Relative contribution of different altered motor unit control to muscle weakness in stroke: a simulation study

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Abstract

Objective. Chronic muscle weakness impacts the majority of individuals after a stroke. The origins of this hemiparesis are multifaceted, and an altered spinal control of the motor unit (MU) pool can lead to muscle weakness. However, the relative contribution of different MU recruitment and discharge organization is not well understood. In this study, we sought to examine these different effects by utilizing a MU simulation with variations set to mimic the changes of MU control in stroke. Approach. Using a well-established model of the MU pool, this study quantified the changes in force output caused by changes in MU recruitment range and recruitment order, as well as MU firing rate organization at the population level. We additionally expanded the original model to include a fatigue component, which variably decreased the output force with increasing length of contraction. Differences in the force output at both the peak and fatigued time points across different excitation levels were quantified and compared across different sets of MU parameters. Main results. Across the different simulation parameters, we found that the main driving factor of the reduced force output was due to the compressed range of MU recruitment. Recruitment compression caused a decrease in total force across all excitation levels. Additionally, a compression of the range of MU firing rates also demonstrated a decrease in the force output mainly at the higher excitation levels. Lastly, changes to the recruitment order of MUs appeared to minimally impact the force output. Significance. We found that altered control of MUs alone, as simulated in this study, can lead to a substantial reduction in muscle force generation in stroke survivors. These findings may provide valuable insight for both clinicians and researchers in prescribing and developing different types of therapies for the rehabilitation and restoration of lost strength after stroke.

Keywords: motor unit simulation, stroke, muscle weakness, fatigue

(Some figures may appear in colour only in the online journal)
Introduction

Hemispheric stroke is a major cause of disability, and commonly leads to muscle weakness. The affected limb of stroke survivors exhibits profound differences in coordination and strength during voluntary force generation [1, 2]. Various neurological and peripheral mechanical factors in the brain, spinal cord, and muscles are thought to contribute to these motor deficits. Specifically, altered cortical activation and changes in the muscular properties (e.g. muscle atrophy, contracture, and passive tissue infiltration) have been well documented [3]. Altered spinal cord activation of the motoneuron pool has also been observed [4]. Recent studies utilizing advanced motor unit (MU) decomposition techniques on post-stroke paretic muscles have elucidated various changes in the recruitment and firing organizations of MUs [5–7]. However, the relative contribution of these different altered MU properties to muscle weakness is not clear.

Physiologically, force generation at the MU level is mainly controlled by the recruitment of new MUs and their subsequent increase in firing rate [8]. In neurologically intact muscles, MU recruitments are distributed across different levels of force output. MUs also exhibit an orderly recruitment from small to large size motoneurons [9], termed the ‘size principle’. Smaller MUs also tend to be more fatigue resistant, and therefore it holds that these fatigue-resistant, early-recruited, smaller MUs can maintain fine control of force output at a lower excitation drive. With further increase of the excitation drive, the large and more fatigable MUs are recruited for more powerful, though less sustainable, force output. Besides well-organized recruitment patterns, these MUs typically exhibit firing rates inversely related to their recruitment order, termed the ‘onion-skin’ pattern. Namely, earlier recruited units tend to reach higher firing rates, which results in the MUs appearing to be layered together when plotted as a function of firing rate over time [10]. This onion-skin pattern can lead to sustained force output with low firing rates in the later recruited fatigable MUs.

Alterations in these MU recruitment and firing rate patterns have been observed in a few studies utilizing intra-muscular recordings of a few MUs as well as an investigation of the global pool of MUs using advanced surface electromyography (EMG) techniques [4–7, 11]. Specifically, compared to contralateral muscles, control of MUs in paretic muscles tend to exhibit disturbances and potential reorganizations. One of these changes is the compression of the range of recruitment thresholds (RTs) of different MUs [5]. This was observed as a clustering of RTs at lower levels of forces, and would cause more MUs to be active earlier than typically expected. In addition to the compression of the recruitment range (RR) of MUs, changes to the range of firing rates of MUs have also been observed in paretic muscles [6]. Specifically, MUs of paretic muscles have shown to also have a greater overlap of firing rates in a tighter range, resulting from a reduced firing rate in the earlier recruited MUs and an increase of the firing rate of the later recruited fatigable MUs. This change in rate organization across the MU pool could also impact force generation and result in muscle weakness. Lastly, the recruitment of MUs has shown to be disturbed from its typical small-to-large order [5]. A disturbance of this orderly recruitment could result in early recruitment of fatigable MUs with unsustainable twitch forces, which can also potentially lead to muscle weakness. Although these various changes in MU properties have been observed, their relative contributions to overall muscle weakness is not clear based on experimental data.

