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## Nonlinear Computational Analysis of Postural Stability and its Relationship to Estrogen Deficiency in Postmenopausal Women

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NONLINEAR COMPUTATIONAL ANALYSIS OF POSTURAL  
STABILITY AND ITS RELATIONSHIP TO ESTROGEN  
DEFICIENCY IN POSTMENOPAUSAL WOMEN

by  
Zachary Mitchell

A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of  
the requirements of the Sally McDonnell Barksdale Honors College.

Oxford  
May 2018

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## ABSTRACT

This study aims to determine if multi-scale entropy analysis will more accurately differentiate the postural stability of postmenopausal women as a function of their estrogen status than traditional measures of postural assessment. The study participants included 7 non-Hormone Replacement Therapy (HRT) postmenopausal women (mean age = 57) and 4 HRT postmenopausal women (mean age = 55). Postural stability was measured with the NeuroCom Equitest and the use of conditions 1-4 of the Sensory Organization Test (SOT). The subjects received an equilibrium score for each condition with a score near 100 representing good postural stability. A modification of the “Multi-Scale Entropy Analysis” Matlab program created by Costa et al. was used to analyze the raw center of pressure (COP) trajectory data measured for each condition in both the medial lateral (x-direction) and anterior posterior (y-direction) directions. The Matlab program created complexity index (CI) scores where a high CI is indicative of low postural stability and a low CI is representative of good postural stability.

A basic t-test of unequal variances was performed on the CI scores between non-HRT and HRT subjects, in addition to the equilibrium scores between non-HRT and HRT subjects. The t-test revealed both the NeuroCom Equitest and MSE analysis identified a significant difference in postural stability between non-HRT subjects and HRT subjects an equal number of times (n=2), where HRT subjects exhibited better postural stability than non-HRT. The MSE analysis method was able to significantly differentiate postural stability between non-HRT and HRT subjects in SOT 1 (p=0.0432), whereas the NeuroCom Equitest did not. This is of significance

because the subject is standing still on the force plate without having their balance disrupted. Previous studies have had to manipulate the surroundings and perturb the subject's balance to significantly differentiate postural stability between non-HRT and HRT subjects. The findings from this study indicate that MSE analysis may provide a higher level of sensitivity necessary to assess postural stability as a function of estrogen status. The effect of estrogen on the preservation of postural stability in postmenopausal women may provide further evidence for the consideration of estrogen as a neuro-protectant.

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## INTRODUCTION

As women reach the ages of 46 to 52 they enter menopause, which is characterized by a decrease in the sex steroid, estrogen [1]. Recent studies show postmenopausal women are more likely to fall than their younger counterparts who have not yet entered menopause [2]. It is considered that the increased risk of falls is related to estrogen deficiency in postmenopausal women [3]. This estrogen deficiency experienced by postmenopausal women has been shown to result in low bone mineral density (BMD) and a reduction in muscle strength [4, 5]. The reduction in muscle strength predisposes postmenopausal women to falls due to their inability to respond to external stimuli appropriately [6]. Thus, by combining the effect of a reduction in muscle strength and low BMD, postmenopausal women become more susceptible to fractures following a fall. A fall resulting in a fracture places postmenopausal women at a greater risk of developing further complications that could potentially lead to death [3, 7].

Hormone replacement therapy (HRT) has been introduced as a preventative measure for falling and fractures by increasing postural stability in postmenopausal women. Studies have shown that HRT has increased muscle strength and prevented further BMD loss, which has led to the consideration they contribute to a decrease in falls [5]. However, despite estrogen deficiency decreasing BMD and subsequently increasing the risk of fracture upon falling, it has been identified that there is no relationship between an increase in risk for falls and BMD. Cangussu found there was no statistical difference between postural stability and the relationship of BMD for postmenopausal

women on HRT and BMD for postmenopausal women not on HRT. Therefore, HRT's effect on postmenopausal women regarding BMD is a decrease in risk in fracture upon falling; not a decrease in risk of falling [8].

Despite the positive effects HRT has on BMD and muscle strength, studies have shown routinely exercising, such as resistance training, has the same results of decreasing the risk of falling in postmenopausal women [9]. Teixeira et al. concluded HRT showed no effects on body composition; however, it did protect postmenopausal women from losing muscle strength. In the study, one group of postmenopausal women received HRT while the additional group of postmenopausal women did not receive HRT; however, both groups were enrolled in a one-year resistance-training program. Upon completion of the program, it was concluded the muscle strength of both groups improved significantly regardless if HRT was administered [10]. Along with the increase in muscle strength, women experienced a greater postural balance [9].

Although postmenopausal women have exhibited an increase in postural stability while performing resistance training, they have shown the same results while only receiving HRT [11, 12]. Specifically, long-term administration of HRT shortly after the onset of menopause rapidly increases postural stability to that seen in premenopausal women [13, 14]. With multiple studies finding HRT maintains postural stability in women without supplemental exercises; muscle weakness can be ruled out as a key factor in the risk of falls in postmenopausal women [10-12, 15].

