

# Non-Linear Techniques Reveal Adaptive and Maladaptive Postural Control Dynamics in Persons with Multiple Sclerosis

Busa MA<sup>1,2\*</sup>, Ducharme SW<sup>1</sup> and van Emmerik REA<sup>1,2</sup><sup>1</sup>Department of Kinesiology, University of Massachusetts Amherst, Amherst, MA 01003, USA<sup>2</sup>Center for Personalized Health Monitoring, Institute for Applied Life Sciences, University of Massachusetts Amherst, Amherst, MA 01003, USA

## Abstract

In this commentary we discuss how complex and nonlinear analysis methods, multiscale entropy (MSE) and detrended fluctuation analysis (DFA) can provide insights into postural changes in people with multiple sclerosis (MS). Here we highlight key methodological considerations for both MSE and DFA, specifically discuss how MS and aging impact the complexity and adaptability of postural control. As MSE and DFA are both sensitive to technical considerations, we directly address how changes in signal processing and equation parameterization impact outcomes and how these may in turn influence the interpretation of results. Furthermore, we identify how MSE and DFA identify different features of disease progression and how the associated breakdowns in physiological function manifest as postural fluctuation changes within and between different time scales. Finally, we propose a framework that combines these techniques to identify the adaptive and maladaptive changes that accompany MS progression.

**Keywords:** Multiscale entropy; Detrended fluctuation analysis; Posture; Center of pressure

## Introduction

The robust control of upright standing posture is influenced by many physiological (e.g., muscular, motor and sensory) and environmental (e.g., support surface and context) factors. In this commentary, we will focus on how two complex systems analysis techniques, multiscale entropy (MSE) and detrended fluctuation analysis (DFA), can provide insights into the nature of postural fluctuations within and between different time scales. Finally, we discuss the generalized pattern of results observed in MSE and DFA and suggest that, when used together, these techniques may reveal how the system responds to disease progression and how this can be used to identify both adaptive and maladaptive changes in postural fluctuations.

Dynamical systems techniques are increasingly being applied in the assessment of postural control changes due to aging and disease [1-3]. In this commentary we focus on MSE and DFA as they have been used empirically to reveal how disease and aging affect the complexity and fractality of postural fluctuations, respectively. MSE reveals the complexity of COP fluctuations, whereby a signal is considered to be complex if it displays point-to-point fluctuations that are indicative of a high entropy value across a range of physiologically relevant time scales [4,5]. By evaluating several time scales, MSE can distinguish random, maladaptive changes in physiological fluctuations from those of a healthy system [2]. Single time scale approaches may yield confusing results such that, depending on the time scale evaluated, physiological fluctuations derived from pathological systems (e.g. heart disease) may exhibit entropy values that are both larger and smaller than those from healthy systems [2]. DFA is a technique that provides information regarding the adaptability of postural control through an assessment of the COP fluctuations at different time scales, and how these fluctuations at various time scales relate to each other. Specifically, we will provide examples of adaptive and maladaptive changes in postural control based on DFA analysis, and how these changes can provide insights into the limitations and redundancy of the physiological systems underlying the control of upright standing in health and disease.

## Multiscale Entropy

Approximate entropy is a measure of entropy that has been used to demonstrate that persons with MS display increased regularity in their COP fluctuations [6]. However, this technique has substantial

