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RESEARCH ARTICLE

New Algorithm for Computing Step Percentage of Compound Muscle Action Potential Scan in Modeling Motor Unit Number Estimate

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ABSTRACT Introduction: Compound Muscle Action Potential Scan (CMAP) Scan is an electrophysiological method for diagnosing neuromuscular diseases with axonal loss. Significant differences between CMAPs are termed as Steps. The percentage ratio of all detected steps to the maximum CMAP, a parameter being evidence of motor unit loss and enlargement due to reinnervation is defined as Step Percentage. Materials and Methods: Motor neuron groups were created and stimulated gradually through a simulator software for CMAP Scan. CMAPs were utilized to compute the step sizes. Their cumulative sum greater than two standard deviations were taken for computing Step Percentage. The simulator data were exported for processing in a MATLAB®Code for these calculations and for computing regression coefficients of the model for step percentage and the number of axons by the Least Square Method. Results: The greatest step percentage value corresponded to the lowest motor unit number. A steep reduction was observed from 5 axons to 120 axons with increasing axon numbers. The step percentages converged to a steady-state value for the axon numbers between 120 and 300. Discussion and Conclusion: Step percentage values were found greater for lower axon numbers as in the case of Motor Unit loss in neurogenic diseases. They tended to decrease with increasing axon numbers approaching a steady-state value as the presence of intact Motor Units. A new algorithm was proposed to determine the lowest step size quantitatively rather than detecting by inspection as in routine clinical applications for estimating the step percentage. A mathematical model was built to demonstrate the relationship between the step percentage and the number of axons.

INDEX TERMS Compound muscle action potential (CMAP) scan, motor unit number estimate (MUNE), neuromuscular diseases, non-linear regression, step percentage, stimulus-response curve.

I. INTRODUCTION

Compound Muscle Action Potential (CMAP) is the summated bioelectrical activities emerging from the synchronous stimulation muscle fibers innervated by all motor axons innervating the muscle under the investigation [1], [2], [3], [4].

Compound Muscle Action Potential (CMAP) Scan is an electrophysiological method used for diagnosing and monitoring neuromuscular diseases caused by motoneuronal or axonal loss. It is obtained by recording the responses to gradually increasing or decreasing stimulus intensities [5]. These are graphically represented by the stimulus-response (SR) curve [5], [6]. In healthy individuals, the SR curve is in sigmoid form as illustrated in Figure 1. However, there exist abrupt jumps between several consecutive responses in the SR-curve in the case of neuromuscular disease characterized by motoneuronal loss (e.g., Amyotrophic Lateral Sclerosis-ALS) [7]. They represent large visible MU potential differences between consecutive CMAPs, and they are referred to as steps. They exist in case of large MUs or if the MU number is severely reduced [8]. An SR-curve possessing some steps is shown in Figure 2. The steps may be suggested to ensure information about the extent of collateral

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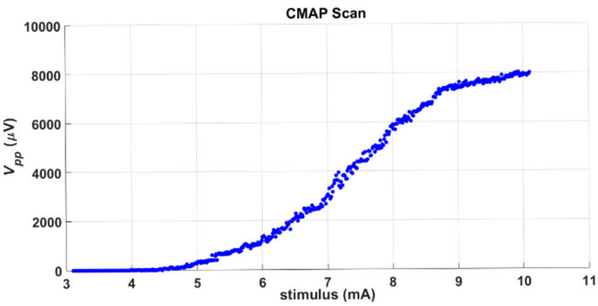

FIGURE 1. The Stimulus-Response curve of a healthy individual.

