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Influence of central and peripheral motor unit properties on isometric muscle force entropy: A computer simulation study

Jakob Dideriksen [a,*], Leonardo Abdala Elias [b,c], Ellen Pereira Zambalde [b,c], Carina Marconi Germer [d], Ricardo Gonçalves Molinari [b,c], Francesco Negro [e]

[a] Department of Health Science and Technology, Aalborg University, Aalborg, Denmark
[b] Neural Engineering Research Laboratory, Center for Biomedical Engineering, University of Campinas, Campinas, SP, Brazil
[c] Department of Electronics and Biomedical Engineering, School of Electrical and Computer Engineering, University of Campinas, Campinas, SP, Brazil
[d] Department of Biomedical Engineering, Federal University of Pernambuco, Recife, PE, Brazil
[e] Department of Clinical and Experimental Sciences, Research Centre for Neuromuscular Function and Adapted Physical Activity "Teresa Camplani", Università degli Studi di Brescia, Brescia, Italy

A R T I C L E I N F O

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A B S T R A C T

Approximate entropy of isometric force is a popular measure to characterize behavioral changes across muscle contraction conditions. The degree to which force entropy characterizes the randomness of the motor control strategy, however, is not known. In this study, we used a computational model to investigate the correlation between approximate entropy of the synaptic input to a motor neuron pool, the neural drive to muscle (cumulative spike train; CST), and the force. This comparison was made across several simulation conditions, that included different synaptic command signal bandwidths, motor neuron pool sizes, and muscle contractile properties. The results indicated that although force entropy to some degree reflects the entropy of the synaptic command to motor neurons, it is biased by changes in motor unit properties. As a consequence, there was a low correlation between approximate entropy of force and the motor neuron input signal across all simulation conditions ($r^2 = 0.13$). Therefore, force entropy should only be used to compare motor control strategies across conditions where motor neuron properties can be assumed to be maintained. Instead, we recommend that the entropy of the descending motor commands should be estimated from CSTs comprising spike trains of multiple motor units.

1. Introduction

The characteristics of isometric force reflect the neural activation of muscles (Negro et al., 2009). For this reason, force is commonly used to analyze the strategies by which the central nervous system controls the motor output. One popular way to analyze force in this context is approximate entropy (ApEn), which is a measure of the complexity of a signal (Pincus and Goldberger, 1994). For example, a highly regular signal (e.g., a sine wave) would yield low ApEn, while a random, white noise shows high ApEn. In this way, ApEn of force is expected to capture changes in the regularity/complexity by which the central nervous system controls the activation signal, or motor command, to a muscle. Force ApEn has been shown to vary across different conditions, including contraction levels (Slifkin and Newell, 1999; Temprado et al., 2015), visual force feedback characteristics (Prodoehl and Vaillancourt, 2010; Schiffman et al., 2006), fatigue (Pethick et al., 2019b, 2019a), age (Deutsch and Newell, 2002; Vaillancourt and Newell, 2003), and neuromuscular diseases (Lodha et al., 2010; Vaillancourt et al., 2001).

The force characteristics, however, are also affected by spinal and peripheral motor unit properties. Spinal motor neurons receive not only the descending activation commands but also uncorrelated inputs from various other sources, which are often referred to as synaptic noise (Faisal et al., 2008; Stein et al., 2005). The impact of this synaptic noise on the degree to which the descending activation commands are transmitted accurately to the compound motor neuron output varies with the number of recruited motor units (Dideriksen et al., 2012). Furthermore, since generation of motor unit force can be described in a simplified way (i.e. disregarding some non-linear properties; see Methods) as the convolution between the motor unit spike train and the motor unit twitch, the contractile properties of the muscles determine the output

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[*] Corresponding author at: Fredrik Bajers Vej 7D, 9220 Aalborg Ø, Denmark.
E-mail address: jldi@hst.aau.dk (J. Dideriksen).

