A Quantitative Comparison of the Cardiac Ventricular Single Cell Models

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Abstract— Cardiac cell modelling provides a logical framework for integrating and understanding the results of experimental study of cardiac cellular physiology. Many computational models of cardiac ventricular cell have been developed to understand the work, out of these, three already existing models, namely Beeler-Reuter model, Luo-Rudy phase-I model and Luo-Rudy phase-II model is analyzed and their comparative study has been performed. These models are compared on the basis of action potential characteristics; peak overshoot potential, resting membrane potential, amplitude, notch potential, plateau potential, action potential duration and diastolic interval, at cycle length of 1000msec. These models are also analyzed one by one for action potential, transmembrane currents and calcium transients at different cycle lengths of 1000msec, 750msec, 500msec and 400msec. Our study reveals, when cycle length is decreased, wave shape of the action potential, all transmembrane currents (except INa) and intracellular calcium concentration becomes narrower for all the models. In LR-II model potassium time dependent current IK is approximately doubled as compared with the other two models, enhancing its ability to repolarize the membrane, so APD is smaller as compared with the other two models.

Keywords: Cardiac cell modelling, action potential, BR model, LR-I model, LR-II model, cycle length

I. INTRODUCTION

The human body is a complex system made up of many complicated and interrelated processes. For example, the heart has four different chambers, that each has different functions. It functions as a mechanical pump that expels blood throughout the body and transport critical nutrients and removes waste products from the tissues. For efficient pumping action, it requires highly organized and synchronized contraction of the heart. Each cardiac cell contributes to the heart's contraction by sending out small electrical impulses called action potentials.

Mathematical models are used to study the dynamics of action potential in an accurate way. A mathematical model of a cardiac cell is a promising technique to extend our knowledge in this field. Experimental studies in this field give detailed information about time–varying functions of ion channels, pump, transporter and intracellular processes. Computer based modelling provides the logical framework for integrating and understanding the results of detailed experimental study of cardiac cellular physiology. By modelling the observed electrical behavior can be interpreted. However, modelling can also be used to make inferences about phenomena that cannot be readily measured.

This field has the potential to improve the understanding of how small scale processes interact to form the whole functioning organ. In addition to their efficacy, experiments based on mathematical models and computation often represent a simpler and less expensive, alternative to experiment with real hearts[1].

In 1952 Hodgkin and Huxley published the first biophysically based model[2] of the electrophysiology of a single cell. This model was the foundation for much of the electrical modelling of cardiac cells. A biophysically based cardiac cell models are derived from extensive experimental observations and are designed to model the underlying physiological mechanisms rather than just reproduce features. Due to the inclusion of the physiological detail, these models are more predictive than the simplified models, but due to the large number of differential equations, complexity increases.

The two ventricular cell models namely, Grandi-Pasqualini-Bers (GPB) model [3] and the O'HaraVira´g-Varro´-Rudy (OVVR) model [4] are compared by Mohamed M. Elshrif1 [5].

In this work, groundbreaking ventricular models, namely, Beeler –Reuter model[6], Luo-Rudy phase-I model[7] and Luo-Rudy phase-II model[8] are compared on the basis of various parameters. The Beeler-Reuter model was the first mathematical model of a mammalian cardiac ventricle muscle cell. Luo-Rudy phase-I model was based on the Beeler-Reuter model, adjusting the parameters to reproduce more recent experimental results and additional currents to more accurately represent potassium ion dynamics. Luo-Rudy phase-II model has become a widely used model. This model was based on experimental findings regarding the channel kinetics, pump, exchangers and intra-cellular processes.

II. ELECTROPHYSIOLOGICAL MODEL FORMULATIONS

In this study, we focused on three already published biophysically based models of cardiac ventricular cells, namely: Beeler–Reuter (BR) model, Luo-Rudy phase-I(LR-I) model and Luo-Rudy phase-II(LR-II) model. These models have different formulations. The details of the state variables and transmembrane currents used by each model are given in table1 and have been taken from the original published papers [6,7,8].

The BR model was the first ventricular cell model, but the data of the BR model was subject to limitations in available voltage-clamp techniques and their applications to multicellular preparation of cardiac muscle. In 1980's the limitations of voltage-clamp measurements were overcome and the intracellular and extracellular ionic environments could be controlled. In LR-I model, the BR model data was modified with additional experimental information. In LR-I model single cell-single channel preparation was used.