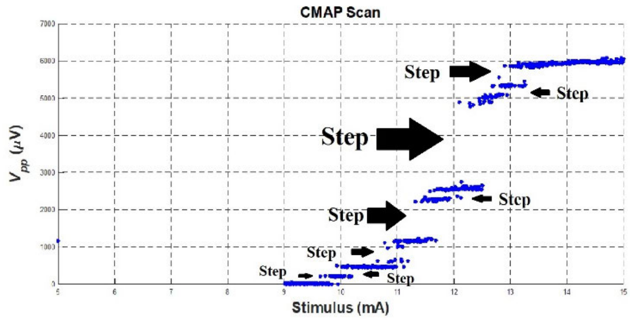

FIGURE 2. The Stimulus-Response curve of a patient with Anterior-Horn Disease (Steps are shown with arrows with different sizes indicating those of the steps).

reinnervation besides being an indicator of motor unit loss [9], [10]. The SR Curves plotted in Figure 1 and Figure 2 were obtained from the CMAP Scan Data acquired by means of the EMG System (Nicolet, Viking, Natus, USA) in the Clinical Neurophysiology Laboratory of the Department of Neurology of İstanbul Faculty of Medicine. The presented study was approved by the Local Ethics Committee.

Motor Unit Number Estimate (MUNE) which had been previously termed as "motor unit counting" is a quantitative electrophysiological technique enabling the clinicians to numerically estimate the number of functional motor axons innervating a muscle addressed in clinical studies [11] [12]. This method has a significant role in the diagnosis and monitoring of motor neuron diseases and peripheral neuropathies characterized by axon loss [11], [12], [13], [14].

The development of a satisfactory MUNE method has been a major challenge in the field of neurophysiology and neurology for several decades and it remains a current biomedical engineering problem [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26]. Some attempts to develop mathematical models have been established for this purpose [27], [28]. In some studies, several CMAP scan parameters such as step size, step number, and step percentage were depicted for MUNE [8], [29].

These parameters are utilized to describe the steps quantitatively [8]. Step percentage (Step % or SP) which is the percentage of the maximum CMAP calculated by summing all the detected steps is the commonly used parameter among them [30]. As the severity of MU loss increases and few MU are intact, Step % approaches 100% of the maximum CMAP [8], [31]. This fact might point out also a relationship between the step percentage and the motor unit number represented by the number of axons.

The selection of the steps to be used in the estimation of step percentage is found by inspection in clinical routine depending on the experience of the operator. The lowest value of all step sizes is chosen by the researcher visually [31].

The aim of this study is to develop an algorithm for estimating the step percentage by determining the lowest step size in a quantitative manner. In addition, a preliminary mathematical model was built via numerical methods to contribute to the development of a satisfactory MUNE method by eliciting the relationship between the step percentage and motor unit number.

The originality and the technical contributions of this work can be summarized as follows: (i) the development of a novel algorithm to compute Step Percentage in a Stimulus-Response Curve of Compound Muscle Action Potential Scan (CMAP Scan) more quantitatively to ensure more reliable and more reproducible clinical data, (ii) building of a preliminary model based on the relationship between the motor unit numbers or axons numbers and the step percentage, (iii) To reveal the potential of evaluating Step Percentage as a feature in complex mathematical models to be built for Motor Unit Number Estimation (MUNE).

II. MATERIALS AND METHODS

A. BUILDING DATA SETS

Data sets were built by utilizing a simulator software ((Motor Nerve Conduction Studies (MNCS) Neurography Simulator version 2.4, Keypoint Club, Uppsala, Sweden).

Motor neurons groups that consist of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 220,225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295 and 300 axons were constituted via this simulator."

Each motor neuron group was stimulated by currents ranging from 0 to 99 mA from the distal locations of these neurons with 1-mA increments. Five different scenarios were constituted for each motor neuron group.

The interface of this simulator software is shown in Figure 3. The waveforms of CMAP traces can be monitored also in the simulator software and these traces were recorded in ".txt" format via the "export" menu of the simulator and then these files were processed by the MATLAB Code developed for the data analysis.

