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SPIKE-TRIGGERED AVERAGING PROVIDES INACCURATE ESTIMATES OF MOTOR UNIT TWITCH PROPERTIES UNDER OPTIMAL CONDITIONS

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ABSTRACT

Spike-triggered averaging is a commonly used technique for the estimation of motor unit twitches during voluntary contractions, although the obtained twitch estimates are known to be inaccurate in several conditions. Nevertheless, it is commonly assumed that a careful selection of the triggers may reduce the inaccuracy. This study aimed to analyze the impact of trigger selection criteria and thereby to identify the minimum estimation errors using a computational neuromuscular model. Force signals of five-minute duration were simulated at 10 contraction levels between 1 and 30% of the maximal voluntary contraction level (MVC) for motor unit pools of varying size (100, 300, and 800 motor units). Triggers were selected based on the inter-spike intervals (minimal value: 90-175 ms) and the number of triggers (minimal value: 100-800). The simulation results indicated that a minimum of 400 triggers with inter-spike intervals >125 ms are needed to achieve the most accurate twitch estimates. Even under these conditions, however, a substantial estimation error remained (11.8-31.2% for different twitch parameters for simulations with 100 motor units). The error increased with the innervation number. The study demonstrates the fundamental inaccuracy of twitch estimates from spike-triggered averaging, which has important implications for our understanding of muscular adaptations.

INTRODUCTION

The output of the neuromuscular system is determined by the activity of the motor units and their contractile properties. For this reason, the pattern of motor unit action potentials (recruitment, rate coding) during voluntary contractions and the characteristics of the contractile response to action potentials (motor unit twitch) have been extensively studied. Examples of such studies include investigations of the effect of acute and chronic adaptations such as e.g. muscle fatigue (Carpentier et al., 2001), pain (Farina et al., 2008), training (Van Cutsem et al., 1998) on these parameters. The discharge patterns of a subset of the active motor units can be identified in an unbiased way by decomposing intramuscular and/or surface electromyographic (EMG) signals (Marateb et al., 2011; McGill et al., 2005; Negro et al., 2016). Accurate estimates of the motor unit twitches during voluntary contractions, however, are more difficult to obtain. Typically, the twitch is estimated using spike-triggered averaging (STA), which involves averaging muscle force in short windows centered around the motor unit discharges (triggers) (Buchthal and Schmalbruch, 1970; Stein et al., 1972), enabling calculation of the twitch properties such as amplitude, contraction time and half relaxation time. The estimated twitch parameters from the STA technique, however, has been shown to be inaccurate in several conditions (Lim et al., 1995; Negro et al., 2014; Taylor et al., 2002).

There are two fundamental sources of errors in the twitch estimates from the STA. First, when the inter-spike intervals of the trigger motor unit are sufficiently short, the consequent twitch summation may distort the twitch estimate. The phenomenon has been demonstrated experimentally by applying STA to the force evoked by electrically stimulated twitches of single motor axons at different frequencies (Calancie and Bawa, 1986; Thomas et al., 1990). Specifically, these studies found that increasing the frequency of action potentials implied an underestimation of the twitch properties. Accordingly, the length of the ISI before and after each trigger substantially impacts the twitch estimate during voluntary contractions (Gossen et al., 2003; Milner-Brown et al., 1973; Nordstrom et al., 1989). These observations have led to some studies imposing a minimum inter-spike interval (ISI-threshold; range: 100-150 ms) as inclusion criteria for triggers (Farina et al., 2008, 2005; Roatta et al., 2008; Van Cutsem et al., 1998). However, a recent investigation showed that this strict selection may even be detrimental for the estimation in some conditions (Negro et al., 2014). Second, the force produced by other motor units imposes noise on the estimate of the target unit twitch. Under the assumption that the forces produced by different motor units are uncorrelated, a sufficient number of triggers should largely reduce this error. Moreover, a certain number of triggers is necessary to account for the natural short-term variability in the twitch shape (Celichowski et al., 2014). Consequently, most studies have imposed a lower limit for the number of triggers (trigger-threshold), but this limit varies largely across different study, e.g. <50 (Carpentier et al., 2001; Stephens and Usherwood, 1977), a few hundreds (Farina et al., 2008, 2005; Milner-Brown et al., 1973; Van Cutsem et al., 1998), and >1000 (Roatta et al., 2008; Semmler et al., 2000). The assumption of uncorrelated forces generated by different motor units, however, is violated when motor unit synchronization is present, which is usually the case during voluntary contractions (Keen et al., 2012). In general, high levels of motor unit synchronization impair accurate twitch estimation (Negro et al., 2014; Taylor et al., 2002).

