A Novel Model of Electrical Action Potentials of Teleost Fish Ventricular Myocytes

Hamsa Naser[1], Dominic G. Whittaker[2], Holly A. Shiels[1], Mark R. Boyett[1], Henggui Zhang[1]

[1]The University of Manchester, Manchester, UK
[2]The University of Leeds, Leeds, UK

Abstract

Mathematical modelling, combined with experimental approaches, has become a powerful method for investigating the heart functions. So far, different models of cardiac electrical activities of variant species have been developed. However, models of fish cardiomycytes are less developed. Given the prominent problem of global warming, sea temperature changes will have a significant impact on the development of cardiac arrhythmias in the fish heart, leading to their sudden death, which may impose a heavy burden to the economy of the society.

This study aimed to develop a biophysically detailed computer model for the teleost fish ventricular myocytes in warm acclimation (18°C). A set of Hodgkin-Huxley (HH) formulations have been developed for the major ion currents that were based on experimental data from different teleost species.

With a series of supra-threshold stimuli (amplitude of -41 pA/pF; duration of 10 ms and time interval (between two successive stimuli) of 1000 ms) the teleost fish model generates a successful sequence of action potentials (APs). The characteristics of the (APs) matched quantitatively the available experimental findings. In conclusion, a mathematical model for the electrical action potential of the teleost fish cardiac myocytes has been developed and validated.

1. Introduction

Cardiac modelling provides an alternative method to experimental cardiology for the study of the function of the heart. Since 1950s, a set of mathematical models for simulating cardiac membrane action potentials (APs) have been developed based on detailed experimental data on ion channel properties and kinetics, as well as intracellular ionic homeostasis [1,2]. So far, a large set of cardiac cell models have been developed for variant mammalian species such as rat, mouse, sheep, rabbit and human, whereas mathematical models for fish heart has not been developed yet.

There are distinctive differences between cardiac anatomy and electrophysiology between the heart of mammals and fish. Most teleost fish are ectothermic animals (their hearts are very sensitive to changes in the ambient temperature) while most mammals are euthermic (can keep their body temperature apart from their environment temperature). Fish as ectothermic species live in a thermal variety of aquatic habitats and their thermal tolerances vary from −2.5°C to +44°C [3]. It has been seen that temperature change has vital effects on the molecular interactions of the fish heart, leading to irregularity in the electrical, biochemical and biomechanical activities of the system [4].

Therefore, it is important to understand possible membrane mechanism(s) for the fish heart to respond to changing environment temperature as the fact of climate change makes global warming as a serious problem that affects ectothermic animal life in the near future [3].

The main goal of the present study was to develop a novel computer model for the cardiac action potential (AP) of fish ventricular myocytes that will provide insight into the ionic basis of cardiac electrical activity. The equations in the model were based on experimental data on the properties of some major ionic channels in myocytes isolated from ventricles of the rainbow trout and Bluefin tuna teleost fish. The developed model is validated by its ability to reproduce the AP characteristics that match to experimental data.

2. Methods

2.1. Model development

A schematic illustration for the mathematical model of cardiac cell of the ventricular teleost fish heart is shown in Figure 1. The model consists of a family of mathematical equations for membrane ion channel currents responsible for generating the electrical APs of teleost fish ventricular myocytes. These membrane ion channel current models are in the Hodgkin-Huxley formulations inherited from existing mathematical models of mammal hearts. All of the ion channel current models

were validated by comparing voltage clamp simulation data to experimental recordings.

To obtain parameters of the model equations for each of the ion channels (such as steady-state activation, inactivation and time constant), the Nelder-Mead simplex algorithm [5] was used to optimally fit the model equations to experimental data (not shown in this paper), which were taken from different fish species: rainbow trout and bluefin tuna.

Simulated current–voltage (I-V) relationships of the main ionic currents including (I_{Na}, I_{CaL}, I_{Kr}, and I_{K1}) with the respective experimental findings are shown in (Figure 2). The model also included formulations for the other currents including; I_{Nab} sodium background current, I_{Cab}, calcium background current, I_{pCa}, calcium pump, I_{Kp}, potassium pump and $I_{K(ATP)}$, ATP sensitive potassium current, I_{NaCa}, sodium-calcium exchanger current, I_{NaK}, sodium-potassium pump and I_{stim} is the stimulus current. These formulations are similar to those previously developed by Luo and Rudy in 1994 [6], which forms the basal framework of our mathematical model.

