Modelling the Electrophysiology of the Zebrafish Heart: A Computational Study

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1. Introduction

Recent studies suggest that the physiology of the zebrafish heart resembles that of the human in many aspects, namely: spontaneous heart rates are found to be similar, its cardiac action potential much more closely resembles that of the human, and QT-interval in electrocardiograms is heart rate dependent [1]. Thus, zebrafish has been proposed as a potential model for genetic and pharmacological screening of factors affecting heart functions. However, despite this rising interest, very few studies concern the development of computational models of the zebrafish heart [2]. This work aims at developing a reliable computational model of the zebrafish heart to evaluate the main electrophysiological parameters with the ultimate purpose of better understanding their correlation with pathologies and drug administration.

2. Methods

A full electrophysiological model of the heart + body of a zebrafish 3 days post fertilization (dpf) is developed. The model (Figure 1a), which includes 550974 elements and 97307 nodes, is based on the geometry reported in *Crowcombe et al.* [2] and is composed of three main parts: body, heart chambers, and heart myocardium. The latter is, in turn, divided into four regions: ventricular wall, atrio-ventricular band (AV band), atrial wall, and sinoatrial region (SAR), where the stimulus is delivered. In addition, the AV band and ventricle have been divided into other sub-parts in order to account for heterogeneities in electric conductance [3]. The AV band includes two distinct rings, an atrium side (AVband1) and a ventricle side (AVband2).

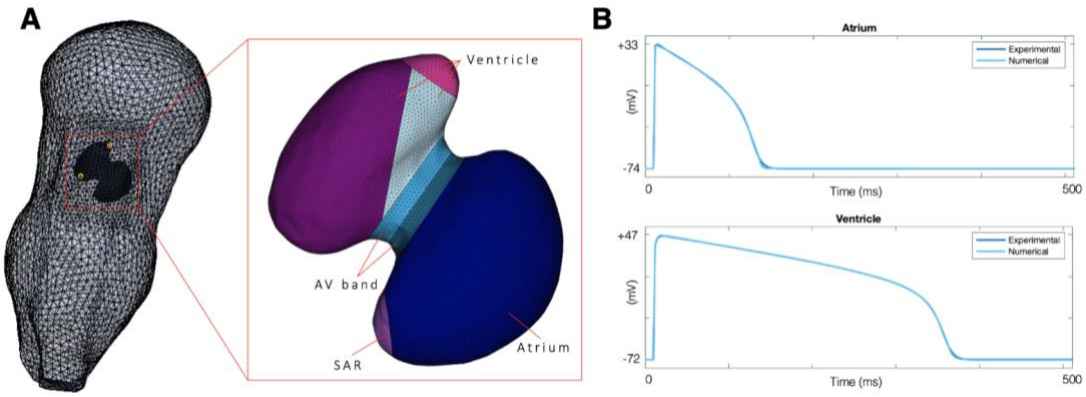

Figure 1. *A) Model geometry: the complete model and in detail the heart and its different parts. In yellow the electrodes used to compute the ECG (positive: ventricular base, negative: ventricular apex) are shown. B) Experimental and numerical AP for atrium and ventricle.*

Different action potential (AP) models have been assigned to the atrium and ventricle, as shown in Figure 1b. To AVband1 has been assigned the action potential model of the atrium and to AVband2 the one of the ventricle. The ventricle has been divided into three different regions, i.e., Ventricle1, Ventricle2, and Ventricle3, (see Figure 1a) following the activation sequence, and according to the study by *Panáková et al.* [3].

Different conductance values have been assigned to these regions in order to reproduce the activation pattern reported in literature [3]. The heart tissue is assumed as isotropic with conductances shown in Table 1. The value of the conductances has been chosen such that the activation sequence of the model and the amplitude of the ECG agree with reported experimental data [3].

Table 1. *Tissue conductances used in the model.*

Part	Intracellular conductance (cm^2/s)	Extracellular conductance (cm^2/s)
SAR	2.01e-06	2.01e-06
Atrium	2.01e-06	2.01e-06
AVband1	8.00e-08	8.00e-08
AVband2	1.00e-07	1.00e-07
Ventricle1	1.00e-06	1.00e-06
Ventricle2	3.00e-07	3.00e-07
Ventricle3	9.50e-08	9.50e-08
Body	-	1.60e-04

The action potential of the different heart regions has been simulated using the Bueno-Orovio four-variables minimal model (BV4) proposed by *Bueno-Orovio et al.* [4]. This model reproduces realistic AP shapes by using only four state variables. This phenomenological model allows reproducing a large variety of AP shapes while accurately reproducing the action potential and conduction velocity (CV) restitution curves. In this work, the BV4 model has been adjusted to fit experimentally reported action potentials of the zebrafish to reproduce a correct heart rhythm dependence of the QT [5]. Figure 1b shows the experimental and numerical AP for the atrium and ventricle.

The bidomain model has been used to model the electric propagation in the heart, whereas the body has been modeled as a volume conductor. The complete set of equations has been solved in the software LS-DYNA (ANSYS, Canonsburg, PA, USA) using a semi-implicit numerical scheme with a fixed time step of 0.02 ms. The model has been stimulated with three beats at a basic cycle length (BCL) of 500ms (heart frequency of 2.0 Hz) close to the spontaneous heart rhythm of the zebrafish [3].