Accordingly, the objective of this study was to quantify the individual contributions of altered MU pool organization to reduced muscle strength as observed in stroke survivors. To isolate the altered MU recruitment and firing patterns, a previously developed mathematical model of a MU pool was utilized to simulate these changes in MU parameters. In particular, the motoneuron pool and force generation model developed by Fuglevand et al was used [12]. The current study also introduced an expansion of the original model to include muscle fatigue, or the decrease of total force with prolonged contractions, a common feature in muscle force generation and further manifested in stroke populations [13].

In summary, we found that a compression of the RT range resulted in a significant reduction in total force output. A reduced firing rate range was also shown to affect total force generation at higher levels of contraction. Lastly, the disruption in the organization of MU recruitment and firing rates appeared to have minimal impact in the total force generation. Our findings indicate that although various changes in MU properties in paretic muscle exist, the change in the RR of MUs may be the more important factor contributing to muscle weakness. The findings of this study can help us better understand how changes in the recruitment and firing rate organizations of MUs impact muscle force generation after a stroke. The outcome can also have clinical implications in developing more targeted rehabilitation strategies that can help improve motor functions.

Methods

In order to evaluate the influence of the altered MU pool organization on muscle weakness, we simulated the changes in MU pool properties observed in stroke, including the compressed recruitment and firing rate ranges as well as the disrupted recruitment order. We utilized a previously developed MU pool model [12] which allowed us to separately evaluate the factors that could contribute to reduced muscle force generation. The model is first described below briefly.

MU pool model

The model contained three main components: recruitment and firing rates of the motoneuron pool, force output based on MU twitch properties, and a simulated surface EMG based on MUAP properties. For the purpose of our study, only the former two were considered—the motoneuron pool and isometric force models. Building on the original model, simulations of MU synchronization [14] and a MU fatigue mechanism were also implemented.
were modelled as an exponential function: 

The following equation related the PFR of a motoneuron with the overall range of the PFR variations across the pool. The recruitment of each MU is visualized as the location on the x-axis that each line starts to rise, and the RR estimates the recruitment of the last MU. The RR effectively determines how many levels of excitatory drive, and only a few were recruited close to the end of the RR. The RR effectively determines how many MUs are active at a particular level of the excitatory drive, and therefore variations in the RR provide insight into how the number of active MUs contribute to the overall force output.

Firing rate synchronization. The firing times of random MUs were also synchronized to mimic the common drive experienced in different motoneurons. Based on previous MU simulation studies [14], a moderate 10% synchrony was applied across the motoneuron pool. This resulted in a randomly

Figure 1. Sample excitation versus firing rate plots. The overall firing rate for every 10th MU in the MU Pool have been plotted. (A) ‘Normal’ model parameters (RR = 30, PFRR = 25). (B) ‘Compressed’ model parameters (RR = 15, PFRR = 10). The model was only run until the last MU reached its PFR, but these figures were extended just for display purposes.

The MU pool model consisted of 120 MUs with adjustable parameters including the RR, RT, and peak firing rates (PFR), as well as the ordered distribution of these values across the pool. The simulated changes of the MU firing and recruitment properties are shown in figure 1. The input to the MU pool was modeled using a uniformly distributed excitatory drive, and the output of the model was the net muscle force generated by the summated MU twitch forces. Both the input and output values were originally quantified in arbitrary units (au) based on the minimum excitation and twitch force of the first MU.

