

Fractal Analysis of Center of Pressure Velocity

Time Series in Parkinson's Disease

BY

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Submitted to the graduate program in Mechanical Engineering

and the Graduate Faculty of the University of Kansas

in partial fulfillment of the requirements for the degree of

Master of Science

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That this is the approved Version of the following thesis:

Fractal Analysis of Center of Pressure Velocity

Time Series in Parkinson's Disease

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Date Approved:

Abstract

The purpose of this study was to test the sensitivity of system parameters of the Center of Pressure velocity (COPv) time series using Detrended Fluctuation Analysis to pre-clinical postural instability (PI) in PD, the progression of PI due to PD progression, and ultimately fall risk. The long term goal is to create quantitative clinically significant measures of pre-clinical PD PI, the progression of PI due to PD progression, and fall risk. Postural sway data collected in a previous study, including participants with mild PD (PD-Mi), moderate PD (PD-Mo) and age-range-matched healthy controls (HC), were analyzed in this study. Ground reaction forces and moments were collected from subjects standing on force plates in quiet postural sway in eyes open (EO) and eyes closed (EC) conditions. COPv was calculated and analyzed as a non-stationary time series. We investigated the temporal parameter of Absolute Average Maximal Velocity (AAMV), the system order parameter of Approximate Entropy (ApEn), and fractal parameters from the DFA which were the short (α_1) and long (α_2) term scaling behavior of the time series and the time scale at which the behavior changes – the crossover index (CrI).

AAMV showed significant group differences between HC and PD-Mo and significant condition differences. In the fractal analysis, α_1 showed significant group differences between HC and PD-Mo and α_2 showed significant differences between conditions. Due to the pilot nature of the study, power analysis was conducted on all non-significant measures in order to investigate required subject numbers for significance. Feasible subject numbers were found for many of the measures. These results suggest that the temporal and fractal analysis of the COPv time series are sensitive measures of the differences between PD and HC and can be used in concert with traditional measures to further benefit clinical analysis, understanding of disease pathology, and development of computer simulation models of postural control in PD.

Acknowledgements

I am deeply thankful to so many for helping me to during my graduate career. Without the advice and direction provided by so many, I would not have succeeded in my efforts.

Although the list is certainly long, I would like to thank a few in particular below:

- Firstly, my wife Carla Fernandez who convinced me to go to graduate school in the first place, and agreed to marry me even after I went. She is truly my most trusted and valued peer who has kept me on track and given me the confidence to tackle ideas I never thought I could. I will always be deeply grateful for her spirit. Thanks Carla!
- Secondly, my advisor, Carl Luchies, who has guided me through this period of my life as a mentor and as a friend. His knowledge and expertise were absolutely critical to this project, and his kindness was absolutely critical to my ability to finish this degree. I am immensely grateful to the patience and understanding he has given me.
- My committee members who are an integral part of the research team.
- The individuals with Parkinson's disease and members of the community who volunteered to participate in this study. The research is impossible without their dedication.
- My sisters who have overcome so much and have never given up. They are a constant reminder to me of what a precious gift life is.
- My mother, who first inspired my love for science and my father who has often been my guide through happy and difficult times. My parents have always supported me in every way possible and I am deeply grateful to them.
- My lab mates, Annaria, Molly, Sommer, Corbin, Kaushik, Srisha and Eshwar, whose patience and support provided much more than just engineering expertise.
- My good friend Saman who studied through many classes with me. We enjoyed many good conversations and I will always remember them.
- Laurita for always giving me a place to stay in Lawrence.
- Barron Jackson who first inspired my love for math and went out of his way to see that I learned it.

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Chapter1: Introduction

Background and Motivation

Parkinson's disease (PD) is a neurodegenerative disorder characterized by tremor, rigidity, bradykinesia and postural instability (Bartolić, Šantić, & Ribarić, 2009). PD is caused by a loss of dopamine producing cells in the Basal Ganglia (BG) which can ultimately effect motor planning and motor skills (Centonze, Calabresi, Giacomini, & Bernardi, 1999). While there is no known cure for PD, there are several treatment options, the most popular of which is levodopa, a dopamine delivering drug which is known to ameliorate the symptoms of PD.

Postural instability significantly increases the fall risk of those with PD compared to age matched healthy controls (HC) (Bloem, Grimbergen, Cramer, Willemsen, & Zwinderman, 2001; Dibble & Lange, 2006; Grimbergen, Munneke, & Bloem, 2004). A fall often significantly reduces quality of life since it is often accompanied by extended hospital stays, general wariness of one's balance (Bloem et al., 2001), and depression (Cummings & Masterman, 1999). Current clinical diagnoses and measures of PD severity are not sufficiently sensitive to detect postural instability prior to a first fall or robustly distinguish between severity levels. According to Visser et al, the most accurate clinical measure of postural stability is retropulsion (UPDRS item 30)(Fahn, 1986), where a backward shoulder pull is performed unexpectedly and only once. A two-step recovery from this perturbation is considered to be an abnormal response (Visser et al.). Given the progressive nature of the disease and the often late diagnosis of postural instability, accurate clinical assessment is crucial in order to ensure appropriate treatment or therapy.

Other more quantitative measures of postural stability have focused on postural sway. Center of Pressure (COP) measures such as sway path length, area, range, peak velocity and maximal direction (Schoneburg, Mancini, Horak, & Nutt, 2013; Stylianou, McVey, Lyons, Pahwa, & Luchies, 2011) have been shown to accurately characterize hallmark tendencies in PD

during postural sway. While these measures have proved useful, they assume the COP time series is a stationary signal, however there is growing consensus in the literature which claims that COP is a non-stationary with time varying statistical properties (Carroll & Freedman, 1993; Loughlin, Redfern, & Furman, 2003; Newell, Slobounov, Slobounova, & Molenaar, 1997; Ramdani, Seigle, Lagarde, Bouchara, & Bernard, 2009; Riley, Balasubramaniam, & Turvey, 1999; Schumann, Redfern, Furman, el-Jaroudi, & Chaparro, 1995). While this knowledge does not necessarily refute conclusions drawn from stationary analyses, it does suggest that there is a potential wealth of data hidden in the non-stationary structure which could further describe the postural instability of PD.

Previous research has also indicated that velocity is an important characteristic of postural sway that distinguishes PD from HC (Stylianou et al., 2011). Other studies have pointed to a control model of postural sway that is based on intermittent velocity based control (Delignières, Torre, & Bernard, 2011; Jeka, Kiemel, Creath, Horak, & Peterka, 2004). Delignières et al. used Detrended Fluctuation Analysis (DFA) as introduced by Peng et al. (Peng, Havlin, Stanley, & Goldberger, 1995) to describe the power law scaling behavior of the COP velocity time series (COPv). It was shown that the bi-logarithmic plot of fluctuation vs. time scale exemplified crossover behavior consistent with open loop and closed loop control (Collins & De Luca, 1993). Taken together and based on this literature, we can consider postural sway to be an intermittent velocity based control process with both open loop (reflexive) and closed loop (somatosensory feedback) structures.

Specific Aims

The purpose of this study was to test the sensitivity of system parameters of the COPv time series to pre-clinical PI in PD, the progression of PI due to PD progression, and ultimately fall risk using DFA. We hypothesize that both short term and long term scaling behavior will be modulated by PD vs. HC and by PD progression. A secondary goal of this study is to investigate the implications the scaling behavior has on postural control as suggested by Collins et al.(Collins & De Luca, 1993). Further understanding of the controls system may not only benefit clinical assessment of PD, but may also help with the development of a computer simulated model of postural sway.

Thesis Content

This document contains four chapters. Chapter 1 contains an introduction to the field of study. Chapter 2 contains a detailed background of relevant literature on which the current study stands. Chapter 3 contains a manuscript of the background, motivation, methods, and results of the study on the effectiveness of fractal analysis in identifying clinically significant scaling behavior of the non-stationary Center of Pressure velocity time series. Chapter 4 summarizes the current study and makes recommendations for future directions.

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Chapter 2: Background

Parkinson's Disease: Symptoms and Behavior

Parkinson's disease (PD) is a neurodegenerative disease which affects 1-2% of people over the age of 60, which is an estimated 5 million people throughout the world (1 million in the USA). With the currently aging population it is expected that these numbers will increase (Olanow, Stern, & Sethi, 2009). PD has a significant negative effect on the daily lives of those who suffer from it, especially in the context of motor tasks and motor planning. The disease is characterized by tremor, rigidity, bradykinesia and postural instability (Bartolić, Šantić, & Ribarič, 2009; Kerr, Morrison, & Silburn, 2008). Disease severity largely determines quality of life experienced by those with PD as stability and mobility become impaired. A significant decrease in quality of life accompanies an increase in fall risk, with falls occurring more often in people with PD compared to age matched controls (Dibble & Lange, 2006; Grimbergen, Munneke, & Bloem, 2004) (Bloem, Grimbergen, Cramer, Willemsen, & Zwinderman, 2001). Falling can culminate in long term hospital care and decreased mobility due to injuries sustained. There is also a significant mental effect that comes from no longer trusting one's balance after a fall (Bloem et al., 2001), which is compounded by an up to 90% depression rate in those with PD (Cummings & Masterman, 1999; Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008) . It can be very disconcerting to no longer be able to trust one's own balance, which can lead to fearful behavior that further limits mobility beyond what may actually be dictated by physiological symptoms.

There is no known cure for PD, and as such therapies focus on mitigating the symptoms of PD in order to improve the quality of life for those afflicted. While there are a large number of caring and skilled individuals who contribute greatly to the care of those with PD, current clinical diagnosis and objective measures of PD severity fail to adequately characterize the

disease or robustly distinguish between severity levels. Clinicians are highly skilled at experience driven PD level assessment, however the tasks that lead to severity level scores are largely subjective and lack the quantitative data that accompany many scientific assessments in modern medicine.

The Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn, 1986) and Hoehn and Yahr (H&Y) (Hoehn MM, 1967) are the two methods currently used to assess PD severity. UPDRS involves four scoring stages: 1) Mentation, behavior and mood; 2) Activities of daily living; 3) Motor examination; and 4) Complications of therapy. The first two and the fourth are written questions which must be completed by the patient and the third stage is a clinical assessment of various motor capabilities that encompass many aspects of movement, expression and speech.

H&Y is a more targeted assessment of postural stability consisting of 0-5 severity levels as seen below:

0. No symptoms
1. Unilateral involvement only, usually with minimal or no functional disability
bilateral involvement, without impairment of balance
2. Bilateral or midline involvement without impairment of balance
3. Bilateral disease: mild to moderate disability with impaired postural reflexes;
physically independent
4. Severely disabling disease; still able to walk or stand unassisted
5. Confinement to bed or wheelchair unless aided

As can be seen, while the scales are descriptive, they lack the sensitivity that would be required to quantitatively describe the complex progression of a neurodegenerative disease.

Postural instability is one of the most quality of life threatening symptoms of PD since it is most closely linked with fall risk. However, it is a complex issue that is affected by the other hallmark PD symptoms as well (bradykinesia, rigidity, and tremor). In a cross sectional reliability and validity study, Visser et al. found that the most reliable test for postural instability in PD is the unexpected shoulder pull (UPDRS item 30), executed once. If the subject takes two steps backward to recover, it is considered an abnormal response (Visser et al.). While this coarse measure may be capable of identifying a person with moderate Parkinsonian symptoms, it is unlikely that it is sensitive enough to distinguish small changes associated with the onset of postural instability that happens during PD progression. Furthermore, the likelihood that this measure would distinguish between PD and other diseases which cause postural instability is unknown. Sensitive, accurate and reliable measures of postural instability are needed in clinical assessments of PD in order to assess fall risk and to justify introducing an intervention to reduce fall risk.

While there is no known cure for PD, there are several treatments that successfully ameliorate PD symptoms. The most common is levodopa, although deep brain stimulation is also used in advanced cases. PD is thought to be caused by a dopamine deficiency in the substantia nigra (SNc) of the basal ganglia (BG). The main effect of this deficiency is decreased stimulation of the motor cortex (Centonze, Calabresi, Giacomini, & Bernardi, 1999). The BG is associated with both motor control and cognitive function depending on the connectivity considered (Middleton & Strick, 2000). Levodopa provides a dose of the missing dopamine and effectively reduces the severity of PD symptoms. Studies show that patients *on* vs. *off* levodopa exhibit

significantly different postural and tremor behavior, indicating the effectiveness of the medication (Morrison, Kerr, Newell, & Silburn, 2008; Rocchi, Chiari, Cappello, & Horak, 2006). However, PD patients *on* levodopa still exhibit parkinsonian tendencies in postural sway when compared to age matched, healthy controls (HC) (Beuter, Barbo, Rigal, & Blanchet, 2005). Levodopa treatment may mask changes caused by PD, compared to HC, during postural instability assessment. Allowing patients to maintain a regular dosing schedule is easier on patients. Thus clinical measures of postural instability that do not require patients to go off levodopa and still distinguish PD related deficits should be pursued.

Parkinson's Disease and Center of Pressure

The effect of PD on postural stability during postural sway is well documented in the literature (Bartolić, Pirtošek, Rozman, & Ribarič, 2005; Kerr et al., 2008; Morrison et al., 2008). One common measure that provides robust contrast between PD and HC during postural sway is the Center of Pressure (COP) (Schmit et al., 2006). Through calculations involving the forces and moments exerted on the floor by the base of support (feet), the resultant COP is the point location of the resultant force of the feet during stance. The COP can be viewed as the neuromuscular response to fluctuations in the COM. COP can be measured by having someone stand on a force plate or an array of force plates in quiet stance. COP in the x-y plane can be calculated using the following equations:

$$COP_x = \frac{M_y + F_x \times d_z}{F_z}$$

$$COP_y = \frac{M_x + F_y \times d_z}{F_z}$$

where COP_x is the COP position in the x direction, COP_y is the COP position in the y direction, F_x and F_y are the forces parallel to the top of the force plate, F_z is the force normal to the force plate, M_x and M_y are the moments parallel to the force plate and d_z is the distance below the surface of the force plate at which the origin is located.

COP is also indicative of the postural control system which provides sensory input from visual, somatosensory and vestibular systems (Mancini et al., 2011; David A Winter, Patla, & Frank, 1990). Many studies have focused on COP parameters in an attempt to accurately characterize hallmark tendencies of PD during postural sway for use in a clinical setting, such as sway path length, area and range (Stylianou, McVey, Lyons, Pahwa, & Luchies, 2011), as well as velocity and maximal direction (Schoneburg, Mancini, Horak, & Nutt, 2013) (Rocchi et al., 2006). These studies report larger sway path length, larger sway area and range and larger velocity in the COP of PD subjects when compared with age matched HC. It is relatively intuitive to believe that postural instability in PD could lead to such findings, however there is an argument for postural control being a function of stability alone without consideration for sway minimization (T. Kiemel, Zhang, & Jeka, 2011). Kiemel et al. argue that control models which minimize muscle activation better predict characteristics of postural sway than those which seek to minimize sway.

Other hallmark PD symptoms have been shown to affect COP as well. Sasagawa et al. report the effect of hip motion during quiet standing as having a substantial effect on body kinematics (Sasagawa, Ushiyama, Kouzaki, & Kanehisa, 2009). Increased rigidity that comes with PD could reduce or eliminate hip joint movement which would, in turn, lead to a more unstable system. Kerr et al. also show the effect of limb tremor on postural sway. Coherence analysis of COP signals for PD participants *on* and *off* levodopa show a significant coupling

between a 4-7 Hz tremor in an extended limb and a 4-7 Hz peak in the spectral analysis of COP (Kerr et al., 2008). The results show the potential effect of tremor on sway dynamics. Despite observed differences between COP parameters in PD and HC, the sensitivity of these measures has not been shown to distinguish between severity levels in PD or to distinguish early postural instability in PD, compared to HC.

In addition to the clinical significance of COP parameters that distinguish PD and HC, these very parameters may be a window into the differences in neural control of postural stability between the two groups. Consideration of differences in control parameters could potentially be useful in a clinical setting, but may also shed light on the specific regions of the brain or physiological operations that are affected by PD. Bartolić et al. studied tremor amplitude as an effect of activity and synchronization of central oscillators in the BG (Bartolic, Pirtosek, Rozman, & Ribaric, 2010). The results showed that the reduction in tremor amplitude widened the spectrum of tremor frequency in rest tremor, and vice versa. Subjects with PD were tested without medication where a clinically visible hand rest tremor was evident. Amplitude and frequency of tremor were monitored in real time for the duration of the test. At the beginning of the test, amplitude was high and frequency had a small bandwidth. The subjects were given apomorphine (APO), which is a drug that is known to dramatically and quickly reduce or eliminate parkinsonian tremor, and the tremor amplitude dropped to nearly zero while the frequency spectrum increased significantly in bandwidth. Once the drug lost effectiveness the amplitude increased again and the frequency bandwidth decreased dramatically. The results suggest that increased amplitude of tremor is a product of synchronization and activity of central oscillators in the BG, whereas dopaminergic effects are seen to de-couple the synchronicity.

Vaillancourt et al. extended this research by showing that the effect of synchronization can be seen in PD subjects who have no clinical signs of PD tremor in postural finger, postural hand and resting hand positions (Vaillancourt & Newell, 2000). They compared finger accelerations and EMG activity between mild to moderate PD subjects and HC. Through a measurement of approximate entropy (ApEn), which shows the regularity of a time series, it was demonstrated that PD tremor is more regular than physiological tremor in HC. It is suggested that this increased regularity comes from greater motor unit synchrony and reduction in neuronal activity consistent with loss of independent sources of control in PD.

While the previous studies focused on limb tremor in PD, Morrison et al. extended the research to postural sway. An experiment was developed and performed to compare postural limb tremor time series structure with that of postural sway in HC controls vs. age matched PD patients *on* and *off* medication. They also used ApEn to measure the regularity of the data. The results confirmed previous ApEn results in postural tremor between PD and HC (i.e. there is greater regularity in PD data), but also revealed the opposite effect in postural sway. PD subjects displayed greater ApEn and, thus, less regularity in postural sway when compared to HC. This phenomenon is attributed to the fact that there is coupling between limb tremor and postural sway and, as such, postural sway in PD represents the additive effect of the normal sway pattern coupled with the postural tremor. Morrison et al. went on to show that there is a lack of inter-limb tremor relation in PD, which implies that the coupling between postural tremor and postural sway is likely a result of neural control signals rather than mechanical wave transmission. This implication highlights the effect PD has on the postural control system through alteration of control commands or parameters involved in postural control, not merely as an additive effect of symptom based mechanical transmission throughout the body. This means that the differences

witnessed in COP parameters between PD and HC as well as the documented symptom of postural instability in PD is not merely a collection of effects driven by bradykinesia, tremor or rigidity, but a fundamental deficit or change in control properties governing postural sway.

