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Modified Motor Unit Number Index: A Simulation Study of the First Dorsal Interosseous Muscle

Xiaoyan Li[1], **Sanjeev D Nandedkar**[2], and **Ping Zhou**[1,3]

[1]Department of Physical Medicine and Rehabilitation, University of Texas Health Science Center, and TIRR Memorial Hermann Research Center, Houston, TX, USA

[2]Natus Medical Inc., Middleton, WI, USA

[3]Guangdong Work Injury Rehabilitation Center, Guangzhou, China

Abstract

The motor unit number index (MUNIX) technique has provided a quick and convenient approach to estimating motor unit population changes in a muscle. Reduction in motor unit action potential (MUAP) amplitude can lead to underestimation of motor unit numbers using the standard MUNIX technique. This study aims to overcome this limitation by developing a modified MUNIX (mMUNIX) technique. The mMUNIX uses a variable that is associated with the area of compound muscle action potential (CMAP) rather than an arbitrary fixed value (20 mV·ms) as used in the standard MUNIX to define the output. The performance of the mMUNIX was evaluated using motoneuron pool and surface electromyography (EMG) models. With a fixed motor unit number, the mMUNIX output remained relatively constant with varying degrees of MUAP amplitude changes, while the standard MUNIX substantially underestimated the motor unit number in such cases. However, when MUAP amplitude remained unchanged, the mMUNIX showed less sensitivity than the standard MUNIX in tracking motor unit loss. The current simulation study demonstrated both the advantages and limitations of the standard and modified MUNIX techniques, which can help guide appropriate application and interpretation of MUNIX measurements.

I. INTRODUCTION

The recent advent of the motor unit number index (MUNIX) technique has provided a quick and convenient approach to estimating the number of functioning motor units in a muscle [1, 2]. It uses compound muscle action potential (CMAP) and surface electromyography (EMG) signals (or interference patterns) at different contraction levels to produce an index that is proportional to the number of motor units in the muscle. Compared with the conventional

Address Correspondence to: Xiaoyan Li, PhD, 1333B Moursund St., Houston, TX 77030, Xiaoyan.Li@uth.tmc.edu.

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motor unit number estimation (MUNE) techniques using laborious incremental stimulations or EMG decomposition based spike triggered averaging (for estimating the average motor unit size) [3-5], the MUNIX technique is quick and easy to implement and can minimize discomfort caused by electrical stimuli. Thus, there have been an increasing number of applications of MUNIX measurements on assessing motor unit loss or tracking disease progress in amyotrophic lateral sclerosis (ALS)[1, 6-10], as well as in aging [11-14] and neurological injury studies [15-17].

To evaluate the MUNIX technique and its applications in different circumstances, multiple studies have been conducted to examine the reproducibility, validity and sensitivity of the MUNIX estimate [6, 7, 9, 18-20]. For example, the reproducibility of MUNIX was assessed in the thenar and hypothenar muscles by independent operators for both ALS patients and control subjects [6, 9]. Comparison of MUNIX with MUNE methods was also made and a positive correlation was found in ALS patients [7, 8]. In our previous study [18], we employed motoneuron pool and surface EMG models to explore the sensitivity of MUNIX technique to changes of motoneuron and muscle properties. The findings indicated that MUNIX estimates are not sensitive to changes in motor unit control property including motor unit rate coding strategies, and modulations of motor unit recruitment and firing rate ranges [18]. However, reduction in motor unit action potential (MUAP) amplitude can have a substantial impact on MUNIX calculations, leading to an underestimation of the MUNIX. This suggests that there are potential limitations when the MUNIX method is applied in atrophied muscles, where the atrophy is dominantly accompanied by loss of muscle fiber size (decrease of muscle fiber cross-sectional area) or/and reduced number of innervated muscle fibers.