Naessen demonstrated the positive effects of long-term HRT on postural stability in postmenopausal women when compared to postmenopausal women not using HRT and concluded the dynamics between HRT and fracture risk were too rapid to influence

BMD. Therefore, the increase in postural stability is considered either an effect on the central nervous system or the preservation of muscle strength, connective tissue and improvement in mood that lead to an increase in physical activity [11, 12, 16]. However, since resistance training can preserve muscle strength and connective tissue, estrogen's role in maintaining postural stability is best explained as an effect on the central nervous system [11]. Further consideration of estrogen's effect on the central nervous system is supported by its role in the facilitation of the neuronal transmission function [1, 17]. Sufficient levels of estrogen in the blood enable adequate excitation of the sensorimotor cortex, which is necessary for the maintenance of both the function of motor learning and coordination. When the level of estrogen decreases to that seen in postmenopausal women, a decrease in the function of the sensorimotor cortex is observed [17]. This decrease in function ultimately leads to the insufficient use of the somatosensory and vestibular systems, thus leading to a decrease in postural stability [11].

Additional studies have examined the relationship between estrogen and postural stability in the central nervous system; however, they have all only performed linear analysis on their data to determine the causal effects of estrogen deficiency [11, 17, 18]. To our knowledge, postural stability in postmenopausal women either on HRT or not on HRT has not been examined with nonlinear analysis. Nonlinear analysis can examine the variability in recorded data and uncover overlooked information that is not normally detected using linear analysis [19, 20]. The variability in center of pressure (COP) data reveals an important condition in the function of motor movements. The function of variability in human movement used to be considered problematic, however, Stergiou identified variability as an important characteristic of movement [19].

The present study aims to build off the consideration that estrogen's effect on the central nervous system plays a vital role in the maintenance of postural stability [11, 12]. Through nonlinear analysis of the variability in movement of postmenopausal women, we expect to identify a decrease in estrogen in postmenopausal women results in a decrease in postural stability and an increase in risk of falling compared to postmenopausal women on HRT. The nonlinear analysis of variability in movement will give insight into the complexity of the subject's physiological system. If the subject exhibits a large amount of complexity, then their physiological system is considered to possess the required flexibility to adequately respond to external stimuli, thus providing sufficient postural stability. Whereas, a subject displaying low levels of complexity cannot sufficiently respond to external stimuli and will, therefore, exhibit low postural stability [21]. According to the "Loss of Complexity Hypothesis," as individuals age, the complexity of interactions in their physiological system begins to decrease [22, 23]. Since the average age of the subjects is  $n= 56$ , independent of menopause, they are already experiencing a decrease in complexity in their system due to the process of aging.

The results of the study are expected to show postmenopausal women on HRT exhibit a greater amount of complexity in their movement compared to non-HRT users. The rationale behind this consideration is based on the results that elderly long-term HRT postmenopausal women reported a better postural balance function than non-HRT users [11]. Therefore, if HRT users exhibit a better postural balance than non-HRT users, then their physiological system will possess a larger degree of complexity than that of non-HRT users [21].

## CHAPTER I: TESTING STABILITY

Postural stability is measured using the NeuroCom Balance Manager assessment device through the Sensory Organization Test (SOT) and the Motor Control Test (MCT). The NeuroCom Balance Manager records the center of pressure (COP) movements of the subject throughout the tests by utilizing the force platform beneath the subject. The SOT examines somatosensory, visual and vestibular systems. Whereas, the MCT determines the subject's ability to recover from an unexpected disturbance in the force platform. Together, the results from both the SOT and MCT are interpreted together to depict an accurate profile of the subject's postural stability [24].

During the SOT, sway referencing is utilized because the force platform beneath the patient moves in addition to the surroundings in response to the subject's anterior/posterior (AP) sway. Sway referencing refers to the tilting of the force platform or visual surrounding as the subject's AP sway fluctuates. Involving sway referencing requires the subject to rely on their nervous system to more accurately interpret the sensory inputs from their surroundings. Combining sway referencing with the presence or absence of eyesight in the subject further increases the subject's reliance on their vestibular and somatosensory systems [24].

There are six different conditions in the SOT, however, for this study only conditions one through four are performed due to their real-world applicability. The four conditions consist of (1) eyes open and fixed platform; (2) eyes closed and fixed platform; (3) eyes open and sway-referenced surrounding; (4) eyes open and sway-

referenced platform (Fig.1). For each of the four conditions, three trials are performed for twenty seconds each time. Before each trial, the subject is instructed to stand with their feet on the designated area on the platform (shoulder width apart), stand quietly, and maintain their balance. At the start of the trial, the subject is also counted down and given confirmation that the trial has begun [24].