S.No.	Model	Static variables	Transmembrane currents
1.	Beeler-	8- m,h,j,d,f,$[Ca^{2+}]_i$,X_1,V	4-I_{Na}, I_K, I_{X1}, I_S

	Reuter Model		
2.	Luo-Rudy Phase-I Model	8-m,h,j, $[Ca^{2+}]_i$,d,f,X,V	6- I_{Na}, I_K, I_{X1}, $I_{Si,}$, I_{K1}, I_{Kp}
3.	Luo-Rudy Phase-I I Model	12- m,h,j,d,f,X,V,$[Ca^{2+}]_{JSR,}$,$[Ca^{2+}]_{NSR}$,$[Ca^{2+}]_{i,}$ $[K^+]_{i,}$ $[Na^+]_i$	11- I_{Na}, I_K, I_{K1}, I_{Kp}, $I_{Ca(L)}$, I_{NaCa}, I_{Nak}, I_{nsCa}, I_{PCa}, I_{bCa}, I_{bNa}

Table 1: Static variables and transmembrane currents for BR, LR-I and LR-II model

The LR-II model was modification of LR-I model. In LR-I model Ca^{2+} current through L-type calcium channel was not reformulated for recent experimental findings about channel kinetics, for fast activation [9] and inactivation that was both voltage and Ca^{2+} dependent [10-14]. Another important feature of LR-II model was calcium uptake and release by the sarcoplasmic reticulum (SR), which regulates $[Ca^{2+}]_i$ not included in LR-I model. In LR-I model only ionic currents through gated channel in sarcolemma are included but other membrane processes (i.e. pump and exchangers) were not included, which contribute to changes in ionic concentration.

The experiments on mammalian ventricular cell have been measured by several groups [15-20] .On this basis shape of the cell in this model was represented by a circular cylinder of 100µm length and 11µm in radius. The SR appears to be functionally and structurally divided into two compartments: the JSR and the NSR. Volume fraction of sarcoplasmic reticulum (F_{SR}) is 6% of cell volume. The SR volume is divided into JSR (8%) and NSR (92%). The mitochondria volume fraction (F_{mito}) was set to 26%. The remaining volume is occupied by myoplasm (F_{myo}=68%).Ion channel accumulation in extracellular clefts, F_{cell}:F_{cleft} is assumed to be 88%:12%.

III. Measurement of Parameters

In this work, dynamic(steady-state) restitution protocol[21] is used to obtain action potential, all transmembrane currents and calcium intracellular concentration at a cycle length (CL) of 1000msec, 750msec, 500msec and 400msec. Action potential duration(APD) is measured using the voltage threshold at 90% of repolarization, at a CL of 1000msec. For analysis APD of fifth pulse and preceding diastolic interval (DI) pair is recorded. Similarly resting membrane potential, peak overshoot potential, amplitude, notch potential and plateau potential is recorded for CL of 1000msec.

IV. Numerical Methods

For all models, the rate of change of cell membrane potential V_m follows an ordinary differential equation which is given by following equation.

$$\frac{dV_m}{dt} = \frac{-(I_{ion}+I_{st})}{C_m} \quad (1.1)$$

Where, I_{ion} = sum of the ionic currents given by the model formulation, I_{st} = Stimulus current, C_m = Membrane capacitance, which is set to 0.01µF/mm^2 for all models.

These models account for dynamic changes of ionic concentration during the action potential. The rate of change of ionic concentration is given by following equation.

$$\frac{d[B]}{dt} = \frac{-I_B \cdot A_{cap}}{V_C \cdot Z_B \cdot F} \quad (1.2)$$

Where, A_{cap} = capacitive membrane area.
V_c = volume of the compartment where [B] is updated.
Z_B = valency of ion.
F = Faraday's constant.

For all models Runga–kutta method is used to solve differential equations. The time step used for all three models is 0.01msec. All equations and parameters are specified in the original papers. MATLAB 2013a is used for simulation.

V. Results

Action potentials, transmembrane currents and calcium transients

We compared the single cell ventricular models(BR, LR-I and LR-II models) on the basis of action potential characteristics; peak overshoot potential, resting membrane potential, amplitude, notch potential, plateau potential, action potential duration and diastolic interval, at a cycle length of 1000msec. The results of the same are shown in table(2). These models are also compared on the basis of t action potential, the transmembrane currents and calcium transients at different cycle lengths of 1000msec, 750msec, 500msec and 400msec. The results are shown in figure(1), figure(2), and figure(3) for BR, LR-I and LR-II models respectively.

