A Resonant Model of the Action Potential in Cardiac Cells

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Abstract

Mathematical models of the bioelectric activity in the cardiac conduction system can be used to study the impact of drugs, conduct hypothetical experiments, and for closed-loop validation of cardiac devices. These applications demand real-time performance.

To meet the goal of real-time simulations, we have developed a high-fidelity mathematical model of cardiac cells. These models, called as Resonant Model (RM), are based on truncated Fourier Series and are adaptable for parallel execution. In this paper, the RM is developed for human atrial myocyte, human inferior nodal extension, and human atrioventricular node. The RMs of these cardiac cells are validated with the experimental data and data obtained from detailed electrophysiology cell models.

The RM cells were accurately able to generate the non-linear AP morphologies with Pearson correlation coefficient above 0.99 between generated and simulated AP morphologies of the detailed cardiac cell models.

1. Introduction

Computational models of the electrophysiology of cardiac cells have become an important resource for the investigation of drugs, studying the mechanisms underlying cardiac arrhythmias, and formal verification of implantable cardiac devices [1–3]. As cardiac electrophysiological models have emerged as important investigative tools, models have grown in number, specificity, accuracy and complexity [4]. The models of cardiac cells can be broadly classified as ionic models [5, 6] and simplified models [7–9]. Ionic models integrate descriptions of ion fluxes through various ion channels, transporters and exchangers and can be useful for accurate electrophysiological studies at the cellular level. However, these models contain 7-100 state variables coupled in non-linear differential equations which include computationally expensive functions. These computational constraints seriously limit their use for large scale simulations. On the other hand, simplified models are efficient in tissue simulations for the investigation of multicellular effects, but they lack accuracy with respect to the AP waveshape [7, 8], which may be important for problems like electrocardiography. In addition, the solution of the ordinary differential equations in the cardiac cell models are approximated by numerical procedures and the models may become unstable [10, 11].

To address these, in previous work [12] we developed the general RM framework which does not include ordinary differential equations. It is easily adaptable to different cell types and features with the modification of the underline behavioral equation. The RM is amenable to parallel execution in computer hardware and therefore, is computationally inexpensive. We developed the models of human and rabbit sinoatrial node cells, human ventricular myocyte and squid giant axon to reproduce their non-linear potential morphologies.

To further extend the methodology, here we develop the RM for a human atrial myocyte and autorhythmic cells present in the human atrioventricular conduction axis. We quantify the ability of the model to produce electrical activity of the cardiac cells by correlating to the reference AP waveshapes and experimentally obtained AP features.

2. Methods

The methodology for the development of the RM of biological cells is detailed in [12]. In brief, the RM uses the modified truncated Fourier Series (FS), as described in Equation (1), to reproduce the bioelectric behavior of a variety of cells.

$$V(t,\gamma) = a_0(\gamma) + \sum_{i=1}^{n} c_i(\gamma)\cos(i\omega t - \phi_i(\gamma)) \qquad (1)$$

The Fourier coefficients, a_0, c_i, ϕ_i, are the dynamic parameters of the RM. The model parameters change with the change in the operating condition of a cell (represented as γ), such as current blockage level (modelled in [12]). For the normal operating conditions, the Fourier coefficients were obtained using an iterative Levenberg-Marquardt algorithm by fitting to the reference waveshape generated by the detailed electrophysiology cell models. The initial values of the FS coefficients to be used in the fitting algorithm

