Web Applications Supporting the Development of Models of Chagas' Disease for Left Ventricular Myocytes of Adult Rats

Caroline Mendonça Costa, Ricardo Silva Campos, Fernando Otaviano Campos,
and Rodrigo Weber dos Santos

FISIOCOMP, the Laboratory of Computational Physiology,
Dept. of Computer Science and Master Program in Computational Modeling
Federal University of Juiz de Fora
Campus Martelos,
Juiz de Fora, MG 36036-330, Brazil
mendonca.carol@yahoo.com.br, ricardosilvacampos@terra.com.br,
fcampos1981@gmail.com, rodrigo.weber@ufjf.edu.br
<http://www.fisiocomp.ufjf.br>

Abstract. Chagas' Disease is an endemic infection in many areas of South and Central America that may cause a fatal type of myocarditis. In the acute phase of the disease, ventricular extrasystoles and tachycardia have been reported. Experiments with cardiac myocytes in the acute stage of Chagas' Disease have suggested a depression of I_{to} , the Ca^{2+} -independent K^+ Transient Outward current. In this work we use computational models of left ventricular myocytes of adult rats to qualify the effects of I_{to} reduction that appear during the acute phase of Chagas' Disease. The simulations are carried out by Web applications based on the CellML language, a recently emerged international standard for the description of biological models. The computational framework supports the development of mathematical models, simulations and visualization of the results. Our preliminary simulation results suggest that the reduction of I_{to} density elicits modifications of electrophysiological mechanisms that are strongly related to the phenomena of arrhythmia.

Keywords: Cardiac Modeling, Web-based Simulations, Problem Solving Environment, Myocarditis, Arrhythmia, Chagas' Disease.

1 Introduction

Chagas' Disease is an endemic infection in many areas of South and Central America causing a distinctive, often fatal myocarditis. Approximately 10 to 20 million individuals are infected, and 50,000 deaths annually are associated with this disease [1].

In the acute period ventricular extrasystoles and tachycardia have been reported in the cases of acute myocarditis [2,3]. Experiments with cardiac myocytes in the acute stage of Chagas' Disease [4] have suggested a depression of I_{to} ,

the Ca^{2+} -independent K^{+} Transient Outward current in canine hearts. Animal models of myocarditis have also reported the depression of I_{to} in rat heart. The availability of many different genetically altered mouse models of known defects in the human cardiovascular system, the recent completion of the rat genome [5] and improvements in methods for genetically modifying rat progeny [6] create a strong demand for a more quantitative understanding of murine cardiovascular physiology.

In this work we use computational models of the left ventricular myocytes of adult rats to qualify the effects of the I_{to} reduction that appear during the acute phase of Chagas' Disease. Due to the multi-scale and multi-physics nature of these biological models, their development becomes particularly challenging, not only from a biological or biophysical viewpoint, but also from a mathematical and computational perspective. A Web-based computational framework that provides support for cardiac electrophysiology modeling is under development [7,8]. Such framework integrates different tools and allows one to bypass many complex steps during the development and use of cardiac models that are based on systems of ordinary differential equations. The implementation of cardiac cell models is supported by a code generator named AGOS [7] that generates C++ code by translating models described in the CellML language [9], a recently emerged international open standard for the description of biological models. The generated code allows one to manipulate and solve the mathematical models numerically. The set up and use of the computational models is supported by a user-friendly graphical interface that offers the tasks of simulation configuration, execution in a computer cluster, storage of results and visualization. All these tools are integrated in a Web portal [10]. The Web portal allows one to develop and simulate cardiac models efficiently via this user-friendly integrated environment. As a result, the complex techniques behind cardiac modeling are taken care of by the Web distributed applications.

A series of in-silico experiments were performed in order to better understand how the depression of I_{to} relates to the reported extrasystoles and tachycardia in the acute phase of the disease. The simulations focused on obtaining insights to better describe three important landmarks of arrhythmia: APD (Action Potential Duration) restitution curves; dispersion of repolarization; and the dynamics of intracellular Ca^{2+} concentration. The APD restitution curve seeks an indication of pro-arrhythmic behavior. During pacing and reentrant cardiac arrhythmias, APD restitution slope has been shown to be an important determinant of wave stability. In addition of promoting APD alternans, a steep (modulus greater than 1) APD restitution slope can promote breakup of electrical waves into a fibrillation-like state [11]. It is well known that amplification of dispersion of repolarization underlies the development of life-threatening ventricular arrhythmias [12]. The dispersion of repolarization is influenced by the dispersion of APDs of the ventricular myocytes and the propagation velocity of the depolarization wave. In this work we have taken the difference between endocardial and epicardial APDs as an indication of transmural APD dispersion. Finally, alterations in intracellular calcium handling play a prominent role in the generation

of arrhythmias in the failing heart. Abnormal intracellular calcium dynamics are usually correlated to the occurrence of Early (EAD) and Delayed (DAD) Afterdepolarization, i.e. the strong candidates for triggers of arrhythmia [13].