The RT in this model is the minimum excitatory drive needed to cause a motoneuron to discharge. Using the following equation, recruitment variations across the pool were modelled as an exponential function:

where RT(i) is the RT of the ith MU, ln is the natural logarithm, RR is the range of recruitment (unitless multiple of the recruitment of the first MU), and n is the total number of MUs in the pool. The recruitment of each MU is visualized in figure 1 as the location on the x-axis that each line starts to rise, and the RR estimates the recruitment of the last MU. In this setting, a majority of the MUs were recruited at lower levels of excitatory drive, and only a few were recruited close to the end of the RR. The RR effectively determines how many MUs are active at a particular level of the excitatory drive, and therefore variations in the RR provide insight into how the number of active MUs contribute to the overall force output.

PFR and range. Based on previous physiological studies and other MU simulations [15–17], the minimum firing rate (MFR) at the RT was set at a constant 5 pulses per second (pps) across all MUs. From this minimum rate, two additional parameters were determined for the MU pool: the PFR of each unit and the overall range of the PFR variations across the pool. The following equation related the PFR of a motoneuron i (PFRi) to be inversely proportional to its RT:

where PFRi is the PFR assigned to the first MU, PFRR is the desired PFR range between the first and last recruited MUs, and the RT/RR is the ratio of the current RT of motoneuron i with the RR of the motoneuron pool. Additionally, the amount of increase of the firing rate with an increase in excitation drive, or the input–output gain, was determined using the following equation:

where Gi is the excitation-rate gain of MU i based on its PFR over the difference between the highest PFR of the pool and the RR/RT1 (unitless). In brief, based on the previous PFR equations, later recruited MUs reach lower PFRs and also have lower gains so they reach their PFR slower than earlier recruited MUs [18]. Together, these equations model the aforementioned onion-skin phenomenon of MU firing patterns where early recruited units rise faster to higher firing rates and later recruited units rise slower to lower rates. This effect is seen in figure 1 through the differing slopes of rise between adjacent MU lines. In summary, the firing rate (FRi) of MUi at a given time is governed by the following equation until it reached its PFR:

where Gi, RTi, and MFR are as previously defined and E(t) is the excitation drive at time t. In order to mimic physiologic variations of the instantaneous firing rate in the simulation, a coefficient of variation (CV) of 20% was also applied to the inter-spike interval (ISI) of each firing time based on the original model.
selected 10% of an MU’s firings to be aligned if they were within 15 ms of another MU’s firings. The firing alignment followed a Gaussian distribution with a mean at the firing reference time and a standard deviation of 1.67 ms.

**Twitch force.** The conversion of the MU firing times to MU force output utilized a modular MU twitch force. The desired impulse response was modelled as a second-order critically damped impulse response, according to the original model [12]. The range of twitch forces used in the current simulation ranged from 1 au force and time-to-peak of 90 ms (MU 1) to 100 au force and 30 ms time-to-peak (MU 120). Similar to the RTs, these twitch forces were distributed exponentially across the MU pool so that most twitches had lower and longer twitch forces and a few had higher and shorter ones. The non-linear force-stimulation rate relation from the original model was also used as the gain to amplify the MU impulse response. The force generated by each MU was then summated linearly across all the MUs to obtain the total force of the simulated muscle contraction.

**Fatigue index.** Building upon the original model, we also introduced a mechanism to emulate physiological fatigue. Fatigue was modelled as a decrease in the MU twitch force as a function of the MU index number, the time-since-recruitment, and the PFR of the MUs. The following equation was used to scale the twitch force across the pool:

$$F_i = e^{- \left( \frac{\text{time since recruitment}}{\text{m}} \right)}$$  \hspace{1cm} (5)

where the fatigue index ($F_i$) of the $i$th MU was calculated based on its PFR, the time since its recruitment ($t$), and the total number of MUs ($n$). The coefficient $m$ was set at 600 in order to match the degree of force decline observed experimentally [19]. Figure 2 shows a sample time course of the decay of the twitch force for every tenth MU. Based on physiologic observations of MU fatigue [19], the fatigue index was scaled using an exponential function to proportionally induce a greater decrease of the twitch force of the later recruited MUs. The twitch force at a given time was the fatigue index multiplied by the original, un-fatigued peak twitch force. This fatigue model assumes other parameters, i.e., the firing rate and twitch duration, remain constant. The simulated effect of the fatigue to the total force output at the ten different excitation levels is also shown in figure 3, which illustrated a more evident force decline at higher force levels. To quantify the levels of force output, the maximum force as indicated by the vertical arrows, and the force at 30 s were analyzed.

