

Simplified Models for Electromechanics of Cardiac Myocyte

João Gabriel Rocha Silva[1,3(✉)], Ricardo Silva Campos[1(✉)], Carolina Ribeiro Xavier[2(✉)], and Rodrigo Weber dos Santos[1(✉)]

[1] Postgraduate Program in Computational Modeling, Federal University of Juiz de Fora, Juiz de Fora, Brazil
joaogabriel.comp@gmail.com, rodrico.weber@ufjj.edu.br
[2] Postgraduate Program in Computer Science, Federal University of São João del Rei, São João del-Rei, Brazil
carolinaxavier@ufsj.edu.br
[3] Federal Institute of Education, Science and Technology of Mato Grosso, Pontes e Lacerda, Brazil
joao.silva@plc.ifmt.edu.br

Abstract. The study of the electromechanical activity of the heart through computational models is important for the interpretation of several cardiac phenomena. However, computational models for this purpose can be computationally expensive. In this work, we present the simplified models at the cellular level which were able to qualitatively reproduce the cardiac electromechanical activity based on the contraction of myocytes. To create these models a parameter adjustment was performed via genetic algorithms. The proposed models with adjusted parameters presented satisfactory results for the reproduction of the active force of the heart with the advantage of being based on only two ordinary differential equations.

Keywords: Simplified models · Electromechanical · Genetic algorithms

1 Introduction

The heart is a vital organ. It is responsible for pumping oxygenated blood throughout the body. Its division is defined by four chambers: two ventricles and two atria. These chambers aid in the procedure of receiving and pumping blood through the organ. The study of the behavior and development of treatments, diagnoses and drugs related to the heart are of high importance by their clinical interest [13].

In Brazil, 20% of all deaths in the adult population over 30 years are caused by cardiovascular diseases [6]. In a global sphere, it is estimated that one-third of all causes of death in the world are from cardiovascular diseases [3]. In addition, in 2010, it was estimated that around U$ 315 billions were applied in research

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and development of cardiovascular diseases cases [3]. In this way, debates and studies on this subject are increasingly recurrent in the scientific community.

The treatment, diagnosis and interpretation of these diseases are of fundamental importance contributing to the study, for example, of the electrical and mechanical properties of the heart.

In this aspect, mathematical modeling has become a widely used tool in the study of different phenomena, among them, models that describe the behavior of the heart stand out. They can be used for the development and testing of new drugs [2] and for the identification of diseases [8].

The earliest models of electrophysiology were simplified as: [5] with only four differential equations and [10]. Over time the models have become more complex, and to introduce, for example, the mechanical part [9] and [12] have 11 differential equations and 45 algebraic equations, due to the high complexity of these representations the models have become larger, which requires a longer computational time for the simulation.

For larger simulations, less computational expensive models are needed. In this sense [7] and [4] presented simplified models for the connection between the electrical and mechanical part of the heart.

In this work, we evaluated the ability of simple models to reproduce more realistic electromechanical simulations, coming from more complex models. In addition, we propose modifications that significantly improve the results of the models and further reduce it's computational.

2 Cardiac Electromechanics

The cardiac electromechanical activity can be defined, in a simplified way, as: given an electrical stimulus (action potential) the increase of calcium concentration in the cell's intracellular medium begins, this causes the actin filaments to bind to myosin. After this connection, the size of the sarcomere is reduced due to the sliding of these filaments. This slip generates a force, this force results in the process of contraction.

2.1 The Electrical System

The Action Potential (AP) can be defined as a variation in the electrical potential of the cell membrane. This variation is due to the differences in concentrations between the ions that surround the intra and extracellular medium. In the heart, AP has the function of synchronizing the rhythm of contraction and relaxation of the heart. The AP is generated in a region called the sinoatrial node also known as the heart's natural pacemaker.

The AP cycle can be described by the following stages: the initial stage is associated with rest, and consists of the state of equilibrium between the potentials of the intra- and extracellular medium, which guarantees an integrity of the cellular structure. When the cell is stimulated, a sodium influx (Na^+) leads to

the accentuated growth of action potential, leaving the inside of the cell less negative, causing depolarization. Quickly the sodium channels close and a potassium efflux (K^+) starts and the potential initiates a repolarization process. Then, a phase called a plateau is initiated, and is characterized by a depolarizing current of calcium, in which the calcium influx equilibrates with the potassium efflux, maintaining for a period the almost constant potential value. It is during this period that the contraction of the cardiomyocyte occurs due to the fact that calcium entry stimulates the release of calcium into the sarcoplasmic reticulum. Over time the calcium channels close and the output of potassium to the extracellular medium intensifies, characterizing the repolarization. In this stage the potential tends to its initial equilibrium (rest).