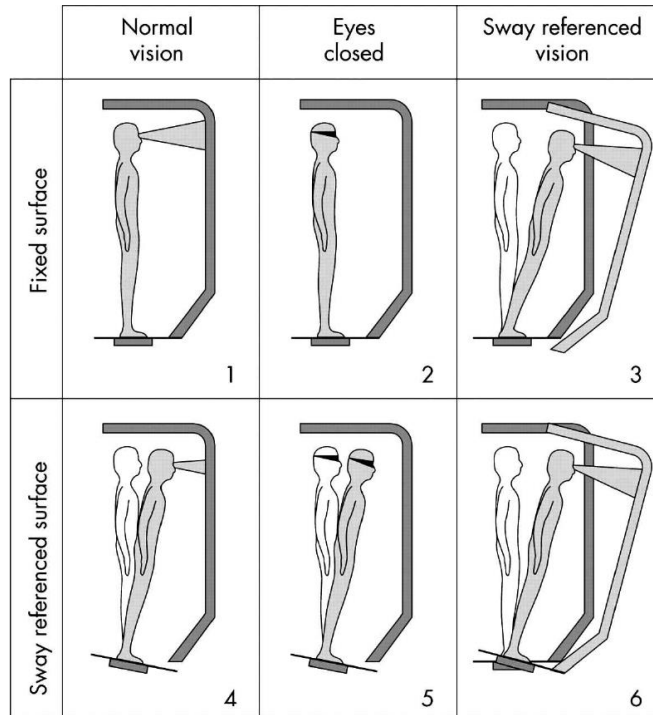


Figure 1. The six conditions of the Sensory Organization Test [30]

After the completion of each condition, the NeuroCom Balance Manager displays the results from the three trials in the form of an equilibrium score (Fig. 2). The equilibrium score is a comparison of the subject's AP sway during the trial and the theoretical sway stability limit (12.5 degrees). If the subject's equilibrium score is near 100, then they experienced minimal sway and adequate postural stability (green bars). A low score is indicative of the subject swaying to the limit of stability and therefore experiencing poor postural stability (red bars). The shaded area of the graph is

representative of the age-matched normative results. Therefore, a green bar indicates the subject is either at or above the normative results, and a red bar indicates the subject is below the normative results [24].

The equilibrium scores for the three trials of each condition are then averaged together to create an average equilibrium score for conditions 1-4. The average equilibrium scores are used to identify the subject's reliance on the somatosensory and visual systems. The ratio condition 2: condition 1 represents the subject's reliance on their somatosensory system to maintain their postural stability. The subject's reliance on their visual system to maintain their postural stability is found from the ratio condition 4: condition 1 [24].

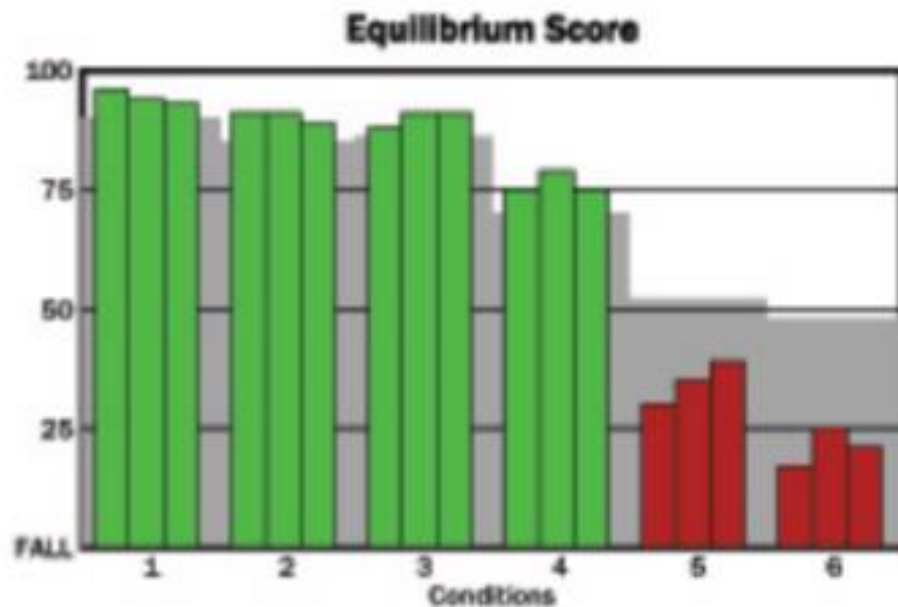


Figure 2. Sensory Organization Test Example Results [30]

The SOT is then followed by the MCT to evaluate the autonomic motor system's involvement in maintaining the subject's postural stability. The MCT consists of six conditions: (1) small backward translation; (2) medium backward translation; (3) large

backward translation; (4) small forward translation; (5) medium forward translation; (6) large forward translation (Fig. 3). [30] The small translations are indicative of a minimum threshold, whereas, the large translations elicit an extreme response from the subject. There are three trials for each condition with a randomized delay of 1.5 to 2.5 seconds between each trial [25]. The size of each translation is scaled to the subject's height, therefore each subject experiences equivalent translational forces in both the forward and backward direction [24].