**Post-stroke muscle model**

The MU pool model was utilized to explore the contributions of different MU parameters to overall force generation. Various changes to the RR, the peak firing rate range, and the recruitment order have been previously observed in muscles of stroke survivors [5–7, 11]. The main changes examined in this paper were compressed RR, a weaker onion-skin layering effect (smaller range of PFRs), and disturbances in the recruitment order.

**Recruitment compression.** MUs in the FDI of the affected side after stroke have shown to be recruited at lower forces than those of the contralateral side (as shown in figure 4) (adapted from [20] with permission). In order to observe the changes due to recruitment compression to the output force as seen in the affected muscle in stroke, the RR was set at four different ranges (in au): 10, 15, 20, and 30. 30 au was considered the ‘normal’ RR and the remaining three ranges represented different degrees of recruitment compression. The different extent of recruitment compression was simulated to mimic experimental data with varying degrees of recruitment compression.

**Reduced onion-skin.** MUs in affected muscles have also been shown to have more overlapping firing rates during steady state isometric contractions. Namely, the onion-skin...
Disturbed recruitment order. This simulation also implemented a disturbance in the recruitment order of MUs within the RR to mimic the changes in the recruitment order of MUs seen in affected muscles of stroke survivors [5]. Specifically, close-to-random order of recruitment was observed in a majority of the tested stroke cohort, while others showed a weaker ordering pattern in the affected side compared with the contralateral side. We were not aware of existing models for disturbed recruitment. Therefore, in our simulation, we added random noise to the RT as one way of perturbing the recruitment order. With more noise added, a close-to-random recruitment can be simulated. Specifically, a coefficient of recruitment disorder between 0 and 1 was utilized to control the degree of RT shuffling as a way to disturb the recruitment order. The following equation was used to determine the changes in the individual RTs:

\[
RT_{\text{new}} = RT_{\text{old}} \pm (RR \times c_{rd} \times r)
\]  

(6)

where \(RT_{\text{new}}\) was the shifted RT of a MU based on the old RT \((RT_{\text{old}})\), the RR, coefficient of recruitment disorder \((c_{rd})\), and \(r\), a uniformly distributed random number between 0 and 0.5. This equation resulted in any RT potentially being shifted up or down at most half of the RR (when \(c_{rd} = 1\)). All the RTs were bounded within the range of 1 to RR au. Four different coefficients (0.1, 0.6, 0.8, and 1) were tested to compare a low level of recruitment order disturbance and varying levels of disturbance observed experimentally.

Procedure

As described above, both the excitation drive and force were quantified in arbitrary units based on the properties of the first MU. This results in varying amounts of total force for each set of RT, RR, and PFR parameters. Therefore, the excitatory drive and muscle forces were subsequently normalized as a percentage of the maximum drive and the maximum peak force, respectively. The maximum excitation drive was always calculated from the drive needed to have the last recruited MU reach its PFR, and the absolute value of the peak excitation across different parameters could be different as shown in figure 1. For example, a MU pool with compressed RR requires less peak excitation drive to activate the pool maximally. The maximum peak force was selected from the force trace of the ‘normal’ condition with RR = 30 and PFR = 25, which was 11920 au. This maximum force was considered the maximum voluntary contraction (MVC), which was used as the MVC across all the simulated conditions. Ten different excitation levels for each set of tested MU parameters were completed based on a percentage of the maximum drive for each condition. A simulation of each parameter set was then run at every 10% of the maximum excitation drive for a duration of 30 s at a sampling interval of 20 ms (figure 3). All simulations started with an initial ramp of 20% excitation per second until the corresponding steady state excitation was reached (e.g. 10% trial starts with 0.5 s ramp, 100% trial starts with 5 s ramp), and this ramp pattern was simulated to match typical experimental conditions. The interaction of the recruitment compression and reduced onion-skin effects were also tested by combining the changed parameters. The four RRs were simulated in combination with peak firing rate ranges of 15 and 25 pps, and the 4 PFRRs were simulated at RRs of 15 and 30 au. The four recruitment disorder coefficients were run at a normal range of recruitment (RR = 30) and a normal range of peak firing rates (PFR = 25). Due to the fatigue component, the output force first reaches a single maximum before gradually declining with longer contraction. This peak force as well as the declined force level at 30 s (figure 3) was calculated to summarize the resultant muscle force due to each parameter set. The forces were estimated based on a 1 s window to reduce the effect of force variability. The force at 30 s was compared in order to evaluate the influence of muscle fatigue on the force output. Since there are stochastic components built into the model, each simulated condition at each excitation level was repeated 10 times, and the averaged peak force or force at 30 s of the 10 repetitions were calculated to further reduce the potential influence of force variability.