Non-stationarity of COP

In many of the previously mentioned studies, COP parameters have been a significant indicator of PD postural dynamics vs. HC postural dynamics, however little consideration has been given to the fact that sway is a time series and not a constant measure that can be averaged across trials without unwanted filtering of potentially valuable information. There has been much documentation on the non-stationary nature of postural sway (Carroll & Freedman, 1993; Loughlin, Redfern, & Furman, 2003; Newell, Slobounov, Slobounova, & Molenaar, 1997; Ramdani, Seigle, Lagarde, Bouchara, & Bernard, 2009; Riley, Balasubramaniam, & Turvey, 1999; Schumann, Redfern, Furman, el-Jaroudi, & Chaparro, 1995). A non-stationary signal is considered to be one which has time varying statistical properties (e.g. mean and standard deviation). The reality of COP as a non-stationary signal casts doubt on many of the traditional measures taken to characterize postural sway or at least forces a re-evaluation of the conclusions drawn from these measures. Reducing a non-stationary signal to a single characteristic value is the equivalent of filtering out all signal sources except one and expecting that measure to characterize the process. Although great strides have been made in understanding postural sway and particularly postural sway deficits in diseased states using these methods, the knowledge of the non-stationarity of COP allows researchers to investigate COP not merely as a stochastic entity, but as a highly sophisticated time series output of postural control, the fluctuations of which hold important information regarding system properties and control structure.

COP Velocity

While many studies have investigated the non-stationary properties of COP position (Loughlin, Redfern, & Tacer, 1996; Sabatini, 2000; Schumann et al., 1995; Tacer & Loughlin, 1998), few have investigated COP velocity as a non-stationary time series and, to the best of our knowledge; none have investigated this in PD. Furthermore, it is known from the previously mentioned studies which performed stationary analysis of COP with traditional measures that COP velocity is a good differentiator between PD and HC. From this point on, “COP time series” will be used to refer to non-stationary COP analysis.

Ramdani et al. investigated the entropy of the COP velocity time series in eyes open (EO) and eyes closed (EC) conditions of young healthy subjects (Ramdani et al., 2009). Statistically significant effects were seen between the two conditions, indicating a change in the organized quality of information when there is no visual feedback. Jeka et al. also report that between position, velocity and acceleration feedback, velocity is the most sensitive form of information in postural sway feedback control (Jeka, Kiemel, Creath, Horak, & Peterka, 2004). Further studies echo this conclusion that velocity information is the most accurate in postural control and offer several different control models that display similar behavior to experimental data and highlight the importance of velocity feedback (Tim Kiemel, Oie, & Jeka, 2002). There is also much evidence in the literature to suggest that postural control can be modeled as an inverted pendulum (Gage, Winter, Frank, & Adkin, 2004; Gawthrop & Wang, 2006; D. A. Winter, 1995), although there is some discussion about the number of segments necessary to construct an accurate model (Pinter, Van Swigchem, van Soest, & Rozendaal, 2008; Sasagawa et al., 2009).

Thus far we have shown that the literature supports COP as a non-stationary time series, that postural sway can be modeled as an inverted pendulum and that COP velocity can be

considered the most accurate and sensitive feedback delivered to the neural controller. Furthermore we have shown that certain conditions, such as EO vs. EC, as well as neurological disorders, such as PD, can alter the control properties of the postural sway dynamics by increasing traditional COP parameters when compared with HC (assuming stationary signals) and by altering the complexity of the COP time series data. Delignières et al. extended the assertion that velocity feedback information is the most accurate and sensitive by arguing that postural sway is really a process governed by velocity based, intermittent control (Delignières, Torre, & Bernard, 2011). They argue that a transition from persistent to anti-persistent correlations in the COP velocity time series indicate a bounded interval over which velocity based control operates using a fractal method of analysis called Detrended Fluctuation Analysis (DFA). They also compare these results to a Stabilogram-Diffusion Analysis (SDA) used by Collins et al. (Collins & De Luca, 1993) and a modified version of Spectral Analysis.

The results from all three were consistent in showing that velocity, not position, are instrumental in postural control. Delignières et al. also introduced a new type of velocity measure called Average Absolute Maximal Velocity (AAMV). This measure is similar to a traditional COP measure in that it averages across the time series, however it is different in that it splits the time series into n segments, takes the average of the rectified peaks of each segment, then takes the grand average of all the n segment averages of peak velocity. In this way the non-stationary aspect of the COP velocity time series is somewhat accounted for when compared to reporting the average velocity or the maximum velocity as with traditional measures previously discussed. In their study, Delignières et al. showed with statistical significance that AAMV increases with age and in the absence of vision. To the best of our knowledge, neither AAMV nor DFA have been applied to the COP velocity time series of PD.

Fractal Analysis of Physiological Systems

Recent advances in understanding of fractal methods have revealed that there is strong evidence for the existence of fractal structures within physiological processes. There are two types of discretely sampled pure fractal signals: 1) fractional Gaussian noise (fGn) and 2) fractional Brownian motion (fBm) where fGn is considered to be a stationary signal and fBm is considered to be non-stationary. These signals are often defined by a power law scaling parameter, the Hurst exponent (H). The power law scaling equation is in the form:

$$SD(\Delta x) \propto \Delta t^H$$

where $SD(\Delta x)$ is the variance of displacement of the time series and Δt^H represents the power law scaling of various time scales with H being the Hurst exponent (Delignières et al., 2011).

Often physiological signals are viewed as random and summary statistics such as mean and standard deviation are considered to be a good description of the witnessed phenomenon. There is growing evidence that physiological systems that may look random in fact display self-similar characteristics that lend themselves better to fractal analysis methods (Eke et al., 2000). Fractal methods are also superior to spectral analysis in the case of self-similar time series because they are capable of handling non-stationary as well as stationary signals. Fractal analysis allows researchers to view a system as its properties change over time. As Delignières et al. points out (Delignieres et al., 2006), this has been used in many different fields of physiological research for processes which have long been considered to be stationary such as self-esteem (Delignières, Fortes, & Ninot, 2004), finger tapping (Gilden, Thornton, & Mallon, 1995), and, as previously mentioned, COP displacement and velocity in upright stance (Collins & De Luca, 1993; Delignières et al., 2011). Glenny et al. offer an in depth review of the various applications

and methods of fractal analysis to physiology (Glenny, Robertson, Yamashiro, & Bassingthwaigte, 1991). Most importantly, fractal analysis is useful to physiology in that it describes the temporal or spatial correlations in the irregularity of physiological systems rather than simply treating the irregularity as randomness.

Peng et al. first introduced Detrended Fluctuation Analysis (DFA) as a way to analyze the fluctuations of the interbeat intervals of the heart in healthy and diseased patients. The interbeat interval time series is a highly irregular process that is known to be non-stationary. Through this analysis, they were able to characterize statistical differences in the scaling behavior over short and long ranges between healthy hearts and those with congestive heart failure using the Hurst exponent (H). This analysis is meant to extend the classical random walk analysis (Peng, Havlin, Stanley, & Goldberger, 1995). (The classical random walk analysis is used by Collins et al. to investigate COP position time series (Collins & De Luca, 1993)). In this analysis, a crossover point was witnessed in the bi-logarithmic plot of fluctuation vs. scale where H changed significantly for short range vs. long range. A Hurst exponent from $0.5 < H < 1$ is considered to be fBm while a Hurst exponent from $0 < H < 0.5$ is considered to be fGn in when using DFA. The crossover in Peng et al. exhibited opposite behavior for healthy vs. diseased hearts. For healthy hearts, H changed from 1.5 to 1, while for diseased hearts H changed from 0.5 to 1.3.

DFA has also been applied to the COP trajectory and the Hurst exponent calculated for HC vs. PD subjects in a study conducted by Stylianou et al. (Stylianou et al., 2011). In this study, the COP position time series was used to classify the Hurst exponent between the two groups. Results showed a statistical difference between HC and PD in both anterior-posterior (AP) and medio-lateral (ML) directions and in eyes opened and eyes closed conditions. The study did not

strike different degrees of PD severity, but compared a group of PD subjects with young HC and age matched HC. No crossover phenomenon were found.

Delignières et al. showed that DFA could be applied to the COP velocity time series (Delignières et al., 2011). In this analysis, the same crossover phenomenon witnessed by Peng et al. was witnessed in the COP velocity time series. This suggests that the COP velocity scales differently in the short range than in the long range. In fact, H in the short range resembles fBm and H in the long range resembles fGn. This implies that short range COP velocity is non-stationary and long range COP velocity is stationary. Furthermore, it shows that long range COP velocity is anti-persistent; meaning the evolution of the series reverses direction at some upper and lower limit. Delignières et al. go on to argue that this implies intermittent velocity based control for postural sway since there is a threshold boundary at which the signal reverses direction, there must be a control scheme driving this reversal. DFA for COP position does not yield these bounded results, rather there is no crossover phenomenon and H remains fBm. This is consistent with a random walk model (Stylianou et al., 2011).

Limitations to Fractal Analysis

Although the value of fractal analysis in physiological systems is evident in the literature, there are some limitations that must be considered. DFA can be sensitive to certain types of non-stationarities as reported by Chen et al. (Chen, Ivanov, Hu, & Stanley, 2002). The first point of concern is signals with data missing which must be patched together, the second is data with random spikes and the third is data with different properties at different times. While these non-stationarities can cause problems if they are not considered in the analysis, they do not render the method useless and should be dealt with in accordance to the recommendations proposed by

Chen et al. As is true with all computationally heavy analysis, great care should be taken to logically and intentionally define all parameters used to obtain analysis results. With proper attention to detail, correct and meaningful conclusions can be drawn as seen in the literature previously mentioned.

Summary

Parkinson's disease (PD) is a debilitating, neurodegenerative disease that, among other things, causes postural instability. The most significant impact of postural instability on quality of life is fall risk, which is linked with extended hospital stays, large economic costs, and demobilizing fear. While clinical methods of PD diagnosis and severity assessment are used with great skill and accomplishment by clinicians, they fail to adequately indicate fall risk and how it relates to disease progression. Furthermore, traditional measures of postural sway assuming a stationary COP signal are inadvertently filtering valuable system information which could be used to improve clinical assessment or understand the underlying control scheme which governs postural stability. Fractal methods of analysis have been shown to be relevant to physiological systems, including COP measurements, and are capable of robustly describing non-stationary processes. While COP position is most often studied, COP velocity has been shown to be more important to postural control and, through traditional measures, has been shown to distinguish PD from HC. To the best of our knowledge, fractal methods have not been applied to COP velocity in PD.

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Chapter 3: Study

Abstract

Background: Postural instability (PI) is a hallmark symptom of Parkinson's disease (PD) with associated decreases in quality of life, largely due to falls. No current clinical method exists which is sensitive enough to detect and accurate enough to quantify PI as PD progresses. Assessment of postural control through the quantitative analysis of the Center of Pressure (COP) time series has been proposed as a solution to this unmet need. This study investigates the use of the fractal behavior of COP velocity (COPv) in mild and moderate PD and age-range matched healthy controls to quantify the development of PI.

Methods: Data were analyzed from a previous study that measured quiet postural sway in mild PD (n=13), moderate PD (n=10) and age-range matched healthy controls (n=21) in eyes open (EO) and eyes closed (EC) conditions. Foot to floor reaction forces and moments were measured to calculate COP and COPv. The following parameters were determined: the COPv power law scaling exponents and associated crossover index using Detrended Fluctuation Analysis (DFA), the Absolute Average Maximal Velocity (AAMV) and Approximate Entropy (ApEn). ANOVA was used to determine the effects of group, condition, and group*condition on all parameters.

Findings: Scaling behavior showed significant group effects in the short term and condition effects in the long term in PD-Mo versus HC. Absolute Average Maximal Velocity (AAMV) was significantly higher in PD-Mo versus HC. ApEn had no significant effect.

Interpretation: Velocity information is an important part of postural control and a sensitive measure of PD versus HC. AAMV has clinical value as it shows group and condition effects. Fractal analysis identifies group and condition effects in short and long term scaling behavior respectively. Given the proper study power, these measures could be useful as a clinical assessment tool of early PD, disease progression and fall risk.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by tremor, rigidity, bradykinesia and postural instability (Bartolić, Šantić, & Ribarić, 2009). Postural instability (PI) significantly increases the fall risk of those with PD compared to age matched healthy controls (HC) (Bloem, Grimbergen, Cramer, Willemsen, & Zwinderman, 2001; Dibble & Lange, 2006; Grimbergen, Munneke, & Bloem, 2004). A fall can significantly impact quality of life since it is often accompanied by extended hospital stays, general wariness of one's balance (Bloem et al., 2001), and depression (Cummings & Masterman, 1999). PD is caused by a loss of dopamine producing cells in the Basal Ganglia (BG) which can ultimately effect motor planning and motor skills (Centonze, Calabresi, Giacomini, & Bernardi, 1999). While there is no known cure for PD, there are several treatment options focused on symptom management, the most popular of which is levodopa, a dopamine delivering drug which is known to ameliorate PD symptoms.

Given the progressive nature of the disease and the often late diagnosis of postural instability, accurate clinical assessment is crucial in order to ensure a timely and appropriate treatment or therapy. The most accurate clinical measure of postural stability is retropulsion (UPDRS item 30), where a backward shoulder pull is performed unexpectedly and only once (Visser et al.). A two-step recovery from this perturbation is considered to be an abnormal response (Visser et al.). Current clinical diagnoses and measures of PD severity are not sufficiently sensitive to detect the onset of postural instability prior to the first fall or robustly quantify the change in PI as a result of PD progression (increasing trend) or an intervention (decreasing trend).

Other more quantitative measures of postural stability have focused on postural sway. The Center of Pressure (COP) time series is often quantified using measures, such as the total sway path length, area, range, peak velocity and maximal direction (Schoneburg, Mancini, Horak, & Nutt, 2013; Stylianou, McVey, Lyons, Pahwa, & Luchies, 2011), that have been shown to accurately characterize hallmark tendencies in PD during postural sway. While these measures have proved useful, they assume the COP time series is a stationary signal, however there is growing consensus in the literature which claims that COP is a non-stationary signal, meaning statistical properties such as mean and standard deviation (SD) vary with time (Carroll & Freedman, 1993; Loughlin, Redfern, & Furman, 2003; Newell, Slobounov, Slobounova, & Molenaar, 1997; Ramdani, Seigle, Lagarde, Bouchara, & Bernard, 2009; Riley, Balasubramaniam, & Turvey, 1999; Schumann, Redfern, Furman, el-Jaroudi, & Chaparro, 1995). While this knowledge does not necessarily refute conclusions drawn from stationary analyses, it does suggest that there is a potential wealth of information hidden within the non-stationary structure which could further describe the postural instability of PD.

Previous research has also indicated that velocity is an important characteristic of postural sway that distinguishes PD from HC (Stylianou et al., 2011). Other studies have pointed to a control model of postural sway that is based on intermittent velocity based control (Delignières, Torre, & Bernard, 2011; Jeka, Kiemel, Creath, Horak, & Peterka, 2004). Delignières et al. also used Detrended Fluctuation Analysis (DFA) as introduced by Peng et al. (Peng, Havlin, Stanley, & Goldberger, 1995) to describe the power law scaling behavior of the COP velocity time series (COPv). It was shown that the bi-logarithmic plot of fluctuation versus time scale exemplified crossover behavior consistent with open loop and closed loop control (Collins & De Luca, 1993). Taken together and based on this literature, we can consider postural

sway to be an intermittent velocity based control process with both open loop (reflexive) and closed loop (somatosensory feedback) structures.

The purpose of this study is to test the sensitivity of system parameters of the COPv time series to onset of postural instability (i.e. pre-clinical assessment), the postural instability development associated with PD progression, postural instability reduction resulting from a successful intervention, and ultimately the assessment of fall risk using DFA. Power analyses will be performed where necessary on the pilot data in order to determine the number of subjects required to find significance, which provides information that is necessary to design a full scale study. We hypothesize that both short term and long term scaling behavior will be modulated by PD versus HC and by PD progression. A secondary goal of this study is to investigate the implications the scaling behavior has on postural control as suggested by Collins et al. (Collins & De Luca, 1993). Further understanding of the controls system may not only benefit clinical assessment of PD, but may also help with the development of a computer simulated model of postural sway.

Methods

Participants

As reported previously by Barnds et al. (Barnds, 2015), twenty-three patients with PD and twenty-one age matched healthy controls (HC) participated in this study of a postural sway task. The data was compiled from two previous studies which investigated the differences between HC and PD in postural sway (Barnds, 2015; Stylianou et al., 2011). All individuals gave informed, written consent as approved by the University's Institutional Review Board. PD patients were further divided into the two sub-categories of Mild PD (PD-Mi) in which no

postural deficits were apparent and Moderate PD (PD-Mo) in which postural deficits were present. Placement into the two PD groups was based on clinically assessment performed by a movement disorders specialist, as discussed in Barnds et al.

All PD patients were recruited from the University of Kansas Medical Center (KUMC) Parkinson's disease and Movement Disorder Center. All patients who had PD were confirmed by a neurologist specializing in movement disorders (RP). PD participants were able to walk without assistance, were without severe depression (BDI<30/63), dementia (MMSE>24/30), and musculoskeletal or neurologic impairments unrelated to PD, had an H&Y score of 2 (PD-Mi) or 3 (PD-Mo) and had not had neurosurgery for PD. HC participants were recruited from the surrounding community and were without any significant cognitive, musculoskeletal or neurologic impairment.

Task

The task used for this study has been discussed in detail in a previously published paper (Stylianou et al., 2011). Postural sway task details are summarized in the following. Participants wearing standardized footwear were asked to stand on a force plate with naturally selected stance width, with their arms at their side and looking forward. Six trials of data were collected in 30 second epochs. Three trials each of Eyes Opened (EO) and Eyes Closed (EC) conditions were randomly selected for order. PD participants were instructed to maintain their normal medication schedule and were tested *on* medication (mean (SD) time since last antiparkinsonian dosage: 2.1 (1.0) hours).

Experimental Measurements and Data Analysis

Postural sway kinetic data were collected using AMTI six-channel force plates (Advanced Mechanical Technology Inc., Watertown, MA, USA) and sampled at 1000 Hz using

a 16-bit A/D data acquisition system (National Instruments, Austin, TX, USA). Video data were used to ensure subject compliance with postural sway task instructions.

Kinetic data were low pass filtered with a fourth-order, zero phase shift, Butterworth filter with a cut-off frequency of 10 Hz. COP path (COPp) was then calculated in the anterior-posterior (AP) direction and COP velocity (COPv) was calculated with a fourth order accuracy numerical derivative of the COP. COP velocity was then down sampled to 100 Hz. Each participant's set of three trials per condition were concatenated to form a single COPv time series for each condition. This was preferred over averaging across trials since averaging would be a form of filtering the data towards the mean. Whereas, concatenation of similar epochs of an infinite time series (i.e. taken from the same steady state, non-fatigued period) is assumed to have little effect on the structure of the data. The cautions issued in Chen et al. (Chen, Ivanov, Hu, & Stanley, 2002) were considered and followed for data with missing sections. All data analysis was completed using MATLAB (MATLAB, Natick, MA, USA).

