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The effects of model composition design choices on high-fidelity simulations of motoneuron recruitment and firing behaviors

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Abstract

Objective—Computational models often require tradeoffs, such as balancing detail with efficiency; yet optimal balance should incorporate sound design features that do not bias the results of the specific scientific question under investigation. The present study examines how model design choices impact simulation results.

Approach—We developed a rigorously-validated high-fidelity computational model of the spinal motoneuron pool to study three long-standing model design practices which have yet to be examined for their impact on motoneuron recruitment, firing rate, and force simulations. The practices examined were the use of: 1) Generic cell models to simulate different motoneuron types, 2) discrete property ranges for different motoneuron types, and 3) biological homogeneity of cell properties within motoneuron types.

Main results—Our results show that each of these practices accentuates conditions of motoneuron recruitment based on the size principle, and minimizes conditions of mixed and reversed recruitment orders, which have been observed in animal and human recordings. Specifically, strict motoneuron orderly size recruitment occurs, but in a compressed range, after which mixed and reverse motoneuron recruitment occurs due to the overlap in electrical properties of different motoneuron types. Additionally, these practices underestimate the motoneuron firing rates and force data simulated by existing models.

Significance—Our results indicate that current modeling practices increase conditions of motoneuron recruitment based on the size principle, and decrease conditions of mixed and reversed recruitment order, which, in turn, impacts the predictions made by existing models on motoneuron recruitment, firing rate, and force. Additionally, mixed and reverse motoneuron recruitment generated higher muscle force than orderly size motoneuron recruitment in these simulations and represents one potential scheme to increase muscle efficiency. The examined

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model design practices, as well as the present results, are applicable to neuronal modeling throughout the nervous system.

INTRODUCTION

Since Wilfrid Rall first adapted the cable theory to develop computer models of neurons (1), computational modeling has become useful for providing insights and assisting in the interpretation of experimental findings. However, some limitations are present in even the most “realistic” models. First, models are, by their nature, constrained by the quality and quantity of experimental data available on the system described (2). Additionally, models must attempt to find solutions to systems with many independent variables, which is challenging, particularly in larger models such as those used in systems biology (3). However, modern computational resources, such as the Neuroscience Gateway (4), do much to alleviate constraints on available computational power.

While reduced models employing simplified neuronal morphology remain useful for examining research questions of conditions which these models can accurately simulate, recent work has shown that significant abstractions in the modeling process can result in inaccurate predictions in other conditions. One example is the case of spinal motoneuron models, especially for firing behaviors mediated by dendritic active conductances (5). Therefore, the development process for computational models must balance design tradeoffs so that simulations incorporate sound design features appropriate for the scientific question and conditions under investigation.

The overarching goal of the present study is to examine how model design choices influence simulation results. To achieve that, we first developed a multi-scale, high-fidelity computational model of the spinal motoneuron pool that innervates the cat MG muscle, including its respective motoneuron types: Small, slow-firing S-types, intermediate FR-types, and large, fast-firing FF-types. The cat MG is one of the most studied and well-characterized muscles in literature. Thus, there exist sufficient data to accurately simulate the process of spinal motoneuron recruitment and firing rates. Our model incorporated great detail on the cellular and electrical properties that influence the motoneuron recruitment process then underwent a rigorous verification process to validate its parameters and results against numerous independent experimental datasets. Second, we used the developed model to examine three key model design features: 1) The effect of overlapping cell properties of modeled motoneuron types, 2) the effect of representing motoneuron types with discrete versus generic cell models, and 3) the effect of simulating biological variability in the cell properties of modeled motoneurons. We studied these three design features because a) these cellular properties are important to firing behaviors and thus are expected to be important to replicating experimental data more closely, and b) because published computational models of motoneuron pools do not incorporate these features (6–12). Thus, the impact of their absence on simulation results is currently unknown.

Our results show that incorporating overlap and biological heterogeneity of cell properties in modeled motoneurons and representing motoneuron types with discrete cell models expand the recruitment ranges of all motoneuron types and result in conditions of mixed and reverse

recruitment of motoneuron types. Together, these effects limit strict orderly size recruitment (i.e., the size principle) to a reduced range, produce a larger range of concurrent orderly, mixed, and reversed recruitment, generate high variability in motoneuron firing rates, and underestimate the force generated by the pool model. Accordingly, these results demonstrate that current, long-standing model design practices reinforce conditions that lead to strict cell recruitment based on the size principle and minimize conditions of mixed and reverse recruitment order, which have been observed experimentally in animals and humans (see Discussion). These results underscore the necessity of careful selection of the many design features available as well as the importance of understanding the impact those features have on results. Although the three features studied here are discussed in the context of spinal motoneuron simulations, these specific model design features and the general practice of careful feature selection are both relevant to simulations of neurons and systems throughout the nervous system.

METHODS

A multi-scale (synaptic, cellular, and system scales), high-fidelity (built from anatomically detailed motoneuron models) spinal motor pool model of the cat medial gastrocnemius (MG) muscle was developed in the NEURON simulation environment version 7.4 (13). Synaptic input to spinal motoneurons generated firing of individual motoneurons and spike trains of the full pool (fig. 1A). The total muscle force was also calculated from the spike train of individual motor units. The following sections detail the development process of each module of the spinal motor pool model.

Model of α -motoneuron types

We employed anatomically detailed motoneuron models, as opposed to simplified motoneuron models, because the latter have been shown to generate large errors in simulating motoneuron firing behaviors and active properties (5, 14). Additionally, incorporating detailed dendritic morphology has been shown to constrain model parameters and match experimental data with unique parameter sets (5, 15, 16). Individual α -motoneuron models were initially developed in NEURON and run on a personal computer. Three template models were developed - one for S, one for FR, and one for FF motoneurons. The previously developed and published active model of an FR α -motoneuron from the cat MG by Elbasiouny, Bennett (17) was used as a reference and an initial base point for the development of the S and FF models. Following the process used for development of the published FR model, models of S- and FF-type motoneurons were developed as follows:

Model morphologies—The motoneuron models employed realistic 3-dimensional (3D) dendritic morphology, obtained experimentally from type-identified motoneurons innervating the cat MG muscle. Respectively, the S, FR, and FF models used the dendritic morphologies of cells 36/4, 43/5, and 41/2 (fig. 1A, 18, 19). The soma diameters for these cells are 60, 48.8, and 49.2 μm , respectively (18). These morphologic data are available from NeuroMorpho (20, RRID: SCR_002145). Additional compartments representing the initial segment (IS) and axon hillock (AH) were also added to all three models as described in Elbasiouny, Bennett (17).

Passive properties—The passive parameters that determine the cable properties of the template motoneuron models were set according to the values reported by Fleshman, Segev (21) for cells 36/4, 43/5, and 41/2. For all cells, the resting membrane potential (V_{rest}) was set to -70 mV, the specific membrane capacitance (C_m) was set to $1 \mu\text{F}/\text{cm}^2$, and the specific axial resistance (R_a) was set to $70 \Omega\cdot\text{cm}$, for all compartments in the model (21–23). The soma, IS, and AH had specific membrane resistance (R_m) set to 455, 225, and $70 \Omega\cdot\text{cm}^2$ for cells 36/4, 43/5, and 41/2, respectively. The dendrites had R_m set to 15500, 11000, and $20000 \Omega\cdot\text{cm}^2$ for cells 36/4, 43/5, and 41/2, respectively. These values matched input resistance and time constant experimental data recorded from those individual cells (21). Starting with these values, R_m was then varied across the model cells in the pool in order to adjust the cells' individual input resistance and time constant within the 95% confidence interval of experimental data, resulting in the range of parameters in Table 1. In the simulations, input resistance and time constant were measured in the same way as in the experiments. Specifically, input resistance was measured by injecting long pulses of hyperpolarizing currents of varying magnitude into the soma while measuring the voltage deflection from V_{rest} to each. The time constant was measured by injecting a hyperpolarizing current pulse into the soma, and the somatic voltage traced during the return to V_{rest} using the graphical peeling method (24).