We further selected three exemplar excitation levels (low, medium, and high), in order to quantify the relative influence...
of individual parameters on the force output across different excitation levels. Specifically, the 20%, 60%, and 100% peak force values were taken from the two sets of RR variations and two sets of PFR range variations. At each excitation level, the force of each parameter value was normalized as a percent of the force taken from the widest RR or PFR range. The 30 s fatigue forces were ignored in this analysis as most trends were similar between the peak and fatigue force traces. For all the simulation results, we did not perform any statistical tests, given that the variation of the simulation outcome is relatively small and an arbitrary number of repetitions can be simulated that could skew the test results.

Results

Recruitment compression

Figure 5 shows the output force values obtained from the varied RRs for the 25 pulses per second (pps) PFR range. Each force profile represented the RT range chosen for the model, and each point corresponded to the peak force (left) and 30 s force (right) of each simulated excitation level. The force range at both time points gradually increased with increasing drive until it reached a plateau, following a sigmoidal shape. The wider RRs reached their plateau earlier than the more compressed ranges, and the plateau itself was also found at

Figure 5. Recruitment compression force output at normal PFR range. Left graph contains the peak forces at each excitation level and simulation condition. Right graph contains the output force level after 30 s of a sustained excitation level.

Figure 6. Recruitment compression force output at small PFR Range. Left graph contains the peak forces at each excitation level and simulation condition. Right graph contains the output force level after 30 s of a sustained excitation level.
a higher percentage of the total MVC force. The most compressed RR (10 fold) also showed a substantial decrease in the force output across all the excitation levels. For example, at 60% excitation, the four threshold ranges (30, 20, 15, and 10 au) exhibited peak forces of 87.5%, 67.7%, 52.5%, and 37.2% of the MVC, respectively. After 30 s of sustained contraction, the forces declined further to 64.5%, 56.6%, 43.5%, and 31.3%, respectively.

At the reduced onion-skin condition (15 pps range), the force output at different threshold ranges are illustrated in figure 6. Although the overall plateau levels were lower than in the 25 pps range condition, the general trend of the force as a function of excitation level were not notably different.

Figure 7. Compressed onion-skin force output at wide RR. Left graph contains the peak forces at each excitation level and simulation condition. Right graph contains the output force level after 30 s of a sustained excitation level.

Figure 8. Compressed onion-skin force output at narrow RR. Left graph contains the peak forces at each excitation level and simulation condition. Right graph contains the output force level after 30 s of a sustained excitation level.

Compressed onion-skin

Alternatively, the four PFRR conditions (25, 20, 15, and 10 pps) were tested at threshold ranges of 30 and 15 au. These conditions resulted in force outputs that had a linear initial increase at lower excitation levels until reaching a plateau at a higher excitation. All the force profiles appeared to have a similar trend across different excitation levels, but differed in the maximum force output. At the wide RR (figure 7), there was a progressive increase in the differences of the force output, and the difference seemed to be more pronounced at higher levels of activation. For example, at 40% excitation, the four PFR ranges (25, 20, 15, 10 pps) exhibited peak forces of 62.0%, 57.3%, 51.4%,

Compressed onion-skin
and 42.6% of the MVC, respectively. In contrast, at 60% excitation, the four ranges peak forces were 87.5%, 78.62, 64.5%, 54.9% of the MVC, which were more noticeably different. With muscle fatigue (force at 30s), the magnitude of force decline over the four ranges was lessened compared with the peak force. At 60% excitation, the force outputs were 57.3%, 54.1%, 49.5%, 42.6% of the MVC after 30s. When the RR was compressed (figure 8), the contribution of the weak onion-skin to a reduction in force output was also progressively increased at higher levels of excitation. This effect was especially evident in the forces under fatigue (at 30s).

