305 - Multiscale Methods for Definition of Ionic Variables in Electrophysiological Models

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I. Introduction

Models of gating currents are usually built by fitting the expression of individual gating variables to experimental data, thus considering each gate as independent of others. In this work, we present a methodology to fit ionic currents while considering the interaction with other elements defining the current as well as the effects at cell and tissue levels.

II. Methods

The Carro-Rodríguez-Laguna-Pueyo (CRLP) human ventricular action potential (AP) model [1] was used as the basis for this study. In silico simulations of experimental protocols were run to optimally define voltage-dependent L-type calcium (I_{CaL}) current inactivation gates (f, f_2). The parameters describing steady-state gating inactivation were identified by solving an optimization problem using a response surface methodology [2]. A number of constraints were considered, and each result validated, at the ionic level, based on experimental evidence: steady-state voltage-dependent I_{CaL} inactivation was required to decrease monotonically for negative voltage values and have only one inflection point. The effects of introducing those changes in the model were evaluated at cell and tissue level. In this regard, a set of arrhythmic risk markers, including systolic and diastolic intracellular calcium concentration ($[Ca^{2+}]_i$), AP duration (APD), AP triangulation and the slow time constant of APD adaptation to abrupt cycle length changes (τ_{slow}) were required to lie within experimental ranges.

III. Results

The redefined I_{CaL} current satisfactorily reproduced experimental observations, with mean square errors between simulated and experimental steady-state inactivation current values being 20% lower than for the original CRLP model. At cell and tissue levels, APD, Triangulation and τ_{slow} lay within physiological ranges, and systolic and diastolic $[Ca^{2+}]_i$ values were of the same order than for the original CRLP model.

IV. Conclusions

The methodology proposed in this study can greatly help to define ionic current models in good concordance with experimental results. To avoid model overfitting, validation at all involved scales is advised.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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