Although the limitations of the STA technique have been well documented, many studies implicitly assume that STA is able to provide reliable estimates of twitch properties if the triggers are selected based on specific criteria. However, the appropriate values for the ISI- and number of trigger-thresholds as well as the relative magnitude of the errors in the estimated twitch properties that can be expected in the optimal case are unknown. In this study, we used a computational model to systematically investigate the quality of the estimates of twitch properties by STA obtained with different values of these thresholds and across a number of realistic conditions.

METHODS

Simulations

The study adopted the model of motor unit activity and isometric force generation developed by (Fuglevand et al., 1993) with the distribution of minimum and peak discharge rates proposed by (Barry et al., 2007). As in other more recent applications of this model, the variability in the timing of the discharges was introduced by adding Gaussian noise to the motor neuron input (Dideriksen et al., 2012, 2010). The magnitude of this noise was scaled to obtain a coefficient of variation for inter-spike intervals between 10% and 30% (Clamann, 1969; Moritz et al., 2005). The number of motor units in the model was set to 100, 300, or 800 representing the range of motor unit numbers for typical small and large muscles (Heckman and Enoka, 2004).

For each type of muscle, simulations were carried out with 10 different excitation levels (1, 2, 3, ..., 10), evoking a range of contraction levels below 30% of the maximum voluntary contraction level (MVC). Each simulation had a duration of 300 s. For each excitation level, simulations were carried out with or without a relation between twitch amplitude and contraction time. As in the original model, the relation between these parameters was modelled by a power function (Fuglevand et al., 1993).

Analysis

For each motor unit, the number of motor unit discharges for which the ISI were below the pre-assigned threshold (ISI-threshold) were excluded as suitable triggers. If the number of the included motor unit discharges was larger than the pre-assigned threshold of number of triggers (trigger-threshold), spike-triggered averaging was performed for the included motor unit twitch. The spike-triggered averaging involved selecting windows from the muscle force (duration: 600 ms), starting at the time of each trigger and calculating the average force across all windows. In this way, the average recurrent twitch waveform following each motor unit discharge was estimated. From each of these estimated motor unit twitches, the peak amplitude (maximum value in the first 150 ms), the contraction time (time to reach the maximum value in the first 150 ms) was calculated, and the half relaxation time (time from the peak amplitude to the twitch estimate has half that amplitude). In each simulation, spike-triggered averaging was performed with 18 different ISI-thresholds (90, 95, 100, ..., 175 ms) and four different trigger-thresholds (100, 200, 400, 800). The trigger-threshold also served as the maximum number of motor unit discharges included, which implied that additional motor unit discharges that complied with the ISI-threshold were excluded once the trigger-threshold was reached. This procedure was implemented to ensure the consistency of the calculated results across simulations with different discharge properties.

The calculations described above were performed at each contraction level and resulted in a vector with the estimated twitch parameters for each individual motor unit that was included. If the same motor unit fulfilled the inclusion criteria in more than one contraction level, one estimate was randomly selected for further analysis. For each motor unit twitch estimation, the normalized rectified error of twitch amplitude, contraction time, and half relaxation time were calculated. Across the population of motor units, the two estimated parameters were log-log transformed (to linearize their relation) and linear regression was applied. This procedure was repeated 20 times to accommodate the random selection of parameters for motor units included in more than one contraction level. The average value for the normalized errors and correlation coefficients across the 20 repetitions were calculated.

RESULTS

Figure 1 shows an example of the output of the simulations with 300 motor units. Across the 10 simulations, the contraction level varied between 0.5% MVC to 29% MVC (Fig. 1A). The number of recruited motor units and their discharge rates increased at higher contraction levels (Fig. 1B). At the highest simulated contraction levels (>20% MVC), all motor units were recruited, although the largest motor units were only active sporadically due to fluctuations in the synaptic noise (i.e. the average discharge rates were below their assigned minimum discharge rates). Figure 1C shows the range of motor units for which at least 400 accepted triggers with ISI-thresholds above 110 ms occurred across the simulations. At the low contraction levels, only the smallest motor units could fulfil the criteria for inclusion. On the other hand, at higher force levels, the discharge rates of the same motor units were too high to allow 400 triggers within the ISI limits (>110 ms). Using this combination of the two inclusion criteria (ISI-threshold: 110 ms; trigger-threshold: 400), almost all (293/300) motor units were included in the analysis for at least one of the 10 simulated contraction levels, while some motor units fulfilled the criteria at more than one contraction level. When the values for the two thresholds increased, however, the number of included motor units and the occurrence of motor units included at multiple simulations decreased.

