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Mathematical Modeling and Computer Simulation of ATP Metabolism in the Excitation-Contraction Coupling Phenomenon in the Rat Ventricular Myocyte

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Mathematical modeling and computer simulation of ATP metabolism in the excitation-contraction coupling phenomenon in the rat ventricular myocyte

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Abstract— **Several mathematical and computational models have already been developed to describe the complex process of cardiac excitation-contraction (EC) coupling. The model of Mullins & Bondarenko (2013) is cited as an example, which describes detailed mechanisms ranging from the function of individual ion channels to other important transporters, and satisfactorily simulates the characteristics of Action Potential (AP) and contraction in the mouse ventricular myocyte. However, the mathematical modeling did not include the equations of energy production and consumption used during the EC process, so it cannot be used to simulate possible problems in the production and consumption of ATP (Adenosine Triphosphate), the main source of energy for cells. In this context, the aim of the present paper is to present the implementation of the model describing ATP metabolism proposed by Cortassa et al. (2006) in the electromechanical model of Mullins & Bondarenko (2013). From this new mathematical model, and using the MATLAB platform, the EnergyECLab tool was developed. As an application of the tool, *"in silico"* experiments were performed to obtain the time course of ATP and phosphocreatine (CrP) concentration and, as well as, the inhibition of Ca^{2+}-ATPase (SERCA) by Adenosine Diphosphate (ADP). The computational tool (EnergyECLab) developed to solve the system of Coupled Differential Equations (CDE's), has a friendly graphic interface and several didactic resources. The first *"in silico"* experiment showed a satisfactory qualitative result of ATP concentration was obtained when compared to the work of Cortassa et al. (2006). As a result of the second *"in silico"* experiment, inhibition of SERCA by the ADP mechanism produced an increase in contraction force (30.7%) when compared to the control.**

Keywords — **mathematical modeling, cardiac electrophysiology, ventricular myocyte, ATP metabolism.**

I. Introduction

According to the World Health Organization (WHO), about 17.5 million people die each year from cardiovascular disease [1]. This is the number one cause of death worldwide. In this context, it is necessary to use mathematical models applied to computational methods for the understanding of the complex phenomenon of excitation-contraction (EC) coupling of the heart cell, which for more than 50 years have been able to identify, on a cellular scale, the causes of cardiac arrhythmias [2].

There are several models divided into electrical [3] and mechanical [4], and also intersection models that are called electromechanical [5]. However, much of it disregards the modeling of Adenosine Triphosphate (ATP) formation and consumption in the cardiac cell, which directly influences the generation of contraction force and cardiac Action Potential (AP) [6].

ATP is produced in the mitochondria by a 3-step process: Glycolysis, Krebs Cycle, and Oxidative Phosphorylation [7] and is used in important cellular structures, such as in the Ca^{2+}-ATPase Sarcoplasmic Reticulum (SR); in the Sodium-Potassium pump located in the sarcolemma; and in the mechanical process of contraction and relaxation of the cardiac cell [8].

Therefore, this paper has the objective of presenting the coupling of the ATP modeling of Cortassa et al. (2006) [8] to the electromechanical model of Mullins & Bondarenko (2013) [9]. For this, a computational tool (EnergyECLab) was developed to solve the CDE's and display the results of the *"in silico"* experiments graphically. As an application of EnergyECLab, the influence of the ATP mechanism on contraction force and cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) was tested.

II. Methods

A. Developing the Mathematical Model

To obtain the electromechanical model that takes into account ATP consumption and production, bidirectional coupling of the energy model of Cortassa et al. (2006) [8] into the electromechanical model of Mullins & Bondarenko (2013) [9] was performed.