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(force) by low-pass filtering the motor neuron input (Baldissera et al., 1998; Dideriksen et al., 2020). The characteristics of this filter depend on muscle fiber type (the longer twitch duration, the lower the cut-off frequency). In this way, the filter depends on predominant muscle fiber type (slow/fast contracting) and may change acutely or chronically due to several phenomena, such as fatigue or training (Pääsuke et al., 1999; Thomas et al., 1991). To summarize, these neuromuscular properties affect the characteristics of the generated force, but their impact on ApEn of force has never been investigated. For this reason, the ability of this measure to accurately characterize the nature of the descending activation commands to muscles across conditions is not known.

In this study, we used a computer simulation approach to systematically investigate the impact of motor unit properties on the ApEn of isometric force. In this context, an analysis based on computational models is particularly useful, since it allows independent control of the descending activation command, the motor neuron characteristics, and the muscular contractile properties. These variables cannot all be measured experimentally during natural behavior in humans. Furthermore, they are likely to adapt in dependent ways across conditions, which means that it would not be possible to identify their respective effects on ApEn. For example, muscle fatigue usually implies concurrent adaptations in the characteristics of the central control of force, the motor neuron recruitment pattern, and the muscle contractile properties (Enoka and Duchateau, 2008; Gandevia, 2001). For these reasons, the study aimed to identify the influence of motor unit properties on the force ApEn ability to characterize the randomness of the descending activation signal using a computational model.

2. Methods

2.1. Simulations

The study used the same computational model as in a previous study (Dideriksen and Negro, 2018). It was based on the model of motor neuron behavior and isometric force initially proposed by Fuglevand and colleagues (Fuglevand et al., 1993), which has been used in several studies by our (Dideriksen et al., 2010a, 2010b) and other groups (Barry et al., 2007; Herbert and Gandevia, 1999; Taylor et al., 2002). The model was implemented in Matlab 2019a (Mathworks) and had a sampling frequency of 1000 Hz. In the model, the motor neuron discharge patterns were determined by a value representing the net excitatory input which was common to all motor neurons. Furthermore, each motor neuron was assigned a recruitment threshold indicating which excitation level it started generating action potentials. Independent noise (low-passed filtered white noise <100 Hz) was imposed on the input of each motor neuron to generate a realistic steady-state variability of the inter-spike interval (Matthews, 1996; Moritz et al., 2005). The relative magnitude of the independent noise was constant in all simulations. Furthermore, each motor unit was assigned a set of parameters determining its temporal twitch characteristics. From the motor neuron discharge patterns and their respective twitches, the force generated by the individual motor units was simulated as a non-linear summation process (Fuglevand et al., 1993). The net force of the muscle was obtained as the algrebraic sum of all motor unit forces.

The simulations included 10-s contractions at 10% of maximal voluntary contraction level (MVC), obtained with different motor unit properties. Specifically, the number of motor units was set to 100, 500, or 900, representing realistic numbers across different muscles (Heckman and Enoka, 2012). In addition, the motor unit twitch contraction speeds were systematically varied. In the default setting, the twitch contraction times were distributed according to motor unit size so that the small low-threshold units had relatively long contraction times (up to 90 ms) and the large high-threshold units had faster contraction times (down to 30 ms) (Fuglevand et al., 1993). In addition to these default settings, simulations were also performed where this range of contraction times were scaled by a factor of 0.6 or 1.4, which represents the range of adaptations that have been observed experimentally in previous studies (Jenkins et al., 2016; Pääsuke et al., 1999; Thomas et al., 1991).

To determine the appropriate excitation level to generate the target force (10% MVC) in each realization of the model, a 20-s ramp contraction from 0 to maximum excitation was simulated before the sustained 10-s contraction at the target. From this ramp contraction, the excitation level at 10% of the peak force during the ramp was identified and imposed as the offset during the following 10-s contraction. To emulate the voluntary command to the motor neurons, low-passed filtered white noise was superimposed on the common excitation signal. Across simulations, this noise was filtered at 1 Hz, 3 Hz, or 5 Hz and scaled, so the standard deviation was 0.25 or 0.5 arbitrary units of excitation, equivalent to 0.6% and 1.1% of the excitation level required for maximum activation of all motor units (maximum value of Emax; Eq. (8) in (Fuglevand et al., 1993)), respectively. The different magnitudes of the variability of the descending command implied different signal-to-noise ratios (SNR) in the motor neuron input as the relative magnitude of the independent noise was constant in all simulations.

