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Adaptation of the Calcium-dependent Tension Development in Ventricular Cardiomyocytes

Abstract: Today a variety of models describe the physiological behavior of the heart on a cellular level. The intracellular calcium concentration plays an important role, since it is the main driver for the active contraction of the heart. Due to different implementations of the calcium dynamics, simulating cardiac electromechanics can lead to severely different behaviors of the active tension when coupling the same tension model with different electrophysiological models. To handle these variations, we present an optimization tool that adapts the parameters of the most recent, human based tension model. The goal is to generate a physiologically valid tension development when coupled to an electrophysiological cellular model independent of the specifics of that model's calcium transient. In this work, we focus on a ventricular cell model. In order to identify the calcium-sensitive parameters, a sensitivity analysis of the tension model was carried out. In a further step, the cell model was adapted to reproduce the sarcomere length-dependent behavior of troponin C. With a maximum relative deviation of 20.3% per defined characteristic of the tension development, satisfactory results could be obtained for isometric twitch tension. Considering the length-dependent troponin handling, physiological behavior could be reproduced. In conclusion, we propose an algorithm to adapt the tension development model to any calcium transient input to achieve a physiologically valid active contraction on a cellular level. As a proof of concept, the algorithm is successfully applied to one of the most recent human ventricular cell models. This is an important step towards fully coupled electromechanical heart models, which are a valuable tool in personalized health care.

Keywords: Human Cardiac Contraction, Parameter Optimization, Sensitivity Analysis, Computer Simulation

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1 Introduction

Calcium ions act as direct activators of the contractile apparatus in the heart. The sarcomere length-dependent concentration of calcium bound to troponin C (TnC) $[Ca^{2+}]_{TRPN}$ causes a conformational change of tropomyosin, which leads to a shortening of the sarcomere as described in the cross-bridge cycle. Thus, the intracellular calcium concentration $[Ca^{2+}]_i$ has a significant impact on the development of active tension and thus on the contraction of the heart. For this reason, the standard procedure to model electromechanical coupling is to transfer the calcium transient from the electrophysiological cellular model to the tension model. Due to different implementations of calcium handling leading to different calcium transients, the resulting tension development (TD) in a given tension model can differ significantly in magnitude and dynamics depending on the electrophysiological. To achieve physiologically reasonable tension developments in combination with these calcium transients, a calibration of the electromechanical coupling becomes necessary. Therefore, we developed a parameter optimization referring to experimental data. In the recent publication of Margara et al. [1], a similar approach was used to address this matter. In our case, the parameters of the ventricular tension model proposed by Land et al. [2] were adapted. Land et al. used the experimentally determined calcium transient reported by Coppini et al. [3] to parametrize the model. It is also one of the few models based on human experimental data, which additionally characterizes the length and velocity dependence of TD. The Land et al. model was coupled to the ventricular electrophysiology model proposed by O'Hara et al. [4]. To overcome deficiencies of the original model with respect to tissue simulations, activation and inactivation of the sodium current I_{Na} were adapted as suggested in [5].

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2 Methods

2.1 Sensitivity Analysis

To identify the calcium-sensitive parameters of the tension model, a sensitivity analysis regarding all input parameters from [2] was performed at a constant stretch of $\lambda = 1$ and under excitation with the calcium transient from [3]. For this purpose, features were defined, that characterized the TD with respect to its dynamics and magnitude (Figure 1): diastolic tension (DT), force of contraction (FOC), duration of tension development (DTD), time to peak tension (TPT) and relaxation time (RT). RT is differentiated into RT₅₀ and RT₉₅, whereby the time is measured until 50/95% of the maximum active tension (TD_{max}) has been dissipated.

The sensitivity coefficients were determined using the central difference approximation normalized to the output value and a change of the input parameter by 50%:

$$S = \frac{Y(x + \Delta x) - Y(x - \Delta x)}{2 \cdot Y(x)} \cdot 100\% \quad (1)$$

We chose the initial values of the input variables x as in [2] and changed them by $\pm 50\%$: $\Delta x = \pm 0.5 \cdot x$. The output values Y correspond to the characteristics of TD.

2.2 Parameter Optimization

Compared to Margara et al. [1], we optimized a larger set of parameters to also consider length-dependent effects. Therefore, it is necessary to calculate the TD for multiple stretch values λ_{opt} .

$$\lambda_{opt} = \{0.85, 0.9, 1.0, 1.1, 1.2\} \quad (2)$$

Since the parameters β_1 and β_0 have an influence on the active tension for $\lambda \neq 1$, they were also optimized. A list of all considered parameters and their bounds [2] is given in Table 1.

