A Mathematical Model of the Neuromuscular Junction and Muscle Force Generation in the Pathological Condition Myasthenia Gravis

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Abstract

At the neuromuscular junction, motor neurons stimulate muscle fibers to contract through many detailed processes. This paper discusses a model to connect the many processes involved in muscle contraction from the electrical activity of nerve impulses to the mechanical force generation. Through the use of differential equations to describe calcium dynamics and muscle force, coupled to end plate potentials at the neuromuscular junction, we model this process in both a healthy system and a damaged system. As an application of our model, we focus on the neuromuscular disease myasthenia gravis and how it affects muscle force generation in our model, as well as the effect of acetylcholinesterase inhibiting treatment.

1 Introduction

Figure 1: The neuromuscular junction.

Our goal is to design a mathematical model that bridges the gap between the electrical activity of neurons and the mechanical action of muscle contraction. This so-called “gap” is known as the neuromuscular junction (Figure 1), an important biological feature in humans, as well as other animals, that allows for the transmission of signals from a motor neuron to a muscle fiber [7]. The motor neuron axon is a long projection of the motor neuron that conducts electrical

1
impulses known as action potentials. At every muscle fiber a neuromuscular junction exists, where the motor neuron axon releases synaptic vesicles, each containing a ‘quantum’ of the neurotransmitter. In mammals, the neurotransmitter is acetylcholine and each ‘quantum’ contains approximately 10,000 molecules of acetylcholine [6]. Upon the arrival of a single neuronal action potential, a number of quanta are released. Once released, acetylcholine crosses the synaptic cleft, the gap between the motor neuron axon and the muscle fiber, and binds to acetylcholine receptors on ion channels on the motor end plate, a folded area of the muscle fiber membrane [3]. This allows the channels to open and exchange ions, causing a depolarization, or end plate potential (EPP), at the motor end plate, which generates an action potential in the muscle fiber [7]. The action potential propagates across the muscle fiber membrane and down extensions of the membrane that connect the surface to the center of the muscle fiber [3]. At the center, the sarcoplasmic reticulum (SR), which is a network of tubules that regulate calcium concentration, then releases calcium so that calcium can bind to contractile filaments in the muscle fiber. The binding of calcium to the contractile filaments (CF) causes a shift in these filaments which allows them to bind to each other and contract [3]. The simultaneous contraction of many muscle fibers is what generates force and allows the movement of muscles.

Unfortunately, there are many places where this complex process of neuromuscular transmission can go wrong, and thus there exist a variety of neuromuscular diseases [3]. Myasthenia gravis is a neuromuscular disease known for fluctuating muscle weakness and fatigue [6]. Most patients with myasthenia gravis have autoantibodies that attack the acetylcholine receptors on the motor end plate of the neuromuscular junction [6]. As the acetylcholine receptors are attacked, less ion channels are activated, which results in a smaller, insufficient EPP [1]. As the EPP does not reach the threshold to activate an action potential in the muscle fiber, the muscle does not generate enough force and the patient will experience muscle weakness. The main treatments for this type of myasthenia gravis are acetylcholinesterase inhibiting drugs [6]. As acetylcholinesterase is the protein that breaks down acetylcholine molecules at the neuromuscular junction [3], the treatment inhibits this protein in an effort to prolong the binding time of acetylcholine and enhance neuromuscular transmission [6]. In addition to designing a model, it is our goal to use this model to investigate mechanisms of the neuromuscular disease myasthenia gravis and its treatment.

Many spiking neuron models exist and are used to describe electrical impulses generated by motor neurons. In addition, several mechanochemical models exist for muscle contraction in response to those incoming signals, like the work of Williams et al. [9]. We designed one cohesive model to describe how electrical impulses from motor neurons lead to muscle contraction and force generation. Our model consists of three main components, including: (1) neuronal action potential and neurotransmitter release (2) end plate potential (EPP) and muscle fiber activity (3) calcium dynamics and muscle contraction. We start by working backwards from muscle contraction to neuronal action potentials. We then apply this model under the conditions of myasthenia gravis to observe the effects of the disease and the acetylcholinesterase inhibiting treatment.

