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EFFECTS OF ABSTRACTION AND ASSUMPTIONS ON MODELING

MOTONEURON POOL OUTPUT

A thesis submitted in partial fulfillment
of the requirement for the degree of
Master of Science

By

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BS in Biomedical Engineering, Wright State University, 2014

2017
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ABSTRACT


Computational modeling has long been used in neuroscience as a supplement to more traditional experimental techniques, as it provides some advantages in terms of the level and detail of control available over the system being studied. At the same time, modeling has significant disadvantages by virtue of adding additional uncertainty to results and forcing the definition of potentially unclear physiological mechanisms. Nevertheless, modeling can provide useful insights when carefully defined and constrained. In this thesis, a model of the α-MN pool innervating the cat medial gastrocnemius was constructed. This model was then used to address two major questions, one regarding modeling technique and the other physiological methods of motor control.

Regarding modeling technique, the original pool model was developed with distinct properties representing the different physiological types of α-MNs. Properties of these types were spread such that significant overlap was present between them, as shown in experimental results. However, similar models are often developed without inclusion of this feature. By removing the overlap from this model, it was shown that inclusion, or lack thereof, of electrophysiological property overlap has significant impact on model results.
Additionally, experimental evidence has shown that α-MNs of lower input resistance innervating muscles of the cat hind limb receive greater synaptic current from volitional input than do those of higher input resistance. To test the significance of this finding, a control scheme was adopted in which input to cells varied as $I_{N,S} < I_{N,FR} < I_{N,FP}$. The results of this test seem to support assertions made by others, that the size principle, which is often considered in an AHP depth and duration dependent manner, is most applicable when comparing to *in vitro* electrical stimulation, and that an “onion-skin” pattern of recruitment, in which the fastest-firing units are recruited first, is more applicable when considering volitional input.
ACKNOWLEDGEMENTS

It is probably not possible to account for everyone who has helped me make it to this point, but I would be remiss not to provide some highlights. First, I would like to thank Dr. Larry Ream, for being one of many to take a chance on me, and giving me the opportunity to join this wonderful program. I would also like to thank the other professors teaching the core courses for providing me with a strong foundation for understanding what I have needed to in order develop this project.

When I first showed up in Dr. Sherif Elbasiouny’s office almost three years ago with only a vague idea of what I might want to do, I was surprised when he was willing to let come on board. He also took a big chance with me, and for that, along with his consistent support and encouragement since, I would like to thank him. As for the other members of the Elbasiouny lab, there are frankly too many of us to acknowledge everyone in the fashion they deserve, but I would like to thank them all. Whether providing help with understanding some concept or another, or just a good conversation or a laugh, their contributions cannot be overstated.

Without extensive consultation from Dr. Ted Carnevale at Yale as I got things running on supercomputer architecture, a lot of these simulations would probably still be very slowly running on a dusty PC somewhere; thanks are due to him for his many insights. I would also like to thank my committee members Drs. Mark Rich and Nasser Kashou for their feedback, and willingness to listen as I stammer through trying to explain two years of work in half an hour.

I would also like to thank Shae for her unfailing patience and support throughout this journey. I told her 7 years ago that I wanted to go back to school for a few years to get my bachelor’s degree, an increasingly inaccurate statement as time goes on, but she still seems willing to go along with it. Maybe I’ll shock her and actually be finished someday.

As of this writing, it has been something like two weeks since I last properly slept, so it is almost a certainty that I forgot someone who I mean to thank here. If I forgot to include you, I hope you can understand.

Finally: This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) BTO under the auspices of Dr. Doug Weber through the DARPA Contracts Management Office Contract No. HR0011-15-C-0083.
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LIST OF ABBREVIATIONS

5-HT: serotonin

α-MN: α-motoneuron

AH: Axon hillock

AHP: Afterhyperpolarization

Ca\textsubscript{v}1.3: Low-voltage activated, persistent L-type calcium channel

FTR: Failure to reject

HPC: high performance computer (supercomputer)

IS: Axon initial segment

MG: medial gastrocnemius

MU: Motor unit

NRNIV: Neuron simulation software

PIC: persistent inward current

PSD: Power spectrum density

RMP: resting membrane potential
I. BACKGROUND AND INTRODUCTION
Purpose

The ultimate purpose of the work present herein is threefold. First, it seeks to provide insight and understanding to some of the pitfalls faced by studies seeking to incorporate modeling work. While the goal is by no means to stifle the use of *in silico* methods, it is necessary to be aware of some of the risks and limitations associated with them when undertaking such studies.

Second, this thesis seeks to examine, and possibly rationalize, some inherent disparity in different findings of motor unit recruitment. In particular, the size principle (Henneman, 1957; Henneman et al, 1965) and onion-skin recruitment scheme (De Luca and Contessa, 2015) are considered.

Finally, the models presented herein are currently being used to further the development of detailed motor decoding algorithms by other laboratory personnel (unpublished work, Elbasiouny lab), which will be used in conjunction with direct peripheral nerve interfaces to control advanced prosthetics in human subjects. Although these results are not presented in this document, they represent the most immediate clinical relevance of this work.

Figure 1 provides a flow diagram outlining the overall scope of work being done for this project.
Figure 1: Flow diagram for model development and experimental protocols
Historical Context

Almost as soon as the selective ionic mechanisms underlying the action potential were described in giant squid axons (Hodgkin, et al 1949; Hodgkin and Katz, 1949), development began of mathematical and equivalent circuit models of these findings (Hodgkin and Huxley, 1952). Less than a decade later, Wilfred Rall published several papers describing how to adapt models from cable theory for use in reducing the anatomy of neurons to allow modeling study of their electrophysiological properties (Rall 1959; Rall 1962). The Rall method provided a means to reduce a large series of branching passive cables, as dendrites were thought to be at the time (Rall, 1962), to a single, finite length cable of similar electrical properties, allowing vast simplification of the models, provided certain conditions were carefully followed. Among other things, these historical examples show that, while modeling of neurons may not have existed yet when Cajal was first describing the anatomy of these cells, it has had ample time to grow and develop in tandem with our understanding of the mechanisms underlying neuronal behavior.

The rest of the 1960’s continued to bring dramatic changes to the way in which spinal motoneurons, and by extension motor units were understood. In terms of significance and lasting field impact, it is impossible to overstate the importance of the Size Principle, developed following experiments in the cat triceps surae, which states that motor units are recruited in order of size, from smallest to largest, and cease firing in the reverse of recruitment order when excitation is removed (Henneman et al, 1965). An additional significant step toward motor unit type identification, made in the same species and muscle group, in an initial distinction between fast-twitch, F-type units, and slow-twitch, S-type units was made in the cat based on the twitch properties of individual motor units (Burke,
This classification system was further expanded into a system of three distinct types: slow firing, fatigue-resistant S; fast firing, intermediate fatigue-resistant FR; and fast firing, fatigable FF based on physiological properties and histochemical staining of muscle fibers (Burke et al, 1971). This classification system was shortly thereafter extended to include the motoneurons innervating the motor units, although it required first identifying the muscle unit, the group of muscle fibers belonging to a single motor unit, and tracing these back axonally to their innervating α-MNs (Burke et al, 1973).

The three-type classification system was later adapted to allow type identification of motor units of the cat medial gastrocnemius solely based on the electrophysiological properties their α-MNs in a herculean effort (Zengel et al, 1985). Classification in this method served in some respects to complicate matters, as it was exhaustively shown that any single electrophysiological parameter was catastrophically insufficient to serve as a sole means of classification. Around the same time, 5-HT induced Ca^{2+} current responsible for plateau potentials and bistable firing in neurons was identified across multiple species (Hounsgaard and Kiehn, 1985), while anatomically-accurate computerized reconstructions of neuronal morphology were used to examine the passive properties of α-MNs (Cullheim et al, 1987). However, even in view of methodological capability to utilize fully-detailed morphology in computational procedures, a hard cap in the computational power of computers at the time served to effectively constrain models in terms of size and complexity when examining more complex properties of motor neurons; at the time, there was also the lack of a clear standard for use in computational modeling of neurons and systems thereof. Two such standards were made available in the early 1990’s: GENESIS in 1991 (Beeman et al, 1997) and NEURON in 1993 (Hines, 1993), both of which had
advantages by being both generalized and freely available to members of the scientific community. As of this writing, both GENESIS and NEURON are still in use for scientific publications, although the most recent developer-driven version of GENESIS was released in 2007.