B. MATLAB CODE FOR DATA ANALYSIS

To analyze the CMAP data being exported from the simulator in ".txt" format, a MATLAB® (Version R2015a) (MathWorks, USA) Code was built. The peak-to-peak voltage values of CMAP traces and the consecutive differences of

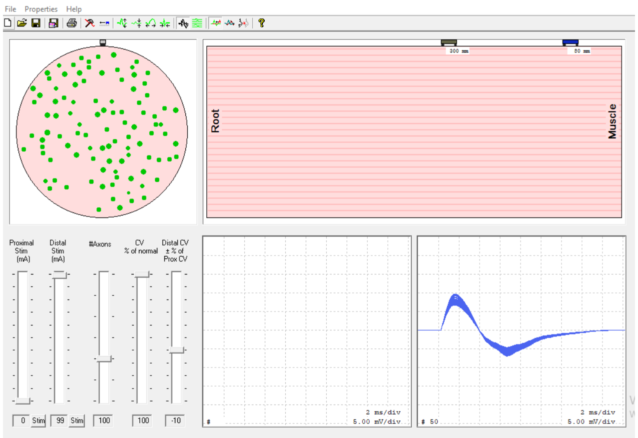

FIGURE 3. The generation of CMAP responses from the gradual stimulations in the "Motor Nerve Conduction Studies" simulator.

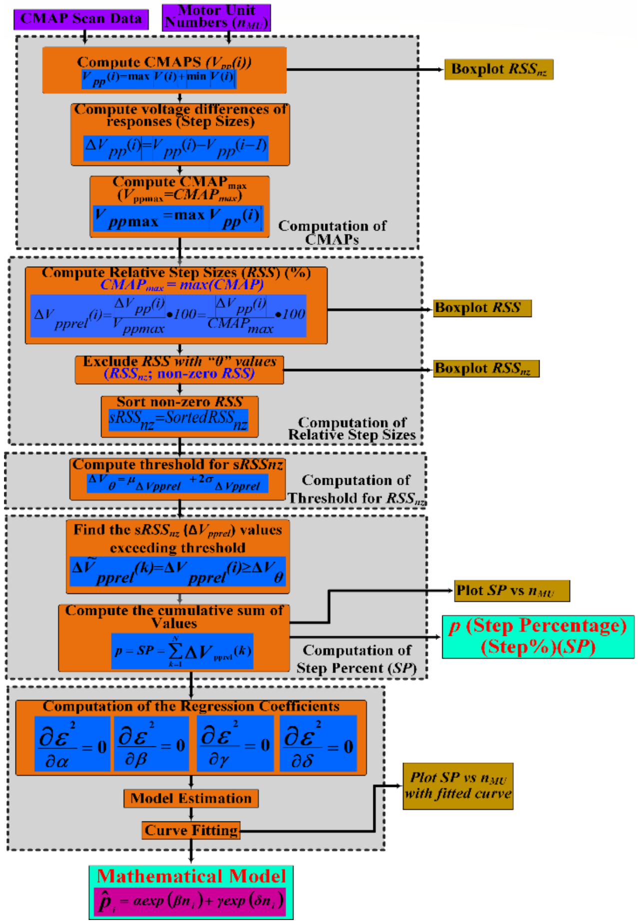

FIGURE 4. The algorithm for computing step percentage (SP).

these voltages were computed by this code. The flowchart of this code is shown in Figure 4.

C. COMPUTATION OF STEP PERCENTAGE:

CMAPs are the peak-to-peak voltages V_{pp} of the waveforms of CMAP traces. They represent the responses to stimuli on the vertical axis of the SR-curve. In determining the steps, initially, the absolute value of voltage differences $|\Delta V_{pp}|$ should be calculated as follows:

$$\left|\Delta V_{pp}\left(i\right)\right| = \left|V_{pp}\left(i\right) - V_{pp}(i-1)\right| \tag{1}$$

In (1), i is the index of the corresponding stimulus.

The relative voltage difference is the percent difference relative to CMAPmax being the maximum CMAP or maximum V_{pp} (V_{ppmax}) which is the maximum response obtained by stimulating stimulation muscle fibers innervated by all motor axons innervating the muscle under the investigation. This is expressed as follow:

$$V_{pprel}\left(i\right) = \frac{\left|\Delta V_{pp}(i)\right|}{V_{ppmax}} \cdot 100 \tag{2a}$$

$$V_{pprel}\left(i\right) = \frac{\left|\Delta V_{pp}(i)\right|}{\text{CMAP}_{max}} \cdot 100 = \frac{\left|\Delta V_{pp}(i)\right|}{\max(CMAP)} \cdot 100 \tag{2b}$$