Figure 1: Illustrative tension development with the features characterizing its course.

To set up the optimization problem, different cost functions were considered initially. However, cost functions including only selected characteristics of TD did not yield satisfactory results, hence the final minimization problem was chosen as the squared difference of the TD courses:

$$\min_{\theta} \sum_i \sum_m (TD(t_m, \lambda_i, \theta) - TD_{GT}(t_m, \lambda_i, \theta))^2 \quad (3)$$

with $\theta = \{[Ca^{2+}]_i, TRPN_{50}, n_{TRPN}, k_{TRPN}, r_s, r_w, A_{eff}, k_u, \beta_1, \beta_0, \gamma_s, \gamma_w, \phi, n_{Tm}, [Ca^{2+}]_{T50}^{ref}, T_{ref}, \nu, \mu\}$.

As ground truth (GT), the sequence of tension developments resulting from the stretches in λ_{opt} was chosen, when the tension model was excited with the calcium transient according to [3].

To evaluate the fit of the optimized parameters towards the ground truth, the following criterion was used:

$$\frac{1}{M} \sum_{m=1}^M \frac{|d(featopt(m), [a(m), b(m)])|}{|feat_{GT}(m)|} \quad (4)$$

with $feat_x = \{DT_x, TD_x, TPT_x, RT_{50,x}, RT_{95,x}\}$, $|feat_x| = M$ and $a(m) = 0.9 \cdot feat_{GT}(m)$, $b(m) = 1.1 \cdot feat_{GT}(m)$.

If the mean relative deviation of a characteristic was smaller than 50%, the new parameter set was considered. In that case, the robustness towards changes in sarcomere length was investigated. For a robust parameter set, the criterion in (4) had to be fulfilled for all stretches in λ_{robust} , with $\lambda_{typ}(t)$ representing a typical course of the sarcomere in tissue simulations (Figure 3).

$$\lambda_{robust} = \{0.875, 0.925, 0.95, 0.975, 1.025, 1.05, 1.075, 1.125, 1.175, \lambda_{typ}(t)\} \quad (5)$$

2.3 Strong Coupling

As the interaction between calcium and TnC plays an important role in the electromechanical coupling, we extended the implementation of the electrophysiological model to

Table 1: Parameter bounds for the optimization that lead to the parameter set P_{opt} . P_{sc} represents the optimal parameter set for the strongly coupled system.

	$TRPN_{50}$	n_{TRPN}	r_w	n_{Tm}	$[Ca^{2+}]_{T50}^{ref}$	μ	β_1	β_0
Lower bound	0	1.6	0.25	0	0μM	1	-Inf	0
Upper bound	Inf	2.0	0.75	Inf	Inf	12	0	Inf
P_{opt}	0.40	2.0	0.75	9.01	0.33μM	1.51	-0.86	2.37
P_{sc}	0.14	2.0	0.75	3.57	0.73μM	1.48	-1.76	3.90

include the corresponding description from [2]. This allowed taking the sarcomere length-dependant behavior of $[Ca^{2+}]_{TRPN}$ into account. All modifications to the model by O'Hara et al. are detailed in [6, p.21-22]. They led to an extended parameter set of the modified cell model.

The new formulation of $[Ca^{2+}]_i$ incorporated the calcium sensitive parameters n_{TRPN} , $[Ca^{2+}]_{T50}^{ref}$ and β_1 . Due to the change of $[Ca^{2+}]_i$, another parameter optimization became necessary. Therefore, the optimization tool was adjusted, such that the calcium transient was no longer interpreted as a fixed input. Instead, the modified coupled system was solved at each time step. This provided a parameter set P_{sc} that yielded optimized tension development for the stretches listed in (2) while including the troponin feedback.

3 Results

3.1 Sensitivity Analysis

The sensitivity coefficients (Table 2) were determined for a $\pm 50\%$ change of the input parameters. The predominantly negative coefficients indicate a tendency to decrease the output parameter when increasing the input parameter. We additionally grouped the calcium-sensitive parameters by evaluating the impact on TD: The parameters r_s , r_w and μ particularly affected the dynamics of TD. The amplitude of TD was mainly or exclusively influenced by $TRPN_{50}$, n_{TRPN} , n_{Tm} , $[Ca^{2+}]_{T50}^{ref}$ and T_{ref} . For k_{TRPN} , k_u and ν , only a very small effect was observed. Changing the other parameters had no effect on static TD, since they only influence the length-dependent behavior of the model.