The Ca\(^{2+}\) conductance responsible for bistable firing and plateau potentials was localized to the dendrites by its’ discoverers (Hounsgaard and Kiehn, 1993), although it was not until significantly later that more specific localization of these channels to specific regions of the dendritic arbor would occur (Elbasiouny et al, 2005; Bui et al, 2006).

In a modern context, the large existing library of data regarding the cat triceps surae, in particular the medial gastrocnenius, makes it an attractive target for modeling to extend insights from previous experiments.

**First Hypothesis: Abstractions in development of models of MN pools will have a significant impact on simulation results.**

**Background**

Any computational model is, by nature, a digital abstraction of an experimenter’s interpretation of an analog reality; in effect, a model of a model. This imposes some rather severe constraints upon the modeler. For one, a modeler is constrained by a combination of the quality and quantity of available data on the system to be modeled, as well as their own ability (or lack thereof) to perform experiments to generate further data. Additionally, access to and power of available computer resources has historically placed limits on the size and complexity of computational models. Finally, as an extension of the first constraint, models (especially large models such as those used to study biological systems)
often deal with large systems of independent, unknown variables, for which many disparate solutions can provide extremely similar results (Gutenkunst et al, 2007). Considering these limitations and confounds, many decision points throughout the modeling process require the modeler to decide whether to include greater physiological detail, or develop more simplified models with a concomitant reduction in the number of variables that might serve to confound results.

When modeling pools of α-MNs, as well as extending these models to motor units, one practice sometimes used is to develop a single model, and vary the properties of that model to encompass the entire range of cells being modeled (Heckman and Binder, 1991a; Fuglevand et al, 1993; Powers and Heckman, 2017).

Modern computational resources, such as the Neuroscience Gateway (Sivagnanam et al, 2013), serve to largely alleviate many concerns of computational speed and efficiency that might otherwise impeded the execution of large, highly detailed models of individual or grouped neurons. In addition, it has been recently shown that highly simplified models of single neurons introduce significant error when attempts are made to generating models of cells with active channels present on their dendrites (Elbasiouny, 2014). This begs the question of whether it is a worthy endeavor, or in fact absolutely necessary for models to include more the variability shown in experimental data, despite the expansion of confounds it brings.

**Hypothesis and Methods**

I hypothesized that failure to include the overlapping of electrical parameters between types of α-MNs shown experimentally when developing a model would significantly impact the results of that model. This was examined by developing a computer model of
a pool of \(\alpha\)-MNs with full type overlap, and a second version of this model which removed that overlap in a single parameter dimension.

**Second Hypothesis: Non-uniform input to motor units will violate the size principle**

**Background**

In vivo experiments in decerebrate animals have been undertaken by another group to provide, as completely as possible, a quantification of all the different inputs received by \(\alpha\)-MNs of the triceps surae muscle group in the distal hind limb of the cat (Heckman and Binder, 1991b; Powers et al, 1993; Westcott et al, 1995; Binder et al, 1998). This group of experiments was undertaken with the one stated goal of driving further modeling work to describe the relation between input and output of these neuron pools (Binder et al, 1998). While their findings regarding peripheral (Heckman and Binder, 1991b) and descending (Westcott et al, 1995) proprioceptive inputs indicated similar or only slightly non-uniform input current across all cells, their findings regarding descending volitional input were more interesting.

Descending inputs from the rubrospinal (Powers et al, 1993) and pyramidal tracts (Binder et al, 1998) were shown to vary systematically between low and high input resistance \(\alpha\)-MNs in the cat triceps surae motor pool, such that low input resistance cells received significantly more input current from these pathways than high input resistance cells. Because input resistance tends to vary such that \(R_{FF} < R_{FR} < R_S\) (Zengel et al, 1985), this could be tested by varying applied input current as \(I_{N,S} < I_{N,FR} < I_{N,FF}\).
Hypothesis and Methods

I hypothesized that non-uniform input current to a pool of cells representing a muscle of the triceps surae following the schedule described above would result in a reversal of recruitment order contrary to the size principle, as interpreted by properties obtained under electrical stimulation. This was tested by varying the synaptic input by motor unit type across a pool of α-MNs representing the cat medial gastrocnemius.
II. METHODS
MN Models

Pool model development was preceded by development of a representative model to serve as a template for each type of α-MN. Individual α-MN models were developed in Neuron version 7.4 (Carnevale and Hines, 2006), and executed on a personal computer running Microsoft Windows 7. A previously developed and published model of an FR-type α-MN (Elbasiouny et al 2005; Elbasiouny et al, 2006) was provided as a reference and an initial base point for further development.

Morphology

Detailed, type-identified, experimentally-obtained morphometric data for the dendritic arbors of cat medial gastrocnemius α-MNs, specifically S-type cell 36/4, FR-type 43/5, and FF-type 41/2, as reported by Cullheim et al (1987), were imported into NRNIV from anatomical text files. The morphological data used are available in standardized format at NeuroMorpho.org (Halavi et al, 2008) under accession numbers NMO_0604, NMO_0606, and NMO_0608. Somata of α-MNs were treated as uniform cylindrical compartments of diameter and height both equivalent to the cross-sectional area reported for these specific cells in literature: 60, 48.8, and 49.2 μm for S, FR, and FF-type α-MNs, respectively (Cullheim et al, 1987).

Additionally, AH and IS compartments were connected to the midpoint of the membrane of the soma compartment of each model (Elbasiouny et al, 2005). The AH consisted of a series of 11 conic frusta, tapering from 13 μm adjacent to the soma to 3 μm distal to the soma, over the course of a 20 μm total length, while the IS was treated as a cylindrical compartment of 3.3 μm diameter and 30 μm length which connected to the distalmost section of the AH (Elbasiouny et al, 2005; Kellerth et al, 1979). Figure 2 shows
dendritic morphology used, with S-type in a blue circle at left, FR centered in a purple circle, and FF at right in a red circle. S-type additionally includes a zoomed view of the soma, AH, and IS, with AH and IS noted by a bright blue oval.
Figure 2

Detailed morphometric data used for α-MN Models.

Dendritic morphology used for all three α-MN types with addition of somata is shown. S-type is rotated to show the addition of AH and IS, and zoomed panel further demonstrates the location of these compartments. Note: morphometric data is sized for similar visual weight across α-MN types, and is not shown on an absolute scale.
**Model Electrophysiological Properties**

Models were developed to match electrophysiological properties taken from one or both of a combination of two main datasets: Zengel et al (1985) and Hochman and McCrea (1994).

*Passive Properties*

The earliest version of each model consisted of a wholly-passive membrane applied to the morphometric data described in the preceding section. All compartments of each α-MN received the passive membrane mechanism provided by NRNIV. In all α-MN models the parameters for membrane capacitance, axial (longitudinal) resistance, and resting membrane potential were assigned values of 1 μF/cm², 70 Ω·cm, and -70 mV, respectively.