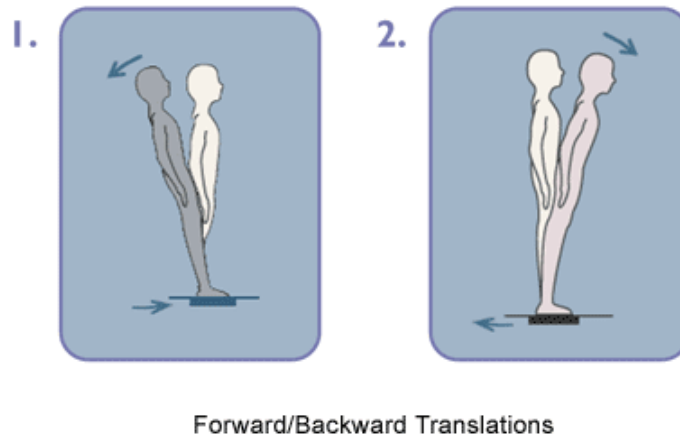


Figure 3. The Six Condition of the Motor Control Test [30]

The results from each condition of the MCT are displayed as Weight Symmetry, Latency, and Amplitude Scaling (Fig. 4). These values are determined independently for the left leg and the right leg. Similar to the graph of the equilibrium scores for the SOT, the subject's scores for Weight Symmetry, Latency, and Amplitude Scaling are compared to age-matched normative results. The shaded regions in the graphs in Figure 4 indicate the age-matched normative data to which the subject's results are compared [24].



The Weight Symmetry value represents the subject's weight distribution in both the left and right legs. A Weight Symmetry score near 100 indicates the subject had their weight relatively centered between both of their legs prior to the initiation of the force platform translation. The Latency score of the subject is the time (in milliseconds) between the force platform translation and the subject's active force response. Since Latency is measured in milliseconds, a low Latency score for the subject is indicative of a quick active force response in the legs. Analysis of the Latency results reveals a red bar indicates the subject generated a slower active force response than their respective age group, whereas, the green bars indicate the subject generated a similar or better active force response than their age group. The strength of the active force response in each leg resulting from the translations is represented by the value of Amplitude Scaling. This value reflects the subject's ability to produce a response in each leg that is proportional to the force platform translations. Amplitude Scaling scores representative of sufficient active force response strength in proportion to the force platform translation will lie between the shaded regions of the graph (Fig. 4) [24].

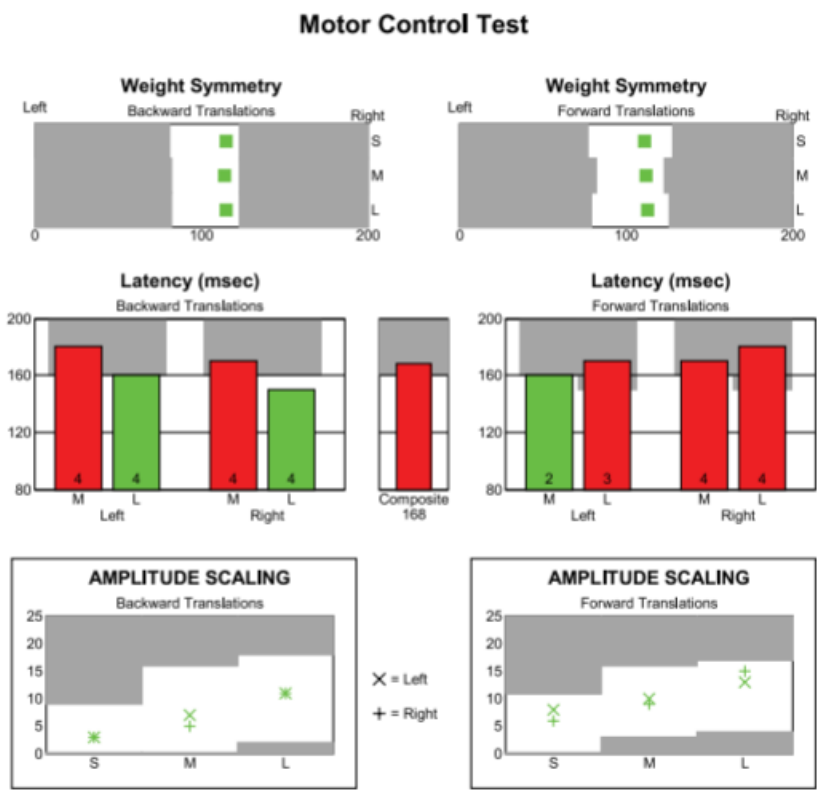


Figure 4. Motor Control Test Sample Results [30]