methodological shortcomings and we therefore recommend against its use [4,7]. The advantages of MSE over other entropy techniques are two fold: 1) It allows an examination of the complexity of postural fluctuations over a range of physiologically relevant time scales, and 2) it uses the sample entropy algorithm to assess complexity at each time scale. Sample entropy eliminates the self-matching bias found in the approximate entropy technique [7]. Furthermore, the numerical integration of the entropy values across the time scales of interest allows for a more comprehensive estimation of the complexity in the system [2]. Several data acquisition and analysis aspects need to be taking into account when applying MSE, including: length of time series, filtering and MSE parameters (see [2,4,5,7] for more detailed discussion). MSE quantifies the point-to-point fluctuations over a range of time scales. This analysis requires a large amount of meaningful data (i.e., not just high sampling frequencies). Specifically, we and others have previously noted that MSE requires 200 data points at any time scale to provide stable and reliable results [4,8]. As MSE requires signal stationarity, a number of different methods have been used to achieve this, including detrending the time series using empirical mode decomposition, high pass filtering the data to remove slow drifts, and differentiating the COP position time series to remove non-stationarities [1,9]. Furthermore, determining the similarity criterion ( $r$ ) for points in the time series can have a major impact on the results [2,4,5]. Comparing and interpreting the results of studies that use different  $r$  values is difficult and could result in erroneous conclusions of difference/similarity in entropy and complexity. Additionally,  $m$  is the parameter in the MSE process that defines the distance between data points that is being compared for similarity. This value is often set to the minimum of  $m=2$ . In single time scale approaches, this parameter can be changed to observe the similarity of fluctuations over different time scales. However, the course

**\*Corresponding author:** Michael A Busa, University of Massachusetts Amherst 30 Eastman Lane, Amherst, MA 01003, USA, Tel: 413-545-1332; E-mail: [mbusa@umass.edu](mailto:mbusa@umass.edu)

Received April 23, 2016; Accepted May 23, 2016; Published May 30, 2016

**Citation:** Busa MA, Ducharme SW, van Emmerik REA (2016) Non-Linear Techniques Reveal Adaptive and Maladaptive Postural Control Dynamics in Persons with Multiple Sclerosis. J Mult Scler (Foster City) 3:177. doi:[10.4172/2376-0389.1000177](https://doi.org/10.4172/2376-0389.1000177)

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graining procedure in MSE, which averages non-overlapping windows of the original dataset to create new time series, largely replaces the use of different values of  $m$  other than 2 as a way to gain insight into fluctuations at different time scales.

We recently evaluated changes in postural fluctuations using MSE in people with MS and observed lower COP complexity during quiet and perturbed standing compared to controls [1]. These results while yet to be replicated, are consistent with other reports of changes in complexity with aging and in those with a history of falls [9]. Costa and colleagues also showed that application of subsensory vibrations to the soles of the feet, stochastic resonance, increased MSE values (i.e., postural complexity) in healthy older adults to values similar to those observed in younger participants [9]. These results suggest that subsensory noise added to the soles of the feet can improve postural control affected by frailty due to aging and disease.

### Detrended Fluctuation Analysis

The MSE analysis presented above can be used to identify changes in postural control processes at a range of different time scales, and provides an overall measure of postural complexity. Similarly, DFA is a technique that is used to identify interactivity between processes occurring at different temporal scales. In a healthy system, physiological fluctuations occurring at short time scales are correlated to those at longer time scales, and these correlations breakdown with aging and disease [10-12]. A system exhibits structured yet complex behavior when fundamental biological processes (e.g. protein or cellular function) are reflected in systemic fluctuations (e.g. whole body sway). DFA is a modified random walk analysis (for detailed description of the algorithm, see Peng et al. [10]), in which the signal is integrated and sectioned into non-overlapping windows of various lengths. Within each window, a root-mean-square analysis of the local trend line is used to quantify the magnitude of fluctuations. Displaying the amplitudes of fluctuations and scale sizes on a double logarithmic plot, the slope of the relationship, known as the scaling exponent ( $\alpha$ ), represents the degree to which fluctuations are scale invariant, also known as fractality.  $\alpha=1.0$  represents signals that are scale invariant (e.g. 'pink noise'). When  $0.5 < \alpha \leq 1.0$ , the signal is correlated, whereby fluctuations in one direction tend to be followed by fluctuations in the same direction. White noise has  $\alpha=0.5$ , indicating that the signal is absent of long-range correlations. Finally, when  $\alpha > 1.0$ , the signal approaches Brownian motion ( $\alpha=1.5$ ), that is the signal has random steps on short time scales but the total distance traveled is a function of the number of steps taken.