Temporal Analysis

Absolute Average Maximal Velocity (AAMV) was used to analyze the temporal aspect of the non-stationary COP velocity time series (Delignières et al., 2011). We calculated AAMV using the following steps with $n = 24$ and $m = 375$:

1. From the COP Velocity, rectify the signal and divide into n divisions of m data points.
2. Find the peaks of each n divisions. This will give you the local maxima for each division.
3. Find the average value of the peaks for each n division. This will give an average maximal velocity per division.
4. Find the average of each of the n averages. This value is the AAMV.

System Order Analysis

Approximate Entropy (ApEn) analysis was used to assess the order/disorder of the time series data (Pincus & Goldberger, 1994; Slifkin & Newell, 1999; Vaillancourt & Newell, 2000). Details of the calculation of ApEn can be found in Pincus et al. and Slifkin et al. ApEn characterizes the regularity of the time series. Two parameters m and r must be set before starting the analysis. We chose $m = 2$ and $r = 0.2$ in accordance with Slifkin et al. The quantity m determines the length of the template and condition vectors to be used, and the quantity r determines the quantity by which the standard deviation of the time series is multiplied to create an acceptable similarity range with the template vector. The process of ApEn calculation is summarized below.

There is considered to be a vector connecting each data point in the time series, such that if there are 1000 points in the series, there are 999 vectors. For each step in the iteration i , each vector in the time series is compared to a template vector $[u(i,), u(i+1)]$. Vectors that fall within the range of similarity determined by $r \times SD$ become conditioning vectors. The number of conditioning vectors found becomes the denominator term B . A third point is considered in the construction of vectors using the second point of the conditioning vectors and the next adjacent point in the series (e.g. if a conditioning vector is of the form $[u(4), u(5)]$ then the vector constructed for this portion of the calculation will be $[u(5), u(6)]$). The number of *these* vectors which still fall within the similarity criterion are recorded as the numerator term A . The ratio A/B is constructed and the absolute value of the log of A/B is reported as the conditional probability that all the vectors in the series will be the same as the template vector. This process is then iterated for the entire length of the series and the average of the conditional probabilities is

reported as the ApEn. This value can range from 0 showing no order, which is apparent in white Gaussian noise, to 1 showing a highly ordered system, which is apparent in a sine wave.

Fractal Analysis

Detrended Fluctuation Analysis (DFA) was performed on the COPv time series as consistent with Peng et al. and Delignières et al. (Delignières et al., 2011; Peng et al., 1995). DFA is a method of analysis that measures the fluctuation of the time series data at specific time scales defined by the user. In the present study, we used a time scale range from 10 ms to the time length of the full data (9000 ms) increasing by 10 ms at each step. DFA is completed in the four steps outlined below and derived from Delignières et al.:

1. Integrate the signal of length N using the equation: $y(k) = \sum_{i=1}^k [B(i) - B_{ave}]$ where $B(i)$ is the i th interval and B_{ave} is the average interval.
2. Divide the integrated time series into non-overlapping boxes of equal length n . Fit a least squares line to the data in the box. This line represents the trend in the box. The y coordinate of the straight line segment is denoted by $y_n(k)$.
3. De-trend the integrated time series, $y(k)$, by subtracting the local trend, $y_n(k)$, in each box.
4. Calculate the root-mean-square fluctuation using the following equation

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [y(k) - y_n(k)]^2}$$

5. Plot $F(n)$ vs. n (fluctuation vs. scale) on a bi-logarithmic plot.

A linear relationship on the fluctuation vs. scale plot indicates a power scaling behavior of the time series. The quantity α represents the slope of the least squares fit regression line relating

$F(n)$ to n on the bi-logarithmic plot. It is analogous to the Hurst exponent (H) in other fractal methods of power law scaling behavior following the equation:

$$SD(\Delta x) \propto \Delta t^H$$

where $SD(\Delta x)$ is the variance of displacement of the time series and Δt^H represents the power law scaling of various time scales with H being the Hurst exponent (Delignières et al., 2011).

As seen in Figure 2 and previously reported in Delignières et al. and Peng et al., there exists two distinct regions of power law scaling in the COPv time series: 1) α_1 - representing the short range time scaling behavior, and 2) α_2 representing the long range time scaling behavior. Both quantities were calculated using a least squares linear fit to the respective portions of the $F(n)$ vs. n plot with a correlation coefficient of at least $R^2 = 0.8$. The Crossover Index (CrI) was calculated as the scale n at which the lines defined by α_1 and α_2 intersect as shown in Figure 2.

Statistical Analysis

A 3-way Analysis of Variance was used to compare effects of Group (HC, PD-Mi, PD-Mo), Condition (EO, EC) and the interaction between group and condition (group*condition) for each of the five analysis parameters (AAMV, ApEn, α_1 , α_2 , CrI). Significance was considered for $p < 0.05$. Post-hoc Tukey-Kramer analysis was used on measures which showed statistical significance ($p < 0.05$) to identify which group comparisons within the ANOVA were driving the main effect differences. All statistical analyses were completed using MATLAB (MATLAB, Natick, MA, USA).

Results

Anthropometric data (age, height and mass) were analyzed in a previous study (Barnds et al.) and no significant differences between groups were reported.

Temporal Analysis

AAMV: Significant main effects were found in groups between HC and PD-Mo and across conditions ($p<0.05$). In EO and EC conditions, PD-Mo had significantly higher AAMV than HC ($p<0.001$). PD-Mi tended to have higher AAMV than HC and lower AAMV than PD-Mo in both conditions; however there was no statistical significance (Table 1, Figure 3). Power analysis revealed the need for a sample size of $n=22$ in order to differentiate between the means of PD-Mi and HC ($p<0.05$), and $n = 25$ for PD-Mi and PD-Mo ($p<0.05$) (Table 2).

System Order Analysis

ApEn: No significant main effects were found, however EO, compared to EC, tended to have higher mean values (Table 1, Figure 4). Power analysis showed the need for sample size of $n >> 200$ for significance (Table 2).

Fractal Analysis

Alpha1: Significant main effects were found in Groups between HC and PD-Mo ($p<0.05$). In EO and EC conditions, PD-Mo had significantly lower α_1 than in HC ($p<0.05$). PD-Mo also had lower α_1 than PD-Mi, but there was no statistical significance. Power analysis revealed the need for a sample size of $n = 194$ to differentiate between PD-Mo and PD-Mi ($p<0.05$) (Table 2). PD-Mi had lower α_1 than HC in both conditions; however there was no statistical significance. Power analysis showed the need for a sample size of $n = 39$ in order to differentiate between PD-Mi and HC ($p<0.5$) (Table 1, Figure 5).

Alpha2: Significant main effects were found in condition ($p<0.05$). EC, compared to EO condition, had significantly lower group means ($p<0.05$). Power analysis showed the need for a sample size of $n = 72$ to differentiate HC from PD-Mo, $n = 56$ to differentiate between PD-Mi and PD-Mo, and $n >> 200$ for HC from PD-Mi. While there was no statistical significant

group*condition interaction effect, condition did appear to have a larger effect on PD-Mo than the other two groups (Table 1 & 2, Figure 6).

CrI: No significant main effects were found. There was a consistent trend in group and condition. EC CrI tended to be lower than EO CrI. The HC CrI tended to be lower than in PD-Mi, with a sample size of $n = 79$ necessary for significance ($p < 0.05$), and the HC CrI tended to be higher than PD-Mo with a sample size of $n = 76$ necessary for significance ($p < 0.05$). PD-Mi tended to have a higher CrI than PD-Mo with a sample size of $n = 22$ necessary for significance ($p < 0.05$) (see Table 1, Table 2 and Figure 7).

Discussion

The purpose of this study was to identify specific system characteristics of the COPv time series for use in clinical assessment of postural instability resulting from PD. More specifically, with the consideration of COPv time series as a non-stationary signal, these measures should provide a higher degree of information density than previous clinical measures (e.g. Retropulsion test) or traditional COPp measures (e.g. sway path, range, peak velocity). This could allow for earlier detection of PD induced postural instability and/or tracking the development of postural instability. As previously stated, fall risk is a major concern for PD patients as it often leads to a significant decrease in quality of life. Quantitative clinical measures would be a very useful tool in identifying those at risk for a fall earlier, and thus in need of therapeutic or compensatory intervention.

The results of this study also have application to the differences in neural control properties of PD vs. HC, especially as it relates to the combination of open and closed loop velocity based control, which is argued to be important in postural sway (Collins & De Luca,

1993). While this knowledge alone may not be a direct measure for use in a clinical setting, it can help to guide future research into computer simulation of Parkinsonian postural sway, which would be a valuable clinical tool in itself.

Temporal Analysis

AAMV proved to be the most clinically significant measure taken, showing significant differences between groups and conditions. The calculation method of the AAMV more accurately reflects the time varying, non-stationary nature of the COP signal in that it more accurately accounts for the time varying mean of the COP trajectory. As PD progression increases, AAMV also increases. Removal of visual feedback also increases AAMV across groups in a fairly uniform manner. It is interesting to note that removal of visual feedback increases the HC AAMV to a value very near the PD-Mi AAMV in the EO condition (Figure 3). Similarly, PD-Mi in the EC condition is comparable to PD-Mo AAMV in the EO.

The increase in AAMV from HC to PD-Mi to PD-Mo is to be expected given the volume of research showing larger sway range, area, and peak velocities as previously mentioned (Rocchi, Chiari, Cappello, & Horak, 2006; Schoneburg et al., 2013; Stylianou et al., 2011). In order to cover more distance in the same amount of time, it is logical to assume that velocity would have to increase, however it is not obvious whether this increase is driven by a trend that persists throughout the entire trial, or several large peak changes in trajectory. The AAMV measure shows that the increase in velocity is consistent over the entire trial duration.

The relative sensitivity of the AAMV calculation offers much potential use to clinical assessment of PD. The pilot nature of this study does not have the power to distinguish between HC and PD-Mi means, but power analysis reveals a feasible sample size in order to gain significance between these two subgroups (Table 2). This shows that AAMV could be a useful

tool in pre-clinical determination of postural instability as well as an indicator of disease progression. AAMV is also a simple calculation which could easily be implemented into clinical instrumentation, allowing for fast results and intuitive interpretations.

AAMV is also considered to be the velocity boundary condition of the controller, assuming intermittent velocity based control (Delignières et al., 2011). A steady increase in AAMV from HC to PD-Mo indicates an increase in the acceptable boundary condition prior to controlled stabilization around a set point. This means, as PD progressives, the velocity of sway is allowed to reach higher values before the system takes corrective action to restore the system toward the fully “upright” configuration. From AAMV alone, it is difficult to speculate what could be causing this change, since the control system is known to have both open loop and closed loop components (Collins & De Luca, 1993; Delignières et al., 2011; Mitchell, Collin, De Luca, Burrows, & Lipsitz, 1995). Furthermore, the effect of condition was consistent across groups which could suggest that visual feedback sensory information is not corrupted in PD.

System Order Analysis

ApEn: The lack of statistical significance in the ApEn analysis between groups and across conditions reveals that, across the groups tested, the regularity of the COPv is similar. There were clearly visible trends; however sample sizes necessary to find significance between the means of groups or across conditions were too large to consider the measure to have much power as a clinical tool. The means fell between 0.5 and 0.6 ($SD \cong 0.05$) (Table 1) which shows a moderate level of regularity in the data when compared to a value of zero which represents white Gaussian noise. The lack of significant difference shows that, although there is evidence for a difference in control strategy between HC and PD in both the literature and in this study, there is still much control occurring at this stage in the disease. The lack of significance could

also be indicative of the fact that the PD groups in this study were individuals who had only moderate postural instability at worst. The ApEn measure may not be sensitive enough to moderate and mild PD to be used successfully as a pre-clinical assessment tool.

Fractal Analysis

Crossover Index: Although there is no statistical difference between groups or between conditions at the current power of the study, the existence of the crossover point is evident from the bi-logarithmic plots (Figure 1). The crossover index (CrI) exists for all subjects and defines the time scale at which the data changes scaling behavior from α_1 to α_2 . The implication of a CrI is that the time series changes scaling behavior at a particular time scale. Clinically speaking, this may not be a useful measure since it is indicative of the exchange of open loop control (short time scale) for closed loop control (long time scale) (Collins & De Luca, 1993), however power analysis does reveal the sample size necessary to distinguish means (Table 2).

The suggestion that CrI indicates transition from open loop to closed loop control is consistent with this study since the CrI occurs between 100-150 ms for all groups. Miall et al. (Miall & Wolpert, 1996) suggests that delays in spinal reflex tasks could be around 30 ms while delays in visually guided feedback tasks could be around 200-300 ms. A CrI between 100-150 ms is consistent with the transition from spinal reflex, or open loop, to feedback guided (with vision or without) closed loop control.

Alpha1: The group differences seen in α_1 are indicative of a change in short range scaling behavior between HC and PD-Mo and between the two PD groups. In fractal analysis of this type, there are two types of classification of time series: fractional Gaussian noise (fGn) ($\alpha < 0.5$) and fractional Brownian motion (fBm) ($\alpha > 0.5$) with $\alpha = 1$ being pure fractional Brownian motion. In EO and EC, $\alpha_1 > 0.5$ for all groups meaning in the short range the data behaves like

fBm. This also suggests positively correlated fBm, meaning each successive value of COP velocity is likely to move in the same direction as the previous value (e.g. if it is increasing it is likely to keep increasing).

Furthermore, increasing severity of PD leads to decreasing values of α_1 with no effect of condition (Figure 8). Since α_1 is considered to be the short term scaling behavior of the series, it is no surprise that loss of visual feedback would not affect the scaling behavior since short term is linked with open loop control. Decreasing values of α_1 are also indicative of a slight move toward fGn compared to higher values of α_1 . This could indicate less positively correlated trends in the scaling behavior which may have unknown effects on system dynamics. Whether this could lead to more postural instability can only be determined analogously since PD groups portray this behavior and are known to have less postural stability. Further analysis is needed to understand the stability effects of decreasing α_1 values on an open loop/closed loop velocity based control inverted pendulum system.

Alpha2: The significant differences in α_2 between the groups and across the conditions without the cross term shows that removal of visual feedback has a common effect across the groups on the longer time scaling behavior of the COP velocity (see Figure 9). This is consistent with the idea that α_2 is indicative of closed loop control, and it is no surprise that removal of one of these feedback sources would move the system behavior more toward pure fGn since less information is being delivered to the controller. What is surprising is the common effect this has on group regardless of diseased state. This is not definitive evidence that loss of visual feedback effects PD and HC alike, but in terms of scaling behavior, there is no measureable difference.

For EO condition, the group means were $\alpha_2 = 0.270$ and for EC condition the group means were $\alpha_2 = .211$ (Table 1), indicating strong evidence for fGn with negative correlations,

meaning each successive value of COP velocity is likely to move in the opposite direction as the previous value (e.g. if it is increasing it is likely to start decreasing). This is also consistent with the behavior of closed loop, intermittent control in steady state behavior.

Combined Effects: The result of the DFA analysis must be considered as a whole and in combination with other measures in order to draw an appropriate conclusion. The α_1 group effect coupled with the α_2 condition effect suggests that PD has a greater impact on the open loop control of the system, and responds similarly to HC during loss of visual feedback. It is important to remember that previous research has indicated the influence other hallmark PD characteristics have on postural instability, such as rigidity and tremor (Kerr, Morrison, & Silburn, 2008; Morrison, Kerr, & Silburn, 2008; Sasagawa, Ushiyama, Kouzaki, & Kanehisa, 2009). Increased rigidity of the biomechanical system could certainly cause a more noise-like characteristic in reflexive, open loop control similar to the high frequency vibration seen in stiff systems in the presence of a perturbation. Tremor has also been shown to have the capability of affecting postural sway in the 4-7 Hz range (Kerr et al., 2008), however it is argued that the effect of tremor on postural sway arises from descending neural control commands and not merely mechanical wave transmission. Neural connectivity and its relation to PD and open/closed loop control is beyond the scope of this paper, however it should be considered in future studies since there is strong evidence for the effect of PD on open loop velocity based control that has not previously been discussed.

Conclusion

The investigation of temporal, organizational and fractal characteristics of COPv as a non-stationary, time varying series yields marked differences in behavior between HC and PD,

even in pre-clinical populations. AAMV proved to be the most clinically significant measure due to the low sample size required to find statistical differences ($p<0.5$) between HC, PD-Mi and PD-Mo, and its relative ease of calculation and interpretation. ApEn showed that there is a common change in the regularity of COPv time series between groups and across conditions, but offered little clinical significance. The fractal method of analysis, DFA, revealed a difference in scaling behavior between groups and across conditions for short time scales indicating a change in open loop control. DFA also showed a common reaction across groups to the removal of visual feedback in the long time scale, indicating similar closed loop control characteristics.

This study serves to show that the traditional treatment of COP as a stationary signal in current clinical methods oversimplifies the complexity data information contained within. In order to develop quantitative clinical assessments of postural instability in PD, accurately track disease progression and effectively detect fall risk, future efforts should focus on the non-stationary analysis of COP. Furthermore, COPv may hold key information related to velocity based control of postural stability that could further benefit clinical analysis, understanding of disease pathology, and development of computer simulation models of postural control in PD.

Limitations: There were limitations to this study which should be considered. Due to the pilot nature of this study, there were a relatively small number of subjects considered. Also, due to natural self-selection of stance width by the subjects on the force plates, the medio-lateral (ML) direction was not considered in the analysis. Further studies should investigate these effects in ML COPv as well, since there is evidence of differences between PD and HC in the ML direction. Since the data was collected in 30 s epochs which were concatenated to form a longer time series, it would also be helpful to collect long samples of data. Longer time series improve the definition of fluctuation analysis, and other aspects of PD vs. HC could be explored,

such as the effect of fatigue on scaling. Lastly, the analyses performed require careful and methodical selection of non-dimensional parameters (e.g. window length in DFA, sample rate of data, vector length in ApEn, etc...). As such, careful consideration of the limitations of these methods should always be applied before usage.

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Table 1: Summary Statistics. Group means and standard deviations for each measure and each condition.