A modified MUNIX (mMUNIX) method is presented in the current study to provide a more appropriate approach (than the standard MUNIX) to estimating an index of motor unit population in atrophied muscles with concurrent MUAP amplitude reduction. This modified method uses a variable that is associated with each muscle's CMAP area rather than an arbitrary constant value (for example, 20 mV·ms was used in the standard MUNIX) to define the mMUNIX. To understand the difference between standard MUNIX and mMUNIX estimates, a simulation approach using established models of motoneuron pool and surface EMG was implemented. Based on the simulation outputs, the applicable situations as well as the limitations for standard and modified MUNIX techniques were discussed.

II. METHODS

2.1 Model description

Surface EMG signals were simulated based on the established motoneuron pool model developed by Fuglevand et al. [21]. Similar to our previous study, a single MUAP recorded at the skin surface was simplified as the first order derivative of the Hermite-Rodriguez function [18, 22-25]. It was assumed that MUAP amplitude changed linearly with twitch force, which was proportional to the number of muscle fibers. All muscle fibers were assigned the same cross-sectional area [21]. Different motor units were assumed to be widely distributed within the muscle, and resultant MUAPs were simulated to have the same

duration (~ 12 ms). The amplitude of MUAPs was simulated to be exponentially distributed over a wide range:

$$Amp_i = exp\left(\frac{ln\left(Amp_{range}\right)}{n} i\right) \quad (1)$$

where Amp_{range} is the amplitude range of MUAPs which was set to be 100, n is the number of motor units in a muscle which was set to be 120, and i is motor unit index. Similarly, the motor unit recruitment threshold (*RTE*) was also exponentially distributed:

$$RTE_i = exp\left(\frac{ln\left(RTE_{range}\right)}{n} i\right) \quad (2)$$

where RTE_{range} is the range of motor unit recruitment threshold. Two RTE_{range} settings (40% excitation and 80% excitation) were implemented in the current study. A motor unit remained inactive if the excitation was lower than the recruitment threshold. As the excitation exceeded the recruitment threshold, it became active and discharged in a rate linearly proportional to the excitation drive above the recruitment threshold. The inter-firing interval of each motor unit was modeled as a Gaussian distribution. All the motor units were set to have the same minimum firing rate of 8 pulses per second (pps). The lower and upper limits of the motor unit peak firing rate were set to be 23 pps and 52 pps respectively. Two rate coding patterns (the 'onion-skin' pattern and the reverse 'onion-skin' pattern) were also implemented [21, 25]. The surface EMG signal, or surface EMG interference pattern, was composed of the superposition of multiple MUAP trains from all active motor units. We simulated 15 steady-state surface interference pattern signals for MUNIX calculation with excitation ranging from 5% to 50% excitation at 5% increments and from 50% to 100% excitation at 10% increments (examples shown in Figure 1). The duration of a typical steady state surface EMG signal (or interference pattern) corresponding to each excitation level lasted for 3s.

The CMAP represents the electrical equivalent of the recruitment of all the motor units in a muscle. It was simulated as a linear summation of all the MUAPs in a synchronous mode [24]:

$$CMAP = \sum_{i=1}^{n} x_i\left(t_i\right) \quad (3)$$

where x_i is the *i*th MUAP, n is the total number of motor units, and t_i indicates the time instance when the *i*th MUAP reaches the recording electrode. The time variation of all the different motor units reaching the electrode was limited within a 2 ms period. An example of CMAP simulation is shown in Figure 1.

2.2 Calculation of standard MUNIX

Estimation of standard MUNIX involves three steps (Figure 1). The first step was to calculate the area and power of the individual surface EMG interference pattern as well as the area and power of the CMAP. The surface interference patterns were rectified prior to computation of their area and power. The parameters were calculated over the 3 s steady

state period and normalized to 1s epoch. The parameters of CMAP, including peak-to-baseline amplitude, area and power, were obtained from the first negative phase of the waveform. Next, the surface EMG interference pattern and CMAP parameters were used to calculate the "ideal case motor unit count (ICMUC)" [1, 2]:

$$ICMUC=\frac{M_p S_{area}}{M_{area} S_p} \quad (4)$$

where M_p and M_{area} represent the power and area of the CMAP, S_p and S_{area} represent the power and area of the surface EMG interference pattern, respectively. A typical trial contains 15 simulated surface interference patterns, which produce 15 corresponding ICMUC values. Selection of valid ICMUC values for MUNIX calculation must meet the following criteria [1]: 1) CMAP amplitude > 0.5 mV; 2) S_{area} > 20 mV·ms; 3) S_{area} / M_{area} > 1; 4) ICMUC < 100. The selected values of the ICMUC and the corresponding area of the surface interference pattern were plotted in a figure (as shown in the bottom plot of Figure 1). The relation between the ICMUC and the surface interference pattern area was then determined via a non-linear regression analysis:

$$ICMUC=\beta^*(S_{area})^{\tau} \quad (5)$$

where β and τ are constant coefficients determined by the relation between the ICMUC and the surface interference pattern area. The standard MUNIX is defined as the ICMUC value when the surface interference pattern area equals to 20 mV·ms:

$$MUNIX=\beta^*(20)^{\tau} \quad (6)$$

The area of surface interference pattern at 20 mV·ms reflects a very low contraction level during which most of recruited motor units have small amplitude and discharge at low rates. As a result, the extent of MUAP superposition is relatively low, which approaches the "ideal" condition as defined by ICMUC [1].

2.3 Calculation of mMUNIX

In contrast to the standard MUNIX which uses an arbitrary constant value of the surface interference pattern area, the mMUNIX is defined as the ICMUC value when the surface EMG interference pattern area equals to a given percentile of the muscle's CMAP (the first negative phase) area:

$$mMUNIX=\beta^*(coeff * M_{area})^{\tau} \quad (7)$$

where 0 < *coeff* < 1. The mMUNIX depends on two parameters: the CMAP area (M_{area}) and the selection of the coefficient (*coeff*). To understand the relation between the mMUNIX and the different percentiles of a muscle's CMAP area, we varied the coefficient values from 10% to 100% at 10% increments. Thus, we calculated 10 mMUNIX values from a single relation between the ICMUC and the surface interference pattern area while the latter was selected from 10% CMAP area, 20% CMAP area, 30% CMAP area, and progressively to 100% CMAP area. An appropriate coefficient was then determined to have the mMUNIX

match the standard MUNIX values. This coefficient was used in the following analysis for tracking motor unit loss in different simulated situations.

2.4 Model assessment of mMUNIX

To understand the mMUNIX method and its differences from the standard MUNIX, we performed the following analysis.

1. The sensitivity of the standard MUNIX and mMUNIX methods to changes in motor unit number was explored. By modifying the number of motor units from the default value (120) to 108, 96, 84, 72, 60, 48, 36, 24, and 12, we were able to simulate motor unit loss in mild to severe conditions (loss of 10% to 90% motor unit population).
2. The effect of decreased MUAP amplitude on mMUNIX and standard MUNIX estimation was also explored by reducing the MUAP amplitude to 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20% and 10% of the default MUAP amplitude.

Twenty trials of surface EMG and CMAP signals were simulated for each motor unit loss or MUAP amplitude reduction situation. The average mMUNIX and standard MUNIX values were calculated and comparisons were made between the two measurements. Regression analysis was performed to examine whether the two measurements were sensitive to changes in motor unit number or MUAP amplitude.

III. RESULTS

The mMUNIX and standard MUNIX were calculated from two motor unit firing rate strategies (“onion skin” strategy and reverse “onion skin” strategy), and from two motor unit recruitment ranges (40% excitation and 80% excitation) [21]. It was found that different motor unit firing rate strategies or different motor unit recruitment ranges did not have a significant effect on the MUNIX or mMUNIX estimates. Thus we only presented results from one motor unit firing rate strategy (“onion skin” strategy) and motor unit recruitment range (40% excitation).