In Mullins & Bondarenko (2013) model [9], which describes the electromechanical mathematical modeling for the mouse ventricular myocyte, the AP is given by Equation (1):

$$\frac{dV}{dt} = \frac{-1}{C_m}.\left(I_{CaL} + I_{p(Ca)} + I_{NaCa} + I_{Cab} + I_{Na} + I_{Nab} + I_{NaK} + I_{Kto,f} + I_{Kto,s} + I_{K1} + I_{Ks} + I_{Kur} + I_{Kss} + I_{Kr} + I_{Cl,Ca} - I_{stim}\right) \quad (1)$$

Where C_m is the membrane capacitance in µF/cm^2, I_{CaL}, $I_{p(Ca)}$, I_{NaCa}, I_{Cab}, $I_{Cl,Ca}$, I_{Na}, I_{Nab} and I_{NaK} the currents, respectively of Ca^{2+} L-Type, of sarcolemma Ca^{2+} pump, of the sodium (Na^+)/Ca^{2+} exchanger, Ca^{2+} background, Ca^{2+} activated by chlorine (Cl^-), Na^+ fast, Na^+ background and of Na^+/potassium (K^+) pump in pA/pF. Whereas, $I_{Kto,f}$, $I_{Kto,s}$, I_{K1}, I_{Ks}, I_{Kur}, I_{Kss} and I_{Kr} indicate the main K^+ currents and I_{stim} is the external stimulus in pA/pF.

The calculation of the contraction force is described by Equation (2) based on the model by Rice et al. (1999) [4]:

$$F_{contr} = \alpha.\frac{P1 + N1 + 2.(P2) + 3.(P3)}{P1_{max} + 2.(P2_{max}) + 3.(P3_{max})} \quad (2)$$

The contraction force F_{contr} is equated based on two non-permissive states ($N0$ and $N1$) and four permissive states of Tropomyosin ($P0$, $P1$, $P2$ and $P3$). Already, the constant α is a model fit factor [4].

The model of Cortassa et al. (2006) [8] describes ATP production and consumption during the EC coupling process. Equation (3) provides the ATP concentration during the entire process.

$$\frac{d[ATP]_i}{dt} = V_{ANT}.\frac{V_{mito}}{V_{myo}} - V_{CK}^{mito} - V_{AM} - \frac{1}{2}.J_{up} - \left(I_{p(Ca)} + I_{NaK}\right).\frac{A_{cap}}{V_{myo}.F} \quad (3)$$

Being, V_{ANT} e V_{CK}^{mito} parameters for the cytosolic reaction rate, F the Faraday constant, V_{myo} and V_{mito} are volume constants of the cytosol and mitochondria, A_{cap} capacitive area of the cell surface; $I_{p(Ca)}$ is the sarcolemma Ca^{2+} pump; I_{NaK} the current of Na^+/K^+ pump and J_{up} the Ca^{2+} flux of SERCA from the SR.

B. Development of the Computational Tool

The computational tool developed from the mathematical model, was implemented using the MATLAB platform version R2018a. The method used for solving the system of CDE's was the 4th order Runge-Kutta's with variable integration step contained in the ode15s routine.

C. Simulation protocols

The simulations used the following protocol: stimulation pulse of 20 pA/pF with a width of 1 ms applied at the instant of 1000 ms and with a frequency of 0.25 Hz. The simulation time was 20000 ms, and in each simulation the final steady-state interval is presented. The initial sarcomere and cell lengths are given by 2.1 µm and 100 µm, respectively. Using these protocols the following *"in silico"* experiments were performed:

1. Time course of [ATP] and [CrP] related to the EC process.
2. Influence of SERCA Inhibition by ADP on contraction force and $[Ca^{2+}]_i$, using the parameters described in Table 1.

The following variables were used for analysis: the diastole (Dia), peak (Peak), amplitude (Δ) peak time (t_{peak}) and half time decline ($t_{0.5}$) values of the contraction force and Ca^{2+} transient.

Values of the main parameters used to simulate ATP consumption during the EC process and SERCA inhibition are shown in Table 1.