DFA is sensitive to a number of methodological considerations including parameterization and data reduction. The main parameter consideration is the sizes of the windows. It has been recommended that these windows should not be shorter than 4 data points and no larger than  $N/4$  data points, where  $N$  is the number of samples in the data set [12]. Applying a low-pass filter (for example, at 5 Hz) reduces small-amplitude fluctuations within the smaller window sizes, and has been suggested as a means of observing aspects of 'central' control, and display fractal scaling exponents between  $1.0 > \alpha > 1.5$  [13]. That is, the dynamics exhibit highly persistent and borderline Brownian patterns. Applying a high pass filter (for example, 10 Hz) will reduce large-amplitude fluctuations in the larger windows, and has been proposed as a mechanism to observe 'peripheral' control, and display scaling exponent values between 0.55 and 0.75 [13]. These fundamentally different  $\alpha$  values highlight how changes in signal processing can impact the interpretation of the fractal nature of the signal. Postural COP signals of young, healthy adults have been examined and indicate the presence of fractality [13-15]. However, it is currently not clear

how the onset or progression of MS impacts the fractal dynamics of postural control. This is important, considering those with MS exhibit multifactorial deficits occurring across numerous sensorimotor time scales, and these deficits may manifest as altered fractality. We recently examined the relationship between cutaneous sensory thresholds at the feet and the fractal nature of postural fluctuations in healthy young subjects [16]. We found that when the sensory thresholds are elevated by cooling the soles of the feet (i.e., impairing sensation) to threshold levels observed in individuals with MS, DFA values are significantly higher, deviating farther from a value of 1.0, indicative of a breakdown in fractality. The application of stochastic resonance resulted in increased fractality (i.e.,  $\alpha$  moved significantly toward 1.0) in postural fluctuations, regardless of sensory status [16]. Furthermore, studies of fractality in older adults have been mixed. In two recent studies, fractal scaling in postural COP patterns displayed deviations away from  $\alpha=1.0$  in older adults compared to young adults, indicating a reduction in long-range interactions and complexity in this group [11,12]. Conversely, fractal scaling in a separate study was lower in older adults compared to young adults, but neither group was different from  $\alpha=1$  [15]. However, the difference in trial length is the most probable explanation for these discrepancies. The two studies that reported age differences entailed 20 s trials [11,12], while the study that did not observe fractal scaling deviation away from  $\alpha=1.0$  consisted of 60 s and 30 min trials [15]. Collectively, these results suggest that fractal scaling is also reduced in those with MS, but empirical confirmation is needed. Examining the effects of postural task on fractal dynamics has identified some mechanisms that may lead to a breakdown in healthy fractality. Specifically, in addition to the altering cutaneous sensation, paradigms have been developed to simulate the consequences of reduced somatosensory information by applying constraints such as eyes-closed conditions [13]. When young healthy adults stand quietly with their eyes closed,  $\alpha$  shifts closer to 1.0 compared to when they stand with their eyes open, irrespective of filtering methods (Figure 1B, 'Adaptive') [13]. This phenomenon may indicate stronger interactions between time scales based on task demands. On the other hand, older adults exhibit scaling exponents that deviate from optimal (i.e., closer to  $\alpha \sim 1.6$ ) when eyes are closed (Figure 1B, 'Maladaptive'), which may