Active properties—Following Elbasiouny, Bennett (17), active conductances were included at the soma, IS, AH, and dendrites of the S, FR, and FF models. Channels on the soma included fast sodium (Naf), delayed-rectifier potassium (Kdr), small-conductance calcium-dependent potassium (SK), and N-type calcium (CaN) channels, as well as calcium dynamics. The AH and IS included Naf, Kdr, and persistent sodium (Nap) channels. These ion channels have been previously identified experimentally in spinal motoneurons (25–28) and their kinetic equations have been previously described (17, 29). The proper conductance values for these channels were determined by using the *Multiple Run Fitter*, a built-in optimization tool in NEURON, in order to generate action potential spikes with similar properties to those recorded experimentally in each motoneuron type (30–32). Starting with these values, channel conductances were then varied across the model cells in the pool and re-tuned per cell in order to produce the cells' individual electrical properties within the 95% confidence interval of experimental data, resulting in the range of parameters in Table 1.

The dendrites included voltage-gated $\text{Ca}_v1.3$ channels (33, 34), which mediate a calcium persistent inward current (PIC) responsible for the generation of self-sustained and bistable firing behaviors exhibited by spinal motoneurons (35–37). The model of $\text{Ca}_v1.3$ channels and its equations followed that developed in Elbasiouny, Bennett (17). The $\text{Ca}_v1.3$ channels were distributed uniformly over the dendritic band as previously shown in simulation studies (5, 17). The conductance of $\text{Ca}_v1.3$ channels was adjusted so that the total Ca^{+2} PIC reaching the soma matched experimental values obtained from cat motoneurons (38). The range of $\text{Ca}_v1.3$ conductance values as they varied across the motoneuron types and their dendritic location in the motoneuron models are shown in Table 1.

Synaptic inputs—Synaptic contacts were uniformly distributed over the dendritic arbors of model cells (fig. 1A, black dots on the dendrites). The excitatory monosynaptic Ia-

afferent input was included in each motoneuron model as previously described in Elbasiouny, Bennett (17) (Fig. 1A). The Ia-afferent synapses were uniformly distributed over the dendrites and their conductances were adjusted such that the Ia effective synaptic current (I_{I_N}) that reached the soma - when Ia afferents discharged at 180 Hz and when the soma was voltage-clamped at V_{rest} - was approximately 4.8 nA. 4.8nA is the value of I_{I_N} measured experimentally from MG cat motoneurons (36). The synaptic conductance was described by an alpha function with reversal potential and time-to-peak set according to previous experimental and modeling studies (17, 23, 39), as follows.

$$I_{syn}(t) = g_{syn}(t) \times (V_m - E_{syn}) \quad (\text{Eq. 1})$$

$$g_{syn}(t) = \bar{g}_{syn} \times [t/\tau_{syn}] \times e^{\left(1 - (t/\tau_{syn})\right)} \quad (\text{Eq. 2})$$

$$\tau_{syn} = 0.2 \text{ ms} \quad E_{syn} = 0.0 \text{ mV} \quad (\text{Eq. 3})$$

We then used Ia afferent conductances to activate the model motoneurons using ramp-and-hold (figs. 3, 4, 5) and triangular synaptic inputs (figs. 7 and 8). These figures show the effective synaptic current (calculated from different simulations under voltage clamp conditions) that resulted from Ia synapse activation. Because synaptic inputs used in this study were deterministic, the resulting spike trains were not random.

Axon models—A myelinated axon was connected to the IS of each motoneuron in the pool (40, 41). The myelinated axon was based on the model developed by McIntyre, Richardson (42), in which nodes of Ranvier and myelin were electrically represented. Node of Ranvier included Na^+ , Na^+ , and slow K^+ channels. For the S, FR, and FF models, the electrical parameters of the myelinated axon were adjusted to have conduction velocity of 74.43 m/s, 82 m/s, and 90.1 m/s, respectively, which are comparable to experimental data (table 2, 32, 43).

Force model—The total muscle force was simulated using the original model described by Fuglevand, Winter (6) in which the spike train of a given cell was converted into force using the original equations. Because the original Fuglevand, Winter (6) force model had the force in arbitrary units (i.e., not in Newtons), we included one modification to one force equation to introduce a multiplicative conversion factor (FCF), as follows:

$$f_{ij}(t) = g_{ij} \times \frac{TF_i \times t}{TD_i} \times e^{1 - t/TD_i} \times FCF \quad (\text{Eq. 4})$$

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 peak amplitude of the twitch force of the motor unit i , TD_i is the time to peak (or contraction time) of the motor unit i . The values of these parameters are shown in table 1. The FCF multiplicative factor then converts the force from arbitrary units to Newton, allowing the pool model to simulate force as generated by the cat MG muscle. Specifically, the value of FCF was determined such that it converts the spike train of individual motor units to twitch force (in Newtons) that matches experimental twitch force recordings from the cat MG muscle (44). In our simulations, the value of FCF was 4.8 and twitch times ranged from 20 ms to 110 ms to match the data from the cat MG muscle (45). The values of TF ranged from 4.8 – 15.91 mN for S cells, 17.44 – 52.72 mN for FR cells, and 57.81 – 528 mN for FF cells. The values of TD ranged from 71.23 – 110 ms for S cells, 46.13 – 68.89 ms for FR cells, and 20 – 44.61 ms for FF cells.

Experimental Design and Statistical Analysis

To evaluate the similarity, or lack thereof, between the motoneuron pool model properties (simulated outputs) and experimental datasets, statistical analysis of key model properties was undertaken, in the form of comparisons between pool model and experimental data. Analysis was performed for four important electrical properties: Rheobase, input resistance, AHP $\frac{1}{2}$ -decay, and time constant. These four properties have been previously identified to provide correct α -motoneuron type identification within the cat MG muscle for 97% of cases when used in combination (30). Tukey's honestly significant difference (HSD) test, or the Tukey-Kramer method (46), was used to perform pair-wise comparisons between model and experimental datasets. Several criteria were considered for selecting this studentized range statistic (also known as the q-statistic) methodology over the commonly used Student's t-test. First, the Tukey-Kramer method is robust enough to test data of normal and non-normal distributions (47). Second, the test can analyze datasets of unequal sample sizes (46). Third, the experimental datasets against which we compared simulation results used both statistic q and Student t-test methods in their original statistical analysis (30). Model data was compared to samples generated from the statistical summary data (i.e., mean, standard deviation or error, and sample size) published in experimental studies. Directly comparing model data to statistical summary data necessitated generating samples with the characteristics of the published summary data. To reduce sampling and type II errors, the comparison between model data and experimental data for each property was repeated 10 times. Model data was considered similar to experimental data when the test resulted in a *failure-to-reject* (FTR) for more than 5 of the 10 repeated comparisons for at least one of the experimental datasets. This statistical analysis was carried out in R Studio, version 3.2.3 (R Studio Team, 2015). In all tests, the null hypothesis was $H_0: \mu_{\text{model}} = \mu_{\text{experimental}}$, and significance level was $\alpha = 0.05$.