Figure 2 shows the mMUNIX and standard MUNIX calculation with the same relation between the ICMUC and the surface interference pattern area (with 120 input motor units). The standard MUNIX value was determined with the surface interference pattern area set as 20 mV·ms. The selection of different surface interference pattern areas associated with the CMAP area resulted in multiple mMUNIX values. When the surface interference pattern area for defining mMUNIX was progressively increased from 10% to 100% of the CMAP area, the mMUNIX averaged from 20 trials decreased from 1284 ± 12 (mean ± standard error) to 133 ± 1, in an exponential trend. The averaged standard MUNIX value was 330 ± 3, which is most similar to the mMUNIX estimate (331 ± 3) when 40% of the CMAP area was used. Therefore, 40% CMAP area was used in the following analysis for the mMUNIX calculation.

Different levels of motor unit loss were simulated by gradually decreasing the number of motor units by 12 (or by 10%). Nine relations between the ICMUC and the surface

interference pattern area were simulated in Figure 3 corresponding to each condition. The mMUNIX and standard MUNIX values were then calculated respectively. In this example, with motor unit number decreasing from 108 to 12 motor units (curves from right to left), the standard MUNIX estimates progressively decreased from 297 to 25. In contrast, the mMUNIX estimates decreased from 330 to 153 (Figure 3a). The standard MUNIX and mMUNIX values averaged over 20 trials for each motor unit loss situation are presented in Table 1. Regression analysis indicates a strong linear relationship between the standard MUNIX decrease and the degree of motor unit loss ($r^2 = 0.999$, $p < 0.0001$), whereas the mMUNIX showed a slower and nonlinear reduction with motor unit loss (Figure 3b). The mMUNIX value remained relatively stable until 30% motor unit loss and then started to decrease slowly and progressively with further motor unit loss (Figure 3b). When the motor unit pool was reduced by 90%, the mMUNIX revealed approximately 50% loss of the original value.

An example of the mMUNIX and standard MUNIX measures from conditions with reduced MUAP amplitude is displayed in Figure 4. From right to left there are 9 relations of the ICMUC and the surface interference pattern area, representing the MUAP amplitude progressively decreasing by 10% of the original amplitude. With reduction of the MUAP amplitude, the standard MUNIX decreased remarkably from 304 (90% MUAP amplitude) to 34 (10% MUAP amplitude). In contrast, the mMUNIX remained stable regardless of the changes of MUAP amplitude (Figure 4a). The standard MUNIX and mMUNIX values were averaged over 20 trials for each situation of MUAP amplitude reduction. The results are shown in Table 2. Regression analysis demonstrated a strong linear relation ($r^2=0.999$, $p<0.0001$) between the standard MUNIX decrease and the amount of MUAP amplitude reduction. Such a relation was not observed for the mMUNIX (Figure 4b).

IV. DISCUSSION

The concept of a modified MUNIX (mMUNIX) was introduced and assessed by a simulation study. The main motivation for development of the mMUNIX technique was to overcome the effects reduced MUAP amplitudes on the standard MUNIX. Model simulations demonstrated a clear difference between standard and modified MUNIX techniques.

The sensitivity of both mMUNIX and standard MUNIX estimates to changes of MUAP amplitude was examined respectively. The analysis confirmed previous findings that when the amplitude of an individual MUAP (rather than the number of motor units) is reduced, the standard MUNIX may substantially underestimate the motor unit number [18]. In contrast, the mMUNIX can achieve appropriate estimation manifested as relatively constant values regardless of the extent of MUAP amplitude changes. The different performance of the two methods is attributed to the selected surface interference pattern area used to define or calculate the output (i.e. standard MUNIX or mMUNIX). Reducing the individual MUAP amplitude and keeping the motor unit number unchanged can lead to reduction of both the CMAP area and the area of surface interference pattern signals, which would drive the relation between the ICMUC and the surface interference pattern area toward both the x-axis (surface interference pattern area) and y-axis (ICMUC) as shown in Figure 4a.