2.2 Cellular Contraction

The increase of the concentration of an ion in the intracellular medium is allowed during the period of activation of the AP, due to ion channel openings that allow ion exchange between the intra and extracellular media. The contraction is basically due to the increase in internal calcium concentration during an electrical stimulus (AP).

The increase in internal calcium concentration alone is not able to promote the onset of sarcomere contraction. However, this step serves as a flag for the sarcoplasmic reticulum, due to calcium ion channels on the cell membrane. Thus, the sarcoplasmic reticulum (SR), the calcium reservoir of the cell, causes an efflux of the calcium that added to the calcium coming from the extracellular environment characterizes the process of release of calcium induced by calcium. In this way, the contraction process begins. Relaxation is related to the reuptake of calcium into the reticulum. Thus, the concentration of calcium within the cell decreases, characterizing the diastole process.

Cardiac myocytes are composed of structures called myofibrils. In the composition of these structures are contractile substances, the sarcomeres. These are responsible for myocyte contraction and relaxation. Sarcomers are composed of filaments called actin and myosin.

These filaments overlap in stretches of their length. The excess of calcium in the intracellular medium causes the sliding of the myosin filaments to that of actin to generate a reduction in the size of the sarcomere, producing a tension (force), characterizing the process of contraction.

3 Computational Models for Cardiac Physiology

Cellular models for physiology are basically divided into two groups according to their characteristics: simplified models and detailed biophysical models. The simplified models are characterized by the use of few equations to describe a physiological phenomenon based on a phenomenological approach. The detailed biophysical models use numerous considerations on biological factors that influence the activity to be reproduced, such as ion channels, ion exchangers, among

others. Thus, these models can count on many equations and consequently have a high computational cost for simulation.

3.1 Cellular Model of TenTuscher (2004)

A detailed biophysical mathematical model for reproduction of human action potential is presented in [14]. For this simulation the model is supported by 19 differential equations.

In [14], the behavior of the cell membrane is associated with the behavior of a capacitor in parallel with variable non linear resistors. The ionic currents that surround the membrane and ion exchange pumps are modeled as non linear resistors. Thus, the electrophysiological behavior for one cell is described by Eq. 1.

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{I_{ion} + I_{stim}}{C_m} \tag{1}$$

where I_{stim} refers to the external stimulus current, C_m means the capacitance per surface area and I_{ion} is the sum of all ionic currents (potassium, calcium, sodium, for example).

3.2 Mechanical Models

Mechanical Model of Rice (2008). A model for active force in rat cardiac myocytes is shown in [12]. This model belongs to the class of detailed biophysical models, since it considers numerous biological components.

This model is described by 11 ordinary differential equations and 45 algebraic equations. Among other topics, Rice considers the detailing of sarcomere geometry, filament slip, ionic concentrations of calcium and cross-bridges.

The Rice model is based on states of a Markov chain. Where state of N_{XB} is a non-permissive state, with the task of preventing the formation of cross-bridges, the state P_{XB} refers to a permissive conformation of the proteins. XB_{PreR} is the strongly bonded state, prior to rotation of the myosin head, and the state XB_{PorstR} occurs at the time the myosin is twisted causing force generation. In addition, states transition rates depend on the calcium binding to troponin. A detailed description of the equations and considerations on the parameters used can be found in [12].

Mechanical Model of Nash-Panfilov (2004). In order to present a simplified model for the mechanical activity and consequently for the electromechanical coupling, [7] approximated the active tension of canine cardiac myocytes using only one differential and one algebraic equation.

The work presented in action potential used for coupling the active force equation was presented in [1], another simplified model for dogs AP.

The reproduction of the active force of the model proposed by Nash & Panfilov is given by:

$$\begin{aligned} \frac{\mathrm{d}Ta}{\mathrm{d}t} &= \epsilon(V)(k_{Ta}V - Ta), \\ \epsilon(V) &= \begin{cases} e_0 & for\ V < 0.05 \\ 10e_0 & for\ V \geq 0.05 \end{cases} \end{aligned} \tag{2}$$

where k_{Ta} controls the active force amplitude and the $\epsilon(V)$ moderates the delay in development (V < 0.05) and recuperation (V ≥ 0.05) of the force in relation to the AP.