2 Mathematical Model

2.1 Model of Calcium Dynamics and Muscle Contraction

The calcium dynamics and muscle contraction part of our model is based on the work of Williams, which appears in McMillen et al. [5] and Williams et al. [9]. The model uses simple mass action kinetics to describe calcium dynamics in the muscle. Mass action kinetics proposes that the rate of a chemical reaction is directly proportional to the concentration of the reactants. Figure 2 shows the rates of calcium release from the SR, of calcium binding to the CF, of calcium unbinding from the CF, and of calcium rebinding to the SR, as rates dependent on the concentrations of calcium, SR binding sites, and CF binding sites. Williams deviates from simple mass action kinetics by having $k_1$, the rate constant for release of calcium from the SR, equal to zero when the stimulus is off, and $k_2$, the rate constant for binding of calcium to the SR, equal to zero when the stimulus is on. In addition, in order to account for cooperativity in the release of calcium from the CF, the rate of release is made proportional to the concentrations of both bound and unbound CF sites with rate constant $k_1$.

These rates and their modifications from simple mass action kinetics lead to the following differential equations:
\[
\frac{dc}{dt} = k_1[cs] - k_2[c][s] - k_3[c][f] + k_4[cf][f], \quad (1)
\]
\[
\frac{d[cs]}{dt} = -k_1[cs] + k_2[c][s], \quad (2)
\]
\[
\frac{d[s]}{dt} = k_1[cs] - k_2[c][s], \quad (3)
\]
\[
\frac{d[cf]}{dt} = k_3[c][f] - k_4[cf][f], \quad (4)
\]
\[
\frac{d[f]}{dt} = -k_3[c][f] + k_4[cf][f], \quad (5)
\]

where \([c]\) is the concentration of free calcium ions, \([s]\) is the concentration of unbound SR calcium-binding sites, \([f]\) is the concentration of unbound CF calcium-binding sites, \([cs]\) is the concentration of calcium-bound SR sites, \([cf]\) is the concentration of calcium-bound CF sites, and \(k_1 - k_4\) are rate constants for binding and release.

Assuming the total amount of calcium is constant, as is the total number of bound and unbound SR and CF sites, the following conservation laws arise:

\[
[c] + [cs] + [cf] = C, \quad (6)
\]
\[
[s] + [cs] = S, \quad (7)
\]
\[
[f] + [cf] = F \quad (8)
\]

where \(C\) is the total amount of calcium, \(S\) is the total number of SR sites, and \(F\) is the total number of CF sites.

Scaling by \(F\), we introduce the new variables:

\[
Ca f = [cf]/F, \quad (9)
\]
\[
Ca = [c]/F, \quad (10)
\]
\[
\tilde{C} = C/F, \quad (11)
\]
\[
\tilde{S} = S/F. \quad (12)
\]

As the number of bound filament sites cannot exceed \(F\), \(Ca f \leq 1\) and \(Ca \leq C\) \([5]\).

Combining Equations 1-12, we simplify the system to only two equations describing free calcium ions and calcium-bound CF sites, respectively:

\[
\frac{d(Ca)}{dt} = (k_4Ca f - k_3Ca)(1 - Ca f) + k_1(\tilde{C} - Ca - Ca f) + k_2Ca(\tilde{C} - \tilde{S} - Ca - Ca f), \quad (13)
\]
\[
\frac{d(Caf)}{dt} = -(k_4Ca f - k_3Ca)(1 - Ca f), \quad (14)
\]

where \(k_1\) is zero when the tetanic stimulus is off and \(k_2\) is zero when the tetanic stimulus in on.
There exist several models to couple the calcium kinetics with the mechanical action of the muscle. Following Williams, we use the Hill formulation [2] where the muscle is modeled as a contractile element connected in series with a linearly elastic spring element, as seen in Figure 3. The contractile element is activated by the release of calcium ions from the SR, while the elastic spring element is a passive component. Hill’s model [2] says that the total length of the muscle \( L \) is equivalent to the length of the elastic spring element \( l_s \) plus the length of the contractile element \( l_c \):

\[
L = l_s + l_c. \tag{15}
\]

We assume the linearly elastic spring element satisfies Hooke’s Law, which describes the force of a linear spring when it is stretched:

\[
P_s = \mu_s (l_s - l_{s0}), \tag{16}
\]

where \( P_s \) is the force exerted by the elastic spring element, \( \mu_s \) is the stiffness constant of the elastic spring element, \( l_s \) is the length of the elastic spring element, and \( l_{s0} \) is the resting length of the elastic spring element.

