An Electrophysiologic Computational Model of the Zebrafish Heart

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Abstract

In recent years there has been a growing interest in the zebrafish thanks to its physiological characteristics similar to humans'. The following work aims to create a full electrophysiological computational model of the zebrafish heart with the ultimate purpose of assessing the influence of pathologies and drug administration. The model considers a full body and the two-chambers of a 3 days post fertilization zebrafish. A four-variable phenomenological Action Potential model is used to describe the action potential of different regions of the heart. Tissue conductivity has been calibrated in order to reproduce the activation sequence described in literature. This model allows the evaluation of the main electrophysiological parameters in terms of activation sequence and timing, AP morphology (i.e., APD_{90}, AP amplitude, maximum and minimum AP derivatives), and ECG morphology (i.e., P-wave, T-wave, and QRS-complex amplitudes and durations).

1. Introduction

Recent studies suggest that the zebrafish's heart physiology resembles that of humans in several aspects. In particular, the heart of the zebrafish shows similar spontaneous heart rates, the QT-interval is heart rate dependent [1], it has comparable action potential (AP) shape and duration, and it also shows the presence of orthologues of human ion channels. For all these reasons, the zebrafish has been proposed as a potential model for genetic and pharmacological screenings of factors that could affect heart functions.

Though the rising interest in the zebrafish in the last years, very few studies concern the development of a computational model of the zebrafish heart [2].

Hence, this work aims to create a consistent computational model of the zebrafish heart, with the final purpose of assessing the main electrophysiological parameters and their correlation with pathologies and drug administration.

2. Methods

A full electrophysiological model of a 3 days post fertilization (dpf) zebrafish heart and body has been modeled in this work.

The complete set of equations has been solved using a semi-implicit numerical scheme with a fixed time step of 0.02 ms in the multiphysics simulation software LS-DYNA (ANSYS, Canonsburg, PA, USA). The electric propagation in the heart was modeled using a bidomain model, while the heart has been considered as a passive volume conductor. The model has been stimulated with three beats at a basic cycle length (BCL) of 500 ms corresponding to a heart frequency of 2 Hz, close to the spontaneous heart rhythm of the zebrafish [3].

2.1. Model geometry

The model (Figure 1.) is based on the geometry reported in the work of *Crowcombe et al.* [2] and includes 550974 elements and 97307 nodes.

It comprises three main parts: the body, the heart chambers, and the heart myocardium. The latter is in turn divided into four other regions: the sinoatrial region (SAR), which is the area where the stimulus is delivered, the atrial wall, the atrio-ventricular band (AV band), and the ventricular wall.
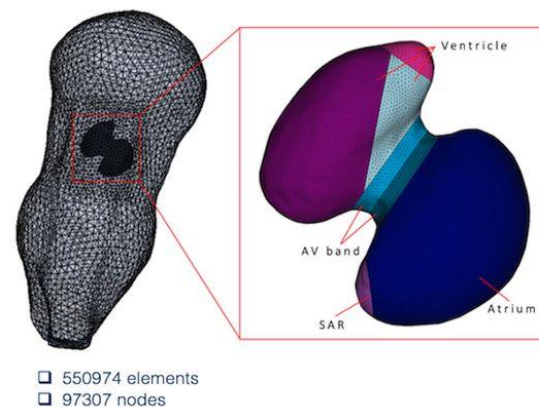

□ 550974 elements
□ 97307 nodes

Figure 1. Ventral view of the complete geometry of the zebrafish model (on the right) and in detail the heart and its different parts (on the left).

Further, the AV band and ventricular wall were split into sub-parts to account for the heterogeneities in the electric propagation [3].

The AV band is composed of two rings (Figure 2.), one on the atrium side and one on the ventricle side, named AVband1 and AVband2, respectively. To these two parts, different action potential models have been assigned. Namely, to AVband1 has been assigned the action potential model of the atrium, and to AVband2 the action potential of the ventricle. Instead, the ventricular wall has been divided into three regions (Figure 2.) named Ventricle1, Ventricle2, and Ventricle3 following the activation sequence and according to *Panáková et al.* [3].
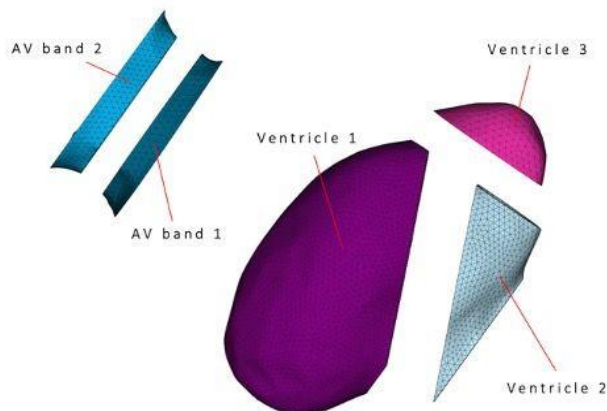

Figure 2. Sub-parts of the model used to recreate the correct activation sequence and times.