RESULTS

I) Pool model development, fitting of parameters, and verification results

The first goal of the present study was to develop a multi-scale, high-fidelity computational model of the spinal motor pool of the MG cat muscle. This section details the development,

fitting, and verification processes of the resultant pool model using the template models described in Methods. High fidelity S, FR, and FF template cell models (see Methods for detail) were developed, then used to generate a computational model to represent the motoneuron pool innervating the cat MG muscle (fig. 1A). The pool model consisted of a total of 51 model cells in which 13 cells (~25%) were of S type, 13 cells (~25%) of FR type, and 25 cells (~50%) of FF type, which matches the relative ratios of motoneuron types reported experimentally from the cat MG muscle (30, 48, 49). Simulations of the pool model were executed in NEURON running on high-performance computer hardware using the Neuroscience Gateway (4).

To optimize the electrical properties of the motoneuron pool, we varied electrical, channel conductance, and force parameters of the somatic, dendritic, and axonal membranes across the model cells in the pool model (fitting parameters shown in table 1), until we matched the pool model's electrical output properties to a wide range of experimental measurements within their mean and standard deviation data range for each motoneuron type (see table 2). The experimental datasets published in Zengel, Reid (30) and Hochman and McCrea (32) provided the primary target values to guide model development and match pool model property values; therefore, we call them the "source datasets". These studies were selected as the source datasets because they provide detailed examination of the electrical properties of identified motoneuron types innervating the cat MG muscle. Additionally, because some properties were measured in one study but not the other [e.g., AHP $\frac{1}{2}$ decay time was measured in Zengel, Reid (30) but not measured in Hochman and McCrea (32), whereas voltage threshold was measured in Hochman and McCrea (32) but not in Zengel, Reid (30)], the combination of the two studies provided comprehensive datasets of electrical properties of the cat MG motoneuron pool with identified types. When tested using somatic current injection, the model cells exhibited bistability and self-sustained firing behaviors as distinct to each motoneuron type (fig. 2). Additionally, when the pool model data were plotted against experimental data of identified motoneurons, the model data showed comparable relationships among electrical properties for each motoneuron type (fig. 3A shows the relationship between the rheobase and input resistance of the pool model plotted versus experimental data - obtained with permission - from the Zengel, Reid (30) study).

II) Sensitivity analysis

To test the robustness of the model parameters and simulation results, a comprehensive sensitivity analysis was conducted. This analysis involved: 1) an iterative process of comparison of model properties against the source experimental datasets and adjustment of model parameters to improve the match, 2) independent validation of model properties against external experimental datasets not used in model development, and 3) examination of the effect of varying the number of cells in the pool model on motoneuron recruitment and firing rates.

1) Statistical analysis of the pool model parameters - comparison to source datasets—To further verify that the pool model faithfully replicates the experimental data of the source datasets used in model development, we used the Tukey-Kramer pair-wise test, for comparison of means between samples of different n (46), to compare the model

properties versus the source datasets. We executed the Tukey-Kramer pair-wise test using tools from the R library *asbio* (51). Specifically, we provide the Tukey-Kramer pair-wise test with the pool model raw data of a given property, as well as a sample generated from the statistical summary of experimental data of that property (i.e., mean, standard deviation or standard error, and *n*) from the experimental study. The sample data from the experimental statistical summaries were generated using a boundable uniform distribution from the *Runuran* R library (52). The outcome of the Tukey-Kramer test would be either *reject* or *failed-to-reject (FTR)*, depending on how well the model data matches the statistical characteristics of experimental data. An FTR outcome would indicate that the model data and experimental data have similar statistical characteristics, whereas a *reject* outcome would indicate that they have different statistical characteristics. Because of the randomization process and to account for the variability in samples among different test runs, we ran, for each property, 10 runs of the Tukey-Kramer test to compare the model data and experimental data, then measured the number of runs with FTR outcome (# of FTR). We report the # of FTR in table 3 and use it as a measure of the goodness of fit between the model data and experimental data for that property. The higher the # of FTR in table 3, the higher the likelihood of statistical similarity between the model and experimental datasets.

We ran this statistical comparison between model data and the source datasets on four key electrical properties: 1) Input resistance, 2) rheobase, 3) AHP $\frac{1}{2}$ -duration, and 4) time constant. These were selected over other electrical properties for this analysis because it has been previously shown that these four properties, when used in combination, provide 97% correct motoneuron type identification of the cat MG muscle (30). Table 3 shows the results of such analysis in which the model data were compared, for each property, versus the source datasets for each motoneuron type. Because a range, as opposed to a specific value, of sample size for the electrical properties was reported in the Hochman and McCrea (32) study for each motoneuron type, we ran for each property two sets of the Tukey-Kramer test, one using the lower end of the sample size range (denoted by 'low *n*' in table 3) and another using the upper end of the sample size range (denoted by 'high *n*' in table 3). We cycled through several iterations of adjusting model parameters and testing model data versus the source datasets for all key properties until we reached an optimal set of model parameters that replicated experimental data well, as shown in table 3. Our results show that, for all key properties, the pool model data had similar statistical characteristics to at least one experimental study of the source datasets, as indicated by the high FTR numbers in table 3. Interestingly, in some instances the model data matched the data of one experimental study very well but matched the data of the other experimental study poorly (see for example the rheobase data of FF cells and the time constant data of all types in table 3). Upon further investigation, we found differences among the experimental datasets in those properties (see the difference in means in time constant data between the Zengel, Reid (30) and Hochman and McCrea (32) studies in table 2), indicating that the inability of the model to match both datasets for some properties is due to the differences in reported values among the experimental studies. In sum, this analysis confirmed that the pool model replicates the experimental data of the source datasets robustly.

2) Statistical analysis of the pool model parameters - comparison to external datasets—

To validate that the pool model replicates the experimental data of type-identified cat MG motoneurons, we compared the pool model data to independent experimental datasets of cat MG motoneurons that were not used in the pool model development (called “external datasets”). Specifically, the Tukey-Kramer pair-wise test was used to compare the four key electrical properties (input resistance, rheobase, AHP $\frac{1}{2}$ -duration, and time constant) between the pool model data versus the external datasets of either Foehring, Sybert (31) or Ulfhake and Kellerth (53) on cat MG motoneurons. Table 4 shows that, for all electrical properties and for all motoneuron types, the pool model has electrical data similar to experimental datasets. The only exception to this was in the AHP $\frac{1}{2}$ -decay of FF cells, which showed a poor match to the external dataset (table 4) despite the perfect match with the source dataset (table 3). This discrepancy resulted from the dissimilarity in the AHP $\frac{1}{2}$ -decay means between the source (30) and external (31) datasets (see table 2), as well as the reported standard error of zero for this parameter by Zengel, Reid (30) despite measuring from 83 cells. In any case, among the source and external experimental datasets, all four key properties matched either one (as for the AHP $\frac{1}{2}$ -decay), two (as for the time constant and rheobase of FF cells), or three (as for the rheobase and input resistance) independent experimental datasets on type-identified MG cat motoneurons.

In conclusion, this analysis demonstrates that the pool model, as developed, is able to robustly replicate data obtained from different experiments and is not specifically tied to the datasets from which it was developed.

3) Pool granularity analysis—

In this section, we tested the sensitivity of the pool model results to variations in the number of cells in the pool model. Specifically, we assessed the changes in motoneuron recruitment profile and firings when the number of cells in the pool model was varied (i.e., mini pool models of $n=13$ and $n=27$ were compared to the standard pool model of $n=51$). The relative overlap in cell properties among the motoneuron types was not changed. In these simulations, cells in the mini pool models were generated within the same parameter boundary values as the standard pool model, and had similar median values for all cell properties and similar motoneuron type proportions (i.e., the 13-cell pool model had 3 S, 3 FR, and 7 FF cells; the 27-cell pool model had 7 S, 7 FR, and 13 FF cells).