By combining Equations 15 and 16, we derive the following equation for the length of the contractile element:

\[
l_c(t) = L(t) - l_{s0} - P_s(t)/\mu_x. \tag{17}
\]

By taking the time derivative of Equation 17, we get the following equation for the velocity of the contractile element:

\[
v_c(t) = V(t) - (dP_s/dt)/\mu_x, \tag{18}
\]

where \( V(t) \) and \( v_c(t) \) are the time derivatives of \( L(t) \) and \( l_c(t) \), respectively. For simplicity, we focus on an isometric contraction, in which tension is generated without changing the length of the muscle. Thus, we assume \( L(t) \) is a constant, and consequently \( V(t) \) is equal to zero.

We assume that the force \( (P_c) \) exerted by the contractile element can be described by independent factors of its length \( (l_c) \) and velocity \( (v_c) \), as McMillen does [5]. As the binding of calcium to the CF is what allows the filaments to contract, the force \( (P_c) \) is also dependent on the amount of calcium-bound CF sites \( (Caf) \). Therefore, the equation for the force of the contractile element is:

\[
P_c = P_o \lambda(l_c)\alpha(v_c)Caf, \tag{19}
\]

where \( P_o \) is the peak force in an isometric tetanic contraction at the optimum length \( l_{c0} \). The functions \( \lambda(l_c) \) and \( \alpha(v_c) \) are estimated from force measurements in Williams et al. [9], where experiments were performed using a tetanic stimulus on a lamprey muscle. Because a positive velocity means that the muscle fiber is lengthening, while a negative
velocity means that the muscle fiber is shortening, we assume the function $\alpha(v_c)$ to be piecewise linear for simplicity, as Williams does [9]. Therefore, the equations for $\lambda(l_c)$ and $\alpha(v_c)$ are:

$$\lambda(l_c) = 1 + \lambda_1(l_c - l_{co})^2,$$

$$\alpha(v_c) = 1 + \begin{cases} \alpha_m v_c & \text{if } v_c < 0 \\ \alpha_p v_c & \text{if } v_c \geq 0 \end{cases},$$

where $l_{co}$ is the optimum length of the contractile element. In addition, we restrict these functions so that $0 \leq \alpha(v_c) \leq \alpha_{max}$ and $0 \leq \lambda(l_c) \leq 1$. The fact that $\alpha_p > \alpha_m > 0$ (see Table 1) reflects the ability of muscle fibers to exert progressively greater forces during lengthening than during shortening [9].

The forces $P_s$ and $P_c$ must be equal in the steady state since the linearly elastic spring element and the contractile element are connected in series. However, if $P_s = P_c$ then Equations 18 and 19 reduce to one expression for $v_c$, which depends on the derivatives of Equations 20 and 21. As Equation 21 is not differentiable when $v_c = 0$, this would result in an instability in our equations. Furthermore, in reality the stretch of the elastic spring element from the activation of the contractile element is not instantaneous [3]. Therefore, we assume the transfer of force to be modeled by simple linear kinetics:

$$\frac{dP}{dt} = k_5(P_c - P_s),$$

where $P$ is the total force exerted by the entire muscle, and $k_5$ is chosen large enough so that $P_s$ and $P_c$ are nearly identical.

Combining Equations 15-22, we get one more differential equation describing the total muscle force in addition to Equations 13 and 14:

$$\frac{dP}{dt} = k_5\mu(P_c\lambda C_{af}(1 + \alpha_1 V) - P/(\mu + k_5 P_c \lambda \alpha_1 C_{af}),$$

where $\alpha_1 = \alpha_m$ if $v_c < 0$ or $\alpha_1 = \alpha_p$ if $v_c \geq 0$.

Therefore, we are left with a system of three differential equations describing free calcium ions (Equation 13), calcium-bound CF sites (Equation 14), and the total muscle force (Equation 23):

$$\frac{d(Ca)}{dt} = (k_4 C_{af} - k_3 C_a)(1 - C_{af}) + k_1(\tilde{C} - C_a - C_{af}) + k_2 C_a(\tilde{C} - \tilde{S} - C_a - C_{af}),$$

$$\frac{d(C_{af})}{dt} = -(k_4 C_{af} - k_3 C_a)(1 - C_{af}),$$

$$\frac{dP}{dt} = k_5\mu(P_c\lambda C_{af}(1 + \alpha_1 V) - P/(\mu + k_5 P_c \lambda \alpha_1 C_{af}).$$

The three equations are coupled together as both free calcium ions and calcium-bound CF sites depend on the concentrations of each other, and the force depends on the concentration of calcium-bound CF sites. Thus, the amount of free calcium ions ($C_a$), the amount of calcium-bound CF sites ($C_{af}$), and the amount of muscle force generated ($P$) are the unknowns of the system. The parameters of the system are provided in Table 1.

