Evaluation and Preliminary Integration of the Most Recent Human Ventricular Action Potential Models

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Abstract

In the last few decades, computational models have been increasingly used to study the cardiac physiology, due to the productive synergy between the in-silico approach and the collection of experimental data. However, no model can correctly reproduce all the experimental results but is accurate only in the context in which the investigation was intended.

The purpose of this work is to integrate the main innovations of the two most recent action potential ventricular models and create a more detailed one, then we proceed to compare the performance of this new model, using different protocols, with the available experimental data and the simulations of the starting models used for its realization.

It was found that the new model can reproduce the negative dependence of the APD on the extracellular calcium. In addition, there is a notable improvement in the results of the activation protocol, we can see the I-V curve obtained with the new model is very close to the experimental data.

Unlike the ToRORd the new model fails to reproduce the negative ino-tropic effect of sodium blockade but at least we do not have a strong pro-inotropic effect like in the ORd model.

1. Introduction

One of the main causes of death all over the world is sudden cardiac death, which is correlated with the basic pro-arrhythmic mechanisms at the level of ion currents and single ventricular myocyte action potential (AP). Computational models of AP are a very useful tools that can help us understand the mechanisms underlying these phenomena.

Currently, the "gold standard" for in silico human ventricular cellular electrophysiology is the O'Hara-Rudy (ORd) [1] model. however like all models being an incomplete representation of biological phenomena, it is not possible to faithfully reproduce all the behaviours observed experimentally. Each model has its own field of validity and the choice of the appropriate model depends on the type of research for which the model is used.

In this work we want to answer the question: is it possible to integrate the innovations introduced by the two most recent models of ventricular action potential? We have combined the major innovations deriving from Bartolucci et al. [2] and Tomek et al. [3] models. These two models use the ORd [1] model as starting point but adopt different formulations of some ionic currents, this means that the responses of the models to test protocols are different.

The Bartolucci et al. [2] primary aim was to develop a model able to simulate the physiological inverse APD-[Ca2+]o dependence, observed both in vitro and in vivo, while the Tomek et al. [3] model aims to eliminate all inconsistencies that are observed between simulations with previous models and experimental data.

We then compared the new model with the respective starting models and experimental data currently available to see if the results are closer to the experimental data and if the peculiarities and positive results that each model has shown are maintained.

2. Materials and methods

In this work we consider the O'Hara et al. [1] model published in 2011 the actual "gold standard" of the human ventricular AP models and two more recent model, Tomek et al. [3] and Bartolucci et al. [2], published in 2019 and 2020.

Hereafter the models will be referred to as follows: ORd, ToRORd, BPS. Although all these models simulate the human ventricular AP, their different parameters and ionic current formulations produce distinct AP morphologies, properties, and every model responds to test protocols differently.

Model differential equations were implemented in Matlab (Mathworks Inc., Natick, MA, USA) and solved with a variable order solver (ode15s), based on numerical

differentiation formulas. APDX was measured once membrane voltage reached X% of the resting value.

2.1. Model formulation

For the development of this new model, we started from the analysis of the differences in the formulations between the BPS and ToRORd models.

This new model follows the general ORd structure, and we reformulated some currents/fluxes as described below while for others we only tuned the maximal conductance.

The I_{CaL} formulation is adopted from the BPS [2] model, where the original Hodgkin-Huxley formulation was replaced by a new Markov model. This new formulation separates voltage-dependent inactivation (VDI) and calcium-dependent inactivation (CDI) in two loops, each consisting of the same four states: one closed (C), one open (O) and two inactivated (I1 and I2) states. The CDI and VDI loops are connected by up/down rates (r_{up}/r_{down}), modulated by intracellular Ca^{2+} concentration, and controlled by the n gate.

