ENTROPY ANALYSIS OF KINETIC AND KINEMATIC GAIT PARAMETERS AS A POTENTIAL TOOL TO PREDICT OSTEOARTHRITIS ONSET

By

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Osteoarthritis (OA) is a debilitating joint degenerative disease that is expected to drastically increase in prevalence by 2050. Therefore, it is necessary to find innovative ways to predict OA onset with the hopes of implementing preventative measures early on.

OA incidence is positively correlated with increasing age and the female gender. Furthermore, gait analysis has been used to elucidate the biomechanical differences that arise from OA onset. Modern gait analysis research has moved towards non-linear analysis due to the understanding of the deterministic properties of human movement. Approximate Entropy (ApEn) and Fuzzy Entropy (FuzzyEn) are both tools that assess signal regularity under the theory of Optimal Movement Variability, and ApEn has been used in a limited capacity to investigate gait imbalance. The goal of this study was to investigate the efficacy of ApEn and FuzzyEn in assessing differences in gait imbalance parameters between males and females of a fixed age, and females of younger and older age groups, under the context of OA onset factors.

Healthy young males (n=20) and females (n=20) between the ages of 18-25 were analyzed in the first study, while younger females of age 18-25 (n=8) and older females of age 50-60 (n=8) were analyzed in the second study. Subjects walked barefoot on a force sensitive treadmill surrounded by six motion capture cameras at a self-selected speed. ApEn and FuzzyEn calculations were then performed at varying k values on the signals of the peak ground reaction force during heel strike and toe off, medial-lateral center of pressure displacement and range of motion of the hip, knee and ankle.

Our results confirmed that gait was a chaotic and deterministic process, since all subjects showed high entropy values at an input parameter k value of 0.2. FuzzyEn and ApEn values were within 22% for all parameters at k=0.2, showing agreement. ApEn found more significant differences between groups, however FuzzyEn showed higher relative consistency. Therefore FuzzyEn remains a promising tool in the investigation of OA and as a future OA prediction tool.

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INTRODUCTION

I.1. Statement of Hypothesis and Specific Aims

The primary goal of this research was to test the efficacy of entropy-based methods in assessing kinetic and kinematic gait parameters between groups in order to develop a potential osteoarthritis prediction tool. Specifically, we aimed to test the use of Approximate Entropy (ApEn) and Fuzzy Entropy (FuzzyEn) tools in investigating the variability of peak ground reaction forces during the heel strike ($pGRF_{HS}$) and toe-off ($pGRF_{TO}$) phases of gait, medial-lateral center of pressure displacement of the foot during the stance phase (mlCOP) and range of motion at the ankle, knee and hip joints (ankleROM, kneeROM and hipROM respectively) between males and females, and younger and older females. Our research was based on the long-term goal of developing reliable gait-assessment methods to identify the risk of osteoarthritis (OA) onset in healthy adults at a young age. If this can be done, strength training protocols may be implemented to delay or prevent the onset of OA at an early age.

OA is a degenerative joint disease which involves the gradual disappearance of bone cartilage that protects the bones from wear and tear, resulting in pain, stiffness, swelling and impaired locomotion (Felson, 1998). It affects approximately 27 million US adults, most of whom are over the age of 65, and is typically observed in the hand, knee and hip joints (Lawrence, 2008). The most recent statistic by Barbour et al. in 2017 (Barbour, 2017) indicates

that half of Americans over the age of 65 suffer from a form of arthritis, of which OA is the most common. Since the number of adults over the age of 60 is expected to double by 2050 (Ortman, 2014), it is reasonable to expect a significant increase in OA occurrences by then. It is therefore critical to develop efficient screening protocols to enable the early detection of OA in young adults, with the hope of implementing corrective measures early on.

The incidence of radiographic OA with increasing age has been well documented and has led to the identification of increasing age as one of the factors behind OA onset (Felson & Zhang, 1998) (Lawrence, 2008). Furthermore, it has been found that OA is prevalent among females than males at all ages, especially after the age of 50 (Oliveria, 1995). Females are also twice as likely to develop OA in the knee joint (Felson, 2000) (Felson, 1997) (Davis, 1988). Despite the age and gender relationship in OA, the exact cause of OA is still debated due to a multitude of factors which simultaneously drive the condition (Felson, 1998). The factors can be grouped under two main umbrellas: systemic factors such as genetics, age and gender and local biomechanical factors such as joint laxity (rotation) and muscle weakness (Felson., 2000). The relationship of OA with biomechanical factors remains vague because the onset of OA itself further aggravates existing biomechanical imbalances and leads to OA progression to adjacent joints (Guilak, 2011) (Kaufman, 2001). The blurring of this line between the biomechanical causes of OA and the biomechanical results of OA onset has thus allowed research in this field to continue to this day. Therefore, an OA prediction tool would require an unconventional analysis method of biomechanical parameters that has not been used for this specific task before.

One of the main tools in studying lower body biomechanical imbalances has been gait analysis. The mechanics of walking on a flat surface are well understood and normative and pathological gait has been well defined (Bresler, 1950) (Perry, 2010). Gait analysis has revealed differences in kinetic and kinematic parameters between males and females, younger and older as well as healthy and OA affected individuals (Kerrigan, 1998) (Hausdorff, 2010) (Childs, 2004). These results have often been obtained through linear analysis methods (mean, standard

displacement, coefficient of variation). However, recent research has found that linear methods fail to capture all aspects of movement and are unable to differentiate between pathology (Stergiou, 2011). This is because linear equations can only lead to solutions that decay, grow or maintain a steady state while many physiological responses show nonlinear behavior (E.A. van Emmerik, 2016). An example of this would be the variability of human movement. Consider, for example, an experiment where a subject is asked to repeat a movement in the exact same way. Despite the number of repetitions, no single movement can be replicated with the exact same joint trajectories and muscular force outputs (Bernstein, 1967). When it comes to human gait, linear tools mask this structure of true variability since the average picture obtained involves time normalization which stretches the data and results in the loss of temporal variations. The emergence of the theory of Optimal Movement Variability in 2006 (Stergiou, 2006) further necessitated a shift away from linear analysis techniques. The theory proposed that human movement possessed an optimal range of variability that was necessary for the body to react to environmental stimuli and stresses. A loss of this optimal state has been associated with pathology and even fatigue (Pincus, 1994). This led to the development of non-linear analysis methods as tools to analyze human movement. These tools have focused on understanding how variations in signal patterns change over time. In application, non-linear analysis methods have increased sensitivity in the detection of this variability based on past and future events, compared to linear techniques.

There are a range of non-linear methods that have been used to investigate gait parameters in recent literature. These fall under the umbrella of local stability measures or under entropy. Local stability measures include the Lyapunov exponent (LyE), Floquet multiplier and Detrended Fluctuation Analysis (DFA). Despite the efficiency of these tools in uncovering gait abnormalities between younger and older adults (Granata, 2008), investigating local stability has not been entirely appropriate in gait analysis due to the negligence of the global stability of the system (E.A. van Emmerik, 2016). For example, adjusting gait to respond to an external

perturbation may result in poor local stability however it would be a positive adaptation on the global level and be indicative of a stable and adaptable system. Thus, movement scientists have turned to entropy analysis to better understand the complexities of human movement. Entropy is the amount of information needed to describe a system (Cover, 2006). Approximate Entropy (ApEn) has been one of the most commonly used complexity measures of this kind and has been used to quantify regularity in in time-series data (Pincus S. , 1995). In biological systems, high ApEn values suggest complexity and adaptability while lower ApEn values signify pathology due to less variability (Pincus S. , 1995). In gait analysis, ApEn has been used to investigate age-related effects of spatio-temporal variables such as minimum toe clearance (Karmakar, 2007), variability patterns in kinematic parameters such as joint angles (Estep, 2018) and in the investigation of variability in anterior cruciate ligament deficient knees during walking (Georgoulis, 2006). However, there has been a noticeable gap in literature when it comes to entropy analysis of kinetic parameters. ApEn has received criticism due to its sensitivity to the length of the time series and the presence of a self-matching feature in the algorithm that provides a bias towards regularity (E.A. van Emmerik, 2016).

ApEn and other entropy tools require three input parameters, “m” which determines the length of the template vectors in the algorithm, “k” which determines the bandwidth where conditioning vectors are found (where r = k*standard deviation), and “N” which is the number of data points that the algorithm processes. These input parameters play a critical role in the output and may result in a “flip-flop effect” of the results (Yentes, 2013). Many modifications to the ApEn algorithm have hence emerged to mitigate the negative aspects such as its self-matching feature and interaction of input parameters, such as Sample Entropy and Multiscale Entropy. However, the dependence on input parameters in other entropy measures has continued to be an issue (Yentes, 2018). Hence Yentes (2018) recommended that the range of input “k” values be displayed in results of future research, so that the performance of the algorithm can be accurately deduced.

Fuzzy Entropy (FuzzyEn), which is based on the concept of Fuzzy logic, was developed as an improvement to existing entropy measures (Chen, 2009). Unlike prior entropy methods, FuzzyEn considered the imprecise environments from which biological data sets arose and used an exponential function instead of the traditional Heaviside function. This fluidity in its core algorithm allowed for greater independence from data length and relative consistency compared to ApEn (Chen, 2007). FuzzyEn has shown its superiority in robustness to noise, input parameter selections and in eliminating the bias towards regularity (Chen, 2009). Despite its power, however, FuzzyEn has been used solely in the investigation of muscle physiology and its performance in investigating kinetics and kinematics gait parameters thus remains unknown.

With the hopes of developing a tool to predict OA onset in young adults, this research focused on testing the efficacy of ApEn and FuzzyEn as tools to detect kinetic and kinematic imbalances in two studies. The first study involved healthy younger males and females (controlled for age), while the second study involved healthy females of younger and older age groups (controlled for gender). We selected the gait imbalance parameters of peak ground reaction force during heel strike ($pGRF_{HS}$) and toe off ($pGRF_{TO}$), medial-lateral center of pressure of the foot displacement during stance phase (mlCOP) and the range of motion at the ankle, knee and hip (ankleROM, kneeROM, hipROM) over the entire trial. We compared the performance of ApEn and FuzzyEn in detecting differences in variability between the two groups in each study based on current knowledge of gender and age-based differences that have been elucidated using linear methodologies.

I.2. Parameters studied

The parameters investigated in this research were based on kinetic and kinematic gait parameters that have been investigated in literature (O. Riley, 2007) (Jamshidi, 2010). Peak ground reaction forces at heel strike and toe off ($pGRF_{HS}$ and $pGRF_{TO}$, respectively) were

computed for each gait cycle as the first and second peak of the total ground reaction force curve, respectively (Figure 1.a).

$$pGRFHS\ (\%) = \frac{First\ peak\ (N)}{Body\ Weight\ (N)} * 100$$

$$pGRFTO\ (\%) = \frac{Second\ peak\ (N)}{Body\ Weight\ (N)} * 100$$

The medio-lateral center of pressure location (mlCOP) was determined by finding the range of displacement of the center of pressure trajectory from the heel-toe line during the stance phase of each gait cycle (Jamshidi, 2010). This value was then normalized by foot length (Figure 1.b).

$$mlCOP\ (\%) = \frac{Deviation\ of\ COP\ trajectory\ (mm)}{Foot\ length\ (mm)} * 100$$

Joint ranges of motion values were computed for each stance phase based on the following equation:

$$ROM\ (\%) = \frac{Max.angle - Min.angle}{Theoretical\ range} * 100$$

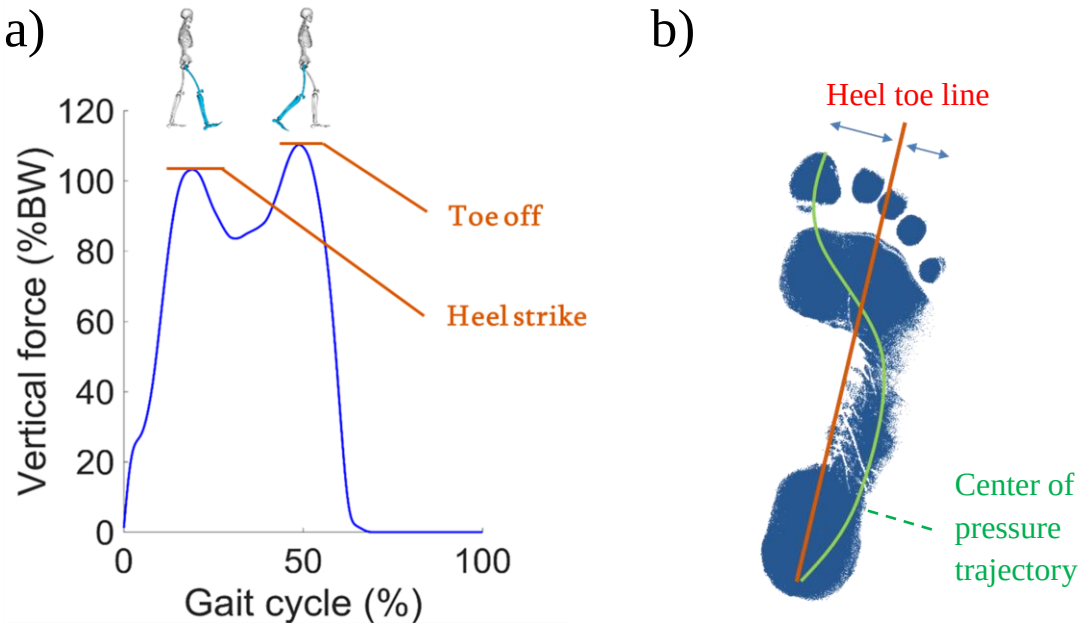

Figure 1. Parameters: a) Vertical ground reaction force curve, and b) center of pressure location under the right foot.

I.3. Hypothesis

This research sought to investigate the performance of ApEn and FuzzyEn in detecting variability differences between two groups in two studies: healthy males vs healthy females (gender study), and younger healthy females vs older healthy females (age study), based on the knowledge of existing gait differences between these groups. We thus hypothesize that ApEn and FuzzyEn can be used to successfully detect differences in variability between healthy groups.

CHAPTER II

LITERATURE REVIEW

II.1. Variability of Human Movement

One of the earliest observations of human motion has been that it is variable. Not only are there multiple degrees of freedom for each limb, but also various combinations of muscles that can be utilized to perform the same motor task (Bernstein, 1967). This gives rise to a few important questions such as "how is this variability controlled while learning a new skill?" or "is this variability associated with disease/health" and "what are the sources of this variability?". In the 20th century, there was an increased effort from scientists and researchers to answer some of these fundamental questions. Prior to 1960, the field of motor behavior was dominated by a "task-oriented" approach (Pew, 1974) that emphasized "global" motor learning theories or sometimes no theories at all (Hull, 1943). Researchers investigated the relationship of many independent variables in the learning and performance of motor tasks and objectives and the results were often poorly defined (Schmidt, 1975). The 1960's showed a shift towards motor skills research which led to the creation of many "closed-loop" theories which suggested that movement was controlled via continuous feedback loops (Sokolov, 1969) (Anokhin, 1969) (Konorski, 1967) and "open loop" theories which proposed that all the necessary information for a movement (usually ballistic or explosive) were already present within the system. Jack Adams improved upon these theories by introducing a closed loop theory in 1971 that was testable and repeatable and was

hence known as “The Adams Theory” (Adams, 1971). He proposed 2 states of memory, memory trace (which was responsible for initiating movement and choosing its overall direction) and perceptual trace (which was responsible for guiding the limb to the correct end point based on past experience and current feedback) that best explained how a motor system with intrinsic feedback would work (Adams, 1971). However, some of the criticisms of Adam’s theory revolved around the massive neurological storage requirements of a one to one mapping system and the question of how novel movements would be performed if perceptual trace was based on historical movements. Schmidt proposed Schema theory in 1975 which addressed these issues, by suggesting that there were 3 parts to movement i) A generalized motor program (GMP) ii) Recall Schema iii) Recognition Schema (Schmidt, 1975). His theory received much acclaim, particularly due to the proposition of a GMP, which is still a prominent theory today. Generalized Motor Program theory (GMPT) considers movement variations to be a result of error (Summers, 1995). It postulates that there is an error in predicting the required parameters to employ the GMP which results in variation, and that prediction error is gradually eliminated with practice (Schmidt R., 2003) (Schmidt, 2005). A competing theory that emerged in the 1980’s was the Dynamical Systems Theory (DST) which assumed that order and regularity were not pre-programmed and stored but emerged from the dynamic interactions of many degrees of freedom within the motor system (Schmidt, 2003). DST understood biological systems to be self-organizing according to environmental, biomechanical and morphological constraints and thus movements sought the most stable solution from these. The current state of human movement research has scientists in either “camp” of GMPT or DST (Schmidt, 2003), however a common theme in both theories is that decreased variability is good and portrays an efficient execution of a movement.

