A NUMERICAL MODEL FOR ZEBRAFISH VENTRICULAR ACTION POTENTIAL

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Introduction

The use of zebrafish in the field of cardiac electrophysiology has grown in the last decades thanks to its action potential (AP) morphology and the functional similarities in cardiac ion channels [1] related to the existence of ~69% human gene orthologues [2]. Considering the exponential growth in using this animal model to help in studying the ionic mechanism involved in the development of cardiac pathologies and the response to pharmacological therapies, it seems to be very helpful the development of an *in-silico* AP model to also allow reducing the number of animals used for the experimentation. Thus, the objective of this work was to develop a mathematical model for the zebrafish ventricular AP.

Methods

After accurate research to identify individual ion channel experimental data (*i.e.*, by patch-clamp) associated with the main currents responsible for the AP, a detailed AP based on the TenTusscher and Panfilov AP model from 2006 (TP06) [3] was adapted to the adult zebrafish. Therefore, the main 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, essential for restoring ionic balance during the resting phase. The transient outward K^+ current, I_{to}, was removed from the TP06 model since it is not present in zebrafish [1].

The model was implemented in Matlab. To identify the best combination of parameters that fits the recorded AP shape while ensuring model stability, the Monte Carlo method was used with 11000 combinations of 34 parameters. A sensitivity analysis was conducted by varying one parameter at a time for the maximum conductances, the time constants, and the activation and inactivation gating variables.

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

Figure 1 shows a comparison of the numerical against experimental AP recordings for a pacing frequency of 2Hz (left) and restitution behavior of the upstroke for protocol S1-S2 (right), whereas Table 1 gives a detailed comparison of AP morphology for the same stimulation frequency.

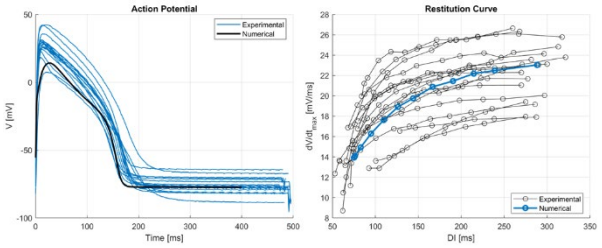

Figure 1: Comparison of ventricular experimental and numerical APs (left) and upstroke restitution curves for S1-S2 protocol (right).

AP marker	Model	Experimental
RMP [mV]	-77.42	-88.42 ÷ -68.48
APA [mV]	91.67	96.27 ÷ 111.20
APD_{20} [ms]	74.97	53.06 ÷ 94.48
APD_{50} [ms]	138.36	114.92 ÷ 158.07
APD_{80} [ms]	156.64	146.88 ÷ 200.25
APD_{90} [ms]	162.1	156.48 ÷ 219.66
dV/dt_{max} [V/s]	23.12	13.73 ÷ 25.98
V_{max} [mV]	14.22	7.85 ÷ 42.56

Table 1: Morphology of ventricular experimental and numerical APs.

Discussion

This work represents the first attempt to develop an electrophysiological detailed AP model of an adult zebrafish. The model is able to describe in-vitro experimental data from isolated adult zebrafish hearts in both static and dynamic stimulation protocols. However, further examination of the model response to additional stimulation protocols and to drugs is required for further validation of the model.

References

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