### 2.2 Model of End Plate Potential (EPP) and Muscle Fiber Activity

A muscle fiber action potential produces changes in muscle fiber voltage, which triggers the release of calcium ions from the SR [3]. We created a stimulus to represent this change in muscle fiber voltage by directly relating the voltage changes to the amount of calcium released from the SR, which is described by the rate constant $k_1$. We designed $k_1$ to be a function of time so that we can control the form and frequency of the stimulus. Similarly, we designed $k_2$, the rate constant for the binding of calcium to the SR, to be a function dependent on $k_1$, since $k_2$ is “off” when $k_1$ is “on”, as assumed by Williams. The models of McMillen et al. [5] and Williams et al. [9] both use a tetanic stimulus, which is a high-frequency sequence of individual stimulations from a neuron [9]. In our model, we used a square wave stimulus, representing this tetanic stimulus, as well as an exponential stimulus, modeling individual electrical impulses.
The equations for $k_1$ and $k_2$ for a square wave stimulus are:

$$k_1 = \begin{cases} k_{10} & \text{if } t_{on} < t < t_{off} \\ 0 & \text{otherwise} \end{cases},$$

$$k_2 = \begin{cases} k_{20} & \text{if } k_1 = 0 \\ 0 & \text{otherwise} \end{cases},$$

where $k_{10}$ is the value of $k_1$ when the stimulus is on, $k_{20}$ is the value of $k_2$ when the stimulus is off, $t_{on}$ is the time that the stimulus turns on, and $t_{off}$ is the time that the stimulus turns off. The equations for $k_1$ and $k_2$ for an exponential stimulus are:

$$k_1 = k_{10} \exp \left( -\frac{t - t_p}{\tau} \right),$$

$$k_2 = \begin{cases} k_{20} & \text{if } |\frac{dk_1}{dt}| < tol \\ 0 & \text{otherwise} \end{cases},$$

where $t_p$ is the time of the stimulation impulse, $\tau$ is the decay time constant for the exponential, and $tol$ is the tolerance for the slope of $k_1$. With an exponential stimulus, $k_1$ is no longer all or nothing (on/off). Therefore, $k_{10}$ is the maximum value of $k_1$, as the values for $k_1$ change with exponential decay. As the exponential decay of $k_1$ never reaches zero, $k_2$ is designed to be on when the slope of $k_1$ is very small, which indicates that $k_1$ values are close to zero. Therefore, $k_{20}$ is the value of $k_2$ when the slope of $k_1$ is less than the tolerance. See Table 1 for a list of parameter values.

We want to relate these muscle fiber voltage equations ($k_1,k_2$) to the EPP produced from the activation of ion channels bound by acetylcholine. For a single neuronal action potential, enough quanta of acetylcholine are released to generate an EPP above the threshold to initiate an action potential in the muscle fiber [3]. The EPP is a sum of the miniature end plate potentials (mEPPs) that each quantum generates [3]. We model each mEPP as an exponential:

$$m k_1 = m k_{10} \exp \left( -\frac{t - t_p}{\tau_q} \right),$$

where $m k_{10}$ is the value for $k_{10}$ divided by the number of quanta released ($M$), and either $q = n$ under normal conditions or $q = a$ under acetylcholinesterase inhibiting treatment. Values for $M$, $\tau_n$, $\tau_a$ are provided in Table 1. We then model the EPP as a sum of the mEPPs for each quantum, thus modifying Equation 26 to be:

$$k_1 = \sum_{i=1}^{M} m k_{10} \exp \left( -\frac{t - t_p}{\tau_q(i)} \right),$$

where $M$ is the number of quanta released, and $\tau_q(i)$ is the decay time constant for the $i^{th}$ mEPP.

### 2.3 Connection between Neuronal Action Potential and Neurotransmitter Release

A single neuronal action potential is enough to generate an action potential in the muscle fiber. Humans release only about 20 quanta for one neuronal action potential [7]. We designed our model to input the amount of quanta released ($M$) from a single neuronal action potential, as seen in Equation 29. We also designed our model with the ability to control the frequency of the nerve impulses to observe the effects of multiple neuronal action potentials.