Mechanical Model of Goktepe and Kuhl (2010). With the objective of smoothing the simplified active force equation proposed by [7]. In [4] a new equation was presented for this approximation in cardiomyocytes, which is given by:

$$\begin{aligned} \frac{\mathrm{d}Ta}{\mathrm{d}t} &= \epsilon(V)(k(V - V_r) - Ta), \\ \epsilon(V) &= e_0 + (e_\infty - e_0)e^{-e^{(\xi(V - vs))}} \end{aligned} \tag{3}$$

where e_0, e_∞, ξ, vs and k are model parameters, which indicate: e_0 and e_∞ constant concentration rates that delimit the value of $\epsilon(V)$, ξ refers to the transition rate, vs the rate of phase change, and k is the saturation control of the active force. In addition, V_r is the value of the resting potential.

4 Evaluation of Electromechanical Models

4.1 TenTuscher/Rice Excitation-Contraction Coupling Model

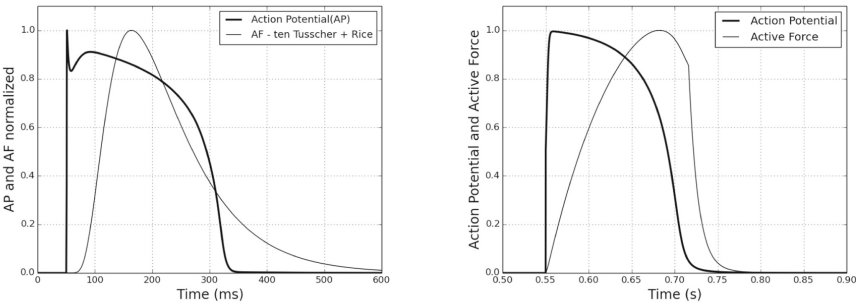
In [11] a model is presented for coupling between the electrical and mechanical system for human cardiac myocytes. For this, two models of the literature [14] and [12] were used, where the first model is responsible for the electrical system while the second is responsible for the mechanical system.

Figure 1(a) shows the normalized active potential and active force of the coupled model proposed in [11] from the [14] and [12] models.

The advantages of using this coupled model in a simulation are supported by the fact of the reproductive quality of the mechanical activity for human cardiac myocytes. However, it is a more complex model, and consequently more differential equations can lead to a high computational cost for a scenario of large simulations (for example for cardiac tissue), thus characterizing the disadvantage in the use this model.

4.2 Aliev-Panfilov/Nash-Panfilov Excitation-Contraction Coupling Model

An electromechanical model based on the Eqs. 2 and the excitation model proposed by [1] is presented in [7]. Both models were developed to describe canine myocytes, however a small adjustment of parameters was necessary.



(a) TenTusscher/Rice coupling (b) Aliev/NashPanfilov coupling

Fig. 1. Action Potential and Active Force for coupled models analyzed.

The Fig. 1(b) shows the action potential and the active force proposed [7]. On the results presented by this coupling it is possible to notice that the model does not present good quality in the reproduction of the active force, based on the physiological behavior described by [11] for the active force, characterizing a disadvantage.

The advantage in choosing this coupled model for a research can then be justified in computational cost issues, since the mechanical model has only one differential equation and another algebraic equations for the generation of the active force.

5 Creation of Models and Results for Each Step

After the study and evaluation process of these coupled models, we propose two new models (Model A and Model B) for electromechanical coupling based on the concepts of these evaluations. After the development of these models, a third model (Model C) is presented, based on empirical considerations during the process of creating the first models.

The purpose of developing new electromechanical models is motivated by the minimization of computational cost (advantage presented by [7]) together with a quality in the simulation of the active force, (benefit presented in [11]). A model that reproduces quickly and with quality the electromechanical coupling can be very useful.

5.1 Step 1 - Direct Coupling

The first phase of the development of the models consists of the direct coupling of the dependent variables between the electric and the mechanical model. Thus, the cellular model of [14] was coupled directly to the mechanical model of [7] (Model A). Analogously, the electric model is coupled to the mechanical model of [4] (Model B).

As a first study, the values of all parameters for both coupled models were maintained according to each of the original proposals [4,7,14].