Model	B-R Model	LR-I Model	LR-II Model
Resting membrane voltage(mV)	-84.4261	-84.4389	-86.0683
Peak overshoot potential(mV)	32.2318	46.9394	47.4106
Amplitude(mV)	116.6579	131.3783	133.4969
Notch voltage(mV)	13.72	9.2	-
Plateu voltage(mV)	16.84	11	30
APD(msec)	288.1	342.4	200.1
DI(msec)	711.9	657.6	799.9

Table 2: Action potential characteristics for BR, LR-I, and LR-II models

Figure 1(A), 2(A), 3(A) shows action potential of BR, LR-I and LR-II models respectively. The LR-I, in contrast to the BR model, produce an AP with a faster upstroke more consistent with experimental observations. LR-I model is reformulated the opening and closing rate coefficients for the sodium current from the BR-model making it a faster process, because of faster sodium dynamics, the APD produced by the LR-I model will be longer, with higher depolarization and so this model will be more excitable.

Action potential shape of BR model and LR-I model is similar but peak overshoot potential and amplitude of LR-I model is greater than the BR model. Peak overshoot potential and amplitude depends on sodium channel conductance, which is increased in LR-I model($\overline{g_{Na}}$ is equal

to 0.04mS/mm^2 for BR model and $\overline{g_{Na}}$ is equal to 0.23mS/mm^2 for LR-I model.

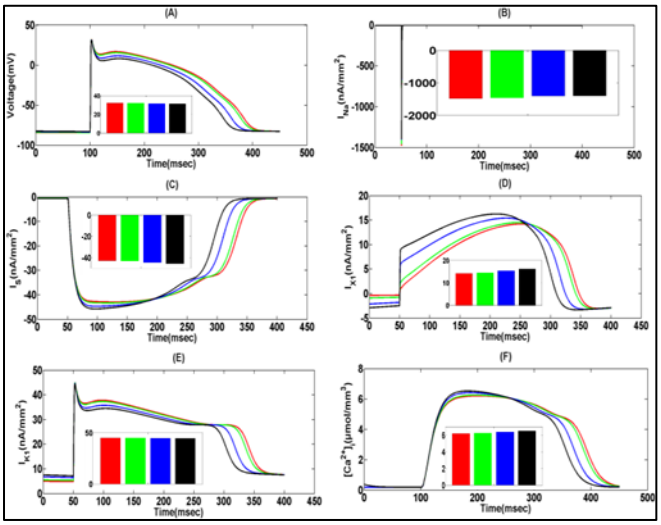

Fig 1: Rate dependence of action potentials(A), transmembrane currents(B-E), and intracellular calcium concentration(F) for B-R Model, for cycle lengths of 1000msec(red), 750msec(green), 500msec(blue), 400msec(black). Bar charts show peak voltage, current, and concentration values for the same cycle lengths following the same color scheme.

Action potential shape of LR—II model is different than BR and LR-I model. LR-II model action potential does not have notch and a slope of plateau phase is higher than the other two models. Notch potential and the plateau potential of BR model is higher than that of LR-I model. The LR-II model has maximum plateau potential of 30mV, because of large value of I_K for the guinea pig type of ventricular cell. For other species, including the rabbit, dog, and rat, I_K is relatively small [5]. LR-II model has minimum APD 200.1msec and LR-I model has highest APD 342.4msec at a cycle length of 1000msec. The LR-I, in contrast to the BR model, produce an AP with a faster upstroke more consistent with experimental observations. The resting membrane potential (RMP) for BR and LR-I model is approximately same which is equal to -84.4mV. In LR-II model RMP is decreased by 2mV as compared to other two models. Amplitude of action potential for LR-I and LR-II model is approximately same, but BR model action potential amplitude is less by approximately 15-17mV. LR-II model is less rate dependent as compared to other two models. The Peak overshoot potential of LR-I and LR-II model is approximately equal despite of different maximum sodium channel conductance, $\overline{g_{Na}}$ is decreased from 0.23mS/mm^2 to 0.16mS/mm^2 to compensate for increased reversal potential(E_{Na} ,from 54.4mv to 70mV).

