TOWARDS THE DEVELOPMENT OF A ZEBRAFISH ACTION POTENTIAL MODEL

Ludovica Cestariolo (1), Jose Maria Ferrero (2), Zachary Long (3), T Alexander Quinn (3), Jose Felix Rodriguez Matas (1)

1. Politecnico di Milano, Milan, Italy; 2. Universitat Politècnica de València, Valencia, Spain; 3. Dalhousie University, Halifax, NS, Canada

Introduction

During the last 30 years, the use of zebrafish for studies of cardiac electrophysiology has exponentially increased. Of particular interest are the similarities in action potential (AP) characteristics, owing to the presence of ~69% human gene orthologues [1], which lead to functional similarities in cardiac ion channels [2]. Given the growing importance of this animal model, the development of an *in-silico* AP model is warranted, to help in understanding ionic mechanisms involved in the development of cardiac pathologies and the response to pharmacological therapies, while reducing the number of animals needed for experimentation. For this purpose, our goal was to develop a mathematical model of the zebrafish AP.

Methods

This work developed a detailed AP model for the adult zebrafish by including the main ionic currents involved. The TenTusscher and Panfilov AP model from 2006 (TP06) [3] was adapted to the zebrafish. A literature review was performed to identify individual ion channel experimental data (*i.e.*, by patch-clamp) related to the principal currents responsible for the zebrafish AP. According to previous reports, the principal currents involved are the: i) fast Na^+ current, I_{Na}, responsible for the rapid depolarization of the AP; ii) T-type Ca^{2+} current, I_{CaT} (added to the TP06 model), which contributes to the initial AP upstroke; iii) L-type Ca^{2+} current, I_{CaL}, which maintains the AP plateau and provides the Ca^{2+} necessary for contraction; iv) rapid and slow delayed rectifier K^+ currents, I_{Kr} and I_{Ks}, involved in repolarization; v) inward rectifier K^+ current, I_{K1}, which contributes to late repolarization and maintains resting membrane potential; and vi) Na^+/K^+ pump and Na^+/Ca^{2+} exchanger, important for restoring ionic balance during the resting phase. The transient outward K^+ current, I_{to}, was removed from the TP06 model since it has been shown not to be present in zebrafish [2]. The newly developed AP model was parameterized by fitting to sharp electrode AP recordings from the ventricle of adult zebrafish isolated hearts maintained in 28°C HEPES-buffered saline solution and paced from the ventricular apex.

Results

After formulating the behavior for the different gating variables, the gates were integrated using the Rush-Larsen scheme, and simulations were run with a fixed time step of 0.02 ms. The Monte Carlo method was used to select which of the 11000 combinations of 34 parameters best fit the shape of the experimentally recorded AP while preserving model stability. Figure 1 shows the best numerical AP (black) compared to experimental AP recordings (blue), while the numerical and experimental AP features are reported in Table 1.

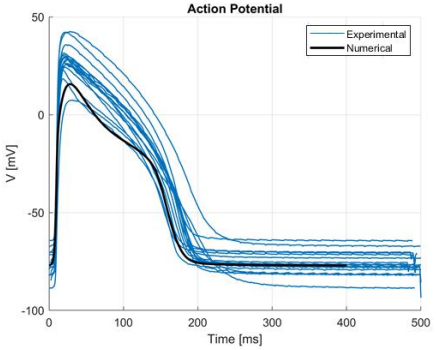

Figure 1: Comparison of ventricular experimental and numerical APs.

AP marker	Model	Experimental
RMP [mV]	-78.48	-88.42 ÷ -68.48
APA [mV]	95.42	96.27 ÷ 111.20
APD_{20} [ms]	54.43	53.06 ÷ 94.48
APD_{50} [ms]	133.05	114.92 ÷ 158.07
APD_{80} [ms]	154.01	146.88 ÷ 200.25
APD_{90} [ms]	163.92	156.48 ÷ 219.66
dV/dt_{max} [V/s]	27.6	13.73 ÷ 25.98
V_{max}	16.95	7.85 ÷ 42.56

Table 1: Characteristics of ventricular experimental and numerical APs.

Discussion

This work represents the first attempt to develop an AP model for adult zebrafish. The model accounts for the main transmembrane currents that have been characterized in zebrafish and generally reproduce measured AP morphology. However, these results are considered preliminary, as the effect of heart rate (or stimulation frequency) on the AP (*i.e.*, restitution) and the response to drugs must be examined to determine the validity and utility of the proposed model.

References

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