Table 1 Parameters used in the simulation of SERCA inhibition

Symbol	Control	Test	Unit	Description
$K_{m,up}^{ATP}$	0.01	0.01	mM	ATP Half Saturation Constant
$K_{i,up}$	0.14	0.14	mM	ADP inhibition constant
$K'_{i,up}$	5.1	0.051	mM	ADP inhibition constant

III. Results

A. Mathematical Model

The new mathematical model consists of 51 CDE's that describe ATP production and consumption during the EC process [8].The following describes the main equations that were implemented in the model model Mullins & Bondarenko (2013) [9]:

ATP consumption by the sarcolemma Ca^{2+} pump (Eq. 4).

$$I_{pCa} = I_{pCa_{max}}.\left[\left(1 + \frac{K_{m1_{pCa}}^{ATP}}{[ATP]_i}.\left(1 + \frac{[ADP]_i}{K_{i_{pCa}}^{ADP}}\right)\right)^{-1} + \left(1 + \frac{K_{m2_{pCa}}^{ATP}}{[ATP]_i}\right)^{-1}\right]. \quad (4)$$

Table 2 Parameters used in ATP consumption by the sarcolemma Ca^{2+} pump

Symbol	Value	Unit	Description
$I_{pCa_{max}}$	0.575	μA/μF	Maximum Ca^{2+} pump current
K_m^{pCa}	5x10^{-4}	mM	ATP half saturation constant for Ca^{2+} pump
$K_{m1_{pCa}}^{ATP}$	0.012	mM	First half ATP saturation constant for Ca^{2+} pump
$K_{m2_{pCa}}^{ATP}$	0.23	mM	Second half ATP saturation constant for the Ca^{2+} pump
$K_{i_{pCa}}^{ADP}$	1.0	mM	ADP inhibition constant for Ca^{2+} pump

ATP consumption of Na^+/K^+ pump (Eq.5).

$$f_{NaK}^{ATP} = \left(1 + \frac{K_{NaK}^{1,ATP}}{[ATP]_i}.\left(1 + \frac{[ADP]_i}{K_{NaK}^{i,ADP}}\right)\right)^{-1} \quad (5)$$

Table 3 Parameters used in modeling ATP consumption by Na^+/K^+ pump

Symbol	Value	Unit	Description
I_{NaK}	3.147	μA/μF	Maximum Na^+/K^+ pump current
$K_{m,Nai}$	10	mM	Half saturation of Na^+ for the Na^+/K^+ pump
$K_{m,Ko}$	1.5	mM	Half saturation of K^+ for the Na^+/K^+ pump
$K_{NaK}^{1,ATP}$	8x10^{-3}	mM	ATP half saturation constant for the Na^+/K^+ pump
$K_{NaK}^{i,ADP}$	0.1	mM	ADP inhibition constant for the Na^+/K^+ pump

ATP consumption in the generation of contraction force (Eq. 6)

$$V_{AM} = V_{AM}^{max} \cdot \left(\frac{f_{01}.[P_0] + f_{12}.[P_1] + f_{23}.[P_2]}{f_{01} + f_{12} + f_{23}}\right). \left(1 + \frac{K_{M,AM}^{ATP}}{[ATP]_i}.\left[1 + \frac{[ADP]_i}{K_{i,AM}}\right]\right) \quad (6)$$

Table 4 Parameters used in modeling ATP consumption for contraction force generation

Symbol	Value	Unit	Description
V_{AM}^{max}	7.2x10^{-3}	mM/ms	Maximum rate of ATP hydrolysis by myofibrils (AM ATPase)
$K_{M,AM}^{ATP}$	0.03	mM	AM ATPase half-saturation constant
$K_{i,AM}$	0.26	mM	ADP inhibition constant for AM ATPase

B. EnergyECLab Tool

The EnergyECLab tool was developed so as to present a friendly and intuitive graphical interface. EnergyECLab is structured in a main panel (Fig. 1) with a top menu containing the options START, CONTROL vs TEST, VIEW GRAPH, RESOURCE, RETURN and EXIT (Fig. 2). By clicking on the START tab, the user has the option to change parameters related to ATP consumption. Then the simulation protocols such as pulse width, stimulation frequency, cell length, sarcomere length, stimulus current, and plotting interval are entered. The results of each simulation can be viewed via graphs (VIEW GRAPH) that indicate ATP, ADP, CrP and Ca^{2+} concentrations as well as the time course of the contraction force. In CONTROL VS TEST, you have the option to select two simulations for comparison. In RESOURCE you have access to educational content such as videos on the functioning of important cellular structures. Finally, the last tabs RETURN and EXIT allow you to return to the main tab or quit the tool, respectively.