Disturbed recruitment. For the disturbed recruitment order condition at normal RR and PFR (figure 9), all of the force profiles behaved similarly with some minor changes in output force levels. There appeared to be no obvious difference between the force profiles across the different levels of recruitment disorder, except a consistent decline of force at 30s.

Relative contributions of altered parameters. Given that the altered RR and firing rate range were the primary contributors of reduced muscle force output, here we further summarized the relative force decline at three representative excitation levels spanning the entire simulated range. Only the peak force was summarized, since the force at 30s tended to show similar trends across the different excitation levels.

To quantify the relative contribution, the forces at each excitation level with a specific MU parameter was normalized by the force from the condition we previously determined to be ‘normal’: The 30 fold range of recruitment for the RR variations (figure 10(A)); and the 25 pps firing rate range for the PFR variations (figure 10(B)). With a stronger onion-skin pattern (figure 10(A), left), a compression of recruitment tended to have a stronger influence on the relative reduction of force output at lower excitation levels (e.g. 20%), and a similar trend was found with a weaker onion-skin pattern (figure 10(A), right).

The influence of the firing rate range on force output is summarized in figure 10(B). With a wider RR, a weaker onion-skin pattern (i.e. a narrow firing rate range) tended to have a stronger influence on the relative force output at higher excitation levels (figure 10(B), left). In contrast, with a narrow RR (figure 10(B), right), the influence of the onion-skin pattern on the relative force tended to show a comparable effect across different excitation levels.

Discussion

By utilizing a MU pool model, this study explored the individual impacts of various changes to MU control properties on the overall impairment of force generation in chronic stroke survivors. The force output was simulated at different levels of excitation comparing different normal and abnormal organization patterns of MU recruitment and firing rate modulation. We found that the reduced range of the MU RTs has the most pronounced impact on the total output force, and the influence is more evident at low to moderate excitation levels.

A weaker onion-skin condition with a more compressed range of MU firing rates also appeared to show an effect on the force during higher levels of simulated activation, although this effect is reduced when recruitment compression comes into play. Surprisingly, the disturbance of the MU recruitment order was not a significant factor in causing muscle weakness. Each of these main factors are further discussed below.

Compressed RR. MUs in post-stroke affected muscle tend to be recruited at small forces compared with the contralateral muscles and neurologically intact muscles [4, 5, 20], and this altered recruitment pattern is observed consistently across different stroke survivors. In our simulation, the compression of the RR has a widespread influence across the entire force range, especially evident at low to moderate excitation levels. We also found that the compressed RR has a stronger influence on reducing muscle output, compared with the reduced

![Figure 9](https://example.com/figure9.png)  
Disturbed recruitment order force output. RR = 30 and PFRD = 25. Left graph contains the peak forces at each excitation level and simulation condition. Right graph contains the output force level after 30s of a sustained excitation level.
It is important to note that there is a difference in the RT measurement between the experimental and the simulation conditions. Experimentally, the RT was measured by the muscle force at which an MU begins firing, whereas the threshold in the simulation was determined by the relative excitation drive. Although the excitation drive and muscle force output have a curvilinear relation as described in the original model [12], these two measurements do not have a direct linear match, especially in the conditions simulated for MUs in stroke survivors as shown in our current simulation. As a consequence, the simulated degree of recruitment compression could underestimate the experimentally observed recruitment compression. We used the excitation measure to be consistent with other measures, e.g. the excitation level rather than the force level was used to quantify the muscle contraction levels. Given that the simulated RR covered a large range (from 10 to 30-fold), which should have covered the experimentally observed range, and that the goal of the stimulation was to quantify how alterations of particular MU parameters can influence muscle weakness, we believe that the excitation based measures can still capture the influence of the recruitment compression on force output.

