Chaos Based Quantitative Electro-Diagnostic Marker for Diagnosis of Myopathy, Neuropathy and Motor Neuron Disease

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Abstract

Background: Myopathies (MYO) are a group of disorders in which the muscle fibers do not function for any one of many reasons, resulting in muscular weakness and/or muscle dysfunction. Neuropathies (NEURO) describe damage to the peripheral nervous system which transmits information from the brain and spinal cord to every other part of the body. The analysis of Electromyography (EMG) signals provides important information to aid in the diagnosis and characterization of Motor Neuron Disease (MND) and any neuromuscular disorders like myopathy and neuropathy.

Methods and findings: In this paper we have proposed a rigorous and robust non-linear technique (multifractal detrended fluctuation analysis, MF-DFA) to study the multifractal properties of EMG signals of two subjects with neuromuscular disorders (myopathy and neuropathy). We observed that a quantitative parameter, multifractal width, which signifies the degree of complexity of the signals, is significantly different for subjects of neuromuscular disorders compared to healthy subject. Another quantity, the auto-correlation exponent shows significant differences in the degree of auto-correlation for different signals.

Conclusion: These quantitative parameters, multifractal width and auto-correlation exponent can be used as a biomarker for diagnosis and prognosis of both MYO and NEURO, and even for early detection of MND.

Keywords: Electromyography; Myopathy; Neuropathy; Non-stationary time series; Multifractality; Multifractal width; Auto-correlation exponent

Introduction

Motor neurone disease (MND) is a rare but devastating illness which leads to progressive paralysis and eventual death. Although rare, many patients are both aware and fearful of it [1]. MND is a progressive degenerative disease of the motor nerve cells of the brain and spinal cord. Neurons control muscle movement of all kinds of physical activities. When the nerves become inactive, muscles gradually weaken leading to paralysis and impaired speaking as well. However, it has been observed that the senses, intellect or memory remains unaffected in most of the cases. Though MND is still incurable, but through proper and continuous treatment several symptoms can be controlled.

Myopathy (MYO) is a sign of pathology with widely varying etiologies, including congenital or inherited, idiopathic, infectious, metabolic, inflammatory, endocrine, and drug-induced or toxic. The primary symptom of this disorder is muscle weakness due to dysfunction of muscle fiber, while it can include other symptoms like muscle cramps, stiffness, and spasm also [2].

Neuropathy (NEURO), generally known as damage to nerves, may be caused either by diseases or trauma to the nerve or as a component of systemic illness.

An electromyography (EMG) signal is obtained by measurement of the electrical activity of a muscle during contraction, and reflects the electrical depolarization of excitable muscle fiber membranes that create electrical signals called muscle fibers potentials (MFPs) [3]. EMG is of two types: surface EMG (SEMG), and intramuscular EMG [4]. SEMG and intramuscular EMG signals are recorded by non-invasive electrodes and invasive electrodes, respectively. These days, surface-detected signals are preferably used to obtain information about the time or intensity of superficial muscle activation [5]. The EMG signal has been widely applied in fatigue studies [6-10] rehabilitation and prosthetic control [11-15], neurology, as a means in clinical diagnosis [16,17], and even in EMG augmented speech recognition [18].

Several complex dynamical systems found in nature are characterized by a set of nonlinear differential equations. The reason for the chaotic behavior of these complex systems is attributed to nonlinearity [19]. Physiological systems are also complex systems involving several nonlinearities [20,21]. Myopathies (MYO), Neuropathies (NEURO) and Motor Neuron Disease (MND) also have such inherent nonlinear character.

Different linear analysis techniques have been applied to describe the characteristics of EMG signals. Time-domain features have been studied by zero crossings and root mean square (RMS) [15] techniques; stochastic features by autoregressive model coefficients [22], cepstral coefficients [11], mean frequency and median frequency (MDN) [6,23] etc. But there are certain limitations with these methods as realized by the scientists. Like every other system found in nature, EMG signals are also of complex character, as they are composed of many subsystems which are strongly correlated to each other, but not in a linear fashion. Conventional linear techniques like amplitude, root mean square or Fourier analysis cannot provide detail information about these subsystems. The development of nonlinear methods has significantly helped in studying complex nonlinear systems in detail by providing accurate and precise information about them such as in studying the multi-resolution features of EMG signals, wavelet coefficients have high level of accuracy [12]. Recurrence quantification analysis (RQA) provides additional information on the underlying motor strategies [24,25], hidden rhythms [26] or fatigue [27,28].