2.2. Conductance values

Different conductances have been assigned to each part of the model in order to reproduce the activation pattern reported in literature [3].

The heart tissue was considered as isotropic with conductance values shown in Table 1. According to the experimental data [3], these values were fitted to reproduce the activation sequence of the model and the ECG amplitude.

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

2.3. Action potential model

The Bueno-Orovio four-variables minimal model (BV4) proposed by *Bueno-Orovio et al.* [4] has been used to simulate the action potential of the different parts of the model. The BV4 is a phenomenological model that allows to reproduce a large variety of AP shapes while accurately reproducing the AP duration (APD) and conduction velocity (CV) restitution curves by using just four state variables. The parameters of the BV4 model were obtained by fitting the numerical AP model to experimental recording of the zebrafish action potential in different regions of the heart [2].

Figure 3. shows the experimental and numerical APs for the atrium and ventricle obtained by adjusting the BV4 in order to fit experimentally reported action potentials of the zebrafish to reproduce a correct heart rhythm dependence of the QT [5].
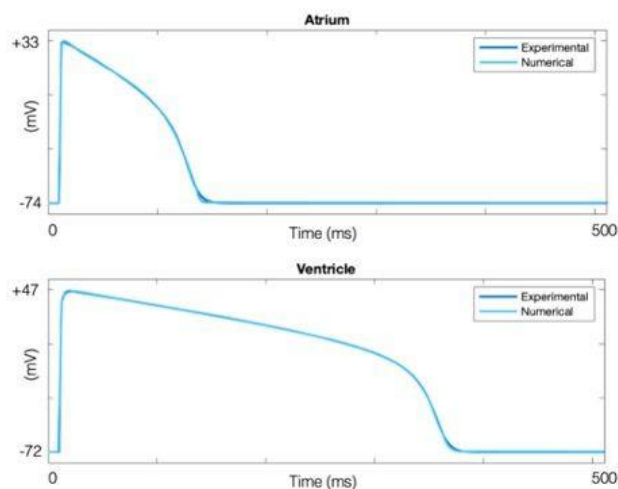

Figure 3. Experimental and numerical action potential for atrium and ventricle.

3. Results

The analyses of the results focus on the main electrophysiological parameters such as the activation sequence, activation times, and the main characteristics of the action potential morphology. Additionally, an in-silico bipolar ECG was computed between two electrodes.

3.1. Activation times and sequence

Analyzing the activation sequence and times, the activation of the atrium occurred in 36 ms, starting from the SAR region where the stimulus is applied. A 14 ms delay in the AVband followed this activation, and finally, the activation of the ventricle occurred in 59 ms with an apex-to-base activation pattern (Figure 4.).
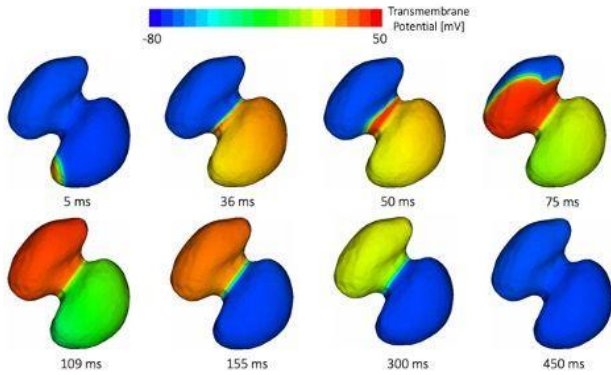
Figure 4. Activation sequence of the 3 dpf zebrafish heart.

These results compare well with the experimental data reported in [3] for which the atrium depolarizes in 35 ms, with a delay of the order of 25 ms in the AVband, and 75 ms for the depolarization of the ventricle.

3.2. Action potential

The main characteristics of the action potential morphology (i.e., APD_{90}, AP amplitude, maximum and minimum AP derivatives) have been evaluated and compared with experimental values reported in literature.

The AP duration, calculated as the time interval between the peak and the time at 90% of repolarization, was found to be 122.48 and 348.40 ms for the atrium and the ventricle, respectively. The AP amplitude was 107.759 mV for the atrium and 118.361 mV for the ventricle. 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.