In addition to this new formulation introduced by the BPS model, we have inserted a modification to the driving force taken from the ToRORd [3] model. To compute the ionic driving force via the Goldman-Hodgkin-Katz equation, it is necessary to know the ionic activity coefficients of the intracellular (γ_i) and extracellular (γ_o) space, in previous models this was fixed as constant while now it is calculated using the Davies equation [4] every step of the simulation. Another modification is represented by a new formulation for the I_{CaL} activation curve. In this new model, as well as the ToRORd model, the activation curve is obtained by dividing the I-V curve from Magyar et al. [5] by the GHK-based driving force, computed the Davies equation for the ionic activity coefficients and intracellular and extracellular ionic concentrations as in Magyar et al. [5]. We have found that the data thus obtained can be well traced by a function which is the product of two sigmoids:

$$d_\infty = \frac{1}{1+e^{-(v+9.698)/2.843}} \frac{1}{1+e^{-(v-5.621)/10.17}}$$

In addition, we decided to keep the sarcoplasmic reticulum (SR) as single compartment like in the BPS model and SR Ca^{2+} release flux (J_{rel}) via the ryanodine (RyR)-sensitive channels was kept as in BPS.

We decided to adopt the I_{Kr} formulation of the BPS model as it is optimized for simulations of ion channel block and dynamic drug-channel interactions and uses a newer Markov model than the formulation used in the ToRORd model.

The I_{K1} model was replaced with the human-based formulation (Fink et. al. [6]) and we have also introduced the calcium-sensitive chloride current $I_{(Ca)Cl}$ and background chloride current I_{Clb} formulation like the ToRORd model does.

The steady state inactivation and recovery from inactivation gates for I_{NaF} were modified as in the BPS model.

Other changes include the current stimulus duration, which is set to 1 ms, with -53 mA/mF amplitude, like the BPS model, and stimulus current is included in the chloride balance. We have also introduced all the changes to the conductances present in the BPS model.

3. Results

In figure 1, the behaviour of the four models can be observed in terms of APs while in the figure 2 we can see the comparison of the calcium transients. We can observe that the new model has an AP closer to the results obtained by the BPS model but can also be noted that the plateau is like the ORd model. The intracellular calcium transient peak is higher regard that of the BPS model but is in line with the values assumed by the transient in the ToRORd and ORd models, the duration of calcium transient is shorter than the ORd and ToRORd, but still is similar to the BPS model.

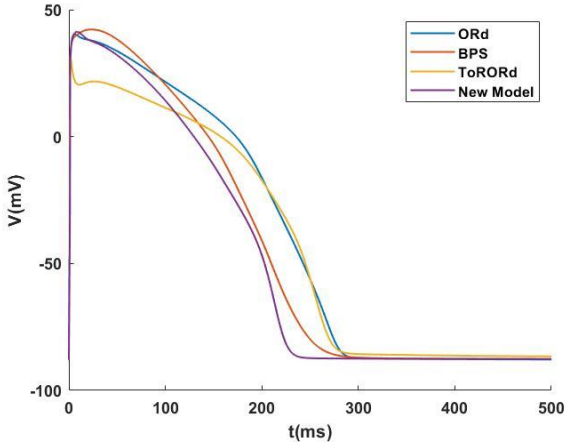

Figure 1. Action potentials comparison between the four models (Ko=5.4mM, Cao=1.8mM, Nao=144mM).

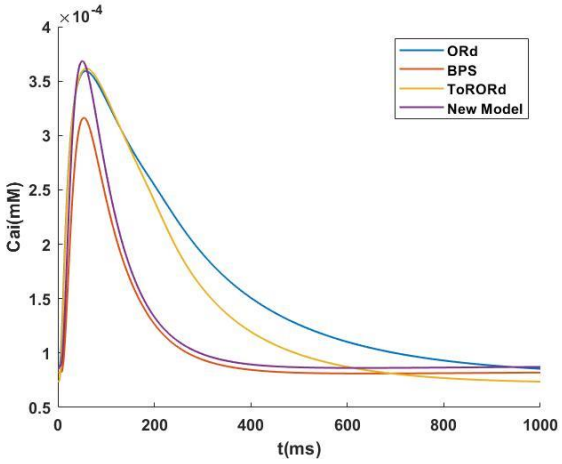

Figure 2. Calcium transient comparison between the four models (Ko=5.4mM, Cao=1.8mM, Nao=144mM).