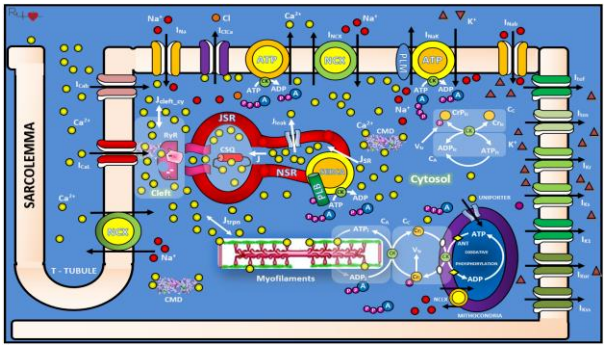

Fig. 1 EnergyECLab simulator main interface

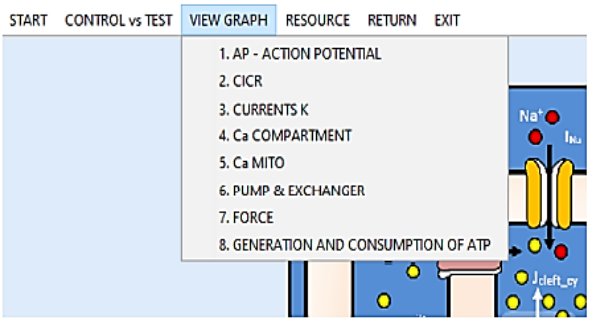

Fig. 2 EnergyECLab simulator options menu

C. In silico experiments

As an application of the tool the following simulations were performed:

"In silico" experiment 1 – The results of the simulations provide us as main output data: the time courses of ATP and CrP (Fig. 3).

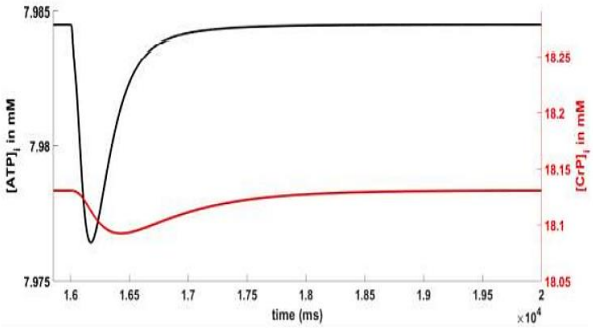

Fig. 3 Time course of ATP and CrP concentrations related to the EC process

"In silico" experiment 2 – Simulations whose output data are the graphs of the rate of Ca^{2+} uptake by the SR pump (Fig. 4) and the Ca^{2+} transient ($[Ca^{2+}]_i$) (Fig. 5) and contraction force (Fig. 6). Quantitative data regarding $[Ca^{2+}]_i$ and contraction force are shown in Tables 5 and 6, respectively.

