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Compartment calcium model of frog skeletal muscle during activation

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HIGHLIGHTS

- Developed a voltage dependent calcium dynamics model in frog skeletal muscle fibers.
- An electrical model was developed to describe voltage at the surface membrane.
- Calcium in the myofibrillar space is examined for twitch and tetanus.
- Force generation in tetanus changes due to variations in parameters.

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ABSTRACT

Skeletal muscle contraction is triggered by a rise in calcium (Ca^{2+}) concentration in the myofibrillar space. The objective of this study was to develop a voltage dependent compartment model of Ca^{2+} dynamics in frog skeletal muscle fibers. The compartment model corresponds to the myofibrillar space (MS) and a calcium store, the sarcoplasmic reticulum (SR). Ca^{2+} is released from the SR to the MS based on the voltage and is able to bind to several proteins in the MS. We use a detailed model to account for voltage dependent Ca^{2+} release and inactivation. With this model, we are able to match previous experimental data for Ca^{2+} release and binding to proteins for an applied (fixed) voltage. We explore the sensitivity of parameters in the model and illustrate the importance of inactivation of the SR; during a long depolarization, the SR must be inactivated in order to achieve realistic Ca^{2+} concentrations in the MS. A Hodgkin Huxley type model was also developed to describe voltage at the surface membrane using electrophysiological data from previous experiments. This voltage model was then used as the time dependent voltage to determine Ca^{2+} release from the SR. With this fully coupled model, we were able to match previous experimental results for Ca^{2+} concentrations for a given applied current. Additionally, we examined simulated Ca^{2+} concentrations in the case of twitch and tetanus, corresponding to different applied currents. The developed model is robust and reproduces many aspects of voltage dependent calcium signaling in frog skeletal muscle fibers. This modeling framework provides a platform for future studies of excitation contraction coupling in skeletal muscle fibers.

1. Introduction

In skeletal muscles, muscular force production is primarily controlled by changes in the intracellular calcium (Ca^{2+}) concentration. In general, when Ca^{2+} rises, the muscles contract, and when calcium decreases, the muscles relax (Berchtold et al., 2000). Normal activation of a skeletal muscle fiber involves a motor neuron receiving a signal from the central nervous system. This signal causes a depolarization corresponding to an action potential at the level of the sarcolemma, the cell membrane of the skeletal muscle fiber. The change in voltage causes Ca^{2+} to be released from the sarcoplasmic reticulum (SR) (Posterino et al., 2000). This Ca^{2+} release allows the muscle to contract. In frog muscle fibers, Ca^{2+} release channels are located near the Z lines of the sarcomeres. The sarcomere is composed of many myofilaments and the Z line corresponds to the region where adjacent sarcomeres come together (thin dark line when viewed with a microscope, Peachey, 1965).

The Ca^{2+} is released from the SR into the myofibrillar space (MS). This is accomplished via voltage dependent conformational changes in receptors and activation of other receptors. A single depolarization or signal from the motor neuron is a twitch. When there are multiple depolarizations within a short period of time, this will result in a sustained increase in Ca^{2+} in the MS, which will cause a sustained muscle contraction and generation of force, corresponding to tetanus (Berchtold et al., 2000; Posterino et al., 2000). Modeling and understanding Ca^{2+} concentrations in the SR and the MS will lead to an understanding of normal and mutant skeletal muscles.

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Several models of Ca^{2+} release and distribution in amphibian (mainly frog) and mammalian skeletal muscle fibers have been proposed and developed. The first model of calcium movement and diffusion was developed by Cannell and Allen (1984). In this model, they were able to solve partial differential equations for Ca^{2+} concentration and included several region specific Ca^{2+} reactions with different proteins. This initial study was able to account for gradients in Ca^{2+} throughout the SR and match well with experimental data for average Ca^{2+} in the MS (Cannell and Allen, 1984). An extension to Cannell and Allen (1984) was developed by Holly and Poledna (1989) to include terms for Ca^{2+} binding to ATPase, but only accounted for one region within the MS. In a later model (Baylor and Hollingworth, 1998), the full role of ATP was modeled. Baylor et al. also modified the model to account for Ca^{2+} release due to sparks in (Baylor et al., 2002) and modified the model further to be an accurate description of mammalian skeletal muscle (Baylor and Hollingworth, 2007, 2012). In these models an accurate voltage model was not used; the Ca^{2+} release was governed by an exponential permeability model, corresponding to release at the Z line in response to an action potential.

In another set of complementary modeling and experimental studies, the voltage dependent Ca^{2+} release was examined (Melzer et al., 1986; Rios et al., 1993; Simon and Hill, 1992). Several other modeling studies have been completed that have developed coupled equations to describe the sarcolemma and tubular system membrane potential (Cannon et al., 1993; Henneberg and Roberge, 1997), primarily for mammalian skeletal muscle. Shorten et al. (2007) have used this membrane potential model coupled to Ca^{2+} release to study fatigue in mammalian skeletal muscle.