The dynamical course of membrane potential (V) over time (t) in the fish model was described by the following differential equation:

$$\frac{dV}{dt} = -\frac{I_{tot}}{C_m} \qquad (1)$$

where (I_{tot}) is the total membrane current and (C_m) is the membrane capacitance; I_{tot} is calculated by summing up the individual ion currents shown in Figure 1.

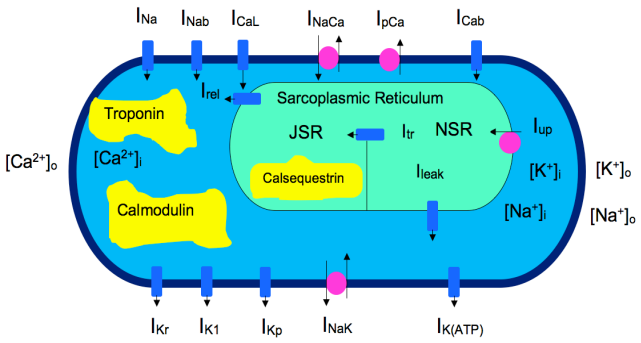

Figure 1. Schematic diagram of the fish model with variant ionic currents and Ca^{2+} fluxes that are responsible for generating APs. The fluxes within the cell are uptake of Ca^{2+} from the cytosol to the network sarcoplasmic reticulum (SR) (I_{up}), Ca^{2+} release from the junctional SR (I_{rel}), Ca^{2+} flux from the network SR (NSR) to junctional SR (JSR) (I_{tr}), Ca^{2+} leak from the SR to the cytosol (I_{leak}).

Figure 2 shows simulated I_{Na}, I_{CaL}, I_{Kr} and I_{K1} currents, which are compared to experimental data from whole-cell voltage clamp recordings of teleost fish ventricular myocytes, performed at 17-19 °C [7-10].

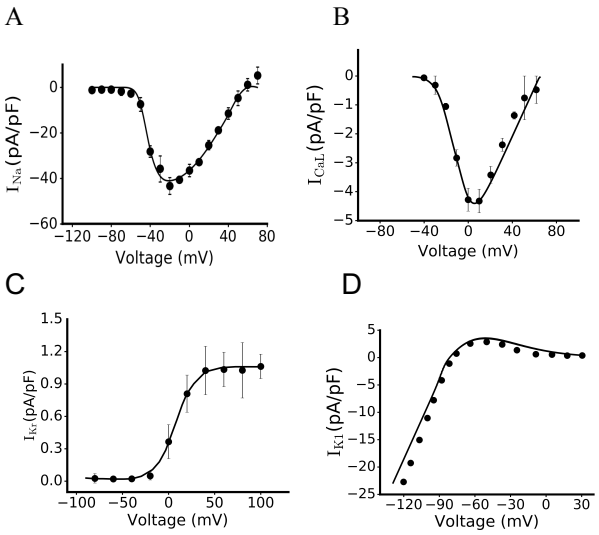

Figure 2. Simulated current – voltage (I-V) relationships with experimental data for teleost ventricular cells. Filled circles represent the experimental data while the lines show results from a simulated voltage clamp using the fish ventricular cell model. A, is the I-V curve for I_{Na} adapted from [11]. B, is the I-V curve for I_{CaL} adapted from [8]. C, is the I-V curve for I_{Kr} adapted from [9]. D, is the I-V curve for I_{K1} adapted from [12]. The I_{Na} and I_{K1} currents were recorded experimentally at 18°C while I_{CaL} current was at 17°C and I_{Kr} at 19°C.

The model at warm acclimation was coded in C programing language using a Rush and Larsen numerical integration method [6] to solve the ordinary differential equations. The time step for the model was 0.01ms, which gives a stable solution of the equations and maintains the accuracy of the computation of membrane potentials.