With the development of nonlinear dynamics it is now very clear that simple nonlinear systems exhibit highly complex [29-34] and chaotic behavior as they are extremely sensitive to initial conditions, since any perturbation, no matter how minute, will forever alter the future of the systems. In complex signal there exists self-similarity phenomenon, in that there is a smaller scale structure that resembles the larger scale structure in complex medical signals such as EMG, EEG (electroencephalography) and ECG (electrocardiograph) signals [33]. Fractals exhibit this self-similar property [35]. The source of SEMG is a set of similar action potentials originating from different locations in the muscles. Because of the self - similarity of the action potentials that are the source of the SEMG recordings over a range of scales, SEMG is expected to have fractals properties.

Fractals refer to objects or signal patterns that have fractional dimension. The measured property of the fractal process is scale dependant and has self-similar variations in different time scales. Fractal dimension (FD) is a measure of the fractal properties of any structure. Fractals can be classified into two categories: monofractals and multifractals. Monofractals are those whose scaling properties are the same in different regions of the system and multifractals are more complicated self-similar objects that consist of differently weighted fractals with different non-integer dimensions. Thus the fundamental characteristic of multifractality is the scaling properties may be different in different regions of the systems [36].

Several researchers applied different nonlinear methods to characterize the geometry and fractal properties of the EMG signals [37-47]. Some authors have directly applied geometrical methods e.g., Katz method [48] and box-counting method [49] on the EMG signal interference pattern to acquire an estimate of the fractal dimension.

Other nonlinear methods such as nonlinear entropy analysis and fractal analysis have been proposed to analyze SEMG signals for extracting information that can detect the changes in different muscle statuses. Zhao Jing-Dong et al. extracted sample entropy and wavelet transform coefficients from three channels of SEMG signals for classifying six fingers movements [50]. Naik et al. used the fractal dimension features for identifying finger movements [51]. In a study Dang et al. showed EMG to be a powerful tool for investigating the relationship between jaw imbalance and the loss of arm strength with Higuchi Fractal dimension (HFD) analysis [52]. Zhang et al. observed, though the traditional time-domain and frequency-domain analyzing methods used in EMG pattern recognition have a satisfactory capability to track muscular changes, but as far as detection of critical features of SEMG signals during transient human movements are concerned, nonlinear methods like nonlinear entropy analysis or fractal analysis are more reliable than the conventional linear analysis methods [53]. Naeem et al. used a combination of linear and nonlinear techniques to estimate their ability to recognize uterine EMG records of term and preterm deliveries using artificial neural network [54]. In another work Patidar et al. applied the back propagation neural network classifier for classification of myopathy patients and healthy subjects with the help of EMG signal [3]. Lei and Meng, investigated the stochastic, deterministic and chaotic behavior of SEMG signals with several nonlinear techniques such as surrogate data method, VWK model method, chaotic analysis method, symplectic geometry method and fractal analysis method. They observed the necessity of multifractal analysis, as it was found very difficult to describe SEMG using single fractal dimension [55]. Way back in 2007 Gang et al. [56] observed SEMG signals from biceps brachii on the skin surface of right forearm of human subjects' characterized multifractality during a static contraction applying multifractal analysis technique as an indicator for assessing muscle fatigue. Several other authors have also extensively analyzed the classical (mono-) fractal aspects [57-61] in the domain of force of contraction of different muscles [62].

In this paper we have proposed multifractal detrended fluctuation analysis (MF-DFA) method to study the multifractal properties of EMG signals of three human subjects of which one contains healthy EMG data and the other two MYO and NEURO data respectively. We may mention that we do not have access to any other data of EMG time series.

Kantelhardt et al. introduced multifractal detrended fluctuation analysis (MF-DFA) as a generalization of the standard DFA [63]. For the study of multifractal scaling behavior of various non-stationary time series, MF-DFA has been applied quite successfully in different fields of science and engineering [64-70]. MF-DFA is a nonlinear analysis technique, the application of which on a given set of data provides information about any evidence of self-similarity or persistence in the series [71]. MF-DFA allows a global detection of multifractal behavior, while the WTMM method is suited for the local characterization of the scaling properties of signals. Moreover the MFDFA does not require a big effort in programming but provides reliable results [72].