Figure 4 shows the results of these simulations. In response to a ramp-and-hold synaptic input of equal magnitude to all cells, motoneuron recruitment was measured during the ramp phase (plotted on the x-axis of figs. 4A–C) and the firing rate of each cell was averaged over the last portion of the hold phase (marked in red in fig. 4D, plotted on the y-axis of figs. 4A–C). The 27-cell (fig. 4B) and 13-cell (fig. 4C) mini pool models had similar motoneuron recruitment patterns, similar firing rates of different motoneuron types, and to some extent, similar percentages of recruited motoneurons to that of the standard 51-cell pool model (fig. 4A). Specifically, the 13-cell pool model recruited a total of 9 cells (69%), the 27-cell pool recruited 21 cells (77.7%), and the 51-cell pool recruited 40 cells (78.4%). The percentage of recruited motoneurons of each type changed for the smaller version of the pool (i.e., 13-cell pool model) due to the presence of much fewer model cells with intermediate values between the median and most excitable extreme for each type. This is particularly exemplified by the FR-type motoneurons in the 13-cell pool model because there are only 3

cells of this type present and, therefore, no cells of this type between the median and the most excitable extreme cells. As a result, only $\frac{2}{3}$ of FR-type motoneurons are recruited in this version of the pool, even though 6/7 and 11/13 FR cells were recruited in the 27-cell and 51-cell versions of the pool model, respectively.

In sum, this analysis shows that 1) the pool model is developed in such a way as to have robust results even with changing numbers of constituent cells, and 2) the standard pool model of 51 cells has an adequate number of constituent cells to simulate the pool firing with adequate resolution. The latter is critical, especially given that we need to represent overlap in the cell properties' ranges among the motoneuron types, as occurs in experimental data.

III) The effect of model composition design choices

In this section, we used the standard 51-cell pool model to examine the effect of model design choices on the simulation results. Three design features were examined: 1) The effect of overlap in cell properties of modeled motoneurons, 2) the effect of modeling motoneuron types using discrete versus generic cell models, and 3) the effect of simulating biological variability in cell properties of modeled motoneurons. We studied these three design features because published computational models of motoneuron pools do not incorporate them (6–12). Thus, the impact of these features' absence on simulation results is currently unknown.

1) Effect of overlap in cell properties of modeled motoneurons—To examine the effect of overlap in cell properties among motoneuron types, we compared motoneuron recruitment order of the standard 51-cell pool model to another version of the pool model in which the overlap in cell properties was removed (i.e., see fig. 5A, compare to fig. 3A). In the latter, the number of cells and proportions of each type in the pool were the same to the standard pool model with overlap (n=51 cells), but the boundary values for each motoneuron type were reduced equally such that no overlap in the rheobase and input resistance took place between motoneuron types. However, the cells of each type were distributed between the new boundaries without altering their mean values. Our results show that, in response to a ramp-and-hold synaptic input of equal magnitude to all cells, motoneurons in the standard pool model with overlap were initially recruited in the order of their size (i.e., the size principle), after which their recruitment was spread over a large overlapping range (fig. 5D). For instance, S motoneurons were recruited over 1%-80%, FR motoneurons over 28%-100%, and FF motoneurons over 45%-98% of activated cells (see fig. 6B for illustration of the recruitment ranges). There were also many instances of mixed recruitment in which motoneurons of two, and sometimes all three, different types were activated around the same time (see the dotted rectangle in fig. 3B for recruitment over time). Additionally, many instances of reverse recruitment were observed in which FF cells were recruited before S or FR cells (black arrows in fig. 5D show some examples). Interestingly, the average motoneuron firing rates differed significantly among the motoneuron types. While the synaptic current had the strongest effect on S motoneurons (due to their highest input resistance) their firing rates were limited by their long AHPs. Synaptic current, on the contrary, did not drive FF motoneurons at their full capacity (due to their lowest input resistance), yet they fired at comparable rates to S motoneurons due to their much shorter

AHPs. Due to FR motoneurons' intermediate input resistance and AHP values, as well as their large intermediate range that spans the S and FF motoneuron properties, the same synaptic current caused FR motoneurons to have the highest firing rates in the pool (higher than S and FF motoneurons). Additionally, there is some variability in firing rate within each motoneuron type (see the range of the blue and purple dots over the y-axis in fig. 5D).

Cells in the pool model without overlap had a comparable number of activated cells, were recruited at comparable firing rates, and the average motoneuron firing rates also differed among the motoneuron types. However, the recruitment range of each cell type was much smaller, particularly for S and FR motoneurons (i.e., S motoneurons were recruited over 1%-33%, FR motoneurons over 35%-85%, and FF motoneurons over 60%-100% of activated cells; compare recruitment ranges in fig. 6B and C). Also, there was less frequent reversed or mixed recruitment of two cell types and no mixed recruitment of 3 cell types. Additionally, motoneuron firing rates exhibited less variability (compare the range of the purple dots over the y-axis in figs. 5D and E).

The effect of these motoneuron recruitment changes on the simulated total muscle force is shown in fig. 7. In response to a triangular input, the pool model without overlap underestimated the force magnitude throughout the ascending and descending input phases relative to that of the standard pool model with overlap (compare green vs. black traces in fig. 7A). This underestimation of force in the standard pool model without overlap is due to lack of early recruitment of FR and FF motoneurons, which contribute higher force than S motoneurons. The reason there is sustained force after the termination of the triangular input (black and green traces do not go down to zero after $t=5000$ in fig. 7A) is due to the self-sustained firing of S motoneurons due to activation of their Na^+ and Ca^{2+} PICs.

Taken collectively, the lack of overlap in cell properties of modeled motoneurons compresses the recruitment ranges of all motoneuron types and accentuates orderly size recruitment ($S > FR > FF$), and consequently underestimates the magnitude of total pool force.

2) Discrete vs. generic representation of motoneuron types—In the simulations of the pool model without overlap, we modeled each motoneuron type separately (indicated by the different dot colors in fig. 5A for each motoneuron type), based on discrete templates of distinct electrical and morphological properties. However, motoneuron computational studies in literature usually represent the motoneuron pool with generic cell models whose electrical parameters are extended to span the full range of S to FF motoneuron properties (6–12). Consequently, there is no overlap in cell properties of modeled motoneurons in these simulations. Therefore, to assess the effect of modeling motoneuron types using discrete versus generic cell models, we developed a homogeneous pool model of 51 cells using only a single template cell model (i.e., the FR template) to create the entire pool, and the data were compared to that of the standard pool model without overlap (compare figs. 5A and B). The FR template was chosen for this purpose as the electrical and morphological properties of FR cells are intermediate between those of S and FF type motoneurons (18, 19, 21). However, the parameters of the FR-based model cells were extended to span the electrical properties of all three motoneuron types and cover the same range of rheobase and input

resistance of the standard pool model without overlap, as shown in fig. 5B. In response to the same ramp-and-hold synaptic input of equal magnitude to all cells, the homogenous pool model had very different motoneuron recruitment and firing rate profiles than that of the standard pool model without overlap: 1) There were fewer activated cells in the homogenous pool model (see the max x-axis value in fig. 5F); 2) all cells in the pool were recruited in the order of their size with a much compressed recruitment range (S motoneurons were recruited over 1%-35%, FR motoneurons over 38%-70%, and FF motoneurons over 73%-100% of activated cells, see fig. 6D for recruitment ranges); 3) fewer FF cells were recruited in the homogeneous model (~30% less, fig. 5F); 4) there were no instances of reverse or mixed recruitment at all; 5) motoneurons of the homogenous model fired at much higher firing rates (fig. 5F); 6) the average motoneuron firing rate was comparable among all motoneuron types and had an intermediate value compared to those of different motoneuron types in the standard pool model without overlap (fig. 5F); and 7) average motoneuron firing rates showed much less variability for the vast majority of cells, except those with the highest firing threshold (fig. 5F, compare to figs. 6C and 6G in Moritz, Barry (54)).