Figure 2 illustrates the process of spike-triggered averaging for one simulated motor unit (ISI-threshold: 110 ms). When the twitch estimate was derived from only a few triggers, substantial errors were observed for the three twitch properties (Fig. 2B, 2C, 2D). In this case, the estimates of twitch amplitude and contraction time tended to converge to a stable value at approximately 200 triggers. Whereas the estimates of twitch amplitude and half relaxation time underestimated those of the real twitch, the estimated contraction time converged to a near-correct value in this example.

Figures 3 shows the actual and estimated motor unit twitch parameters (amplitude and contraction time) for all included motor units (ISI-threshold: 140 ms, trigger-threshold: 400) in simulations with 100 motor units. In this way, the figure contain estimates of twitch properties from simulations at all 10 contraction levels. Overall, the estimates are relatively accurate, as indicated by the average normalized rectified errors (twitch amplitude: 15.5%, contraction time 13.9%) and by the relation between the estimated amplitude and contraction time (similarity between grey and black line). The average error in half relaxation time (not shown), however, was 63.7%. Slow, low-amplitude units tended to display the largest errors. Figure 4 compiles the average normalized rectified errors for all three twitch parameters as functions of the ISI- and trigger-thresholds for simulations with 300 motor units. At low values for the ISI-threshold, the errors were high, but decreased steadily when this threshold was increased. Table 1 shows the average ISI-threshold required for the errors to be within 25% of the minimum error. For simulations with 300 motor units (as shown in Figure 4), this critical value for the ISI-threshold was 135-140 ms. Furthermore, an increase in the trigger-threshold implied a decrease in the error for all parameters. When the ISI-threshold was assigned values > 145 ms, none of the motor units in any of the simulations displayed 800 triggers. For this reason, the lines indicating errors estimated with trigger-threshold=800 are only shown for ISI-thresholds between 90 and 145 ms.

Figure 5 shows the average errors in the twitch parameters calculated with ISI-thresholds above the critical values (Table 1) across the trigger-thresholds. As also indicated by Figure 4, an increase in the trigger-threshold improves the estimate of the twitch parameter. In some cases, however, the estimates are worse at 800 triggers compared to 400 triggers. This reflects that only a small subset of the motor units were included when 800 triggers were required (5-8% of the motor unit pool, as opposed to >75% of the motor unit pool at 400 triggers). Together, the results illustrated in Table 1, Figure 4, and 5 indicate the optimal thresholds for STA. Figure 6 summarizes the average errors in the estimated twitch parameters when these optimal thresholds were applied. For all three parameters, the errors increased with the number of motor units. For muscles innervated by 100 motor neurons average errors of 13.2% and 11.8% were found for twitch amplitude and contraction time, respectively. Accordingly, the correlation coefficient for the log-log transformed linear relation between estimates of twitch amplitude and contraction time was -0.73, -0.47, and -0.29 for simulations with 100, 300, and 800 motor units, respectively. For half relaxation time, the error at 100 motor units was 31.2%.