Description of the data

We obtained the data from https://physionet.org/physiobank/database/emgdb/

Data were collected with a Medelec Synergy N2 EMG Monitoring System (Oxford Instruments Medical, Old Woking, United Kingdom). EMG data from: 1) A 44-year-old man without history of neuromuscular disease; 2) A 57-year-old man with myopathy due to longstanding history of polymyositis, treated effectively with steroids and low-dose methotrexate; and 3) A 62-year-old man with chronic low back pain and neuropathy due to a right L5 radiculopathy. The data were recorded at 50 KHz and then down-sampled to 4 KHz. During the recording process two analog filters were used: A 20 Hz high-pass filter and a 5K Hz low-pass filter. The data were further divided into five equal sets for each subject.

Method of analysis

We have performed a multifractal analysis of the EMG recordings of three human subjects, one healthy, one with myopathy and one with neuropathy respectively using methodology of Kantelhardt et al. [63].

Let us consider x(i) for i =1, ..., N, be a non-stationary time series of length N. The mean of the above series is given by

$$X_{ave} = \frac{1}{N}\sum_{i=1}^{N} X(i) \tag{1}$$

Assuming x(i) as the increments of a random walk process around the average, the trajectory can be obtained by integration of the signal.

$$Y(i) = \sum_{k=1}^{i} \left[X(k) - X_{ave} \right] \text{ for } i =1....... N \tag{2}$$

The level of measurement noise present in experimental records and the finite data are also reduced by the integration thereby dividing the integrated time series into N_s non-overlapping bins, where N_s = int(N/S) and where s is the length of the bin. As N is not a multiple of s, a small portion of the series is left at the end.

Again, to include that left part, the entire process is repeated in a similar way starting from the opposite end, leaving a small portion at the beginning. Hence, $2N_s$ bins are obtained altogether and for each bin least-square fit of the series is done followed by determination of the variance.

$$F^2(s,v) = \frac{1}{s}\sum_{i=1}^{s} \left\{ Y\left[(v-1)s+i \right] - y_v(i) \right\}^2$$

For each bin v, v =1 .... N_s and

$$F^2(s,v) = \frac{1}{s}\sum_{i=1}^{s} \left\{ Y\left[N-(v-N_s)s+i \right] - y_v(i) \right\}^2 \tag{4}$$

For v = N_s + 1........, 2 N_s, where $y_v(i)$ is the least square fitted value in the bin v. In our research work we have performed a least square linear fit (MFDFA -1). The study can also be extended to higher orders by fitting quadratic, cubic, or higher order polynomials.

The qth order fluctuation function $F_q(s)$ is obtained after averaging over 2 N_s bins,

$$F_0(s) \equiv \sim \exp\left\{ \frac{1}{2} N_s \sum_{V=1}^{2N_s} In\left[F^2(s,v)^{\frac{q}{2}} \right] \right\}^{\frac{1}{q}} \tag{5}$$

where q is an index which can take all possible values except zero, as the factor 1/q becomes infinite with zero value. The procedure can be repeated by varying the value of s. With the increase in the value of s F_q (s) , increases and for the long range power correlated series F_q (s) shows power law behavior,

$$F_q(s) \alpha s^{h(q)}$$

If such a scaling exists, In F_q will depend linearly on s with slope h(q). In general, the exponent h(q) depends on q. For a stationary time series, h(2) is identical with the Hurst exponent H. h(q) is said to be the generalised exponent. The value of h(0) cannot be obtained directly, because F_q blows up at q = 0. F_q cannot be obtained by normal averaging procedure; instead a logarithmic averaging procedure is applied.

$$F_0(s) \equiv \exp\left\{ \frac{1}{4} N_s \sum_{V=1}^{2N_s} In\left[F^2(s,v) \right] \right\} \sim s^{h(0)} \tag{6}$$

A monofractal time series is characterized by unique h(q) for all values of q. If small and large fluctuations scale differently, then h(q) will depend on q, or in other words the time series is multifractal. Kantelhardt et al. have explained that the values of h(q) for q < 0 will be larger than that for q > 0 [73].