When the force traces were compared in response to a triangular input, we found that the homogenous pool model generally underestimated the total muscle force throughout the ascending and descending ramps, but showed a much higher sustained force after input termination, relative to the standard pool model without overlap (compare the gray and green traces in fig. 7A). Force underestimation is due to the reduced recruitment number and more compressed recruitment range of FF motoneurons, which contribute the highest force amongst all types, in the homogenous pool model. The longer sustained force was due to the higher self-sustained firing rate of S motoneurons in the homogeneous pool model.

In sum, modeling motoneuron types using generic cell models, as opposed to discrete templates of distinct properties, reinforces orderly size recruitment and abolishes reverse or mixed recruitment of motoneurons (fig. 6D), causing the homogeneous pool model to generate altered motoneuron firing rates and force results.

3) Effect of biological variability—One of the important design questions in developing a realistic network or pool model is whether biological variability in cell properties of the modeled cells will be incorporated. Fig. 3A shows that our standard 51-cell pool model was able to capture the ‘average’ relationship between rheobase and input resistance successfully; however, the model does not reproduce the biological variability or heterogeneity in electrical properties observed experimentally (i.e., there are multiple cells of different rheobase values at a given input resistance value, as well as multiple cells of different input resistance values at a given rheobase value). This biological variability is critical because it increases the overlap in electrical properties among motoneuron types and causes multiple motoneurons of different types to be recruited at the same current threshold. This, in turn, leads to less orderly recruitment of motoneurons and higher variability in their firing rates, which have been observed experimentally (see Discussion). We, therefore, tested the effect of incorporating biological variability in the properties of modeled cells on motoneuron recruitment patterns in response to a ramp-and-hold synaptic input of equal magnitude to all cells. To achieve that, a heterogeneous version of the pool model was developed, which was formed of 153 cells generated within the same parameter boundary

values, and with similar mean values for cell properties and similar motoneuron type proportions to the standard pool model (fig. 5C). The action potential spike threshold of various cells of the heterogeneous pool model was depolarized or hyperpolarized, which caused upward and downward shifts around the means of the model properties and captured the biological variability in experimental data (fig. 5C shows the relationship between rheobase and input resistance for the pool as compared to the experimental data of Zengel, Reid (30)). Many differences in motoneuron recruitment were seen in the heterogeneous model relative to the standard pool model: 1) Many more cells were activated by the same synaptic input (see the max x-axis value in fig. 5G), due to the addition of more excitable cells to the pool (46 additional cells were recruited in the heterogeneous pool model); 2) the range of recruitment was expanded for all cell types (S motoneurons were recruited over 1%-98%, FR motoneurons over 23%-100%, and FF motoneurons over 37%-99% of activated cells, fig. 6A); 3) recruitment based on the size principle was limited to the first 28% cells, after which mixed and reverse recruitment among all motoneuron types were pronounced (fig. 5G); and 4) there is large variability in firing rates within each motoneuron type and among the different types (fig. 5G). Because the heterogeneous pool model has a larger number of motoneurons than the other pool model versions, we could not compare its force data against the other pool model versions. However, for the same number of motoneurons, a heterogeneous pool model would be expected to generate higher force than any other model, due to both the activation of a higher percentage of FR and FF cells at lower firing thresholds and the larger variability in firing rates.

Together, these results show that simulating biological variability of modeled cell properties enhances the variability in motoneuron firing rates and recruitment ranges, increases conditions of mixed and reverse recruitment among motoneuron types, and limits strict orderly size recruitment to a smaller initial range.

IV) Effect of uniform vs. non-uniform synaptic inputs

Our simulations heretofore have used uniform synaptic inputs of equal magnitude to all motoneuron types. This simulates the condition of excitatory inputs from Ia afferents to motoneurons (55). However, in this set of simulations, we used non-uniform synaptic inputs of varying magnitudes to motoneuron types ($FF > FR > S$) to simulate the effect of excitatory inputs from descending tracts to the motoneuron pool innervating the MG muscle in the cat (56–58). To achieve this, the synaptic conductances were varied among the motoneuron types (but equal within each type) in the standard pool model of fig. 3, such that $I_{N, FF} = 6.5 \text{ nA} > I_{N, FR} = 4 \text{ nA} > I_{N, S} = 1.5 \text{ nA}$ (fig. 8D), which simulates the difference in nonuniform synaptic current to the motoneuron pool from the contralateral pyramidal tract (56). The results were then compared to those of the standard pool model with uniform synaptic input of 4 nA (fig. 8B). In this way, the mean synaptic current to the pool was comparable ($= 4 \text{ nA}$) between the simulations of uniform and non-uniform current conditions, only differing in the distribution of synaptic current among motoneuron types (compare fig. 8B and D). Because of the difference in distribution of synaptic inputs to cells in the pool, motoneuron recruitment was completely reversed, as expected, in the non-uniform input simulation (compare fig. 8A to 8C). Specifically, FF motoneurons were recruited first, followed by FR motoneurons, then S motoneurons (fig. 8C), which is

opposite to motoneuron recruitment in the uniform input simulation (fig. 8A). In both uniform and non-uniform input simulations, motoneurons exhibited mixed recruitment, and the recruitment ranges were comparable for all motoneuron types (the same number of S and FR cells were recruited in both simulations, but slightly more FF cells in the non-uniform simulation, given the higher synaptic current they received). Additionally, the firing rates of S and FF motoneurons were comparable in the two input conditions (compare the y-axis range of the blue and purple dots in figs. 8A and C), and FR motoneurons always had the highest firing rates in the pool (fig. 8C).

When the force traces were compared in response to a triangular input, we observed that the nonuniform input condition showed a significantly higher sustained force after the termination of the input current, relative to that of the uniform input condition (compare the cyan and black traces in fig. 8E; note that no inhibitory synaptic input was applied to turn off the PIC, resulting in sustained force). This was counter-intuitive, because the firing rate of S motoneurons (shown in figs. 8A and C) and their self-sustained firing rates are comparable in the two input conditions; thus comparable sustained force should be generated. Upon further investigation, we found that the higher sustained force resulted from the way the Fuglevand, Winter (6) force model is designed. Specifically, because the Fuglevand force model was originally designed to work with a homogenous pool model, in which motoneurons are recruited based on the size principle (S cells, followed by FR cells, then FF cells), the model then assigns motor unit properties based on recruitment order, determined by the cell firing order. This method of force assignment is correct as long as motoneuron recruitment order follows the size principle strictly, as is the case with the homogeneous model. However, in situations of mixed or reverse recruitment orders, the original Fuglevand force model will not generate correct estimation of the force, because the model will treat an early-recruited FR or FF cell as an S cell and underestimates the generated force; or will treat a late-recruited S cell as an FR or FF cell and overestimates the generated force. To dissociate this dependency between force assignment and recruitment, we modified the process of motor unit force property assignment in the Fuglevand force model to make it by fixed cell index, as opposed to by recruitment order. In this way, any given cell in the pool will be always assigned consistent force properties regardless of when it is recruited (early or late). This modified Fuglevand force model is thus compatible to work with motoneuron pool models experiencing irregular recruitment order, including ones deviating from the size principle. Using this modified Fuglevand force model, our simulations show that a non-uniform synaptic input generates much higher muscle force than does a uniform input, due to early and stronger recruitment of FF cells (compare the black and green traces in fig. 8E). Importantly, the sustained force was comparable between the uniform and non-uniform input conditions, in agreement with the firing rate data of S motoneurons.

In sum, these simulations show that recruitment deviating from the size principle, as the ones generated by the descending tracts, are more efficient in generating high forces from muscles.

