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The sensitivity of fast muscle contractile function to the major components of the sarcomere Ca^{2+}-cycling system

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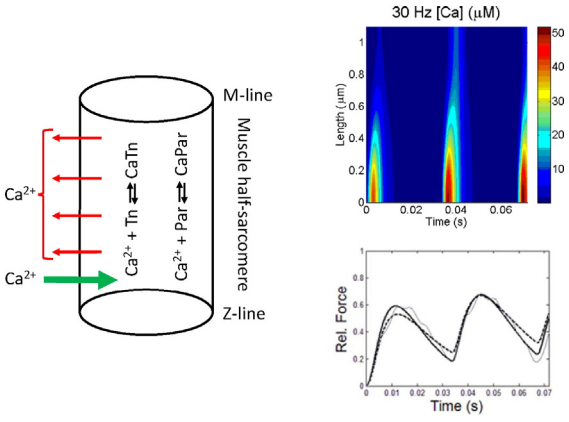
HIGHLIGHTS

- Reaction–diffusion model of a sarcomere matched experimental force measurements.
- Steep concentration gradients were present, but diffusion did not limit contraction.
- Increases in Ca^{2+} release rate enhance force slightly, but are energetically costly.
- Effects of variation in the parameter set that defines a sarcomere are described.

GRAPHICAL ABSTRACT



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ABSTRACT

A reaction–diffusion model of a muscle sarcomere was developed to evaluate the sensitivity of force characteristics to diffusion and Ca^{2+}-cycling components. The model compared well to experimental force measurements. Diffusion led to Ca^{2+} gradients that enhanced maximal force and accelerated relaxation compared to when diffusion was infinitely fast. However, a modest increase in sarcomere length or radius led to a decrease in maximal force. Lowering the Ca^{2+} release rate caused a lower maximal force, but increasing the rate led to only modest gains in maximal force while incurring much greater ATP costs associated with reuptake. Greater parvalbumin binding rates decreased maximal force but enhanced relaxation, and this effect was magnified when Ca^{2+} uptake rates were lowered as may occur during fatigue. These results show a physiological set of parameters that lead to a functional sarcomere of known dimensions and contractile function, and the effects of parameter variation on muscle function.

1. Introduction

Muscle contraction begins when a wave of depolarization radiates from the neuromuscular junction to the t-tubules activating voltage-gated Ca^{2+} channels that release Ca^{2+} from the sarcoplasmic reticulum (SR). Ca^{2+} then diffuses across the sarcoplasm and binds to troponin C (Tn) in the sarcomeres, which facilitates cross-bridge attachment and

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thus contraction. Relaxation of muscle is induced by the reuptake of Ca^{2+} via the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA), as well as by sequestration of Ca^{2+} by the soluble Ca^{2+} binding protein parvalbumin (Fig. 1A) [4,6,12,16]. Maximal contractile frequency is therefore largely dictated by the rate at which Ca^{2+} cycling allows muscle to switch between phases of contraction and relaxation.

Several prior studies have developed reaction–diffusion models of sarcomere Ca^{2+} cycling in skeletal muscle. Cannell and Allen [5] demonstrated steep Ca^{2+} concentration gradients along the sarcomere, and their model compared well to Ca^{2+} transients measured experimentally in frog muscle. Baylor and Hollingworth [1] expanded on this approach and confirmed the presence of Ca^{2+} gradients and also showed that ATP had a Ca^{2+} buffering role in frog muscle. These authors further adapted their model to mouse fast-twitch muscle, and evaluated the effects of the location of the Ca^{2+} release site, sarcomere length, the Ca^{2+} binding protein, parvalbumin (Par), as well as mitochondrial uptake of Ca^{2+} [2,3]. Similarly, Novo et al. [13] and Groenendaal et al. [7] found that the location of the Ca^{2+} release site from the SR was an important contributor to the Ca^{2+} dynamics during contraction/relaxation cycles. More recently, Liu and Olson [11] developed a model for frog muscle that incorporated voltage sensitivity of Ca^{2+} release.

The present study integrated reaction and diffusion components of Ca^{2+} cycling with force production, allowing comparison of the model output to experimental contractile data. In addition, we evaluated the role of Ca^{2+} diffusion by comparing normal diffusion results to those with infinitely fast diffusion rates, and we conducted a sensitivity analysis of the major components of the Ca^{2+} cycling system. A model base case was generated using experimental contractile data from fish white muscle. This experimental system was selected because fish white muscle has a uniform fiber type, thus eliminating confounding effects of mixed fiber muscles with different contractile properties, and because it has a high maximal contractile frequency, which allows the evaluation of a relatively high performance muscle that may be near functional limits of Ca^{2+} cycling. This analysis sheds insight into the parameters that influence muscle contractile function, and it will have application to future modeling efforts as well as tissue engineering studies.