Membrane resistance was applied in a step model, with significantly lower resistance at the cell soma as compared to the dendrites. This resistance distribution has been shown to provide similar fidelity in reproducing experimental results as compared to a sigmoidal distribution in which resistance increases with distance from the soma, and significantly better results as compared to a uniform membrane resistance model (Fleshman et al, 1988). Membrane resistance for the AH and IS compartments was treated as equivalent to that of the soma compartment (Elbasiouny et al, 2005). Furthermore, membrane resistance varied between α-MN types, as well as the ratio of resistance between somatic and dendritic compartments (Fleshman et al, 1988). Values for passive properties are included in Table 1.
Values used for membrane resistance were tested and adjusted by measuring $\alpha$-MN input resistance ($R_N$) and time constant ($\tau_0$) in ms as observed at the soma. Input resistance was measured by placing a member of the impedance object class at the center of the soma compartment, and measuring as input resistance the value of this object. The results obtained from this method of measurement were found to be equivalent to those obtained using a steady state somatic current clamp and the resulting voltage displacement to measure input resistance. Time constant was measured by injecting a hyperpolarizing current spike to the cell soma, then graphical peeling the of the somatic voltage trace during return to RMP (Rall, 1969).
Table 1

α-MN Model Properties

Passive membrane and active channel conductance values used for all model α-MNs are shown. Ranges are provided for values which were varied within cell type. Only active channels included in each section are listed with that section.
<table>
<thead>
<tr>
<th></th>
<th>S Cells</th>
<th>FR Cells</th>
<th>FF Cells</th>
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<tbody>
<tr>
<td><strong>Somatic Properties</strong></td>
<td></td>
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<tr>
<td>$R_m$ (Ω)</td>
<td>230-496</td>
<td>77.9-245</td>
<td>22-94</td>
</tr>
<tr>
<td>$\overline{g}$ Naf (S/cm$^2$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\overline{g}$ Kdr (S/cm$^2$)</td>
<td></td>
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<tr>
<td>$\overline{g}$ K(Ca) (S/cm$^2$)</td>
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<tr>
<td>$\overline{g}$ CaN (S/cm$^2$)</td>
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<tr>
<td><strong>Axon Hillock &amp; Initial Segment</strong></td>
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<td></td>
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<tr>
<td>$R_m$ (Ω)</td>
<td>230-496</td>
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<td>$\overline{g}$ Kdr (S/cm$^2$)</td>
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<td>$\overline{g}$ NaP (mS/cm$^2$)</td>
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<td><strong>Dendrites</strong></td>
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<tr>
<td>$R_m$ (Ω)</td>
<td>6900-14900</td>
<td>3890-12300</td>
<td>5500-23500</td>
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<tr>
<td>$\overline{g}$ CaL (mS/cm$^2$)</td>
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Active Somatic Properties

A variety of gated-conductance ion channel models were added to the soma, axon hillock, and initial segment compartments to allow the α-MN models to generate basic firing behavior. Somata received fast sodium (Naf), delayed-rectifier potassium (Kdr), calcium-dependent potassium (K(Ca)), and N-type calcium (CaN) channels. AH and IS compartments received Naf, Kdr, and persistent sodium (Nap) channels as described by Elbasiouny et al (2005). The specific kinetic models for these channels have been previously published (McIntyre and Grill, 2002; Elbasiouny et al, 2005).

All membrane ion channels were applied uniformly to their respective compartments. Channel conductance values were obtained using multiple run fitter tool in NEURON (Brette et al, 2007) to first loosely constrain α-MN behavior to match a stereotyped single action potential with a minimal degree of calculated error. The results of this process were then manually adjusted to enable a given α-MN model to produce an action potential with greater resemblance to one generated in vitro by the corresponding type. Conductance values for ion channels used for each MN type may be found in Table 1.

Active Dendritic Properties

Slow activating, voltage-gated Cav1.3 channels were added to the dendritic compartments of models (Lee and Heckman, 1998a; Li and Bennett, 2003) to allow generation of the calcium PIC responsible for generation of bistable behavior exhibited by mammalian α-MNs under repetitive firing conditions in vitro (Bennett et al, 1998; Lee and Heckman, 1998b; Lee and Heckman, 2000; Hamm et al, 2010). The mathematical model
used for these channels was originally developed in context of a turtle spinal motoneuron model (Booth et al, 1997) but has been successfully adapted for use previously in a cat model as well (Elbasiouny et al, 2005). Cav1.3 channels were applied uniformly over the dendritic arbor of the α-MN models (Elbasiouny et al, 2005), but the conductance density of these channels was increased in a band determined by electrotonic distance, as a percentage of electrotonic length $\lambda$, of the dendritic compartments from the soma, which was calculated by somatofugal voltage attenuation. Channels located outside the band had their conductance set to zero, eliminating any effect of their presence on results. The electrotonic distance from the soma at which channels were activated was determined by starting with a band corresponding to a similar physical distance as was used by Elbasiouny, et al (2005), then adjusting the distances as necessary.

The results of band placement were measured by determining the frequency-current (F-I) relationship for the given cell. This was executed using a current clamp protocol, applied to the soma, to allow for the most direct comparison to the in vitro studies in which this property has been shown. A triangular current command was used, increasing from an initial value of zero nA to 20 nA over the course of a 10 second increasing ramp, and returning to zero nA over a 10 second decreasing ramp. The time values were chosen to give the current ramp a slope of 4 nA/s for both the ascending and descending ramps, similar to what has been used experimentally in vitro (Lee and Heckman, 1998a). The voltage membrane voltage was measured, and peaks of magnitude greater than 35 mV from resting membrane potential were considered as action potentials. Frequency of action potentials were calculated, and plotted against current to obtain F-I relationships. Testing revealed that it was necessary to inject the FF-type models with a maximum current of 25
nA to demonstrate bistable firing; the simulation time was increased to 12.5 seconds for each ramp of the injected current to hold the slope constant for this case. Figure 3 shows an F-I plot for each type of α-MN. Substantial overlap existed in the electrotonic distance of the final band distribution for activated channel conductance between α-MN types, with active channels on S-type α-MNs placed from 0.42-0.9λ, and 0.4-0.9λ for both FR and FF-type α-MNs, although these measurements do not necessarily equate to similar physical distances. Table 1 includes the specific conductance value used for dendritic Cav1.3 channels on each cell type.
**Figure 3**

**F-I Plots for representative members of each α-MN type**

(Top) FI plots are shown for median model cell of each type, generated under a triangular current clamp protocol applied at the soma. In all cases, the slope of the input current was held constant at 4 nA/s. As shown, the S-type α-MNs display the greatest amount of bistability in their firing pattern. FF type MNs do not display bistable firing patterns unless driven to higher current than is required for S or FR type MNs; current for FF type was 25 nA rather than 20 as used in other cases. (Bottom) FI plots are shown for the median model cell of each type under triangular synaptic current. Bistable firing as shown in current injection is not displayed, because PICs are immediately activated by synaptic current.
Pool Model Development

The pool model was developed to capture a broader section of behaviors of the grouped α-MNs innervating the cat medial gastrocnemius. It was determined that this would require a generation of a minimum of 51 total modeled α-MNs, 13 each S-type and FR-type, and 25 FF-type, to reasonably approximate the relative ratios of MU types reported experimentally for this muscle (Burke and Tsairis, 1973; Fleshman et al, 1981; Zengel et al, 1985) while allowing for an odd number of α-MNs of each type, such that a distinct median member of each cell type would always remain present.

Converting from discrete, individual MN models to a pool model required several adjustments. First, each model α-MN discussed in the previous subsection was converted to an object class template using the Cell Builder tool in NRNIV. Treatment of each α-MN as an object class allows for rapid generation of many instance of that class, although it leads to generation of model cells within each α-MN type having the same morphology and basic properties upon generation. However, properties of an object generated from a template are capable of being changed independently of the same properties for other objects generated from the same template, allowing for variation within a given α-MN type.

In the pool model, the first method of variation between members of a given class of α-MNs applied was change in input resistance. To accomplish this, upper and lower boundary values for the input resistance of each cell type were established, and membrane resistance adjusted to meet these boundaries, while maintaining the ratio between somatic and dendritic resistance established during development of the single α-MN model. Once boundary values for membrane resistance each cell class were established, additional
members of that class were generated by linearly spreading values of membrane resistance between the boundary values.

Dendritic channel conductance values were held constant within each α-MN type, but kinetic parameters within the channel models, which underlie voltage threshold for spiking, were adjusted to allow variation in the voltage threshold for individual α-MN firing. This provided a more nuanced method of varying model α-MN rheobase than could be accomplished through variation of membrane resistance alone. Appropriate parameter values were determined for highest, median and lowest input resistance members of each type of α-MN, and linearly distributed between those values.