DISCUSSION

The present study provides a systematic analysis of the impact of several long-standing model design practices on the predictions of motoneuron recruitment, firing rate, and force simulations. The practices examined were the use of: generic cell models to simulate different motoneuron types; discrete property ranges for different motoneuron types; and biological homogeneity of cell properties within motoneuron types. Our approach compared motoneuron recruitment, firing rate, and force data between motor unit pool models of similar parameters, except for the design features mentioned above. Our results show that each practice accentuates cell recruitment based on the size principle and minimizes conditions of mixed and reverse recruitment order. Thus, current simulations might be under-representing the occurrence of mixed/reverse recruitment, which has been observed in animals and humans (see below). Although discussed here in the context of spinal motoneurons, these design practices are relevant to simulations throughout the nervous system.

Novelty of the present work

The present study models the spinal motoneuron pool at a higher level of realistic detail than has been previously incorporated, to the authors' knowledge. Different motoneuron types (S, FR, and FF) were represented by discrete models with distinct electrical properties and 3D morphological reconstructions specific to their respective types for MG cat motoneurons. These models and their synaptic inputs were optimized, following our published approach, to incorporate somatic and dendritic active conductances that match multiple sets of experimental data under various pharmacological and voltage-clamp conditions. They successfully replicate motoneuron firing behaviors (e.g., bistability and self-sustained firing) under various current-clamp conditions (5, 17, 59). Overlap in motoneuron type properties and biological heterogeneity in cell properties were additionally modeled as observed experimentally in MG cat motoneurons (30).

Furthermore, we developed and validated the electrical properties of each motoneuron type against multiple experimental datasets on type-identified MG cat motoneurons, with a level of rigor not previously implemented, to the authors' knowledge. This analysis involved 1) iterative comparisons to source experimental datasets, 2) comparisons to independent experimental datasets not used in model development, and 3) sensitivity analysis on pool model parameters. Comparisons against the source and external experimental datasets relied on repeated, randomized statistical analyses that assessed the similarity of several statistical characteristics between model and experimental data samples. Our results show that the pool model robustly replicates both the source and external experimental datasets and is not coupled to the datasets used in its development. Importantly, the firing behavior of model motoneurons in the present study resembles those measured from MG cat motoneurons (60).

The present study has some critical differences from earlier simulation studies that examined motoneuron recruitment and its effects on firing rate profiles and muscle force (61, 62). In earlier studies, pool models were constructed and validated such that motoneurons would be recruited following the size principle and the resulting force computed. Therefore, their results are based on strict orderly recruitment of motoneurons that only differ in activation

ranges. Our study, on the other hand, constructed and validated a pool model that incorporated a high level of detail and simulated overlap and heterogeneity in the cellular properties of different motoneuron types. Therefore, motoneuron recruitment in the present study was not preset, but rather an outcome of the rich variation in model motoneuron cellular properties. The resulting motoneuron recruitment profiles exhibited a mix of orderly, mixed, and reversed recruitment. Thus, predictions of motoneuron recruitment and resulting force in the present study differ fundamentally from those examined in earlier studies.

Evidence on mixed and reverse motoneuron recruitment

Although abundant evidence on ordered recruitment of motoneurons is reported in literature, evidence on mixed and reversed recruitment has been also observed in animals and humans (for review, see 63, 64, 65). For instance, mixed and reverse motoneuron recruitment has been observed in ballistic (66–68) and eccentric (69) contractions, as well as within (70, 71) and across muscles (72, 73). These data indicate that mixed and reverse motoneuron recruitment indeed occurs in biological systems and could increase under conditions of ageing, re-innervation, pain, and fatigue (64).

Modeling practices' ramifications

Although spinal motoneurons have multiple types with distinct morphological and functional properties, their electrical properties are usually considered to form a continuum. Thus, published motoneuron pool models usually simulate the motoneuron pool using generic cell models with a few properties adjusted to discretely represent S, FR, or FF electrical properties (6–8, 10, 12). There are ramifications of this simplification: 1) No overlap in cell properties among motoneuron types occurs, and 2) no biological variability in cell properties is incorporated. However, these modeling design features are critical, because their presence causes multiple motoneurons of different types to be recruited around similar current thresholds, thereby affecting motoneuron recruitment order. More importantly, the impact of the lack of these design features has not been assessed until the present study.

Beyond the pool model design considerations discussed above, design choices for motoneuron cellular properties also impact simulation accuracy. Our group and others have shown that motoneuron models with simplified dendrites have significant errors in simulating firing behaviors (5, 14), especially those resulting from dendritic active conductances (5). This is because the major target for reduction is the dendrites. However, simplified representation of dendrites to simulate firing behaviors generated by dendrites (e.g., bistability and self-sustained firing, which result from dendritic PIC) is an unsubstantiated design choice. More importantly, employing many cell models with reduced dendrites in pool simulations may magnify the total error, which is especially problematic when such simplified motoneuron models are used to build pool models to study motoneuron firing behaviors and rates, and force (7, 10, 12, 54, 74).

Orderly size recruitment of motoneurons: An over-emphasized principle

Since its presentation by Elwood Henneman in 1957 (75), the size principle has been very useful in explaining how the central nervous system could recruit motor units in a graded manner for fine movement control, and in linking basic neuronal properties, such as cell size

and membrane resistance, to overall cell function and generation of a coordinated behavior. Although the correlation between motoneuron size and type is strong, it is not 1:1 [i.e., motoneurons types overlap largely in soma and cell size (18, 53)]. This makes application of the size principle to predict motoneuron type recruitment less straightforward. Situations of mixed (recruitment of several motoneuron types at the same time) or reverse (FF>FR>S) recruitment would be supported by the wide overlap and large biological variability in rheobase and input resistance of motoneurons observed experimentally. Furthermore, multiple motoneuron types with similar rheobase values and motoneurons of similar resistances with different rheobase values have both been observed (30); such highly variable motoneuron electrical properties would also support mixed/reversed recruitment. Finally, as discussed above, situations of mixed and reverse recruitment have been observed in animals and humans. However, regardless of this evidence, motoneuron computer models, unintentionally and via common modeling practices discussed above, continue to reinforce conditions of extremely orderly size recruitment and lessen conditions of reverse and mixed recruitment. Our simulations results suggest that strict orderly size recruitment of motoneurons occurs, but in a compressed range (in the initial 30% range of recruitment), after which orderly, mixed, and reverse motoneuron recruitment occurs frequently due to the overlap in electrical properties among the different types. In fact, mixed and reverse motoneuron recruitment could provide functional advantages over orderly size recruitment, because an early, expanded FF motoneuron recruitment range would allow these high-force cells to contribute to the brief weak-to-moderate contractions performed most of the time. Strict orderly recruitment would allow FF cells to only contribute to intense contractions. Mixed and reverse motoneuron recruitment would be particularly advantageous in muscles with predominant fast-fiber composition (FR and FF types), such as the MG and many other muscles exhibit. Our simulations show that mixed and reverse motoneuron recruitment generates higher muscle force than orderly motoneuron recruitment, and could represent one scheme for more efficient activation. It is also important to note that human motor units sometimes show differences in properties, and potentially innervation patterns, from those of animal motor units. For instance, motor units of the human thenar muscle show weak correlation among various twitch parameters known to exist in animals (76), indicating a potential deviation from the innervation pattern expected from the size principle. Accordingly, investigators would need to consider these differences when developing models of human motor units.

Modified Fuglevand force model

Since its publication in 1993, the Fuglevand, Winter (6) force model has been very useful and widely used in simulating force data from motoneuron pool models (8–11, 54). However, because this model was originally developed to work with a homogenous pool model, the Fuglevand model is most compatible with orderly size recruitment of motoneurons and is limited when used with mixed or reverse motoneuron recruitment. To address this limitation, we have modified the Fuglevand force model such that motor unit force property assignment is made by cell index rather than recruitment order, which makes the modified model more compatible with any recruitment order.

