Mechano-Chemical Interactions in Cardiac Sarcomere Shortening

Lauren J Dupuis[1], Joost Lumens[1,2], Theo Arts[1], Tammo Delhaas[1]

[1]Maastricht University, Maastricht, the Netherlands
[2] Université de Bordeaux, Bordeaux, France

Abstract

Tension development in the cardiac sarcomere is highly cooperative, yet the mechanism is not known. We have developed the MechChem model of sarcomere mechanics, which incorporates a mechano-chemical interaction-based cooperativity mechanism in which the thin filament has an intrinsic chemical cooperativity that is boosted by mechanical tension in the thin filament.. In the current study, we extend the MechChem model to include the possibility for the sarcomere to change length when contracting against different afterloads. The model was tested at various afterloads and compared to experimental data. The MechChem model successfully reproduced isotonic twitch experiments.

1. Introduction

The most basic functional unit of cardiac contraction, a sarcomere, is composed of thick and thin filaments. The binding of a calcium ion (Ca^{2+}) to a troponin complex (*Tn*) on the thin filament triggers conformational changes that unblock binding sites [1]. Cross-bridges (*XB*) can form and generate force when myosin heads on thick filaments bind to unblocked binding sites on a thin filament. Force generation in the cardiac sarcomere is cooperative, meaning that small increases in the intracellular Ca^{2+} concentration produce disproportionately large increases in force [2]. We have proposed a novel mechanism of cooperativity in which an intrinsic chemical cooperativity in the thin filament is boosted by mechanical tension [3]. High tension locally along the thin filament impedes the unbinding of Ca^{2+} from the *Tn*, thereby hindering relaxation. Based on this proposed mechanism of cooperativity, we developed the MechChem model of mechano-chemical interactions in cardiac sarcomere contractions [3] that was validated against experimental data on steady-state isometric contraction in skinned muscle [2] and isometric twitches in myofibers [4, 5]. The aim of this study is to extend the MechChem model to mimic isotonic twitch experiments where the sarcomere can contract and shorten against different afterloads. Model validity will be evaluated by comparison of simulated and measured isotonic twitch experiments at various afterloads.

2. Methods

2.1. Model Setup

The setup of the MechChem model is based on several assumptions. First, we assume that binding of Ca^{2+} to a *Tn* results in the movement of tropomyosin (*Tm*) away from its rest position, unblocking the XB binding sites on the thin filament. We assume there is an intrinsic chemical cooperativity in the binding of Ca^{2+} to *Tn* [6] that is boosted by mechanical tension in the thin filament. When binding sites are unblocked for XB binding, we assume a XB can either be in the attached or detached states. Each bound XB is assumed to generate a discrete force on the thin filament that sums up to the tension at position *x* along the single overlap region (*SOR*) from the start of the mid line to the z-disk. The final assumption is that the sarcomere length (L_{sarc}) changes with a Hill-type model [7].

At rest, the binding sites for myosin are blocked by *Tm* molecules that wrap around the thin filament. They are anchored in place by *Tn* complexes. When Ca^{2+} binds to the *Tn*, conformational changes occur that result in the movement of *Tm* away from the position in which it blocks the binding sites on the thin filament. We refer to this as the activation of the *Tn*. The proportion of activated *Tn* at time *t* and position *x* along the thin filament, *P*(*x*,*t*), is modeled with the following partial differential equation:

$$\frac{\partial P(x,t)}{\partial t} = \left(1 - P(x,t)\right)\left(\frac{[Ca^{2+}](t)}{K_{Ca}(t)}\right)^{n} f_{Ca_{DA}} - f_{Ca_{AD}} P(x,t) e^{-nC_s S_x(x,t)} \quad (1)$$