In this work, we use a modified version of the Pandit *et al* [14] model to simulate action potentials (APs) in adult rat left ventricular myocytes. The mathematical description of the Pandit model was obtained from the CellML repository [15]. Our Web Portal supported the modification of the model, the simulation of many experiments and the visualization of results. Our simulation results suggest that the reduction of I_{to} density observed during the acute phase of Chagas' Disease elicits the modification of many important electrophysiological mechanisms and features at the cellular level. The reduction of I_{to} was followed by $[Ca^{2+}]_i$ overload and promoted the occurrence of EADs, acting thus in a pro-arrhythmic fashion. However, reduction of I_{to} also decreased the transmural dispersion of APDs, indicating an anti-arrhythmic response. Therefore, the observed modifications do not converge to the same direction in what concerns the prevention or induction of arrhythmia.

2 Methods

We have used a modified version of the Pandit *et al.* [14] model to simulate action potentials (APs) in adult rat left ventricular myocytes. The Pandit model was used to simulate both epicardial and endocardial myocytes as described in [14]. The original model exhibits Early Afterdepolarizations (EAD) at pacing rates greater than 2Hz due to insufficient inactivation and excessive reactivation of the L-type Ca^{2+} current $I_{Ca,L}$ [16]. To solve these limitations the modifications proposed in [16] were implemented to avoid the occurrence of EAD at physiological rates: the time constant of fast inactivation related to the Ca^{2+} -independent K^+ Transient Outward Current I_{to} was reduced by 5%; and the inactivation time constant τ_{11} of $I_{Ca,L}$ was modified according to [16] in order to accelerate its kinetics.

These modifications were performed on the Web via a CellML editor which is one of the applications of a Web-based computational framework that provides support for cardiac electrophysiology modeling [7,8]. In addition, all simulations and the visualization of results were performed on the web with the support of our computational framework. After applying the above modifications to the original CellML model, the AGOS tool [7] translated the new description to an Application Program Interface (API) which is an object oriented C++ code. Functions are created for initialization of parameters like the number of iterations, discretization interval and initial values of variables. There are functions for the numerical solution of the system of ordinary differential equations and for results storage. In addition, the API offers functions which allow the automatic creation of model-specific interfaces. This feature is used by another web application that enables one to set any model initial condition or parameter of the model, displaying their actual names, as documented in the CellML input file, as shown in Figure 1. The Web server is currently connected to a small cluster via the SGE engine [17] which enables the simulations to be executed.

Expand all | Collapse all

Eq. Parameters

Free Variables

environment

membrane

R

8.314500e+03

millijoule_

T

2.950000e+02

kelvin

Q

9.648700e+04

coulomb_J

Cm

1.000000e-04

microF

stim_start

0.000000e+00

s

stim_end

1.000000e+01

se

stim_period

5.000000e-01

stim_duration

5.000000e-03

stim_amplitude

-6.000000e-0

sodium_current

L_type_Ca_channel

g_Ca_L

3.100000e-02

E_Ca_L

6.500000e+01

L_type_Ca_channel_d

L_type_Ca_channel_f

L_type_Ca_channel_f

L_type_Ca_channel_C

Ca_independent_transien

steady_state_outward_K

inward_rectifier

hyperpolarisation_activat

background_currents

sodium_potassium_pump

sarcolemmal_calcium_pu

Na_Ca_ion_exchanger_α

RESULT VISUALIZATION

Number of visualizations:

1

time

☒

V

☒

m

☐

time

☒

V

☒

m

☐

time

☒

V

☒

m

☐

SIMULATION SETUP

Discretization:

dtime

Number of iterations:

Ni

Numerical Method:

☒ Explicit Euler

☐ Backward Differentiation (CVODE)

☐ Adams-Moulton (CVODE)

Implicit Method Tolerance:

Abstol

1.0E-6

Reltol

1.0E-6

Save Configuration as:

☐ Overwrite any existing file with this name.