Conflicts among experimental datasets

In the process of comparing model data against experimental datasets, we observed instances in which the model data for some properties matched one dataset very well, but not the other (time constant in table 3 is an example). Upon further analysis, we found that this discrepancy resulted from differences among experimental datasets in values for those properties. This point is important for modeling studies, as discrepancies among experimental datasets do exist. One possible explanation for the inconsistency among experimental datasets for a given property is the difference in the methods used to measure this property in one study versus another. It is therefore important for the modeler to decide and justify what key properties they need to simulate and which experimental datasets provide the best guidance. Taken together, the results of this study ultimately suggest that it is critical for the field to examine the underlying assumptions of computational models and assess the compatibility of published models and methods before applying them to their own research questions.

CONCLUSION

In conclusion, we examine three long-standing model design practices: 1) Generic cell models to simulate different motoneuron types, 2) discrete property ranges for different motoneuron types, and 3) biological homogeneity of cell properties within motoneuron types. Our results indicate that each practice accentuates conditions of motoneuron recruitment based on the size principle, and minimizes conditions of mixed and reversed recruitment orders. This, in turn, impacts motoneuron recruitment, firing rate, and force predictions made by existing models. The present results are applicable to neuronal modeling throughout the nervous system.

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Figure 1.

Schematic diagram of pool model structure and cell distribution. **A)** Morphometric data used for development of S (blue), FR (purple), and FF (red) type motoneuron models. A total of 51 cells were included in the pool model to simulate the cat MG muscle, with 13 S cells (~25%), 13 FR cells (~25%), and 25 FF cells (~50%) as observed experimentally (18–20). Dots on motoneuron dendrites illustrate synaptic inputs distributed uniformly over the cell dendrites. The black triangular traces illustrate the triangular synaptic inputs used to activate the motoneurons in the pool model, and the repetitive colored traces illustrate which cells fire action potential (AP) spikes. The spike train of each motoneuron (MN) in the pool is used to calculate the individual motor unit (MU) force; these were then summed for total muscle force. Dendrites and traces are sized for visual clarity, not presented to scale. **B)** Distribution of motoneuron types (by input resistance) within the pool model.

Figure 2. Representative frequency-current (FI) relationships for motoneuron types in the pool model. S cell shown in blue, FR in purple, and FF in red. FI relationships were measured in response to a somatic triangular current input. Data were measured from the median cell of each type.

Figure 3.

A) Comparison of rheobase versus input resistance for the pool model (colored dots) and experimental data from Zengel, Reid (30, black letters). Model data is shown in color, with S cells in blue, FR in purple, and FF in red. Model data is overlaid on top of fig. 8 from Zengel, Reid (30), which shows S cells as 'S', FR as 'R', and FF as 'F' letters. Dotted lines denote approximate boundaries between cell types as identified by Zengel, Reid (30). Figure used with permission. **B)** Recruitment of motoneuron types in the pool model in response to a ramp-and-hold effective synaptic current (illustrated in **C**) that evoked 47% of the

maximum voluntary contraction (maximum voluntary contraction corresponds to the force level generated when all cells in the pool are activated at their maximum firing rates). The dotted box in B illustrates situations of reverse (in which FF cells are recruited before FR and S cells) and mixed (in which two cells types are recruited at the same time) recruitment.

Figure 4.

Sensitivity analysis showing comparable steady-state firing data from pool models with varying number of cells. Panels **A–D** plot steady-state firing frequency (measured as the average firing frequency during the hold period illustrated by the red box in **D**) versus motoneuron recruitment order in response to a ramp-and-hold synaptic input shown in **D**. Steady-state firing from a pool of 51 cells (**A**), 27 cells (**B**), and 13 cells (**C**). The maximum x-axis value in each panel indicates the total number of recruited cells in each pool model. **D**) Effective synaptic input current vs. time used to generate steady-state firing data. Interval used for steady-state firing rate calculations is highlighted in red. For all panels, S cells are shown in blue, FR in purple, and FF in red.

Figure 5.

Alternate versions of the pool model. **A)** The rheobase vs. input resistance for the standard pool model of 51 cells, without overlapping cell properties among motoneuron types. **B)** The rheobase vs. input resistance for a homogeneous pool model containing 51 cells in which motoneuron types were modeled using generic cell templates with varying electrical properties. The vertical dotted lines indicate the ranges of different motoneuron types. **C)** The rheobase vs. input resistance for a heterogeneous pool model containing 153 cells with biological variability simulated. This figure follows the format of fig. 3A, in which model data (in color) is overlaid on experimental data of fig. 8 of Zengel, Reid (30, black letters, figure used with permission). Following the same format in fig. 4, the steady state firing is

shown from the standard pool model with overlap (**D**), the standard pool model without overlap (**E**), the homogeneous model (**F**, in which all cells are shown in gray but the borders between cell types is shown by the vertical dotted lines), and the heterogeneous pool model (**G**) in response to a ramp-and-hold effective synaptic current shown versus time in **H**, which has been used to activate the motoneurons. The maximum x-axis value in panels D–G indicates the total number of recruited cells in each pool model. For all panels, S cells are shown in blue, FR in purple, and FF in red. The arrows in D show instances of reverse recruitment.

Figure 6.

Range of recruitment of the various motoneuron types in the different pool models in response to the ramp-and-hold synaptic input shown in fig. 5H. Consistent with our format, the recruitment range of S cells for each pool model is shown in blue, FR in purple, and FF in red.

Figure 7.

Force data for the alternate versions of pool models in response to a triangular synaptic input shown in B. **A)** Comparison of the force data generated from the standard pool model with overlap (black), the standard pool model without overlap (green), and the homogeneous pool model (gray). Note that sustained force after the termination of the input is seen because no inhibitory input in D was applied to deactivate PICs and stop motoneurons' self-sustained firing. **B)** Triangular synaptic input command to all models.

Figure 8.

Comparison of motoneuron recruitment, and force results from uniform and non-uniform inputs to the standard pool model with overlap. The steady-state firing rate of motoneuron types (A) in response to a uniform ramp-and-hold synaptic input (shown in B), as shown in fig. 4A. The steady-state firing rate of motoneuron types (C) in response to a non-uniform ramp-and-hold synaptic input (shown in D). In panels A–D, the firing and input of S cells is shown in blue, FR in purple, and FF in red. E) Comparison of force data generated by the standard pool model with overlap under various conditions. The black trace shows force in response to a uniform triangular synaptic input. The cyan trace shows force in response to a non-uniform triangular synaptic input using the original Fuglevand Model. The green trace shows force in response to a non-uniform triangular synaptic input using the modified Fuglevand model (see text for detail). F) The effective synaptic current vs. time used to generate the force data. For the uniform input condition, all cell types received a uniform triangular input, shown in fig. 7B, of effective synaptic current of 10 nA. For the non-uniform input condition, the peak input to FF cells is 12.5 nA, to FR cells is 10 nA, and to S cells is 7.5 nA.

Table 1

The ranges of the pool model parameters, as varied across all motoneuron types.