In this paper, we present a compartment model of Ca^{2+} movement in skeletal muscle that is coupled to voltage. We first use a simplified compartment model with a prescribed voltage and novel coupling of SR Ca^{2+} release and inactivation to the voltage and MS Ca^{2+} concentration. This model is compared to experimental data of Simon and Hill (1992). We then develop a model to describe voltage at the surface membrane based on electrophysiological data. This allows us to explore Ca^{2+} release and Ca^{2+} concentrations in response to different applied currents, corresponding to a twitch and tetanus. The full model reproduces experimental results of Cannell and Allen (1984). With the novel coupling of voltage equations to the Ca^{2+} release, we are able to show the importance of Ca^{2+} inactivation in the MS. We also study the effects of parameters that could be related to mutations and skeletal muscle disorders to understand Ca^{2+} release from the SR and Ca^{2+} concentrations in the MS.

2. Mathematical model

2.1. Overview

We are interested in tracking the total amount of calcium that ultimately affects the activation of muscle in force generation, versus its distribution and diffusion. Thus, we propose a simplified geometry of the sarcomere of frog skeletal muscle myofibril. This is in contrast to previous studies where diffusion and calcium movement within the myofibril were modeled in detail (Cannell and Allen, 1984; Baylor and Hollingworth, 1998; Baylor et al., 2002; Baylor and Hollingworth, 2012; Holly and Poledna, 1989).

We simplify the different regions of the sarcomere and focus on two compartments. The top compartment is the sarcoplasmic reticulum (SR). The second connected compartment is the myofibrillar space (MS), where Ca^{2+} can bind to different proteins. The compartments are illustrated in Fig. 1. The SR will release Ca^{2+} into the MS after an activation or nerve stimulation. In contrast to previous models (Cannell and Allen, 1984; Baylor and Hollingworth, 1998; Baylor et al., 2002; Baylor and Hollingworth, 2012; Holly and Poledna, 1989), we couple SR release to voltage. We will first explore using a prescribed voltage and then we develop a time dependent voltage governed by Hodgkin Huxley equations to accurately account for a nerve stimulation or applied input current.

2.2. Compartment calcium model

We will track the free Ca^{2+} concentration in the two compartments through a system of differential equations. The concentration of free Ca^{2+} in the SR and the MS will be given by C_{SR} (μM) and C_{MS} (μM), respectively. The rate of change of Ca^{2+} concentration with respect to time t (ms) in the SR is determined by

$$\frac{dC_{SR}}{dt} = -\mathcal{R}(V) + V_{max}\frac{C_{MS}}{C_{MS}+K_{MS}} - L_p, \tag{1}$$

where $\mathcal{R}(V)$ ($\mu M\, ms^{-1}$) is the Ca^{2+} release from the SR that depends on the strength of the nerve stimulation (or applied input current) and the resulting membrane voltage. The second term in Eq. (1) corresponds to Ca^{2+} uptake by SERCA, an ATP dependent pump that moves Ca^{2+} from the MS to the lumen of the SR (Berchtold et al., 2000). The movement or pumping of excess Ca^{2+} from the MS into the SR is important since it reduces available Ca^{2+} in the MS to relax the muscle. Increasing the SR Ca^{2+} allows it to be stored and ready for release with the next stimulation from the motor neurons. Current experimental data supports the theory that a single conformational change of the pump allows the movement of Ca^{2+} across the membrane and into the SR (Berchtold et al., 2000; Salviati et al., 1984). We use a standard Hill type equation to model the SERCA, as in other modeling studies, assuming that the pumping rate can saturate and that it is first order (Hill coefficient of 1, Cannell and Allen, 1984; Holly and Poledna, 1989; Koivumaki et al., 2009). The parameters for SERCA include a maximal pumping rate V_{max} ($\mu M\, ms^{-1}$) and dissociation constant K_{MS} (μM). The last term in Eq. (1) is a leak term for Ca^{2+} moving into the MS due to the large difference in concentration. The leak parameter to capture the permeability of Ca^{2+} to leak from the SR into the MS is given by L_p ($\mu M\, ms^{-1}$). We do not include terms for PMCA, another Ca^{2+}-ATPase pump, and the sodium calcium exchanger NCX, which could be playing a role in Ca^{2+} movement between the MS and SR compartments (Berchtold et al., 2000).

The differential equation governing Ca^{2+} in the MS will include the corresponding SERCA, voltage dependent Ca^{2+} release, and leak term with opposite signs of that in Eq. (1). The total free Ca^{2+} in the MS will also depend on how Ca^{2+} is binding to several proteins in the MS. The Ca^{2+} concentration in the MS, C_{MS} (μM), is

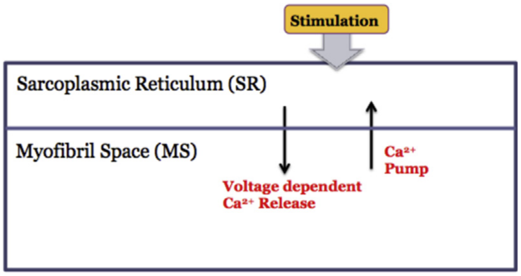

Fig. 1. Model geometry for the two compartment model. The stimulation from an applied current or specified voltage at the level of the sarcolemma will then cause Ca^{2+} release from the sarcoplasmic reticulum (SR) to the myofibril space (MS). Several channels and pumps allow Ca^{2+} movement between the SR and the MS. Several proteins and reactions also take place in the MS.