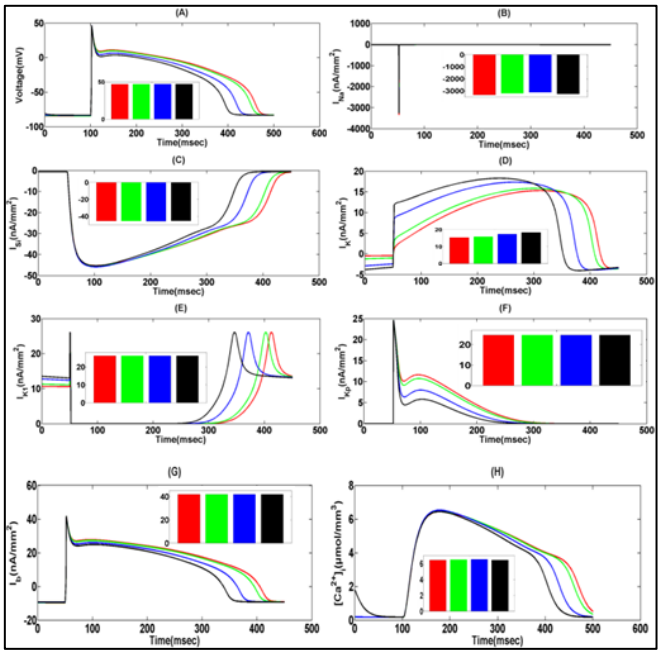

Fig 2. Rate dependence of action potentials(A), transmembrane currents(B-G), and intracellular calcium concentration(H) for LR-I Model, for cycle lengths of 1000msec(red), 750msec(green), 500msec(blue), 400msec(black). Bar charts show peak voltage, current, and concentration values for the same cycle lengths following the same color scheme.

B-R model is rate dependent for some parameters. When CL changes from 1000msec to 400msec resting membrane potential is decreased by 1.41mV, whereas, peak overshot potential and amplitude is decreased by 0.97mV and 2.28mV respectively. Notch voltage and plateau voltage are sensitive to cycle length. At CL of 1000msec notch voltage is 13.72 mV and plateau voltage is 16.84mV, when CL is 400msec notch voltage is 5.562mV and plateau voltage is 8.156mV, it is approximately decreased by 50%. Similarly APD is also decreased by 38.7mV. Diastolic interval is strongly dependent on CL, at 1000msec DI is 711.9mec which is decreased by 244.5msec, 476.1msec and 561.3msec when CL is 750msec, 500sec and 400msec respectively. The results of BR model are shown in figure (1).

The results obtained from LR-I model are different from BR model. When CL changes from 1000msec to 400msec resting membrane potential is decreased by 0.8mV, whereas, peak overshot potential is increased by 0.11mV and amplitude is decreased by 0.75mV. The notch voltage and plateau voltage are sensitive to cycle length. At CL of 1000msec notch voltage is 9.2mV and plateau voltage is 11mV, when CL is 400msec notch voltage is 1.65mV and plateau voltage is 3.73mV, it is decreased by 82% and 66% respectively. Similarly APD is also decreased by 48.7mV. The diastolic interval is strongly dependent on CL, at 1000msec DI is 657.6mec which is decreased by 257.5msec, 476.3msec and 551.3msec when CL is 750msec, 500sec and 400msec respectively. The results of LR-I model are shown in figure (2). When cycle length is decreased, wave shape of the action potential, all transmembrane currents (except I_{Na}) and intracellular calcium concentration becomes narrower for all the models as shown in figure (1, 2 and 3).