However, this understanding of movement from either side begs a simple question. How are some movements that appear highly stable performed in highly variable ways? For example, a general observation of elite athletes and musicians (considered as people of high motor skills) shows that they have extremely stable outputs yet have developed multiple ways to

achieve these. The idea that variability decreases with increased skill does not hold in such instances and therefore questions the validity of GMPT and DST. This argument has been echoed before and Schmidt himself called for a new theory in 2003, asking researchers to abandon their "camps" and to move forward with a new theory that incorporated the surviving aspects GMPT and DST (Schmidt, 2003). Stergiou et al. took a different approach to this question and proposed that the paradoxes and controversies of GMPT and DST could be explained by the way in which variability had been traditionally measured (Stergiou, 2011). Traditionally, movement research had focused on linear statistical measures such as mean, standard deviation and coefficient of variation. These tools were statistical measures of centrality and showed us how far a set of data deviated around a central point, treating variations as random and independent and disregarding the temporal organization (or structure) of the variability with respect to time (Lomax, 2007). While linear methods were useful for linear systems, several studies indicated that human movement variations had deterministic properties (Dingwell, 1999) (Dingwell, 2007) (Harbourne, 2009) (Stergiou, 2011) and thus nonlinear methods of analysis would have been more appropriate, thus affirming Stergiou's approach. This was seen especially in human gait where a non-linear method such as DFA revealed that fluctuations in stride interval time showed long range correlations (Hausdorff, 1995) which degraded with age and neurological diseases (Hausdorff, 2009) (Stergiou, 2006). Stergiou and Harbourne (Stergiou, 2006) thus proposed a new model called "Optimal Movement Variability" which suggested that there was an optimal range of variability that existed between a purely stochastic system and a purely periodic one. Thus, under this new theory, variability was viewed as a deterministic structure that showed the adaptability of the system to environmental stimuli and stresses. A decrease or loss of this state was found to be associated with pathology and even fatigue, through non-linear methods (Pincus, 1994) (Cignetti, 2009). Optimal movement variability theory proposed that motor development and learning processes obeyed methods by which optimal variability was reached and that abnormal development, pathology and aging resulted in rigid, inflexible and highly predictable

behavior outside of the optimal range (Stergiou, 2011). Therefore, this paper functions under the assumptions of the prevailing Optimal Movement Variability theory, and the generalized consensus in literature is that there is a "functional" aspect to variability that is characterized by chaotic structure (Caballero, 2014). This paper hence seeks to test the veracity of non-linear methods as a diagnostic tool of chaotic signals in human movement, particularly gait imbalance parameters as a tool to predict osteoarthritis onset.

II.2. Non-Linear methods

Nonlinear methods in the investigation of human movement are the product of mathematical tools that have been used in the study of deterministic chaos. Biological signals have been found to exhibit deterministic patterns which have been defined as chaotic. In the instance of hearth rhythms, these chaotic states have been found to indicate healthy states (Denton, 1990) (Glass, 1988) contrary to prior theories believing that they were pathological. Currently, it is believed that chaotic behavior in a biological system may represent the physiologic capability to adapt to external stresses (Lipsitz, 2002).

In the application of non-linear methods in investigating motor variability, these tools look at how motor behavior changes over time, considering the temporal dynamics and complexity. They take the fuller picture of movement into account by understanding the "hidden" temporal structure of movement fluctuations (Stergiou, 2011). There have been many nonlinear methods that have been used to study human movement. The Lyapunov exponent (LyE), for example, measures the exponential rate of divergence of neighboring trajectories of a state space (obtained from human kinematic data) (Dingwell, 2006) and is a measure of the dynamic stability of a system. It has been used to estimate fall risk in elderly human subjects by quantifying local dynamic stability (Lockhart, 2008) (Brujin, 2013). Local dynamic stability is the degree of sensitivity of a system to small perturbations (Buzzi, 2003). Another way to analyze variability is to look at the degree of irregularity of the time series. Recurrence Quantification Analysis (RQA),

a tool that quantifies system properties by visualizing trajectories in phase space, has been used to analyze postural fluctuations (Riley, 1999) and even analyze changes in heart rate variability (Javorka, 2008). Detrended Fluctuation Analysis (DFA) is another non-linear tool that looks at the long-range power-law correlations in signals (Peng, 1995). DFA estimates fractal scaling properties of a times series where a scaling index value (α) of 1 indicates pink noise with fractal characteristics (Holden, 2005). DFA has been widely used in variability analysis to investigate heart rate variability (Ahmad, 2009) and gait analysis (Kirchner, 2014). Entropy measures are another type of non-linear approach to assess the degree of irregularity. Entropy refers to disorder or chaos and it's meaning in information theory is akin to that of thermodynamics. Claude Shannon was the first researcher to introduce entropy as a tool to investigate time series data (Shannon, 1948). Under the theory of Shannon Entropy, entropy quantifies the uniformity or regularity of a time series, therefore higher entropy values would indicate increased irregularity while lower values would indicate increased periodicity and regularity (Shannon, 1948). The work of Shannon has been improved upon by various researchers and in 1995, Steve Pincus introduced Approximate Entropy to investigate biological signals ranging from endocrine hormone secretion data to infant heart rates (Pincus S. , 1995). Due to the work of Pincus, there have been many subsequent entropy algorithms developed such as Sample Entropy, Multiscale Entropy, Increment Entropy and so on, with an increasing use in the investigation of biological signals. It has generally been found that aging and diseased systems show reduced entropy values when compared to the dynamics of a healthy system, although there are anomalies to this understanding likely due to an increase in noise (Goldberger, 2002). The following section will take a deeper look at the mechanisms and uses of the different entropy methods available.

II.3. Entropy-based methods

Approximate Entropy (ApEn) was pioneered by mathematician Steven Pincus in the early 90's and was introduced as a method of quantifying the complexity and regularity of time-

series data. It has since been implemented in a wide range of investigations ranging from financial markets to weather patterns (Yentes, 2018). Its development pertaining to the analysis of human biological signals was motivated by data length constraints and noise commonly encountered in heart rate, endocrine and EEG data sets (Pincus S. , 1995). Its primary benefit appears in instances where classical statistics (such as mean, standard deviation) fail to show clear group distinctions (Fleisher, 1993).

To compute ApEn, three input parameters are required. “m” is the length of the compared runs and “k” functions essentially as a filter (commonly multiplied to the standard deviation of the time series data to give a value “r”). “N” is the number of data points in the data (Figure 2).

Standard ApEn

For a time series T containing N data points $\{u(i):1 \le i \le N\}$, the following vector sequence can be formed[29]

$$X_i^m = \{u(i), u(i+1), \ldots, u(i+m-1)\}$$
$$1 \le i \le N-m+1 \quad (1)$$

Here, X_i^m represents m consecutive u values, commencing with the ith point. The distance d_{ij}^m between X_i^m and X_j^m is defined as

$$d_{ij}^m = d[X_i^m, X_j^m] = \max_{k\in(0,m-1)} |u(i+k) - u(j+k)| \quad (2)$$

For each vector X_i^m, a measure that describes the similarity between the vector X_i^m and the other vector X_j^m can be constructed as

$$C_r^m(i) = \frac{1}{N-m+1} \cdot \sum_{j=1, j\neq i}^{N-m+1} \Theta\left(d_{ij}^m - r\right) \quad (3)$$

where Θ is the Heaviside function

$$\Theta(z) = \begin{cases} 1 & \text{if } z \le 0 \\ 0 & \text{if } z > 0 \end{cases} \quad (4)$$

The symbol r in Eq. (3) represents a predetermined tolerance value, which is defined as

$$r = k \cdot \text{std}(T) \quad (5)$$

where k is a constant ($k > 0$), and std($\cdot$) represents the standard deviation of the time series. By defining

$$\phi^m(r) = \frac{1}{N-m+1} \cdot \sum_{i=1}^{N-m+1} \ln\left[C_r^m(i)\right] \quad (6)$$

The ApEn value of the time series can be calculated as

$$\text{ApEn}(m, r) = \lim_{N\to\infty} \left[\phi^m(r) - \phi^{m+1}(r)\right] \quad (7)$$

For practical applications, a finite time series consisting of N data points is used to estimate the ApEn value of the time series, which is defined as

$$\text{ApEn}(m, r, N) = \phi^m(r) - \phi^{m+1}(r) \quad (8)$$

Figure 2. Algorithm for the standard ApEn (from Xie, 2010).

It can be understood that ApEn measures the likelihood (in logarithms) that runs of patterns that are close for "m" observations remain close in subsequent incremental comparisons (Pincus, 1994). The range of ApEn is from 0 to 2, with larger ApEn values signifying independent sequential processes (chaotic nature) while smaller ApEn values indicate relative

regularity of sequences (for example a sinusoidal wave). Pincus concluded that for data sets of N=1000, values of m=2 and r=0.1 to 0.2 times the standard deviation (SD) produced good statistical validity of ApEn for many models (Pincus & Goldberger, 1994). It was noted that "r" values smaller than 0.1*SD (i.e k=0.1) gave poor conditional probability estimates while r values larger than 0.25*SD (i.e. k=0.25) allowed for the loss of detailed system information (Pincus, 1994). Pincus agreed that the choice of "r" was perhaps the most significant input parameter and must be chosen carefully, since a decreasing "r" caused ApEn to increase (Pincus S. , 1995). This variability of ApEn based on input parameters has been one of its biggest flaws, however Pincus advised that maintaining fixed input parameters across investigations would answer the simple question of regularity vs irregularity in signals (Pincus S. , 1995). Hence, a good technique would be to select the "r" value that provides the maximum value of ApEn based on the findings of Chon et al. (Chon, 2009). There has been some suggestion in literature to use a fixed "r" value based on the sampling rate, however this has been demonstrated to produce a different outcome compared to using r*SD (standard deviation), often flipping the results (Forrest, 2014). The suggested "m" value for clinical data, based on the findings of Yentes et al. is 2 (Yentes, 2018). In terms of gait analysis, an m of 2 would represent a comparison between one set of consecutive steps to another set of consecutive steps while an "m" value of 3 would indicate 3 steps compared with the next 3 and so forth (Yentes, 2013). However, it seems that in gait analysis, an m=3 provides more consistent results for ApEn along a range of N values (Yentes, 2018). All human movement studies that have used ApEn have utilized an m value of 2 and an r value between 0.2 and 0.25 (Georgoulis, 2006).

ApEn, however, does possess its imperfections. The algorithm to compute ApEn includes a self-matching feature of vectors (which was intentionally developed by Pincus to avoid taking the natural logarithm of 0, leading to an undefined answer). This adds a bias towards a more regular result. Furthermore, ApEn shows relative inconsistency when input parameters such as "N" are altered and may even "flip" its results depending on the input parameters used, where

lower entropy would falsely be found or vice versa (Chen, 2009) . These shortcomings were investigated by Yentes et al. especially in regards to its effect on human movement where she found that ApEn differed based on the input combinations of "m", "r" and "N", however showed relative consistency when m was 2 and the smallest r values were used (r=0.2*SD) (Yentes, 2013). Sample Entropy (SampEn) was developed as a solution to this by Richman and Moorman and was a modification of the ApEn algorithm. It excluded the self-matching feature present in the former. It was hence argued to be a better tool since it behaved independent of data length and showed relative consistency (Richman, 2000). However, the subsequent investigations by Yentes concluded that both SampEn and ApEn were susceptible to a 3-way interaction between the input parameters "m"," r" and "N", significant enough to generate incorrect signal analysis results. The only benefit of SampEn appeared to be its independence of data length (Yentes, 2013). Her advice, and that shown by Karmarkar et al (Karmakar, 2007), is to reveal the effect of a range of "r" values on the output of ApEn or SampEn so that any flipping of entropy results may be observed.

Fuzzy Entropy analysis is one of the more recent innovations in the use of non-linear methods to investigate biological signals. It was first developed by Bart Kosko based on the concept of "fuzzy sets" introduced by Zadeh in 1965 (Kosko, 1986) (Zadeh, 1965). It's power in investigating biological signals was sparked by the work of Chen et al. with their renowned paper "Characterization of Surface EMG Signal based on Fuzzy Entropy" (Chen, 2007).

Theoretically, FuzzyEn is more applicable to biological signals since it understands the imprecise environments from which data sets arise and shows lenience in classifying vector similarity. While ApEn and SampEn determine the similarity of two vectors based on a Heaviside function which assigns a binary 1 or 0 (yes or no), FuzzyEn determines this based on a "membership degree" in the form of a number between 0 and 1. The algorithm developed by Chen et al. is hence similar to the ApEn algorithm involving an N sample time series $\{u(i): 1 \leq I \leq N\}$ with vector sequences $X^m_i = \{u(i),u(i+1),\ldots,u(i+m-1)\} - u0(i)$. The distance d^m_{ij} between

two vectors X^m_i and X^m_j is given as the maximum absolute difference between their corresponding scalar components. The algorithm deviates thereafter, involving a similarity degree D^m_{ij} through a fuzzy function $\mu(d^m_{ij},n,r) = \exp(-d^m_{ij})^n/r$. The functions $\varphi^m(r) = (1/(N-m)) \sum^{N-m}_{i=1} ((N-m-1)^{-1} \sum^{N-m}_{j=1} D^m_{ij}$ and $\varphi^{m+1}(r)$ are then used to define the FuzzyEn output using the negative natural logarithm of the deviation of the two: $FuzzyEn(m,n,r) = \lim_{N-\infty}[\ln \varphi^m(n,r) - \ln \varphi^{m+1}(n,r)]$. The main benefit of this approach is the replacement of the binary Heaviside function with a continuum-based approach, which is thus capable of considering the imprecise environments from which biological data sets arise.

As in ApEn, FuzzyEn requires an "m" input parameter which describes the length of the vector sequences to be compared. The "r" and "n" parameters describe the width (often used as r multiplied by the standard deviation, r*SD) and gradient of the boundary of the exponential function respectively. In the investigation of surface EMG signals from the right forearm, Chen et. al selected a FuzzyEn m value of 2, an r value of 0.3 and an n value of 2 based on the clarity of results from experimental data involving random numbers and sinusoidal signals. Their results proved the superiority of FuzzyEn in investigating EMG, as it was shown to have the lowest standard deviation and the best characterizing result compared to ApEn and SampEn (Chen, 2007). This was echoed in a 2009 study investigating all big three entropy measures, ApEn, SampEn and FuzzyEn by Chen et al. (Chen, 2009) where FuzzyEn was found to closely follow theoretical hypotheses and show freer parameter selections and robustness to noise. However, its use has centered around EMG and its performance in gait analysis of kinetic and kinematic parameters remains unknown. Therefore, exploring FuzzyEn in gait analysis would offer novel insights into the tool's abilities.