Condition	Group		$\alpha 1$	$\alpha 2$	CrI	AAMV	ApEnt
EO	HC	Mean	1.379	0.261	131.905	9.234	0.592
		STDEV	0.104	0.089	46.327	2.212	0.052
	PD-Mi	Mean	1.315	0.255	152.500	13.476	0.594
		STDEV	0.206	0.111	49.198	5.891	0.073
EC	HC	Mean	1.258	0.308	110.909	22.900	0.591
		STDEV	0.253	0.164	55.037	19.481	0.085
	PD-Mi	Mean	1.427	0.230	116.190	13.937	0.571
		STDEV	0.100	0.095	32.323	5.754	0.055
EC	PD-Mo	Mean	1.413	0.178	131.667	22.333	0.560
		STDEV	0.190	0.102	52.541	14.239	0.069
	PD-Mo	Mean	1.295	0.211	126.364	36.492	0.577
		STDEV	0.233	0.090	61.850	27.506	0.080

Table 2: Tukey-Kramer and Power Analysis for combinations of each possible group.
Either significance is noted (*sig*) or the number of subjects required for significance
($p<0.05$) is noted ($n = \text{'number'}$).

(I) Group	(J) Group	$\alpha 1$	$\alpha 2$	CrI	AAMV	ApEnt
1	2	$n = 39$	$n = 1091$	$n = 79$	$n = 21$	$n = 3532$
	3	<i>sig</i>	$n = 72$	$n = 76$	<i>sig</i>	$n = 14128$
2	1	$n = 39$	$n = 1091$	$n = 79$	$n = 21$	$n = 3532$
	3	$n = 194$	$n = 56$	$n = 22$	$n = 25$	$n = 1570$
3	1	<i>sig</i>	$n = 72$	$n = 76$	<i>sig</i>	$n = 14128$
	2	$n = 194$	$n = 56$	$n = 22$	$n = 25$	$n = 1570$

**sig* indicates significant difference between groups at the current power

** $n = \text{"number"}$ indicates the required sample size for significance

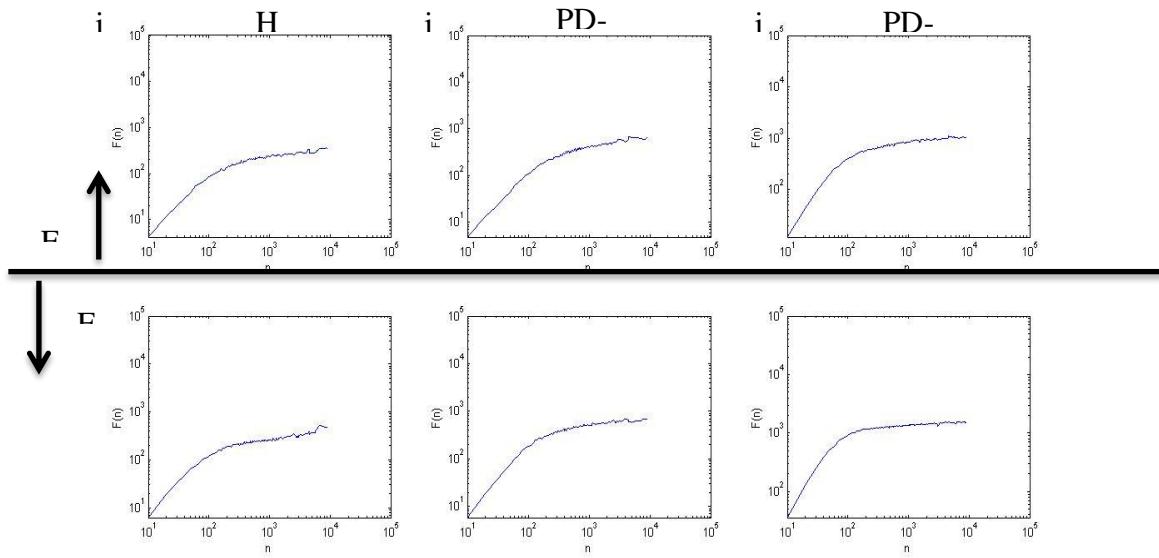


Figure 1: Fluctuation vs. scale. A typical fluctuation vs. scale plot for each group (i) HC, ii) PD-Mi, iii) PD-Mo) in both condition conditions (EO, EC).

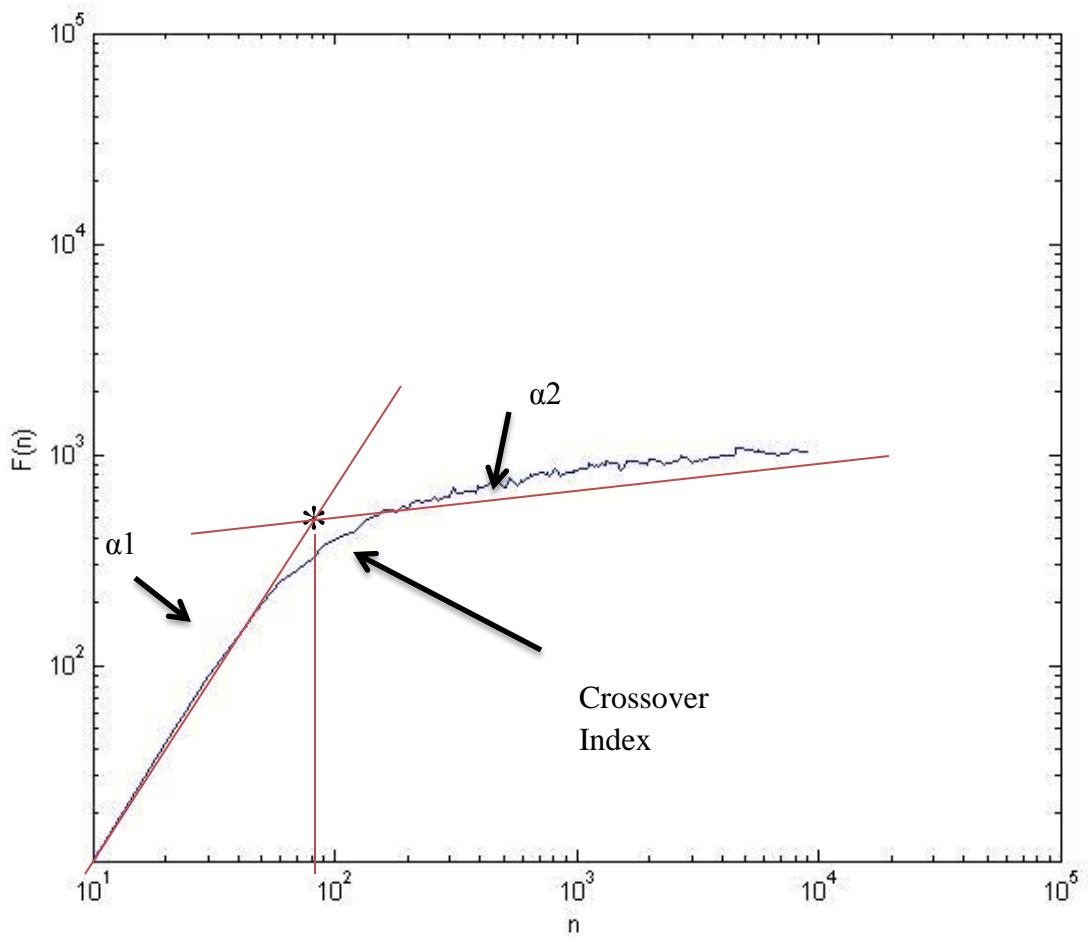


Figure 2: Construction of α_1 , α_2 and CrI from a fluctuation vs. scale plot.

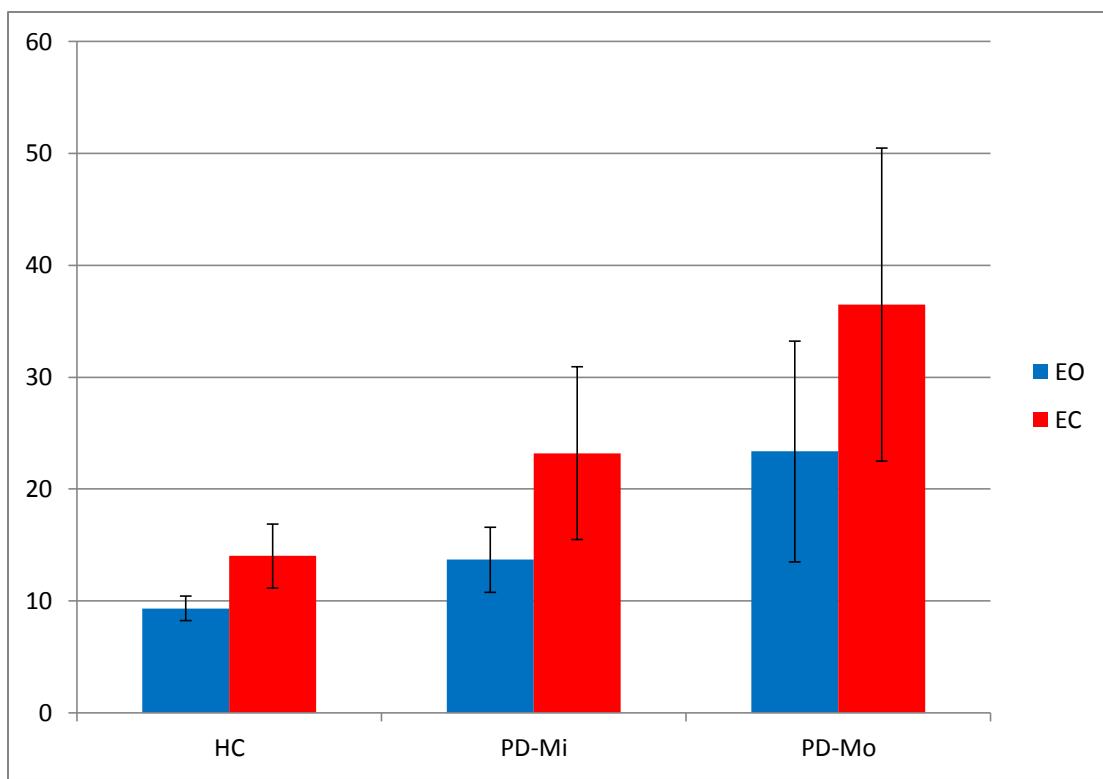


Figure 3: Bar plot of the means and standard deviations of AAMV results by group and condition.

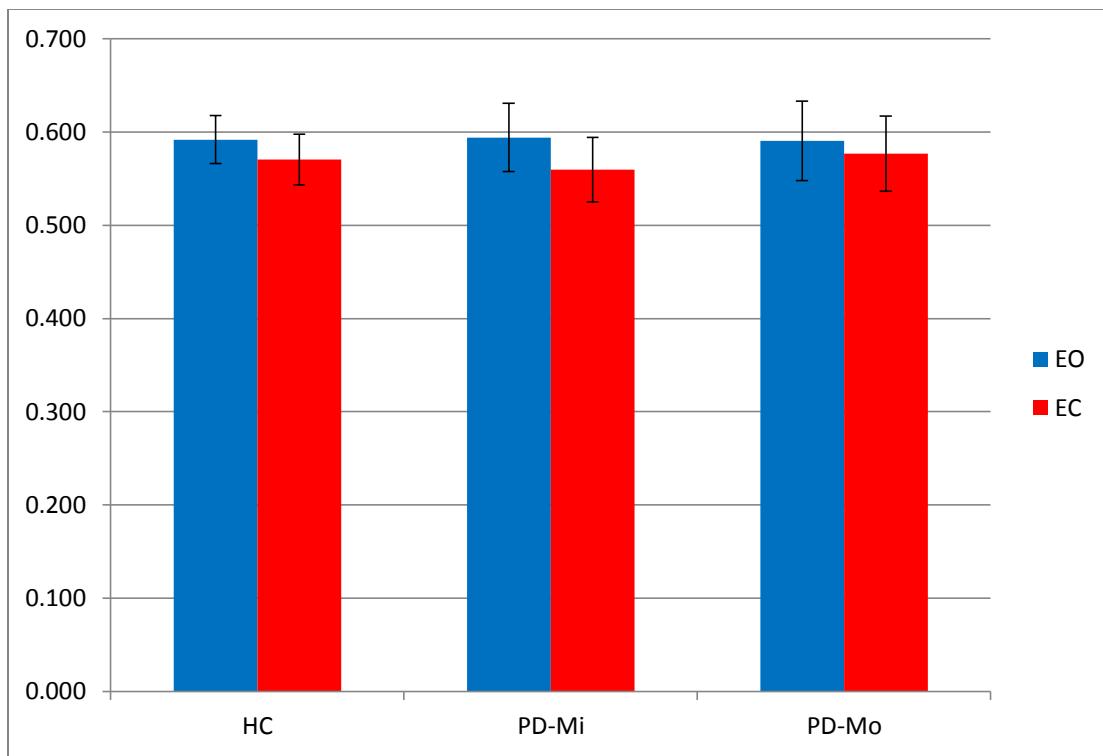


Figure 4: Bar plot of the means and standard deviations of the ApEn results by group and condition.

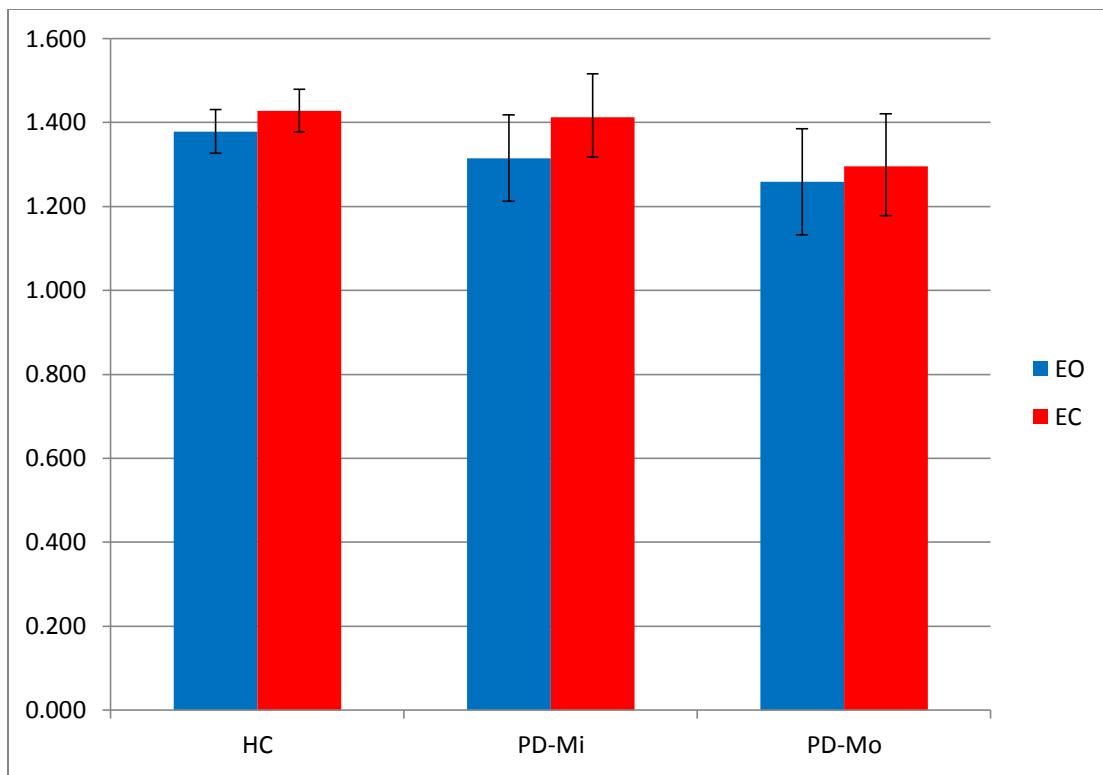


Figure 5: Bar plot of the means and standard deviations of the Alpha1 results by group and condition.

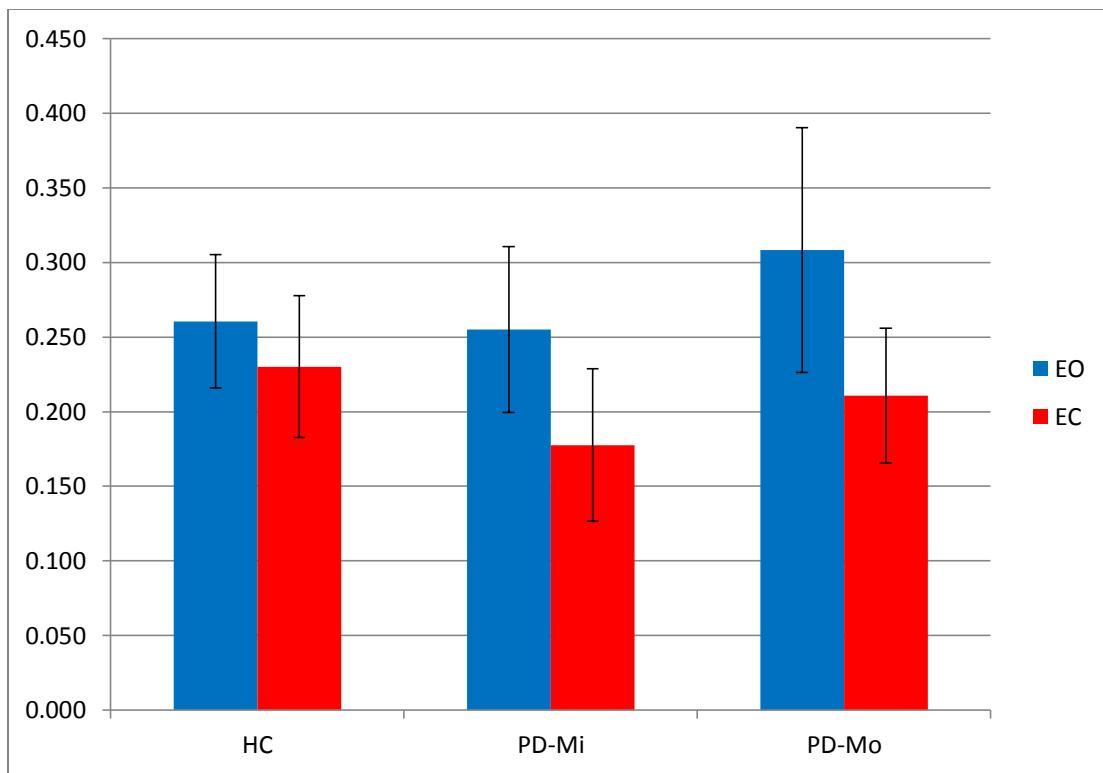


Figure 6: Bar plot of the means and standard deviations of the Alpha2 results by group and condition.