Figure 4 provides a variety of parameter comparisons; 4A shows rheobase vs. input resistance, and qualitatively plots very well to the top panel of Figure 8 from Zengel et al (1985). Panels 4B and 4C show AHP half-decay and input time constant versus input resistance, respectively. This serves to illustrate that, although there is some systematic variation between types of α-MN, overlap between types is sufficient to require several parameters to provide the basis of any effective classification system.
Figure 4:
Two-parameter comparisons of pool model single-spike data
Panel 4A shows modeled cell rheobase vs input resistance. Compared to Zengel et al (1985) figure 8, model qualitative matches experimental data. Panel 4B shows AHP half-decay vs input resistance. S cells are clearly separated from both fast types, although FF and FR overlap significantly. Panel 4C shows input time constant vs input resistance. In this case, FF-type cells are discriminated, but FR and S are not clearly separate.
Statistical Analysis of Single-Spike Parameters

After careful consideration, it was determined that qualitative visual analysis of pool suitability was not, in isolation, sufficient as a form of model validation. As such, statistical analysis of some model parameters was undertaken, in the form of comparisons between pool model and experimental data. Analysis was performed for four key parameters: rheobase, input resistance, membrane time constant, and AHP half-decay, which had been previously identified to provide correct α-MN type identification within the cat medial gastrocnemius for 97% of cases when used in combination (Zengel et al, 1985). Analysis was carried out in R Studio, version 3.2.3 (R Core Team, 2015).

For each parameter, the pool model data was compared to both sets of experimental data used in model development (Zengel et al, 1985; Hochman and McCrea 1994) as well as one external data set from either Foehring et al (1986) or Ulfhake and Kellerth (1984). All data were analyzed using Tukey-Kramer pairwise testing for comparison of means between samples of different n (Kramer, 1954). The function `pairw.anova()` from the R package asbio (Aho, 2016) was used for all comparisons. In all tests, the null hypothesis was $H_0: \mu_{\text{model}}=\mu_{\text{experimental}}$, and significance level was $\alpha=0.05$.

Because published summary data was used for both model development analysis, sample data for comparison testing was generated using the bounded, pseudo-normal distribution function `urnorm()` found in R package Runuran (Leydold and Hormann, 2015). The boundary property of this distribution was used to apply a lower bound to the range of MN parameters in cases where only positive values are appropriate, such as input resistance. No lower bound was used for parameters where negative values have been previously reported for the MN parameter in question, specifically rheobase (Lee and
Heckman, 1998). For consistency, the urnorm() function was used to generate both the unbounded normal and bounded pseudo-normal distributions.

As this process introduced a degree of additional sampling error to the proceedings, each sample draw was repeated 10 times with the goal of reducing both sampling and type II error. Because Hochman and McCrea (1994) reported a range of n for all data parameters, all comparison groups including data from this set were run an equal number of times for each extreme of the range of reported n for that parameter. This includes all parameters except AHP ½-decay, which was not included by Hochman and McCrea (1994). Additionally, comparisons were made between the various sets of experimental data to examine possible differences between data sets gathered from similar animals and motor pools.

In context of this analysis, it is also important to reiterate that the pool model was generated by uniformly distributing properties between extrema, rather than in a normally-distributed fashion. However, the Tukey-Kramer comparison is based on the studentized q-statistic, which is considered robust to non-normally distributed data (Brown 1974).

Table 2 provides a summary of experimental data used to develop comparisons, as well as summary data for the same parameters in the pool model. The appendix includes sample R code identical to that used to generate, analyze, and display the statistical comparisons.
Table 2:

Summary single-spike data for model parameters and experimental data
<table>
<thead>
<tr>
<th>Property</th>
<th>Cell Type</th>
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</tr>
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<tr>
<td></td>
<td>S</td>
<td>FR</td>
<td>FF</td>
<td></td>
</tr>
<tr>
<td><strong>Rheobase [nA]</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(72)</td>
<td>(70)</td>
<td>(153)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hochman and McCrea (1994)</td>
<td>4.3 ± 2.5</td>
<td>11.6 ± 3.1</td>
<td>19.7 ± 5.1</td>
<td></td>
</tr>
<tr>
<td>(20-45)</td>
<td>(14-31)</td>
<td>(28-48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foehring et al (1986)</td>
<td>5 ± 0.0</td>
<td>11 ± 6.08</td>
<td>20 ± 8.37</td>
<td></td>
</tr>
<tr>
<td>(34)</td>
<td>(37)</td>
<td>(70)</td>
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<tr>
<td>Model Data‡</td>
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<td>17.03 ± 9.81</td>
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<td></td>
<td>(13)</td>
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<td>(25)</td>
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<td><strong>Input Resistance [MΩ]</strong></td>
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<td>Zengel et al (1985)</td>
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<td>0.6 ± 0.0</td>
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<td>(61)</td>
<td>(62)</td>
<td>(153)</td>
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<td></td>
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<tr>
<td>Hochman and McCrea (1994)</td>
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<td>0.62 ± 0.15</td>
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<tr>
<td>(20-45)</td>
<td>(14-31)</td>
<td>(28-48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foehring et al (1986)</td>
<td>1.5 ± 0.0</td>
<td>1.1 ± 0.0</td>
<td>0.6 ± 0.0</td>
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<tr>
<td>(28)</td>
<td>(30)</td>
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<tr>
<td>Model Data‡</td>
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<td>1.02 ± 0.26</td>
<td>0.62 ± 0.21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(13)</td>
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<td><strong>Time Constant [ms]</strong></td>
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<td>(12)</td>
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<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Ulfhake and Kellerth (1984)</td>
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<td>4.9 ± 2.3 †</td>
<td>4.9 ± 2.3 †</td>
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</tr>
<tr>
<td>(7)</td>
<td>(10) †</td>
<td>(10) †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model Data‡</td>
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<td>5.23 ± 1.29</td>
<td>5.61 ± 1.26</td>
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</tr>
<tr>
<td></td>
<td>(13)</td>
<td>(13)</td>
<td>(25)</td>
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</tr>
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<td><strong>AHP Half-Decay time [ms]</strong></td>
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<td></td>
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<td>Zengel et al (1985)</td>
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<td>22 ± 5.57</td>
<td>18 ± 0.0</td>
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<tr>
<td>(23)</td>
<td>(31)</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>Not reported</td>
<td>Not reported</td>
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</tr>
<tr>
<td>Foehring et al (1986)</td>
<td>49 ± 15.87</td>
<td>25 ± 5.57</td>
<td>22 ± 7.35</td>
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<td>(31)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Model Data‡</td>
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<td>20.88 ± 0.65</td>
<td>19.05 ± 0.66</td>
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<tr>
<td></td>
<td>(13)</td>
<td>(13)</td>
<td>(25)</td>
<td></td>
</tr>
</tbody>
</table>

Data is shown as mean ± standard deviation
‡ Uniformly distributed
† Reported values for FF and FR MNs were combined
Parallelization

Due to the size and complexity of the pool model, it very rapidly became impractical to execute pool simulations on a personal computer. As such, all pool simulations after initial testing of code were carried out using HPC hardware via Neuroscience Gateway (Sivagnanam et al, 2013). Due to the significant degree of discreteness between each individual α-MN model, a bulletin board parallelization method (Nugala et al, 1997) was used to distribute the necessary tasks to execute a pool simulation across available CPU cores on a per-cell basis. In this parallelization scheme, one or more cores act as a master, posting a bulletin-board list of available jobs for many worker cores. As they become available, worker cores accept and execute a job, returning only the results to the master core(s). This implementation resulted in an approximately 30-fold decrease in model runtime, allowing for more rapid execution of simulations and production of additional results.

Force and EMG Models

To provide an additional means of evaluating pool output, models to simulate muscle force and EMG were implemented as described in previously published work (Fuglevand et al, 1992; Fuglevand et al, 1993). Briefly, each MU is assigned a value of twitch force (TF) in arbitrary units, twitch duration (TD) in milliseconds, as well as the number of muscle fibers innervated (nf) following an exponential schedule in which each MU is assigned an integer identifier, $i$, based upon recruitment order. In the standard model, if all α-MNs were recruited, the first recruited α-MN would be assigned to a MU designated $i=1$ and the last recruited α-MN assigned to a MU designated $i=51$. 