To summarize, the simulations included all combinations of three sizes of the motor unit pool (100, 500, 900), three values assigned as a scale factor of the motor unit twitch contraction times (0.6, 1, 1.4), three different bandwidths of the voluntary descending command signal (<1 Hz, <3 Hz, <5 Hz), as well as low and high SNR. In total, this yielded 54 different simulation settings. Each setting was repeated 10 times similar to our previous simulation studies (Dideriksen et al., 2020; Dideriksen and Negro, 2018). Furthermore, pilot simulations indicated that 10 repetitions were sufficient to obtain a full representation of the variability in the outcome measures arising from the randomly assigned model parameters. In addition, for illustrative purposes, one simulation was conducted with a constant descending command (500 motor units, twitch contraction time scale factor 1).

2.2. Analysis

For each simulation, ApEn of the descending command signal (motor neuron input), the cumulative spike train (motor neuron output), and the muscle force was calculated. The first second of the simulated data was discarded to exclude the transient phase of the force. As in previous studies, the cumulative spike train (CST) was calculated as the algebraic sum of multiple single motor unit spike trains and was smoothed (low-pass filtered < 5 Hz) prior to further analysis (Farina et al., 2014; Negro et al., 2012). CSTs were calculated with 10, 20, 30, 40, 50 motor units randomly selected from all recruited motor units, or with all recruited motor units (i.e. 100, 500, or 900). In this way, CSTs with 10–50 motor units represent the estimate of the neural drive to the muscle the can be obtained in realistic experimental conditions (i.e the number of motor units that can be decomposed from the same contraction with current state-of-the-art methods (Muceli et al., 2015; Negro et al., 2016)), while CSTs comprising all motor units represent the ideal estimate of the neural drive. All signals were down-sampled to 100 Hz prior to the calculation of ApEn. To calculate ApEn, the Matlab function "approximateEntropy" (dimensions: 2, lag: 1, radius: 0.2*variance of the signal) was employed. Linear correlation analysis between ApEn of force or CST and the command signal was applied for all simulations with either low or high SNR.

3. Results

Fig. 1 illustrates representative examples of the simulated signals and their ApEn. Specifically, the figure includes simulations with different characteristics of the voluntary command signal in the high-SNR setting (500 motor units, twitch scale factor: 1). When the motor command signal is constant (fully deterministic), it has zero ApEn. Increasing the bandwidth from <1 Hz to < 5 Hz implied an increase in ApEn of the command signal from 0.21 to 0.58 (Fig. 1B). This difference related to the bandwidth was also reflected in the ApEn of the motor neuron