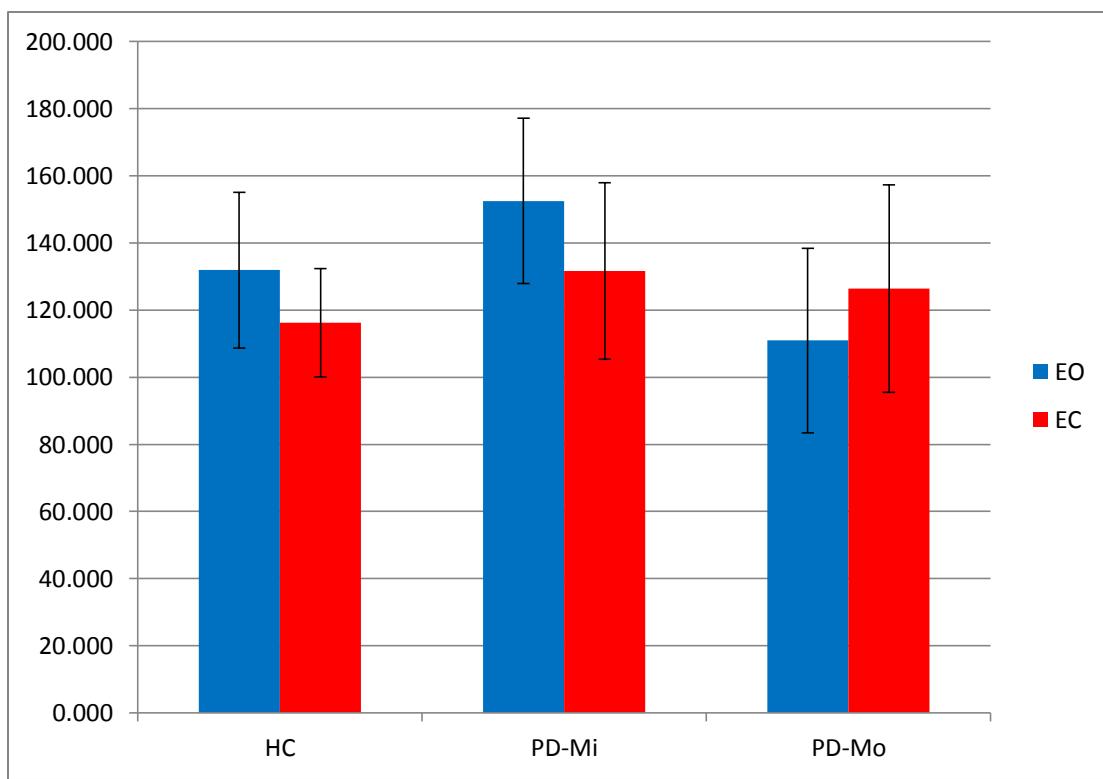


Figure 7: Bar plot of the means and standard deviations of the CrI results by group and by condition.

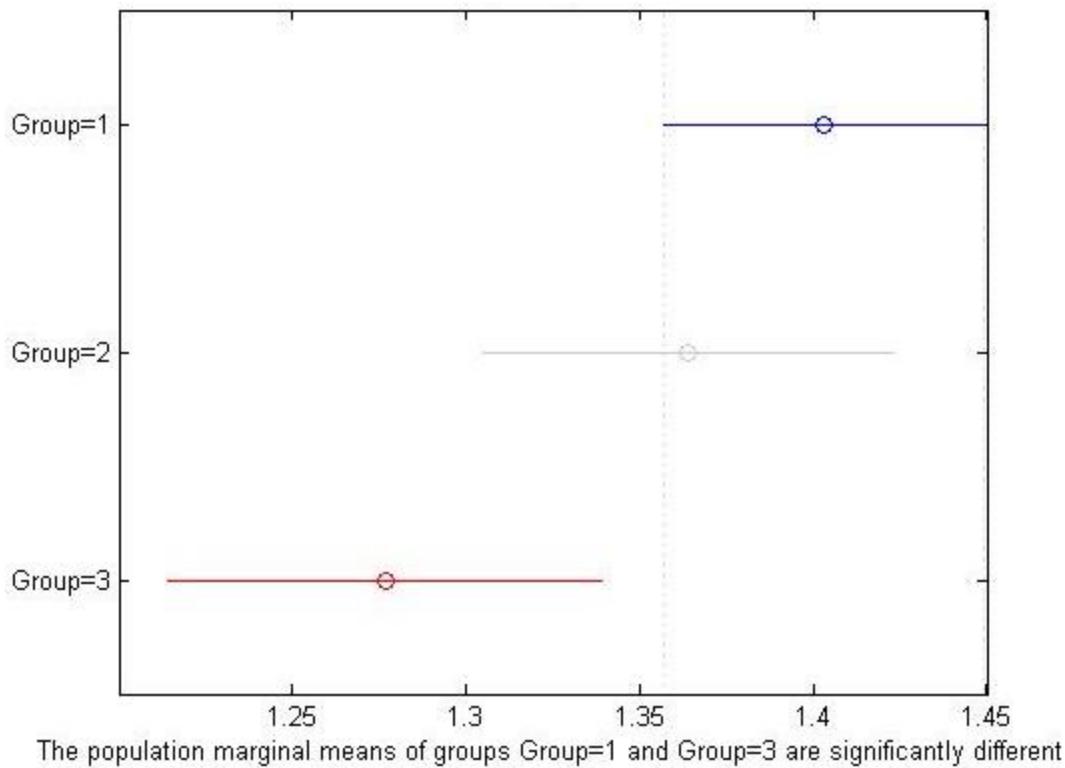


Figure 8: A multiple comparison Tukey-Kramer plot of the mean and standard deviation showing group significance for Alpha1. Group=1 is HC, Group=2 is PD-Mi and Group=3 is PD-Mo. The plot shows significant difference between HC and PD-Mo.

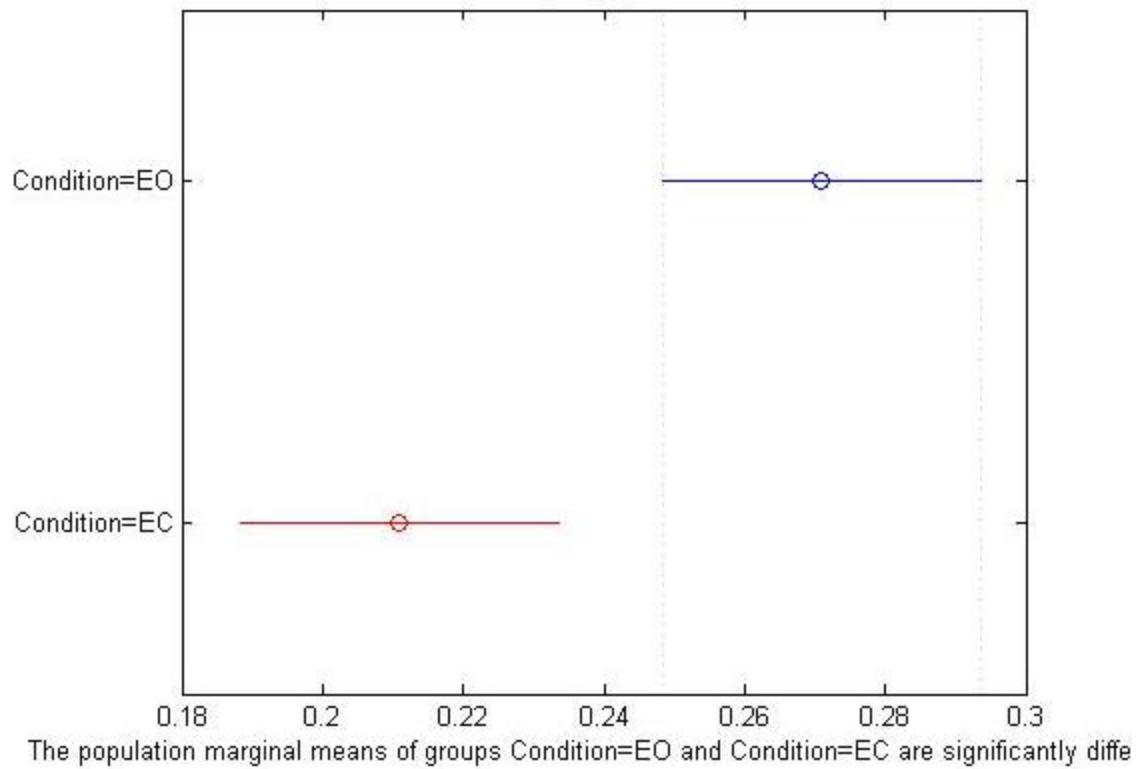


Figure 9: Multiple comparison Tukey-Kramer plot of the mean and standard deviation showing condition significance for Alpha2. The plot shows that the two conditions are significantly different from one another.

Chapter Four: Summary

Summary of Study

The purpose of this study was to test the sensitivity of system parameters of the Center of Pressure velocity (COPv) time series to pre-clinical postural instability (PI) in PD, the progression of PI due to PD progression, and ultimately fall risk using DFA. Subjects with mild PD (PD-Mi), moderate PD (PD-Mo) and age-range-matched healthy controls (HC) participated in this study of a postural sway task. Ground reaction forces and moments were collected from subjects standing on force plates in quiet postural sway in eyes open (EO) and eyes closed (EC) conditions. COPv was calculated and analyzed as a non-stationary time series with varying statistical properties. We investigated the temporal parameter of Absolute Average Maximal Velocity (AAMV), the system order parameter of Approximate Entropy (ApEn), and fractal parameters from the DFA which were the short term scaling behavior of the time series (α_1), the long term scaling behavior of the time series (α_2) and the time scale at which the scaling behavior changes – the crossover index (CrI).

Taken together, the parameters showed differences between groups and conditions. In the temporal analysis, AAMV showed significant group differences between HC and PD-Mo and significant condition differences. In the fractal analysis, α_1 showed significant group differences between HC and PD-Mo and α_2 showed significant differences between conditions. Due to the pilot nature of the study, power analysis was conducted on all non-significant findings in order to inform the design of a full study. Feasible subject numbers were found for many of the measures that did not show significance in the pilot study.

Conclusions and Recommendations

The investigation of temporal, organizational and fractal characteristics of COPv as a non-stationary, time varying series yields marked differences in behavior between HC and PD,

even in pre-clinical populations. AAMV proved to be the most sensitive measure of differences between HC, PD-Mi and PD-Mo. The fractal parameters $\alpha 1$ and $\alpha 2$ not only have merit as clinical tools, but also give insight into the differences in open and closed loop control between the groups. This study shows the importance of the COPv time series as a clinical assessment tool of pre-clinical PD postural instability, disease progression and fall risk. Furthermore, COPv may hold key information related to velocity based control of postural stability. Further study is needed to develop these measures as a clinical tool. Further study is also needed in order to connect the measurements of postural instability in PD (COP, COPv) to the neural control systems that govern these processes. The present study shows that aspects of this control system can be seen in the postural sway data, however more targeted experimentation is needed to strengthen this connection. Challenges to postural sway, such as a narrow or compliant base of support, could also be introduced to see if there is different degrees of parameter modulation between groups. Given the neurodegenerative nature of PD, a better understanding of this connection could further benefit clinical analysis, understanding of disease pathology, and development of computer simulation models of postural control in PD.

Study Limitations

Limitations in this study are largely due to the pilot nature of the subject pool. Many measures were underpowered, and thus only trends in data could be reported. Since subjects were asked to self-select stance width, we were not able to investigate the ML direction of postural sway due to the fact that certain postural deficits might have been compensated for or unequally modulated in this direction by wider or narrower stance width.

Further Study

Further study of this subject should extend the methods to the medial-lateral (ML) direction of the COPv time series. A larger sample population should also be considered following the power analyses performed in this study. It would also be beneficial to increase the time of each trial taken in order to witness more of the data structure in time. A study conducted in this way would need to work with clinicians in order to ascertain how long a clinical assessment of PD using force plates should take. An assessment that takes too long to collect would be less likely to be helpful in a clinical setting.

For the purpose of understanding the control system changes between HC and PD, a study should be designed in which perturbations to feedback systems in closed loop control are investigated beyond the removal of visual feedback. Since this study showed little difference between groups with the removal of visual feedback, perhaps control systems in PD leading to postural instability are more sensitive to other types of feedback. Lastly, the study should be safely extended to PD populations who already have a history of falls in order to further assess the sensitivity of these parameters to PD progression.

Appendix A: Matlab code used in the analysis

i. Initial Parameters

The file Init_Parameters.m is M code specifying initial parameter definitions and organization for use with all analysis code is copied below. The file was written jointly by Josh Harper and Dr. Carl Luchies.

```
%Init_Parameters.m
%Initial parameters needed for swat analysis
%Written by Carl W. Luchies, 2014

%%%%%%%%%%%%% THE USER MUST SELECT APPROPRIATE SETTINGS IN THIS CELL BREAK %%%%%%
%%%%% choose the test mode. 1 = real data analysis; 2 = known signal analysis
test_mode = 1;
%%%%% NOTE
%%%%% if test_mode = 2, select: ifreq = 2; i_filter = 2; testyear = 3; and set
%the following parameters:
if test_mode == 2
    Mdl = arima('Constant',0,'AR',{0.8,-0.4},'Variance',10^2);
    signal_time = 1:1:600;

    %simulate the model
    rng('default');
    [Y, E] = simulate(Mdl,600);

    %(expm(-((ti-500)^2)/(2*200^2)))*
    count = 0;
    for ti = 1:1:600
        count = count + 1;
        signal_data(ti,:) = Y(ti,:);
    end

    figure('Name', 'Known Signal')
    plot(signal_time, signal_data)
    title(['Known Signal with'])
end
%%%%% choose the sampling frequency (1=100hz, 2=1000hz, 3=1080hz)
i_freq=2;

%Choose to downsample at a particular rate. setting a rate of "1" will keep
%the original sample rate which is normally 1000hz. choosing a downsample
%rate of 10 will decimate the signal to a sample rate of 100hz, 100 to
```

```

% 10hz.
downsample_rate = 10;

%to save or not to save: 1=yes, 2=no
i_save=2;

%filter the data: 1=yes, filter, 2=no filter
i_filter=1;

%Testing year: 1= HC and Mild PD; 2= HC and Moderate PD 3: Model data or
%known signal data if test_mode = 2.
testyear=[1:2];

%groups: 1=HC, 2=PD (for test_mode = 2: 1 = stationary; 2 =
%non-stationary)
group=[1:2];

%Testing condition: 1=EO; 2=EC (for test_mode = 2: 1 = clean; 2 = white noise)
condition=[1,2];

%trials
trials=[1:3];

%choose the sway direction analyzed. 1 = Radius of COP; 2 = AP; 3 = ML
%(for test_mode = 2 use COP_direction = 2)
COP_direction = 2;

%choose type of analysis. 1 = position, 2 = velocity, 3 = acceleration
analysis = 2;

%Set statistical preferences for use in Process results
pval = 0.05;

%setup the experiments to be run by setting the variables to 1 (enable) or
%0 (disable)

i_DFA = 1; %Detrended Fluctuation Analysis 1 enables DFA analysis per trial or with trials averaged,
2 enables DFA analysis with trials chained together into a single time series
DFA_Save = 2; %Specify whether to save the DFA data or load previous results. 0 = Do Nothing, 1 =
save, 2 = load previous analysis
i_ApEnt = 0; %Approximate Entropy Analysis
ApEnt_Save = 0; %Specify whether to save the Approximate Entropy data or load previous results. 0 =
Do Nothing, 1 = save, 2 = load previous analysis
i_spectral_analysis = 0; %Spectral Analysis
i_spectrogram = 0; %Time Frequency Analysis

%%%%%%%%%%%%% THE REST OF THE CODE INITIATES DATA GATHERING
%%%%%%%%%%%%%

```

```

%choose sample frequencies
if i_freq ==1
    fsample = 100;
elseif i_freq == 2
    fsample = 1000;
elseif i_freq ==3
    fsample = 1080;
end

%groups, subjects, trials, conditions to analyze
% 1_1001_EO1
% testingyear_subjectnum_trialcondition
%
% testingyear = 1, HC (1-14) and mild PD (1-14)
% testingyear = 2, HC (1-10) and moderate PD (1-12)
%
% subjectnum = 1000's HC; 3000's Mild; 4000's Moderate (4009 is mild)
% trialcondition: EO is eyes open, EC is eyes closed, 1,2,3 trial number

%Subject number range for each group: start:stop
subject_range=[1 11;... %max is 11
               1 12; ... %max is 12
               1 10;... %max is 10
               1 11]; %max is 11

HC_groupnum1 = max(subject_range(1,:));
HC_groupnum2 = max(subject_range(3,:));
PDMi_groupnum = max(subject_range(2,:));
PDMo_groupnum = max(subject_range(4,:));

if test_mode == 2
    subject_range = [1 1; 1 1; 1 1; 1 1];
end

condition_string={'EO'; 'EC'};

if test_mode == 2
    condition_string = {'Stationary'; 'Non_Stationary'};
end

yr1_HC_subnum=['1001'; ...
               '% '1002'; ...
               '1003'; ...
               '% '1004'; ...
               '% '1005'; ...
               '1006'; ...
               '1007'; ...
               '1008'; ...
               '1009'; ...
               '1010'; ...
               '1011'; ...

