9 ionic currents in the model as; inward Na^+ current, I_{Na}, responsible for the initial upstroke, L-type Ca^{2+} current, I_{CaL}, responsible for the plateau phase, transient outward K^+ current (I_t), steady-state outward K^+ current (I_{ss}), inwardly rectifying K^+ current (I_{K1}) mainly responsible for the membrane resting potential, small hyperpolarization-activated inward current (I_f), background current and I_B is a sum of three linear background currents due to a Na^+ current, a Ca^{2+} current and a K^+ current. Pumps and exchanger currents Na^+- K^+ pump current (I_{NaK}), the Na^+- Ca^{2+} exchanger current (I_{NaCa}) and a Ca^{2+} pump (I_{CaP}) current are also included.

We are interested in Ca^{2+} channel dynamics during cardiac action potential. Ca^{2+}-current together with its gating variables are modeled as:

$$I_{CaL}=g_{CaL}d\,[(0.9+\frac{Ca_{inact}}{10})f_{11}+(0.1-\frac{Ca_{inact}}{10})f_{12}](V_m-E_{CaL}) \quad (2)$$

$$\frac{dd}{dt}=\frac{d_\infty-d}{\tau_d},\ \frac{df_{11}}{dt}=\frac{f_{11\infty}-f_{11}}{\tau_{f_{11}}},\ \frac{df_{12}}{dt}=\frac{f_{12\infty}-f_{12}}{\tau_{f_{12}}} \quad (3)$$

$$d_\infty=\frac{1}{1+e^{(V_m+15)/-4}},\quad f_{11\infty}=f_{12\infty}=\frac{1}{1+e^{(V_m+26)/5}} \quad (4)$$

$$\tau_d=3.05e^{-0.0045(V_m+7.02)^2}+1.05e^{-0.002(V_m-18)^2}+0.25 \quad (5)$$

$$\tau_{f_{11}}=105e^{-((V_m+45)/12)^2}+\frac{40}{(1+e^{(-V_m+25)/25})}+\frac{15}{(1+e^{(V_m+75)/25})}+17 \quad (6)$$

$$\tau_{f_{12}}=41e^{-((V_m+47)/12)^2}+\frac{80}{(1+e^{(V_m+55)/-5})}+\frac{15}{(1+e^{(V_m+75)/25})}+17 \quad (7)$$

To examine whether our mathematical model of the cardiomyocytes can catch the key features of the cardiac action potential, we changed ionic current parameters in the model that correspond to currents implicated in the control of cardiac excitability and optimized according to the action potential recorded from rat cardiomyocytes (Fig 1A and 1B). The stability ranges of this differential equations is very small because of high difference between coefficients. So that Matlab stiff differential equation solver ode15s function was used with Gear's method (dt=0.01) that is very convenient for solving stiff systems (1). In optimization part, model codes were converted to C language to calibrate model results with experimental data. As optimization tool, nlopt-nonlinear optimization library was integrated to our code that includes a variety of optimization functions. After optimization, maximal conductances of the model is taken as g_{Na} = 1255.36 nS, g_{CaL} = 14.61 nS, g_t = 15.17 nS, g_{ss} = 19.40 nS, g_{K1} = 24.44 nS, g_f = 30.44 nS, g_{BNa} = 1.15 nS, g_{BK} = 5.38 nS, g_{BCa} = 0.0024 nS. Figure 1A and 1B shows both the model and experimental cardiac cell exhibiting spontaneous cardiac action potential over the first 120 ms. The modeled action potential is generated with an applied current of 0.55 nA for 5 seconds which is adapted with the experimental protocol used to evoke action potentials in rat ventricular myocytes.

2.2 Contribution Analysis:

Experimentally it is too difficult or sometimes impossible to see the contribution of each ion channel state to the cardiac action potential generation. Mathematical approaches in computational biology have progressed from analysis of abstract systems to more biologically realistic situations with the increasing detailed electrophysiological data about cardiomyocytes. Our approach relies on contribution analysis method, a technique that measures the relative contributions of each feedback processes to AP initiation and termination, defined by a dynamical system of ordinary differential equations (ODEs) [7] as long as dynamics are changing linearly during the active and silent phases of the spikes. The new approach in this paper allows using the technique in a large class of biological system, even though the derivative of fast and negative feedback processes are changing signs during the region we want to measure its contribution. To find the contribution of Ca^{2+} channel dynamics to cardiac action potential we find the points that the

curvature of activation-inactivation curves change as in Fig 1C.