For the present study, nonlinear analysis is performed on the results from the SOT and MCT. The reasoning for using nonlinear analysis on the SOT and MCT results is that healthy systems exhibit dynamics representative of an extremely adaptable neuromuscular system. Through nonlinear analysis using entropy techniques, the extreme adaptability of a healthy physiological system can be identified as complexity in the system [34]. Lipsitz and Goldberger proposed the “Loss of Complexity Hypothesis,” which describes that the deterioration of the physiological system is induced by a reduction in the system’s ability to adequately respond to external stimuli. Specifically, this hypothesis suggests as physiological functions deteriorate, through aging and disease, interactions between components in the system break down and cause a reduction in variability in the system, which ultimately leads to a decrease in complexity in the system

(Fig. 5) [22, 23]. It is considered that non-HRT postmenopausal women are experiencing this decrease in complexity while postmenopausal women on HRT are not exhibiting as rapid of a decline in complexity as non-HRT [16]. By utilizing analysis of entropy, the complexity of the physiological system can be used as a representation of the level of postural stability in postmenopausal women [21].

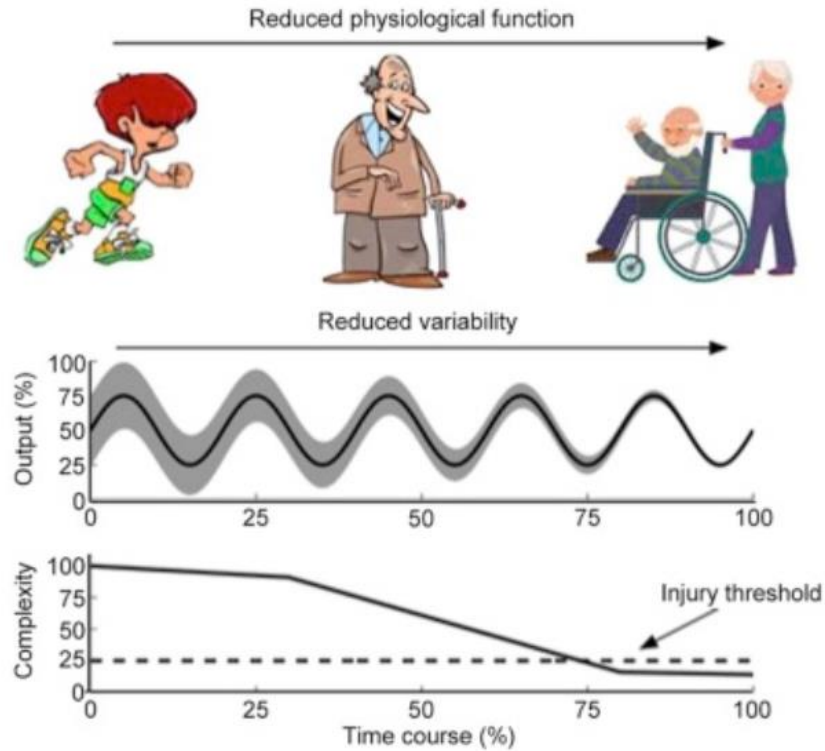


Figure 5. The Relationship Between Age, Variability, and Complexity [21]

Stergiou performed nonlinear analysis with approximate entropy (ApEn) on COP data and discovered variability in gait allows the central nervous system to react and adapt to variable external stimuli one might experience [19]. High values of ApEn signify data sets recorded at different times do not have similarities, whereas low values of ApEn signify similarities between the data sets. Therefore, subjects who record a low ApEn value show a more predictable pattern in their postural stability, which corresponds to

both low variability and postural stability. Whereas, higher values of ApEn correspond to data that do not show similarities, and therefore correspond to both greater variability and postural stability [19, 26]. Although ApEn measures the predictability of the data, it is quite sensitive to the length of data [26]. As for SampEn, it has been observed to show much less sensitivity than ApEn to the length of data it is processing [27]. However, in both ApEn and SampEn, higher values correspond to greater variability and less predictability, whereas lower values resemble low variability and greater predictability. Despite the similarities of ApEn and SampEn in their function, SampEn provides more consistent results while remaining less sensitive to the data length [26-28].

While the use of ApEn and SampEn provide an insight into the regularity and predictability of variability, they only consider a one-time scale of measurement. Analyzing physiological functions at a single time scale does not fully incorporate the complexity of the entire system. Investigating multiple time scales can detect the relationship between the various elements of the physiological system that contribute to the maintenance of postural stability. Therefore, for this study, multiple scale entropy (MSE) is applied due to its inclusion of multiple time scales. MSE utilizes the SampEn method by including a coarse-graining procedure, which allows the identification variations over multiple time scales. The advantages of including multiple time scales are the complexity can be analyzed at shorter or longer time scales and the measurement of the overall complexity of the physiological system [21].