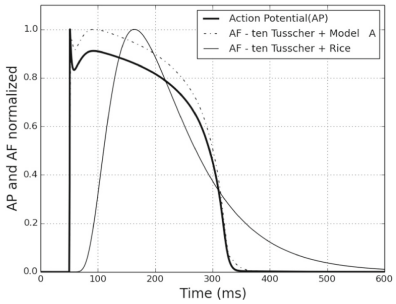
Considering the fact that the action potential is a dimensionless variable in [7], the action potential used in all the coupled simulations was also normalized.

In Model B, the activation rate controlling function is prepared to receive the parameter V in a non-normalized physiological domain, around $[-86, 31]$, for the cellular model of [14]. Thus, the action potential is readapted in this term from the equation to a normalized domain on a real scale according to Eq. 4:

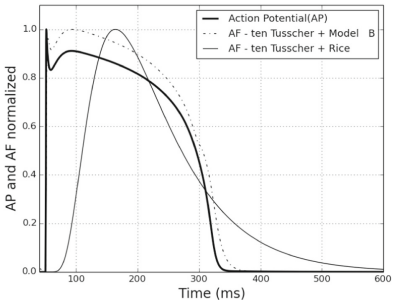
$$V^* = V * 143 - 94, \tag{4}$$

Where V^* is the action potential adapted to be used in the activation function of Model B and V is the action potential coming from [14].

The Fig. 2 presents the result of the direct coupling between the [14] model and the models [7] in (a) and [4] in (b) the direct coupling.



(a) ten Tusccher + Nash-Panfilov



(b) ten Tusccher + Ellen Kuhl

Fig. 2. Action Potential and Active Force (TA) for the coupled models ten Tusscher + Nash-Panfilov and ten Tusscher + Ellen Kuhl.

As it is possible to see, the direct coupling does not present a suitable behavior for the active force in either of the two proposals. This phenomenon can be related to values of unsuitable parameters, making the active force tend to the behavior of the action potential.

5.2 Step 2 - Adjustment of Parameters with Genetic Algorithm

The second step for the creation to models consisted of small considerations in the mathematical model and in the adjustment of model's parameters by a genetic algorithm developed find a set of parameters that show a smaller difference between the simulation of the active force of the presented models and active force coming from to [11].

From this stage the mechanical models underwent changes of parameter values via genetic algorithm. The Eq. 5 presents the equations for the active force

in Model A, where it is evidenced, the parameters to be adjusted by the Genetic Algorithm. They are: kTa, e_0 and e_t.

$$\frac{\mathrm{d}Ta}{\mathrm{d}t} = \epsilon(V)(\mathbf{k_{Ta}}V - Ta),$$
$$\epsilon(V) = \begin{cases} \mathbf{e_0} & \text{for V}< \mathbf{e_t} \\ 10\mathbf{e_0} & \text{for V}\geq \mathbf{e_t} \end{cases} \tag{5}$$

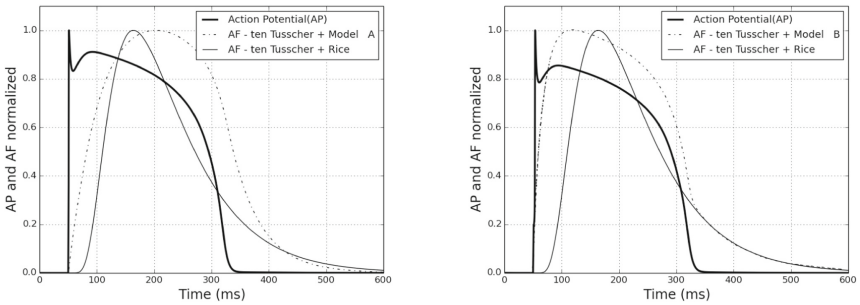
In order to use the genetic algorithm it is necessary to define the domain of the values that each parameter can assume (search space). The e_t is the domain of the action potential (since it controls values for phase changes of the action potential, acting as a threshold). The e_0 domain suggests values close to the values shown in [7]. Finally, the domain for kTa follows the domain of action potential due to its normalization. Thus, the parameters e_0, e_t and kTa belong to the domain [0, 1].