II.4. Effects of osteoarthritis

This paper focuses on a tool to predict osteoarthritis (OA) onset in the lower body. It is thus necessary to understand the factors behind OA and the biomechanical symptoms of OA onset in the lower body.

OA is a disease characterized by localized cartilage erosion at a specific joint, resulting in bone-to-bone contact accompanied by pain, swelling, stiffness and anatomical changes to the underlying bone (Felson, 2000). It is the most common form of arthritis today and affects approximately 27 million Americans (Prevention, 2018). Felson and Zhang have highlighted that systemic and local factors contribute towards the onset of OA (Felson, 1998), with systemic factors including a person's age, sex, racial characteristics and estrogen replacement therapy among others. It is believed that such systemic factors increase the vulnerability of the cartilage to injuries and reduces its ability to regenerate (Felson, 1998). Once these are in place, local biomechanical factors begin to take affect and may include joint injury, obesity, joint deformity and muscle weakness (Felson, 1998).

A comprehensive study quantifying the incidence of hand, hip and knee OA in men and women of varying age groups from Massachusetts found that there was a correlation in the incidence of OA in all joints with age and gender (Oliveria, 1995). After the age of 50, women had a higher prevalence and incidence of OA, along with a drastic increase in the number of radiographically valid OA diagnoses (Oliveria, 1995). The largest study into OA onset in the knee to date is the Framingham Osteoarthritis Study, which used 1424 radiographs of older subjects between the ages of 63 and 94 years. It found that radiographic evidence of OA increased with age from 27% in subjects younger than 70, to 44% in subjects over the age of 80 (Felson, 1987). Furthermore, this study found that the proportion of women with symptomatic knee OA was significantly higher than that of men, thus confirming the understanding that OA of the lower body is related to old age and the female gender.

The effect of OA on the biomechanical functioning of the lower body has been investigated thoroughly using linear tools. Gait analysis of 24 subjects with unilateral symptomatic knee OA against 24 age and gender matched control subjects by Childs et. al found that disease affected subjects had an increased knee angle at heel contact, decreased knee flexion excursion (range of motion) during the loading response phase, decreased vertical ground reaction force during loading and push off and a prolonged activation of the tibialis anterior and medial gastrocnemius muscles compared to controls (Childs, 2004). Another study involving 47 males and 92 females (mean age of 57 ± 12.5 years) with Grade II knee OA found that patients with knee OA exhibited reduced internal knee extensor moments and walked slower than those without knee OA (despite normalizing for shorter stride length) (Kaufman, 2001). A gender difference was also observed with female OA patients exhibiting greater peak knee flexion angles and knee extensor moments compared to males.

Despite these findings, there is a blurring of the line between the biomechanical causes of OA and the biomechanical symptoms of OA, since OA onset requires biomechanical imbalances and the disease itself results in biomechanical imbalances. This paradox necessitates an unconventional approach in detecting OA onset using traditional gait analysis tools.

II.5. Gender and gait

It is relevant to this study to understand the anatomical differences in the musculoskeletal system of the lower body between healthy males and females since it is known that females are at an increased risk of knee osteoarthritis and certain knee injuries such as non-contact anterior cruciate ligament tears (Felson, 2000) (Arendt, 1999). This section hopes to offer insight into the resulting variations in female gait.

Prior to the onset of puberty, there are very few differences in male and female anatomy. Studies report no difference in prepubescent femur and tibia lengths, knee laxity, tibiofemoral angles or hip anteversion (Smith, 2005) (Baxter, 1988) (Svenningsen, 1989) (Cahuzac, 1995) between males and females. However, with the onset of hormonal changes associated with puberty, there is a gradual shift in stature and muscle mass between the 2 genders. The static musculoskeletal differences found by Shultz et al. (Schultz, 2007) in a study of 50 males and 50 females (aged 23 ± 4 and 22 ± 3 respectively) revealed that females possessed a significantly greater pelvic angle (anterior pelvic tilt), hip anteversion (femoral internal rotation), standing quadriceps angle and tibiofemoral angle (resulting in knee valgus and genu recurvatum (knee hyperextension)). These differences were mainly found proximal to the pelvis, and no differences were found in the alignment of lower legs, ankles or feet (tibial torsion, standing rearfoot angle or navicular drop. The proximality of these differences to the female hip may be related to the anatomical differences between the male and female pelvis. The female pelvis is wider and rounder than the male pelvis, with a wider sacrum. The acetabula are further apart in females, which results in greater lateral angles and a valgus inclination (Heyden). Female skeletons are also less dense and possess comparatively weaker tendons and ligaments compared to males (Nieves, 2005). The overall muscle mass in females is also lower compared to males as gross measures of body strength have revealed that females range from 42 to 63% of male strength (Frontera, 1991). However, in a study of 11 males and 11 females by Krishnan et al. (Chandramouli, 2009), it was found that during knee extension trials females showed higher

vastus medialis activity compared to males. Furthermore, in knee flexion trials, females showed higher vastus lateralis, vastus medialis and rectus femoris activity than males. The study found no significant differences in hamstring activation between males and females. These differences are thought to stem from the prevalence of slower type I muscle fibers present in females (Haizlip, 2015). Especially in the vastus lateralis, it has been found that the cross-sectional area of all 3 muscle fiber types was larger for men, but that Type 2A was largest in men while Type 1 was largest in women (Staron, 2000). Females are also found to recruit a larger number of motor unites compared to males at a given contraction intensity and opt for increasing motor unit recruitment as opposed to increasing motor unit firing rates when faced with increased force demands (Giannini, 1994).

These differences are evident in the kinetics and kinematics of females in gait analysis studies involving comparisons between the two genders. A study by Kerrigan et al. measured the sagittal kinematic and kinetic (joint torque and power) data of the lower limbs of 99 young adult subjects (49 females and 50 males of ages 20 to 40 years) using a force platform and an optoelectronic motion analysis system. They found that females had significantly greater mean hip flexion, reduced mean knee extension before initial contact, and higher mean ankle power generation during pre-swing compared to males (Kerrigan, 1998). Another study by Chumanov et al. investigated the kinematics and EMG activity of the lower limbs of 34 subjects walking at varying speeds and inclinations on a treadmill. Kinematics were recorded using 40 reflective markers on 21 anatomical landmarks and the utilization of an 8-camera motion analysis system. EMG data was recorded using surface electrodes on the hip adductors, gluteus medius, gluteus maximus and vastus lateralis muscles of the lower right limb. Their results indicated that females had significantly greater peak hip internal rotation and adduction during the stance phase as well as greater hip excursion, lateral pelvic tilt excursion and peak knee flexion during stance at all walking and running speeds and inclinations, when compared to males (Chumanov, 2008). In addition to this, females had higher gluteus maximus and vastus lateralis activity compared to

males in all conditions (Chumanov, 2008). In terms of kinetics, Chiu & Wang conducted a similar study involving 15 males and 15 females, where EMG, joint motion and ground reaction force data were captured using wireless EMG surface electrodes, a six-camera motion capture system and a force platform. They found no differences in cadence between the 2 genders but found that females had higher tibialis anterior activity which correlated with higher vertical ground reaction forces in the loading response and pre-swing phase, compared to males (Chiu, 2007). A comprehensive report into the gender based differences in gait, based on a thorough literature review of all research in the field, was released in 2014 by the Air Force Research Laboratory and was undertaken by Frimenko et al. (Frimenko, 2014). Their findings can be summarized as follows: Female gait speed decreases with age proportionally compared to men. Males possess greater step length in every age group, while females possess greater cadence in every age group (findings of 80 studies). In terms of sagittal plane kinematics, females have generally lower hip ROM compared to males, varying knee ROM's (sometimes higher, sometimes lower) compared to males and significantly greater ankle ROM's compared to males (Frimenko, 2014). While these results have been found using linear analysis, it is important to understand its limitations in understanding OA onset due to the negligence of the temporal nature of the signal, for which non-linear methods are best suited. There is a noticeable gap in literature when it comes to non-linear analysis of gender related gait differences specifically, since most non-linear analyses have been conducted on normal vs. pathologic groups. Often times, investigations revolve around the use of non-linear methods in understanding the differences in variability between running and walking (Jordan, 2008), or involve strictly male or female subjects (Jordan, 2009) (Costa, 2003). Therefore, this paper seeks to establish normative data on the differences in variability between males and females of a healthy group, while assessing the efficacy of such non-linear methods.

II.6. Age and variability

It is well documented that OA onset is correlated with increasing age (Oliveria, 1995). Hence, it is important to understand the anatomical and physiological changes that occur with old age.

Older individuals experience a decrease in skeletal muscle mass (Frontera, 2000). Sarcopenia, which is defined as the age-related loss of muscle mass, leads to a decrease in muscle strength and aerobic capacity (Evans, 1993). It contributes to the most "striking and consistent" changes of lean body mass with age (where lean body mass implies skeletal muscle and bone mass) (Evans, 2010). From ages 20 to 80 there is an approximately 30% reduction of muscle mass while the cross-sectional area of the muscles decreases by approximately 20% (Frontera, 2000). There is also a preferential loss of type 2 muscle fibers over type 1 with advancing age (Larsson, 1983) (Porter, 1995) although the consensus among researchers is still varied. The factors behind these are complex, yet can bet attributed to decreased physical activity, declining androgen concentrations, nutritional imbalances, inflammation and insulin resistance that appear with age (Kortebein, 2007) (Morley, 2003). Furthermore, there is a loss of bone mineral density, metabolic rate and an increase in body fat with age (Evans, 2010). Bone loss with age has been well investigated in the Framingham osteoporosis study, where a total of 800 subjects were longitudinally examined over a four-year period (Hannan, 2010). It was found that bone mineral density decreased significantly in both elderly men and women and that women had a greater loss compared to men (which is relevant in our gender-based hypothesis as well). Murray et al. have found that age decreases isometric and isokinetic torques of the knee flexor and extensor muscles in men (Murray, 1980) (Frontera, 1991), similar to the results of Frontera et al. who found that flexor and extensor strength of the knee was significantly reduced in older people (Frontera, 1991). The loss of muscle mass and strength is important to our understanding of movement, since these are required by an individual to stabilize forces at a joint. In the lower body, proper muscle activation and force generation is a vital component of shock attenuation between foot

and ground (Wakeling, 2003). The loss of muscle mass has also been associated with an increased risk of falling and injury (LaStayo, 2003). In terms of sensory function, it was found in a longitudinal study by Baloh et al. (Baloh, 2003) that vestibular function as well as visual, auditory and somatosensation were significantly decreased with age, however this was only weakly correlated with a 29% measured change in resulting gait and balance.

There are several important changes that happen in the foot with age. In a study by Scott et al. (Scott, 2007) where 50 younger and 50 older subjects were investigated, it was found that older subjects possessed flatter, pronated feet and exhibited reduced range of motion at the ankles with a higher prevalence of hallux valgus as well as toe plantar flexor weakness. These were associated with reduced magnitude of plantar forces and pressure under the heel, midfoot and metatarsophalangeal joints. A decrease in toe plantarflexion strength by up to 29% in older adults has also been found by Endo et al. (Endo, 2002). Interestingly, there has also been an observance of decreased tactile sensitivity of the lower limb (Thornbury, 1981) showing that the sensory change with age is not limited to the visual and auditory and may have an effect in proprioception. These changes could be explained by the anatomical change to cutaneous tissues of the foot which become dry, inelastic and cool with age, often showing callosities in the medial and lateral metatarsal heads and heel due to atrophy of soft tissues (Edelstein, 1988). The loss of plantar tissue response to different impact velocities may also explain variations in the plantar pressure distribution profile with age. This was investigated by Hsu et al. who found that tissue reaction to cyclical stresses are impaired in the elderly, due to the decreased shock absorbency and increased energy dissipation ratio (Hsu, 2005).

These anatomical and physiological changes that occur with age can be witnessed in the change of gait parameters of older adults when compared with healthy younger adults. This has been undertaken in two ways, using linear analysis methods in the past, and more recently using non-linear analysis tools.

In linear analysis investigations, it has been found that older adults generate less power and perform less work about the ankle compared to younger adults while more work and higher power is found about the hip of older adults (DeVita, 2000). This is often described as a distal to proximal shift in control strategy. This was demonstrated by Devita and Hortobagyi in their investigation on the age-related redistribution of joint torques and power during gait (DeVita, 2000). Their study involved 12 elderly (mean 69) and 14 young (mean 21) adults of whom ground reaction force and kinematic data were recorded during gait. They found that elderly adults had 58% increased angular impulse at the hip, 279% increased work at the hip, 50% decreased angular impulse at the knee, 39% less work at the knee, 23% less angular impulse at the ankle accompanied with 29% less work at the ankle. They also found that elderly adults had a 4% shorter step length as well as a 4% increase in cadence. Ko et al. found similar spatiotemporal results in their longitudinal study involving 183 participants (mean 73+= 9 years) with a decreasing gait speed and stride length while cadence was observed to increase. They confirmed the findings of other studies that wider stride width was also observed with older age (Ko, 2011).

A combination of linear and non-linear tools was used by Buzzi et al. in one of the more popular papers that investigated the age and gait variability question (Buzzi, 2003). They looked at the variability of 10 younger females (20-37) to that of 10 older females (71-79) by having subjects walk on a treadmill for 30 gait cycles while measuring the sagittal kinematic data from the right lower extremity (maximum and minimum vertical displacement of ankle, knee and hip as well as maximum and minimum knee joint angles). What they found was that there was a significant increase in standard deviation and coefficient of variation for the minimum vertical displacements of the hip and the minimum and maximum vertical displacements of the ankle as well as the knee angle maximum and minimum. In addition to this they used the largest Lyapunov Exponent method (LyE) and found that LyE values were greater for all parameters in

the elderly group, showing that elderly subjects displayed more local instability than younger subjects.

Kurz and Stergiou utilized non-linear statistical entropy to (Stergiou, 2003) investigate 10 younger (mean aged 25) and 10 older (mean aged 75) individuals. The subjects walked on a treadmill while kinematic data of the right lower extremity were recorded. While their method of entropy analysis differed from ApEn and FuzzyEn (outlined in this paper), they found larger entropy values in the older group which suggested that there was less certainty in selecting a joint range of motion (ROM) for the ankle, knee and hip joints with age. However, it must be noted that their methodology involved stride to stride comparisons of the right leg only and the ROM was defined as the difference between the absolute maximum and minimum angles.

For ApEn investigations, Karmakar et al. (Karmakar, 2007) looked at minimum toe clearance (MTC) between 30 young, 27 healthy elderly and 10 falls risk elderly subjects. The subjects walked at a self-selected speed on a treadmill while a motion capture system was used to collect 2D foot clearance data. ApEn was utilized on a constant 500 gait cycles per subject (to normalize for speed variations), while the m value was set at 3 and r values were varied from 0.1*SD to 0.9*SD in increments of 0.1. Their results showed the ability of ApEn to flip results based on the "r" value, as it was found that below an r value of 0.26*SD, the falls risk group had a higher ApEn than that of the healthy young and healthy older groups. Above an r value of 0.26, the mean ApEn of the falls risk group was found to be smaller than the other two groups. The peak ApEn values were observed for all groups at an r value of 0.4*SD, and if the method of maximum ApEn (described by Chon et al., 2009) is followed, would support the hypothesis that pathology (in this case falls risk) correlates with lower ApEn values, since the falls risk group was found to be lower in ApEn compared to the other two at the peak ApEn.