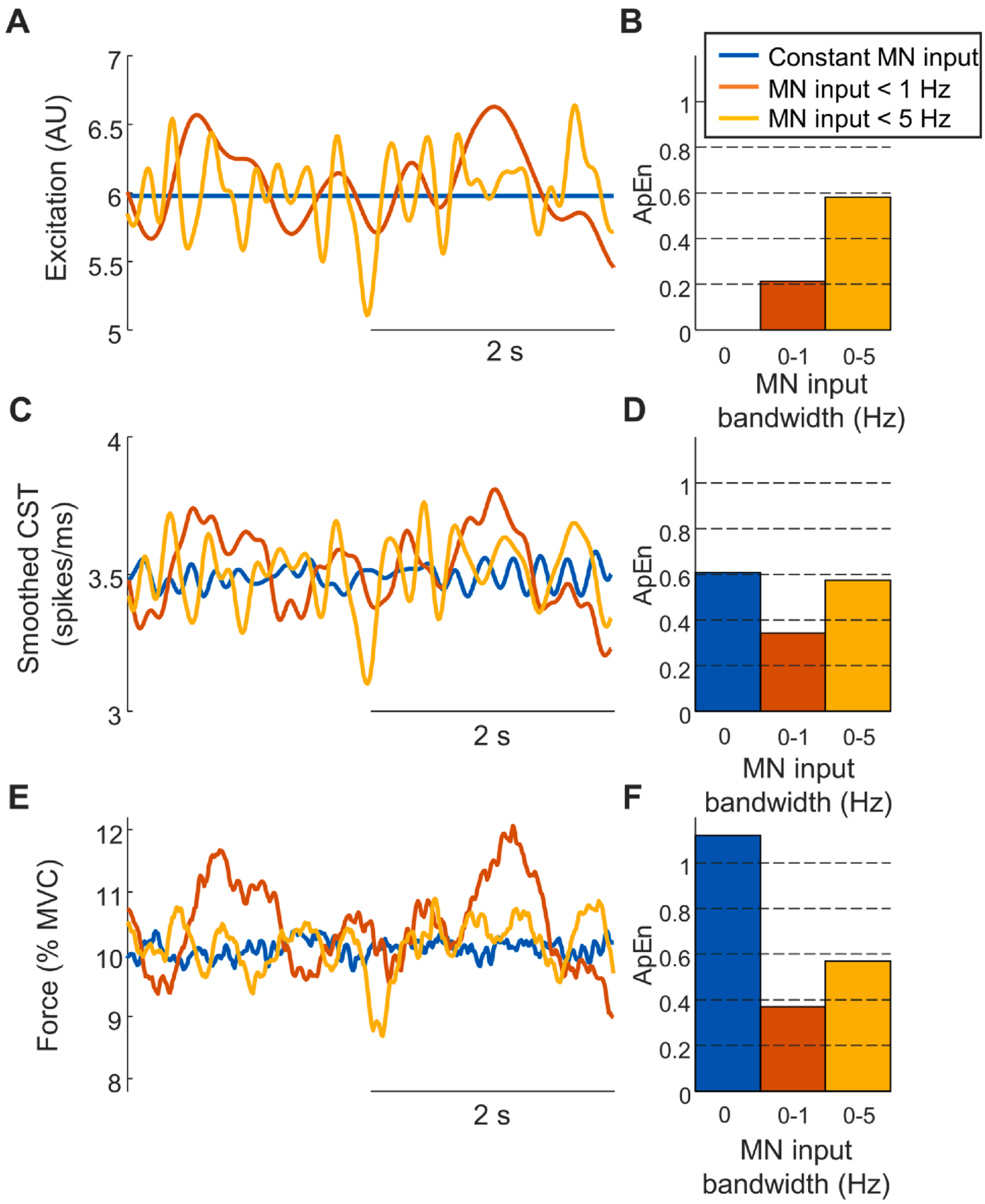

Fig. 1. Representative simulation data for three conditions: Constant input (blue), narrow-bandwidth motor neuron (MN) input (0–1 Hz; yellow), and wide-bandwidth MN input (0–5 Hz; red). The simulated data for MN input (A), MN output (CST consisting of all MNs; C), and force (E), and their respective values for ApEn across the three conditions (B, D, F). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

output (Fig. 1D) and force (1F), although the value of ApEn varied across the three signals; in particular for the <1 Hz case. The highest values of ApEn in these representative simulation examples were from CST and force in the condition with a constant common motor neuron input (CST: 0.61, force: 1.12). Although the variability of these signals was low (blue lines in 1C and 1E), the random independent synaptic noise added to the individual motor neurons implied high entropy.

Fig. 2 summarizes the calculated ApEn values across all simulated conditions. These results confirm that when the bandwidth of the input increases, the ApEn of the motor neuron input followed the same trend, as well as for both motor neuron pool output and force (Fig. 2A, D). The size of the motor neuron pool, however, also affected ApEn (Fig. 2B, E). Specifically, when the number of motor neurons increased, ApEn of motor neuron output and force decreased, reflecting that the independent synaptic noise (generating high ApEn; Fig. 1) is filtered out when more motor units are involved in the contraction (Dideriksen et al., 2012). Similarly, when the average motor unit twitch contraction time increased, the ApEn of the force also decreased (Fig. 2C, F). This relation reflects that an increased duration of the twitch implies a decrease in the cut-off frequency of the low-pass filter it imposes on the motor neuron output (Dideriksen et al., 2020). In both cases (many motor units, slow twitches), the bandwidth of the signal is decreased, thereby transmitting less of the complexity of the motor command to the force signal.