The calcium concentration ($[Ca^{2+}]$) is assumed to be

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uniform across the cell and to vary in time according to Rice et al. [8]. Parameter $n = 3$ represents the intrinsic cooperativity of the binding of Ca^{2+} to *Tn* in the absence of tension as described in Sun et al [6]. C_s represents the tension cooperativity constant. The parameter $f_{Ca_{DA}}$ represents the rate of attachment of a Ca^{2+} to *Tn*, and $f_{Ca_{AD}}$ represents the rate of detachment of Ca^{2+} from *Tn*. K_{Ca} is an equilibrium constant that changes linearly with L_{sarc} according to Equation 2 where parameters *a* and *b* are constants

$$K_{Ca} = -a\,L_{sarc} + b \tag{2}$$

Once myosin heads on the thick filaments bind to unblocked sites, *XBs* can form and generate force. This is only possible in the *SOR* of the sarcomere, defined as the length of thin filament that overlaps with one thick filament and no other thin filaments. We calculate the length of the *SOR* as described previously [3].

The probability of formation of a strong *XB* is represented by $A(x,t)$ (Equation 3).

$$\frac{\partial A(x,t)}{\partial t} = \big(1 - A(x,t)\big) f_{DA} P(x,t) - A(x,t) f_{AD} \tag{3}$$

where the rates of *XB* attachment and detachment are $f_{DA} = 40\ s^{-1}$ and $f_{AD} = 12\ s^{-1}$, respectively [9].

Because the MechChem model represents an average of thousands of sarcomeres, $A(x,t)$ can be viewed as a density of *XBs*. The force density ($F_{XB}(x,t)$) generated by the bound *XBs* can be represented with Equation 4.

$$F_{XB}(x,t) = F_{iso} A(x,t) H(t) \tag{4}$$

In Equation 4, F_{iso} represents the maximum force generated by a single *XB*, and $H(t)$ is a normalized sarcomere length L_{sarc} determined by Equation 5.

$$H(t) = \frac{h_s(t) - h_i(t)}{h_{SE0}} \tag{5}$$

We utilize a Hill-type model to represent the changes in length in the sarcomere. The half L_{sarc} is represented by $h_s(t)$, the length of the intrinsic element is $h_i(t)$, and the length of the series elastic element where maximum force is generated is h_{SE0}. $H(t)$ is a proportion of the current length of the series elastic element, defined as $h_s(t) - h_i(t)$ to the length where the series elastic element generates the most tension (h_{SE0}).

The change in length of the intrinsic element h_i is determined with Equation 6.

$$\frac{dh_i(t)}{dt} = (H(t) - 1) v_{max} \tag{6}$$

where parameter v_{max} refers to the maximum velocity of sarcomere shortening.

The half sarcomere length $h_s(t)$ is determined by Equation 7.

$$h_s(t) = min \begin{cases} h_{iso} \\ \dfrac{h_{SE0}(S_{afterload} - S_{passive}(t))}{F_{iso} A_{Xmax}(t)} + h_i(t) \end{cases} \tag{7}$$

A sarcomere shortens when it develops enough tension at the end of the *SOR* to overcome the afterload ($S_{afterload}$). The afterload re-stretches the sarcomere when there is no longer enough tension developed to overcome it. If the sarcomere does not change length, L_{sarc} is held constant at the same length as the previous step (h_{iso}). A_{Xmax} represents the cumulative sum of the *XB* density at the end of the *SOR*. $S_{passive}$ is the total passive tension in the sarcomere.