More recently, Cavanaugh et al. investigated the step count values of 157 community-dwelling older adults (aged 70 and over) over the span of 2 weeks. Their investigation looked at the step count values at 1-minute intervals throughout the day as a way of assessing minute-to-

minute fluctuations in step count. What they found was that older, physically active participants displayed grater randomness (higher ApEn) values compared to inactive participants. Randomness indicated greater uncertainty in the ordering of a step count. Their conclusion raised the validity of nonlinear methods to assess movement health and supported earlier studies that higher ApEn values allowed for more adaptive movements (Cavanaugh, 2009).

From these studies we can observe that investigations into gait variability and age using non-linear methods have been broad. The studies utilizing ApEn have looked at mainly spatio-temporal and kinematic parameters. It would be of use to contribute to this literature by investigating other gait imbalance parameters such as ground reaction force and center of pressure variations. Furthermore, the performance of FuzzyEn in gait analysis of kinetic and kinematic parameters remains unknown, as its use has centered around EMG analysis. Hence, this study serves to establish normative data for ApEn and FuzzyEn in the investigation of gender based and age-based gait variability differences in addition to testing the efficacy of ApEn and FuzzyEn as tools to assess differences between two groups, with the hopes of developing an OA onset prediction tool.

CHAPTER III

GENDER STUDY: MALES VERSUS FEMALES

Entropy analysis of kinetic and kinematic gait parameters reveals a complex chaotic behavior in both males and females

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III.1. Abstract

Osteoarthritis (OA) is an age-related joint degenerative disease that affects 30.8 million Americans. The number of adults affected by OA incidence is predicted to dramatically increase by 2050 as the population of adults over the age of 60 is expected to double. Thus, there is a critical need for reliable screening protocols for the early detection of this debilitating disease. A variety of variability measurements have been developed in the past decade. Approximate Entropy (ApEn) has been used to identify pathology in biosignals and to investigate gait variability. Fuzzy Entropy (FuzzyEn) was developed as an improvement of ApEn, however its use has primarily been in the study of electromyography signals. This study quantifies the performance of ApEn and FuzzyEn in identifying gait variability in healthy young male and female adults to provide baseline data. Twenty healthy males and females between 18 and 25 years old walked on an instrumented treadmill at a self-selected speed while kinetic and kinematic parameters were recorded. We found that gait is a complex chaotic process, regardless of the gender, since both kinetic and kinematic parameters exhibited step-to-step variability. Overall, males showed lower variability in kinetic parameters while females showed lower variability in kinematic parameters. More importantly, FuzzyEn was less sensitive to input parameters and thus more reliable than ApEn. We believe that this entropy measurement is a promising tool for the early detection of biomechanical imbalances that can lead to OA onset.

III.2. Keywords

Gait, Chaos, Entropy Analysis, Variability, Gender

III.3. Introduction

Almost half of Americans over the age of 65 suffer from arthritis, of which osteoarthritis (OA) is the most common (Barbour, 2017). OA is a painful, debilitating disease that is characterized by a progressive disappearance of the articular cartilage. Since the number of adults over the age of 60 is expected to double by 2050 (Ortman, 2014), it is reasonable to expect a significant increase in OA occurrences in the future. Hence, there is a need to develop efficient screening protocols to enable early detection of OA in young adults, with the hope of implementing corrective measures early on. The investigation of gender-based differences during gait may highlight key parameters for such screening protocols, since females are twice as likely to develop OA in the knee joint (Zhang, 2010). Gait analysis could be an effective screening task since it has been an established tool in investigating kinetic and kinematic variations during gait (Hausdorff, 2001; Andriacchi, 1985).

Traditionally, research into gender-based gait differences has focused on linear statistical measures of centrality such as mean, median, standard deviation and coefficient of variation. These quantities highlight how far a set of data deviates from a central point, treating variations as random and independent, and thus disregarding temporal variations (Lomax, 2007). One of these studies by Kerrigan et al. involved ninety-nine young adult subjects and found that females have significantly greater mean hip flexion, reduced mean knee extension before initial contact, and higher mean ankle power generation during pre-swing compared to males (Kerrigan, 1998). Other kinematic studies have revealed that females show greater internal hip rotation and adduction when compared to males but conflicting results have been found regarding sagittal plane hip and knee kinematics (Ferber, 2003; Chumanov, 2008). Chiu & Wang (2007) also found that females show significantly higher vertical ground reaction forces in the loading response and pre-swing phases and higher tibialis anterior activity compared to males. While these gender differences deduced through linear analysis of gait remain useful, the variability of gait with respect to gender has remained a largely unexplored area and may lead to novel insights into the

higher rate of OA in females, and in the development of efficient screening protocols for early OA detection.

Several studies have indicated that human movement variations possess deterministic properties (Dingwell, 1999; Dingwell, 2007; Harbourne, 2009). Under the theory of Optimal Movement Variability, first proposed by Stergiou & Harbourne (2006), there exists an optimal range of movement variability necessary for the body to react to environmental stimuli and stresses. A loss of this optimal state has been associated with pathology or fatigue (Pincus and Goldberger, 1994). Several non-linear methods have been developed to investigate this variability and fall under the umbrellas of local stability measures or entropy. Since local stability measures neglect the global stability of the system (Van Emmerik, 2016), it is appropriate to use entropy measures in studying gait variability since it is rooted in information theory.

Approximate Entropy (ApEn) is a popular entropy measure that was first used by Steve Pincus (Pincus, 1995) as a method of quantifying the complexity and regularity of biological time-series data. The ApEn algorithm measures the likelihood that runs of patterns that are close for m observations remain close in subsequent incremental comparisons, based on an input parameter (r) related to the standard deviation of the signal (where r = k*standard deviation) and the length of the signal (N, the number of data points). ApEn ranges from 0 to 2, with larger values signifying increased variability and thus adaptability, and lower values signifying regularity, *i.e.* reduced variability or even underlying pathology (Pincus S., 1995). In gait analysis, ApEn has been used to investigate age-related effects of spatio-temporal variables such as minimum toe clearance (Karmakar, 2007), variability patterns in kinematic parameters such as joint angles (Estep, 2018), and in the investigation of variability in anterior cruciate ligament deficient knees during walking (Georgoulis, 2006). However, there is a noticeable gap when it comes to kinetic parameters. ApEn also shows inconsistencies with its dependence on input parameters and its bias towards regularity, due to an inherent self-matching feature. A recent investigation into the performance of ApEn with varying input parameter values by Yentes and

Schmid (2018) found a significant interaction between r and N and hence recommended that r values be listed as a range when depicting results in entropy studies. Many modifications to the ApEn algorithm have thus emerged, such as Sample Entropy and Multiscale Entropy. However, the dependence on input parameters in other entropy measures continues to be an issue (Yentes, 2013).

Chen and Wang (2007) developed Fuzzy Entropy (FuzzyEn), which is based on the concept of Fuzzy logic developed by Zadeh (1965), as an improvement to existing entropy measures. Unlike other entropy measures, FuzzyEn considers the imprecise environments from which biological data sets arise. When analyzing vector similarity, FuzzyEn replaces the binary response of traditional entropy measures (0 or 1), by a continuum. Despite utilizing the same input parameters as ApEn, FuzzyEn has shown its superiority in its robustness to noise and input parameter selections, and in eliminating the bias towards regularity (Chen, 2009). However, despite its power, FuzzyEn has been used solely in the investigation of muscle physiology, *i.e.* electromyographic (EMG) signals, and its performance in investigating kinetics and kinematics gait parameters thus remains unknown.

We thus hypothesize that ApEn and FuzzyEn are effective tools in detecting gender-related variability of kinetic and kinematic parameters. The purpose of this study was thus to assess the efficacy of ApEn and FuzzyEn in detecting gender-related variability and to establish normative kinetics and kinematics variability measures for young healthy subjects during gait. Specifically, we studied the variability of six parameters: (1) peak ground reaction force during heel strike, (2) during toe off, (3) medio-lateral center of pressure location, sagittal range of motion of the (4) hip, (5) knee, (6) and ankle joints.

III.4. Methods

III.4.1. Subjects

Twenty healthy males and twenty healthy females between the ages of 18 and 25 were included in this study (Males: age: 21.9 ± 1.8 years, Females: age: 21.9 ± 1.2 years). The study was conducted under the approval of the university's Institutional Review Board and all participants signed an informed consent form. Participants were screened based on the inclusion criteria of (1) no diagnosed OA, (2) no history of lower limb surgeries, and (3) no existing cardiac conditions. Participants also filled out an intake form providing information about the participant's height, weight, lower body injuries over the past year, neurological disorders, diabetes diagnosis, pregnancy, level of physical activity (active considered as exercise for two and a half hours a week during the past year) and administration or consumption of analgesics prior to participation.

III.4.2. Data collection protocol

A six-camera motion capture system (Natural Point Inc., Corvallis OR, USA) was used to record kinematics data. Twenty-six motion analysis markers were placed on anatomical landmarks according to the Rizzoli Lower Body protocol (Leardini, 2007). Ground reaction forces and plantar pressure distributions were recorded using an instrumented treadmill (Noraxon, Scottsdale AZ, USA).

Instrumented barefoot subjects were asked to step on the treadmill and remain in a standing t-pose for calibration. Subjects then increased the treadmill speed until a comfortable gait speed was achieved. Subjects warmed up for two minutes at this fixed, self-selected speed after which kinetics and kinematics data were then collected for 10 minutes.

III.4.3. Data processing

Force and pressure data were sampled at 100 Hz. Pressure data was filtered using a 4^{th} order Butterworth low-pass filter with a cut-off frequency of 20 Hz to reduce any treadmill-related noise. A custom MATLAB algorithm was used to sort data per subject and per gait cycle.

In order to take into account the differences in speed, 370 gait cycles were selected in the middle of each subject's trial. Peak ground reaction forces at heel strike and toe off ($pGRF_{HS}$ and $pGRF_{TO}$, respectively) were computed for each gait cycle as the first and second peak of the total ground reaction force curve, respectively. To allow for inter-subject comparisons, these values were then normalized by body weight. The medio-lateral center of pressure location (mlCOP) was determined by finding the range of deviation of the center of pressure trajectory from the heel-toe line during the stance phase of each gait cycle (Jamshidi, 2010). This value was then normalized by foot length. To calculate joint kinematics, an existing OpenSim model (Hamner, 2010) was modified to create a 19-degree of freedom template, which was then used to create subject-specific models. A pipeline between Matlab (MathWorks, Natick MA, USA) and OpenSim (Delp, 2007) was developed to automatically scale each model and compute the joint kinematics for each of the 370 gait cycles selected.

ApEn and FuzzyEn values were then computed for step-to-step data for pGRFHS, pGRFTO, mlCOP, and the three joint ROMs, using m = 2, n = 1, and k ranging from 0.1 to 0.9 in 0.1 increments. The ApEn and FuzzyEn algorithms used were downloaded from the Mathworks' File Exchange database and were developed by Lee (Lee, 2012) and Alvarez (Monge-Alvarez, 2015), respectively. Differences between the two methods were estimated by pulling together the data for males and females and computing the normalized difference (nD), defined as follow:

$$nD = \frac{ApEn - FuzzyEn}{FuzzyEn} * 100$$

III.4.4. Statistical analysis

Linear analyses was performed on each parameter using an independent two sample t-test or Wilcoxon Man Whitney test, depending on the distribution of the data, to check for differences between males and females (Box, 2005). ApEn and FuzzyEn outputs were compared for each group (males and females), parameter, and k value using the means and medians based on the condition of normality found by the Jarque-Bera test (Jarque & Bera, 1980). Normal data was

compared using an independent two-sample t-test while non-normal data was investigated using the Wilcoxon Man Whitney test. Significance was set at $p < 0.05$.

III.5. Results

Our results indicate that: (1) gait is a complex process since all the parameters studied exhibited relative variability, with entropy values ranging from 0.2 to 2 (and always superior to 0.9 at k = 0.2), and (2) these variabilities are predominantly non gender-specific. Subjects' characteristics are shown in Figure 3. Males exhibited a significantly higher Body Mass Index in comparison to females ($p = 0.048$).

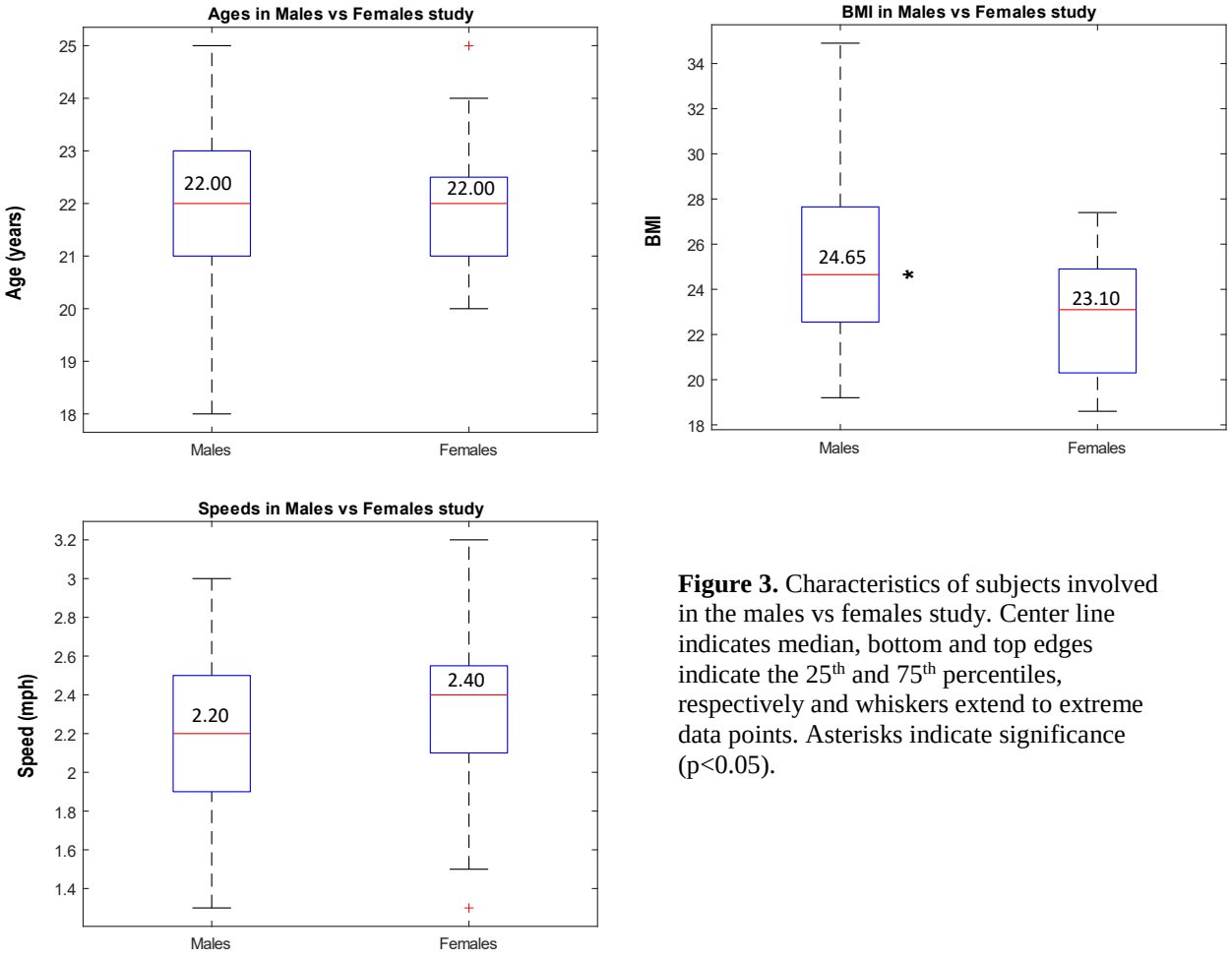

Figure 3. Characteristics of subjects involved in the males vs females study. Center line indicates median, bottom and top edges indicate the 25th and 75th percentiles, respectively and whiskers extend to extreme data points. Asterisks indicate significance ($p<0.05$).