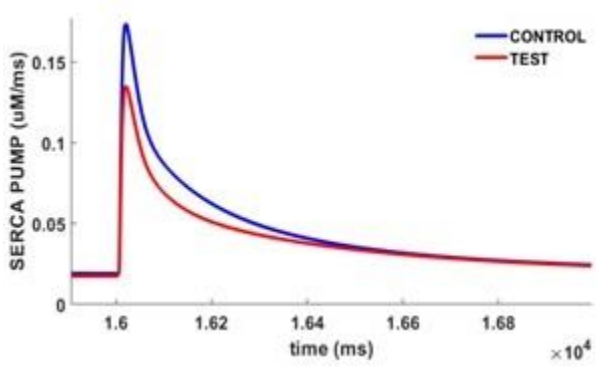

Fig. 4 Speed of Ca^{2+} uptake by SERCA: Control vs Test

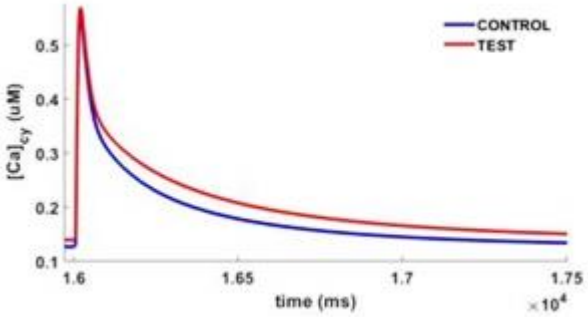

Fig. 5 Ca^{2+} transient: Control vs Test

Table 5 Ca^{2+} transient. In this table the values of diastole (Dia), peak (Peak), amplitude (Δ), peak time (t_{peak}) and half time of decline ($t_{0.5}$) are shown.

Variables	Control	Test
Dia (μM)	0.13	0.14
Peak (μM)	0.56	0.57
Δ (μM)	0.43	0.43
t_{peak} (ms)	20	20
$t_{0.5}$ (ms)	120	180

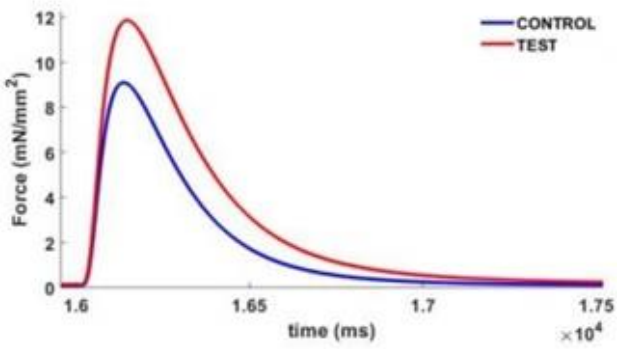

Fig. 6 Contraction force: Control vs Test

Table 6 Contraction force. In this table the values of diastole (Dia), peak (Peak), amplitude (Δ), peak time (t_{peak}) and half time of decline ($t_{0.5}$) are shown.

Variables	Control	Test
Dia (mN/mm^2)	0.13	0.13
Peak (mN/mm^2)	9.1	11.86
Δ (mN/mm^2)	8.97	11.73
t_{peak} (ms)	130	130
$t_{0.5}$ (ms)	180	220

IV. Discussion

The EnergyECLab computational tool has shown to be effective in performing simulations involving the production and consumption of ATP during the complex process of EC coupling, and due to its didactic resources, as well as other computational tools already available: MioLab [10] which describes the contraction force as a function of calcium dynamics, MarkoLab [11] which shows the stochastic process of ion channels and ForceLAB [12] which is used to compare contraction models, EnergyECLab can also be used to complement the teaching of the entire metabolic process that occurs in the cardiac cell.

From the experiment *"in sílico"* 1 it can be seen that the graph of ATP concentration showed a satisfactory qualitative result compared to the graph presented in the work of Cortassa et al. (2006) [8].

In the *"in silico"* experiment 2, according to studies by Sakamoto and Tonomura (1980) [13], ADP can inhibit the SR Ca^{2+} pump (SERCA) either by competitive mechanisms or not. As can be seen in Fig. 4, a reduction in the rate of Ca^{2+} uptake by SERCA did indeed occur (0.1738 μM/ms vs 0.1351 μM/ms).This reduction, as expected directly impacted the Ca^{2+} transient and contraction force presenting in the latter case a 30.7% increase in force compared to the control (Tables 5 and 6).

V. Conclusions

The computational tool was able to satisfactorily reproduce the temporal evolution of ATP concentrations, $[Ca^{2+}]_i$ and contraction force, proving to be capable of enriching the investigation of the EC coupling phenomenon.

Other parameter adjustments will still be necessary to allow simulations to be carried out involving the inhibition of the Na^+/K^+ pump and its influence on the Ca^{2+} transient and contraction force time. The EnergyECLab computational tool is available for download at the link: https://forms.gle/9ejMQ7w5hgrGPqde6

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