```

```

'1012'; ...
'1013'; ...
'1014'];

yr1_PD_subnum=['3001'; ...
'3002'; ...
'3003'; ...
'3004'; ...
'3005'; ...
'3006'; ...
% '3007'; ...
'3008'; ...
'3009'; ...
'3010'; ...
'3011'; ...
% '3012';...
'3013'; ...
'3014'];

yr2_HC_subnum=['1001'; ...
'1002'; ...
'1003'; ...
'1004'; ...
'1005'; ...
'1006'; ...
'1007'; ...
'1008'; ...
'1009'; ...
'1010'];

yr2_PD_subnum=['4001'; ...
'4002'; ...
% '4003'; ...
'4004'; ...
'4005'; ...
'4006'; ...
'4007'; ...
'4008'; ...
'4009'; ...
'4010'; ...
'4011'; ...
'4012'];

COP_direction_name = {'COP_Radius',...
'COP_AP',...
'COP_ML'};

%choose preallocation size for variables that will change size with loop
%iteration.
pre_allocate = length(COP_direction)*length(trials)*length(condition)*((subject_range(1,2)-
subject_range(1,1)+1)+(subject_range(2,2)-subject_range(2,1)+1)+(subject_range(3,2)-
subject_range(3,1)+1)+(subject_range(4,2)-subject_range(4,1)+1));

%for known signal data

```

```

%set up timing parameters
if i_freq==1
    sample_freq=100;      %samples/sec
else
    sample_freq=1000;
end

sample_time=30;           %duration in seconds
t=1/sample_freq:1/sample_freq:sample_time; %time vector
dt=1/sample_freq;         %time between samples

%Low pass filter information
order = 4;                %fourth order filter
nyquist_frequency = sample_freq/2;    %compute the nyquist frequency
cutoff_freq=10;             %cutoff frequency for the lowpass filter
normalized_cutoff = cutoff_freq/nyquist_frequency;

[b,a] = butter(order, normalized_cutoff , 'low');
%b and a are now my filter coefficients

%establish the path to the data
if i_freq==1      % 100Hz data
    %for Harper's structure
    path_data=['C:\Time_Freq_Research\Data_Raw\COP_Data_1000Hz\'];
    path_results=['C:\Time_Freq_Research\Data_Results\Sample_Data\'];

    %for VCL structure from Harper's drive
%    path_data=['\Client\Time_Freq_Research\Data_Raw\COP_Data_1000Hz\'];
%    path_results=['\Client\Time_Freq_Research\Sample_Data\'];

    %for luchie's file structure
    %path_data=['c:\Luchies\data\PD_sway\COP_Data_100Hz\'];
    %path_results=['c:\Luchies\Data_Processing\PD_sway\COP_Data_100Hz\'];
else            % 1000Hz data
    %for Harper's structure
    path_data=['C:\Time_Freq_Research\Data_Raw\COP_Data_1000Hz\'];
    path_results=['C:\Time_Freq_Research\Sample_Data\'];

    %for VCL structure from Harper's drive
%    path_data=['\Client\Time_Freq_Research\Data_Raw\COP_Data_1000Hz\'];
%    path_results=['\Client\Time_Freq_Research\Sample_Data\'];

    %for Luchie's file structure
    %path_data=['c:\Luchies\data\PD_sway\COP_Data_1000Hz\'];
    %path_results=['c:\Luchies\Data_Processing\PD_sway\COP_Data_1000Hz\'];
end

```

ii. Main Process Code

Process.m is the main process code was used to perform common operations on data (e.g. take the derivative of COP to form COPv) and call different analysis based on the selections in Init_Parameters.m.

```
%Process_v3.m
%Calculate the power spectrum of the COP time series
%Written by Josh Harper and Carl Luchies 2015

%clear workspace
clear
%set up all initial parameters
Init_parameters
time_stamp = datestr(now,'yyyymmddTHHMMSS');

%Load any saved data used in the analysis
if ApEntSave == 1 || ApEntSave == 2
    if i_ApEnt == 1
        mkdir(['C:\Time_Freq_Research\Data_Results\ApEnt\' time_stamp]);
    elseif i_ApEnt == 2
        mkdir(['C:\Time_Freq_Research\Data_Results\ApEnt_chain\' time_stamp]);
    end
    result_dir3 = ('C:\Time_Freq_Research\Data_Results\ApEnt\'');
    result_dir5 = ('C:\Time_Freq_Research\Data_Results\ApEnt_chain\'');
    if ApEntSave == 2 && i_ApEnt == 1
        load([result_dir3 '\newest\ApEntropy_collect.mat'],'ApEntropy_collect')
    elseif ApEntSave == 2 && i_ApEnt == 2
        load([result_dir5 '\newest\ApEntropy_collect_sub.mat'],'ApEntropy_collect_sub')
    end
end
%pre-allocate space for variables that change with each iteration
alpha1_mod = zeros(pre_allocate,1);
alpha2_mod = zeros(pre_allocate,1);
AAMV_mod = zeros(pre_allocate,1);
% group_factor = zeros(pre_allocate,1);
% condition_factor = cell(pre_allocate,1);
% subject_factor = zeros(pre_allocate,1);
% trial_factor = zeros(pre_allocate,1);

%delineate between real data signal analysis and known signal analysis
if i_save == 1

    if analysis == 1
        type_dir = ['COP_Position'];
    elseif analysis == 2
        type_dir = ['COP_Velocity'];
    elseif analysis == 3
        type_dir = ['COP_Acceleration'];
    end
    result_dir = (['C:\Time_Freq_Research\Data_Results\' type_dir '\' time_stamp]);
```

```

mkdir(result_dir);

end
%%
%D Data Analysis
call_count1 = 0;
fig_count = 0;
total_trial_iter_count = 0;
total_sub_iter_count = 0;
for idirection = COP_direction
    for icondition = condition
        icondition
        for itestyear=testyear % test year being analyzed

            for igroup=group % group being analyzed within a test year
                igroup
                itestyear
                if itestyear ==1 && igroup ==1
                    subnum=yr1_HC_subnum;
                    subjects=subject_range(1,1):subject_range(1,2);

                elseif itestyear==1 && igroup==2
                    subnum=yr1_PD_subnum;
                    subjects=subject_range(2,1):subject_range(2,2);

                elseif itestyear==2 && igroup==1
                    subnum=yr2_HC_subnum;
                    subjects=subject_range(3,1):subject_range(3,2);

                elseif itestyear==2 && igroup==2
                    subnum=yr2_PD_subnum;
                    subjects=subject_range(4,1):subject_range(4,2);

                elseif itestyear ==3 && igroup==1 && test_mode == 1 %itestyear = 3 cooresponds to model data
                    subnum = ['model_output'];
                    subjects = 1;
                elseif itestyear ==3 && test_mode == 2
                    subnum = ['known signal'];
                    subjects = 1;
                end
                % for icondition=condition %Condidion: EO EC loop
                count_subject = 0;
                for isubject=subjects % subject loop
                    total_sub_iter_count = total_sub_iter_count + 1
                    count_subject = count_subject + 1;
                    count_trial = 0;

                    %set up factor vectors for N-Way ANOVA
                    if itestyear == 1
                        group_factor_sub(total_sub_iter_count,1) = (igroup);
                    elseif itestyear == 2 && igroup == 1
                        group_factor_sub(total_sub_iter_count,1) = (igroup);
                    elseif itestyear == 2 && igroup == 2
                        group_factor_sub(total_sub_iter_count,1) = (igroup+1);

```

```

    end
    condition_factor_sub(total_sub_iter_count,1) = condition_string(icondition);
    direction_factor_sub(total_sub_iter_count,1) = (idirection);

    plot_title_sub=['COP_ ' COP_direction_name{idirection} '_Test
Yr_',int2str(itestyear),'_Group_',int2str(igroup),...
    '_sub#_',subnum(isubject,:);condition_string{icondition,:}];

for itrial=trials %trial loop
    total_trial_iter_count = total_trial_iter_count +1
    %set up factor vectors for N-Way ANOVA
    if itestyear == 1
        group_factor(total_trial_iter_count,1) = (igroup);
    elseif itestyear == 2 && igrup == 1
        group_factor(total_trial_iter_count,1) = (igroup);
    elseif itestyear == 2 && igrup == 2
        group_factor(total_trial_iter_count,1) = (igroup+1);
    end
    condition_factor(total_trial_iter_count,1) = condition_string(icondition);
    condition_factor_numeric(total_trial_iter_count,1) = icondition;
    direction_factor(total_trial_iter_count,1) = (idirection);
    trial_factor(total_trial_iter_count,1) = (itrial);

    fig_count = fig_count+1
    count_trial = count_trial + 1;

    %load the data
    if test_mode == 1
        if itestyear<3

datafilename=[num2str(itestyear),'_',subnum(isubject,:),'_',condition_string{icondition,:},num2str(itrial)];
        datafilename2=[num2str(itestyear),'_',subnum(isubject,:),'-'-
',condition_string{icondition,:},num2str(itrial)];
        elseif itestyear==3
            datafilename=['model_output'];
        end
        fname=[path_data,datafilename];
        eval(['load ',fname]);
    elseif test_mode == 2
    end

%%%%% - For MODEL DATA - %%%%%%
if test_mode == 1
    if itestyear<3
        if idirection == 1
            COP_raw = sqrt((dt_COPAP_COPML(:,idirection+1)-
mean(dt_COPAP_COPML(:,idirection+1))).^2+(dt_COPAP_COPML(:,idirection+2)-
mean(dt_COPAP_COPML(:,idirection+2))).^2);
        else
            COP_raw=dt_COPAP_COPML(:,idirection);
        end
    elseif itestyear ==3
        if idirection == 1
            COP_raw =
sqrt(Model_dt_COPAP(:,idirection+1).^2+Model_dt_COPAP(:,idirection+2).^2);
        end
    end
end

```

```

    else
        COP_raw=Model_dt_COPAP(:,idirection);
    end
end
elseif test_mode ==2
    COP_raw = signal_data;
end
plot_title=['COP_ ' COP_direction_name{idirection} '_Test
Yr_',int2str(itestyear),'_Group_',int2str(igroup),...
'_sub#_',subnum(isubject,:),condition_string{icondition,:} num2str(itrial)];

if test_mode == 2
    plot_title = ['Known_ ', condition_string{icondition,:}, '_Signal_'];
end

%Filter the data
COP_raw = COP_raw - mean(COP_raw);
if i_filter == 1
    COP_temp = filtfilt(b,a,COP_raw);
elseif i_filter == 2
    COP_temp = COP_raw;
end
%calcuate velocity or acceleration
if analysis == 1
    COP = COP_temp; %position of COP
elseif analysis == 2
    [COP, ~] = derivative(COP_temp,2,sample_time/length(COP_temp)); %velocity of COP
elseif analysis == 3
    [~, COP] = derivative(COP_temp,2,sample_time/length(COP_temp)); %acceleration of COP
end
clear COP_temp COP_raw

%downsample the data in accordance with the
%downsample rate set in init_parameters
COP = COP(1:downsample_rate:end);

%Collect the COP data for each trial for later us
%in COP_chain
COP_collect_tr(:,itrial) = COP;
%test the data for stationarity
% [h, pValue, stat, cValue, reg] = is_stationary(COP_AP);
% ['COP_AP_Test Yr_',int2str(itestyear),'_Group_',int2str(igroup),...
% '_sub#_',subnum(isubject,:),condition_string{icondition,:}]
% h
%plot the data for a check
% figure('Name', ['DQC_ ' plot_title])
% plot(t,COP)
% xlabel('time (sec)')
% ylabel('COP ')
% title(datafilename2)
%

```

```

%%%
if i_DFA == 1
    %perform a DFA analysis. 0 = no, 1 = yes
    DFA_range = 10:20:length(COP);
    if DFASave == 1    %RUN NEW DFA ANALYSIS
        [D,Alpha1,F_n]=DFA_main(COP',DFA_range,2000);
        alpha1_subject(isubject) = Alpha1 ;
    %
    end
    %find the AAMV
    windows = fix(length(COP)/125);
    divisions = 0:(windows-1);
    for irange = 1:windows
        %find the rectified peaks of DATA
        pk = findpeaks(abs(COP((1+125*divisions(irange))):(125 + 125*divisions(irange))))));
        %take the mean of the peaks over teh given range
        mini_mean(irange) = mean(pk);
        clear pk
    end
    %find the average absolute maximal velocity by take the mean of the mini
    %means
    AAMV = mean(mini_mean);
    result_dir2 = ('C:\Time_Freq_Research\Results\F_n');

    %if you wish to save the time consuming to make F_n
    %function for later analysis with the same F_n
    %parameters, use the save code
    if DFASave == 1    %SAVE RESULTS
        save([result_dir2 '\F_n' plot_title '.mat'],F_n')
        delete([result_dir2 '\newest\*.mat'])
        save([result_dir2 '\newest\F_n' plot_title '.mat'],F_n')
    end
    %if you have already saved the F_n's for this run,
    %use the load code.
    if DFASave == 2    %LOAD PREVIOUS RESULTS
        F_n_load = load([result_dir2 '\newest\F_n' plot_title]);
        F_n = F_n_load.F_n;
    end
    AAMV_trial(itrial,isubject,igroup,itestyear,icondition,idirection) = AAMV;

    %%
    %find alpha1 and alpha2
    %specify the number of segments to divide F_n into
    difference = diff(log10(F_n));

    for iter = 1:length(difference)
        if difference(iter,:) <= 0.55
            crossover_index = iter;
            break
        end
    end

```

```

crossover_scale(total_trial_iter_count) = DFA_range(crossover_index);
crossover_scale_collect(itrial,isubject,igroup,itestyear,icondition,idirection) =
DFA_range(crossover_index);
%
difference = difference';
%
figure('Name', ['Alpha for' plot_title])
%
hold on
%
plot(log10(DFA_range(:,1:end-1)),difference)
scatter(log10(DFA_range(:,crossover_index)),difference(:,crossover_index),'*')
set(gca,'YTick',0:0.25:5)
%
hold off
%
index_offset = 15;

A1 = polyfit(log10(DFA_range(1:crossover_index)'),log10(F_n(1:crossover_index)),1);
A2 =
polyfit(log10(DFA_range(crossover_index+index_offset:end)'),log10(F_n(crossover_index+index_offset:end)),1);
alpha1(itrial,isubject,igroup,itestyear,icondition,idirection) = A1(1);
alpha2(itrial,isubject,igroup,itestyear,icondition,idirection) = A2(1);

% modify data collection to work with N-Way ANOVA.
% collapse itestyear and igroup into groups 1-3
% specifyig healthy(1), mild(2) and moderate(3). The
% result should be a nx1 vector which will line up
% with the "factor" variables (group_factor,
% condition_factor, subject_factor and
% trial_factor).
alpha1_mod(total_trial_iter_count) = A1(1);
alpha2_mod(total_trial_iter_count) = A2(1);
AAMV_mod(total_trial_iter_count) = AAMV;

%
B1 = log10(F_n(1))-A1(1)*log10(DFA_range(1));
B2 = log10(F_n(end))-A2(1)*log10(DFA_range(end));
%
y1 = A1(1)*DFA_range + B1;
y2 = A2(1)*DFA_range + B2;

y1 = polyval((A1),log10(DFA_range));
y2 = polyval((A2),log10(DFA_range));
%
figure('Name',[DFA for ' plot_title])
%
hold on
%
scatter(log10(DFA_range),log10(F_n),'o'),
scatter(log10(DFA_range(:,crossover_index)),log10(F_n(crossover_index,:)),'*'),
plot(log10(DFA_range(1:crossover_index)),(y1(1:crossover_index)),'--'),
plot(log10(DFA_range(crossover_index+index_offset:end)),(y2(crossover_index+index_offset:end)),'-');
%
xlabel('n')
ylabel('F(n)')
axis([0 12 0 12])
%
end

%%
% perform an approximate entropy analysis on the
% data
if i_ApEnt == 1 && ApEntSave == 1
tic

```

```

m = 2;
r = 0.2;
ApEntropy_temp = ApEnt(COP_resample,m,r);
%collect the results by subsets and in a single
%column vecotor for later use in ANOVA
ApEntropy_collect(itrial,isubject,igroup,itestyear,icondition,idirection) = ApEntropy_temp;

clear ApEntropy_temp
toc
elseif i_ApEnt == 1 && ApEntSave == 2
    ApEntropy_tr(total_trial_iter_count) =
ApEntropy_collect(itrial,isubject,igroup,itestyear,icondition,idirection);
end

%%%
%do a spectral analysis of the data. 0 = no, 1 = yes

if i_spectral_analysis == 1

[mf,f,mx,amp] = Spectral_analysis(sample_freq,COP);
[pxx,omega] = pwelch(COP);
%median_freq(itrial,ichan)=mf;
%freq_fft(itrial,:,ichan)=f;
%Power_fft(itrial,:,ichan)=mx';
f_trials(:,itrial) = f;
amp_trials(:,itrial)=amp;
mx_trials(:,itrial)=mx;
mf_trials(itrial)=mf;

f_trial_ave = mean(mean(f_trials,2));
amp_trials_ave = mean(mean(amp_trials,2));
mx_trials_ave = mean(mean(amp_trials,2));
mf_trials_ave = mean(mf_trials);
% Generate the plot, title and labels.
iplot=1;
if iplot==1
    figure('name','[spec anal for' plot_title]')
    %
    subplot(2,1,1)
    loglog(omega,pxx); %plot(f(irange),mx(irange));
    %
    axis([0 7 0 50])
    title('Signal Power Spectrum');
    xlabel('Frequency (Hz)');
    ylabel('Power');

    %
    subplot(2,1,2), plot(f,amp)
    axis([0 7 0 15])
    %
    title('Signal Power Spectrum');
    xlabel('Frequency (Hz)');
    ylabel('Amplitude');

```

```

else
end
end

%%

% perform a spectrogram analysis to see the non-stationary characteristics of the signal

if i_spectrogram == 1
    spectro_CWL_JRH
end
%%

% run the data adaptive evolutionary spectrum analysis

% spec = data_adapt(COP_AP,8,9,2);

end %itrial loop end
%%%%% %%%%%% %%%%%% %%%%%% %%%%%% %%%%%% %%%%%% %%%%%% %%%%%% %%%%%% TRIAL RESULTS
%%%%% %%%%%% %%%%%% %%%%%% %%%%%% %%%%%% %%%%%% %%%%%% %%%%%% %%%%%%
% string together each COP trial into a single data set
%for each subject
COP_chain = vertcat(COP_collect_tr(:,1), COP_collect_tr(:,2), COP_collect_tr(:,3));
COP_chain_collect(:,isubject,igroup,itestyear,icondition,idirection) = vertcat(COP_collect_tr(:,1),
COP_collect_tr(:,2), COP_collect_tr(:,3));
% figure(Name', [DQC_ ' plot_title_sub])
%
plot(1:length(COP_chain_collect(:,isubject,igroup,itestyear,icondition,idirection)),COP_chain_collect(:,isubject,igo
up,itestyear,icondition,idirection))
%
xlabel('time (sec)')
%
ylabel('COP ')
%
title(datafilename2)

if i_DFA == 2
    %perform a DFA analysis. 0 = no, 1 = yes
    DFA_range = 10:10:length(COP_chain);
    if DFASave == 1    %RUN NEW DFA ANALYSIS
        tic
        [D,Alpha1,F_n]=DFA_main(COP_chain',DFA_range,2000);
        toc
        %
        alpha1_subject(isubject) = Alpha1;
    end
    %find the AAMV
    windows = fix(length(COP_chain)/2000);
    divisions = 0:(windows-1);
    for irange = 1:windows
        %find the rectified peaks of DATA

```

```

pk = findpeaks(abs(COP_chain((1+2000*divisions(irange)):(2000 + 2000*divisions(irange))))));
%take the mean of the peaks over teh given range
mini_mean(irange) = mean(pk);
clear pk
end
%find the average absolute maximal velocity by take the mean of the mini
%means
AAMV = mean(mini_mean);
result_dir4 = ('C:\Time_Freq_Research\Results\F_n_chain');

%if you wish to save the time consuming to make F_n
%function for later analysis with the same F_n
%parameters, use the save code
if DFASave == 1 %SAVE RESULTS
    save([result_dir4 'F_n' plot_title_sub '.mat'], 'F_n')
    delete([result_dir4 'newest*.mat'])
    save([result_dir4 'newest\F_n' plot_title_sub '.mat'], 'F_n')
end
%if you have already saved the F_n's for this run,
%use the load code.
if DFASave == 2 %LOAD PREVIOUS RESULTS
    F_n_load = load([result_dir4 'newest\F_n' plot_title_sub]);
    F_n = F_n_load.F_n;
end
AAMV_sub_collect(isubject, igroup, itestyear, icondition, idirection) = AAMV;

%%

%find alpha1 and alpha2
%specify the number of segments to divide F_n into
difference = diff(log10(F_n));

cross_deriv = derivative(log10(F_n), 2, 0.01);
ss_mean = mean(abs(cross_deriv((length(cross_deriv) - fix(.35*length(cross_deriv))):end)));
ss_std = std(abs(cross_deriv((length(cross_deriv) - fix(.35*length(cross_deriv))):end)));
for iter = 1:length(cross_deriv)
    temp_val = mean(cross_deriv(iter:iter+20));
    if temp_val < ss_mean+ss_std && temp_val > ss_mean-ss_std
        pickoff_val = cross_deriv(iter);
        pickoff_point = iter;
        break
    end
end
clear iter

for iter = 1:length(difference)
    if difference(iter,:) <= 0.55
        crossover_index = iter;
        break
    end
end