The generalized Hurst exponent h(q) of MFDFA is related to the classical scaling exponent τ(q) by the relation,

$$\tau(q) = qh(q) - 1 \tag{7}$$

a monofractal series with long range correlation is characterized by linearly dependent q- order exponent τ(q) with a single Hurst exponent H. Multifractal signals have multiple Hursts exponent and τ(q) depends nonlinearly on q [74]. The singularity spectrum f(α) is related to τ(q) by Legendre transform [75].

$$\alpha = h(q) + qh(q) \tag{8}$$

$$f(\alpha) = q\left[\alpha - h(q) \right] + 1 \tag{9}$$

In general, the singularity spectrum quantifies the long range correlations property of the time series [76]. The multifractal spectrum is capable of providing information about the relative

importance of various fractal exponents in the time series, e.g., the width of the spectrum denotes range of exponents. A quantitative characterization of the spectra can be done by least-squares fitting it to quadratic function [77] around the position of maximum α_0,

$$f(\alpha) = A(\alpha - \alpha_0)^2 + (\alpha - \alpha_0) + c \qquad (10)$$

where C is a additive constant, C = $f(\alpha_0)$ =1; B indicates the asymmetry of the spectrum, and zero for a symmetric spectrum. The width of the spectrum can be obtained by extrapolating the fitted curve to zero. Width W is defined as W = $\alpha_1 - \alpha_2$ with $f(\alpha_1)$ = $f(\alpha_2)$ = 0. It has been proposed by some workers [78] that the width of the multifractal spectrum is a measure of the degree of multifractality. Singularity strength or Holder exponent α and the dimension of subset series $f(\alpha)$ can be obtained from reln.9 and 10. For a monofractal series, h(q) is independent of q. Hence from relation 9 and 10 it is evident that there will be a unique value of α and f(), the value of α being the generalized Hurst exponent H and the value of $f(\alpha)$ being 1. Hence the width of the spectrum will be zero for a monofractal series. The more the width, the more multifractal is the spectrum.

The autocorrelation exponent γ can be estimated from the relation given below [79,80]:

$$\gamma = 2 - 2(h)(q = 2) \qquad (11)$$

For uncorrelated or short-range correlated data, h(2) is expected to have a value 0.5 while a value greater than 0.5 is expected for long-range correlations. Therefore for uncorrelated data, γ has a value 1 and the lower the value the more correlated is the data.

Superiority of MFDFA over other conventional methods

A time series containing apparent irregularities can be best described with nonlinear scaling analysis. MFDFA, in comparison with the conventional methods such as Fourier analysis, Detrended Fluctuation Analysis (DFA), Detrended Moving Average (DMA), Backward Moving Average (BMA), Modified Detrended Fluctuation Analysis (MDFA), Continuous DFA (CDFA), Wavelet Analysis etc., has achieved the highest degree of precision. It is a very rigorous and robust technique and can be implemented with lesser effort in computer programming as compared to conventional DFA, since it does not require the modulus maxima procedure. Many researchers in this domain have recommended MFDFA due to its better performance than other conventional methods in the analysis of multifractality in both stationary as well as non-stationary time series [63,81,82]. Oswiecimka et al. have established the superiority of MFDFA over other techniques, especially over the most popular one, the Wavelet Transform Modulus Maxima (WTMM) in terms of reliable applications [83].

Certain limitations have also been identified in MFDFA method. Mainly, where a large amount of data is missing or removed due to artifacts, the problem may arise in the identification of correlation properties of real data. However, Ma et al. [84] observed that the major findings are not significantly disturbed even with loss of data.

Results

The non-stationary times series of EMG data of healthy, myopathy and neuropathy respectively recorded in three human subjects are analyzed following the method described above.

Multifractal analysis was employed for each set. The data was transformed to obtain the integrated signal. This process is effective in reducing noise in the data. The integrated time series was divided to N_s bins, where N_s = int(N/s), N is the length of the series. The qth order fluctuation function Fq(s) for q = -10 to +10 in steps of 1 was determined.

Figure 1 depicts the linear dependence of lnFq on lns suggesting scaling behavior for the healthy subjects. **Figure 2** and **Figure 3** also depict the same scaling behavior for myopathy and neuropathy patients respectively.