The same procedure to define parameters to be adjusted was applied to Model B, where the Eq. 6 presents, highlighted, all the parameters submitted to the Genetic Algorithm. One consideration is the exclusion of the parameter V_r (resting potential) because the domain is normalized, so the resting potential is 0.

$$\frac{\mathrm{d}Ta}{\mathrm{d}t} = \epsilon(V)(\mathbf{k}V - Ta),$$
$$\epsilon(V) = (\mathbf{e_0} + (\mathbf{e_\infty} - \mathbf{e_0})e^{-e^{(-\xi(V^* - \mathbf{vs}))}}) \tag{6}$$

For all parameters, the domains were defined by values close to the original parameter values presented by [4]. Another consideration used is the requirement of a proportionality between e_0 and e_∞, this proportionality follows the example presented in the original proposal $e_0 = 10\ e_\infty$.

The Fig. 3 presents the result for small changes in model considerations and submission of the parameters of each models to the genetic algorithm.



(a) Model A (b) Model B

Fig. 3. Action Potential and Active Force for coupled models A and B after adjustment via genetic algorithm - Step 2

It is possible to verify that the active force presented better results when compared to the first phase of the model creation process aiming at an approximation to the active force of the example model. However, the quality of the reproduction is still poor, especially for Model B, which still tends to the action potential in parts of its evolution.

The parameter values found for Model A were: $e_0 = 0.001953$, $e_t = 0.000002$ mV and $kTa = 0.760743$ kPa. For the Model B: $e_0 = 0.007813$ mV, $e_\infty = 0.078125$ mV, $\xi = 0.148438$ mV, $vs = 78.749999$, $k = 0.556641$ mV.

5.3 Step 3 - Mathematical Modifications and Addition of a Continuous Delay

In order to correct behavior and add delay between stimulus and contraction, new strategies at the mathematical level were adopted in Phase 3. The first strategy was to change the term $kTa * V$ in Model A and $(k * V)$ for Model B.

Considering the biological existence of a delay between the electrical stimulus and the beginning of the cardiac muscle contraction, we realized the need of a new differential equation. Thus, a new equation is inserted for the active force called Intermediate Active Force (Ta_i) which assumes the previous Ta equation and the Active Force already considered is now expressed as the multiplication of the activation control (even used in the Intermediate Active Force) by the difference between Ta and Ta_i.

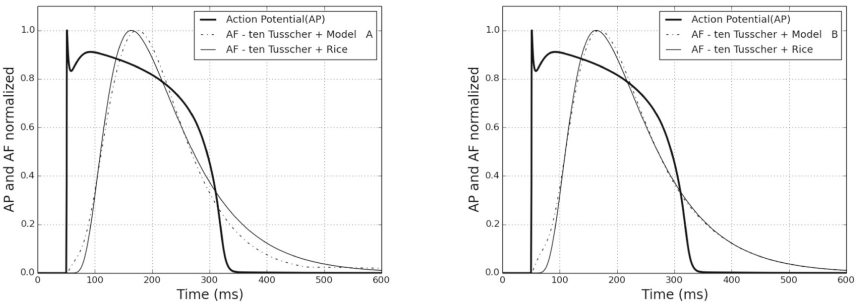
The sets of Eqs. 7 and 8 express Models A and B with the addition of the considerations proposed in this phase as well as, highlighted, the parameters to be submitted to the genetic algorithm with the intention of reproducing the force from a more complex model.

$$\begin{aligned} \frac{\mathrm{d}Ta_i}{\mathrm{d}t} &= \epsilon_0(V)(kTa(V) - Ta_i), \\ \frac{\mathrm{d}Ta}{\mathrm{d}t} &= \epsilon_1(V)(Ta_i - Ta), \\ \epsilon_0(V) = \epsilon_1(V) &= \begin{cases} \mathbf{e_0} \text{ for V} < \mathbf{e_t} \\ \mathbf{e_0} \text{ for V} \geq \mathbf{e_t} \end{cases}, \\ kTa(V) &= \frac{1}{\sigma\sqrt{2\pi}}\, e^{\frac{-1}{2}(\frac{V-1}{\sigma})^2} \end{aligned} \tag{7}$$

The domains of each parameter for the submission in the genetic algorithm continue as in the previous phase and the new parameter added (σ), follows the domain of the action potential for both models ([0.1]).

$$\begin{aligned} \frac{\mathrm{d}Ta_i}{\mathrm{d}t} &= \epsilon_0(V)(k(V) - Ta_i), \\ \frac{\mathrm{d}Ta}{\mathrm{d}t} &= \epsilon_1(V)(Ta_i - Ta), \\ \epsilon_0(V) = \epsilon_1(V) &= (\mathbf{e_0} + (\mathbf{e}_\infty - \mathbf{e_0})e^{-e^{(-\xi}(V - \mathbf{vs}))}), \\ k(V) &= \frac{1}{\sigma\sqrt{2\pi}}\, e^{\frac{-1}{2}(\frac{V-1}{\sigma})^2} \end{aligned} \tag{8}$$

Figure 5 presents the results obtained for the third phase of the development of Models A and B. It is possible to verify a significant increase in the quality in the reproduction of the active tension in both models when compared to the curve of a complex realistic model (Fig. 4).