☒ Plotting time optimization.

☐ Submit to ParaFisio Cluster using Sun Grid Engine*.

*under construction...

Submit

Fig. 1. Web form automatically generated by the AGOS tool for the Pandit model

The in-silico myocyte based on the Pandit model was stimulated by injecting a transmembrane current of 0.6nA during 5 ms. A train of stimuli was simulated in order to reproduce the dynamic restitution protocol described in [18]. Cells were initially paced at a constant BCL (Basic Cycle Length) of 150 ms. After 50 stimuli pacing was stopped and action potential duration (APD90) and the maximal upstroke velocity ($max\ dv/dt$) were measured. APD90, APD at 90% of repolarization, was calculated using the difference between the activation time and repolarization time. Activation times were obtained as the time of maximum rate of rise of the simulated transmembrane potentials. Repolarization times were calculated as the time of crossing a level corresponding to 90% of repolarization to the transmembrane resting potential. Pacing was then restarted at a longer BCL. At every 50 stimuli BCL was increased by 25 ms for the simulation with BCLs ranging from 150 ms to 300 ms; by 50 ms for BCLs ranging from 300 ms to 500 ms; by 250 ms from 500 ms to 1000 ms; and by 500 ms from 1000 ms to 3000 ms.

Fig. 2. Epicardial AP paced at a constant BCL of 250 ms for 50% reduction and control I_{to} densities

Fig. 3. Epicardial APD for different DIs and I_{to} densities

Fig. 4. Difference between endocardial and epicardial APDs for different I_{to} densities

We have also analyzed the dynamics of intracellular Ca^{2+} concentration by using the same steady-state restitution protocol described above. Calcium intracellular concentration was also recorded during 100 pulses at a constant BCL of 750 ms. The density of the I_{to} current was reduced to 50%, 25% and 12.5% in order to investigate the occurrence of EAD and its relation to APD. Transmembrane currents and ion concentrations were computed, stored, visualized and used in subsequent analysis.

3 Results

3.1 Restitution Curves and EADs

Experiments with cardiac myocytes in the acute stage of Chagas' Disease [4] indicate that phase 1 repolarization is attenuated and suggest a depression of I_{to} . In this work we investigated the influence of I_{to} in the APD restitution. For this task we changed the maximum conductance of the I_{to} current varying its density from 12.5% to 100% (control condition).

Figure 2 shows APs using the Modified Pandit Model paced at a BCL of 250 ms for both control (100% of I_{to}) and I_{to} reduced to 50% conditions. At this BCL, Figure 2 shows that a pattern similar to EAD appears after 9 s of simulation when I_{to} is reduced. At BCLs longer than 275 ms we have not observed EADs, i.e. with I_{to} reduced to 50%. However, after further reducing I_{to} density to 25% (12.5%) EAD-like patterns show up again for BCLs shorter than 450 ms

(750 ms). Therefore, these simulations suggest that the reduction of I_{to} density increases the probability of EAD occurrence at physiological rates.

APD restitution curves were calculated and are presented in Figure 3, where APD is plotted versus the diastolic interval (DI). DI was taken as the difference of the BCL and the measured APD90. One may note from Figure 3 that APD decreases for longer BCLs reaching a steady-state condition after 1000 ms. In addition, reducing the maximum conductivity of I_{to} monotonically increases APD. The APD restitution curve may be used as an indication of pro-arrhythmic behavior. During pacing and reentrant cardiac arrhythmias, APD restitution slope has been shown to be an important determinant of wave stability. In addition to promoting APD alternans, a steep (modulus greater than 1) APD restitution slope can promote breakup of electrical waves into a fibrillation-like state [11]. The slopes of the restitution curves presented by Figure 3 were significantly smaller than 1. This agrees with the fact that alternans were not observed in any of the simulation results.

3.2 Dispersion of Repolarization

It is well known that amplification of dispersion of repolarization underlies the development of life-threatening ventricular arrhythmias [12]. The dispersion of repolarization is influenced by the dispersion of APDs of the ventricular myocytes and the propagation velocity of the depolarization wave. In this work we have taken the difference between endocardial and epicardial APDs as an indication of transmural APD dispersion. In addition, since the propagation velocity is proportional to the maximum rise of the action potential, we measured $\max dv/dt$ and considered this as an indication of changes on the propagation velocity.