At healthy human motor end plates, a single quantum opens approximately 1,500 ion channels [1]. However, in myasthenia gravis, where acetylcholine receptors on the ion channels are not working properly, a single quantum opens only about 600 channels [1]. The same amount of quanta is released in myasthenia gravis as in healthy conditions, despite the fact that the amount of ion channels activated is less than normal. Therefore in our model for myasthenia gravis, $M$ does not change, but rather 60% of the mEPPs generated are equal to 0 mV, which results in a smaller EPP that is below the threshold to initiate a muscle fiber action potential. Treatment of myasthenia gravis with
acetylcholinesterase inhibitors has been found to increase the decay time constant of the EPP, as recorded in the work of Cull-Candy et al. [1]. We model the treatment by changing the decay time constant for each mEPP from $\tau_n$ (normal) to $\tau_a$ (treated) where $\tau_a$ is a randomly generated value within a particular range, as seen in Table 1. This increase in the decay time constant represents the extended duration that acetylcholine molecules are able to bind to receptors on the ion channels while acetylcholinesterase inhibiting drugs are present.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>$k_{10}$</td>
<td>9.6 s$^{-1}$</td>
<td>McMillen et al. [5]</td>
</tr>
<tr>
<td>$k_{20}$</td>
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<td>McMillen et al. [5]</td>
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<td>McMillen et al. [5]</td>
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<td>$k_5$</td>
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<td>McMillen et al. [5]</td>
</tr>
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<td>McMillen et al. [5]</td>
</tr>
<tr>
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</tr>
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<td>600 mN/mm</td>
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<tr>
<td>$M$</td>
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<td>My value (based on Slater et al. [7])</td>
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Table 1: Model parameters used in simulations.

3 Results

3.1 Qualitative Comparison of Model

In our simulations, we use both a square wave stimulus and an exponential stimulus (coupled to EPPs and mEPPs) to compare the results to each other as well as to the results from similar models. Figure 4 shows the force and calcium dynamics of each type of stimulus using our model for muscle contraction. To confirm that our model is behaving according to what we expect biologically, we plot the effect of varying parameter values and determine their biological significance. In Figure 5, we observe that as the rate constant for the unbinding of calcium from the SR, $k_1$, increases, the free calcium directly increases, and consequently the filament-bound calcium and the force generation increase as well, which is what we would biologically expect. As the rate constant for the binding of calcium to the SR, $k_2$, increases, the free calcium directly decreases, and consequently the filament-bound calcium and the force generation decrease as well, which is what we would biologically expect as well. As the rate constant for the binding of calcium to the CF, $k_3$, increases, the filament-bound calcium directly increases, and consequently the force generation increases as well, which is what we would biologically expect. For large values, this parameter causes the force to peak again before...
Figure 4: Free calcium, filament-bound calcium, velocity of the contractile element, and muscle force generation for (A) a square stimulus and (B) an exponential stimulus using our model for muscle contraction. All variables are normalized except for time, which is in seconds. Forces ($P$) are given as fractions of $P_o$ and velocities ($v_c$) are given as fractions of $L_o$, where $L_o = l_{co} + l_{so} + P_o/\mu$ (see Table 1).

Figure 5: Parameter effects on muscle force generation. (A)-(D) Observing the effects of increasing the rate constants $k_1$-$k_4$ over a range of values, in which the lowest values are represented in blue and the highest values are represented in green. The arrow on each plot represents the direction in which the respective parameter value is increasing.

its value falls back down to zero, thus representing a muscle that is constantly contracted. As the rate constant for
the unbinding of calcium from the CF, \( k_4 \), increases, the filament-bound calcium directly decreases, and consequently the force generation decreases as well, which is what we would biologically expect. For small values, this parameter causes the force to peak again before its value falls back down to zero, thus representing a muscle that is constantly contracted. As our rate constants and other parameters behave the way we would biologically expect them to when they are varied, we believe that our model is producing output that qualitatively captures certain biological phenomena of muscle contraction.

Figure 6: Effects of varying length on muscle force. Stimulus was applied for 0.36 seconds for each length in both plots. (A) Force at 3 lengths (2.5 mm, 2.7 mm, 2.9 mm), produced by our model with a square stimulus. (B) Force at 3 lengths with a similar tetanic stimulus. Taken from McMillen et al. [5].