(a) Model A (b) Model B

Fig. 4. Action Potential and Active Force for coupled models A and B after adjustment via genetic algorithm - Step 3

Therefore, the development of the new models follows a promising path. However, the delay phenomenon (one of the proposals for adding this phase) has not yet obtained the expected result. Based on the fact that even then, when an electrical stimulus happens, even slowly, the contraction begins, not characterizing the biological behavior for this phenomenon.

The parameter values found for Model A were: $e_0 = 0.001953$, $e_t = 0.000977$ mV, $\sigma = 0.066406$. For the Model B: $e_0 = 0.003906$ mV^{-1}, $e_\infty = 0.039063$ mV^{-1}, $\xi = 0.001953$ mV, $vs = -0.078084$ mV, $\sigma = 0.049805$.

5.4 Step 4 - Delay Correction

The fourth and last stage of the development of the models consists in the correction of the multiplier of the differential equation proposed for the delay due to its still inadequate behavior. Thus, the term multiplier is no longer the same as the differential equation for Ta_i. It breaks down into a function defined by Ta_i-dependent parts and the action potential. The fully developed Model A is given by Eq. 9.

$$\begin{aligned}
\frac{\mathrm{d}Ta_i}{\mathrm{d}t} &= \epsilon_0(V)(kTa(V) - Ta_i) \\
\frac{\mathrm{d}Ta}{\mathrm{d}t} &= \epsilon_1(V, Ta_i)(Ta_i - Ta) \\
\epsilon_0(V) &= \begin{cases} \mathbf{e_0} & \text{for V}< \mathbf{e_t} \\ 10\mathbf{e_0} & \text{for V}\geq \mathbf{e_t} \end{cases} \\
\epsilon_1(V, Ta_i) &= \begin{cases} \mathbf{x_1} & \text{for V}> \mathbf{x_2} \text{ and } Ta_i < \mathbf{x_3} \\ e_0(V) & \text{otherwise} \end{cases} \\
kTa(V) &= \frac{1}{\sigma\sqrt{2\pi}}\, e^{\frac{-1}{2}(\frac{V-1}{\sigma})^2}
\end{aligned} \tag{9}$$

Equations 10 presents Model B. The changes in the multiplier (speed control) $(e_1(V, Ta_i))$ are the same as those for Model A.

$$\begin{aligned}
\frac{\mathrm{d}Ta_i}{\mathrm{d}t} &= \epsilon_0(V)(k(V) - Ta_i) \\
\frac{\mathrm{d}Ta}{\mathrm{d}t} &= \epsilon_1(V)(Ta_i - Ta) \\
\epsilon_0(V) &= (\mathbf{e_0} + (\mathbf{e_\infty} - \mathbf{e_0})e^{-e^{(-\xi(V-\mathbf{vs}))}}) \\
\epsilon_1(V, Ta_i) &= \begin{cases} \mathbf{x_1} & \text{for V} > \mathbf{x_2} \text{ and } Ta_i < \mathbf{x_3} \\ e_0(V) & \text{otherwise} \end{cases} \\
k(V) &= \frac{1}{\sigma\sqrt{2\pi}}\, e^{\frac{-1}{2}(\frac{V-1}{\sigma})^2}
\end{aligned} \tag{10}$$

All the parameters added in this phase belong to the domain [0, 1] in both models. For the last time, after these considerations and modifications presented in this phase the parameters of the models were submitted to the GA developed in order to minimize the difference between the curves of the complex model and the simplified models.