Analysis of the number of motor units required to reach the interference pattern area used for defining MUNIX can also help understand the simulation results. The standard MUNIX is determined as the ICMUC value at a constant surface interference pattern area of 20 mV·ms. Approximately 44 motor units (from our simulation) have to be recruited to produce surface interference pattern area of 20 mV·ms in the baseline or default condition (i.e. no motor unit loss or decrease of MUAP amplitude). Decreasing MUAP amplitude (while other parameters remaining unchanged) would reduce the surface interference pattern area. For example, we found the surface interference pattern area was reduced to 10.03 mV·ms with a 50% decrease of MUAP amplitude (with approximately 44 motor units). To reach the interference pattern area of 20 mV·ms, an additional 15 larger threshold motor units would be needed. It follows that the standard MUNIX using 20 mV·ms tends to underestimate the actual motor unit number. On the other hand, calculation of the mMUNIX is associated with CMAP area, which decreases with MUAP amplitude reduction. For example, the averaged CMAP area with a 50% decrease of MUAP amplitude was 25.08 mV·ms. Multiplied by a coefficient of 0.4 (for defining mMUNIX), it generated a value very close to the interference pattern surface EMG area from approximately 44 motor units with 50% MUAP amplitude reduction.

The standard MUNIX and mMUNIX techniques were applied to track motor unit loss when the number of motor units was simulated to progressively decrease by 10% from 90% to 10% of the original population (while other parameters remaining unchanged). It was found that the standard MUNIX estimates can appropriately reflect actual motor unit number changes in a muscle, which is consistent to our previous simulation study [18]. On the other hand, the mMUNIX estimation remained almost unchanged until 30% of motor units were lost, and then showed a nonlinear and slower reduction with further motor unit loss (Figure 3b). The lower sensitivity of mMUNIX to motor unit number reduction (especially at the beginning stage) needs to be considered during interpretation of mMUNIX findings.

The limitations of the simulation study should be acknowledged. The loss of motor units was simulated to be evenly distributed among the motor unit pool in the current simulation. In real life due to motoneuron diseases or neurologic disorders, the loss of motor units might occur in a more complex pattern (either in a specific trend or randomly). For example, a previous study reported that large motor units may be selectively affected by the trans-synaptic changes of the spinal motoneurons post stroke [26]. Similarly, the reduction of MUAP amplitude across different motor units was simulated to be uniformly distributed. This is again a simplification of complex muscle fiber changes in real life.

The current simulation study demonstrates both advantages and limitations of the standard and modified MUNIX techniques. The mMUNIX can overcome the effects of MUAP amplitude reduction on the standard MUNIX. However, it is less sensitive than the standard MUNIX for tracking changes in motor unit number. It is worth mentioning that the two techniques are mainly used for tracking disease progression or in follow-up studies. One should choose the appropriate method depending upon the underlying disease process. The standard MUNIX with fixed surface interference pattern area is most suitable for motoneuron diseases that demonstrate secondary evidence of muscle fiber reinnervation. As a comparison, the mMUNIX, whose definition is correlated with CMAP area of the

examined muscle, is suitable for applications in atrophied muscles, where the atrophy is dominantly accompanied by muscle fiber shrinkage or muscle fiber loss (which might be the case when tracking motor unit loss in myopathies or with aging). Indeed, in real life various situations may coexist such as loss of motor units, the compensatory muscle fiber hypertrophy, muscle fiber shrinkage, and muscle fiber denervation and reinnervation, etc. It is important to determine the dominant factor to ensure appropriate application and interpretation of MUNIX or mMUNIX measurements.

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Highlights

- The study developed a modified MUNIX technique and evaluated its performance using motoneuron pool and surface EMG models.
- The modified MUNIX can overcome the effects of MUAP amplitude reduction on the standard MUNIX.
- However, the modified MUNIX is less sensitive than the standard MUNIX for tracking motor unit number changes.