When comparing the low-SNR (Fig. 2A, B, C) and high-SNR conditions (Fig. 2D, E, F), it is clear that a low relative amplitude of the motor command signal with respect to the synaptic noise (i.e. low SNR) increases ApEn of motor neuron output (on average by 0.11) and force (on average by 0.35). Conversely, when the SNR was high, the ApEn values tended to be more similar across all three signals. Specifically, the average error between ApEn of common motor neuron input and the CST and force was 0.05 and 0.16, respectively, in the high-SNR condition. Since these two conditions (low/high SNR) involved different amplitudes of the variability in the motor command signals (relative to the independent synaptic noise), the force variability differed

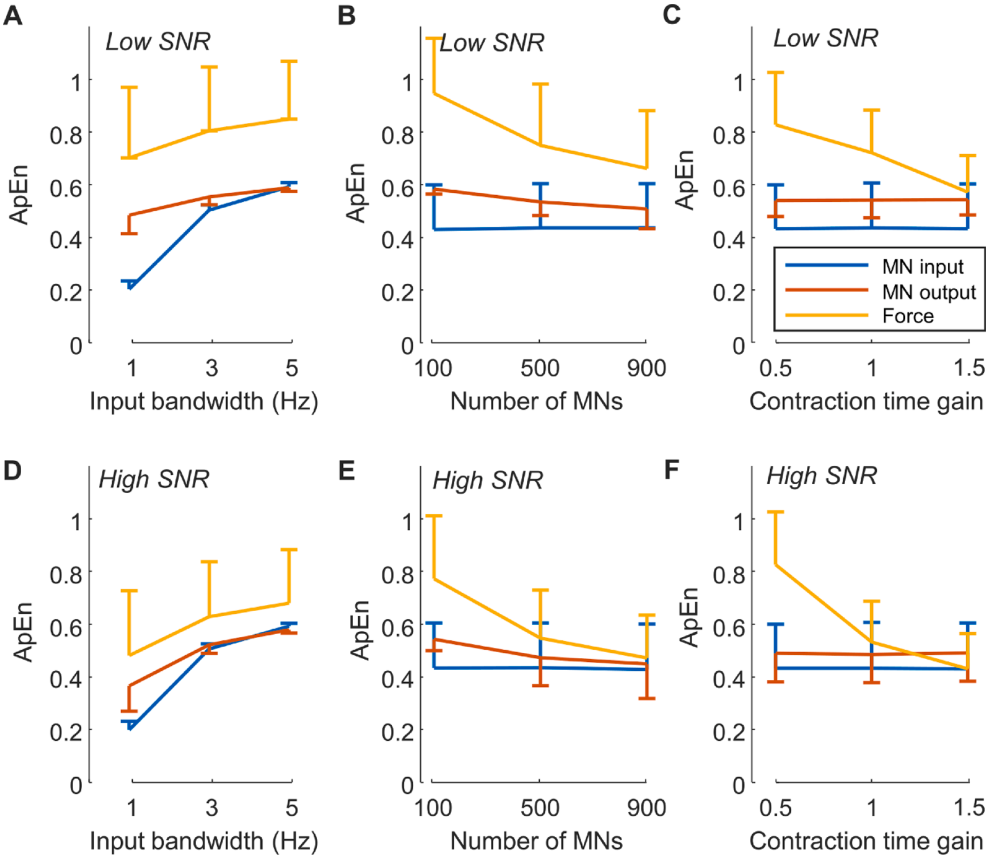

Fig. 2. Average + std values of ApEn across motor neuron (MN) input bandwidth (A, D), number of MNs (B, E), and contraction time scale factor (C, F) for low (A, B, C) and high (D, E, F) SNR.

systematically across these settings. Across conditions with high variability (i.e. high SNR) the coefficient of variation of force were in the range 4–8%, while it was 2.5–5% in the low SNR settings. The relatively large ranges of values within each setting reflect that other model parameters (in particular average twitch contraction time) also affected force variability.