To select the steps, a threshold value in terms of relative voltage differences should be determined as follows:

$$\Delta V_{\theta} = \mu_{\Delta Vpprel} + 2\sigma_{\Delta Vpprel} \tag{3}$$

Then, the zeros are excluded by means of MATLAB® Code. Afterwards, the relative voltage differences were sorted in descending order to form the matrix $[\text{s}\Delta V_{pprel}(k)]$ where ΔV_{θ} is the threshold value for relative voltage differences, $\mu_{\Delta_{Vpprel}}$ is the mean of relative voltage differences and $\sigma_{\Delta_{Vpprel}}$ is the standard deviation of relative voltage differences.

Therefore, any relative voltage difference that will be chosen as step should fulfill the following criterion:

$$s\Delta V_{pprel}\left(k\right) \geq \Delta V_{\theta} \tag{4}$$

The relative step sizes (RSS) that will be used in computing the step percentage can be represented as the following matrix:

$$RSS\left(k\right) = \left[\Delta V_{\theta}, \ldots, \Delta V_{pprel}\left(N\right)\right] \tag{5}$$

where N is the number of the sorted relative voltage differences having values greater than the threshold given in (3) and satisfying the criterion expressed in (4). *RSS* may be considered as a vector of the sorted relative voltage differences in descending order which satisfy (5), to compute the Step Percentage via MATLAB® Code in concordance with the algorithm shown in Figure 4.

The step percentage (Step %) p is the cumulative sum of the relative step sizes expressed in (5) and it can be expressed as follows:

The Flow-Chart of the Data Analysis Code

$$p = Step\% = \sum_{k=1}^{N} RSS\left(k\right) \tag{6}$$

The flow chart of the algorithm is illustrated in Figure 5.

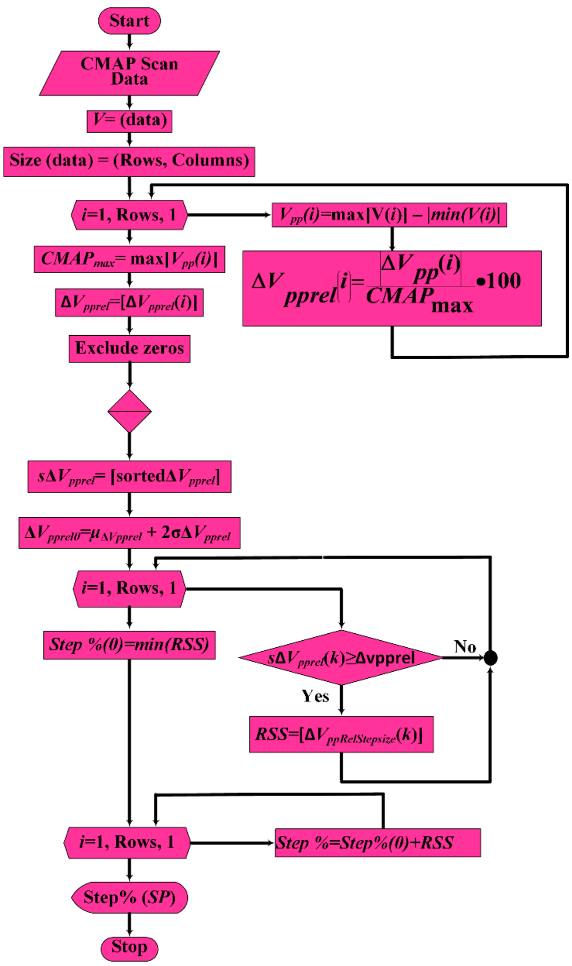

FIGURE 5. The Flow-chart of the data analysis code.

D. MODELLING THE RELATIONSHIP BETWEEN THE STEP PERCENTAGE AND THE NUMBER OF AXONS

From the shape of the curve in Figure 6, which will be discussed in detail later in the Results section, the relationship between Step Percentage and number of axons corresponds to an exponential function. This function can be expressed as follows:

$$\hat{p}_i = \alpha e^{\beta n_i} x + \gamma e^{\delta n_i} \quad (7)$$

where $\hat{p}_i$ is the step percentage, and n_i is the number of axons, α, $\boldsymbol{\beta}$, $\boldsymbol{\gamma}$, $\boldsymbol{\delta}$ are the regression coefficients.