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The principal equations for the force model used were implemented as described in the source material (Fuglevand et al, 1993), with one significant exception. A multiplicative conversion factor was included in the equation used to calculate instantaneous twitch force. This led to the modification of equation 18 from Fuglevand et al (1993) as follows:

\[ f_{ij}(t) = g_{ij} \times \frac{TF_i \times t}{TD_i} \times e^{1-t/TD_i} \times FCF \]

Where \( f_{ij}(t) \) is the time-dependent force generated by motor unit \( i \) in response to spike \( j \); \( g_{ij} \) is the instantaneous gain of the signal between spikes. \( TF_i \) is the twitch force of the motor unit, \( TD_i \) is the twitch duration of the motor unit, and \( FCF \) is the multiplicative factor used to convert from arbitrary units to Newtons allowing the pool to simulate force as generated by the cat medial gastrocnemius. The value of \( FCF \) used for these simulations was 4.8, which was developed to convert the force from arbitrary units as used in the source material (Fuglevand et al, 1993) to units in Newtons comparable to experimental literature in the cat MG (Krutki et al, 2006). Figure 5 shows the assignment order of twitch force to motor units; twitch duration was assigned similarly on a decaying exponential. The values used for the range of twitch times and longest twitch time parameters described in Fuglevand et al (1993) were 5.5x and 110 milliseconds, respectively, which were chose to compare to data from the cat MG (Burke et al, 1971).

The EMG model was implemented as described in the source literature (Fuglevand et al 1992; Fuglevand et al, 1993). The values of some of the constants from this model were adjusted to better represent the cat MG muscle. Model motor units were treated as representative sample taken from a population of 280 and the ideal total
number of muscle fibers was treated as 170,000 (Burke and Tsairis, 1973); however, simulating such a large number of muscle fibers caused computer memory errors, even when code was run on a HPC. To compensate for this, the number of muscle fibers was reduced to 5% of the ideal total, or 8500 fibers, which reduced the absolute magnitude of the signal, but did not change the relative contribution from individual motor units nor the frequency content of the signal.
Figure 5:

Twitch force assignment schedule

Twitch force is assigned by recruitment order, from 1 to n, where n is the number of MNs in the model.
The image shows a graph with the x-axis labeled "MN Number (by recruitment order)" and the y-axis labeled "MU Force [N]." The graph plots data points that form a curve.
**Pool Abstraction**

One abstraction sometimes made during the modeling process is treatment of α-MNs as a single, continuous group (Heckman and Binder, 1991a; Fuglevand et al, 1993; Powers and Heckman, 2017). To evaluate the possible effect of such a treatment, the variation between modeled α-MN types was maintained, but the region of overlap in the plot of rheobase vs input resistance was removed by adjusting the boundary values for each cell type. Figure 6 shows the distribution of rheobase vs input resistance resulting from this shifting. The overall shape of the distribution in Figure 6 maps similarly to that of the original pool model, as shown in figure 4A, despite the significant changes made to produce it. Table 3 provides the boundary values used for membrane and net input resistance in the non-overlapping pool.
Figure 6

Rheobase vs. input resistance for abstracted, non-overlapping model pool

Rheobase vs input resistance is shown for the abstracted pool model in which overlap between \( \alpha \)-MN types has been removed. The overall results still map similarly to those shown previously in Figure 3.
Table 3

Boundary values used for membrane resistance in α-MN types in non-overlapping version of model pool.
<table>
<thead>
<tr>
<th>A-MN Type</th>
<th>Parameter</th>
<th>Lower Boundary (Ω)</th>
<th>Upper Boundary (Ω)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Overlap Pool</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>Rm, Soma</td>
<td>318.8</td>
<td>496.4</td>
</tr>
<tr>
<td></td>
<td>Rm, Dendrites</td>
<td>9564</td>
<td>14892</td>
</tr>
<tr>
<td>FR</td>
<td>Rm, Soma</td>
<td>133.625</td>
<td>203.3125</td>
</tr>
<tr>
<td></td>
<td>Rm, Dendrites</td>
<td>6681.25</td>
<td>10165.625</td>
</tr>
<tr>
<td>FF</td>
<td>Rm, Soma</td>
<td>22</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Rm, Dendrites</td>
<td>5500</td>
<td>18250</td>
</tr>
</tbody>
</table>
Input Standardization

Synaptic contacts were applied to and activated on α-MN models in the pool in a uniform distribution across the dendritic arbor of all α-MNs; this resulted in more synaptic contacts being applied to FF cells than other groups due to their greater number of dendritic segments and branches. The goal of this process was to provide a standardized synaptic input to the α-MN pool. However, similar synaptic currents applied to the dendrites produced widely variable net current at the somata, depending heavily upon the membrane resistance of the dendrites of the cell to which they are applied. To account for this, an input standardization method was adopted as follows:

For all cases, input current to a given type of α-MN was standardized using the median cell of that type. These were the 7th S and FR α-MNs, and the 13th FF-type α-MN, in which all α-MNs of a given type received equivalent synaptic weighting, the value of which was determined using the median cell for that type. Each type of α-MN, in turn, was standardized independently of other types to receive the desired current at the soma. As such, every member of each type of α-MN receives the same quantity of initial synaptic current at the dendrites. While this still results in some variability in current seen at the soma due to variations in membrane resistance between members of each type of α-MN, the variability is effectively reduced by reducing the range of values over which a given input is applied. In the standard test case, the median cell of each type of α-MN was adjusted to receive the same net current over the same timeframe as the others.

To determine the appropriate conductance values to produce a desired current, a fully passive version of each of these cells was used; fully passive in this context indicates no AP generating channels on the soma, AH, or IS, as well as no PIC-generating channels.
on the dendrites. Synapses were applied to the dendritic arbor of each of these cells in the same manner as they would be for simulations. These synapses were then divided into 4 equivalently-sized groups, with each group activated at 180 Hz. To smooth the activation signal, activation between groups was phase-shifted 90 degrees from adjacent groups. A voltage clamp at the cell soma was simulated, and maintained at -70 mV, equal to RMP. Positive influx of current required a negative current to be current applied through the clamp to maintain steady voltage; this value was measured, and its’ inverse taken to be the effective synaptic current (Lee and Heckman, 1998b).

This method of applying and determining synaptic current still resulted in a quite noisy signal. Therefore, standard values for synaptic activation current use the RMS value of the raw signal; where applicable, the raw signal will also be shown to demonstrate the range of the true signal applied to pool cells.

These procedures were repeated for the non-overlapping version of the pool as well. Thus, effective synaptic current at the soma was conserved between pools, but not raw current at the dendrites or net synaptic conductance.

*Input Variation by Type*

Evidence obtained from the cat has suggested some systematic variation in volitional descending input to α-MNs based on their input resistance. Specifically, descending pyramidal and rubrospinal tract input to triceps surae α-MNs has been shown to be as much as 15 nA greater in low input resistance cells as compared to those of high input resistance (Powers et al, 1993; Binder et al, 1998). To simulate this in the pool model, input current was varied by cell type. FR-type α-MNs received the standard current input, while S-type received 2.5 nA less current than standard, and FF-type received 2.5 nA more
current; this produced a variation comparable to what had been suggested experimentally for the pyramidal tract alone (Binder et al., 1998). As discussed above, the synaptic current value applied to each type of α-MN was based upon the parameter settings used to apply that current value to the median member of the respective type.

**Simulation Protocols**

Table 4 provides a summary of current applied to all MNs during all simulations. Descriptions of the specific protocols used to obtain these values follow.
Table 4: RMS of synaptic inputs applied during simulations
<table>
<thead>
<tr>
<th>Simulation</th>
<th>S Current</th>
<th>FR Current</th>
<th>FF Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Pool, Uniform Isometric</td>
<td>4 nA</td>
<td>4 nA</td>
<td>4 nA</td>
</tr>
<tr>
<td>Non-Overlapping Pool, Uniform Isometric</td>
<td>4 nA</td>
<td>4 nA</td>
<td>4 nA</td>
</tr>
<tr>
<td>Standard Pool, Non-Uniform Isometric</td>
<td>1.5 nA</td>
<td>4 nA</td>
<td>6.5 nA</td>
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<tr>
<td>Standard Pool, Uniform Triangle</td>
<td>10 nA</td>
<td>10 nA</td>
<td>10 nA</td>
</tr>
<tr>
<td>Non-Overlapping Pool, Uniform Triangle</td>
<td>10 nA</td>
<td>10 nA</td>
<td>10 nA</td>
</tr>
<tr>
<td>Standard Pool, Non-Uniform Triangle</td>
<td>7.5 nA</td>
<td>10 nA</td>
<td>12.5 nA</td>
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</table>
Steady-State Firing Rate