Linear correlation analysis indicated that the correlation between ApEn of the common motor neuron input signal and force was low. This analysis compiled all simulations ($n = 270$) with either low or high SNR, and showed that the correlation increased only slightly with SNR (low SNR: $r^2 = 0.07$; High SNR: $r^2 = 0.13$) (Fig. 3). This observation implies that a decrease in SNR results not only in a change in the offset of force ApEn (Fig. 2), but also a decrease in the degree to which force ApEn covaries with ApEn of the motor command signal. On the other hand, ApEn of the motor command signal was strongly correlated with the motor neuron output (CST of all motor units) (low-SNR: $r^2 = 0.48$; high-SNR: $r^2 = 0.73$). While ApEn of a single motor unit spike train was not correlated with the motor command signal ApEn, this correlation rapidly increased when considering more motor units in the high-SNR condition. In this condition, the correlation between ApEn of force and the common motor neuron input was exceeded by that of the CST when the spike trains of approximately 15 motor units were included. When 30 motor units were included, r^2 reached 0.47 in the high SNR condition.

4. Discussion

ApEn is a popular way to analyze muscle force, but the underlying assumption that it provides an accurate characterization of the central control of force has never been validated. For this reason, this study aimed to quantify the impact of changes in motor unit properties on ApEn of force. Overall, the simulation results confirmed that while ApEn of force to some degree reflects ApEn of the motor neuron input signal, it is also affected by multiple confounding factors that can change across contraction conditions. First, low magnitudes of the variability in the descending command signal or high levels of synaptic noise (i.e., low SNR) decreases the degree to which ApEn of force reflects motor ApEn of the command signal. In the simulations, the levels of isometric force variability in the low and high-SNR settings were within those typically observed experimentally (Laidlaw et al., 2000; Sosnoff and Newell, 2006; Tracy et al., 2007). Second, an increased number of motor units recruited during the contractions increases the ability of the motor neuron pool to accurately transmit the descending input to the output, thereby limiting the influence of synaptic noise and decreasing the ApEn of the force output (Dideriksen et al., 2012). Finally, the contractile properties of the motor units affect the ApEn of the force by decreasing the signal bandwidth that is an important determinant of the ApEn. For this reason, the results of this study indicate that ApEn of the force should only be used to estimate ApEn of the descending control signal in conditions that minimize the impact of these confounding factors.

The confounding factors are likely to have affected some previous studies on ApEn of the force output. For example, relatively modest changes in ApEn of force (up to 0.1) reported across the full range of contraction levels (Slifkin and Newell, 1999) are likely to reflect not only possible changes in the nature of the central control of the force, but also changes in above-mentioned confounding factors. Specifically, increasing the contraction level implies progressive recruitment of additional motor units (decreasing force ApEn; Fig. 2B, E). Furthermore, it is normally assumed that the low-threshold motor units contain predominantly slow-twitch muscle fibers, while motor units recruited at higher contraction levels consist predominantly of fast-twitch fibers (Fuglevand et al., 1993; Heckman and Enoka, 2012). This observation is