We then compare our simulation results to the results presented by other models in order to determine whether our simulation is producing the desired output. We plot the force for three different muscle lengths using our square wave stimulus, which represents the tetanic stimulus used by McMillen et al. [5]. We then compare our force plots to the force plots produced by McMillen et al. [5] for the same three muscle lengths. Figure 6 shows for both simulations how the force generated increases as the length of the muscle increases. Because our force plots are very similar to the force plots of the McMillen et al. simulation [5], we believe our simulation is producing the desired output while using a square wave stimulus.

However, the McMillen et al. model [5], as well as the Williams et al. model [9], assumes only a tetanic stimulus, rather than individual impulses from a neuron. Therefore, in order to evaluate our force plots using an exponential stimulus we compare our results to the force plots of the Kim et al. model [4], which is a completely different model but uses a similar exponential stimulus. Figure 7 shows how the force generated increases as the frequency of the stimuli is increased in both our simulation and the simulation of the Kim et al. model [4]. By frequency, we mean the rate at which individual impulses are signaled from the motor neuron, as seen in part (A) of Figure 7. In general our force plots look similar to the results of Kim et al. [4], and our model was able to capture the phenomenon of the force building over a series of impulses, as seen in our 10 Hz force plot (Figure 7). However, our 20 Hz and 40 Hz force plots are larger and not as plateaued as the force plots of Kim et al. [4]. This difference in our simulation results is most likely due to the fact that Kim et al. [4] uses a completely different model with a different system of equations than what we use in our model. In addition, the exponential stimulus of the Kim et al. model [4] uses time constants for...
both rise and decay, while our model’s exponential stimulus only uses a decay time constant. Therefore, our stimulus has a higher peak and a more drastic decline, which can account for the larger force values and the less plateaued force
plots. However, as we increase the frequency for our simulation, our force plots become more plateaued and look a lot more like the results of Kim et al. [4]. Therefore, we believe our simulation is producing the desired output while using an exponential stimulus.

Figure 4 shows the differences between our results while using a square wave stimulus and our results while using an exponential stimulus. The exponential stimulus was designed to observe individual nerve impulses, unlike the square wave which represents a constant tetanic stimulus. Thus, we want to know if this exponential stimulus can capture certain biological phenomena better than a square wave stimulus can, given its unique abilities. When we compare our simulation results using a square wave stimulus to the results of Kim et al. [4], we do not get similar force plots and we cannot capture the phenomenon of the force building over a series of impulses like we can with an exponential stimulus. Therefore, we believe our exponential stimulus (coupled to EPPs and mEPPs) provides a more realistic representation of force generation, as it is able to capture certain phenomena of muscle contraction, like impulse frequency dependence, better than a square wave stimulus can.

3.2 Validation of Numerical Method

Even if our model is producing results that are qualitatively comparable to other models, the question still remains whether our numerical method of forward Euler is accurately solving the system of differential equations. We performed a self-convergence test on the simulation to determine the rate of convergence of the error for different time step values. We define the error as the absolute value of the difference between our solution and the solution for the finest time step (0.00005 s). Table 2 shows the errors at the same location (near the middle) in time and their convergence rates. As the errors are fairly small and the rates are close to one, we believe that the forward Euler method is being properly implemented and our method is accurately approximating the solution.

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<td>4.4875 x 10^{-5}</td>
</tr>
</tbody>
</table>

Table 2: Convergence with Exponential Stimulus. Table shows the errors and rates of convergence of the error for our model’s solutions (free calcium, filament-bound calcium, force) for 5 different time step (dt) values using an exponential stimulus. Errors are calculated by taking the absolute value of the difference between our solution at each time step value and the solution for the finest time step (0.00005 s). The convergence rate is calculated by dividing the binary logarithm of the error for a certain time step by that of the previous time step.

In Figure 8, we plot the binary logarithm of each time step value against the binary logarithm of the error produced from each time step value, and observe the trend of a slope that is very close to one. As we expect our model to have a convergence rate of one, a slope of one indicates that the numerical method is accurately solving the system of equations and converging accordingly.