The slope of linear fit to ln Fq(s) versus lns plots gives the values of h(q). The values of τ(q) were also determined. As we have mentioned earlier, nonlinear dependence of on (q) on q suggests multifractality, whereas for a monofractal series τ(q) depends linearly on q. The values of h(q) and τ(q) of all the EMG signals are depicted in **Figures 4 and 5** respectively.
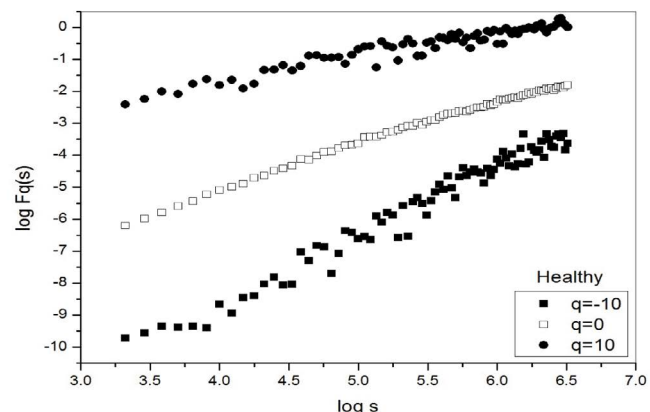

Figure 1 ln*Fq* vs. ln*s* for a particular set of EMG signal of healthy subject.
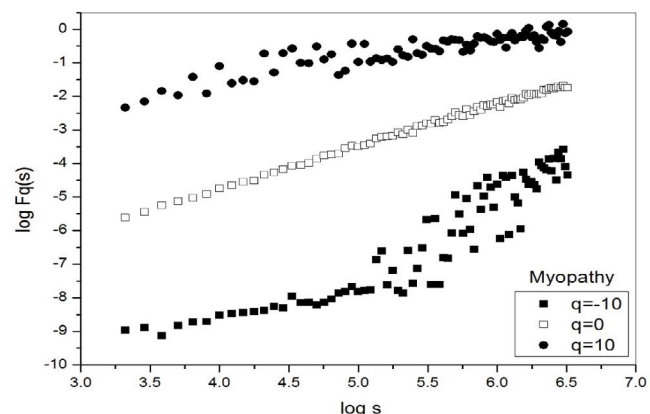

Figure 2 ln*Fq* vs. ln*s* for a particular set of EMG signal of myopathy patient.
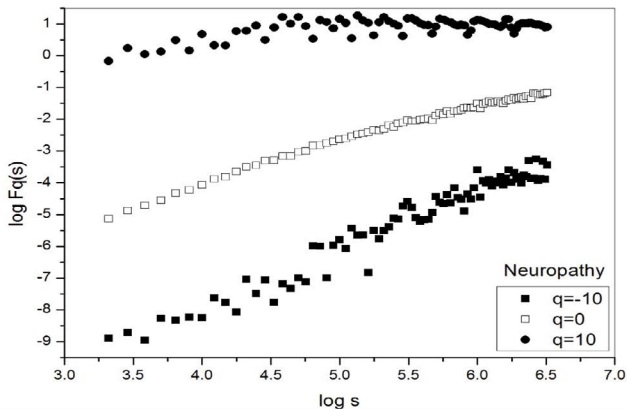
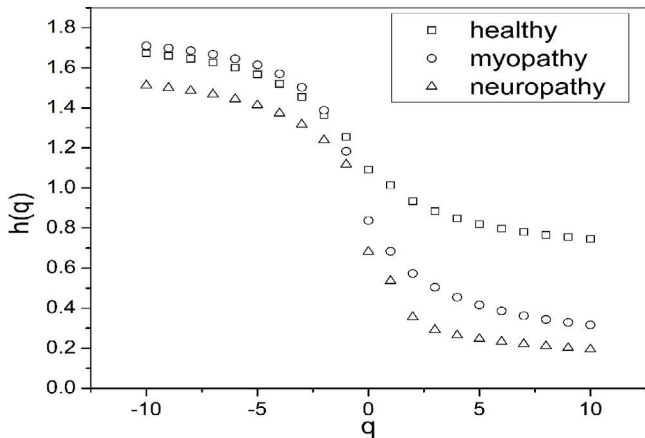**Figure 3** ln*Fq* vs. ln*s* for a particular set of EMG signal of neuropathy patient.