2. Methods

2.1. Model species balance

The species continuity equation for all components (Ca^{2+} (Ca), Mg^{2+} (Mg), troponin-C (Tn), parvalbumin (Par), calcium bound troponin (CaTn), calcium bound parvalbumin (CaPar), and magnesium bound parvalbumin (MgPar)) is given by

$$\frac{\partial C_i}{\partial t} = D_i\left(\frac{\partial^2 C_i}{\partial x^2} + \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C_i}{\partial r}\right)\right) + R_i \tag{1}$$

where C_i is the concentration of the ith component and R_i is the net rate of formation of the ith component by chemical reaction. The boundary conditions are given by Eqs. (2)–(5). (The uptake and release functions are given by Eqs. (15)–(18).) It should be noted that calcium is the only component that has a non-zero flux. In Eqs. (2)–(5), where not specified, i is for all species.

$$-D_i\frac{\partial C_i}{\partial r}\Big]_0 = 0 \tag{2}$$

$$-D_i\frac{\partial C_i}{\partial r}\Big]_R = 0 \text{ where i}\neq[Ca] \tag{3}$$

$$-D_{[Ca]}\frac{\partial [Ca]}{\partial r}\Big]_R = \sum J_i(t,z,[Ca]) \tag{4}$$

$$-D_i\frac{\partial C_i}{\partial x}\Big]_{0 \text{ and } L} = 0 \tag{5}$$

Reaction rates, R_i, are given in Eqs. (6)–(9). The overall model has 3 specified reactions with 7 species: Ca + Tn ⇆ CaTn, Ca + Par ⇆ CaPar, and Mg + Par ⇆ MgPar. In Eqs. (6)–(9) $R_i' = R_i/S_i$ where S_i is a scaling factor for sensitivity analysis (see Eq. (25)).

$$R_{Ca}{}' = \sum_l R_{Ca,l} \tag{6}$$

$$R_{Ca,TnC}{}' = \left(k_{r,CaTn}[CaTn] - k_{f,CaTn}[Ca][Tn]\right) \tag{7}$$

$$R_{Ca,Par}{}' = \left(k_{r,CaPar}[CaPar] - k_{f,CaPar}[Ca][Par]\right) \tag{8}$$

$$R_{Mg,Par}{}' = \left(k_{r,MgPar}[MgCaParATP] - k_{f,MgPar}[Mg][Par]\right) \tag{9}$$

$$R_{Ca} = R_{Ca,Tn} + R_{Ca,Par} \tag{10}$$

The initial conditions for all species were obtained by using the equilibrium of the reaction equations and the known species concentrations at rest of Ca and Mg. Diffusion of each species in the radial direction is very fast and leads to small concentration gradients in the radial direction as depicted by Cannel and Allen[5]. For small gradients in the radial direction, an average in the radial direction (Eq. (11)) can be applied to Eq. (1) and this yields Eq. (12).

$$<\text{Average of } f(r)> = \frac{\int_0^R f(r)r\,dr}{\int_0^R dr} \tag{11}$$

$$\frac{\partial\langle C_i\rangle}{\partial t} = D_i\frac{\partial^2\langle C_i\rangle}{\partial x^2} + \frac{2}{R}D_i\frac{\partial\langle C_i\rangle}{\partial r}\Big]_R + \langle R_i'\rangle \tag{12}$$

The radially averaged model, Eq. (12), is used to analyze the diffusion limitations in the axial direction of the myofibril and is termed here the *Diffusion* model. Averaging again over the axial direction produces a volume averaged model (removing diffusion gradients in all dimensions). There are 3 distinct regions, L_k along the length of the sarcomere which are accounted for by the sum over the index k in Eq. (14).

$$<\text{Average of } f(x)> = \frac{\int_0^L f(x)dx}{\int_0^L dx} \tag{13}$$

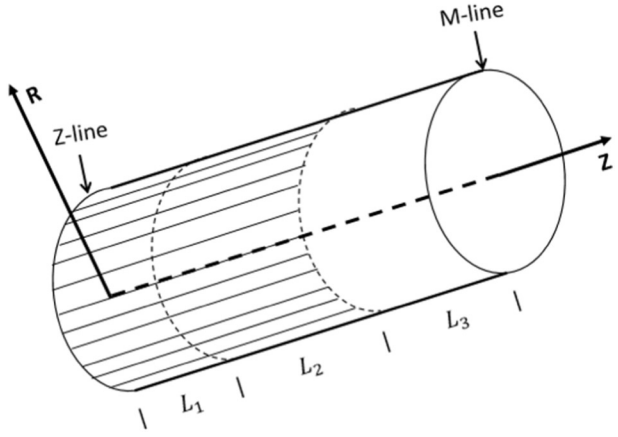

Fig. 1. Model schematic of a half-sarcomere, where the L1 region is the site of Ca^{2+} release, and also sites of Ca^{2+} uptake and the troponin-C reaction. The L2 region contains Ca^{2+} uptake and troponin-C, while the L3 region has only Ca^{2+} uptake. R is the sarcomere radius and Z is the length of the half sarcomere, and diffusion occurs between all 3 regions.