Steady state firing rate analysis was conducted to allow for comparison to isometric contraction tasks that are sometimes used to evaluate motor unit properties in vivo, particularly in human studies (Moritz et al, 2004; Barry et al, 2007; Martinez-Valdes et al, 2017). A ramp-to-hold synaptic command, as shown in figure 7, was used for this evaluation, with current values normalized as discussed above. Input was standardized to an RMS value of 4 nA for steady state tests; this recruited a significant proportion of pool cells by activating dendritic PICs, but induced them to fire at a low rate. The steady-state firing rate was calculated on the final 25% of the α-MN firing rate vs. time vector so as to avoid any errors resulting from non-linear firing rate that might be seen at the initial changeover from the ramp activation to the holding phase.
**Figure 7:**

**Representative input trace for isometric task simulation**

The input signal applied to S cells in the standard pool for isometric simulations is shown. Traces for other cells and simulations were similar. The raw input, as applied to the cell is shown in black; the RMS input, which was used for the reported value, is shown in red. Firing frequency under this input was measured during the time period within the green rectangle.
Force and EMG

Force and EMG signals were simulated using the output of triangular synaptic input that increased from zero to 10 nA as seen at the soma over the course of 2.5 seconds, then returned to an input of zero nA over the following 2.5 seconds. Figure 8 shows both the raw synaptic input used for these experiments, as well as the RMS value used in reporting. Because EMG is a noisy signal, additional analysis of the EMG signal was conducted by calculating a PSD signal, to allow analysis of signal frequency content. Due to reductions in the absolute number of muscle fibers simulated for EMG signals, all PSDs were normalized to the maximum value of the PSD generated from the standard pool.
Figure 8: Representative input trace for force and EMG simulations

A representative example of the input signal used when generating force and EMG traces is shown, taken from an S-type cell. Input signals for other cells types are similar. Raw input is shown in black; RMS input shown in red.
III. RESULTS
Statistical Analysis of Single-Spike Parameters

Table 5 provides a summary of the results of comparisons between 4 key electrophysiological parameters of the pool model and experimental data. As discussed in methods, these parameters are input resistance ($R_{\text{in}}$), input time constant ($\tau_0$), AHP half-decay, and rheobase, which were used in combination to successfully type-identify $\alpha$-MNs 97% of the time (Zengel et al, 1985). In all tests, comparisons were made between model data, the two data sets used in the model development process (Zengel et al, 1985; Hochman and McCrea, 1994), as well as one external set of either Foehring et al, (1986) or Ulfhake and Kellerth (1984). Data from Hochman and McCrea (1994) was reported with a range of values for n, so all comparisons using this data were made for both extrema of the number provided (indicated in table 4 as “low n” and “high n” rows. This allowed verification of the fit of the model data to both the data from which it was derived as well as additional, independent data from similar cells. Finally, to reiterate the methods for these comparisons, experimental data was generated using 10 repeated draws and subsequent comparison tests per parameter from a bounded, pseudo-normal distribution function. Success criteria for these tests was defined as a failure to reject (FTR) between the pool model data and at least one of two data sets used in model development as well as one external data set not used during model development for a minimum of 5 out of 10 trials each. The null hypothesis in all comparisons was defined as an equal population mean between groups. All tests were carried out at the $\alpha=0.05$ confidence level, which would indicate the model electrical properties are similar to the same properties in experimental data.
Table 5 is interpreted as follows, using one specific comparison parameter (S-type rheobase) as an example, which is found in the upper left of the table. When considering the comparison between the rheobase of modeled S cells with data from experimental S cells used in model development (Zengel et al, 1985; Hochman and McCrea, 1994), comparison between pool model and experimental data failed to reject in 10 out of 10 trials. This is indicated by the number shown to the right of the comparison under Number FTR, which must be at least a 5 for either Zengel et al (1985) or Hochman and McCrea (1994). Additionally, when compared to the external data set (Foehring et al, 1986), which appears as the bottom row in each panel, the hypothesis that the model and experimental data were similar failed to reject in all 10 trials. This indicates a very high degree of similarity between the model data and both data from Zengel et al (1985) and Hochman and McCrea (1994) for S cell rheobase.

As shown throughout the table, the model passed both established criteria for all parameters, apart from AHP half-decay in the FF-type α-MNs, which only failed to reject when compared to the external data set in 3 out of the 10 trials. This indicates that the model electrical properties were similar to the same properties in actual cells recorded in vitro for all key parameters as compared to the data used in development and all but one parameter when compared to outside data.

Several inconsistencies between experimental data sets, particularly in those cases where the model was not able to match both experimental data sets used for development of a given parameter, prompted the inclusion of pairwise comparisons of different groups of experimental data in table 6. These comparisons between experimental data sets allow the assessment of the robustness and consistency of the measurement of each given
electrical parameter reported in experimental studies. For most parameters compared, analysis showed that the reported values of electrical properties were consistent among datasets, although there were wide variations among some of the properties thus examined. Because a majority of parameters were consistent between the data sets examined, only parameters which showed repeated, consistent difference between experimental data sets were included; that is, those for which the conclusion of the pairwise comparison test was a rejection of the null hypothesis for more than half of the times the test was executed. Parameters where this was the case between two or more data sets were input resistance for FR cells, AHP half-decay for FF type cells, and time constant for all three types. The differences in reported time constant may result from measurement errors. All three data sets for this parameter used a curve-fitting method to estimate time constant, with one author even noting “…it was difficult to obtain measures of the membrane time constant.” (Zengel et al, 1985). In fact, the method used to provide the reported values of time constant was found to be inconsistent in another study (Fleshman et al, 1988).
Table 5:

Results from single parameter comparisons between model and experimental single-spike data.
<table>
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<tr>
<th></th>
<th>Compared Data</th>
<th>Number FTR</th>
<th>Compared Data</th>
<th>Number FTR</th>
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<td>Ulfhake Kellerth</td>
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Table 6:

Results from single parameter comparisons between experimental single-spike data sets for which repeated difference between sample means was noted.
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<td>Hochman McCrea (high n) vs Zengel et al</td>
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</tr>
<tr>
<td>Ulfhake and Kellerth vs Zengel et al</td>
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<tr>
<td><strong>FR Input Resistance</strong></td>
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<td>Hochman McCrea (high n) vs Foehring et al</td>
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<td>Foehring et al vs Zengel et al</td>
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<td><strong>FR Time Constant</strong></td>
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Abstracted Pool without Overlap

Steady-State Firing Rate

Results from the steady state firing rate task are summarized in figure 9. As shown, both the standard and non-overlapping cases show superficially similar recruitment patterns and firing frequencies, as well as a similar number of MNs recruited, although there are some variations.

In both pools, recruitment proceeded as would be expected by the size principle, such that S cells were recruited first, then FR, and last FF. The main differences visible are in the extrema of the pool range. On the more excitable extreme, the standard version activates most of the S cells first, with a few activating after other cell types, while the non-overlapping version activates all the S cells before the first FR cell becomes active. Considering the least excitable extreme of the model, the pattern of recruitment for that last few cells differs as well. In the standard case, the last 5 cells recruited consist of 3 FF- and 2 FR-type, while in the non-overlapping pool, all 5 are FF type.

Additionally, the types of cells recruited vary between pools. In both cases, all 13 S-type cells are recruited. In the standard pool, 11 FR- and 16-type FF are recruited, while in the non-overlapping pool, all 13 FR- and only 14 FF-type are recruited. This indicates the standard pool will allow for more recruitment of FF cells and more heterogeneity in the source of the spikes from recruited MNs than the non-overlapping pool.
Figure 9:

Steady state firing rate results from standard and non-overlapping pool models

Steady state firing rates is plotted vs recruitment order. Top panel shows results from the standard pool, while middle panel shows results from the non-overlapping pool. Results in both panels are similarly consistent with the size principle. The middle panel (non-overlapping pool) provides a more stereotyped activation, with all of the early cells being S-type, and all of the late cells being FF-type. Bottom Panel provides synaptic input vs time used in this simulation. The bright red rectangle indicates the period for which firing rate was calculated.
Force

Results from simulating force on the output of both pools are shown in Figure 10. The standard pool results are shown in black. As shown, the output force value is reduced by 13.6% in the non-overlapping model as compared to the normal, overlapping pool model. This is due to the changes in recruitment order and firing. Because the twitch force is assigned based upon the order in which MNs firing, changes in the recruitment order, similar to those shown for the isometric task, result in a lower firing frequency for the last several cells recruited. This leads to the cells that contribute most significantly to the overall amplitude of the force generated by the model are ultimately firing at a lower rate in the non-overlapping models.