We wish to know the contributions of each gating variable of Ca^{2+} channel that are activation, d, fast inactivation, f_{11} and slow inactivation dynamics, f_{12}, to cardiac AP generation. We analyzed the Ca^{2+} dynamics through Phase 1 to Phase 4 as shown in Fig. 1. If the activation of the Ca^{2+} channel d contributes to AP phase 1, then slowing down the time constant variable τ_d will increase the duration of phase 1. So we can find the contribution of d to phase 1 by perturbing its time constant τ_d and calculating the fractional change in phase 1 duration as long as d increases or decreases linearly during the phase 1. But if the curvature of d changes then we divided the phase to epochs from the changing points of d curve. Fig 1 shows the epochs of activation curve d changes during the Phase 1 at points 1,2 and 3. To measure the contribution of d to the phase 1, at the start of the phase and the curvature changing points, τ_d is increased by $\delta\tau_d$. This slows down the rise in d during that portion of the phase 1, with a resulting increase in the phase duration of δP11, δP12 and δP13. Therefore, the contribution of d to phase 1 is $C_{P1}^{d} = \frac{\delta P11}{P11}\frac{\tau_d}{\delta\tau_d} + \frac{\delta P12}{P12}\frac{\tau_d}{\delta\tau_d} + \frac{\delta P13}{P13}\frac{\tau_d}{\delta\tau_d}$. Similarly, the contribution of d to phase 2, phase 3 and phase 4 is measured by perturbing τ_d at the beginning of the each curvature changing point, gives $C_{P2}^{d} = \frac{\delta P21}{P21}\frac{\tau_d}{\delta\tau_d}$, $C_{P3}^{d} = \frac{\delta P31}{P31}\frac{\tau_d}{\delta\tau_d}$ and $C_{P4}^{d} = \frac{\delta P41}{P41}\frac{\tau_d}{\delta\tau_d}$, respectively. Similar definitions apply for the f_{11} and f_{12} variables. Fig 1B shows each perturbation points for each state variable of Ca^{2+} channel. The AP durations were determined by finding the epochs as time intervals between each curvature points for each phase regions. The contribution of variable X was calculated using a $\delta\tau_X$ that perturbed by %10, All computational analysis and simulation was performed with Matlab.

3) Results:

Here contribution analysis was performed to investigate the roles of the Ca^{2+} gating variables activation d, fast inactivation f_{11} and slow inactivation f_{12} during the four phases of cardiac action potential defined as Fig 1A. We employ the method for evaluating Ca^{2+} variable contributions that was described in Methods (2.2) and show the results as bar graphs in Fig 1D. We defined a parameter as a multiplication of τ_X equation to vary the time constant. During depolarization as shown in phase 1, C_{AP}^{f11} and C_{AP}^{f12} values are zero which means neither slow nor fast inactivation has a contribution in this phase. Instead, Ca^{2+} channel activation d helps to increase voltage towards E_{Na}, as expected with $C_{AP}^{d} = 0.18$. During the phase 1, rapid Na^{+} influx is observed by fast Na^{+} channel activation with the help of of Ca^{2+} channel activation [6].

Next, we checked the Ca^{2+} channel contributions during phase 2 as shown in 2nd bars in Fig 1D. At depolarized potentials Ca^{2+} inactivation is composed of both fast (f_{11}) and slow (f_{12}) components [9]. The active component of Ca^{2+} channel during this phase in our model is fast inactivation of Ca^{2+} channel f_{11} with $C_{P2}^{f11} = 0.08$. In this phase voltage starts to turn back from its peak value to the 0 mV. Na^{+} channel inactivation together with K^{+} channel activation mainly responsible for the phase 2. Fast Ca^{2+} channel inactivation f_{11} also helps in this phase to returns the voltage toward the 0 mV.

In Fig. 1D, 3rd bar graphs, contribution analysis shows that Ca^{2+} channel dynamics are mainly responsible in phase 3. This is the plateau phase of the cardiac action potential and Ca^{2+} channel activation d together with the slow f_{12} and fast f_{11} inactivation is mainly responsible from phase 3 with the values $C_{AP}^{d} = 0.6$, $C_{P2}^{f11} = 0.3$ and $C_{P2}^{f12} = 0.012$. Influx of Ca^{2+} through L-type Ca^{2+} channels is electrically balanced with K^{+} efflux in this phase.