```

```

    end
%
% crossover_scale_sub(total_sub_iter_count) = DFA_range(crossover_index);
% crossover_scale_collect(isubject,igroup,itestyear,icondition,idirection) =
DFA_range(crossover_index);

crossover_scale_sub(total_sub_iter_count) = DFA_range(pickoff_point);
crossover_scale_collect(isubject,igroup,itestyear,icondition,idirection) = DFA_range(pickoff_point);
difference = difference';
figure('Name', ['Alpha for' plot_title_sub])
hold on
plot(log10(DFA_range(:,1:end)),cross_deriv)
scatter(log10(DFA_range(:,crossover_index)),cross_deriv(crossover_index),'*')
scatter(log10(DFA_range(:,pickoff_point)),cross_deriv(pickoff_point),'X','r')

%
% scatter(log10(DFA_range(:,crossover_index)),difference(:,crossover_index),'*')
% set(gca,'YTick',0:0.25:5)
hold off

index_offset = 15;

A1 = polyfit(log10(DFA_range(1:crossover_index')),log10(F_n(1:crossover_index)),1);
A2 =
polyfit(log10(DFA_range(crossover_index+index_offset:end')),log10(F_n(crossover_index+index_offset:end)),1);
alpha1_sub_collect(isubject,igroup,itestyear,icondition,idirection) = A1(1);
alpha2_sub_collect(isubject,igroup,itestyear,icondition,idirection) = A2(1);

% modify data collection to work with N-Way ANOVA.
% collapse itestyear and igrup into groups 1-3
% specifyig healthy(1), mild(2) and moderate(3). The
% result should be a nx1 vector which will line up
% with the "factor" variables (group_factor,
% condition_factor, subject_factor and
% trial_factor).
alpha1_sub(total_sub_iter_count) = A1(1);
alpha2_sub(total_sub_iter_count) = A2(1);
AAMV_sub(total_sub_iter_count) = AAMV;

%
B1 = log10(F_n(1))-A1(1)*log10(DFA_range(1));
B2 = log10(F_n(end))-A2(1)*log10(DFA_range(end));
%
y1 = A1(1)*DFA_range + B1;
y2 = A2(1)*DFA_range + B2;

y1 = polyval((A1),log10(DFA_range));
y2 = polyval((A2),log10(DFA_range));

%plot the DFA analysis for each subject
figure('Name',[DFA for ' plot_title_sub])
hold on
scatter(log10(DFA_range),log10(F_n),'o'),
scatter(log10(DFA_range(:,crossover_index)),log10(F_n(crossover_index,:)),'*'),

```

```

plot(log10(DFA_range(1:crossover_index)),(y1(1:crossover_index)),'--'),
plot(log10(DFA_range(crossover_index+index_offset:end)),(y2(crossover_index+index_offset:end)),'-');
scatter(log10(DFA_range(:,pickoff_point)),log10(F_n(pickoff_point)),X,'r')
xlabel('n')
ylabel('F(n)')
axis([0 12 0 12])

end

%Approximate Entropy Analysis
if i_ApEnt == 1
    %take the mean and standard deviation across trials
    Ap_Ent_trial_mean(isubject,igroup,itestyear,icondition,idirection) =
mean(ApEntropy_collect(:,isubject,igroup,itestyear,icondition,idirection));
    Ap_Ent_trial_std(isubject,igroup,itestyear,icondition,idirection) =
std(ApEntropy_collect(:,isubject,igroup,itestyear,icondition,idirection));

    ApEntropy_sub(total_sub_iter_count) =
Ap_Ent_trial_mean(isubject,igroup,itestyear,icondition,idirection);
    end

if i_ApEnt == 2 && ApEntSave == 1
tic

m = 2;
r = 0.2;
ApEntropy_temp = ApEnt(COP_chain,m,r);
%collect the results by subsets and in a single
%column vecotor for later use in ANOVA
ApEntropy_collect_sub(isubject,igroup,itestyear,icondition,idirection) = ApEntropy_temp;

clear ApEntropy_temp
toc
elseif i_ApEnt == 2 && ApEntSave == 2
ApEntropy_sub(total_sub_iter_count) =
ApEntropy_collect_sub(isubject,igroup,itestyear,icondition,idirection);
end
%Time Frequency Analysis
if i_spectrogram == 1
end

%Detrended Fluctuation Analysis
if i_DFA == 1
call_count1 = call_count1 + 1;
%           AAMV_sub_ave(:,igroup,itestyear) = mean(AAMV_trial);

```

```

% AAMV_sub_std = std(AAMV_trial);

%
% Marker = ['+' 'o' '*' 'x' 's' '^'];
% figure('Name', 'AAMV_Scatter')
% hold on
% scatter(call_count1,AAMV_sub_ave(isubject),Marker(call_count1))

%take the mean and standard deviation of Alpha1,
%Alpha2 and AAMV and crossover_scale across trials
alpha1_mean_sub(isubject,igroup,itestyear,icondition,idirection) =
mean(alpha1(:,isubject,igroup,itestyear,icondition,idirection));
alpha1_std_sub(isubject,igroup,itestyear,icondition,idirection) =
std(alpha1(:,isubject,igroup,itestyear,icondition,idirection));
alpha1_sub(total_sub_iter_count) = alpha1_mean_sub(isubject,igroup,itestyear,icondition,idirection);

alpha2_mean_sub(isubject,igroup,itestyear,icondition,idirection) =
mean(alpha2(:,isubject,igroup,itestyear,icondition,idirection));
alpha2_std_sub(isubject,igroup,itestyear,icondition,idirection) =
std(alpha2(:,isubject,igroup,itestyear,icondition,idirection));
alpha2_sub(total_sub_iter_count) = alpha2_mean_sub(isubject,igroup,itestyear,icondition,idirection);

AAMV_mean_sub(isubject,igroup,itestyear,icondition,idirection) =
mean(AAMV_trial(:,isubject,igroup,itestyear,icondition,idirection));
AAMV_std_sub(isubject,igroup,itestyear,icondition,idirection) =
std(AAMV_trial(:,isubject,igroup,itestyear,icondition,idirection));
AAMV_sub(total_sub_iter_count) =
AAMV_mean_sub(isubject,igroup,itestyear,icondition,idirection);

crossover_scale_mean(isubject,igroup,itestyear,icondition,idirection) =
mean(crossover_scale_collect(:,isubject,igroup,itestyear,icondition,idirection));
crossover_scale_std(isubject,igroup,itestyear,icondition,idirection) =
std(crossover_scale_collect(:,isubject,igroup,itestyear,icondition,idirection));
crossover_scale_sub(total_sub_iter_count) =
crossover_scale_mean(isubject,igroup,itestyear,icondition,idirection);

end

%Spectral Analysis
if i_spectral_analysis == 1
    mx_ave(:,isubject) = mean(mx_trials)';
    mf_ave(isubject) = mean(mf_trials_ave);
    amp_ave(:,isubject) = mean(amp_trials)';

    mx_std(:,isubject) = std(mx_trials)';
    mf_std(isubject) = std(mf_trials);
    amp_std(:,isubject) = std(amp_trials)';
end
end %isubject loop end
%%%%% SUBJECT RESULTS%%%%%
%Detrended Fluctuation Analysis
if i_DFA == 1
    %run a repeated measures anova on the DFA to see if

```

```

%there is a significant difference between trials
%within subjects
%for alpha1
[A1p_subject A1table_subject] =
anova_rm_cust(alpha1(:,1:max(subjects),igroup,itestyear,icondition,idirection)',on',['Alpha1 RM ANOVA for year '
int2str(itestyear) ' Group ' int2str(igroup) ' condition ' condition_string{icondition,:}
COP_direction_name{idirection,:}]);
A1_RMANOVA{igroup, itestyear,icondition,idirection} = A1table_subject;
clear A1p_subject A1table_subject

%for alpha2
[A2p_subject A2table_subject] =
anova_rm_cust(alpha2(:,1:max(subjects),igroup,itestyear,icondition,idirection)',on,['Alpha2 RM ANOVA for year '
int2str(itestyear) ' Group ' int2str(igroup) ' condition ' condition_string{icondition,:}
COP_direction_name{idirection,:}]);
A2_RMANOVA{igroup, itestyear,icondition,idirection} = A2table_subject;
clear A2p_subject A2table_subject

%for AAMV
[AAMVp_subject AAMVtable_subject] =
anova_rm_cust(AAMV_trial(:,1:max(subjects),igroup,itestyear,icondition,idirection)',on,['AAMV RM ANOVA for
year ' int2str(itestyear) ' Group ' int2str(igroup) ' condition ' condition_string{icondition,:}
COP_direction_name{idirection,:}]);
AAMV_RMANOVA{igroup, itestyear,icondition,idirection} = AAMVtable_subject;
clear AAMVp_subject AAMVtable_subject
end

%Approximate Entropy Analysis
if i_ApEnt == 1
%run a repeated measures anova on the ApEnt to see if
%there is a significant difference between trials
%within subjects
[AEp_subject AEtable_subject] =
anova_rm_cust(ApEntropy_collect(:,1:max(subjects),igroup,itestyear,icondition,idirection)',on,['ApEnt RM
ANOVA for year ' int2str(itestyear) ' Group ' int2str(igroup) ' condition ' condition_string{icondition,:}
COP_direction_name{idirection,:}]);
ApEnt_RMANOVA{igroup, itestyear,icondition,idirection} = AEtable_subject;
clear p_subject table_subject
end

%Time Frequency Analysis
if i_spectrogram == 1
end

%Spectral Analysis
if i_spectral_analysis == 1
mx_group_ave(:,igroup) = mean(mx_ave)';
mf_group_ave(igroup) = mean(mf_ave);
amp_group_ave(:,igroup) = mean(amp_ave)';
mx_group_std(:,igroup) = std(mx_ave)';
mf_group_std(igroup) = std(mf_ave);

```

```

amp_group_std(:,igroup) = std(amp_ave)';
%
clear mx_ave mf_ave amp_ave mx_std mf_std amp_std
% figure(3000*itestyear+100*igroup);
end
end % igrup loop end
%%%%% GROUP RESULTS
%%%%% GROUP RESULTS
if i_DFA == 1 %Detrended Fluctuation Analysis
end
if i_ApEnt == 1 %Approximate Entropy Analysis
end
if i_spectral_analysis == 1 %Spectral Analysis
end
if i_spectrogram == 1 %Time Frequency Analysis
end

end %itestyear loop end
%%%%% TEST YEAR RESULTS
%%%%% TEST YEAR RESULTS
if i_DFA == 1 %Detrended Fluctuation Analysis
end
if i_ApEnt == 1 %Approximate Entropy Analysis
end
if i_spectral_analysis == 1 %Spectral Analysis
end
if i_spectrogram == 1 %Time Frequency Analysis
end

end %icondition loop end
%%%%% CONDITION RESULTS
%%%%% CONDITION RESULTS
if i_DFA == 1 %Detrended Fluctuation Analysis
end
if i_ApEnt == 1 %Approximate Entropy Analysis
end
if i_spectral_analysis == 1 %Spectral Analysis
end
if i_spectrogram == 1 %Time Frequency Analysis
end
end %idirection loop end

%save data that needs to be saved
if DFASave ==1
end
if ApEntSave == 1 && i_ApEnt == 1
    save([result_dir3 time_stamp '\ApEntropy_collect.mat'],'ApEntropy_collect')
    delete([result_dir3 '\newest*.mat'])
    save([result_dir3 '\newest\ApEntropy_collect.mat'],'ApEntropy_collect')
elseif ApEntSave == 1 && i_ApEnt == 2
    save([result_dir5 time_stamp '\ApEntropy_collect_sub.mat'],'ApEntropy_collect_sub')
    delete([result_dir5 '\newest*.mat'])
    save([result_dir5 '\newest\ApEntropy_collect_sub.mat'],'ApEntropy_collect_sub')
end

```

```

varnames = {'Group','Condition','Trial'};

if i_DFA == 1 || i_DFA == 2

    %collect data for SPSS analysis and write to excel
    %file in the results directory (indices 1:44)
    %coorespond to EO and indices 45:88 coorespond to
    %EC. This WILL ONLY WORK with these indices IF
    %idirection is ONLY set to EITHER ML or AP. NOT
    %BOTH).

    % xlswrite('C:\Time_Freq_Research\Data_Results\SPSS_input.xlsx','alpha1_sub(:,1:44)', 1,'C2')
    % xlswrite('C:\Time_Freq_Research\Data_Results\SPSS_input.xlsx','alpha1_sub(:,45:88)', 1,'D2')
    % xlswrite('C:\Time_Freq_Research\Data_Results\SPSS_input.xlsx','alpha2_sub(:,1:44)', 1,'E2')
    % xlswrite('C:\Time_Freq_Research\Data_Results\SPSS_input.xlsx','alpha2_sub(:,45:88)', 1,'F2')
    % xlswrite('C:\Time_Freq_Research\Data_Results\SPSS_input.xlsx','AAMV_sub(:,1:44)', 1,'G2')
    % xlswrite('C:\Time_Freq_Research\Data_Results\SPSS_input.xlsx','AAMV_sub(:,45:88)', 1,'H2')
    % xlswrite('C:\Time_Freq_Research\Data_Results\SPSS_input.xlsx','crossover_scale_sub(:,1:44)', 1,'I2')
    % xlswrite('C:\Time_Freq_Research\Data_Results\SPSS_input.xlsx','crossover_scale_sub(:,45:88)', 1,'J2')

    % %Perform Statistical Analysis on the Results
    %
    % all_collected = [alpha1_mod alpha2_mod AAMV_mod group_factor condition_factor_numeric trial_factor];
    %
    % %perform an N-Way ANOVA and reduce analysis complexity for each anovan by
    % %comparing the p value to the set variable "pval" specified in
    % %Init_parameters.
    %
    % %perform an initial anovan which will include all relevant factors
    % [p1_init, tbl1_init, stats1_init, terms1_init] = anovan(alpha1_mod,{group_factor condition_factor trial_factor},'varnames','varnames','model', 'full');
    % [p2_init, tbl2_init, stats2_init, terms2_init] = anovan(alpha2_mod,{group_factor condition_factor trial_factor},'varnames','varnames', 'model', 'full');
    % [p3_init, tbl3_init, stats3_init, terms3_init] = anovan(AAMV_mod,{group_factor condition_factor trial_factor},'varnames','varnames', 'model', 'full');
    % [p4_init, tbl4_init, stats4_init, terms4_init] = anovan(crossover_scale,{group_factor condition_factor trial_factor},'varnames','varnames', 'model', 'full');
    %
    % [table, chi2, p, factorvals] = crosstab(group_factor,condition_factor,trial_factor);
    %
    % %reduce the number of included factors based on the set pval and the p
    % %values resulting from the initial anovan
    % %for first analysis: alpha1
    % pvals1 = cell2mat(tbl1_init(2:length(tbl1_init)-2,7));
    % ind1 = find(pvals1>pval);
    % terms1_init(ind1,:) = [];
    % [p1, tbl1, stats1, terms1] = anovan(alpha1_mod,{group_factor condition_factor trial_factor},terms1_init,3,varnames');
    %
    % %for second analysis: alpha2
    % pvals2 = cell2mat(tbl2_init(2:length(tbl2_init)-2,7));
    % ind2 = find(pvals2>pval);
    % terms2_init(ind2,:) = [];
    % [p2, tbl2, stats2, terms2] = anovan(alpha2_mod,{group_factor condition_factor trial_factor},terms2_init,3,varnames');


```

```

%
% % for third analysis: AAMV
% pvals3 = cell2mat(tbl3_init(2:length(tbl3_init)-2,7));
% ind3 = find(pvals3>pval);
% terms3_init(ind3,:) = [];
% [p3, tbl3, stats3, terms3] = anovan(AAMV_mod,{group_factor condition_factor
trial_factor},terms3_init,3,varnames');
%
% % for fourth analysis: crossover scale
% pvals4 = cell2mat(tbl4_init(2:length(tbl4_init)-2,7));
% ind4 = find(pvals4>pval);
% terms4_init(ind4,:) = [];
% [p4, tbl4, stats4, terms4] = anovan(crossover_scale,{group_factor condition_factor
trial_factor},terms4_init,3,varnames');
%
% % perform a multiple comparison test (Tukey Test)
% alpha1_tukey = multcompare(stats1,'Dimension',[1 2]);
% alpha2_tukey = multcompare(stats2,'Dimension',[1 2]);
% AAMV_tukey = multcompare(stats3,'Dimension',[1 2]);
% crossover_tukey = multcompare(stats4,'Dimension',[1 2]);

% Perform Statistical Analysis on the Results when trials are averaged
varnames = {'Group','Condition'};
%
% perform an N-Way ANOVA and reduce analysis complexity for each anovan by
% comparing the p value to the set variable "pval" specified in
% Init_parameters.
%
% perform an initial anovan which will include all relevant factors
[p1_init, tbl1_init, stats1_init, terms1_init] = anovan(alpha1_sub,{group_factor_sub
condition_factor_sub},'varnames','varnames','model', 'full');
[p2_init, tbl2_init, stats2_init, terms2_init] = anovan(alpha2_sub,{group_factor_sub
condition_factor_sub},'varnames','varnames', 'model', 'full');
[p3_init, tbl3_init, stats3_init, terms3_init] = anovan(AAMV_sub,{group_factor_sub
condition_factor_sub},'varnames','varnames', 'model', 'full');
[p4_init, tbl4_init, stats4_init, terms4_init] = anovan(crossover_scale_sub,{group_factor_sub
condition_factor_sub},'varnames','varnames', 'model', 'full');

[table, chi2, p, factorvals] = crosstab(group_factor_sub,condition_factor_sub);
%
% reduce the number of included factors based on the set pval and the p
% values resulting from the initial anovan
% for first analysis: alpha1
pvals1 = cell2mat(tbl1_init(2:length(tbl1_init)-2,7));
ind1 = find(pvals1>pval);
terms1_init(ind1,:) = [];
[p1, tbl1, stats1, terms1] = anovan(alpha1_sub,{group_factor_sub
condition_factor_sub},terms1_init,2,varnames');

% for second analysis: alpha2
pvals2 = cell2mat(tbl2_init(2:length(tbl2_init)-2,7));
ind2 = find(pvals2>pval);
terms2_init(ind2,:) = [];