3. Results

3.1. Fish ventricular action potential

Simulated APs were obtained with a 1-Hz stimulation rate and calculated after at least 200 ms of continuous simulation to ensure that a steady-state solution has been reached. The AP for teleost fish ventricular myocytes at 18°C (warm acclimation) is shown in Figure 3.

Five different phases (0-4) have been observed in the ventricular APs of most vertebrate animals including teleost fish. However, in fish cardiac myocytes phase 1 is absent indicating that the transient outward current (I_{to}) (which is mainly carried by K^+ ions generating the phase 1 repolarization) does not exist in the fish heart [3].

Moreover, the main repolarization currents is the rapid component of the delayed rectifier current (I_{Kr}) while the slow component of the delayed rectifier K^+ current (I_{Ks}) is not found in the teleost heart. However, it might be involved in other type of fish [3].

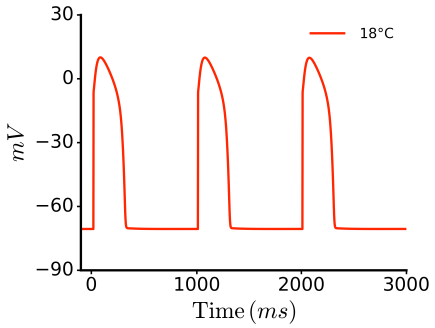

Figure 3. Simulated steady state APs (over a 3000 ms period) of the teleost fish ventricular myocytes at 18°C.

3.2. Model validation

To validate the model, the characteristics of APs were computed and compared to experimental data. Results are shown in Figure 4.

The characteristics include the overshoot (OS) and AP amplitude (APA). In simulations, they were 9.5 and 84 mV respectively, which are in agreement with experimental data [13]. In the model, the computed resting membrane potential (RMP) is -72 mV, which is the same as that of experimental recordings [13].

The simulated APD at 50% of AP repolarisation (APD_{50}) of the ventricular cell is 265 ms and the simulated APD at 90% of AP repolarisation (APD_{90}) is 308.8 ms, all of which match well with experimental findings of different teleost species including (rainbow, perch, pike, burbot, roach, crucian carp) from Haverinen and Vornanen [13]. The maximum upstroke velocity (dV/dt_{max}) is 56 V/s, but no experimental data has been published yet to compare with.

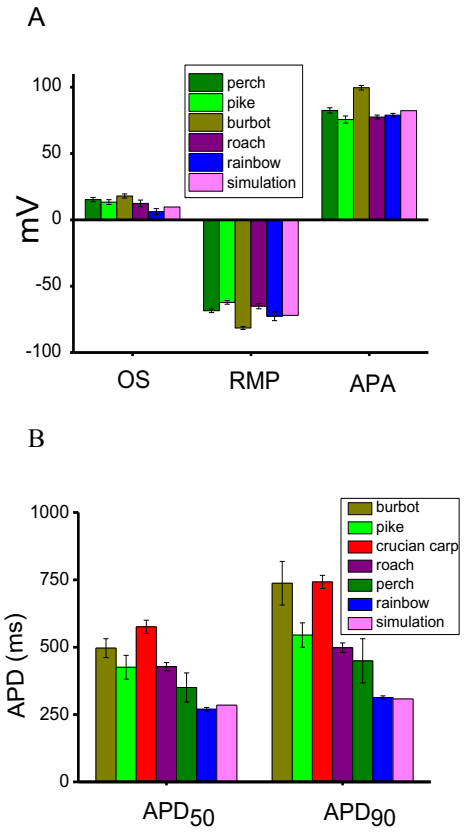

Figure 4. Characteristics of simulated APs compared with available experimental data for teleost fish model. In (A) the overshoot (OS), resting potential (RP) and AP amplitude (APA) are shown for the ventricular cells. APD_{50} and APD_{90} values for ventricular myocytes are shown in (B). The source of the experimental data is from Haverinen and Vornanen [13].

The steady state APD rate-dependence for the APD_{90} of the fish ventricular model is shown in Figure 5. The APD_{90} restitution curve illustrates that at basic cycle lengths (BCLs) below 1000 ms, the model demonstrates a great rate dependency and it becomes more stable at BCLs above 1000 ms.