The output of the MechChem model is the total tension in the thin filament (S_x) at location *x* along the *SOR* and time *t*. It is the sum of the total active tension ($S_{xactive}(x,t)$) and the total passive tension ($S_{passive}(t)$) at time *t*, as shown in Equation 8.

$$S_x(x,t) = S_{x_{active}}(x,t) + S_{passive}(t) \tag{8}$$

$S_{x_{active}}(x,t)$ is modeled with Equation 9. The *XB* density, F_{XB}, is integrated along the *x* dimension at each time point to calculate the active tension locally in the thin filament.

$$\frac{\partial S_{x_{active}}(x,t)}{\partial x} = F_{XB}(x,t) \tag{9}$$

$S_{passive}(t)$ is modeled by the experimental results of Weiwad et al. 2000 [10] (Equation 10), depending on L_{sarc}

$$S_{passive} = 4.41(e^{2.87(L_{sarc} - 1.85)} - 1) \tag{10}$$

2.2. Parameter fitting procedure

The parameters F_{iso}, C_s, *a*, and *b* were fitted using a linear least squares analysis to minimize the difference between the tension data of Katsnelson et al. [11] ($S_{experiment}$) and the tension output by the MechChem model (S_{model}). The objective function to be minimized is presented in Equation 11. The parameter v_{max} was then fit to the length data of Katsnelson et al.

$$error = \frac{\sum_{i=1}^{j} \big(S_{model} - S_{experiment}\big)^2}{j} \tag{11}$$

2.3. Simulation protocol

Simulations were performed to mimic isotonic twitch experiments. Given the fitted parameter values, we evaluated how well the model reproduces length and

tension data as a function of time in comparison to the isotonic twitch experiments of Katsnelson et al [11]. The sarcomere was allowed to contract against seven afterloads ranging from 17mN to 100mN, as was done in the experiments by Katsnelson et al [11]. Throughout all simulations, 2.15 μm was the initial and maximum L_{sarc}. The MechChem model outputs the myofiber tension and L_{sarc} for all steps throughout the cycle.

3. Results

3.1. Isotonic Twitch

Figure 1 displays the comparison between the experimentally measured isotonic twitch data of Katsnelson et al [11] and the MechChem model-generated isotonic twitch results given the fitted parameter values in Table 1. Figure 1A and B display the experimentally measured muscle tension and the MechChem model-generated myofiber tension at various afterloads, respectively. Figure 1C displays the experimentally measured muscle length corresponding to the tension curves in Figure 1A, and Figure 1D displays the MechChem model-generated L_{sarc} curves.

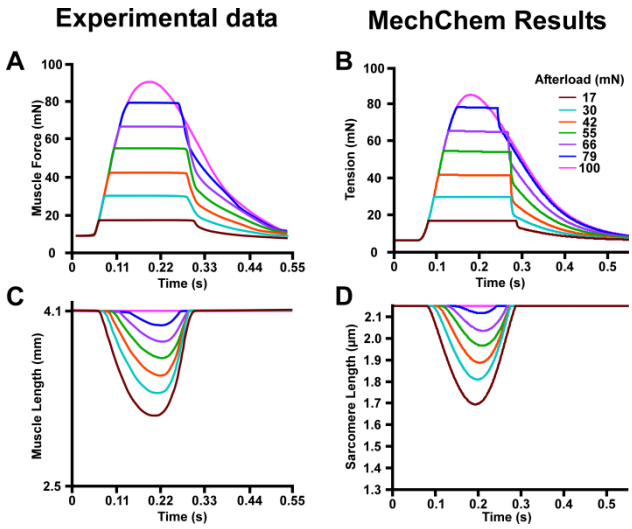

Figure 1: Myofiber tension and length in isotonic twitches with seven different maximum afterloads. The (A) muscle force generated in the experimental results of Katsnelson et al. [11] are compared to (B) MechChem model-generated myofiber tension. (C) experimentally measured muscle length is compared to (D) simulated L_{sarc}.

The MechChem model-generated tension curves are qualitatively similar to the experimental data of Katsnelson et al. The peak tension generated in the isometric contraction (afterload 100 mN) is higher in the experiments. The duration of the shortening phase is similar between the experiments and the simulated data. In the MechChem model-generated results, the duration of the shortening phase decreased from 0.21 seconds at the lowest afterload to 0.095 seconds at an afterload of 79 mN. In the experimental data of Katsnelson et al, the duration of shortening showed a similar decrease in the duration of shortening from 0.23 seconds to 0.12 seconds for the same afterloads.