For the curve fitting of this function, the regression coefficients are calculated by the least squares method with the following differential equations. Therefore, first, the error term is expressed as follows:

$$\epsilon_i = p_i - \hat{p}_i \quad (8)$$

where ϵ_i are the error terms, p_i are the observed Step Percentage values obtained from the simulator data and $\hat{p}_i$ are the Step Percentage values estimated by equation (7). In this case, if equation (7) is substituted into equation (8), the square of the error term can be expressed as follows:

$$\epsilon_i^2 = \sum\nolimits_{i=1}^{N} \left[p_i - \left(\alpha e^{\beta n_i} + \gamma e^{\delta n_i}\right)\right]^2 \quad (9)$$

It is possible to utilize the Least Squares Method, which is a numerical method for determining how to calculate the regression coefficients. The coefficient α can be calculated by solving the following differential equation:

$$\frac{\partial \epsilon^2}{\partial \alpha} = -2\sum_{i=1}^{N} e^{\beta n_i}\left[p_i - \left(\alpha e^{\beta n_i} - \gamma e^{\delta n_i}\right)\right] = 0 \quad (10)$$

As a result of the analytical solution of this differential equation in (10), the coefficient α is expressed as follows:

$$\alpha = \frac{\sum_{i=1}^{N} p_i e^{\beta n_i} - \sum_{i=1}^{N} \gamma e^{(\beta+\delta) n_i}}{\sum\limits_{i=1}^{N} e^{2\beta n_i}} \quad (11)$$

In order to calculate the coefficient β, the following differential equation can be formed by the Least Squares Method:

$$\frac{\partial \epsilon^2}{\partial \beta} = -2\sum_{i=1}^{N} p_i - \left[-\left(\alpha e^{\beta n_i} + \gamma e^{\delta n_i}\right)\right]\left[e^{\beta n_i}\left(\frac{d\alpha}{d\beta} + \alpha n_i\right)\right.$$
$$\left. + e^{\delta n_i}\left(\frac{d\gamma}{d\beta} + \gamma \frac{d\delta}{d\beta}\right)\right] = 0 \quad (12)$$

Equation 12 which is a partial differential equation, can be solved numerically by the Newton-Raphsen method. For this purpose, the right-hand side of (12) can be expressed as $f(\beta)$;

$$f(\beta) = \sum_{i=1}^{N} p_i - \left[-\left(\alpha e^{\beta n_i} + \gamma e^{\delta n_i}\right)\right]\left[e^{\beta n_i}\left(\frac{d\alpha}{d\beta} + \alpha n_i\right)\right.$$
$$\left. + e^{\delta n_i}\left(\frac{d\gamma}{d\beta} + \gamma \frac{d\delta}{d\beta}\right)\right] = 0 \quad (13)$$

The numerical solution of (13) for β by the Newton-Raphsen Method is generally expressed as follows:

$$\beta_{k+1} = \beta_k - \frac{f(\beta_k)}{f'(\beta_k)} \quad (14)$$

The regression coefficient γ can be calculated by the Least Squares Method as follows:

$$\frac{\partial \epsilon^2}{\partial \gamma} = -2\sum_{i=1}^{N} e^{\delta n_i}\left[p_i - \left(\alpha e^{\beta n_i} - \gamma e^{\delta n_i}\right)\right] = 0 \quad (15)$$

As a result of the analytical solution of (15), γ is calculated as given in the following expression:

$$\gamma = \frac{\sum_{i=1}^{N} \alpha e^{(\beta+\delta) n_i} - \sum_{i=1}^{N} p_i e^{\delta n_i}}{\sum_{i=1}^{N} e^{2\delta n_i}} \quad (16)$$