Regarding linear analyses (Figure 3), females exhibited significantly higher peak vertical force at heel strike and toe off, and higher sagittal hip ROM ($p < 0.05$).

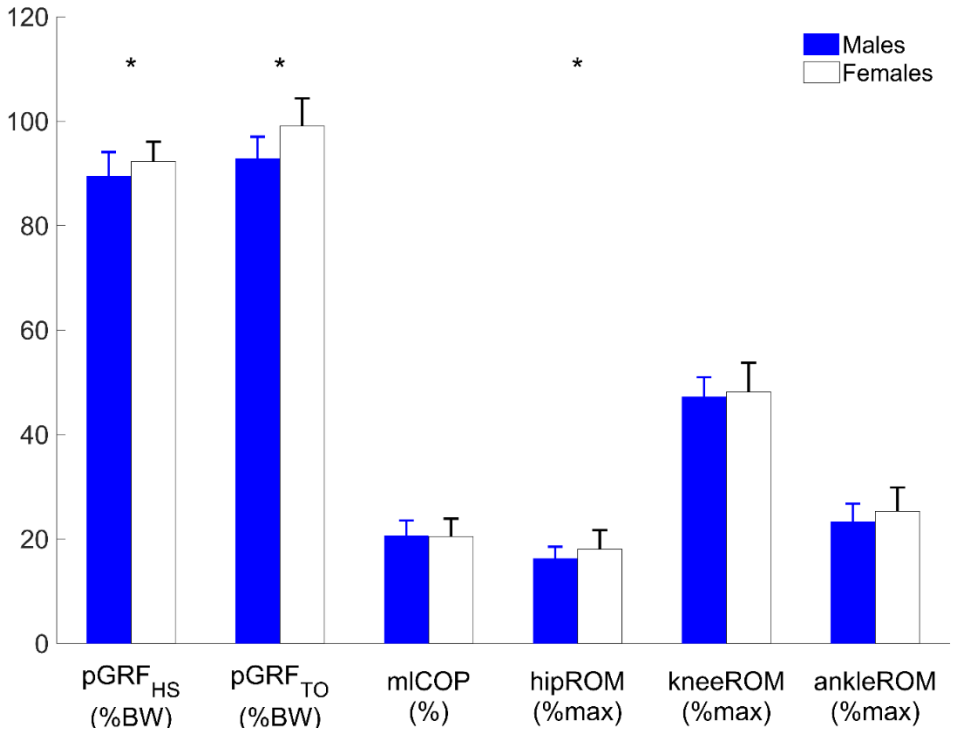

Figure 4. Linear analysis: peak vertical ground reaction force at heel-strike (pGRFHS) and toe-off (pGRFTO), medio-lateral center of pressure displacement (mlCOP), and ankle, knee, and hip ranges of motion (ankleROM, kneeROM, and hipROM, respectively). Bars represent the mean values per group, whiskers represent one standard deviation, and asterisks represent significance ($p < 0.05$).

Regarding variability analysis using ApEn, males exhibited lower variability for peak ground reaction force at heel strike and toe off and for medio-lateral COP displacement (Figure 4). However, significantly lower values for males were only found for the peak ground reaction force during toe off at k = 0.8 ($p = 0.047$) (Figure 4.a) and for the medio-lateral COP displacement at k = 0.2 and 0.3 ($p = 0.002$ and 0.003, respectively). The trends were the same when using FuzzyEn, with significantly lower FuzzyEn values for males in the peak ground reaction force during toe off at k = 0.1 and 0.2 (p =0.040 and 0.049, respectively) (Figure 4.b).

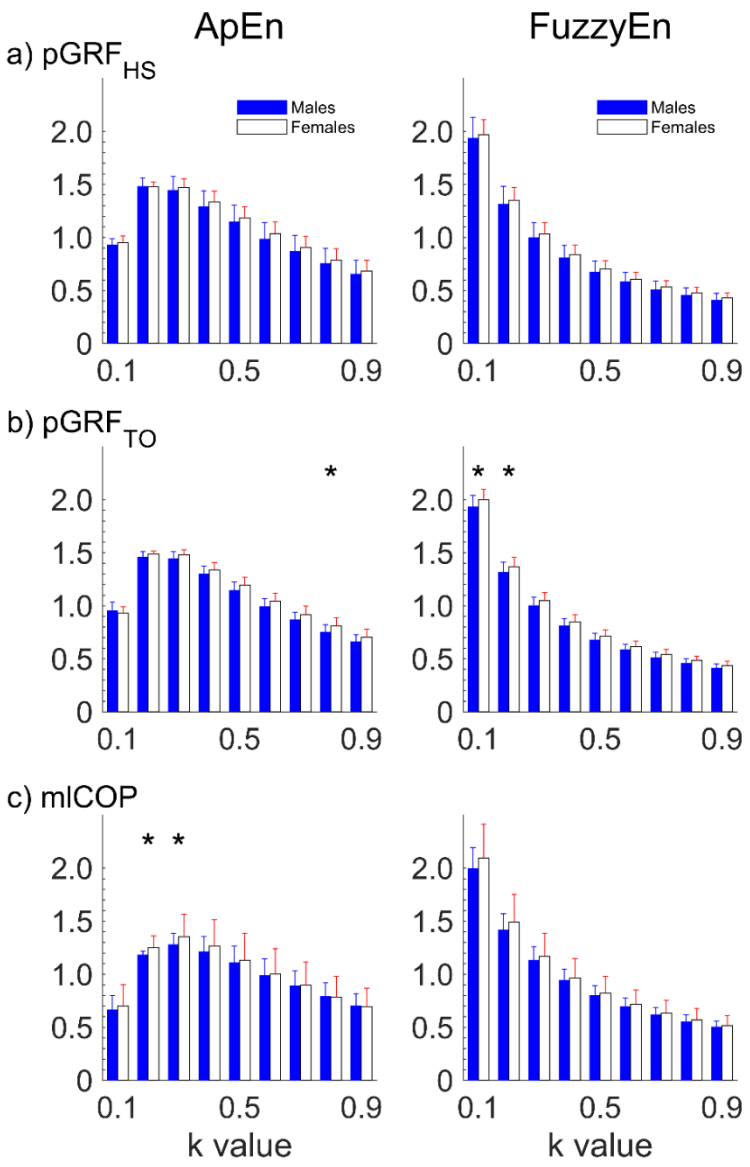

Figure 5. ApEn and FuzzyEn values versus k values for the peak GRF at heel strike (a), the peak GRF at toe off (b), and the medio-lateral COP displacement (c). Bars represent the mean values per group, whiskers represent one standard deviation, and asterisks rep represent significance ($p < 0.05$). Males showed lower entropy values with significantly lower median ApEn values in peak ground reaction force during toe off for $k = 0.8$, and lower mean FuzzyEn values for $k = 0.1$ and 0.2, as well as lower median ApEn values for medio-lateral center of pressure displacement for $k = 0.2$ and 0.3.

Females exhibited lower variability for sagittal ankle, knee and hip ranges of motion, regardless of the entropy method used (Figure 5). ApEn values were significantly lower in females for the ankle ROM (Figure 5.c) at k = 0.1, 0.2, 0.4 and 0.5. FuzzyEn showed similar trends but without significance.

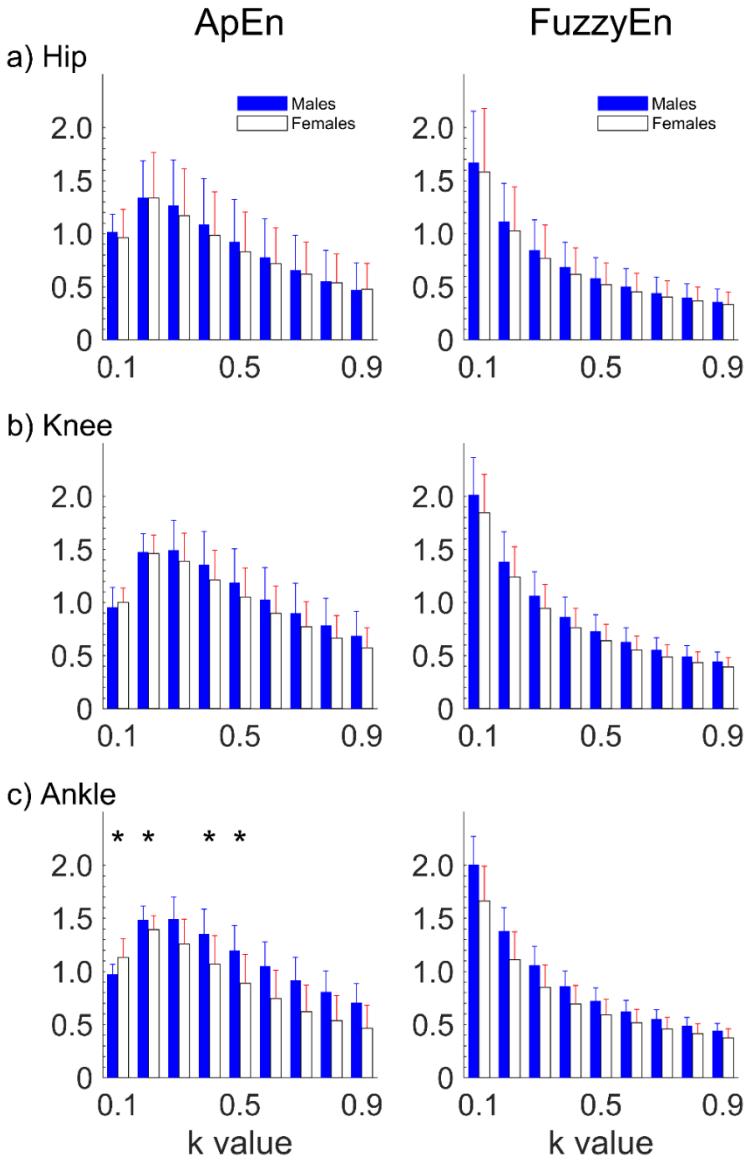

Figure 6. ApEn and FuzzyEn values versus k values for the hip ROM (a), knee ROM (b), and ankle ROM (c). Bars represent the mean values per group, whiskers represent one standard deviation, and asterisks represent significance ($p < 0.05$). Females showed lower entropy values with significantly lower median ApEn values in ankle ROM for k = 0.1, 0.2, 0.4, and 0.5.

Finally, normalized differences between ApEn and FuzzyEn values were all inferior to 20% only for k = 0.2 (Figure 6).

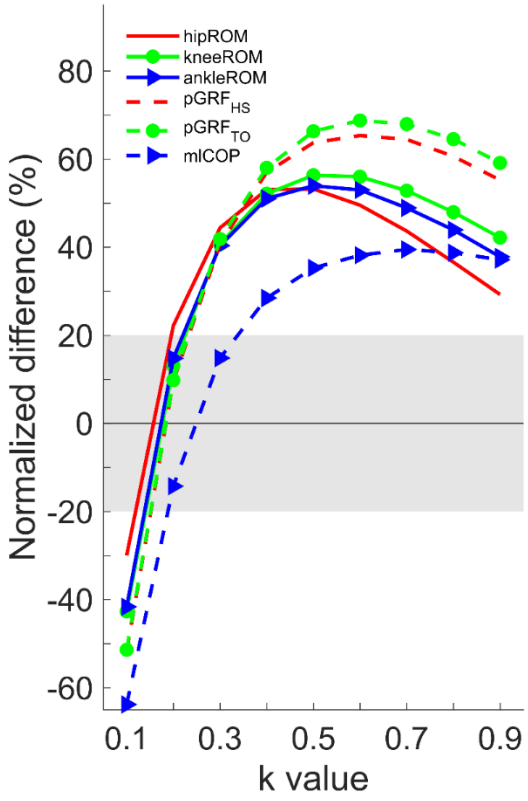

Figure 7. Normalized difference between mean ApEn and FuzzyEn versus k values for the three kinetics and three kinematics parameters. Absolute differences are all inferior to 20% only for k = 0.2.

III.6. Discussion

The purpose of this study was to test the efficacy of approximate and fuzzy entropy in detecting differences in gait variability between healthy males and females as well as to establish normative variability values for kinetic and kinematic gait parameters. Both kinetic and kinematic parameters exhibited step-to-step temporal variability. These results confirm that, for young healthy subjects, gait is not a simple cyclic motion but a complex chaotic process (Stergiou,

2011). Overall, we did not find consistent significant gender-related differences, showing that the processes at play seem to be universal for young healthy humans.

Linear analyses were performed to validate our data collection protocol by comparing our results to previous studies. Males exhibited a significantly higher BMI than females, which is reflective of the male and female population aged 20-39 years old in the United States (Flegal 2006). Females experienced significantly higher peak vertical ground reaction forces during the heel strike and toe off phases of gait, similar to previous findings by Chiu & Wang (2007). However, Keller et al. (1996) found higher vertical thrust forces in males compared to females at speeds of 1.5 and 2.0 m/s in a study comprising of 13 male and 10 female recreational athletes. Since gait speed was not controlled in our study, our contradictory findings can be attributed to the higher average gait speed of females, since it has been found that vertical thrust forces increase with speed (Keller, 1996). The increased hip range of motion in females in comparison to males agrees with previous findings (Kerrigan et al., 1998). We did not a find significant increase in the knee and ankle sagittal ranges of motion in females. However, the trend indicating higher ranges of motion for females agrees with previous findings (Frimenko, 2014). Controlling for gait speed may have revealed significant linear kinematic differences between males and females. However, we chose not to impose a pre-selected speed since our focus remained on gait variability analysis, hence necessitating a natural and comfortable gait speed for the subjects involved.

For non-linear analysis, the embedded dimension of input parameter m = 2 allowed for a step-to-step comparison of gait data and was based on prior studies (Estep, 2018). The data length N was fixed at 740 steps for all subjects for investigating the kinetic and kinematic parameters. We varied our input parameter k (where r = k*standard deviation) incrementally from 0.1 to 0.9 based on the recommendation by Yentes & Schmid (2018) to reveal the performance of the algorithms at different input parameters, and to prevent incorrect assessments of the signal complexity (Chon, 2009). Non-linear analysis using ApEn showed a distinctive pattern for kinetic

and kinematic data that peaked at k = 0.2 or 0.3 and decreased thereafter. A similar pattern was observed in a prior study by Kamarkar et al. (2007), where a peak was observed in healthy young, healthy elderly, and falls risk groups, but for a k value of 0.4. This difference in peak regions may be due to differences in input parameters between the two studies since interactions between input parameters m, k and N produce varying results (Yentes, 2018). However, ApEn peaks coincided with statistical significance in the case of the ankle ROM and medio-lateral COP displacement, which supports the recommendation by Chon to use the k value that provides the maximum ApEn value (Chon, 2009).