Figure 4 h(q) vs. q for a particular set of EMG signals of healthy, myopathy and neuropathy.
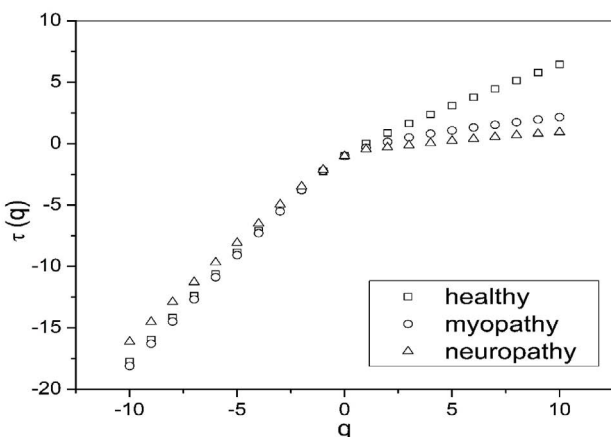

Figure 5 τ(q) vs. q for a particular set of EMG signals of healthy, myopathy and neuropathy.

The nonlinear dependence of τ(q) on q and the dependence of h(q) on q gives evidence for the multifractality of the EMG signals. **Figure 4** also depicts that the degree of dependence of h(q) on

q, or in other words, the degree of multifractality is different in different cases.

Table 1 is formed with the values obtained from **Figure 4** where we can see that for q = 2 the generalized Hurst exponent h(q) of all the EMG signals of healthy and myopathy subjects are greater than 0.5 which means that long range correlation and persistent properties exist in all the sets. For neuropathy, h(q) is less than 0.5, which indicates the existence of anti-persistent properties in all the sets.

A quantitative determination of the degree of multifractality can also be done from the multifractal spectrum. Ashkenazy et al. have associated the width of the multifractal spectrum (f(α) versus α) with the degree of multifractality [78]. **Figure 6** shows the multifractal spectrum of healthy, myopathy and neuropathy EMG signals.

In **Table 2** the values of multifractal width w obtained by fitting the multifractal spectrums to Eq. (8) are listed, where we can observe that the multifractal widths in five sets of all the three healthy, myopathy and neuropathy EMG signals are different ranging from as low as 1.144 to as high as 1.257, from 1.507 to 1.605 and from 1.655 to 1.991 respectively giving a clear indication of increasing complexity from healthy subject to neuropathy subject.

From **Table 3** we can observe that the value of auto-correlation exponent γ for set 5 of the healthy person is 0.035 which indicates a high degree of correlation as we know lower the value of higher is the degree of correlation. Whereas for the same set, for myopathy patient γ is quite high with a close approach to 1,

Table 1 Values of h(q) corresponding to q for a particular set of EMG signals of healthy, myopathy and neuropathy subjects.

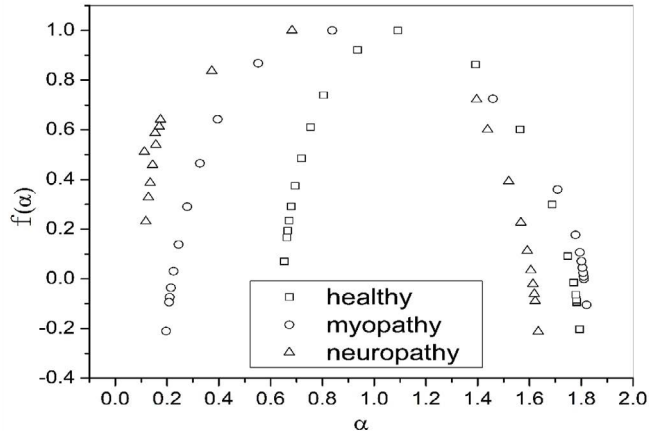| Order q	Generalized Hurst Exponent h(q)		
	Healthy	**Myopathy**	**Neuropathy**
-10	1.67	1.71	1.51
-9	1.66	1.70	1.50
-8	1.65	1.69	1.49
-7	1.63	1.67	1.47
-6	1.60	1.65	1.44
-5	1.57	1.61	1.41
-4	1.52	1.57	1.37
-3	1.45	1.50	1.32
-2	1.36	1.39	1.24
-1	1.26	1.18	1.12
0	1.09	0.84	0.68
1	1.01	0.68	0.54
2	0.93	0.57	0.36
3	0.88	0.51	0.29
4	0.85	0.46	0.26
5	0.82	0.42	0.25
6	0.80	0.39	0.23
7	0.78	0.36	0.22
8	0.77	0.34	0.21
9	0.75	0.33	0.20
10	0.75	0.32	0.19

Figure 6 f(α) vs. α for a particular set of EMG signals of healthy, myopathy and neuropathy.