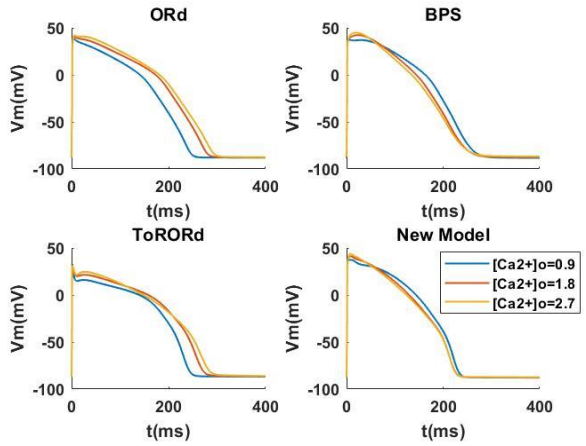

Figure 3. Comparison between the four models action potentials at three different $[Ca^{2+}]_o$ (0.9,1.8,2.7mM), CL=1s in steady-state.

In Figure 3, the behavior of the models in terms of AP can be observed for three different concentration of $[Ca^{2+}]_o$ in steady-state. As shown, $[Ca^{2+}]_o$ markedly affects the AP morphology and duration, and in the four models we can observe different behavior.

It is well-known that extracellular calcium concentration ($[Ca^{2+}]_o$) affects the cardiac AP even if this phenomenon is not entirely understood yet, can be observed that an increase of $[Ca^{2+}]_o$ shortens AP while $[Ca^{2+}]_o$ decrease lengthens it. The dependence between APD and $[Ca^{2+}]_o$ is reported in Figure 4. The new model for calcium values in the range of (0.9 - 1.8 mM) presents the correct trend but beyond this range of values there is a slight increase in the APD, the BPS is the only model reproducing the correct inverse relationship. Conversely, both ORd and ToRORd reproduce a nonphysiological direct dependence.

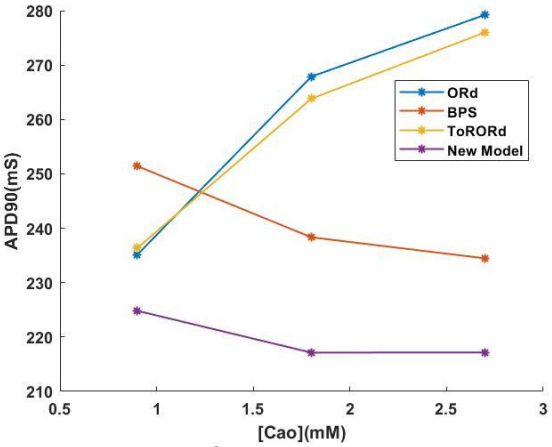

Figure 4. APD-$[Ca^{2+}]_o$ relationship for ORd, BPS, ToRORd and the new model in the range 0.9-2.7 mM

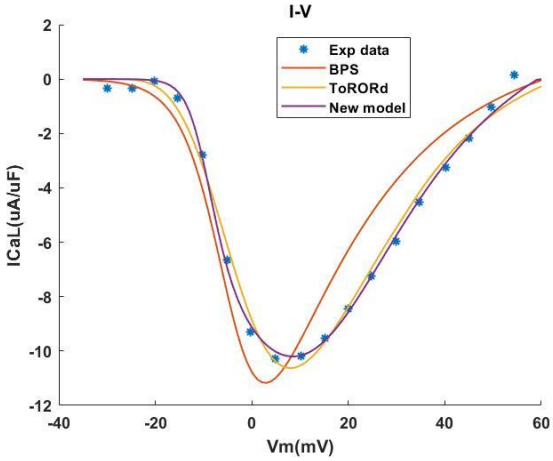

Figure 5. Comparison of the simulated I_{CaL} I–V curve between BPS, ToRORd, the new model, and the experimental data from Magyar et. al. [5]

As described in Model formulation, the new model I_{CaL} activation curve was extracted from experimental data (Magyar et. al. [5]), using the GH-K formulation of the driving force, ensuring theoretical consistency, this change result in a considerable improvement, in figure 5 we can observe how the curve obtained from the new model using the activation protocol for the I_{CaL} fits better the experimental data (Magyar et. al. [5]).