DISCUSSION

In this study, we analysed the ability of the STA technique to provide accurate estimates of motor unit twitches using a computational model of the neuromuscular system. In general, the results showed a significant bias in the estimation of peak twitch force, contraction time, and half relaxation time, for all simulated conditions. This observation is in line with a number of previous investigations (Lim et al., 1995; Negro et al., 2014; Taylor et al., 2002), but this study demonstrated for the first time that accurate twitch estimation by STA cannot be achieved by optimally selecting inclusion criteria for triggers in typical physiological conditions. The results showed that the optimal criteria include a minimum of 400 triggers (Figure 5) with inter-spike intervals of at least 125 ms (Table 1). The ISI-thresholds, however, depended on the size of the motor unit pool and the twitch parameter in question. Consequently, ISI-thresholds >130 ms were required for optimal twitch estimates in most simulated conditions. In a similar way, the minimum estimation error depended on the number of motor units. For a muscle innervated by 100 motor neurons, normalized errors in the range 10-15% could be achieved for estimated twitch amplitude and contraction time, provided that appropriate trigger- and ISI-thresholds were applied. Innervation numbers around 100, however, are only observed for few, small muscles, whereas most muscles have higher innervation numbers (Heckman and Enoka, 2004). This implies inevitably higher estimation errors (Figure 6). This reflects that in STA, the force produced by other motor units represents a noise term, and that magnitude of this noise increases with the number of motor units. Finally, the results indicated that the error in the estimated twitch half relaxation time was always substantially higher compared to the other twitch parameters (>30%; Figure 6), as previously reported (Negro and Orizio, 2017). Importantly, it should be noted that these results reflect conditions without motor unit synchronization, which, if present to a sufficient degree, further corrupts the twitch estimates by STA (Kutch et al., 2007; Taylor et al., 2002).

The results casts doubt on the current knowledge on motor unit twitch properties and their adaptations, since several previous studies applied STA with sub-optimal ISI- and trigger-thresholds. For example, an inverse relation between twitch amplitude and contraction time were presented by Stephens and Usherwood (1977), but the average ISI was 100 ms and in the number of triggers were <100 in many trials. As shown in Figure 4, these settings likely implied large estimation errors. Interestingly, studies using intraneural stimulation have not always been able to confirm this relation (Fuglevand, 2011). Furthermore, the current results indicate that for large muscles the uncertainty related to STA may mask such a relation when present. Another example relates to strength training, where the observed adaptations in the motor unit twitches were likely to have been biased by the applied ISI-threshold of 100 ms with fewer than 400 triggers (Van Cutsem et al., 1998). Finally, it should be noted that, even when appropriate thresholds are applied, a substantial estimation error remains (Figure 6), which implies a risk of misinterpretation. For example, Roatta et al. (2008) found a 15% change in twitch half relaxation time in response to sympathetic activation using an ISI-threshold of 125 and >1,000 triggers. Although, these thresholds are close to the optimal values, the identified difference in half relaxation time is well below the minimum expected error for this parameter (>30% in our study).

The rationale for applying ISI-thresholds is to minimize overlap between consecutive motor unit twitches. Consequently, the optimal ISI-threshold depends on the twitch duration of the trigger motor unit (Nordstrom et al., 1989). Twitch durations varies substantially across the motor unit pool, but since the properties of the trigger unit are not known until after STA is performed, the ISI-threshold must be conservatively selected. In this way, an optimal estimate of the twitch will be obtained irrespective of its duration. This study indicates that this threshold is 130-150 ms which is equivalent to an average discharge rate of approximately 6-8 pps. Conversely, the minimum discharge rate for some motor units (presumably mainly high-threshold units) are >10 pps (Moritz et al., 2005). However, since motor unit discharges are highly variable at recruitment (Matthews, 1996; Moritz et al., 2005), it may still be possible to obtain the necessary amount acceptable triggers if the duration of the contraction is sufficient. Additionally, Negro et al. 2014 have shown that high variability of the ISI can minimize bias in the twitch estimation. On the other hand, long contraction durations may be problematic when investigating twitch properties and their adaptations. Specifically, twitch potentiation (Vandervoort et al., 1983) and muscle fatigue (Bigland-Ritchie et al., 1986) progressively alter twitch shape during sustained contractions. Furthermore, when investigating adaptations in the twitch shape to e.g. muscle pain (Farina et al., 2008), standard pain models cannot maintain a stable pain intensity for more than a few minutes.

These considerations strongly indicate the need of more reliable and robust methods for twitch estimation. A few alternative methods based on system identification techniques have been previously proposed to overcome the limitations of the traditional STA technique in human (Andreassen and Bar-On, 1983; Kutch et al., 2010; Lim et al., 1995; Orizio et al., 2016) and in animal recordings (Drzymała-Celichowska et al., 2016). Recently, an advanced method have been proposed and it has demonstrated the ability to accurately estimate the averaged twitch parameters of a relatively small population of motor units (Negro and Orizio, 2017). The method is based on a model-based deconvolution of the recorded force signal using the identified discharge times of a relatively small (tens) population of motor units. Using the information of the discharge times of multiple motor units and a flexible twitch model, it is able to solve the inverse problem and estimate the averaged twitch profile overcoming the bias introduced by the mean discharge rate of the units. Moreover, in simulations and experimental recordings, it showed less sensitivity to motor unit synchronization and low trigger number compared to the standard STA technique.