```

```

[p2, tbl2, stats2, terms2] = anovan(alpha2_sub,{group_factor_sub
condition_factor_sub},terms2_init,2,varnames');

% for third analysis: AAMV
pvals3 = cell2mat(tbl3_init(2:length(tbl3_init)-2,7));
ind3 = find(pvals3>pval);
terms3_init(ind3,:) = [];
[p3, tbl3, stats3, terms3] = anovan(AAMV_sub,{group_factor_sub
condition_factor_sub},terms3_init,2,varnames');

% for fourth analysis: crossover scale
pvals4 = cell2mat(tbl4_init(2:length(tbl4_init)-2,7));
ind4 = find(pvals4>pval);
terms4_init(ind4,:) = [];
[p4, tbl4, stats4, terms4] = anovan(crossover_scale_sub,{group_factor_sub
condition_factor_sub},terms4_init,2,varnames');

%perform a multiple comparison test (Tukey Test)
alpha1_tukey = multcompare(stats1,'Dimension',[1 2]);
alpha2_tukey = multcompare(stats2,'Dimension',[1 2]);
AAMV_tukey = multcompare(stats3,'Dimension',[1 2]);
crossover_tukey = multcompare(stats4,'Dimension',[1 2]);
end

%statistical analysis of Aproximate Entropy results
if i_ApEnt == 1 || i_ApEnt == 2
% [pAE_init, tblAE_init, statsAE_init, termsAE_init] = anovan(ApEntropy_tr,{group_factor condition_factor
trial_factor},'varnames','varnames','model', 'full');
%
% pvalsAE = cell2mat(tblAE_init(2:length(tblAE_init)-2,7));
% indAE = find(pvalsAE>pval);
% termsAE_init(indAE,:) = [];
% [pAE, tblAE, statsAE, termsAE] = anovan(ApEntropy_tr,{group_factor condition_factor
trial_factor},termsAE_init,3,varnames');
%
% Ap_Ent_Tukey = multcompare(statsAE,'Dimension', [1,2]);
%
%you can also perform ANOVA and Tukey on trial averaged data
varnames = {'Group','Condition'};
[pAE_init, tblAE_init, statsAE_init, termsAE_init] = anovan(ApEntropy_sub,{group_factor_sub
condition_factor_sub},varnames,'varnames','model', 'full');

pvalsAE = cell2mat(tblAE_init(2:length(tblAE_init)-2,7));
indAE = find(pvalsAE>pval);
termsAE_init(indAE,:) = [];
[pAE, tblAE, statsAE, termsAE] = anovan(ApEntropy_sub,{group_factor_sub
condition_factor_sub},termsAE_init,2,varnames');

Ap_Ent_Tukey = multcompare(statsAE,'Dimension', [1,2]);

xlswrite('C:\Time_Freq_Research\Data_Results\SPSS_input.xlsx',ApEntropy_sub(:,1:44)', 1,'K2')
xlswrite('C:\Time_Freq_Research\Data_Results\SPSS_input.xlsx',ApEntropy_sub(:,45:88)', 1,'L2')
end

```

iii. DFA Analysis

DFA_main.m and DFA.m are functions called by Process.m to calculate the fluctuation equation of the Detrended Fluctuation Analysis.

```
function [D,Alpha, F_n, AAMV]=DFA_main(DATA,n,range)
% DATA should be a time series of length(DATA) greater than 2000, and of column vector.
%A is the alpha in the paper
%D is the dimension of the time series
%n can be changed to your interest
%AAMV is the average absolute maximal velocity
%range is the non-overlapping velocity window range used to calculate AAMV
%
%define the number of divisions based on range and length of Data
windows = fix(length(DATA)/range);
divisions = 0:(windows-1);
for irange = 1:windows
    %find the rectified peaks of DATA
    pks = findpeaks(abs(DATA((1+range*divisions(irange)):(range + range*divisions(irange))))));
    %take the mean of the peaks over the given range
    mini_mean(irange) = mean(pks);
    clear pks
end
%find the average absolute maximal velocity by take the mean of the mini
%means
AAMV = mean(mini_mean);
N1=length(n);
F_n=zeros(N1,1);
for i=1:N1
    F_n(i)=DFA(DATA,n(i),1);
end

n=n';
% plot(log(n),log(F_n));
% xlabel('n')
% ylabel('F(n)')
A=polyfit(log(n(1:end)),log(F_n(1:end)),1);
Alpha=A(1);
D=3-A(1);

return

function output1=DFA(DATA,win_length,order)
```

```

N=length(DATA);
n=floor(N/win_length);
N1=n*win_length;
y=zeros(N1,1);
Yn=zeros(N1,1);

fitcoef=zeros(n,order+1);
mean1=mean(DATA(1:N1));
for i=1:N1

    y(i)=sum(DATA(1:i)-mean1);
end
y=y';
for j=1:n
    fitcoef(j,:)=polyfit(1:win_length,y(((j-1)*win_length+1):j*win_length),order);
end

for j=1:n
    Yn(((j-1)*win_length+1):j*win_length)=polyval(fitcoef(j,:),1:win_length);
end

sum1=sum((y'-Yn).^2)/N1;
sum1=sqrt(sum1);
output1=sum1;

```

iv. Approximate Entropy Analysis

The approximate entropy was calculated using a function ApEnt.m called by Process.m.

```

%function estimates approximate entropy of time series u (assumed to be a %column vector)

function [ApEntropy]=ApEnt(u,m,r)
rlim=r*std(u); %establish the limits of similarity for vector components
[N1 N2]=size(u);

%vector sequences x of length m are created from consecutive elements of
%vector u starting with the first element
icount=0;
for i=1:N1-m %starting with the first vector sequence, determine the conditional probability using the current x as
the template
    x_template=u(i:i+m); % this is the template vector
    A=0;
    B=0;

    for j=1:N1-m
        if j ~= i
            x=u(j:j+m); % this is the conditioning vector
            x_diff=abs(x_template-x); %compare the template to each conditioning vector
            if all(x_diff(1:m) < rlim) %check to see if the first m components are similar
                B=B+1;
            end
        end
    end
    ApEntropy=A/(B*(N1-m));
end

```

```

if (x_diff(m+1) < rlim) %check to see if the m+1 components are similar
    A=A+1;
end

end
end
end

if A & B ~= 0 %exclude if either the numerator or denominator is zero
    icount=icount+1;
    cond_prob(icount)=A/B;
end
end

%cond_prob
ApEntropy=-mean(log(cond_prob));

```

v. Derivative calculation

The derivative was calculated using a fourth order accurate derivative function. Called by Process.m.

```

% DERIVATIVE.M Differentiation program to calculate the first and second
% derivatives of numerical data. Select either a
% second (a=1) or fourth (a=2) order accurate scheme.
% These parameters must be defined before calling this function:
% dt = time step
% a = 1 or 2 to chose second or fourth order of accuracy respectively
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function [vel,acc] = derivative(x,a,dt)

[m,n] = size(x);

x0 = x(3:m-2,:);
xp1 = x(4:m-1,:);
xp2 = x(5:m,:);
xm1 = x(2:m-3,:);
xm2 = x(1:m-4,:);

%SECOND ORDER ACCURATE VELOCITY SCHEME
if a==1

c0 = 2;
c1 = 0;
c2 = -1;
c3 = 0;
c4 = 1;

```

```

c5 = 0;

%FOURTH ORDER ACCURATE VELOCITY
elseif a==2

c0 = 12;
c1 = 1;
c2 = -8;
c3 = 0;
c4 = 8;
c5 = -1;
end

DX = (c1*xm2 + c2*xm1 + c3*x0 + c4*xp1 +c5*xp2)/c0;
vel(3:m-2,:) = DX/dt;

clear c0 c1 c2 c3 c4 c5 DX

%SECOND ORDER ACCURATE ACCELERATION SCHEME
if a==1

c0 = 1;
c1 = 0;
c2 = 1;
c3 = -2;
c4 = 1;
c5 = 0;

%FOURTH ORDER ACCURATE ACCELERATION SCHEME
elseif a==2

c0 = 12;
c1 = -1;
c2 = 16;
c3 = -30;
c4 = 16;
c5 = -1;
end

DDX = (c1*xm2 + c2*xm1 + c3*x0 + c4*xp1 +c5*xp2)/c0;
acc(3:m-2,:) = DDX/(dt*dt);

% USE FORWARD FORMULAS FOR INITIAL POINTS AND BACKWARD FORMULAS FOR END POINTS
% VEL AND ACC BEING SECOND AND FIRST ORDER ACCURATE RESPECTIVELY

vel(1,:) = (-3*x(1,:)+4*x(2,:)-x(3,:))/2*dt;
vel(2,:) = (-3*x(2,:)+4*x(3,:)-x(4,:))/2*dt;

acc(1,:) = (x(1,:)-2*x(2,:)+x(3,:))/(dt*dt);
acc(2,:) = (x(2,:)-2*x(3,:)+x(4,:))/(dt*dt);

vel(m-1,:) = (x(m-3,:)-4*x(m-2,:)+3*x(m-1,:))/2*dt;
vel(m,: ) = (x(m-2,:)-4*x(m-1,:)+3*x(m,:))/2*dt;

```

```
acc(m-1,:)= (x(m-3,:)-2*x(m-2,:)+x(m-1,:))/(dt*dt);  
acc(m,:)= (x(m-2,:)-2*x(m-1,:)+x(m,:))/(dt*dt);
```

Appendix B: Further Analysis

i. Time Frequency Analysis

Time frequency analysis (TFA) was explored at the beginning of the previous study, however it was abandoned in favor of DFA since DFA offered a more obvious analysis path and more finite result variables. It is our belief that TFA could be a very useful tool in the study of the COPv time series, since it is used in many non-stationary time series applications. Below is the initial exploratory code which offers a beginning to the study of COPv in PD with TFA. It is also called the Process.m, mentioned in Appendix A.

```
%calculate and plot the spectrogram of the COP_AP signal. This allows  
%visualization of the nonstationarity of the signal
```

```
%Changes made on 1-14-15 by JRH
```

```
%*****  
%the following commands are to be used for model data  
% itestyear=3;  
% igrup=1;  
% isubject=1;  
% subnum=['Model HC'];  
% COP_AP=Model_dt_COPAP(:,2);  
%*****  
  
plot_title=[COP_ COP_direction_name{COP_direction} _Test Yr_,int2str(itestyear),_Group_,int2str(igroup),...  
'_sub#_',subnum(isubject,:),condition_string(icondition,:)];  
  
sample_time=30; %duration in seconds  
SF=1000; %sampling frequency  
t=1/SF:1/SF:sample_time; %time vector  
dt=1/SF; %time between samples  
  
%load the sample data of COP in the AP direction  
%load COP_AP_example.mat  
y = COP;  
N = length(y); % Length of signal  
  
NFFT = 2^nextpow2(N); % Next power of 2 from length of y  
Y = fft(y,NFFT)/N;  
f = SF/2*linspace(0,1,NFFT/2+1);  
  
% % Generate the plot, title and labels.  
% figure(1000*itestyear+100*igrup+isubject);  
% hold on
```

```

% set(fh,'color','white','visible','off');
% subplot(2,1,1); %(311);
% plot(t,y-mean(y),'k');
% title(plot_title);
% axis([0 30 -30 30]);
% xlabel('Time (s)',FontName,'Times New Roman','fontsize',10);
% ylabel('Amplitude',FontName,'Times New Roman','fontsize',10);
% set(gca,FontName,'Times New Roman','fontsize',10);
% %
% % Frequency domain plots
% subplot(2,1,2);%(312);
% plot(f,2*abs(Y(1:NFFT/2+1)));
% irange=[1:100];
% plot(f(irange),2*abs(Y(irange)));
% axis([0 1.5 0 10]);
% xlabel('Frequency (cycles/second)',FontName,'Times New Roman','fontsize',10);
% ylabel('Amplitude',FontName,'Times New Roman','fontsize',10);
% set(gca,FontName,'Times New Roman','fontsize',10);

%define the range of window lengths to use
maxPSD_scale = 1;
L = [7500];
overlap_factor = 0.99;
rows = ceil(sqrt(length(L)));
cols = round(sqrt(length(L)));
countL = 0;
figure('Name',plot_title);
for iL = L
    countL = countL+1;
    %compute the spectrogram for the COP data
    color = (0:1:100);
    %define the window function
    windowL = iL;
    Noverlap = fix(overlap_factor*windowL);
    window=hann(windowL, 'periodic');
    % freq = [0.001:.01:10]; %frequency target range for high freq and smaller windows
    % freq = [0.001:.01:5]; %frequency target range for low and large
    % windows
    [S,F,T,P] = spectrogram(y,window,Noverlap,freq,1000);
    length_time = fix((length(y) - Noverlap)/(length(window)-Noverlap));

    subplot(rows,cols,countL)
    surf(T,F,P./max(max(P)), 'edgecolor','none')
    axis xy; axis tight; colormap(jet); colorbar; view([0,90]); axis([0 fix(T(end))+1 0 (fix(F(end))+1) 0
    maxPSD_scale 0 maxPSD_scale]); %view([-127.5,30])

    title(['hann' num2str(windowL)])
    % xlabel('Time (s)');
    % ylabel('Frequency (cycles/second)');
end
%%

%perform a Fractal Dimension Analysis

% figure('name', ['FD' plot_title]);

```

```

% [n, r] = boxcount(P./max(max(P)), 'slope');
% df = -diff(log(n))./diff(log(r));
% store_df(isubject,igroup,icondition) = mean(df(4:8));
% store_std(isubject,igroup,icondition) = std(df(4:8));
% disp(['Fractal dimension, Df = ' num2str(mean(df(4:8))) ' +/- ' num2str(std(df(4:8)))]);
%%

%perform a PCA Analysis
[number_of_components,explained] = PCA_required(P,90);
store_explained(isubject,igroup,icondition)=explained(1);
store_components(isubject,igroup,icondition) = number_of_components;
figure('name',[['PCA' plot_title]]);
pareto(explained)
title(plot_title)
%%

if i_save == 1
    saveas(gcf,[result_dir '\' plot_title],'jpg')
end
%find the gradient and plot in the freq vs time plane
% [PSDx,PSDy] = gradient(P.,2.,.5085);
% PSDz = sqrt(PSDx.^2 + PSDy.^2);
% figure(3000*itestyear+100*igroup+isubject);
% hold on
% % set(fh,'color','white','visible','off');
% % subplot(2,1,1); %(311);
% % plot(t,y-mean(y),'k');
% % title(plot_title);
% % axis([0 30 -30 30]);
% % xlabel('Time (s)','FontName','Times New Roman','fontsize',10);
% % ylabel('Amplitude','FontName','Times New Roman','fontsize',10);
% % set(gca,'FontName','Times New Roman','fontsize',10);
% % subplot(2,1,2)
% surf(T,F,PSDz); axis xy; axis tight; colormap(jet); colorbar; view([-127.5,30]);title(plot_title);;

%store frequency and power data for each trial. m x n x p where m is
%data, n is isubject and p is igroup
% S_tot(:,:,isubject,igroup,itestyear) = abs(S);
% PSD_tot(:,:,isubject,igroup,itestyear)=P;
%
% mean_S(:,:,isubject,igroup,itestyear) = mean(S_tot(:,:,isubject,igroup,itestyear));
% mean_PSD(:,:,isubject,igroup,itestyear) = mean(PSD_tot(:,:,isubject,igroup,itestyear));
%
% std_S(:,:,isubject,igroup,itestyear) = std(S_tot(:,:,isubject,igroup,itestyear));
% std_PSD(:,:,isubject,igroup,itestyear) = std(PSD_tot(:,:,isubject,igroup,itestyear));
%
% mean_S_group(:,:,igroup,itestyear) = mean(mean_S(:,:,isubject,igroup,itestyear));
% mean_PSD_group(:,:,igroup,itestyear) = mean(mean_PSD(:,:,isubject,igroup,itestyear));
%
% std_S_group(:,:,igroup,itestyear) = std(mean_S(:,:,isubject,igroup,itestyear));
% std_PSD_group(:,:,igroup,itestyear) = std(mean_PSD(:,:,isubject,igroup,itestyear));

```

ii. Spectral Analysis

Time frequency analysis code also calls the m file Spectral_analysis.m seen below. It is used to look at the spectral density of the signal assuming signal stationarity.

```
function [ median_freq,f,mx,amp] = Spectral_analysis(Fs,x)
%Spectral_analysis
% determine the spectrum of the signal x provided
% Fs = sampling frequency
% x = signal of arbitrary length
% edited from routing found on Matlab Central
% http://www.mathworks.com/support/tech-notes/1700/1702.html?BB=1

% Use next highest power of 2 greater than or equal to length(x) to calculate FFT.
nfft= 2^(nextpow2(length(x)));

% Take fft, padding with zeros so that length(fft) is equal to nfft
fftx = fft(x,nfft);

% Calculate the numberof unique points
NumUniquePts = ceil((nfft+1)/2);

% FFT is symmetric, throw away second half
fftx = fftx(1:NumUniquePts);

% Take the magnitude of fft of x and scale the fft so that it is not a function of the length of x
mx = abs(fftx)/length(x);
amp = mx;
% Take the square of the magnitude of fft of x.
mx = mx.^2;

% Since we dropped half the FFT, we multiply mx by 2 to keep the same energy.
% The DC component and Nyquist component, if it exists, are unique and should not be multiplied by 2.

if rem(nfft, 2) % odd nfft excludes Nyquist point
    mx(2:end) = mx(2:end)*2;
    amp(2:end) = amp(2:end)*2;
else
    mx(2:end -1) = mx(2:end -1)*2;
    amp(2:end-1) = amp(2:end-1)*2;
end

% This is an evenly spaced frequency vector with NumUniquePts points.
f = (0:NumUniquePts-1)*Fs/nfft;

% Generate the plot, title and labels.
% figure(20)
% plot(f,mx);
% title('Power Spectrum of your signal');
% xlabel('Frequency (Hz)');
```

```

% ylabel('Power');
% pause

%determine the median frequency, the frequency which divides the power in
%half
[m n]=size(mx);

Area_mx = trapz(mx);
Median_area = .5*Area_mx;

Runn_Int = 0; % Initialize a running integral
for i = 1:m-1
    Lim_int = mx(i:i+1); % Successive points are the limits of integration
    Inst_Int = trapz(Lim_int); % Calculate the integral between two points
    Runn_Int = Runn_Int + Inst_Int; % Update the running integral
    Area_Vector(i) = Runn_Int;
end

Freq_indx = find(Area_Vector > Median_area);
median_freq = f(Freq_indx(1)); % Median freq

```

end