Since changes in the physiological system due to aging and disease cannot be contained to one-time scale, MSE is used to identify the time scales where the deterioration of the physiological system occurs. In postmenopausal women, this

deterioration in the physiological system is attributed to a decrease in estrogen levels in the blood [16]. Through analysis of MSE on the SOT results, the role of estrogen in the nervous system's ability to utilize the sensorimotor and visual systems to maintain postural stability can be identified. Determining the relationship between estrogen deficiency and the timescales when postural stability is most affected can provide valuable evidence for the benefit of HRT in postmenopausal women [21]

## CHAPTER II: SUBJECTS AND METHODS

The study participants included 7 non-HRT postmenopausal women (mean age = 57) and 4 HRT postmenopausal women (mean age = 55). These women were recruited through the “UM Today Daily Edition” and flyers passed out to organizations in the Oxford/Lafayette community. If an individual expressed interest in the study, we contacted them and conducted a preliminary screening over the phone to verify they were a candidate for the study. The preliminary screening consisted of (1) Identifying if the individual is postmenopausal or perimenopausal and (2) If the individual is on or not on HRT. If the individual identifies as perimenopausal, then they are thanked for their interest but removed from consideration for the study. An individual identifying as postmenopausal and on HRT is asked to provide the name of their medication and the dose. Once the individuals are cleared to participate in the study, they provide written consent upon arrival to the Neuromechanics laboratory.

The testing apparatus used for the study is the NeuroCom Balance Manager assessment device (Fig. 6). This device is a commonly used balance testing device found in assessment clinics. It has a medical insurance number for when a physician orders the test. The NeuroCom Balance Manager is connected to a computer that actively records data while each for each test performed.



Figure 6. NeuroCom Balance Equitest [30]

The study used a semi-experimental design. The independent variables in the study were subject height, age, weight and HRT dosage.

When a subject would arrive at the Neuromechanics laboratory, an IRB approved investigator would provide the subject with a consent form, which they were then instructed to fill out in its entirety. Upon completion of the consent form, the investigator would instruct the subject to stand on the force platform of the NeuroCom Balance Manager. The investigator helped position the feet of the subject in the designated location on the platform. Once the subject was positioned correctly, and in a comfortable stance, the investigator proceeded to explain each test the subject will perform (Sensory Organization Test and Motor Control Test). Before the start of each trial for a condition, the investigator would count down the subject and begin the test after saying “go.” Upon completion of each trial, the investigator would instruct the subject to “relax” before the

beginning of the next trial. After the completion of both the Sensory Organization Test and Motor Control Test, the investigator gave the subject a \$20 gift card to Wal Mart for their participation in the study. Upon receiving the gift card, the subject is then instructed by the investigator to fill out an “incentive payment list” verifying they received a gift card for completing the study.

#### *Data Collection and Analysis*

Although both SOT and MCT data were collected for this study, only SOT data will be analyzed and presented as the long time series output of this test is amenable for entropy processing. Complexity Indices for both side-to-side (medial-lateral – ML) and forward-backward sway (anterior-posterior – AP) COP movement were calculated for SOT tests 1-4 and compared with clinical output scores one receives from the NeuroCom unit after each subject is finished with the protocol. Complexity Indices are calculated from the ML and AP time series which make up the center of pressure traces. An exemplar center of pressure trace (Fig. 7) is shown for the SOT1 condition.