The modelling approach adopted for this study involves a number of advantages but also some limitations. The main advantages includes that the true twitch properties are known and can act as a direct reference for the estimated twitch properties. Furthermore, the model allows for systematic evaluation of the effect of different parameters such as innervation number without bias from e.g. twitch adaptations (e.g. fatigue), motor unit synchronization, and force generated by synergistic muscles. On the other hand, this approach requires that the model is an accurate representation of the physiological system. For example, it was recently shown that another computational model of motor unit force provides a poor estimate of tetanic forces generated by slow twitch motor units (Raikova et al., 2016). The model used in this study (Fuglevand et al., 1993), however, has previously been used for a wide range of applications (e.g. (Herbert and Gandevia, 1999; Jones et al., 2002; Taylor et al., 2002)).

In conclusion, the simulation results indicate that estimation of twitch properties using STA is unreliable even when conservative selection criteria for triggers are employed. In addition, the estimation errors depend on the muscle innervation number. These findings indicate the need for new methods for twitch estimation of individual motor unit and the re-evaluation of some aspects of our understanding of twitch properties and their adaptations.

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TABLES

Table 1: Optimal ISI-thresholds for the three twitch parameters across simulations with different number of motor units (MUs)

	100 MUs	300 MUs	800 MUs
Amplitude	150 ms	140 ms	130 ms
Contraction time	140 ms	135 ms	125 ms
Half relaxation time	160 ms	140 ms	130 ms

FIGURE CAPTIONS

Figure 1: The simulated forces (A), the average discharge rates (B) and the range of motor units that complied with one set of inclusion criteria (ISI-threshold = 110 ms, trigger-threshold=400) across all simulated contraction levels (C). In this case, most motor units (293/300) were included in at least one contraction level. The simulations presenting the lowest average force in panel A corresponds to the lowest average discharge rate in panel B, and so forth for higher and higher contraction levels.

Figure 2: The twitch waveform estimated by spike-triggered averaging with 50, 200, or 800 triggers (different shades of grey; A). The ISI-threshold was 110 ms. The real twitch (motor unit #140) is superimposed (thin dashed line). The estimated twitch amplitude (B), contraction time (C), and half relaxation time (D) are shown as functions of the number of triggers. Here, the dashed lines represent the parameters from the real twitch.

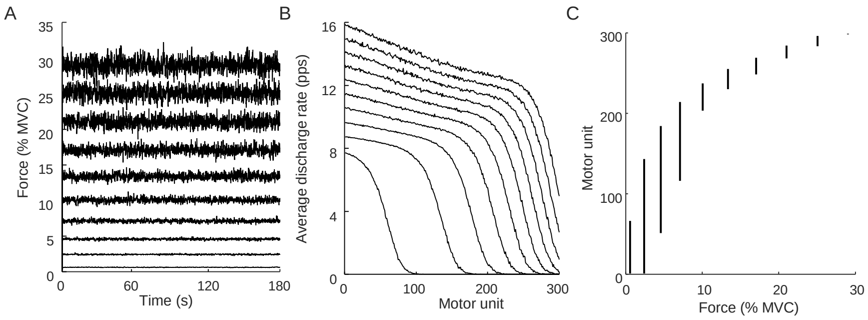
Figure 3: Scatter plot of the real (grey line) and estimated (black circles) motor unit twitch parameters (A). The black line represents the best fit to the estimated data using a power-function. Panels B and C show the mean±SD of the normalized, rectified errors in the estimates of twitch amplitude and contraction time across the range of real values for the two parameters. The data shown in the figure represents simulations 100 motor units. ISI-threshold was set to 140 ms and the trigger-threshold was 400.

Figure 4: Average normalized, rectified errors for twitch amplitude (A), contraction time (B) and half relaxation time (C) as a function of the ISI-threshold for all trigger-thresholds. The data shown in the figure represents simulations 300 motor units.