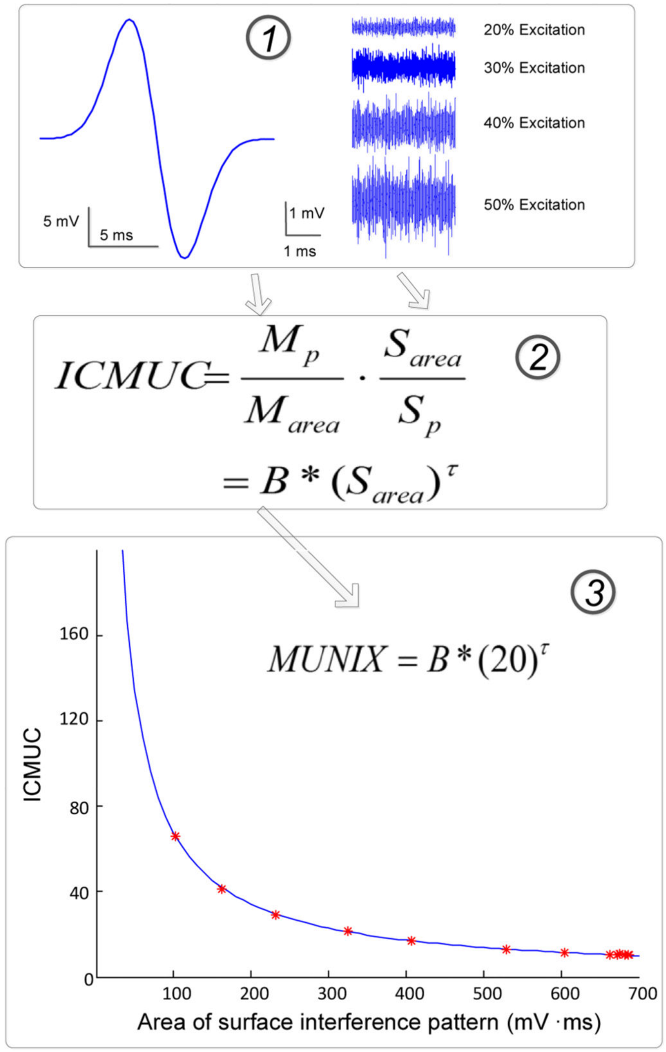

Figure 1.

Three steps for standard MUNIX calculation. (1) Left: simulated CMAP waveform; Right: simulated surface EMG (or interference pattern) at different excitation levels. (2) Calculation of the "ideal case motor unit count (ICMUC)". (3) Nonlinear curve fitting for estimation of the standard MUNIX.

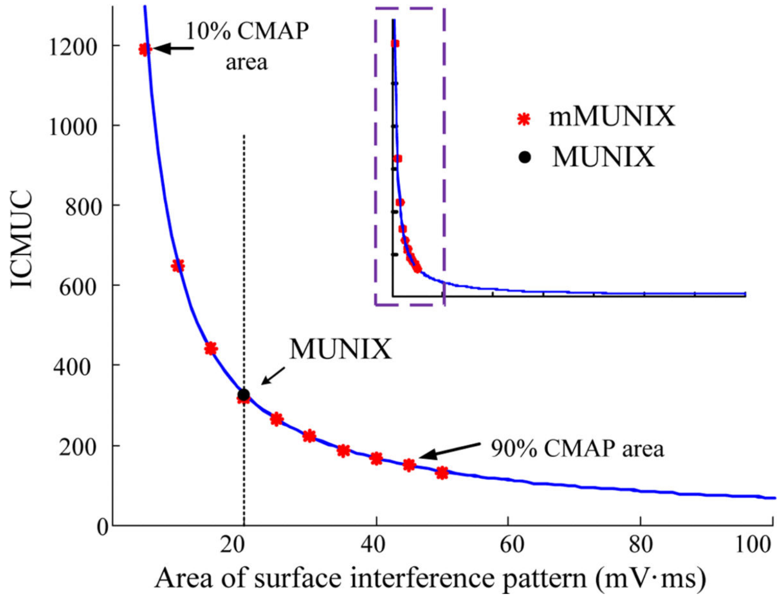

Figure 2.

Simulation of mMUNIX and MUNIX calculation. The mMUNIX (red stars) and MUNIX (black dot) were calculated from the same relation between the ICMUC and the surface interference pattern area. The MUNIX value was determined as the surface interference pattern area equaled to 20 mV·ms. The mMUNIX value varied as a different percentile of the CMAP area was selected. The left plot is part of the curve displayed in the inset.