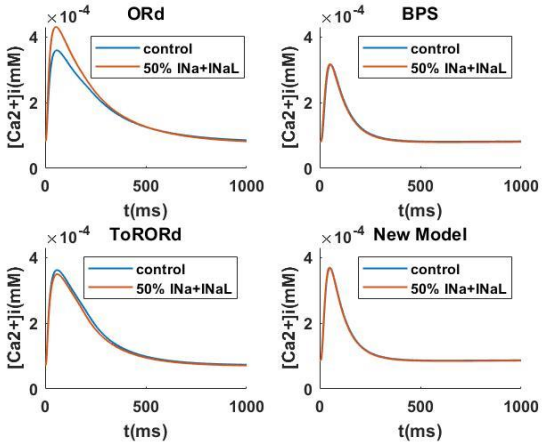

Figure 6. Simulated effect of sodium current block on calcium transient. Control simulations are shown as blue traces, whereas results for 50% block of I_{Na} and I_{NaL} are shown as red traces.

Figure 6 illustrates calcium transient changes caused by the block of sodium currents, sodium blockers act on both the fast (I_{NaF}) and late (I_{NaL}) sodium current, we simulate this effect by a combined partial I_{NaF} and I_{NaL} block (50% block of both I_{NaF} and I_{NaL}).

The ORd model manifests a large increase in calcium

transient amplitude, unlike the ToRORd, which gives a small reduction. On the contrary, in both BPS and the new model only small variations in the calcium transient are noted. This result can be considered an improvement with respect to the ORd model since its behavior does not reflect the real trend of the calcium transient upon a sodium block; however, the only model that presents a correct trend of the calcium transient is ToRORd that is in line with the observed negative inotropy of sodium blockers.

4. Discussion and Conclusion

In this study we tried to combine the main innovations of the two most recent ventricular action potential models, the BPS and ToRORd. Both models have the ORd as their starting point but develop in totally different. The BPS primary aim was to develop a model able to simulate the physiological inverse APD-$[Ca^{2+}]_o$ dependence, observed both in vitro and in vivo, and to reproduce the *in vitro* experiments at the correct $[K^+]_o$. While the ToRORd model aims to eliminate all inconsistencies that are observed between simulations with previous models and experimental data.

With this new model we have tried to reproduce some of those improvements that ToRORd and BPS models have made.

It is well established that a change in $[Ca^{2+}]_o$ may affect many electrogenic transport mechanisms across the membrane. The new model responded with APD shortening to $[Ca^{2+}]_o$ increase till a concentration of extracellular calcium of 1.8mM and beyond this value is observed a small increase in APD. The behavior found beyond this calcium value is in contrast with the experimental results and the simulations results of BPS model, but we can say that the formulations introduced on this new model manage to correct the behavior of the ORd model as regards the $[Ca^{2+}]_o$-APD dependance at least in a physiological range.

The new formulation of the I_{CaL} activation curve brings a substantial improvement in the results obtained through the activation protocol: as we can see the I-V curve obtained with the new model is very close to the experimental data in the whole range of the test potential.

Another partial improved behavior compared to the ORd model is the response to sodium current block, unlike ToRORd model that predicts the negative inotropic effect of sodium blockade, consistent with data, we can observe small variation in calcium transient, this is an improvement since the ORd model suggested a strong pro-inotropic effect.

In conclusion, this new model inherits many of the improvements present in the ToRORd and BPS models, but further modifications are needed so that the formulations introduced in the new model can coexist, allowing the experimental data to be reproduced even more faithfully.

References

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