Table 2 Values of w for all the five sets of EMG signals of healthy, myopathy and neuropathy subjects.

Set	Multifractal Width (w)		
	Healthy	Myopathy	Neuropathy
1	1.161 ± 0.042	1.605 ± 0.078	1.655 ± 0.140
2	1.146 ± 0.041	1.583 ± 0.077	1.848 ± 0.103
3	1.257 ± 0.026	1.598 ± 0.087	1.855 ± 0.105
4	1.230 ± 0.050	1.507 ± 0.078	1.991 ± 0.078
5	1.144 ± 0.041	1.598 ± 0.073	1.813 ± 0.082

Table 3 Values of γ for all the five sets of EMG signals of healthy, myopathy and neuropathy subjects.

Set	Autocorrelation Exponent (γ)		
	Healthy	Myopathy	Neuropathy
1	0.132 ± 0.004	0.852 ± 0.010	1.288 ± 0.007
2	0.075 ± 0.006	0.842 ± 0.011	1.462 ± 0.010
3	0.069 ± 0.005	0.793 ± 0.009	1.442 ± 0.009
4	0.262 ± 0.004	0.73 ± 0.010	1.459 ± 0.009
5	0.035 ± 0.005	0.763 ± 0.010	1.431 ± 0.009

indicating a very less autocorrelation and for neuropathy patient it is greater than 1 which implies there is no correlation at all.

Discussion

Little work has been done on the analysis of EMG data with nonlinear techniques. Gang et al. reported a work [56] which aimed to study muscle fatigue during static contraction. Using a multifractal method developed by Chhabra and Jensen [85] they showed multifractility of SEMG signals. They observed the area of the multifractal spectrum of the SEMG signals to increase significantly during muscle fatigue. Thus they concluded that the area of the multifractal spectrum could then be used as an assessor of muscle fatigue which is more sensitive than the single characteristic frequency such as the median frequency (MDF) or mean frequency (MNF) of the power spectral density (PSD) which was a then popular method of estimating fatigue [86,87]. They also opined that the large area of SEMG multifractal singularity spectrum reflects the strengthened activity of the nervous system

of the body in the process of muscle fatigue [86]. In another study Talebinejad et al. [88] used a bi-phase power spectrum method (BPSM) for fractal analysis of SEMG signals and also included an algorithm for extraction of fractal indicators (FIs). BSPM was evaluated for force and joint angle and the changes that reflect in EMG signals were demonstrated with the help of FIs. They also compared BSPM with geometrical techniques and the $1/f^\alpha$ approach for fractal analysis of electromyography signals and concluded that BPSM provides reliable information, as it consists of components which are capable of sensing force and joint angle effects separately, which could be used as complementary information for confounded conventional measures [88].

However as elaborated earlier Oswiecimka et al. have established the superiority of MFDFA over other techniques, especially the Wavelet Transform Modulus Maxima (WTMM) in terms of reliable applications [83]. Compared to other conventional methods MFDFA has reached the highest precision in scaling analysis. Thus it is considered a rigorous and robust tool for assessing correlation in nonlinear time series. Some other authors too have advocated the better performance of MFDFA than other multifractal analyses methods [63,81,82] as it can detect multifractality in both stationary as well as non-stationary time series.

Conclusion

Using MF-DFA in our work we have been able to distinguish the EMG signals of healthy, myopathy and neuropathy subjects effectively with the help of two parameters the multifractal width (w) and auto-correlation exponent (γ). Not only we observed different degree of multifractility of the EMG signals of healthy, myopathy and neuropathy subjects but we have also observed the significant variation in degree of auto-correlation for all the three subjects where subject with neuropathy shows no correlation at all. Thus the present study proposes a novel, rigorous method of assessment of myopathy and neuropathy using EMG time series from a different perspective and any EMG data available may be analyzed using the method for diagnosis and prognosis of myopathy and neuropathy and even early detection of motor neuron disease.

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Competing and Conflicting Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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