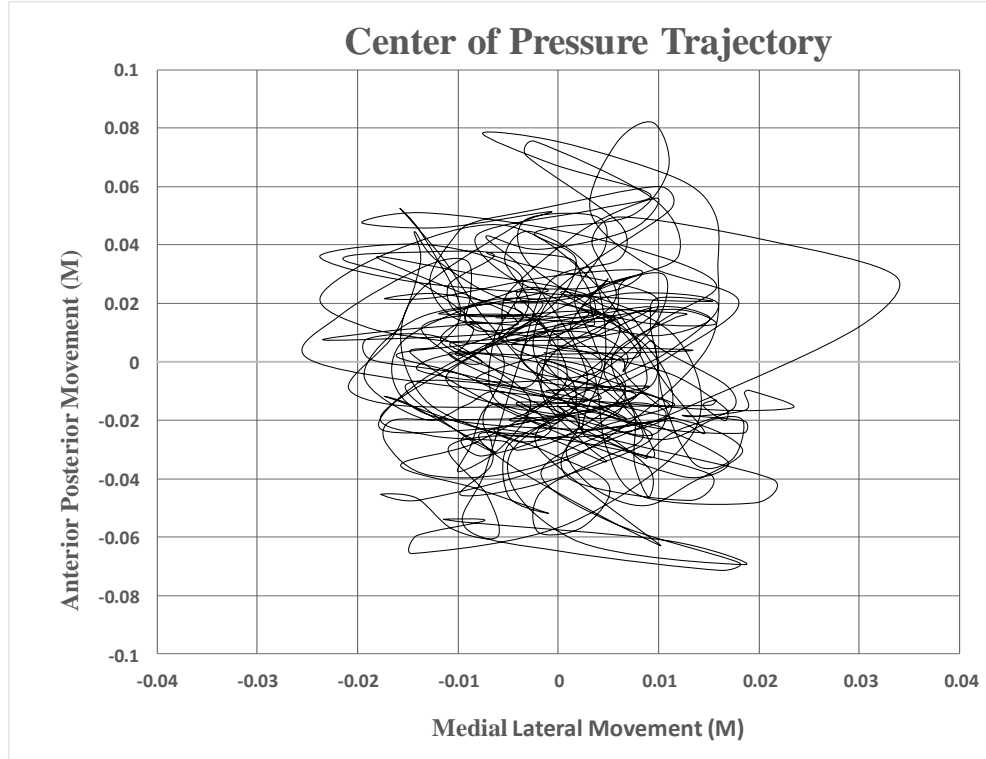


Figure 7. Center of Pressure Trace

A Matlab program was created which was a modification of the “Multi-Scale Entropy Analysis” program, originally created by Costa et al., (2015) through the NIH administered PhysioNet website [29]. The maximum timescale Tau was set to 10 which establishes the granularity of the analysis. The program “creates a set of coarse-grained series with a user-selected range of scales and calculates SampEn for each coarse-grained series.” A complexity Index (CI) is calculated by adding all of the SampEn scores across all Tau values (area under the curve) as shown in exemplar Fig. 8 [30].

We hypothesize that MSE scores will more accurately differentiate the postural stability of post-menopausal women as a function of their hormone status. Basic t-tests (unequal variances) were used to test this hypothesis.

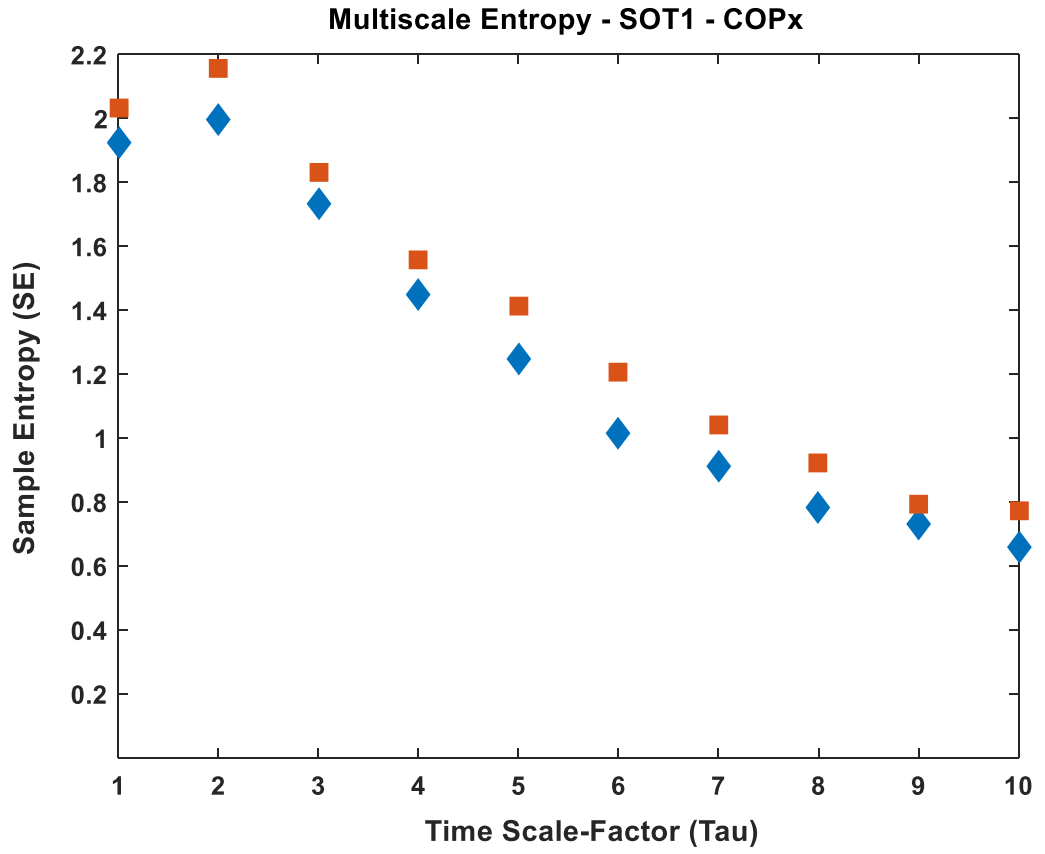


Figure 8. Sample Entropy Scores for Two Different Subjects

### CHAPTER III: RESULTS

The results from the NeuroCom Equitest show HRT subjects exhibit a larger mean equilibrium score than non-HRT subjects, which is indicative of greater postural stability (Table 1). The MSE method created CI scores in both the medial-lateral (x) and anterior/posterior (y) directions where a low CI is representative of good postural stability. In Table 2, it is evident that HRT subjects display a lower CI than non-HRT subjects in all conditions except for SOT 1y and SOT 4y. Therefore, both methods of analysis were able to produce results consistent with those found in previous studies [11, 12].