There were also slight changes in the type of cells recruited in each pool. The non-overlapping pool model tends to recruit slightly fewer FR cells and slightly more FF cells than the standard pool model. This results in a lower overall firing frequency for the non-overlapping pool, as compared to the standard pool, which, coupled with changes in recruitment order, may lead to the lower amplitude of the force trace.
**Figure 10**

**Force results for standard and non-overlapping pool models**

(Top) Results from force simulation are shown for standard and non-overlapping pools. Standard pool is shown in black, while non-overlapping version is shown in green. Both traces are similar, although the magnitude of the peak force for the non-overlapping pool is reduced. (Bottom) RMS synaptic input current ($I_N$) used to stimulate pool when generating this force.
EMG

EMG simulation results are shown in figure 11. As shown, simple visual analysis of the EMG signal was not possible due to the noisy nature of the signal and similar amplitude between the signals in both the standard and non-overlapping pool models.

As the raw EMG signal was not an effective means of comparing between the standard and non-overlapping pool models, frequency content analysis was undertaken by calculating a power spectrum density for both signals, as shown in figure 12. Results from the standard pool are shown in black. This signal displays a single large peak at 36 Hz, with some surrounding activity that does not exceed 20% of the value of the maximum peak. The non-overlapping pool had, a similar main peak to the original at 35 Hz, as well as some additional peaks between 50 and 60% of the amplitude of the main peak in the 25-35 Hz frequency range.

These additional peaks are the result of the changes in recruitment order for the non-overlapping version of the model pool. In the standard version of the MU pool, the last 5 MUs recruited consist of 3 FR and 2 FF, while in the non-overlapping version, all 5 are FF. This is significant because these least-excitable FF cells are the slowest-firing cells in the pool under a uniform input to all MN types, such as is used here, and the Fuglevand-style force model (Fuglevand et al, 1993), which treats later-recruited motor units as larger. The combination of these two factors results in the appearance of these secondary peaks in the PSD, corresponding to activity in the least excitable FF MNs.
Figure 11

EMG Results for standard and non-overlapping pool models.

(Top) Standard pool is shown in black; non-overlapping pool is shown in green. (Bottom) RMS synaptic input current ($I_N$) used to stimulate pool when generating this force.
Figure 12

**EMG power spectra for standard and non-overlapping pool models**

Power spectrum for the standard pool is shown in black; non-overlapping power spectrum is shown in green. The main peak in both cases was similar, occurring at 36 Hz in the standard pool and 35 Hz in the non-overlapping pool. The non-overlapping pool had additional, lower frequency peaks corresponding to low-firing rate FF cells recruited late in the simulation; these peaks are indicated by red arrows. This effect was not seen in the standard pool due to some late recruited cells firing faster.
**Input Variability**

Previous simulations were conducted with uniform synaptic current applied to all MN types. Per the second specific aim, it was also desirable to examine the effect of non-uniform input to the pool model. This was done because some experimental studies have shown systematic variation in synaptic current by input resistance to the MN pool of the cat MG by from volitional spinal tracts (Powers et al, 1993; Binder et al, 1998). These simulations used MN type as representative of input resistance, and varied synaptic input such that $I_{N, FF} > I_{N, FR} > I_{N, S}$. The variation treated FR as the standard case, with current increased and decreased by 2.5 nA for FF and S type cells, respectively, to simulate variations shown in pyramidal tract input (Binder et al, 1998)

**Steady-State Firing Rate**

Results for the steady-state, ramp to hold test of the standard pool under type-variable input are shown in Figure 13. The top panel shows standard pool under uniform input (results shown previously in figure 9). The middle panel shows the results obtained from the standard pool with non-uniform input. In both cases, the pool input was treated as being 4 nA during the holding phase of the applied signal (bottom panel). For the top panel, all MN types received 4nA synaptic current; in the middle panel, FR cells received 4nA, FF 6.5 nA, and S 1.5 nA. As shown, when non-uniform input is applied, the recruitment order in the pool no longer follows orderly recruitment under the size principle. However, FF cells are induced to fire faster than previously, and S cells become the slowest-firing in the pool, which is more consistent with relative firing rates between cells types that would be expected in motor unit typing.
Figure 13:

Steady state firing results for standard pool and pool with non-uniform input

Steady state firing frequency is plotted against recruitment order. Panel A shows results from the standard pool, with uniform input current across cell types. Panel B shows the input used for panel A. Panel C shows results from the pool with non-uniform input across cell types; FR received 4 nA peak input, FF 6.5 nA, and S 1.5 nA. Panel D shows the input used to generate the plot in panel C. Recruitment order is notably different between panels.
Standard Pool

Uniform Input

Non-Uniform Input Pool

Non-Uniform Input
Force

Force traces for the standard pool under uniform input, and the standard pool under non-uniform input are shown in Figure 14. The variable input was designed to provide similar overall input amplitude for both simulations, although there is some differences due to the fact that there are more FF cells than there are other types. As may be seen, the peak force under variable input increased 10.2%. This, in part results from the recruitment of an additional FF cell; 46 fired in the standard case, while 47 fired under variable input. More significantly, the force resulting from tonic firing after removal of stimulus was increased by 120.4%. Tonic force after stimulus results from steady firing of S cells due to the effects of the dendritic Calcium PIC. The increase in amplitude of this force results from a combination of the later recruitment of S cells with the method by which force properties were assigned to cells. Because twitch force is assigned by recruitment order per the size principle, the late-recruited S cells, which fire tonically following stimulus, were assigned to higher than normal force values.
Figure 14:

Force results for standard pool and pool with non-uniform input

Force from the standard pool is shown in black; non-uniform input pool is shown in grey. Shapes are similar, but peak force is increased with non-uniform input. Additionally, force from tonic firing after removal of stimulus is increased with non-uniform input.
EMG

Figure 15 shows the EMG traces for the standard pool as well as the pool under non-uniform input. The trace shown for the standard pool is the same trace shown previously in Figure 11. As can be seen, there is a notable increase in EMG amplitude when the pool receives type-variable input, although more detailed analysis of the raw EMG trace was not undertaken.

Figure 16 shows the normalized power spectra calculated for both the standard pool and the non-uniform input case. The variable input trace has its main peak at a slightly higher frequency than the main peak in the uniform input trace. Furthermore, this trace shows additional low frequency peaks, resulting from the assignment of tonic-firing S cells to larger motor units than would normally be expected.
Figure 15:

EMG results for standard and variable input pools

Top Panel: EMG from the standard pool is shown in black; non-uniform input is shown in grey. Trace shape is similar overall, although the non-uniform input trace shows greater amplitude throughout. Bottom Panel: Standardized input trace. S cells receive 2.5 nA less input than shown throughout, while FF cells receive 2.5 nA more input.
Figure 16:

EMG power spectra for standard and non-uniform input pools

Standard pool is shown in black; non-uniform input is shown in grey. The major peak for the non-uniform input pool is shifted slightly to the right. Under non-uniform input, there are also some smaller, secondary peaks at lower frequency corresponding to S-type motor units receiving assignment of more muscle fibers than they were under the standard case. Red arrows indicate the locations of these secondary peaks.
IV. DISCUSSION & CONCLUSIONS
Statistical Analysis of Single-Spike Parameters

A major confound to model development was the high variation between available experimental parameters. As shown in Table 5, certain parameters failed entirely to match between the different sets of previous experimental data analyzed. This was especially true in the case of input time constant, which showed significant differences between the results reported by Hochman and McCrea (1994) and Zengel et al (1985) for all MN types, as well as between Ulfhake and Kellerth (1984) and Zengel et al (1985) for S and FR types. This was despite all three studies using a similar method to obtain time constant data. There are two likely explanations for these differences. First, although all three studies used similar methodology, all used different amplitude and duration current pulses when measuring the voltage trace used to estimate the time constant. This likely led to some differences in time course between them. Second, this method of estimation has also been shown to be somewhat unreliable (Fleshman et al, 1988), although the more precise graphical peeling method (Fleshman et al, 1988) used in that study also has significant limitations that restrict its’ use.