Lastly, cardiac AP turns to the resting potential after Ca^{2+} channels close and delayed-rectifier K^{+} channels mainly responsible for the downstroke of the voltage curve. When we look at the contribution results, we see the similar case as Ca^{2+} channels are closing with decreasing $C_{AP}^{d} = 0.03$ value and helps to rapid repolarization together with the K^{+} channels activation.

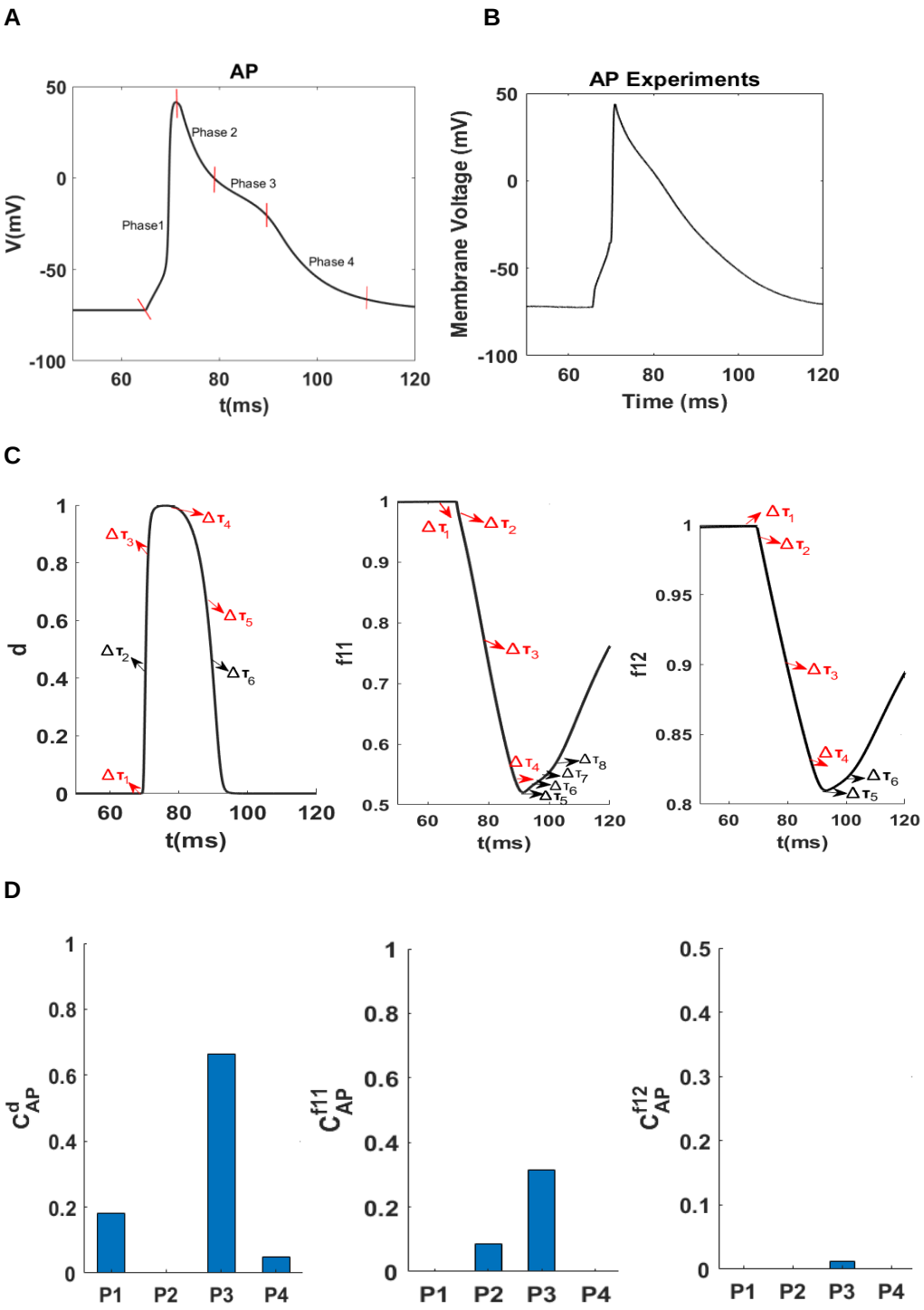

Figure x: (A) Simulated action potential between 50 ms and 120 ms,with four phases shown with red lines starting at 67.40, 71.12, 78.70, 90.42 ms respectively (B) Recorded action potential (C) Curves of activation of Ca^{2+} channel d, fast inactivation gate f_{11} and slow inactivation gate f_{12}. The black and red arrows on the graphs show the points where epochs starts and time constant was increased by %10 percent. While the black arrows represent the changing points of state variables, red arrows represent starting and/or finishing point of action potential phases. (D) P1,P2,P3,P4 represents the relative contribution values of each state variables for each action potential phases.

4) Discussion

In this paper, the new cardiac model described with 26 differential equations is optimized in conjunction with electrophysiological recordings from the rat cardiomyocytes. Hodgkin-Huxley formalism is used to describe ion channel dynamics. Model analysis focused on analyzing the Ca^{2+} channel dynamics during

the cardiac action potential. L-type Ca^{2+} channels are modeled with activation variable d together with fast and slow inactivation gates f_{11} and f_{12} respectively. To understand the role of different components and how these components interact to produce specific dynamical outputs, we defined a mathematical measure contribution analysis for more complex biological oscillators. Since the derivative of the state variables change sign during the AP, we divide it to epochs and find the contributions separately for each of them. As an example, contribution analysis is applied to Ca^{2+} gating variables and the results were consistent with the literature. Ca^{2+} activation had a contribution on depolarization, repolarization and the plateau that was shown as phase 1,2,3 and 4 in Fig 1A. Even though fast inactivation variable