Further analysis of the traditional clinical scores and complexity indices reveals both methods determined there to be a significant difference in postural stability between postmenopausal women on HRT and non-HRT postmenopausal women an equal number of times (n=2). The NeuroCom assessment device identified a significant difference between HRT and non-HRT postmenopausal women in SOT 2 ( $p \leq 0.05$ ) and SOT 3 ( $p \leq 0.05$ ) (Table 1). Whereas, the MSE method determined there to be a significant difference between HRT and non-HRT postmenopausal women in SOT 1x ( $p \leq 0.05$ ) and SOT 4x ( $p \leq 0.05$ ) (Table 2).

Table 1. Clinical Score Analysis

Test	Mean Equilibrium Score for Non-HRT	Mean Equilibrium Score for HRT	P Score	Significance
SOT 1	92.543	95.083	.0974	No
SOT 2	89.381	93	.0050	Yes
SOT 3	86.619	91.667	.0330	Yes
SOT 4	77.619	85.75	.0674	No

Table 2. Multiscale Entropy Analysis

Test	Mean Complexity Index for Non-HRT	Mean Complexity Index for HRT	P Score	Significance
SOT 1x	13.802	13.064	.0432	Yes
SOT 1y	14.605	14.838	.4197	No
SOT 2x	14.245	13.530	.1153	No
SOT 2y	15.969	15.537	.3170	No
SOT 3x	13.864	13.173	.0562	No
SOT 3y	15.527	15.157	.3306	No
SOT 4x	14.369	13.657	.0236	Yes
SOT 4y	15.723	16.074	.2823	No

## CHAPTER IV: CONCLUSION

The results from both the NeuroCom and MSE method were consistent with the findings from previous studies in showing that postmenopausal women on HRT exhibit better postural stability than non-HRT postmenopausal women [11, 12]. The MSE analysis for SOT 1y and SOT 4y showed non-HRT subjects have greater postural stability than HRT subjects, however, these results may be due to the limited availability of subjects on HRT in the present study. Despite SOT 1y and SOT 4y, graphical analysis of all the SampEn scores across all Tau values for the remaining SOT conditions indicates HRT subjects exhibit lower SampEn scores and thus a high degree of complexity in their COP movement (Fig. 8). These findings support the “Loss of Complexity Hypothesis” in showing that HRT subjects exhibit less of a breakdown of complexity in their movements compared to non-HRT subjects [17, 23].

The present study sought to use MSE as a method to more accurately assess the postural stability of postmenopausal women with regards to the presence/absence of estrogen in their system. A t-test performed on both the NeuroCom results and MSE results indicated that both methods accurately detect a significant difference in postural stability between HRT and non-HRT postmenopausal women an equal number of times (n=2). NeuroCom analysis found a significant difference in SOT 2 and SOT 3, however, since the subject is blinded in SOT 2 and their surrounding is sway-referenced in SOT 3, we expected the NeuroCom to detect a difference in the subjects. Previous studies have had success in differentiating postural stability in non-HRT and HRT subjects, however,

they have only done so by creating conditions for the subjects similar to those found in SOT 2 and SOT 3 [12]. For the present study, we are interested in determining if the MSE method can detect a difference in the subjects without needing to manipulate the conditions to elicit a fall.

When the MSE method was applied, a significant difference was identified in SOT 1x and SOT 4x. Although the MSE method was unable to detect more differences than the NeuroCom, it was able to identify a significant difference in SOT 1, whereas, the NeuroCom was not. To our knowledge, this is the first instance to identify a significant difference in the postural stability of non-HRT and HRT postmenopausal women experiencing the conditions present in SOT 1. Previous studies have not shown these results because their use of traditional assessment methods does not possess the required sensitivity to differentiate an HRT subject and a non-HRT subject without trying to elicit a fall in the subject [12]. Therefore, applying the MSE method to analyze COP data may introduce a higher level of sensitivity necessary to assess postural stability as a function of estrogen status.

MSE may be more likely to detect the complex interactions between the sensory, motor and central processing systems involved in postural stability, however, prospective studies are needed to show if the proposed method is more accurate than traditional methods. Currently, if used in conjunction with the NeuroCom, the MSE method can create a more accurate representation of a postmenopausal woman's postural stability as a function of the presence of estrogen than previous traditional methods. Thus, we can apply the results from both methods of analysis to support the assumption presented by Naessen et al that estrogen can counteract the deterioration of complexity in movement

through an effect on the central nervous system. Additional research on the MSE method and its ability to analyze postural stability in postmenopausal women may provide further evidence of estrogen's role as a neuroprotectant and protective factor for risk of falling.

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