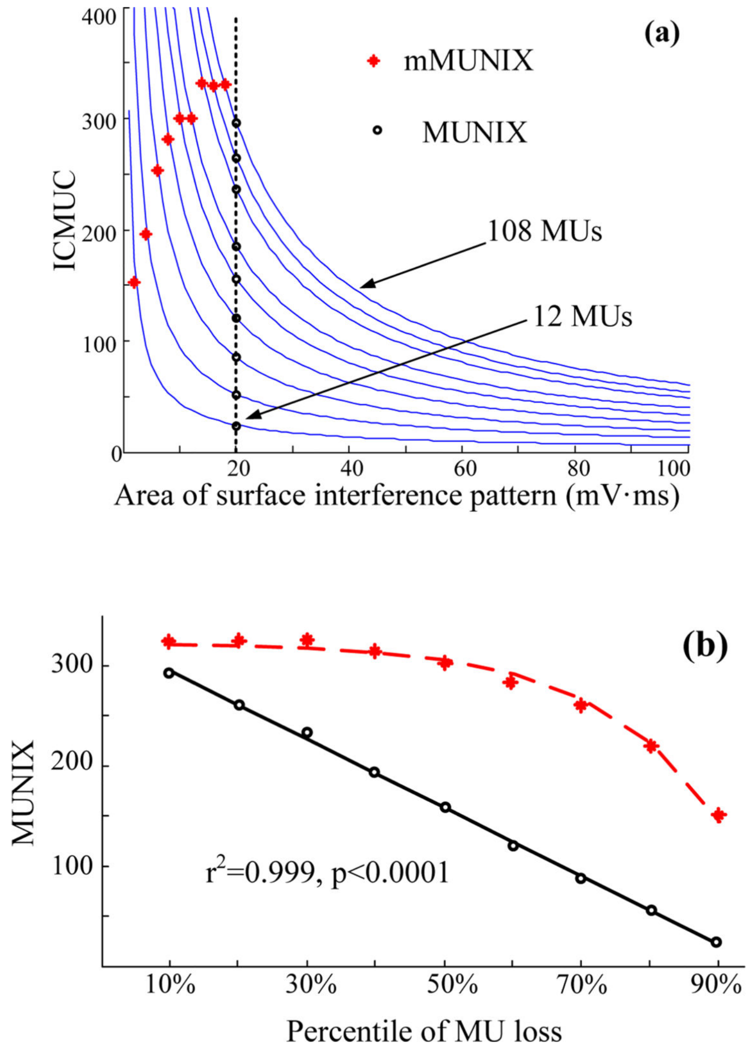

Figure 3.

Comparison of the simulated mMUNIX (stars) and standard MUNIX (open circles) estimation in conditions of motor unit loss. (a) The relations between the ICMUC and the surface interference pattern area at different degrees of motor unit loss (curves from right to left corresponding to motor unit number from 108 to 12, progressively decreased by 12). The standard MUNIX and mMUNIX values can be determined from the relations. (b) The averaged standard MUNIX decreased linearly with motor unit loss (r^2=0.999, p<0.0001), whereas mMUNIX showed a less sensitive and nonlinear reduction with motor unit loss.

