Mechanical Aspects of Crossbridge Muscle Dynamics

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Abstract

In this report we analyze a stochastic model of the crossbridge interactions of the muscle. A computational model and theoretical model will be developed and used to compare quantities such as force and velocity of crossbridge dynamics.

1 Introduction

In the muscle, the basic unit known as the sarcomere consists of thin and thick filaments that interact with each other in the process of muscle contraction or muscle shortening. The thick filament, made of myosin, consists of a large number of microscopically small protrusions called myosin heads or "crossbridges" that interact with the thin filament, made of actin, in a cycle where they attach, pull and detach, known as the crossbridge cycle. We focus on a muscle that is in constant contractile state, meaning it is continuously being electrically stimulated. We restrict our focus to a model of half a sarcomere unit. It can be seen in the bottom image of figure 1 that there is an equilibrium

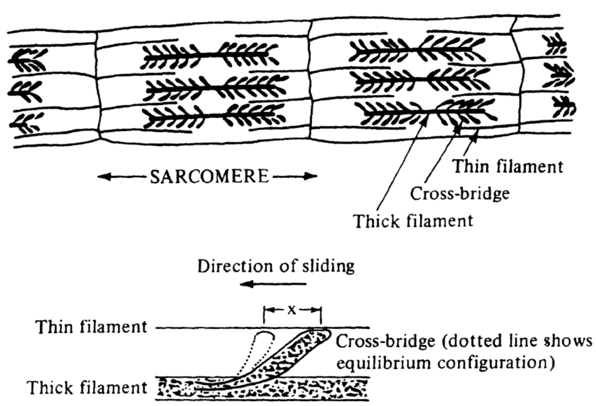

Figure 1: A top diagram shows a series of sarcomere and the bottom image demonstrates the interaction between a crossbridge and the actin thin filaments. Taken from "Modeling and Simulation in Medicine and the Life Sciences" by Peskin and Hoppensteadt.

position where the crossbridge attaches to the thin filament that has no force or strain on it. It is a strained position away from equilibrium that results in the motion that leads to muscle shortening and contraction. The speed of this motion is referred to as the sliding velocity and it is inversely proportional to the load at the end of the muscle unit.

2 Crossbridge Dynamics

In this section we take a look at crossbridge dynamics with the consideration that the rate proportionality of crossbridge attachment and detachment, α and β, are to be constants. This is a special case of the general methodology that could take into account α and β as functions of displacement x. We will derive theoretical equations to model this behavior and also briefly discuss a stochastic computational model.

2.1 Theoretical Model

The crossbridge has an equilibrium position where it exerts zero force on the thin filament. We take this equilibrium position to be $x = 0$ where x is the displacement from equilibrium. Let $p(x)$ be the force exerted on the thin filament by a crossbridge at position x. As stated above, $p(0) = 0$. Let n_0 be the total number of crossbridges in half a sarcomere. We introduce $u(x)$ as the population density function for crossbridges as a function of displacement.

The fraction of attached crossbridges with displacements $x \in (x_1, x_2)$ is given by

$$\int_{x_1}^{x_2} u(x)dx \tag{1}$$

which means that the total fraction of crossbridges attached is given by

$$U = \int_{-\infty}^{\infty} u(x)dx. \tag{2}$$

The number of crossbridges within an infitesmally small interval dx is given by $n_0u(x)dx$ and the force exerted on the thin filament by those crossbridges is $p(x)n_0u(x)dx$ and integrating over the entire region gives the total force:

$$P = n_0 \int_{-\infty}^{\infty} p(x)u(x)dx \tag{3}$$

In order to quantitatively describe the sequence of crossbridge attachment, sliding and detachment (crossbridge cycle) we begin by noting that the number of unattached crossbridges is $n_0(1 - U)$ since $1 - U$ is the proportion of unattached crossbridges. Let α be the rate constant of attachment of the crossbridges. Then $\alpha n_0(1 - U)$ is the rate of attachment of new crossbridges in half a sarcomere. We define movement or sliding of the crossbridges in the negative x direction to denote positive velocity v since we defined v as the shortening velocity:

$$\frac{-dx}{dt} = v \tag{4}$$

Let the rate of attachment of the crossbridges be independent of the position of attachment. There are two ways that crossbridges can leave the thin filament. One is by detaching, where β is the rate constant of detachment, and the other is by sliding past a lower bound x_0. The rate of detachment would thus be the sum of the rates at which these two processes occur by (assume crossbridges are formed at $x = A$):

$$\beta n_0 \int_{x_0}^{A} u(x)dx + vn_0u(x_0) \tag{5}$$

The steady-state assumption we make for this model is that the rate of attachment of the crossbridges is equal to the rate of detachment and sliding off of the crossbridges:

$$n_0\alpha(1 - U) = \beta n_0 \int_{x_0}^{A} u(x)dx + vn_0u(x_0) \tag{6}$$

Dividing by n_0 yields:

$$\alpha(1-U) = \beta \int_{x_0}^{A} u(x)dx + vu(x_0) \tag{7}$$

Taking the derivative and simplifying gives the following:

$$\beta u = v\frac{du}{dx} \tag{8}$$

The solution to this ODE takes the following form:

$$u(x) = u(A)e^{\frac{\beta(x-A)}{v}} \tag{9}$$

To solve for $u(A)$ we take $x_0 \to A$ in (5):

$$u(A) = \frac{\alpha(1-U)}{v} \tag{10}$$

To solve explicitly for U, integrating (9) gives:

$$U = \int_{-\infty}^{A} u(x)dx = \frac{vu(A)}{\beta} \tag{11}$$

This gives the following system of equations:

$$U = \frac{\alpha}{\alpha+\beta} \tag{12}$$

$$u(A) = \frac{\alpha\beta}{v(\alpha+\beta)} \tag{13}$$

The 2×2 linear system has the following solution for $x < A$:

$$u(x) = \frac{e^{\frac{\beta(x-A)}{v}}}{v(\alpha+\beta)}\alpha\beta \tag{14}$$

Using this explicit statement for the population density of the crossbridges we can write the force equation:

$$P = \frac{\alpha\beta}{v(\alpha+\beta)} \int_{-\infty}^{A} n_0 p(x) e^{\frac{\beta(x-A)}{v}} dx \tag{15}$$

We hypothesize that $p(x)$ is of the exponential form:

$$p(x) = p_1(e^{\gamma x} - 1) \tag{16}$$

Plugging (16) into (15) yields a relationship between force and velocity in terms of known parameters:

$$P = \frac{\alpha n_0 p_1}{\alpha+\beta} \frac{(e^{\gamma A} - 1) - (\gamma v/\beta)}{1 + \gamma v/\beta} \tag{17}$$

This will be used to produce a Force Velocity plot with velocity v treated as a given.

2.2 Computational Model

For the computational model of the stochastic process of the crossbridge interactions, we use what is often called a Monte Carlo simulation because it implements the use of random numbers. As above, we take n_0 to be the total number of crossbridges in a half sarcomere. Let $i = 1, ..., n_0$ index each of the crossbridges in the half sarcomere. We use an indicator function to represent the two possible states of the crossbridge i:

$$\mathbf{1}(i) = \begin{cases} 0 & \text{if attached} \\ 1 & \text{if detached} \end{cases} \tag{18}$$

Let $x(i)$ be the displacement from equilibrium of crossbridge i. When $x(i) > 0$ ($x(i) < 0$) the force exerted by that crossbridge is positive (negative). The total force P generated is the sum of the individual forces p of each crossbridge at their various locations:

$$P = \sum_{i=1}^{n_0} p(x(i)) \tag{19}$$

The process where the indicator function changes from a value of 1 to 0 and vise versa is a random one independent for the different crossbridges. In a short time interval Δtwe shall assume that a detached cross bridge has a probability $\alpha \Delta t$ of attaching, and that an attached crossbridge has a probability $\beta \Delta t$ of detaching. We use a pseudo random number generator to choose a random number on the uniformly distributed interval $(0, 1)$ and the range that the number falls in will determine if a crossbridge switches states or not.

3 Results

In order to achieve accurate results we must run the simulation long enough for the value of P, and U to equilibrate for a given v:

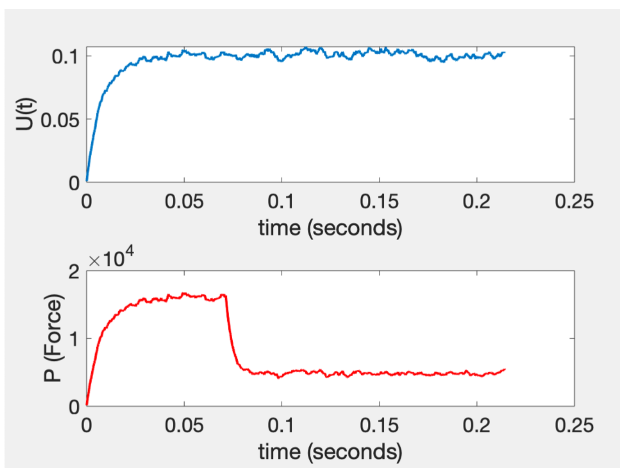

Figure 2: The graph above shows U (the proportion of attached crossbridges) and P (the total force exerted by the family of crossbridges) as functions of time, equilibrating to a steady value. Run for a half sarcomere population of 10,000

It can be seen that there is a lot of noise in the data. These are fluctuations due to the random nature of the computational simulation. We can minimize the noise by either decreasing the time interval that we run the simulation with dt or by increasing the population size of the crossbridges:

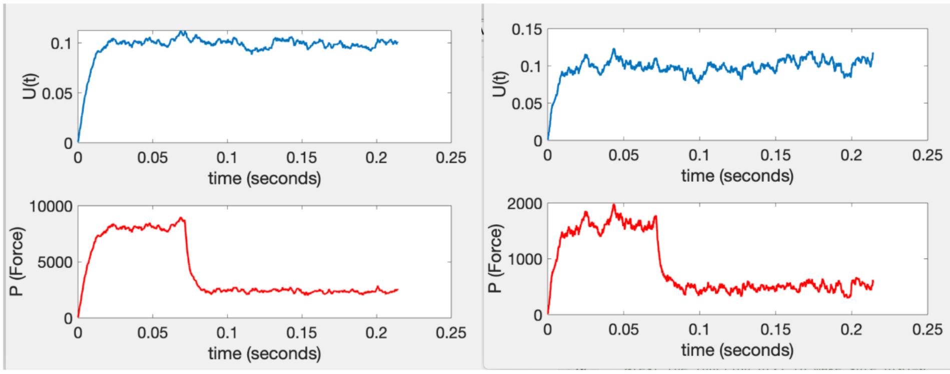

Figure 3: Left figures have a population size of 5000 and right figures have a population size of 1000. As the population size decreases, the noise increases.

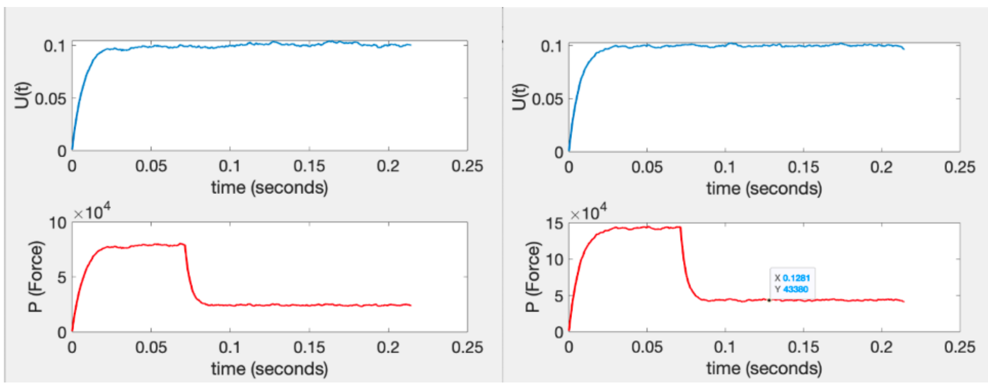

Figure 4: Left figures have a population size of 50,000 and right figures have a population size of 90,000. As the population size increases, the noise decreases.

Now we can plot the force-velocity curve of the crossbridges and compare it with the theory we developed earlier.

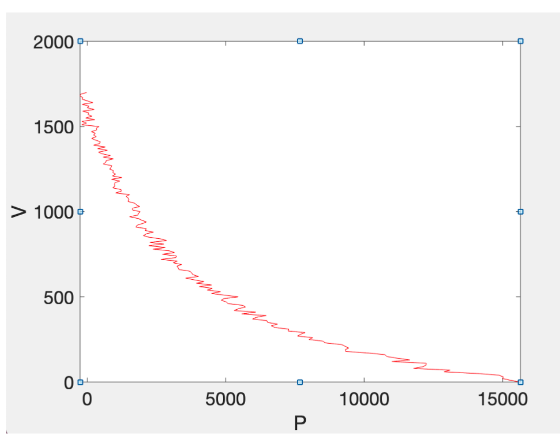

Figure 5: Force velocity curve for a crossbridge population size of 10,000 resulting from the computational model. Taken for a range of given velocities.

The computational model has the qualitative characteristics where the max velocity comes at zero force and the larger the force is the slower the shortening velocity. If our theory is correct, then the force-velocity curve using (17) should result in an identical plot to figure 5, but with no noise:

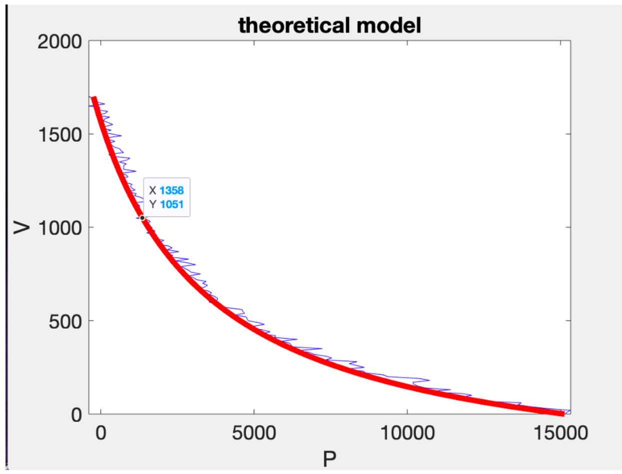

Figure 6: Force-velocity curve: theoretical plot (solid red) and computational model (blue).

In this force-velocity curve we see that the theoretical plot is identical to the curve shown by the compuational model, confirming our theory.