Table 1. Fitted parameter values.

Parameter	Value	Units
C_s	0.02	kPa^{-1}
a	3.25	$\mu M\ \mu m^{-1}$
b	8.56	μM
F_{iso}	0.29	$kPa\ nm^{-1}$
v_{max}	5.77	$\mu m\ s^{-1}$

4. Discussion and conclusions

In this study, we have expanded the MechChem model of mechano-chemical interactions in cardiac sarcomere contraction to simulate an isotonic twitch. The sarcomere was allowed to shorten against various afterloads, and the model-predicted myofiber tension and length. The model-generated results were in qualitative agreement with the experimental results of Katsnelson et al. [11].

In the experimental data of Katsnelson et al, the tension traces show that the fully isometric twitch requires the longest time to relax. It has been proposed that greater tension developed in the sarcomere causes a longer duration of contraction [4]. We propose that the prolongation of contraction is due to the tension dependent mechanism of cooperativity in sarcomere contraction. Greater developed tension in the thin filament hinders relaxation. In this study, the maximum tension was limited by afterload. In experiments, the only shortening phase to peak out past the isometric twitch was that of 79 mN. In our simulations, the contractions with an afterload of 79 mN and 66 mN peaked out past the isometric tension trace. As maximum tension was decreased, the duration of relaxation also decreased.

A greater single overlap length has been shown to allow greater tension to develop in the thin filament [12]. Shortening of sarcomeres results in smaller *SOR*s. If the afterload is low, the sarcomere shortens to a smaller length, decreasing the length where a strongly bound *XB* can develop. Hence, the overall force density decreases. This could help explain the reduced duration of the isotonic twitch at lower afterloads. When Ca^{2+} is decreased in the cytosol, low tension in the thin filament, partially due to the short *SOR*, does not have a large hindering effect on relaxation.

The MechChem model-generated relaxation phase begins quickly following the end of the shortening phase. As L_{sarc} increases, a slower phase of relaxation begins. With a longer *SOR*, there are greater probabilities of strong *XBs* developing, slowing the relaxation phase.

We compare the L_{sarc} generated by the MechChem model to left ventricular papillary muscle length output in the experiments of Katsnelson et al [11]. While muscle length and L_{sarc} are not directly comparable, the general trends in length change remain similar. The shortening phase is slower than the relengthening phase in both experimental data and MechChem model results.

The MechChem model utilizes a prescribed Ca^{2+} transient as input. It has been shown that the free intracellular Ca^{2+} transient is affected by the feedback of force on the Ca^{2+} handling system [13]. However, the Ca^{2+} transient was not measured in the experiments of Katsnelson et al [11], so these effects could not be viewed in the experimental data. In the future, however, the MechChem model can be coupled to a Ca^{2+} handling system to understand changes in the calcium transient due to the feedback of mechanics during sarcomere shortening as well as during the relaxation phase.

The addition of the ability for the sarcomere to shorten is a necessary step added to the MechChem model. In a whole heart, sarcomeres shorten during systole, and blood is ejected from the left ventricle. Hence, for the MechChem model to be utilized within the framework of a full heart contraction model, sarcomere shortening must be possible. With this development, it is a logical next step to insert the MechChem model into the framework of a whole-heart model such as the CircAdapt model of the closed-loop circulation.

The MechChem model has been extended to allow the sarcomere to change length. The model-generated tension and L_{sarc} curves during isotonic twitches at various afterloads are in good qualitative agreement with experimental results. This development step in the MechChem model will allow its use to couple it with a calcium handling system as well as a whole-heart model.

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Address for correspondence.

Name. Lauren Dupuis.
Full postal address. Department of Biomedical Engineering. Universiteitssingel 50, 6229ER Maastricht, the Netherlands
E-mail address. L.dupuis@maastrichtuniversity.nl