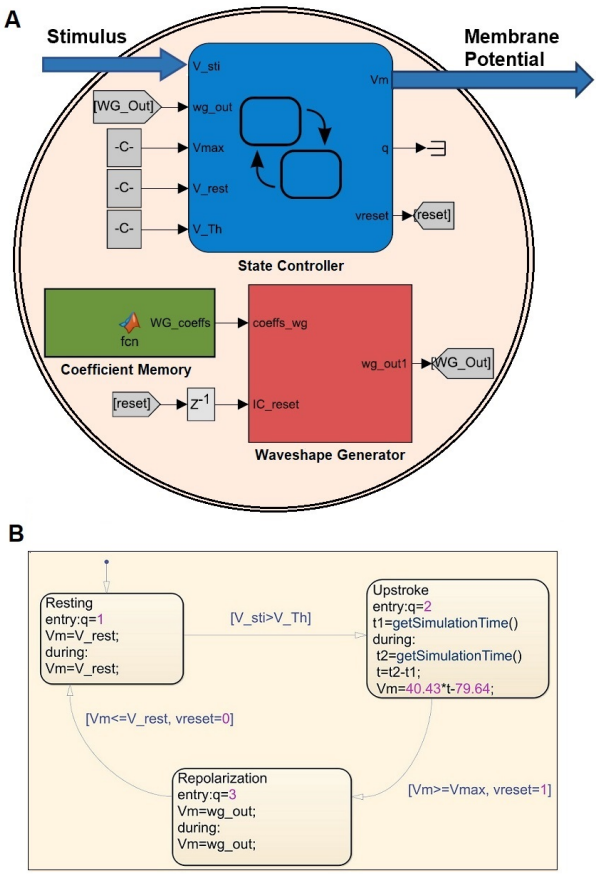

Figure 1. A: Schematic representation of the Resonant model of a cell. B: State controller of a human atrial myocyte implemented in SIMULINK.

were obtained from the frequency spectrum of the reference AP waveshape. This resulted in an increased probability of finding the set of the coefficients within the global minimum region of the root mean squared error. The adjusted R-squared metric was used to determine the number of harmonics in the finite FS. The minimum number of harmonics that resulted in the adjusted R-squared value of 0.99 or higher were included in the RM.

The implementation of the Equation (1) was achieved with the three components of the RM: a waveshape generator (WG), a state controller (SC) and a coefficient memory (CM). Figure 1A shows the diagram of the RM as implemented in SIMULINK. A WG was a set of n sinusoidal oscillators. Each oscillator represents a harmonic in the FS and was constructed using two integrators in series in a closed loop. The WG produced basic AP waveshape of a cell. Coefficients for the WG were stored in the CM.

A SC was designed with the help of a stateflow® to respond to an external stimulus. The SC that implemented the decision and control logic of a human atrial myocyte is shown in Figure 1B. The AP dynamics in the resting, upstroke and repolarization phase was modelled as states q_1, q_2, and q_3, respectively. A piecewise-continuous variable V_m defined the membrane potential. The default transition to q_1 sets the myocyte at its resting potential V_{rest}. The transition from q_1 to q_2 was triggered when the voltage V_{sti} around the myocyte was greater than or equal to the threshold membrane potential (V_{Th}). In this state the myocyte depolarized and the depolarization was modelled with a straight line equation. The myocyte started repolarizing after reaching the maximum potential (V_{max}). The oscillators in the WG were reset to their initial conditions and the non-linear V_m was produced by the WG. After the V_m dropped to V_{rest}, it transitioned back to q_1 where it remained until the arrival of an appropriate stimulus.

3. Results

3.1. Human atrial myocyte

Figure 2 shows the simulated AP morphology generated from the Courtemanche model electrophysiological model of the human atrial myocyte [13] after pacing for 60 s at the basic cycle length of 1000 ms. Also shown in this figure is the RM's equivalent simulation with the WG consisting of 10 oscillators. Comparison of AP features of RM simulations with corresponding experimentally obtained values [14] is shown in Table 1. RM for human atrial myocyte quantitatively reproduced the AP morphology as the RM simulation results lie roughly in the same range of experimental data.

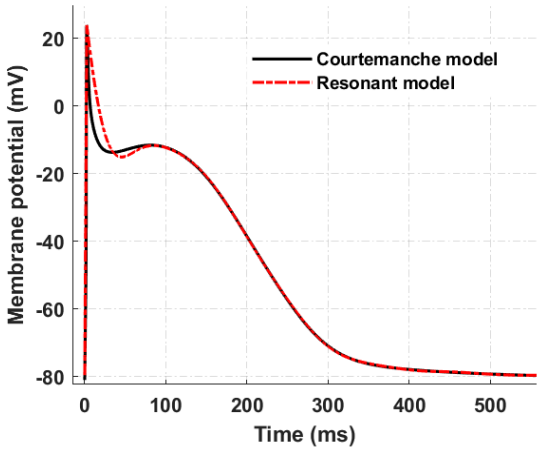

Figure 2. Comparison between the action potential morphologies of human atrial myocyte produced by the Courtemanche model and the Resonant model.

Table 1. Human atrial myocyte action potential features at a basic cycle length of 1000 ms.