3.3 Application to Myasthenia Gravis

Using our model of muscle contraction with an exponential stimulus (coupled to EPPs and mEPPs), we can observe the effects of the neuromuscular disease, myasthenia gravis, and the effects of treatment with acetylcholinesterase inhibiting drugs. In patients with myasthenia gravis, less ion channels are opened so the EPP does not reach the threshold to activate an action potential in the muscle fiber [1]. Therefore, we model the exponential stimulus for a patient with myasthenia gravis to only produce 40% of the mEPPs normally generated by a healthy person (60% equal to 0 mV), resulting in a smaller EPP that is below threshold. In Figure 9, the plots show that this decrease in the number of
mEPPs causes the height of the EPP and the force to decrease as well. Therefore, our model predicts that a patient with myasthenia gravis has a much smaller muscle force generation than a healthy person, as is expected.

The work of Cull-Candy et al. [1] describes how treatment with acetylcholinesterase inhibitors increases the decay time constant of the stimulus. Figure 9 shows the effect of treatment on the muscle force, as we increase the decay time constant of the exponential stimulus to represent the inhibition of acetylcholinesterase. Despite having a stimulus with a relatively small maximum value, the treatment is able to generate a force that is very similar to the force generated by a healthy person. However, our model does show some differences between healthy force values and treated force values. Our model indicates that the treated force takes a slightly longer time to reach its peak than a healthy force, which is an interesting trend that we hope to investigate in the future. But overall, our model can capture results seen in other studies of myasthenia gravis [1], and effectively show how treatment with acetylcholinesterase inhibiting drugs can improve muscle force generation in patients with myasthenia gravis.

4 Discussion

This model builds from the work of Williams et. al [9] and McMillen et al. [5] on calcium kinetics and muscle contraction. Rather than using only a tetanic stimulus that is either on or off at a high frequency, we added an exponential stimulus to model individual nerve impulses and control the frequency of these impulses. The exponential stimulus is able to
capture the biological phenomena of muscle force building over repeated stimulations. Furthermore, we modeled the end plate potential (EPP) as a summation of miniature end plate potentials (mEPPs) that are generated from the opening of ion channels on the motor end plate. We related the activation of these ion channels to the amount of quanta that are released upon the arrival of a neuronal action potential. We designed our model with the ability to change the frequency of the stimuli to observe the effects from the electrical activity of neurons all the way to muscle force generation. By qualitatively comparing our results to the results of similar simulations, we believe our model is reasonably describing qualitative force generation in response to nerve stimulation.

The application of our model to the neuromuscular disease myasthenia gravis, allows us to observe certain biological phenomena in the mechanisms of the disease and its treatment. Our model captures the post-synaptic behavior of the disease, as less ion channels are activated in patients with myasthenia gravis, despite having the same amount of quantal release as a healthy neuromuscular junction. Under the conditions of myasthenia gravis, our model generates an EPP below the threshold for the initiation of an muscle fiber action potential, which results in a force well below the force of a healthy person. This low force generation accounts for the muscle weakness and fatigue seen in myasthenia gravis patients. The effect of treatment is seen in our model by increasing the decay time constant of the mEPPs, thus increasing the EPP decay time. Our model supports the idea that this extension in the decay time is sufficient to return forces to normal values. In biological terms, by extending the binding time of acetylcholine, the treatment allows a greater exchange in ions, thus resulting in a larger depolarization at the motor end plate that will lead to increased force generation.

Although this model is producing desired outputs, it can certainly be improved by adding more details of neuromuscular transmission. The shortcomings of this model are attributed to the over-simplifications we made, and the many small processes that were overlooked in this complex neuromuscular system. For example, we assumed the release
of calcium from the sarcoplasmic reticulum (SR) to be directly proportional to changes in the muscle fiber voltage, which is not biologically true. In the future, we hope to improve our model to describe these mechanisms in a more biologically accurate way. We also hope to couple our current model to a spiking neuron model to show the effects of random spike trains on the system instead of manually increasing the frequency of nerve impulses. In the future we can use our model to investigate the effects of myasthenia gravis on other variables like calcium concentration, which could allow us to propose mechanisms for other possible treatments. We also hope to use our model to study a variety of other neuromuscular diseases.

In conclusion, this model is able to bridge the gap between the electrical activity of neurons and the mechanics of muscle contraction, while producing reasonable qualitative outputs for force generation. The model’s ability to qualitatively capture biological phenomena and the behavior of the neuromuscular disease myasthenia gravis, represents a contribution to the efforts to understand the complex dynamics of the neuromuscular junction and muscle force generation.

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References