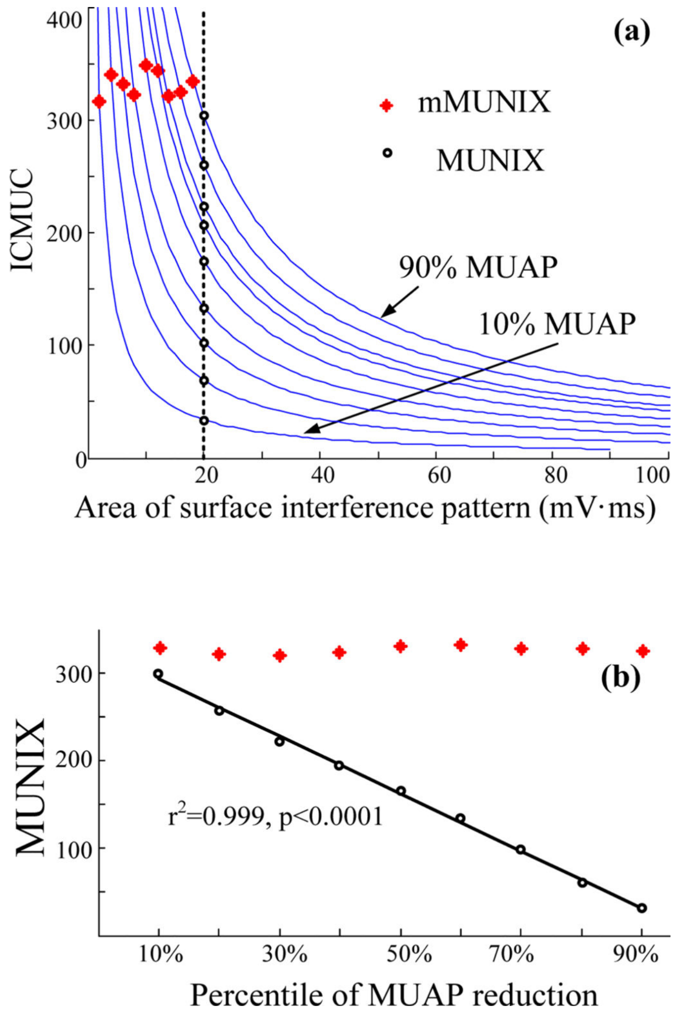

Figure 4.

A comparison of the mMUNIX (stars) and standard MUNIX (open circles) estimation at various degrees of MUAP amplitude reduction. (a) The relations between the ICMUC and the surface interference pattern area with different degrees of MUAP amplitude reduction (curves from right to left corresponding to MUAP amplitude from 90% to 10% of original value, progressively decreased by 10%). The standard MUNIX and mMUNIX values can be determined from the relations. (b) The averaged MUNIX decreased linearly with the MUAP amplitude reduction (r^2=0.999, p<0.0001). Such a relation was not observed for the averaged mMUNIX (p=0.29).

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Table 1

Changes of MUNIX, mMUNIX, and CMAP area with reduction of motor unit numbers. Results were averaged over 20 trials of simulations (mean ± standard error)

MU number	MUNIX	mMUNIX	CMAP area (mV·ms)
120	330 ± 3	331 ± 3	50.11 ± 0.08
108	291 ± 1.6	324 ± 1.6	45.33 ± 0.06
96	261 ± 1.7	325 ± 3.1	40.25 ± 0.05
84	233 ± 1.4	325 ± 2.5	35.32 ± 0.06
72	193 ± 0.7	315 ± 2.6	30.39 ± 0.05
60	157 ± 1.2	303 ± 3.1	25.56 ± 0.03
48	122 ± 0.8	284 ± 1.5	20.35 ± 0.04
36	87 ± 0.5	259 ± 2.1	15.49 ± 0.03
24	56 ± 0.4	221 ± 2.3	10.52 ± 0.03
12	24 ± 0.1	149 ± 1.9	5.60 ± 0.02

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Table 2

Changes of MUNIX, mMUNIX, and CMAP area with reduction of MUAP amplitude. Results were averaged over 20 trials of simulations (mean ± standard error)

MUAP amplitude	MUNIX	mMUNIX	CMAP area (mV·ms)
A	330 ± 3	331 ± 3	50.22 ± 0.12
0.9A	305 ± 2.2	335 ± 2.7	45.02 ± 0.12
0.8A	263 ± 1.8	328 ± 2.5	40.14 ± 0.06
0.7A	227 ± 1.6	326 ± 2.5	35.07 ± 0.06
0.6A	201 ± 1.8	331 ± 3.4	30.10 ± 0.06
0.5A	170 ± 0.9	335 ± 2.5	25.08 ± 0.06
0.4A	138 ± 0.7	339 ± 2.2	20.10 ± 0.04
0.3A	103 ± 0.4	333 ± 2.5	15.03 ± 0.03
0.2A	68 ± 0.2	334 ± 2.5	10.03 ± 0.03
0.1A	34 ± 0.2	332 ± 4.2	5.01 ± 0.01