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

Region	AP marker	Model	Experiment
Atrium	APD_{90} (ms)	122.48	[2,5]
	AP amplitude (mV)	107.759	[2,5,6]
	Max der. (V/s)	58.468	[2,5]
	Min der. (V/s)	-3.758	[2]
Ventricle	APD_{90} (ms)	348.40	[2,5,7,8,9]
	AP amplitude (mV)	118.361	[2,5,6]
	Max der. (V/s)	59.801	[2,5]
	Min der. (V/s)	-2.149	[2]

The significant differences in the upstroke velocity could be related to the calibration process of the AP model, but overall, these values were found to be in line with experimental data reported in literature [2,5,6,7,8,9].

3.3. ECG

In this work, a bipolar ECG was computed between two electrodes (Figure 5.) that have been positioned on the body in correspondence of the ventricular base (electrode +) and ventricular apex (electrode -).
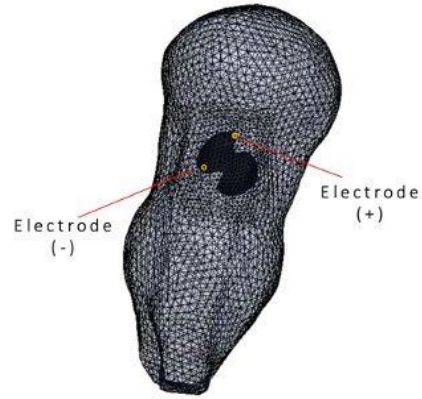

Figure 5. Location of the electrodes for the bipolar ECG.

The in-silico ECG (Figure 6.) has been found to reflect the main characteristics of the recorded zebrafish's ECG. Namely, the P wave showed a duration in line with the total atrial activation (~37 ms) and an amplitude of about 29.6 µV. The relatively high amplitude of the P wave is related to the atrium size that, at 3 dpf, is comparable to the size of the ventricle.

The P wave is followed by the QRS complex that shows a duration of approximately 64 ms, comparable with the ventricular activation, and an amplitude of 129.584 µV, in line with the value of 104 ± 60 [8].

The QRS complex is followed by a slight depression of 52 ms duration corresponding to the total atrial repolarization. Also in this case, the presence of the atrial repolarization in the ECG signal is related to the comparable size between the atrium and the ventricle. The biphasic T wave is consistent with the depolarization-repolarization pattern of a 3 dpf zebrafish.
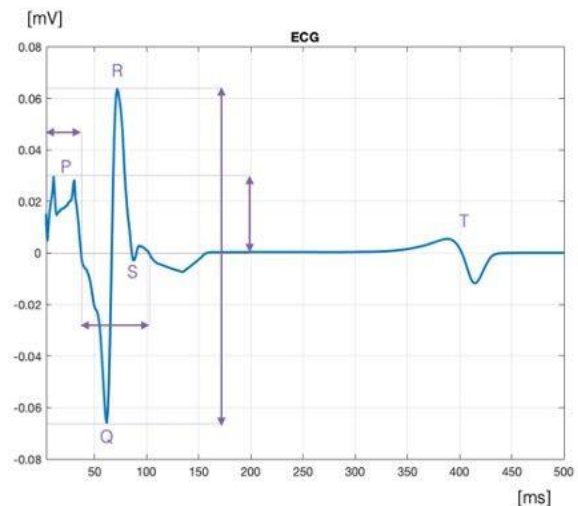

Figure 6. Dipolar ECG computed between two electrodes located at the ventricular base and apex.

4. Discussion

In this work, a full electrophysiological computational model of the zebrafish heart and body was developed.

This model allows the evaluation of the main electrophysiological parameters in terms of activation sequence and timing, AP morphology (i.e., APD_{90}, AP amplitude, maximum and minimum AP derivatives), and ECG morphology (i.e., P-wave, T-wave, and QRS-complex amplitudes and durations).

The model assumes the tissue as isotropic, in part because there is no evidence of tissue anisotropy for the zebrafish cardiac tissue. However, our numerical results indicate that considering conductance heterogeneity in the ventricular tissue as indicated by from *Panáková et al.* [3] may suffice to describe the correct activation of the zebrafish heart and gives a bipolar ECG in good agreement with experimental measurements from literature.

This model comprises a significant improvement with respect to the previous model developed in [2] not only in terms of the activation sequence, but also in terms of the resulting ECG. In general, comparison with the experimental data [2,3,5,6,7,8,9], we can consider the results as promising.

5. Future developments

Future developments will consider incorporating APD restitution data in the fitting process of the parameters of the BV4 model in order to be able to simulate responses to changes in heart rhythm. In addition, geometries of the zebrafish full body and heart at further stages of development (i.e., 4 and 5 dpf) for which the heart rhythm is more stable will be done. Moreover, at these advance stages of development, the size of atrium is significantly lower than that of the ventricle, being close to those of the adult fish. This leads to a more realistic in-silico ECG signals.

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