3.2 Parameter Optimization

The optimized parameter set P_{opt} (Table 1) was used to compare TD for the stretches λ_{opt} using the original and the optimized parameters (Figure 2). For the stretches considered in the optimization, the maximum relative deviation per feature was 20.3%, which occurred for $\lambda = 0.9$. The same applied to all constant stretches included in λ_{robust} . However, the robustness criterion in (4) was not fulfilled for $\lambda_{typ}(t)$ where the deviation was 71%. The respective TD is shown in Figure 3.

Table 2: Sensitivity coefficients for static tension development ($\lambda = 1$) at 50% increase of the input parameters.

	DT	FOC	DTD	TPT	RT ₅₀	RT ₉₅
$TRPN_{50}$	-1563.3	-97.4	-714.4	-25.2	-42.7	-51.6
n_{TRPN}	-2114.6	-53.7	-724.7	1.1	-48.5	-71.0
k_{TRPN}	0	0.7	5.5	-2.8	0.1	-0.2
r_s	0.3	-11.7	952.0	-0.7	8.8	28.1
r_w	-0.7	11.67	-282.9	1.5	-9.3	-28.5
A_{eff}	0	0	0	0	0	0
k_u	0	0.6	-108.0	-15.3	0.4	0.3
β_1	0	0	0	0	0	0
β_0	0	0	0	0	0	0
γ_s	0	0	0	0	0	0
γ_w	0	0	0	0	0	0
ϕ	0	0	0	0	0	0
n_{Tm}	-348.3	-5.2	-76.4	10.8	-18.1	-15.0
$[Ca^{2+}]_{T50}^{ref}$	-1174.6	-104.9	-340.4	-3.8	-52.5	-30.4
T_{ref}	50.0	50.0	0	0	0	0
ν	0	0.1	13.5	1.4	-0.5	-0.4
μ	-0.7	12.1	-294.6	1.7	-10.4	-29.7

S < 0
 S = 0
 S > 0

Figure 2: Influence of P_{opt} on TD, when coupling the considered tension and electrophysiological models for the stretches in λ_{opt} .

Figure 3: Comparison of TD, when using the original parameter set, P_{opt} and GT, with the coupling based on λ_{typ} .

Figure 4: Stationary behavior of the strongly coupled system at various stretches λ for the action potential V_m , the active tension T_a , $[Ca^{2+}]_{TRPN}$ and $[Ca^{2+}]_i$.

3.3 Strongly Coupled System

Strongly coupled optimization yielded the parameter set P_{sc} (Table 1). Based on P_{sc} , the behavior of the strongly coupled system was analysed (Figure 4). The active tension T_a and $[Ca^{2+}]_{TRPN}$ showed a proportional behavior with respect to changes in the sarcomere length. In contrast, $[Ca^{2+}]_i$ showed a significant increase in maximum concentration when the stretch was reduced. At the same time, we observed a faster removal of calcium from the intracellular space.

4 Discussion

In this work, we identified the parameter sets P_{opt} and P_{sc} for the tension model by Land et al. that generate physiological tension courses in simulations with a range of stretch values. The evaluation of the strongly coupled system also showed physiological behavior. A proportional relationship between T_a and $[Ca^{2+}]_{TRPN}$ was observed, as well as an opposite behavior for the magnitudes of the two calcium concentrations. The evaluation criterion was not fulfilled when applying the dynamic stretch course $\lambda_{typ}(t)$ indicating further room for improvement with respect to time-varying stretches. This issue is also relevant for the use of the TD model in tissue simulations, since these usually include time-variable stretches. Future work will extend the parameter optimization to consider time-varying stretches as well.

Nevertheless, with this study we were able to achieve a physiologically more realistic TD by calibrating the electromechanical coupling using a parameter optimization on the ventricular tension model. As an extension to the model considered in this study, we carried out the calibration in combination with other popular ventricular electro-

physiological cellular models as well as for models of the atria. The overall results support the conclusion that the developed optimization tool allows the standardization of tension developments which enables physiologically realistic simulations of the human heart electromechanics.

Author Statement

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