Figure 4 presents the difference of APDs between simulated endocardial and epicardial cells for different densities of I_{to} with a pacing rate of 1Hz. Note the biphasic behavior. APD dispersion is greatly decreased by reducing I_{to} density (a near 4-fold decrease from control to 12.5% of I_{to} density). However, increasing I_{to} beyond the control level also reduces APD dispersion.

Since $\max dv/dt$ is related with the velocity of the wave propagation in the cardiac tissue, we simulated the influence of the I_{to} in the upstroke of the AP. Figure 5 shows that the longer the cycle length the greater the upstroke. Figure 5 also shows that I_{to} marginally affects $\max dv/dt$. The reduction of I_{to} was followed by a 10% decrease of $\max dv/dt$.

3.3 Changes in the Intracellular Ca^{2+} Concentration

Alterations in intracellular calcium handling play a prominent role in the generation of arrhythmias in the failing heart [13]. Figure 6 presents the $[\text{Ca}^{2+}]_i$ versus time for a BCL of 750 ms. By reducing I_{to} density we observe that $[\text{Ca}^{2+}]_i$ reaches a larger steady-state value. The results thus suggest that reduction of I_{to} density is followed by $[\text{Ca}^{2+}]_i$ overload.

Fig. 5. The upstroke velocity $\text{max } dv/dt$ for different DIs

Fig. 6. $[\text{Ca}^{2+}]_i$ for different densities of I_{to} versus time

4 Discussion

In this work we have used a Web-based cardiac computational framework based on the CellML language to simulate mathematical models of the left ventricular myocytes of adult rats. The simulations seek a better understanding of the effects of I_{to} reduction during the acute phase of Chagas' Disease. APD restitution curves were generated, the transmural dispersion of repolarization was investigated and the dynamics of $[Ca^{2+}]_i$ analyzed. We have not observed the phenomenon of alternans during the steady-state pacing protocol adopted. The APD restitution curves were calculated as presented in Figure 3. It is known that a steep APD restitution slope may suggest the breakup of electrical waves into a fibrillation-like state. The absolute values of the slopes of the restitution curves presented by Figure 3 were significantly smaller than 1. This agrees with the fact that alternans were not observed in any of the simulation results.

However, during fast pacing a pattern similar to Early Afterdepolarization (EAD) was present (see Figure 2). In addition, EADs occurred in considerably slower pacing rates after I_{to} density was reduced in the models. Therefore, the results suggest that the reduction of I_{to} density increases the probability of EAD occurrence at physiological rates. The premature occurrence of EADs seems to be in accordance with the accumulation of $[Ca^{2+}]_i$ as a consequence of reduction of I_{to} density (see Figure 6). Calcium entry into myocytes drives myocyte contraction. To prepare for the next contraction, myocytes must extrude calcium from intracellular space via the Na^+/Ca^{2+} exchanger (NCX1) or sequester it into the sarcoplasmic reticulum. Defective calcium extrusion correlates with increased intracellular calcium levels and may be relevant to heart failure and to the generation of arrhythmias [19]. The results presented in Figure 6 suggest that reduction of I_{to} density may be followed by $[Ca^{2+}]_i$ overload.

We have addressed the effects of I_{to} density reduction on the transmural dispersion of repolarization by calculating the changes on endocardial to epicardial APD difference and on the $max dv/dt$, which is related to the velocity of the wave propagation in the cardiac tissue. In our simulations, $max dv/dt$ was marginally affected (see Figure 4). However, the transmural dispersion of APD, as presented in Figure 5, is decreased after I_{to} is reduced. The results indicate an anti-arrhythmic effect associated to the reduction of I_{to} density.

In summary, the computational framework simplified the required modifications and usage of the mathematical model studied in this work. The combination of the XML-based automatic code generator, the CellML editor and the Web portal provided an user-friendly environment for our simulations. Our results suggest that the reduction of I_{to} density observed during the acute phase of Chagas' Disease elicits the modification of many important electrophysiological mechanisms and features. The reduction of I_{to} was followed by $[Ca^{2+}]_i$ overload and promoted the occurrence of EADs, acting thus in a pro-arrhythmic fashion. However, reduction of I_{to} also decreased the dispersion of APDs, indicating an anti-arrhythmic effect. Therefore, the observed modifications do not converge to the same direction in what concerns the prevention or induction of arrhythmia. Further studies are necessary in order to better characterize and understand the electrophysiological changes that underly the acute phase of Chagas' Disease.

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