Section	Parameter	Range
Soma	$R_m (\Omega)$	22 – 496
	$\bar{g}_{\text{Naf}} (\text{S/cm}^2)$	0.06 – 0.08
	$\bar{g}_{\text{Kdr}} (\text{S/cm}^2)$	0.8 – 1.2
	$\bar{g}_{\text{K(Ca)}} (\text{S/cm}^2)$	0.024 – 0.03
	$\bar{g}_{\text{CaN}} (\text{S/cm}^2)$	0.009 – 0.012
Axon hillock and initial segment	$R_m (\Omega)$	22 – 496
	$\bar{g}_{\text{Naf}} (\text{S/cm}^2)$	0.89 – 1.53
	$\bar{g}_{\text{Kdr}} (\text{S/cm}^2)$	0.17
	$\bar{g}_{\text{NaP}} (\text{mS/cm}^2)$	0.033 – 0.041
Dendrites	$R_m (\Omega)$	3890 – 23500
	$\bar{g}_{\text{CaL}} (\text{mS/cm}^2)$	0.201 – 0.203
	Electrotonic Distance (λ) where λ is the electrotonic length	0.4 – 0.9
Force	$TF(\text{mN})$	4.8 – 528.0
	$TD(\text{ms})$	20 – 110

Table 2

Comparison of model properties versus different experimental datasets. Values are mean $\pm$ standard deviation.

Property	Experimental Dataset	S cells	FR cells	FF cells
Input resistance [M Ω]	Model Data	1.48 $\pm$ 0.28 (13)	1.02 $\pm$ 0.26 (13)	0.62 $\pm$ 0.21 (25)
	Hochman and McCrea (32)	1.77 $\pm$ 0.70 (20–45)	0.91 $\pm$ 0.21 (14–31)	0.62 $\pm$ 0.15 (28–48)
	Zengel, Reid (30) *	1.6 $\pm$ 0.78 (61)	0.9 $\pm$ 0.0 (62)	0.6 $\pm$ 0.0 (153)
	Foehring, Svpt (31) *	1.5 $\pm$ 0.0 (28)	1.1 $\pm$ 0.0 (30)	0.6 $\pm$ 0.0 (56)
Time constant [ms]	Model Data	6.98 $\pm$ 1.33 (13)	5.23 $\pm$ 1.29 (13)	5.61 $\pm$ 1.26 (25)
	Hochman and McCrea (32)	7.02 $\pm$ 2.08 (20–45)	5.14 $\pm$ 1.10 (14–31)	4.47 $\pm$ 0.91 (28–48)
	Zengel, Reid (30) *	10.4 $\pm$ 2.42 (12)	8.0 $\pm$ 1.31 (19)	5.9 $\pm$ 1.37 (47)
	Foehring, Svpt (31) *	Not reported	Not reported	Not reported
Rheobase [nA]	Model Data	4.99 $\pm$ 1.70 (13)	10.07 $\pm$ 1.97 (13)	17.03 $\pm$ 9.81 (25)
	Hochman and McCrea (32)	4.3 $\pm$ 2.5 (20–45)	11.6 $\pm$ 3.1 (14–31)	19.7 $\pm$ 5.1 (28–48)
	Zengel, Reid (30) *	5.0 $\pm$ 2.55 (72)	12.0 $\pm$ 3.35 (70)	21.3 $\pm$ 6.18 (153)
	Foehring, Svpt (31) *	5 $\pm$ 0.0 (34)	11 $\pm$ 6.08 (37)	20 $\pm$ 8.37 (70)
AHP $\frac{1}{2}$ decay time [ms]	Model Data	41.49 $\pm$ 2.35 (13)	20.88 $\pm$ 0.65 (13)	19.05 $\pm$ 0.66 (25)
	Hochman and McCrea (32)	Not reported	Not reported	Not reported
	Zengel, Reid (30) *	44 $\pm$ 9.59 (23)	22 $\pm$ 5.57 (31)	18 $\pm$ 0.0 (83)
	Foehring, Svpt (31) *	49 $\pm$ 15.87 (28)	25 $\pm$ 5.57 (31)	22 $\pm$ 7.35 (54)
AHP duration [ms]	Model Data	156.89 $\pm$ 13.65 (13)	73.34 $\pm$ 4.65 (13)	63.58 $\pm$ 5.03 (25)
	Hochman and McCrea (32)	110.5 $\pm$ 31.5 (20–45)	81.9 $\pm$ 17.1 (14–31)	79.5 $\pm$ 214 (28–48)
	Zengel, Reid (30) *	161 $\pm$ 67.14 (23)	78 $\pm$ 22.27 (31)	65 $\pm$ 18 (81)
AHP amplitude [mV]	Model Data	4.77 $\pm$ 0.49 (13)	4.20 $\pm$ 0.41 (13)	2.78 $\pm$ 0.56 (25)
	Hochman and McCrea (32)	4.84 $\pm$ 2.01 (20–45)	3.13 $\pm$ 1.15 (14–31)	2.36 $\pm$ 0.97 (28–48)
	Zengel, Reid (30) *	4.9 $\pm$ 2.4 (16)	4.3 $\pm$ 1.6 (16)	3.0 $\pm$ 1.28 (41)
AP height [mV]	Model Data	80.19 $\pm$ 0.54 (13)	74.95 $\pm$ 1.95 (13)	75.46 $\pm$ 4.02 (25)

Property	Experimental Dataset	S cells	FR cells	FF cells
	Hochman and McCrea (32)	81.3 ± 10.5 (20–45)	81.8 ± 9.3 (14–31)	82.9 ± 8.3 (28–48)
Axon conduction velocity [m/s]	Model Data	76.82 ± 10.36 (13)	83.91 ± 9.80 (13)	90.07 ± 11.92 (25)
	Hochman and McCrea (32)	74.5 ± 14.2 (20–45)	81.9 ± 8.6 (14–31)	88.8 ± 11.5 (28–48)
Axon diameter [μm]	Model Data	$5.7 - 12.6$ (51)		
	Cullheim and Ulfhake (43)	$4.4 - 8.4$ (33)		
FI gain [Hz/nA]	Model Data	1.43 ± 0.18 (51)		
	Kernell (50)	1.7 ± 0.50 (9)		

* Source studies reported values as mean $\pm$ SE. These values were converted here to mean $\pm$ SD for comparison with model and other experimental data.

Table 3

Comparison of the model key properties versus the source experimental datasets. The number of failed-to-reject (FTR) indicates how many trials (of a total of 10) failed to reject similarity between model data and the listed dataset (i.e., the higher the FTR number, the higher the likelihood of similarity between the model and the source experimental dataset).

Property	Experimental dataset	S cells	FR cells	FF cells
		# of FTR	# of FTR	# of FTR
Rheobase	Hochman and McCrea (32) - low n	10/10	10/10	10/10
	Hochman and McCrea (32) - high n	10/10	10/10	10/10
	Zengel, Reid (30)	10/10	10/10	2/10
Input resistance	Hochman and McCrea (32) - low n	10/10	10/10	10/10
	Hochman and McCrea (32) - high n	10/10	5/10	10/10
	Zengel, Reid (30)	10/10	7/10	10/10
AHP $\frac{1}{2}$ -decay	Zengel, Reid (30)	10/10	10/10	10/10
Time constant	Hochman and McCrea (32) - low n	10/10	10/10	1/10
	Hochman and McCrea (32) - high n	10/10	10/10	0/10
	Zengel, Reid (30)	1/10	0/10	10/10

Table 4

Comparison of the model key properties versus the external experimental datasets. The number of failed-to-reject (FTR) indicates how many trials (of a total of 10) failed to reject similarity between model data and the listed dataset (i.e., the higher the FTR number, the higher the likelihood of similarity between the model and the external experimental datasets).

Property	Experimental dataset	S cells	FR cells	FF cells
		# of FTR	# of FTR	# of FTR
Rheobase	Foehring, Sypert (31)	10/10	10/10	9/10
Input resistance	Foehring, Sypert (31)	10/10	10/10	10/10
AHP $\frac{1}{2}$ -decay	Foehring, Sypert (31)	8/10	6/10	3/10
Time constant	Ulfhake and Kellerth (53)	10/10	9/10	9/10