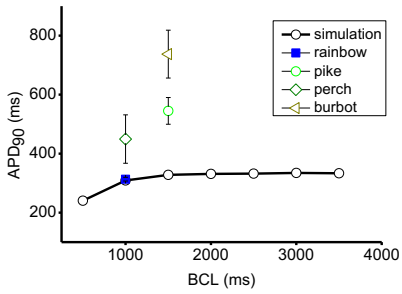

Figure 5. Steady state APD rate dependence of the fish model at 18°C demonstrating the cycle length dependency of the APD_{90} for the fish ventricular model. Experimental data from [13].

4. Discussion and conclusion

A mathematical model for simulating the membrane action potential of the teleost fish ventricular myocytes has been developed. The model was based on, whenever possible, available experimental data of single-cell fish cardiomyocytes. It consists of individual ionic currents that are formulated quantitatively on the basis of experimental data and measured parameter values. The characteristics of simulated action potentials, such as OS, APA, RMP, APD50 and APD90, were in agreement with available experimental data from different teleost species, validating the model development. It is also hoped that the model developed in this study will be used to develop one-, two- or three-dimensional models of the intact ventricular cells, then in the development of a whole heart model for the fish.

Acknowledgment

This project was supported by The Higher Committee for Education Development in Iraq (HCED). H.N. thanks Dr. Matti Vornanen from University of Eastern Finland, Joensuu, Finland, for the useful discussions.

References

[1] Bondarenko VE, Szigeti GP, Bett GCL, et al. Computer model of action potential of mouse ventricular myocytes. *Am J Physiol-Heart Circ Physiol* 2004; 287: H1378–H1403.

[2] Grandi E, Pasqualini FS, Bers DM. A novel computational model of the human ventricular action potential and Ca transient. *J Mol Cell Cardiol* 2010; 48: 112–121.

[3] Vornanen M. The temperature dependence of electrical excitability in fish hearts. *J Exp Biol* 2016; 219: 1941–1952.

[4] Keen AN, Klaiman JM, Shiels HA, et al. Temperature-induced cardiac remodelling in fish. *J Exp Biol* 2017; 220: 147–160.

[5] Russell R. Barton, John S. Ivey, Jr. Nelder-Mead Simplex Modifications for Simulation Optimization. *Manag Sci* 1996; 42: 954–973.

[6] Luo CH, Rudy Y. A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes. *Circ Res* 1994; 74: 1071–1096.

[7] Haverinen J. Significance of Na+ current in the excitability of atrial and ventricular myocardium of the fish heart. *J Exp Biol* 2006; 209: 549–557.

[8] Vornanen M. L-type Ca2+ current in fish cardiac myocytes: Effects of thermal acclimation and β-adrenergic stimulation. *J Exp Biol 201* 1998; 533–547.

[9] Galli GLJ, Lipnick MS, Block BA. Effect of thermal acclimation on action potentials and sarcolemmal K^+ channels from Pacific bluefin tuna cardiomyocytes. *Am J Physiol-Regul Integr Comp Physiol* 2009; 297: R502–R509.

[10] Hassinen M, Paajanen V, Haverinen J, et al. Cloning and expression of cardiac K_{ir} 2.1 and K_{ir} 2.2 channels in thermally acclimated rainbow trout. *Am J Physiol-Regul Integr Comp Physiol* 2007; 292: R2328–R2339.

[11] Haverinen J. Temperature acclimation modifies Na+ current in fish cardiac myocytes. *J Exp Biol* 2004; 207: 2823–2833.

[12] Hassinen M, Paajanen V, Vornanen M. A novel inwardly rectifying K+ channel, Kir2.5, is upregulated under chronic cold stress in fish cardiac myocytes. *J Exp Biol* 2008; 211: 2162–2171.

[13] Haverinen J, Vornanen M. Responses of Action Potential and K^+ Currents to Temperature Acclimation in Fish Hearts: Phylogeny or Thermal Preferences? *Physiol Biochem Zool* 2009; 82: 468–482.

Address for correspondence.
Hamsa Naser
3.06. Schuster Laboratory,
University of Manchester,
Manchester, UK, M13 9PL,
hamsa.naser@postgrad.manchester.ac.uk