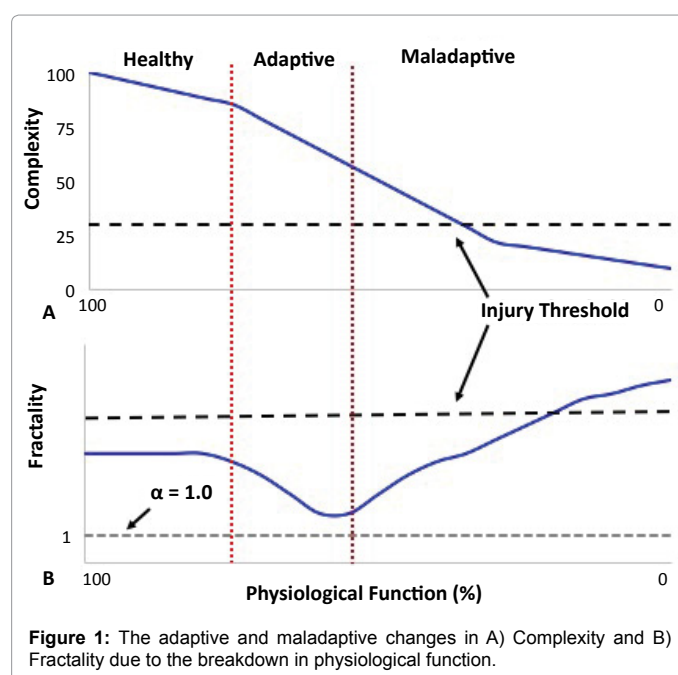


Figure 1: The adaptive and maladaptive changes in A) Complexity and B) Fractality due to the breakdown in physiological function.

reflect a compensatory mechanism by older adults to actively constrain available degrees of freedom to minimize point-to-point fluctuations [11]. To summarize, while analysis of fractal scaling during quiet standing provides valuable information, incorporating conditions such as eyes-closed conditions may also play a key role in understanding how these interactions across time scales change as a function of organism, environmental or task constraints (Figure 1).

The changes in sensorimotor function occurring at different spatio-temporal scales can be revealed by a combined assessment of complexity (through MSE) and fractality (through DFA). For instance, sensorimotor degradation due to MS can be observed in complexity (Figure 1A). DFA results suggest a different pattern (Figure 1B), that is, when the postural system is challenged by removing vision, younger individuals exhibit an adaptable response by increasing the interactivity between spatio-temporal processes at different levels of the system (i.e.,  $\alpha$  shifts toward 1.0), while older individuals display a maladaptive response with decreased coupling strength between levels of the system (i.e.,  $\alpha$  shifts away from 1.0). It is this scale-invariant similarity in the presence of reduced complexity that may identify functional adaptations in the face of physiological impairment. The combination of MSE and DFA appears to be a suitable way to evaluate how the breakdown of sensorimotor function in MS relates to adaptive and maladaptive changes in postural COP fluctuations. Here we present a conceptual framework of the evolution of changes to the COP signal with the onset and progression of disease (Figure 1). With the onset of systemic constraint (imposed by disease and/or task), MSE complexity decreases, while fractality initially display shifts towards  $\alpha=1.0$ , representing a strengthening of interactivity as an adaptation to lost complexity. Further degradation results in a breakdown in the scale invariant COP fluctuations, manifesting as  $\alpha$  shifting away from 1.0. This breakdown in fractality coincides with substantial reductions in complexity observed with advanced aging and disease states. The reductions in complexity and fractality are indicative of maladapted physiological states. More work is needed to identify if these proposed changes in COP dynamics accompany neurological disease (e.g. MS, Parkinson's disease, Huntington's disease, etc.) progression and if they can be used to track such progression.

## Conclusion

Nonlinear analysis techniques such as MSE and DFA are well suited to assess the changes in postural control processes due to aging and disease. A major asset of these methods is that they can reveal the changes in postural control across and within different spatio-temporal scales impacting different populations such as MS. Several methodological considerations for experimental design and interpretations need to be taken into account in the application of these methods. Finally, we propose a conceptual framework that uses both complexity (MSE) and fractality (DFA) analysis that may enhance our ability to track different stages of MS or other neurological disease progression and frailty due to aging and disease in general.

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