AP feature	Unit	Experimental data [14]	Resonant model
APA[1]	mV	98 ± 5	103.5
RMP[2]	mV	-80 ± 3	-79.64
APD_{95}[3]	ms	364 ± 59	341.2
OS[4]	mV	18 ± 4	23.86

[1] action potential amplitude, [2] resting membrane potential, [3] action potential duration at 95% repolarization, [4] Overshoot

3.2. Human atrioventricular conduction axis

Figure 3A and 3B shows the AP morphologies of human AVN and INE, respectively, obtained from the Dobrzynski et al. model [5]. These AP morphologies are compared with the corresponding output of the RM cells. The RM cells generated self-oscillating APs. The RM consisting of 10 oscillators reproduced the AP morphology of the detailed human INE cell model with the Pearson correlation coefficient (PCC) of 0.9874. For the AVN, the PCC was 0.9940 between the Dobrzynski et al. model and the RM cell consisting of 17 oscillators. The PCC values are very close to the ideal value of 1. Also, the AP features of the RM cells are aligned well with the AP features of the detailed electrophysiology model cells are reported in Table 2. These results demonstrate the capability of the developed RM to quantitatively reproduce AP morphologies of the cells present in the human atrioventricular conduction axis.

Table 2. Action potential features of human inferior nodal extension and human atrioventricular node.

AP feature	Inferior nodal extension		Atrioventricular node	
	RM	Detailed Model[5]	RM	Detailed Model[5]
APA[1]	117.26	118.7	107.7	106.8
MDP[2]	-77.1	-78.3	-75.5	-75.6
CL[3]	1039.8	1039.8	853	853
APD_{20}[4]	407.5	399.2	243.4	236.8
APD_{50}[5]	438.2	429.4	268.1	261.5
APD_{90}[6]	487.4	481	301.2	294.5
OS[7]	40.2	40.4	32.2	31.2

[1] action potential amplitude (mV), [2] maximum diastolic potential (mV), [3] cycle length (ms), [4,5,6] action potential duration between 50% depolarization and 20, 50 and 90% repolarization, respectively (ms), [7] Overshoot (mV)

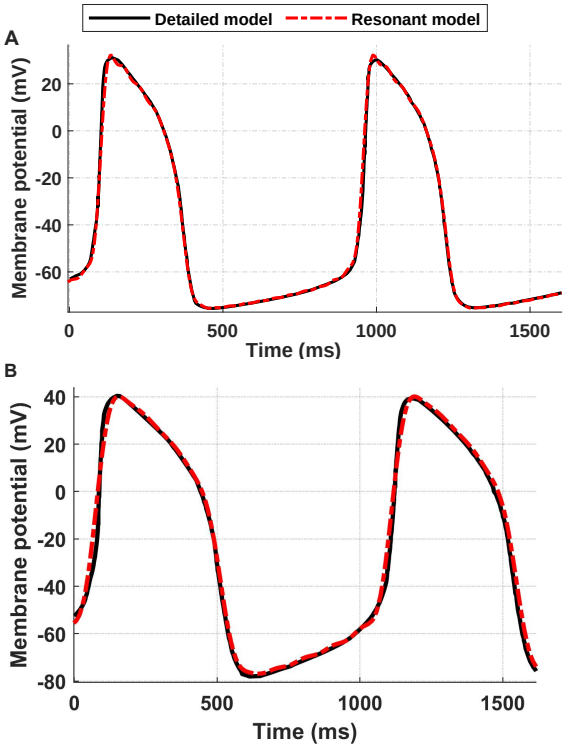

Figure 3. A: Human atrioventricular node and B: inferior nodal extension action potentials produced by the Resonant model and the detailed model (Dobrzynski et al.).

4. Discussion and Conclusions

The RM capture the bioelectric activity of human atrial myocytes and autorhythmic cells present in the human atrioventricular conduction axis with quantitative accuracy. It matches well with the experimental data and the simulated dynamics of the detailed electrophysiology models. The close to ideal values of PCC, suggests that the RM methodology is viable for capturing morphology of a variety of cardiac cells. In particular the model well describes the AP morphology, both during the diastolic depolarization and the upstroke phase. The maximum upstroke velocity of the AP in the INE is 1.82 V/s and in the AVN is 2.31 V/s. These values are known to be this low along the AV conduction axis [5] and are one of the reasons for the slow conduction through the AVN.

In addition to capturing autorhythmic cell's bioelectric behaviour, AP generated by human atrial RM exhibited spike and dome morphology. This morphology was similar to experimentally recorded spike-and-dome APs of cardiac myocytes.

In the future, we hope to improve the RM framework by including dynamic properties possessed by cardiac cells, like action potential duration rate dependence, action potential duration restitution, memory, etc. We will also work

on extending the RM development methodology to other biological periodic or quasi-periodic processes.

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