3. Results

The activation times and the activation sequence were in line with experimental data [3]. Namely, the results showed an activation time of 35 ms for the atrium, starting from the SAR region where

the stimulus has been delivered, followed by a delay of 14 ms in the AV band, and an activation time of 59 ms for the ventricle that shows an apex-to-base depolarization pattern (Figure 2a). These values compare well with the values of 35 ms for the atrium [3], the 25 ms delay in the AV band [3], and the 75 ms of total activation for the ventricle [3].

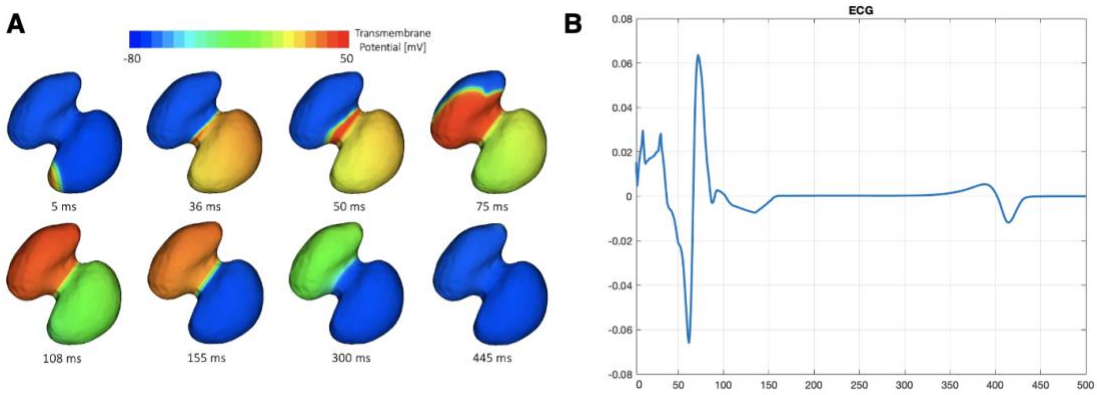

Figure 2. *(A) Transmembrane potential for the main time instants in the activation sequence. (B) Dipolar ECG computed between the two electrodes located at the ventricular base and apex.*

The main characteristics of the AP morphology (i.e., APD_{90}, AP amplitude, and maximum and minimum AP derivative) have been evaluated and compared with values reported in literature [5]. The AP duration has been calculated as the time interval between the peak and the time at 90% of repolarization. APD_{90} for the atrium was found to be 122.48 ms, whereas APD_{90} for the ventricle was 348.40 ms. The AP amplitude was 107.759 mV and 118.361 mV for the atrium and the ventricle, respectively. Maximum and minimum AP derivatives for the atrium were 58.468 and -3.758 mV/ms, while in the ventricle they were 59.801 and -2.149 mV/ms. These values were found to be in good agreement with those reported in literature, as shown in Table 2, except for the upstroke that is found to be 7 times larger.

Table 2. *Comparison of AP characteristics between model and experiments.*

Region	AP marker	Model	Experiment
Atrium	APD_{90} (ms)	122.48	-
	AP amplitude (mV)	107.759	80.10 [2]
	Max. Derivative (V/s)	58.468	8.38 [2]
	Min. Derivative (V/s)	-3.758	-3.99 [2]
Ventricle	APD_{90} (ms)	348.40	235.00 ± 29.00 base, 263.00 ± 23.00 apex [5]
	AP amplitude (mV)	118.361	117.60 [2]
	Max. Derivative (V/s)	59.801	7.15 [2]
	Min. Derivative (V/s)	-2.149	-1.69 [2]

Furthermore, a dipolar ECG was computed between two electrodes (see Figure 1a for the location of the electrodes) and shown in Figure 2b. The shape of the ECG is found to be in good agreement with *in vivo* recordings reported in literature [5].

4. Discussion

In this work, a full electrophysiological model of a zebrafish heart + body has been developed. This model allowed the evaluation of the main electrophysiological parameters such as the activation sequence, activation times, and the main characteristics of AP morphology (i.e., APD_{90}, AP amplitude, maximum and minimum AP derivative). All the results have been found to be in good agreement with experimental data found in literature ([2], [3], [5]). The significant differences in the upstroke velocity are possibly related to the calibration process of the AP model. Future efforts will perform the calibration using a 1D-tissue model in order to minimize the boundary effects.

Even though preliminary, the results are quite encouraging. The obtained in-silico ECG reflects the main characteristics of the zebrafish ECG, a P-wave with a duration of approximately the total atrial activation, followed by a QRS complex of approximately 64 ms corresponding to ventricle activation followed by a small depression of 52 ms corresponding to the total atrial repolarization. The biphasic T-wave is also consistent with the depolarization-repolarization sequence present in the 3 dpf zebrafish heart. The relatively high amplitude of the P-wave is associated with the similar size between the atrium and ventricle, a characteristic of the 3 dpf zebrafish.

Further developments will consider incorporating the APD restitution data to the AP model in order to simulate responses to changes in heart rhythm, as well as to develop the model for zebrafish at a further stage of development, i.e., 4 dpf and 5 dpf, for which the heart rhythm is more stable, and the size of atrium and ventricle are closer to those of the adult fish.

References

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