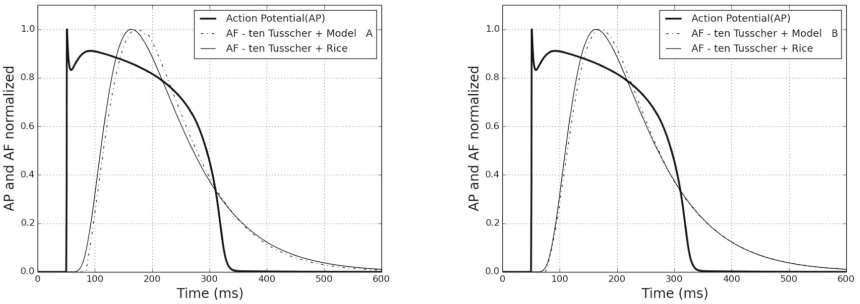
As can be seen in Fig. 5, the proposed models were able to reproduce with excellent quality the active force that generates the contraction based on the comparison of the [11] model, a complex model with numerous considerations.

The parameter values found for Model A were: $e_0 = 0.016602$, $e_t = 0.999024$ mV, $\sigma = 0.050781$, $x_1 = 0.00001$, $x_2 = 0.82594$ mV, $x_3 = 0.42852$. For the Model B: $e_0 = 0.003906$ mV^{-1}, $e_\infty = 0.039063$ mV^{-1}, $\xi = 0.001953$ mV, $vs = -0.312459$ mV, $\sigma = 0.049805$, $x_1 = 0.00001$, $x_2 = 0.8$ mV, $x_3 = 0.22$.

5.5 The Model C

A phenomena observed based on the development of Models A and B is that for both models the smaller the variation of the multiplier $e_0(V)$ the better the result of the reproduction of the active force.

Based on this fact, the creation of a new model for active force generation began: Model C. In this model, all the considerations and phases generated in the process of creating Models A and B are maintained, however, with only the



(a) Model A (b) Model B

Fig. 5. Action Potential and Active Force for coupled models A and B after GA adjustment. - Step 4

modification of the multiplier of the differential equation for Ta_i. This modification consists of replacing the multiplier $e_0(V)$ with an activation constant c_0. The set of Eqs. 11 presents Model C in a complete way with the addition of this change.

$$\begin{aligned} \frac{\mathrm{d}Ta_i}{\mathrm{d}t} &= \mathbf{c_0}(k(V) - Ta_i) \\ \frac{\mathrm{d}Ta}{\mathrm{d}t} &= \epsilon_1(V, Ta_i)(Ta_i - Ta) \\ \epsilon_1(V) &= \begin{cases} \mathbf{x_1} & \text{for V} > \mathbf{x_2} \text{ and } Ta_i < \mathbf{x_3} \\ e_0(V) & \text{otherwise} \end{cases} \\ k(V) &= \frac{1}{\sigma\sqrt{2\pi}}\, e^{\frac{-1}{2}(\frac{V-1}{\sigma})^2} \end{aligned} \tag{11}$$

In Fig. 6 the active force is shown for the electromechanical model C from the parameter adjustment performed by the GA.

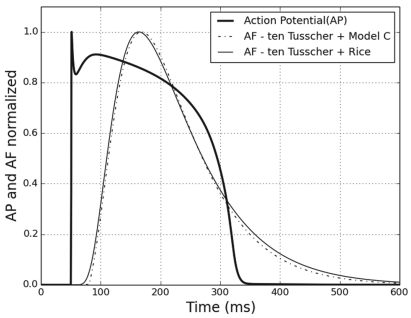


Fig. 6. Potential of Action and Active Force for the electromechanical model C after adjustment via genetic algorithm.

It is possible to observe that just like the previous models, this model was also able to reproduce the active force coming from a more complex model. However, in an even simpler way, eliminating an algebraic equation and two parameters in relation to Model A and three parameters in relation to Model B.

The parameter values found for Model C were: $c_0 = 0.016602$, $\sigma = 0.042969$, $x_1 = 0.0001$, $x_2 = 0.827044$ mV, $x_3 = 0.209961$.

6 Conclusions

In this work three simplified mathematical-computational models are proposed and implemented for the electromechanical coupling of the heart. The objective of the development of these models was to present models with few differential equations and consequently low computational cost for the simulation of the electromechanical activity of the heart without loss of quality in the reproduction of the mechanical activity coming from the active force.

For this, we compared the new models with a complex model presented in [11].

After considering mathematical changes in the equations of the presented models and adjustments using a GA, it was possible to conclude that the simulations achieved were satisfactory for all models developed. The new model was able to reproduce the generation of myocyte force in very clare agreement with a complex and detailed modeled [11] and yet reduced the computational costs by eliminating 11 differential equations and more than 40 algebraic equations.

When dealing with simplified models, we give up allegiance to the biology of the problem. And we are more concerned with the representation of phenomena.

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