For kinetic parameters, *i.e.* peak vertical force at heel-strike and toe-off, and medio-lateral COP displacement, both entropy measures found higher values for females than for males, with significance for peak force at toe-off using FuzzyEn and for medio-lateral COP displacement using ApEn. However, we did not find any simultaneous significance. Nevertheless, these trends suggest that females exhibit relatively higher variability, *i.e.* adaptability, during the stance phase, which may compensate for their higher hip power absorption and ankle power generation in comparison to males (Kerrigan, 1998), as well as the significantly higher hip negative work during running compared to men (Ferber, 2003). Both males and females exhibit high gait variability for k values ranging from 0.2 to 0.3, which is indicative of a healthy biomechanical system (Pincus, 1994).

For kinematic parameters, males exhibited higher entropy values, *i.e.* variability, than females for the ankle ROM, which was significant when using ApEn. This finding is particularly interesting since females walked slightly faster than males, although not significantly, and should have thus shown increased variability (Jordan, 2007; Estep, 2018). The implication could be that, despite the higher ranges of motion and gait speeds, females may lack the kinematic adaptability present in males. A lack of kinematic variability, *i.e.* an ability to adapt to external stimuli and stresses, could result in localized peak contact pressures in the cartilage of the ankle, knee, and hip joints. This local overloading may lead to gradual cartilage damage and may result in

osteoarthritis onset (Zhang, 2010). Our results may thus show insights into the prevalence of lower body osteoarthritis in females.

Comparison of the two entropy measurement methods showed that while trends were similar, there were more cases of significant differences between males and females when using ApEn. Indeed, this is evident in literature where ApEn's sensitivity has been used to show lower variability in pathological groups such as in multiple sclerosis patients where lower ApEn values were found (Kaipust, 2012). However, FuzzyEn showed sensitivity in peak vertical ground reaction force at toe off, where females had significantly higher entropy values compared to males. Although this was echoed in ApEn for k = 0.8, caution should be observed due to weak algorithmic validity of ApEn at such high k values (Pincus, 1994). For all parameters, FuzzyEn showed lower entropy values compared to ApEn, which goes against the current understanding that ApEn shows a bias towards regularity (Yentes, 2018). However, ApEn showed poor relative consistency for k values below 0.2, with male and female results exhibiting the well documented "flip-flop effect" (Boskovic, 2011). The "flip-flop effect" limits the reliability of ApEn at lower k values, and continues to be a strong reason of implementing a range of k input values when analyzing biosignals (Karmakar, 2007). Finally, for solely k = 0.2 did the two methods give similar values, with a normalized difference inferior to 20%. Thus, if varying k is not an option, using k = 0.2 should minimize the discrepancies between ApEn and FuzzyEn outputs. Coincidentally, this value is the one recommended for computing ApEn values (Pincus S. , 1995).

The limitations of this study are related to the data collection protocol. The use of a treadmill has been found to show a bias towards regularity due to the inability to adjust speed and forced cadence (Dingwell, 2001) which has been revealed in ApEn and sample entropy analysis (Yentes, 2018). However, the use of a treadmill in this study enabled the collection of many gait cycles at relative comfort to the subjects and was validated by previous investigations into kinematic variability (Estep, 2018; Georgoulis, 2006). Future work will focus on studying potential age-related effects on gait variability, and effects of this variability on joint contact

forces. The hypothesis to investigate would be that lower variability leads to a higher amount of cartilage damage. This future study will be pave the way for the development of a reliable predictor of the risk of osteoarthritis onset. Another limitation of this study is that the performance of entropy tools on patients with osteoarthritis was not conducted. Future studies have to be performed with healthy and osteoarthritis affected patients in order to understand the true result of such algorithms. Furthermore, longitudinal studies where patients are re-tested over a period of time would elucidate a better understanding behind the development of gait abnormalities with age, through the lens of variability.

III.7. Conclusion

This study assessed the variability of kinetic and kinematic gait behavior to provide baseline data for future studies. Our findings confirmed that gait is a complex chaotic process, regardless of the gender, since both kinetic and kinematic parameters exhibited step-to-step variability. When comparing the two entropy measures used, FuzzyEn appears to be a more reliable tool due to a reduced dependence on input parameters and a lower probability of finding potentially false significant differences. This study was the first to use entropy measurements for characterizing both kinetic and kinematic gait parameters, and hence paves the way for developing novel reliable predictors of early onset of musculoskeletal disorders through gait variability analysis.

III.8. Acknowledgement

The authors would like to thank Mr. William Estep, Mr. Osama Ramadan, and Mr. Landon Grant for their assistance during data collection.

III.9. Conflict of interest statement

The authors have no financial or personal relationships with people or organizations that could have inappropriately influenced this work.

CHAPTER IV

AGE STUDY: YOUNGER VERSUS OLDER

Effect of Age on Gait Variability and its Potential Implications in Osteoarthritis Onset

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IV.1. Abstract

Osteoarthritis (OA) is an age-related joint degenerative disease that is predicted to dramatically increase in prevalence by 2050, as the population of adults over the age of 60 is expected to double. Thus, there is a critical need for reliable screening protocols for the early detection of OA onset. A variety of variability measurements have been developed in the past decade. Approximate Entropy (ApEn) has been used to identify pathology in biosignals and to investigate gait variability. Fuzzy Entropy (FuzzyEn) was developed as an improvement of ApEn, however its use has primarily been in the study of electromyography signals. This study sought to quantify the performance of ApEn and FuzzyEn in identifying gait variability in younger and older females, under the context of OA onset. Eight younger females (of ages 18 to 25 years old) and eight older females (of ages 50 to 60 years old) walked on an instrumented treadmill at a self-selected speed while kinetic and kinematic parameters were recorded. We found that gait remains complex and chaotic into old age. Overall, older females showed relatively lower entropy values in all parameters except for peak ground reaction force during heel strike, showing promise in the variability analysis method. FuzzyEn was less sensitive to input parameters and thus more reliable than ApEn. We believe that this FuzzyEn is a promising tool for the early detection of biomechanical imbalances that can lead to OA onset.

IV.2. Keywords

Gait, Chaos, Entropy Analysis, Variability, Age

IV.3. Introduction

Osteoarthritis (OA) is the most common form of arthritis and affects approximately 27 million Americans today (Health, 2018). The disease is characterized by localized cartilage erosion at a specific joint, resulting in bone-to-bone contact accompanied by pain, swelling, stiffness and anatomical changes to the underlying bone (Felson, 2000). The onset of OA is dependent on a multitude of systemic factors that increases the vulnerability of an individual to the disease, after which local biomechanical factors trigger the disease (Felson, 1998). However, current understanding is unclear on whether systemic factors possess their own biomechanical issues that drive OA onset (Felson, 2000). With the number of doctor-diagnosed arthritis cases in the United States set to increase by 49% by 2040 (Hootman, 2016), there is a critical need to better understand the biomechanics behind osteoarthritis onset so that early preventative measures can be implemented.

One of the systemic factors behind OA onset is age (Felson , 2000). Oliveria et al. (1995) found that OA incidence increases after the age of 50 years old, with knee and hip OA progressing the fastest during this period. While the exact reason for this is unknown, researchers investigating the biomechanical effects of age on gait have found a distal to proximal shift in gait control strategy of older adults. This shift includes less power and work generated at the ankle in exchange for higher power and work generated at the hip (DeVita, 2000). In addition, linear analysis of spatio-temporal gait parameters has revealed that elderly adults walk at slower speeds and with shorter step lengths, despite having higher cadence (Ko, 2010).

Another systemic factor of OA onset is gender. Females over the age of 50 years old have a higher prevalence and incidence of OA for most joints, including the hip and knee (Saase, 1989). Investigations into the biomechanical differences between males and females during gait have revealed a higher pelvic range of motion (ROM) in all planes (Frimenko, 2014), an increased knee valgus angle throughout the gait cycle (Cho, 2004), and higher ankle ROM due to greater ankle flexion at heel strike and toe off (Frimenko, 2014). While these biomechanical

differences may provide clues as to why older females are at a higher risk of osteoarthritis, it is important to note that earlier studies had focused on linear statistical measures of centrality, which sufficed under the popular 'Generalized Motor Program' and 'Dynamical Systems' theories of human movement at the time. However, the emergence of a more recent theory of Optimal Movement Variability has warranted the use of novel non-linear tools in investigating the variability of human movement (Stergiou, 2006). This theory suggests that human movement exists in an optimal range of variability between a purely stochastic system and a purely periodic one (Stergiou, 2006) and that variability is essentially a deterministic process (Dingwell, 1999). Of the many non-linear tools developed for this cause, Approximate Entropy (ApEn) grew in popularity in gait variability studies (Pincus S. , 1995). ApEn is a measure of the likelihood that runs of patterns that are close for "m" observations remain close in subsequent incremental comparisons based on an input parameter related to the standard deviation of the signal r (where r = k*standard deviation) and length of the signal N (where N is the number of data points). The output of ApEn ranges between 0 and 2, with higher values signifying complexity of the signal, and lower value signifying regularity (Pincus, 1994). Due to the an inherent self-matching feature in ApEn that provided a bias towards regularity, and a significant interaction between the input parameters (Yentes, 2018), Chen & Wang developed Fuzzy Entropy to provide a more robust and reliable entropy analysis of biological signals (Chen, 2009). FuzzyEn used the same input parameters as ApEn while replacing the Heaviside function for a Fuzzy function with a "membership degree" (Chen, 2007). Our earlier investigation into the efficacy of ApEn and FuzzyEn in the investigation of variability in gait imbalance parameters of healthy, young males and females showed that FuzzyEn was more reliable due to a lower dependence on input parameters and a lower chance of finding false significant differences (Ekanayake & Hausselle).

Several studies highlighted the effect of age and gait variability Buzzi et al. investigated this relationship by studying gait kinematics of ten younger and ten older females. They found that Lyapunov Exponent values were greater for the sagittal vertical displacements of the hip,

ankle, and knee in the elderly group, concluding that elderly subjects displayed more local instability than younger subjects (Buzzi, 2003). Kurz and Stergiou used non-linear statistical entropy to investigate sagittal kinematics between ten younger and ten older subjects and found larger entropy values in the older group. This suggested that there was less certainty in selecting a joint range of motion for the ankle, knee, and hip joints with age (Stergiou, 2003). Furthermore, Karmakar et al. (Karmakar, 2007) looked at minimum toe clearance between thirty young, twenty seven elderly, and ten elderly subjects with fall risk and found that above an ApEn input "r" value of 0.26*SD, the falls risk group had a lower ApEn than the other two groups. Their study supported the hypothesis proposed by Pincus (Pincus, 1994) that lower ApEn can be related to an underlying pathology. These studies mainly focused on age-related variability of spatio-temporal and kinematic parameters. Since OA onset has been related to higher-than-normal joint contact forces, there is also a critical need to establish the effects of age on the variability of kinetic parameters such as ground reaction forces, center of pressure locations, and muscle activity.

Therefore, the purpose of this study was to assess age-related changes in the variability of kinetic and kinematic gait parameters using Approximate and Fuzzy Entropy. This study is a critical first step towards a better understanding OA onset and the development of efficient preventive measures. Specifically, we studied the variability in females of six parameters: (1) peak ground reaction force during heel strike, (2) during toe off, (3) medio-lateral center of pressure location, and sagittal ROM of the (4) hip, (5) knee, and (6) ankle joints.

IV.4. Methods

IV.4.1. Subjects

The study was conducted under the approval of the university's Institutional Review Board and all participants signed an informed consent form. Eight females between the ages of 18 and 25 years old and eight females between the ages of 50 and 60 years old were included. For subjects aged 18-25, gait data was obtained from our prior study which involved investigating the

efficacy of ApEn and FuzzyEn in finding differences in variability between healthy men and women of this age range. This study utilized the exact same parameters but focused on investigating the performance of entropy tools with respect to age. All participants had to meet the inclusion criteria of i) no diagnosed OA, ii) no history of lower limb surgeries, and iii) no existing cardiac conditions. Eligible participants filled out an additional intake form which provided information about the participant's weight, height, lower body injuries over the past year, neurological disorders, diabetes diagnosis, pregnancy, level of physical activity (active considered as exercise for two and a half hours a week during the past year) and administration or consumption of analgesics prior to participation.

IV.4.2. Data collection protocol

To record kinematic data, a six-camera motion capture system (Natural Point Inc., Corvallis OR, USA) was used along with twenty-six motion analysis markers that were placed on participants' bone anatomical landmarks according to the Rizzoli Lower Body established by Leardini et al. (Leardini, 2007). An instrumented treadmill (Noraxon, Scottsdale AZ, USA) was used to record plantar pressure distributions. Participants remained barefoot for this study. Once instrumented, participants were asked to step on the treadmill and remain in a standing position for calibration. Participants then increased the speed of the treadmill until a comfortable gait speed was achieved and warmed up for two minutes at this fixed speed. Kinetic and kinematic data were then collected for ten minutes at the comfortable self-selected speed of the participant.

IV.4.3. Data processing

Data for younger subjects (ages 18 to 25) were selected from our prior study to match the average BMI and gait speed of the eight older females (ages 50-60) from whom data was collected in this study.

A sampling rate of 120Hz was used for motion capture data while pressure data were sampled at 100Hz. Flickering motion-capture markers were corrected using pattern-based interpolation while a 4^{th} order Butterworth low-pass filter with a cut-off frequency of 4Hz was

applied to reduce noise. Pressure data were filtered using a 4th order Butterworth low-pass filter with a cut-off frequency of 20 Hz to reduce treadmill-related noise. A custom Matlab algorithm was used to sort data per subject and per gait cycle based on the pressure measurements. In order to take into account differences in speed, 370 gait cycles were extracted in the middle of the trial for each subject. Vertical ground reaction forces were computed based on the pressure distributions at each time step. Peak vertical ground reaction forces at heel strike and toe off (pGRFHS and pGRFTO, respectively) were computed for each step as the first and second peak of the total ground reaction force curve, respectively. These values were then normalized by body weight to allow for inter-subject comparisons. The medio-lateral center of pressure location (mlCOP) was determined by finding the range of deviation of the center of pressure trajectory from the heel-toe line during the stance phase of each step (Jamshidi, 2010), and by then normalizing by foot length. To compute joint kinematics, an existing OpenSim (Delp, 2007) model (Hamner, 2010) was modified to create a 19-degree of freedom template to develop subject specific models. Scaling and inverse kinematics procedures were automatically run for each subject and each gait cycle using a custom pipeline between Matlab (MathWorks, Natick MA, USA) and OpenSim.. Sagittal hip, knee, and ankle ROM (HipROM, KneeROM, AnkleROM, respectively) were computed for each subject and each gait cycle as the amplitude of the corresponding angle during the stance phase.

Step-to-step non-linear analysis of the six variables of interest (pGRFHS, pGRFTO, mlCOP, HipROM, KneeROM, AnkleROM) was performed using Approximate and Fuzzy Entropy (FuzzyEn) codes downloaded from the Mathworks' File Exchange database (Lee, 2012) (Monge-Alvarez, 2015) using input parameters of m=2, n=1 and k ranging from 0.1 to 0.9 in 0.1 increments. based on the recommendation by Yentes et al. (Yentes & Schmid, 2018) in order to gauge the performance of each entropy measure and to observe and "flip-flop effect" of results. Differences between the two entropy methods were estimated by pulling together the data for younger vs older groups and computing the normalized difference (nD), defined as follow:

$$nD = \frac{(ApEn - FuzzyEn)}{FuzzyEn} * 100$$

IV.4.4. Statistical analysis

To test for differences between the two age groups (younger and older), linear analyses was performed on each parameters using an independent two sample t-test or Wilcoxon Man Whitney test, depending on the distribution of the data. FuzzyEn values were compared for each group and each k value using the means and medians based on the condition of normality found by the Jarque-Bera test (Jarque & Bera, 1980). Normal data was compared using an independent two-sample t-test while non-normal data was investigated using the Wilcoxon Man Whitney test. Significance was set at $p = 0.05$.