Despite these disparities, it was possible to meet the established success criteria for all but one parameter: FF-type AHP half-decay. In this case, the data used for model development, taken from Zengel et al (1985) was so wildly different from the external comparison group, Foehring et al (1986), that the two were irreconcilable. For the other parameters where there were significant differences, it proved feasible to match well with one of the two data sets used in model development as well as the external comparison dataset, although it was often not possible to compare as similarly as desired to both groups of data used in original development.
These differences underscore a major difficulty in modeling when using external data. The often-wide variability between different datasets can force one to select between them, which further complicates an already uncertain process. However, this forces the modeler to discard potentially valid data sets in favor of those most readily compatible. Under ideal circumstances, the researcher would attempt to replicate some of the findings being modeled in house for validation, although this may not be possible for any of a variety of reasons.

**Removal of Type Overlap**

The effect of this abstraction on pool output was relatively small, although it was sufficient to provide some insights, as well as several ideas for further directions. First, the changes in recruitment order with removal of type overlap appear to adhere to the size principle better, rather than worse, than the standard model case. This is accompanied by some changes in the force trace and EMG power spectrum, although the raw EMG appears little different. Placed in context of the force and EMG models (Fuglevand et al, 1993) as implemented, this tends toward the explanation that changes in the force and EMG results are due to a better match between these models and the α-MN pool model.

Changes in the force trace also serve to highlight a limitation in the assumptions built into the force model. This limitation is particularly significant in models similar to those presented in this document, in which different models are used for each MN type. By modeling each type of MN separately, it was possible to include and then remove the overlap between MN types, which changes how the force assignment schedule interprets the firing of different cells. For instance, if the 15th recruited MN was previously an S cell, but is an FR cell after removing the overlap between MN types, this will result in a
significantly different firing frequency being sent to a certain set of properties in the force model.

The impact of this limitation may be lessened in less specific models, such as those presented by Powers and Heckman (2017). In drawing an entire pool of models from a single template, they ensure that orderly recruitment will almost always proceed from one extreme of the pool to the other, in much the same manner that all MNs of a single type in our model would proceed. As such, these changes to the Fuglevand (1993) force model will be necessary for models that include different MN type characteristics, but may not be for models in which such variations are absent.

Further investigation into the effect of abstraction could be undertaken in a couple of different ways. A pool model could be generated by spreading the characteristics of a single α-MN type over the same range used for the original, multi-type model. Changes in results from this process could be compared to the changes already shown here. Additionally, a single type model could be constructed using a reduced morphology, as was recently done by Powers and Heckman (2017).

The recent Powers and Heckman model (2017) further includes a weighting in the distribution of modeled cells toward the set of properties most commonly seen experimentally. The pool model developed for this thesis effectively includes similar weighting by distributing type-specific modeled α-MNs in a similar proportion to what has been shown experimentally for the cat MG (Burke and Tsairis, 1973).

An additional comparison could be made in generating simplified versions of this model by applying a weighted distribution when generating a pool model from a single
type template, so as to retain the approximate distribution included in the original model as well as the same boundaries, even while making a more severe abstraction. This would provide an additional method to assess the necessity of including type variance and overlap in pool models despite the additional variables this inclusion adds to the system.

**Input Variability**

Recruitment order was effectively reversed in this test case as compared to the standard pool. At first glance, this might seem to violate all reason, especially in light of more than 50 years of research since the coining of the term size principle (Henneman et al, 1965). However, this largely serves to underscore the importance of context in interpretation of findings. De Luca and Contessa (2015) strongly contest the applicability of the size principle, particularly as interpreted from recordings using direct electrical stimulation, to analysis of volitional movements. They note that many of the experiments involved in the development of the size principle were undertaken under conditions of direct electrical stimulation (Henneman, 1957; De Luca and Contessa, 2015), a condition markedly different from the physiological means of delivering excitatory current to groups of cells. While not specifically stating that the size principle is inaccurate, they suggest that the interpretation that recruitment proceeds as S->FR->FF (Kernell, 2003) does not capture the reality of movement in a living subject. Faced with similar difficulties in matching results to neuroscience orthodoxy, other researchers have sought a more congruous explanation, suggesting that human motor units perhaps behave differently than those of other animals, and so defy typing in the traditional three-class system (Fuglevand et al, 1999).
The synaptic control used to excite the pool model seeks to emulate volitional control of a muscle. As such, it may be beneficial to consider these results in comparison to volitional, in vivo recordings rather than in vitro experiments. With this in mind, it would be of interest to perform further tests of the variable input control scheme used here, under a variety of conditions, to determine if the “onion-skin” recruitment scheme (De Luca and Contessa, 2015) best applies in cases of lifelike synaptic control. In the experiments which led to the origination of this term for recruitment, De Luca and Contessa (2015) showed that the earliest-recruited motor units in their human volunteers fired at the highest rate throughout a voluntary contraction, while later-recruited motor units fired at a lower relative rate. Plots of these data vs time showed a layered distribution in firing rate, resembling the layers seen when cutting into an onion.

It should be noted that the tests performed thus far use a very mild case in varying input to MUs by type by adjusting each successive type’s input by 2.5 nA, which represents only the variation in input to the MG MN pool from the contralateral pyramidal tract (Binder et al, 1998). The experiments this test was based on suggested as much as a fivefold increase in overall input for low-resistance cells as compared to those with high resistance. If further simulations are undertaken with a greater difference in input between MN types, it is quite likely that an onion-skin-like recruitment scheme would more clearly emerge.

The force and EMG results obtained under this control scheme also serve as a cautionary point for further modeling work. The Fuglevand force and EMG models implemented here (Fuglevand et al, 1993) were originally designed with the assumption of a strict adherence to the size principle. While this is not, in itself, a problem, when
recruitment proceeds in a method that fails to follow this assumption, the results of these models are significantly skewed. It should be possible to develop a version of this model more compatible with cell type variation and variable input conditions by making some adjustments to the means in which properties are assigned to motor units, e.g. by specifying specific values of $i$ to pertain to certain MU types. While further testing is necessary, this adjustment in assignment strategy should allow the use of the Fuglevand force and EMG models with increasingly complex models of $\alpha$-MN pools. This change will be particularly significant in models similar to those presented in this document, in which different models are used for each MN type.

The effects of non-uniform input may also be significant even in the case of models that use a single template to generate all pool cells. In all cases of uniform input, this type of pool, such as the one described recently by Powers and Heckman (2017), will display orderly recruitment. However, when a non-uniform input is applied, there is the potential for unexpected effects. One possibility would be the emergence of a reversed recruitment order, starting with the lowest input resistance and progressing to the highest, which would change their results but likely not have any adverse effects. Additionally, it would be possible, depending upon the non-uniform input used, to have an irregular recruitment order. This could occur as a result of variability in input resistance coupled with non-uniform input such that, as input resistance and excitability decrease, excitatory input increases. This could lead to a situation in which recruitment of cells near the middle of the pool occurs before those at the extrema. In this case, the results produced by such a model would be strongly adversely impacted, as the recruitment of cells would be strongly disordered.
HAPTIX and Clinical Significance

As a final note on the potential clinical significance of the work presented herein, the model pool is currently being used in the development and testing of motor decoding algorithms which will be used to convert the firing rate from peripheral nerves of patients to a control signal for prostheses (unpublished work, Elbasiouny lab). This work has the potential to provide patients with the ability to use their prostheses in the same manner as a natural hand, greatly improving their quality of life.
V. REFERENCES


gastrocnemius muscle of cat and rat. *Archives italiennes de biologie, 144*(1), 11-23.


library(Runuran)

library(asbio)

Zengel <- urnorm(70, 12, 0.4, -Inf, Inf)

Hochman <- urnorm(31, 11.6, 3.1, -Inf, Inf)

Munson <- urnorm(32, 11, 4, -Inf, Inf)

Allen <- c(7.9, 8, 8.2, 8.5, 8.7, 9, 9.4, 9.9, 10.4, 11.1, 12, 13.1, 14.7)

trt <- as.factor(c(rep("Zengel", 70), rep("Hochman", 31), rep("Munson", 32), rep("Allen", 13)))

dat <- c(Zengel, Hochman, Munson, Allen)

tukey <- pairw.anova(dat, trt, 0.95, "tukey")

tukey

plot(tukey)