f_{11} had contribution on phase 2 and phase 3 as a result of the analysis, the only contribution of slow inactivation variable f_{12} was on phase 3. In general, with experimental approaches cannot be found the relative contributions of different variables to a biological system's activity and the development of a computational model together with the method presented here can be applied to all cardiac channels. But this could be verified experimentally for cardiac cells using the dynamic clamp technique, which allows us to introduce a model-generated ionic current into a real cell.

Acknowledgments: All authors were supported by TÜBİTAK 3501 grant 117f020.

Conflict of interest: The authors declare that they have no conflict of interest.

References

[1] Burt B. Hamrell. 2018. Cardiovascular Physiology. Taylor and Francis.
[2] Pehlivan F. 2015. Biyofizik. Pelikan Yayınları.
[3] Antzelevitch, C., G-X. Yan, W. Shimuzu, and A. Burashnikov. 1999. Electrical Heterogeneity, the ECG, and Cardiac Arrhythmias. In Cardiac Electrophysiology: From Cell to Bedside. D. P. Zipes and J. Jalife, editors. W. B. Saunders Co., Philadelphia. 222–238.
[4] Hodgkin, A. L., and A. F. Huxley. 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. 117:500–544.
[5] Luo, C. H., and Y. Rudy. 1994. A dynamic model of the cardiac ventricular action potential. I. Simulation of ionic currents and concentration changes. Circ. Res. 74:1071–1096.
[6] Beeler, G.W., and H. Reuter. 1977. Reconstruction of the action potential of ventricular myocardial fibres. J. Physiol. 268: 177-210.
[7] Şengül, S., R. Clewley, R. Bertram, and J. Tabak. 2014. Determining the contributions of divisive and subtractive feedback in the Hodgkin-Huxley model. J Comput. Neurosci. 37:403-415.
[8] Sandeep V. Pandit, Robert B. Clark, W. R. Giles, and S. S. Demir. 2001. A Mathematical Model of Action Potential Heterogeneity in Adult Rat Left Ventricular Myocytes. Biophysical Journal. 81:3029–3051.
[9]Katsube, Y., H. Yokoshiki, L. Nguyen, M. Yamamoto, and N. Sperelakis.1998. L-type Ca^{2+} currents in ventricular myocytes from neonatal and adult rats. Can. J. Physiol. Pharmacol. 76:873–881.

2010 Mathematics Subject Classification: 37N25, 92B05
Key Words and Phrases: Mathematical Modeling, Biomathematics, Cardiac action potential