IV.5. Results

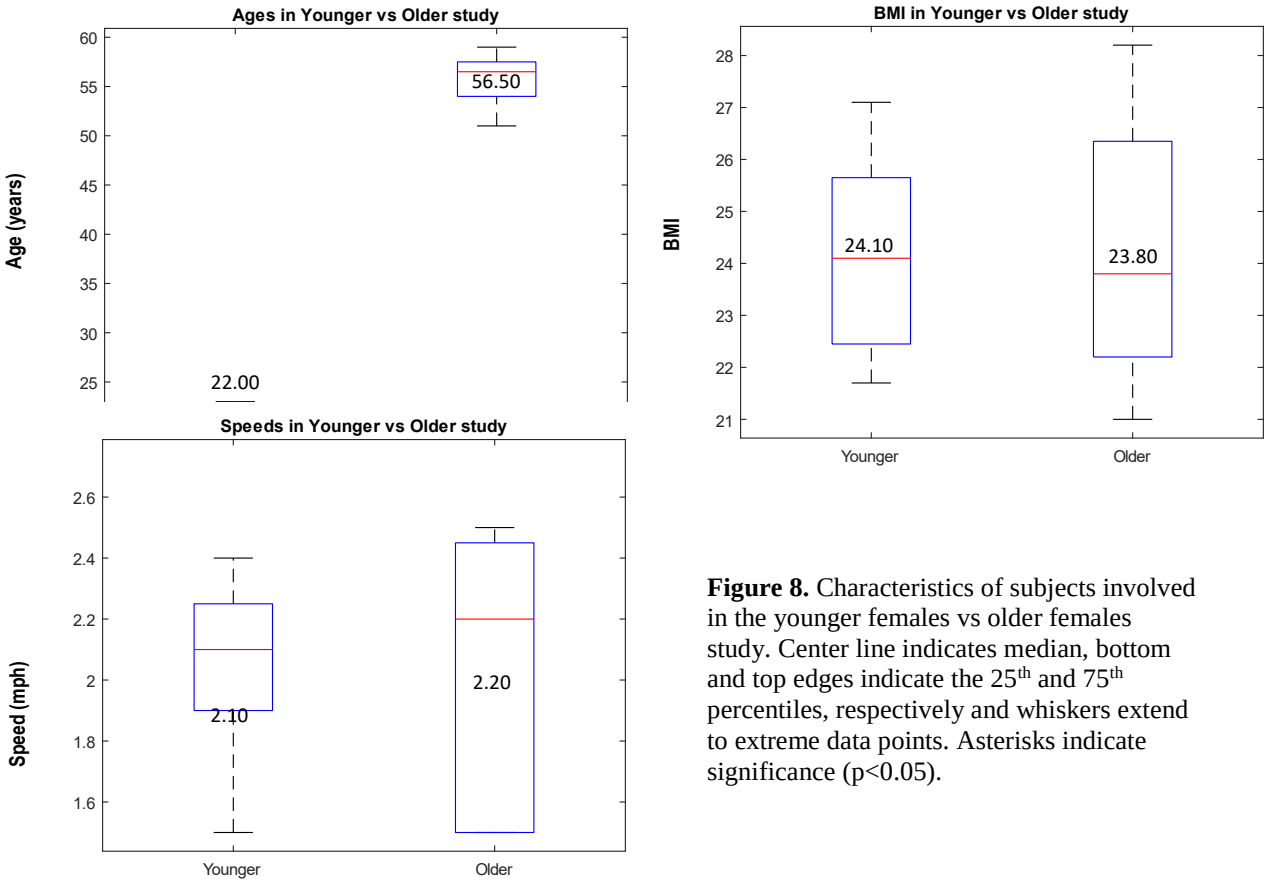

Figure 8. Characteristics of subjects involved in the younger females vs older females study. Center line indicates median, bottom and top edges indicate the 25th and 75th percentiles, respectively and whiskers extend to extreme data points. Asterisks indicate significance ($p<0.05$).

Older females had an average age of 55.75 ± 2.60, BMI of 24.24 ± 2.55 and walked at a gait speed of 0.91 ± 0.21 m/s. Younger females had an average age of 22 ± 0.76, BMI of 24.15 ± 1.96 and walked at a gait speed of 0.92 ± 0.13 m/s (Table 2). There was no significant difference in BMI or gait speed between the two groups, as the data from younger female subjects were intentionally selected to match older subjects' BMI and gait speeds. However, 12.5% of younger females had suffered an injury in the lower extremity in the past year and 100% were physically active (defined the same as earlier), while none of the older subjects had suffered from a lower body injury but only 75% were physically active.

Regarding linear analyses (Figure 7), older females had a significantly higher range of motion in the hip (p = 0.0281). Younger females showed insignificantly higher values for peak ground reaction force during heel strike and toe off and medial-lateral center of pressure. Older females showed marginally higher range of motion at the ankle and marginally lower range of motion at the knee when compared to younger females.

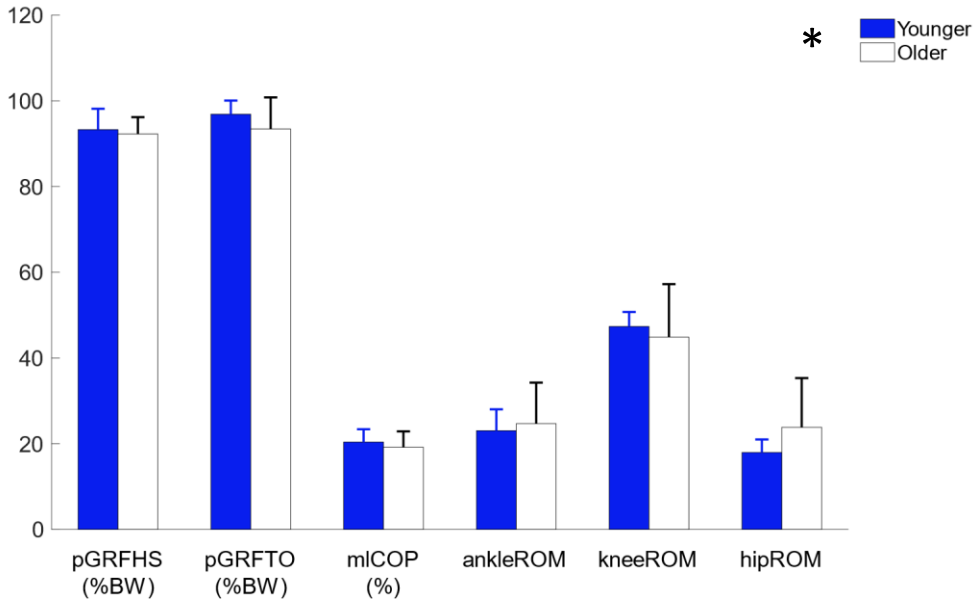

Figure 9. Linear result so investigation into younger vs older females. Bars represent the mean values per group, whiskers represent one standard deviation, and asterisks represent significance ($p < 0.05$).

Non-linear analysis by ApEn and FuzzyEn revealed no significant differences between younger and older subjects in kinetics (peak ground reaction force during heel strike and toe off, medial-lateral center of pressure) (Figure 8) and for range of motion in the hip and ankle (Figure 9). However, older adults had significantly lower entropy values in the range of motion of the knee, which was found by ApEn at k = 0.2 and 0.3 (p= 0.02 and 0.04 respectively) and FuzzyEn at k=0.1 (p = 0.04) (Figure 9). For peak ground reaction force during heel strike, younger adults were observed to have slightly lower entropy values in both measures. For peak ground reaction force during toe off and medial-lateral center of pressure, the opposite was observed (older adults had lower entropy values). For all kinematic parameters (range of motion at the hip, knee and ankle), older adults were observed to have slightly lower entropy values.

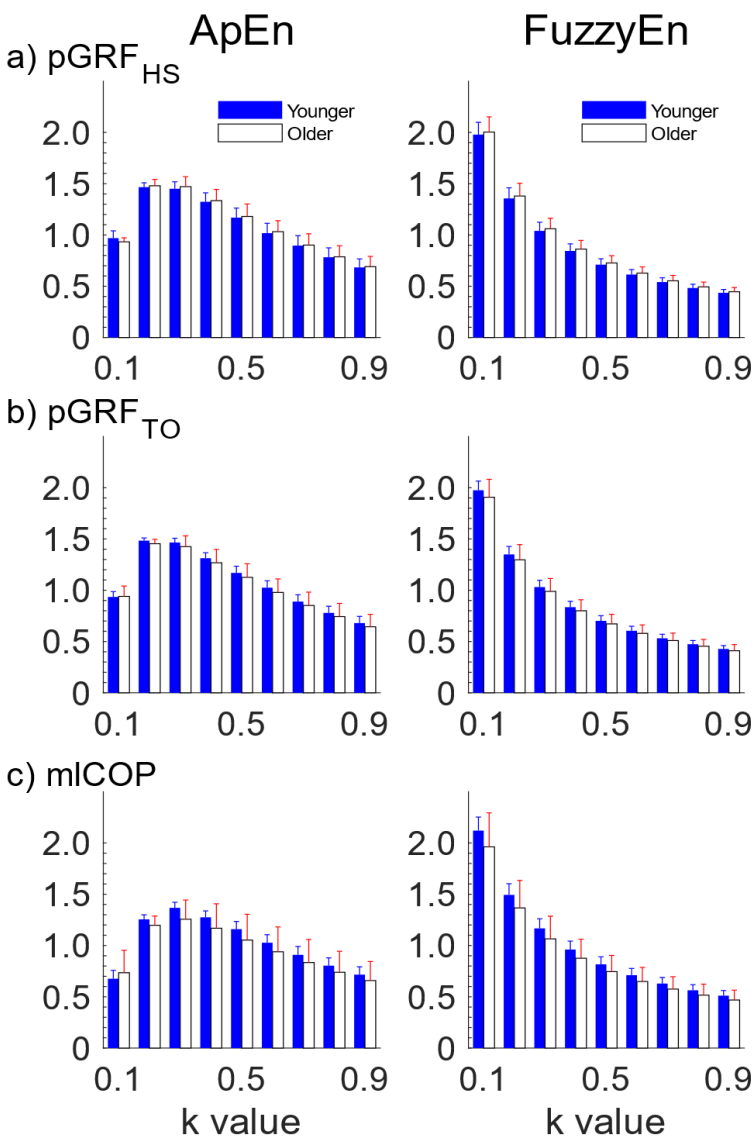

Figure 10. ApEn and FuzzyEn values versus k values for the peak GRF at heel strike (a), the peak GRF at toe off (b), and the medio-lateral COP displacement (c) in younger and older females. Bars represent the mean values per group, whiskers represent one standard deviation, and asterisks represent significance ($p < 0.05$).

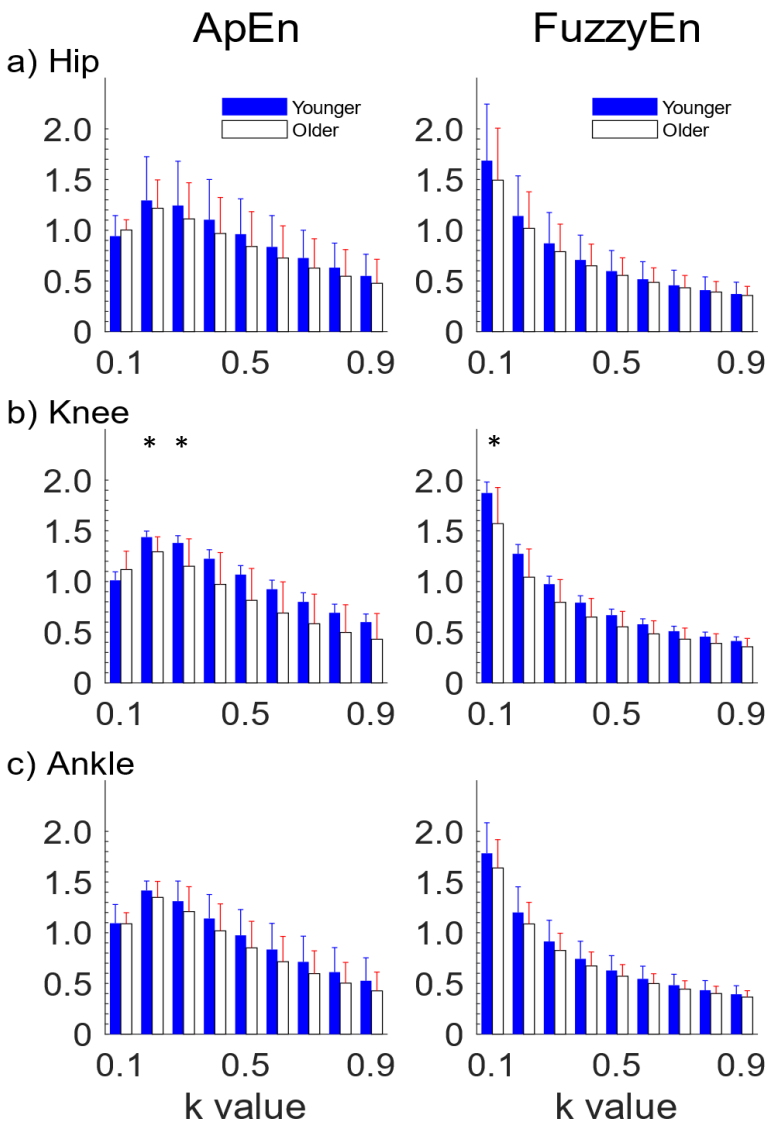

Figure 11. ApEn and FuzzyEn values versus k values for the hip ROM (a), knee ROM (b), and ankle ROM (c) in younger and older females. Bars represent the mean values per group, whiskers represent one standard deviation, and asterisks represent significance ($p < 0.05$).

The comparison of ApEn vs FuzzyEn at varying k values revealed that differences between the two measures under all parameters were inferior to 20% for k = 0.2 except for ROMankle which was at 21% (Figure 10). However, differences were greater than 20% above and below k = 0.2 (Figure 10).

In both investigations, entropy values at k = 0.2 between FuzzyEn and ApEn were no larger than 22%, indicating confidence in the input parameter.

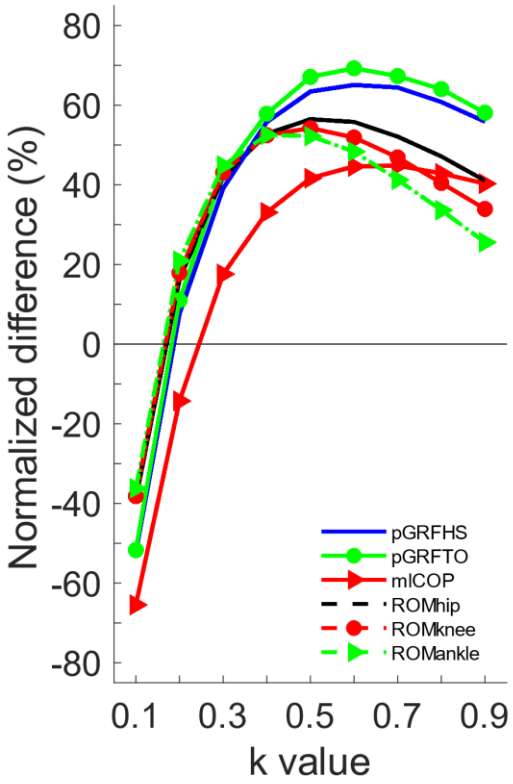

Figure 12. Normalized difference between mean ApEn and FuzzyEn versus k values for the three kinetics and three kinematics parameters. At k=0.2 all parameters had a difference less than 20% except for ROMankle, which was at 21%.