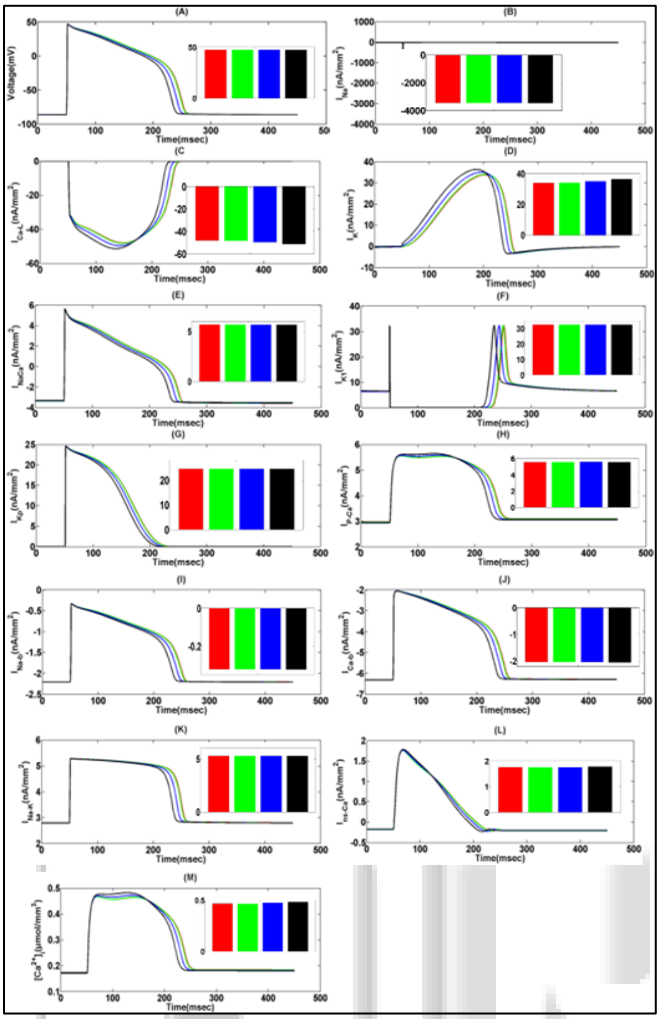

Fig. 3: Rate dependence of action potentials (A), transmembrane currents (B-L), and intracellular calcium concentration (M) for LR-II Model, for cycle lengths of 1000msec (red), 750msec (green), 500msec (blue), 400msec (black). Bar charts show peak voltage, current, and concentration values for the same cycle lengths following the same color scheme.

The shape of the action potential of the LR-II model is different than BR and LR-I model, notch is not present in LR-II model and slope of the plateau phase is higher as compared with the other two models. In LR-II model potassium time dependent current I_K is approximately doubled as compared with the other two models, enhancing its ability to repolarize the membrane, due to which APD is reduced to 200.1msec. As shown in figure 3(M) I_{NaK} strongly depends on membrane potential, I_{NAK} saturates for membrane potential greater than 0mV. When CL changes from 1000msec to 400msec resting membrane potential is decreased by 0.05mV, which is very less as compared with BR and LR-I model. Peak overshoot potential and amplitude is decreased by is decreased by 0.1mV when CL is changed from 1000msec to 400msec. Variation in the APD is 17msec, which is very small as compared with the other two models. Diastolic interval is strongly dependent on CL, at 1000msec DI is 799.9mec which is decreased by 249msec, 491.8msec and 583msec when CL is 750msec, 500sec and 400msec respectively. The results for the LR-II model are shown in figure (3).

VI. Conclusion

Cardiac arrhythmia is a serious disease with multiple involvement at the molecular, cellular, and organ levels and it is essential to understand the electro-pathological behaviors and underlying mechanisms for precise diagnosis and effective treatment. Construction of a cardiac cell model with integration of individual sub-cellular components, including ion channels, dynamic intracellular ionic handling, intracellular organelles and regulatory signaling pathways into the physiologically functioning system of the cardiac cell is necessary to facilitate insights into the interactions and mechanisms underlying electrophysiological behaviors. It is a powerful method which can help recognize and investigate the interactions between components of the cell and study their unique roles in the whole-cell behavior. In this work, three already existing cardiac ventricular single cell models, namely Beeler-Reuter model, Luo-Rudy phase-I model and Luo-Rudy phase-II model are analysed and their comparative study has been performed. These models are compared on the basis of action potential characteristics, at a cycle length of 1000msec. These models are also analyzed one by one for action potential, transmembrane currents and calcium transients at different cycle lengths of 1000msec, 750msec, 500msec and 400msec. Our study reveals, when cycle length is decreased, wave shape of the action potential, all transmembrane currents (except I_{Na}) and intracellular calcium concentration becomes narrower for all the models. In LR-II model potassium time dependent current I_K is approximately doubled as compared with the other two models, enhancing its ability to repolarize the membrane, so APD is smaller as compared with the other two models.

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