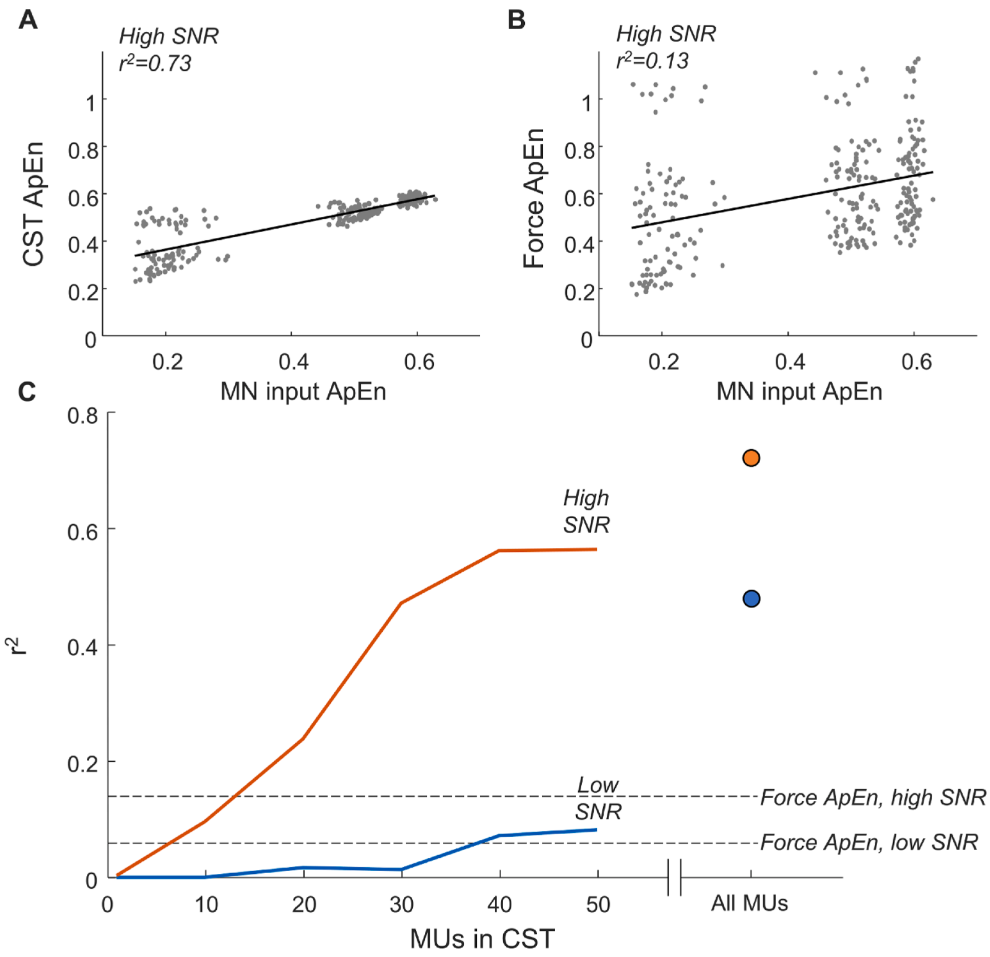

Fig. 3. Linear relation between ApEn of the common motor neuron input and ApEn of CST of all motor neurons (A) and ApEn of force (B) across all simulations with high SNR (each grey dot represents the outcome of one simulation). Panel C shows the values of r^2 between ApEn of common motor neuron input and ApEn of CST (continuous lines, and circles) low (blue) and high (orange) SNR level as a function of motor units in the CST (1–50 motor units or all recruited motor units). In addition, the values of r2 reflecting the correlation between ApEn of the common motor neuron input and ApEn of force are superimposed as horizontal, dashed lines (since they do not depend on the number of motor units in the CST) for the low and high SNR cases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

equivalent to a gradual change in the average motor unit contraction time which decreases ApEn of force (Fig. 2C, F). Another example is the reported changes in ApEn of the force output during sustained contractions evoking muscle fatigue (Pethick et al., 2019b). During fatiguing contractions, additional motor units are progressively recruited, and motor unit twitch contraction times increase (Enoka and Duchateau, 2008; Gandevia, 2001). Furthermore, motor unit discharge rate variability increases (Enoka et al., 1989; Garland et al., 1994; Martinez-Valdes et al., 2020), which indicates an increase in the magnitude of the synaptic noise, resulting in a variation of the SNR. Therefore, this study suggests that the values of ApEn of force reported in these works reflect multiple factors and not exclusively the regularity of the descending control commands. Importantly, methods to measure these confounding factors experimentally during contractions have substantial limitations, which in practice makes it impossible to compensate for their impact on the ApEn of the force.