The following differential equation can be employed to calculate the regression coefficient δ with the Least Squares Method:

$$\frac{\epsilon^2}{\partial \delta} = -2\sum_{i=1}^{N} \left[p_i - \left(\alpha e^{\beta n_i} + \gamma e^{\delta n_i}\right)\right]\left[e^{\delta n_i}\left(\alpha e^{\beta n_i} + \gamma e^{\delta n_i}\right)\right.$$
$$\left. + e^{\beta n_i}\left(\frac{d\alpha}{d\delta} + \gamma \frac{d\beta}{d\delta}\right)\right] = 0 \quad (17)$$

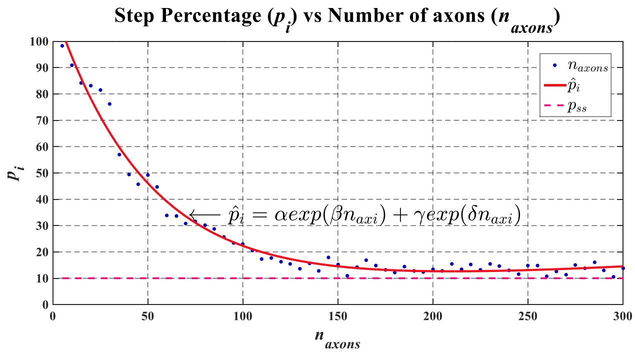

FIGURE 6. The change in step percentage in terms of number of axons.

For the numerical solution of (17), which is a partial differential equation for the regression coefficient δ by the Newton-Raphsen Method, the right-hand side of this equation can be expressed as follows:

$$f(\delta) = -2\sum_{i=1}^{N}\left[p_i - \left(\alpha e^{\beta n_i} + \gamma e^{\delta n_i}\right)\right] \left[e^{\delta n_i}\left(\frac{d\alpha}{d\delta} + \gamma n_i\right) e^{\beta n_i}\left(\frac{d\alpha}{d\delta} + \gamma\frac{d\beta}{d\delta}\right)\right] = 0 \quad (18)$$

The numerical solution of (18) for δ by the Newton-Raphsen Method can be expressed in general terms as follows:

$$\delta_{k+1} = \delta_k - \frac{f(\delta_k)}{f'(\delta_k)} \quad (19)$$

III. RESULTS

The step percentage values computed from the CMAP Scan data generated in the simulator software are summarized in terms of number of axons in Table 1. Moreover, the trend of change in step percentage in terms of number of axons is illustrated in the chart in Figure 6.

For 5 Simulated axons, the Step Percentage is 98.2656± 1.4288 being the greatest value among all of those computed for other axon numbers.

Between 5 and 120 axons, the Step Percentage values exhibit a steep reduction with increasing number of simulated axons.

For the number of simulated axons ranging from 120 to 300, the Step Percentage values tend to converge to almost a steady-state value of 10 and they vary between 10.5666± 4.8119 and 17.8682±13.5381.

IV. DISCUSSION

When the values presented in Table 1 are tackled, a decreasing tendency is seen in step percentage values as the number of axons increases. This is observed also in Figure 5. This trend exhibits almost an exponentially decaying curve converging to a steady-state percentage value which can be expressed

TABLE 1. Step percentage in terms of number of axons.