With a compressed RR, despite a larger number of MUs being recruited at lower excitation levels, these earlier recruited MUs did not contribute to more force output, but rather lead to force decrement. This seemingly unintuitive finding can arise from several factors. First, with a lower RT, MU fatigue can arise earlier since the fatigue index in the model is a function of time-since-recruitment; this being especially applicable to the originally high-threshold fatigable MUs. Therefore, the recruited MUs collectively have reduced twitch amplitudes, and the initially added forces are not sustainable over time. The total MU forces are reduced accordingly, leading to overall muscle weakness. This early fatigue effect is consistent with experimental findings showing that stroke survivors are more susceptible to muscle fatigue [19]. Second, although the MUs are active, the initially recruited ones discharge at a relatively low rate. Based on the sigmoidal rate-force relation, the firing rate can be located at critically low levels that cannot lead to proper fusion of the twitch forces, and the individually spaced twitches would thus yield minimal force contribution. Lastly,
MU atrophy in stroke survivors [21, 22] can also lead to recruitment compression as a compensatory mechanism. Specifically, the atrophied MU produced a lower unit force due to smaller twitches. As a result, additional MUs, potentially more fatigable ones, need to be recruited earlier to reach the desired total force. However, the added forces may not be sustainable in the long term because of earlier onset of MU fatigue.

In our simulation, an open-loop scheme was used, and the reduced force was not compensated by increasing the excitation drive, as in realistic human testing. As the excitation drive increases, the MU firing rates will increase accompanied with additional new unit recruitments. However, the high firing rate can further accelerate the degree of fatigue, and would have detrimental effects on the overall force output. Therefore, our simulation could potentially underestimate the influence of recruitment compression on force output reduction. Further simulation studies involving close-loop control of the force output are necessary to better quantify the contribution of recruitment compression to muscle weakness.

Reduced onion-skin. Earlier studies have found that the MU firing rate layering pattern is considerably weaker in the affected muscle in comparison with the contralateral muscle [6]. This weak onion-skin pattern can be a result of a differentially altered firing rates at different RTs. Namely, an earlier plateau of firing rate in the lower threshold MUs can lead to a compressed firing rate range, possibly due to an impaired rate modulation of MUs in the affected muscles of stroke survivors [23]. Conversely, in order to produce the desired force output, a compensatory increase of the firing rate in the later recruited MUs can also reduce the firing rate range in the pool. In our simulation, we found that a weaker onion-skin firing pattern can lead to reduced force output, both in an absolute and a relative sense, especially at higher excitation levels.

The observed force level decline with a weaker onion-skin firing pattern can arise from a reduced firing rate in the earlier recruited MUs, which could reduce the MU force in those units. On the other hand, an increase of the firing rate in the high threshold units can initiate an early onset of muscle fatigue. This effect can partly explain the observation that the reduced force due to weak onion-skin is more evident at high excitation levels. Specifically, the high threshold units are generally more susceptible to fatigue. With initial higher firing rates in the high threshold MUs at high excitation drive, the rate of decline in the twitches of those units is further accelerated, which can lead to reduced overall muscle forces at high levels of effort in stroke survivors. Conversely, at low excitation levels, the weak onion-skin does not have much impact on the force output, possibly because the extent of MU fatigue in the earlier recruited units is relatively small and the twitch amplitude can be sustained. Our simulation also shows that recruitment compression can dampen the influence of the weak onion-skin on muscle weakness. This is largely because early recruitment of MUs have already induced fatigue onset, leading to lower force output. Therefore, the overall influence of recruitment compression on muscle weakness can overpower the influence of weak onion-skin firing pattern.

Conclusions. Overall, we found that the recruitment compression and weak onion-skin firing pattern tend to show a substantial contribution to muscle weakness. The relative impact is more evident in the low force levels under recruitment compression, while the relative impact is more evident in the high force levels under the weak onion-skin firing.
pattern. We also found that the compressed RR can restrain the impact of weak onion-skin on muscle weakness, but not vice versa. Lastly, we found that a disturbance of the orderly recruitment has minimal impact on muscle weakness. These findings suggest that, besides reduced excitation drive and peripheral atrophy, altered central control of MU pool alone can lead to substantial muscle weakness in stroke survivors. The findings can potentially provide guidance for clinicians during prescription of rehabilitation procedures that include targeted cortical or peripheral stimulation therapies and pharmacological treatments involving neurotrophic factors, in order to maximize functional recovery of stroke survivors.

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