On the other hand, other studies were designed in ways that make the ApEn of force less likely to be biased by these confounding factors. For example, Schiffman et al. investigated the effect of different ways to provide visual force feedback during brief contractions at the same level (Schiffman et al., 2006). Under such conditions, it is reasonable to assume that the number of recruited motor units, their contractile properties, and the magnitude of the synaptic noise did not change. Therefore, it would be expected that the reported changes in ApEn of force across feedback conditions primarily reflect changes in the nature of the central motor command.

Since it is not possible to measure and/or control all the confounding factors during an experiment, the simulation approach is necessary to systematically investigate the degree to which ApEn of force reflects ApEn of the descending command signal. Nevertheless, the simulation approach has a number of limitations. Most importantly, in the context of this study, the models of the neural signals may not fully reflect natural conditions. For example, the descending control signal was modeled as a low-passed filtered white noise. Accordingly, the ApEn of this signal depended on its bandwidth (Fig. 2A, D). Changes in the bandwidth of the common input to motor neurons may reflect alterations in the relative input from different neural sources, including central (Brown et al., 1998) and afferent inputs (Christakos et al., 2006). However, it is also possible that the structure of the input in the same bandwidth (and thus its ApEn) changes across conditions. In this case, the reflection of such changes in the ApEn of force may be less prone to be affected by changes in the filter of the muscle contractile properties (Fig. 2C, F).

A potential methodological approach to limit the effects of the confounding factors of the muscle contractile properties in the estimation of the ApEn of the descending command signal is to analyze motor unit discharge patterns (neural drive) instead of force. One study has previously analyzed ApEn of motor unit discharge trains (Vaillancourt et al., 2003), but this study analyzed only individual motor units. Conversely, our results, as well as previous studies, show that the collective motor neuron pool output can be reliably estimated only if the discharge patterns of multiple motor units are taken into account (Farina et al., 2014). Current decomposition techniques can identify spike trains of tens of single motor units from the same contraction (Muceli et al., 2015). Therefore, a clear recommendation arising from this study is that in order to reliably estimate the structure of the activation signal to muscles, the analysis should be based on the spike trains of multiple motor units rather than on the force output. However, since the SNR (variability in common, descending motor neuron input relative to variability of independent input) would likely vary across subjects and conditions, the results cannot be used to infer a universal minimum number of motor units in the CST for obtaining a reliable estimate of motor neuron input entropy. The simulation approach of the study has some intrinsic limitations that should be acknowledged. The model is relatively simple from a computational perspective, which comes at the expense that it does not fully capture all details of the physiological processes. For example, linear summation of single motor unit forces into the net muscle force may be affected by the properties of connective tissues and tendon dynamics. Moreover, several model parameters exhibit a large natural variability across the human population. Although some model parameters were assigned random values, this variability in the simulated outcome variables does not fully capture realistic variations across a population of human subjects. Instead, many model parameters were assigned values that represent an estimate of the average across such a population (Fuglevand et al., 1993). Accordingly, the simulated variabilities more accurately represent trial-to-trial variability in a single "average" subject. Nevertheless, since we aimed to investigate the impact of certain model parameters on force entropy, these limitations do not affect the primary message of this study. Since the contraction level was 10% MVC in all simulations, the results reflect forces generated by the subset of motor units with lowest recruitment thresholds (slow contracting). However, simulating different motor unit population sizes and average contraction times is effectively the same as simulating different contraction levels (i.e. different absolute number of recruited motor units with different average contractile properties). Furthermore, another recent modelling study illustrated the isometric force variability related to different motor unit types (Raikova et al., 2021).

In conclusion, this study showed that ApEn of force is only a reliable estimator of the structure of the strategies by which the central nervous system controls the motor output in limited conditions. Specifically, confounding factors, including the magnitude of synaptic noise, as well as the number of active motor units and their contractile properties can substantially affect ApEn of force.

CRediT authorship contribution statement

Jakob Dideriksen: Conceptualization, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Leonardo Abdala Elias:** Methodology, Writing - review & editing. **Ellen Pereira Zambalde:** Methodology, Writing - review & editing. **Carina Marconi Germer:** Methodology, Writing - review & editing. **Ricardo Gonçalves Molinari:** Methodology, Writing - review & editing. **Francesco Negro:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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