Number of Simulated Axons (n_{axon})	Step % (Mean ± S.D.)
5	98.2656 ± 1.4288
10	90.9712 ± 8.5564
15	84.1024 ± 12.5811
20	83.2102 ± 15.3142
25	82.1197 ± 16.7817
30	76.1097 ± 15.0426
35	57.0055 ± 18.2968
40	49.3030 ± 10.6215
45	45.6859 ± 12.4668
50	49.1132 ± 16.3570
55	44.6171 ± 10.6287
60	33.8646 ± 7.1155
65	33.6744 ± 9.0445
70	30.6999 ± 10.8683
75	31.6964 ± 6.3449
80	30.0760 ± 5.0019
85	28.7208 ± 15.8509
90	25.7526 ± 8.3838
95	23.3380 ± 9.2480
100	23.0392 ± 6.8451
105	20.6523 ± 8.6581
110	17.3192 ± 6.4755
115	17.5870 ± 8.1967
120	16.2125 ± 13.1773
125	15.5221 ± 7.5891
130	13.5817 ± 6.4762
135	15.6385 ± 9.5750
140	15.1538 ± 4.3908
145	17.8682 ± 13.5381
150	15.3100 ± 9.6282
155	10.9499 ± 3.1421
160	14.1641 ± 6.4920
165	16.9408 ± 7.3740
170	14.8859 ± 8.9652
175	13.1976 ±3.9537
180	12.1954 ± 4.5310
185	14.5085 ± 8.3623
190	12.7188 ± 1.4039
195	12.3881 ± 4.5079
200	13.3726 ± 5.0705
205	12.7413 ± 5.4386
210	15.3400 ± 5.5432
215	13.3398 ± 7.8290
220	15.3070 ± 6.8252
225	13.0891 ± 3.0453
230	15.4717 ± 4.6553
235	14.6240 ± 4.7269
240	13.0151 ± 2.2835
245	15.5071 ± 12.9373
250	14.9261 ± 6.3009
255	14.7894 ± 5.2451
260	10.6898 ± 3.7024
265	12.4982 ± 1.6888
270	11.3194 ± 4.5974
275	14.9510 ± 6.7295
280	13.7702 ± 5.4001
285	11.6728 ± 2.4011
290	12.9458± 7.3939
295	10.5666 ± 4.8119
300	13.8006 ± 3.9081

mathematically as follows:

$$\lim_{n_{\text{axon}} \to \infty} p(n) = p_{ss} \tag{20}$$

where $p(n)$ is the step percentage function with independent variable n being the number of simulated axons. p_{ss} is the steady-state step percentage value.

According to the information from literature, the step percentage will approach to 100% as MU loss takes place (i.e., number of intact axons decreases) [8], [12]. By the way, the data presented in Table 1 seems to be consistent with this fact.

For example, lower numbers of simulated axons such as 5, 10, 15 that can be assumed to represent MU loss in various degrees have step percentage values such 98.2656%, 90.9712% and 84.1024% respectively.

The decrease of step percentage values continues almost in exponential manner until the number of simulated axons reaches to approximately 120 indicating that as the number of intact MUs increases the step percentage approaches to a steady-state value as seen in Figure 5. For the numbers of simulated axons between 120 and 300, the step percentage values vary nearby an asymptotic value p_{ss} as illustrated in Figure 6. This implies that the step percentage values tend to stable when the intact MUs dominate. On the other hand, the variations nearby the steady-state value for the numbers of axons over 120 may be attributed to the stochastic architectural organizations of intact MUs within a muscle (i.e., random distribution of MUs within the cross-section of muscle).

The non-linear regression coefficients were computed as; $\alpha = 102.7$, $\beta = -0.02032$, $\gamma = 6.231$, $\delta = 0.002761$. Therefore, the preliminary mathematical model demonstrating the relationship between the step percentage and the number of axons illustrated by the equation of the fitted curve, and which is represented in Equation 7 can be written as follows:

$$\hat{p}_i = 102.7e^{-0.02032n_i} + 6.231e^{0.002761n_i} \tag{21}$$

The relationship between Step Percentage and Motor Unit Number has already been discussed in a previous study. However, the number of Motor Unit Numbers simulated in that study were limited to between 5 and 120 [32]. In this paper, the maximum number of Motor Units has been increased up to 300. Thus, a more accurate and precise data set was obtained. In this way, it was also possible to build the preliminary model.

V. CONCLUSION

In conclusion, an algorithm that computes more quantitatively was proposed. In future studies, algorithms that would estimate threshold values more accurately can be built for more precise computation of step percentage. Moreover, a preliminary mathematical model that suggests that Step Percentage can be considered as a feature for Motor Unit Number Estimate (MUNE).

In future works, it is aimed to use more involved mapping methods such as Deep Learning techniques to achieve higher accurate models than the proposed one alongside of additional data samples. Furthermore, features such as step size and step number may be involved to these models in addition to step percentage to provide an evidence not only for loss of MU but also reinnervation.

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