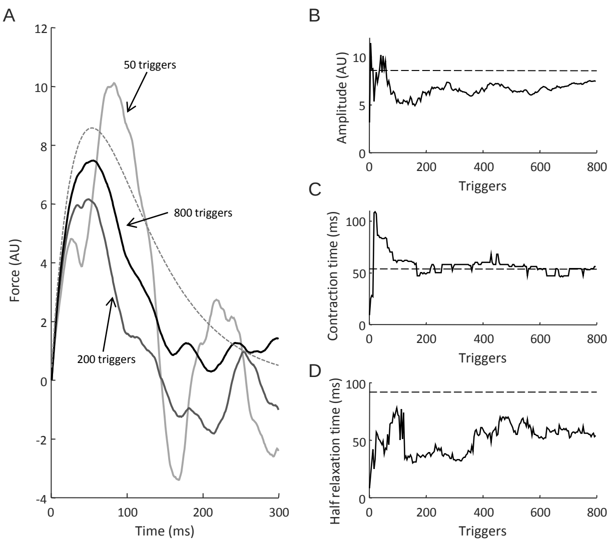
Figure 5: Average normalized, rectified errors for twitch amplitude (A), contraction time (B) and half relaxation time (C) as a function of the trigger-threshold for ISI-thresholds at or higher than the value required for the error to be <25% above the minimum error (see Table 1).

Figure 6: Average normalized, rectified errors for twitch amplitude (A), contraction time (B) and half relaxation time (C) estimated using the optimal values for ISI-threshold and trigger-threshold across the different numbers of motor units.

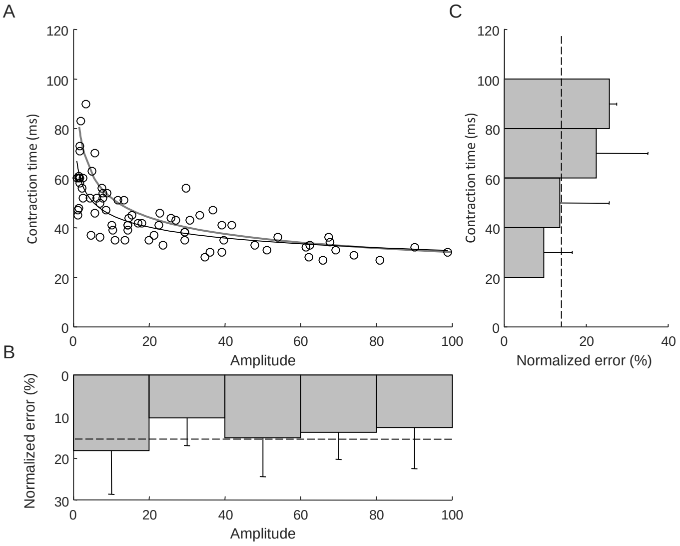
Dideriksen & Negro, Figure 1



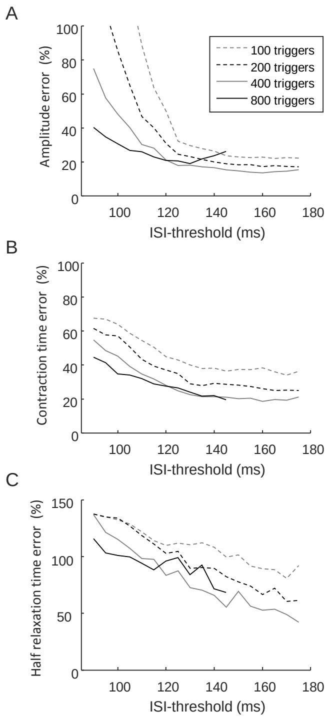
Dideriksen & Negro, Figure 2



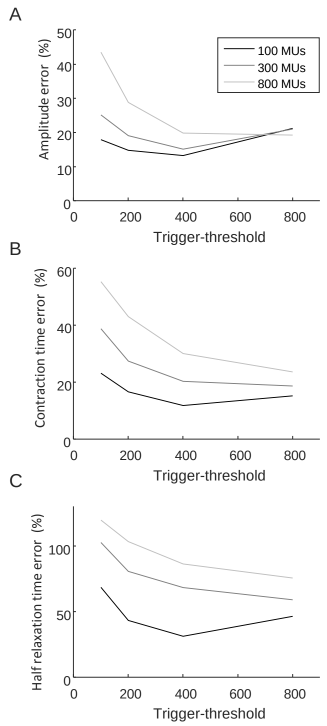
Dideriksen & Negro, Figure 3



Dideriksen & Negro, Figure 4



Dideriksen & Negro, Figure 5



Dideriksen & Negro, Figure 6