IV.6. Discussion

The purpose of this study was to assess the performance of ApEn and FuzzyEn in detecting differences in variability between a healthy younger group and a healthy older group that was controlled for gender (females). Our linear analyses found a significant increase in the hip range of motion of older females, suggesting the beginning of a distal to proximal shift in gait control strategy. This was found by DeVita et al. (2000) in an investigation of twelve young (aged 21 years) and twelve elderly (aged 69 years) adults. Older adults generated more work at the hip

and less work at the ankle. Our linear analyses also revealed a slight decrease in knee range of motion in older adults, which is in agreement with the findings of Ostrosky et al. (1994), who found that older adults demonstrated decreased knee extension during gait at a self-selected speed when compared to younger adults. However, our study showed an unusual observation of older females showing slightly higher ankle ranges of motion compared to younger females. This conflict with the distal to proximal shift in control strategy, however, may be due to our older subjects having been below the age of 60, unlike other studies where significantly older subjects were investigated. Hence, our subjects may have been showing early signs of the purported distal to proximal shift.

Non-linear analyses by ApEn and FuzzyEn found that older females had slightly lower entropy values, with significance in the knee range of motion, except for the peak ground reaction force during heel strike. The significant decrease in knee range of motion variability at $k = 0.2$ indicates that a continual region of knee joint cartilage could be loaded during gait, and combined with knee valgus in females (Schultz, 2007), could explain the higher incidence of knee OA in older females (Felson, 1997). However, it must be noted that the lower entropy observed here is strictly relative and would still be considered complex and part of a healthy adaptable system due to the entropy values being greater than 1.

The significantly higher median hip range of motion values coupled with lower entropy values in older females could highlight an important finding relating to osteoarthritis onset of the hip. Higher hip ranges of motion would cause joint contact forces to act on smaller areas of the femoral head and acetabular labrum during peak hip extension and flexion (as can be found through inverse dynamics). If true, this combination of increased force per unit area and lower variability (as observed in our entropy analysis) would mean that a specific region of femoral and acetabular cartilage is loaded with higher force concentrations during gait cycles in older individuals. This could lead to significant cartilage stress and hence osteoarthritis onset. More research would have to be conducted to determine if cartilage stress is indeed increased with

higher ranges of motion, in order to prove this theory. However, such findings elucidate the benefits of using variability analysis as an approach to better understand osteoarthritis. Out of the six parameters investigated, older females showed slightly lower entropy values for five, with significantly lower entropy values for the knee range of motion, suggesting that our hypothesis was mostly supported in the age investigation.

The performance of ApEn and FuzzyEn were most consistent with each other at an input parameter of k = 0.2, since entropy values were within 20% of each other for all parameters except for the range of motion of the ankle, which was at 21%. This finding supports two observations by previous researchers: that a k-value of 0.2 for ApEn shows the most statistical validity (Pincus S. , 1995) and that the highest ApEn value often depicts the most accurate picture of a signal's complexity (Chon, 2009). Furthermore, this result can be extended to include a recommendation to utilize a k value of 0.2 in future FuzzyEn studies investigating gait parameters. At a k value of 0.2, FuzzyEn showed statistical significances less of often than ApEn. Hence, FuzzyEn exhibits more conservative outputs as observed by Chen et al. (2009). For all parameters, FuzzyEn showed higher relative consistency (compared to ApEn) in its output, when comparing between two groups, at varying k values. However, the same could not be said for ApEn. The notable "flip-flop effect", which was first outlined by Boskovic et al. (2011), was observed. The flip-flop effect is when the entropy values transition from relatively higher to relatively lower (or vice versa) as k-values increase (Boskovic, 2011). However, for all instances of flipping, stability was observed beyond k values of 0.2 in ApEn outputs, which suggests that k values of 0.1 should be avoided in future entropy studies, an assertion that was made by its creator (Pincus S. , 1995). Meanwhile, outputs of FuzzyEn were in agreement at all k values, showing the stability of FuzzyEn across a range of input k values, validating the findings of Chen et al. (2009) who found that FuzzyEn showed more consistency in investigating EMG signals when compared to ApEn and Sample Entropy.

One of the limitations of this study was the data collection protocol. The use of a treadmill has been found to show a bias towards regularity due to the inability to adjust speed and forced cadence (Dingwell, 2001) which has been revealed in ApEn and sample entropy analysis (Yentes, 2018). However, the use of a treadmill in this study enabled the collection of many gait cycles at relative comfort to the subjects and was validated by previous investigations into kinematic variability (Estep, 2018; Georgoulis, 2006). Another limitation was the small sample size used in the age study. A sample size of 20 younger and 20 older females would have been more appropriate and provided clearer results. However, the results of this investigation provides valuable insight into the performance of ApEn and FuzzyEn and potential outcomes of an eventual larger study. Future work will also have to include data from electromyography signals in order to better understand the role of muscle loss and osteoarthritis onset with old age. Another limitation of this study was that the performance of entropy tools on patients affected with OA was not conducted. Future work will include investigating the performance of ApEn and FuzzyEn in detecting differences in gait variability between a healthy and osteoarthritis affected group. A longitudinal study on selected subjects could also better reveal the performance of entropy tools with respect to osteoarthritis onset.

IV.7. Conclusion

The goal of this study was to test the efficacy of using ApEn and FuzzyEn at detecting differences in variability between younger and older females, based on existing knowledge of increased osteoarthritis occurrences in females of older ages and known gait differences between younger and older individuals. Our hypothesis was supported due to the ability of FuzzyEn to detect significant differences in variability of kneeROM between younger and older females. The performance of FuzzyEn was more consistent and less sensitive than ApEn, proving its most

robust nature. This paper demonstrates that FuzzyEn could be a promising tool to pursue the development of an osteoarthritis detection tool by investigating changes in gait variability.

IV.8. Conflict of interest

The authors of this paper have no financial or personal relationships with external people or organizations that could have inappropriately influenced this work.

IV.9. Acknowledgements

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CHAPTER V

OVERALL DISCUSSION

The purpose of this study was to assess the efficacy of using ApEn and FuzzyEn as tools to detect differences in gait variability between males and females as well as younger and older females, based on existing, known linear differences in gait between the two groups, with the hopes of developing an osteoarthritis detection tool in the future. Our hypothesis was that Approximate Entropy (ApEn) and Fuzzy Entropy (FuzzyEn) tools would be successful in detecting differences in variability between healthy groups. Our hypothesis was supported.

Our results indicated that both kinetic and kinematic parameters exhibit step-to-step temporal variability across gender and age groups. These results confirm that, for younger and older subjects that were healthy, gait is not a simple cyclic motion but a complex chaotic process (Stergiou, 2011). Overall, we did not find consistent significant gender-related differences, showing that the processes at play seem to be universal for young healthy humans. In the investigation of younger and older females, we found that gait remained chaotic well into maturity, however a significant loss in the variability of knee range of motion was observed in the older group.

The performance of ApEn and FuzzyEn were in agreement with each other at an input parameter of k=0.2, since both studies showed entropy values within 20% of each other for all parameters except for the range of motion of the ankle in the age study which was at 21%. This finding supports two observations by previous researchers: that a k-value of 0.2 for ApEn shows the most statistical validity (Pincus S. , 1995) and that the highest ApEn value often depicts the

most accurate picture of a signal's complexity (Chon, 2009). Furthermore, this result can be extended to include a recommendation to utilize a k value of 0.2 in future FuzzyEn studies investigating gait parameters. At a k value of 0.2, ApEn showed statistical significance 3 times in both studies, while FuzzyEn showed statistical significance only twice. Hence, FuzzyEn shows more conservative outputs as observed by Chen et al. (2009). For all parameters and in both studies, FuzzyEn showed higher relative consistency in its output (compared to ApEn), when comparing between two groups, at varying k values. However, the same could not be said for ApEn. The notable "flip-flop effect", which was first outlined by Boskovic et al. (2011), was observed in results in nine out of the total twelve ApEn results (when considering both studies). The flip-flop effect is when the entropy values transition from relatively higher to relatively lower (or vice versa) as k-values increase (Boskovic, 2011). However, for all instances of flipping, stability was observed beyond k values of 0.2 in ApEn outputs, which suggests that k values of 0.1 should be avoided in future entropy studies, an assertion that was made by its creator (Pincus S. , 1995). Meanwhile, outputs of FuzzyEn were in agreement at all k-values, showing the relative stability of FuzzyEn across a range of input k-values, validating the findings of Chen et al. (2009) who found that FuzzyEn showed higher relative consistency in investigating EMG signals when compared to ApEn and Sample Entropy.

Our study also revealed that entropy analysis could potentially highlight hidden mechanisms behind OA onset. The combination of increased linear range of motion and reduced non-linear variability was observed in both studies. In the male vs female study, we found that females had a significantly higher hip range of motion coupled with a significantly lower ankle variability. In the younger vs older female study, we found that older females had significantly higher linear hip range of motion, coupled with a significantly lower knee range of motion. This increase in linear range of motion combined with decreased range of motion variability could indicate that specific areas of joint cartilage are being loaded constantly and may contribute to increased OA onset observed in older females. More research would have to be conducted to

investigate this relationship, by building computational models from data already obtained in this study.

One of the limitations of this study was the data collection protocol. The use of a treadmill has been found to show a bias towards regularity due to the inability to adjust speed and forced cadence (Dingwell, 2001) which has been revealed in ApEn and sample entropy analysis (Yentes, 2018). However, the use of a treadmill in this study enabled the collection of many gait cycles at relative comfort to the subjects and was validated by previous investigations into kinematic variability (Estep, 2018; Georgoulis, 2006). Another limitation was the small sample size used in the age study. A sample size of 20 younger and 20 older females would have been more appropriate and provided clearer results. However, the results of this investigation provides valuable insight into the performance of ApEn and FuzzyEn and potential outcomes of an eventual larger study. Future work could include investigating the performance of ApEn and FuzzyEn in subject suffering from OA against healthy non-OA affected subjects, as well as a longitudinal study investigating the differences in gait variability with age in the same sample pool. Such studies would increase the understanding of the ability of ApEn and FuzzyEn to predict OA onset. Other studies could test the repeatability of ApEn and FuzzyEn in investigating the same parameters used in this paper.

CHAPTER VI

CONCLUSION

Our study confirmed that human gait was chaotic and variable in healthy populations. We found that Approximate and Fuzzy Entropy (FuzzyEn) could successfully detect differences in variability when comparing groups based on gender and age. We observed that Approximate Entropy (ApEn) was more sensitive to differences than FuzzyEn, and that ApEn displayed the notable "flip flop" effect at input "k" values that were less than 0.2. FuzzEn, on the other hand, was found to be more stable and consistent and did not display result flipping. We confirmed that the input "k" parameter that produces the maximum entropy value gives a statistically valid result for ApEn as found by Chon et. al (2009). We also found that "k"values less than 0.2 produced poor statistical validity.

Our results displayed that entropy analysis can elucidate potential "hidden" factors behind osteoarthritis onset, such as an increase in linear range of motion coupled with a decrease in kinematic variability. Further research would have to be undertaken to confirm the validity of this claim. The limitations of this study include a bias towards regularity due to the use of a treadmill and the small sample size used in the age study.

Overall, we conclude that entropy analysis is a useful tool in detecting variability differences and suggest that FuzzyEn could be used in the development of an osteoarthritis (OA) prediction tool. Future work would include testing FuzzyEn in the investigation of variability between healthy and OA affected groups. We recommend that future research display a range of "k" values in entropy results as initially suggested by Yentes et al. (2018).

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APPENDIX A

Non-linear analysis results at k=0.2 for ApEn and FuzzyEn in the Male vs Female investigation. (*) indicates higher entropy value of significance at $p<0.05$.

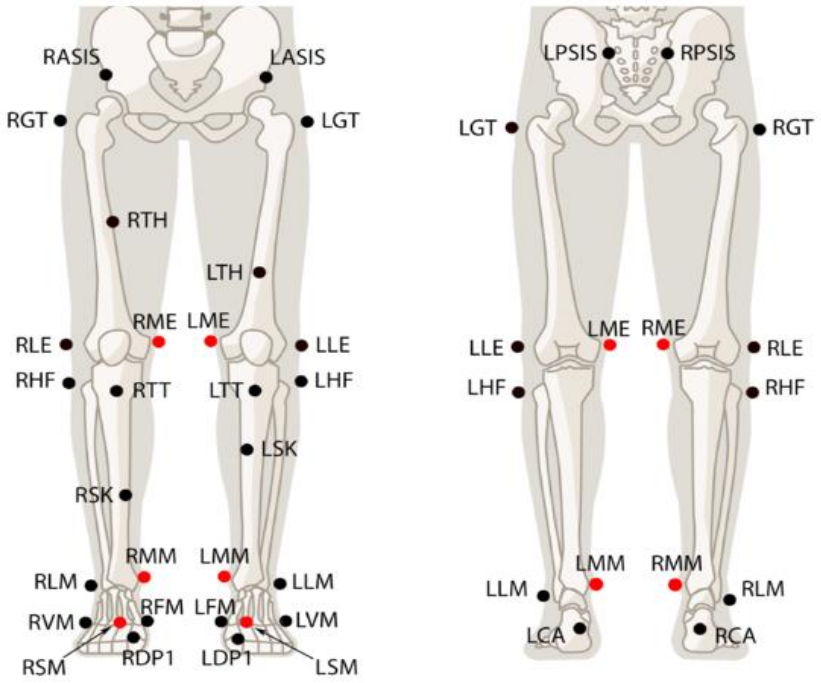
		MALES (n=20)	FEMALES (n=20)	*p*
pGRFHS	ApEn	1.45	1.47	0.382
	FuzzyEn	1.31	1.36	0.249
pGRFTO	ApEn	1.46	1.48	0.144
	FuzzyEn	1.31	*1.37	0.049
mlCOP	ApEn	1.18	*1.25	0.002
	FuzzyEn	1.42	1.49	0.337
ROMhip	ApEn	1.34	1.33	0.860
	FuzzyEn	0.97	0.95	0.900
ROMknee	ApEn	1.48	1.46	0.457
	FuzzyEn	1.38	1.24	0.441
ROMankle	ApEn	*1.49	1.39	0.046
	FuzzyEn	1.38	1.11	0.081

Non-linear analysis results at k=0.2 for ApEn and FuzzyEn in the Younger vs Older (fixed gender, female) investigation. (*) indicates higher entropy value of significance at $p<0.05$.

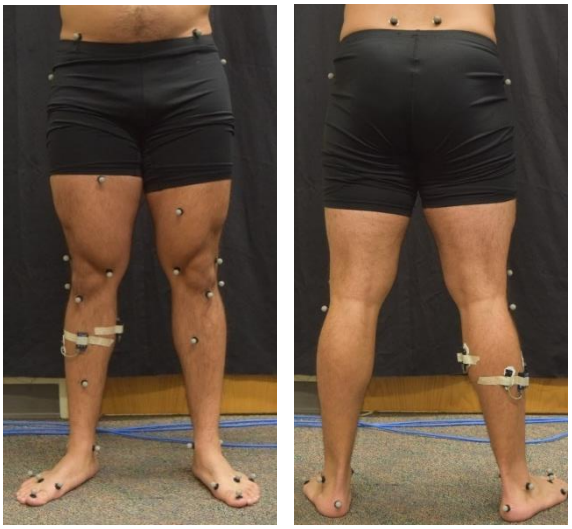
		18-25 GROUP (n=8)	50-60 GROUP (n=8)	*p*
pGRFHS	ApEn	1.47	1.48	0.691
	FuzzyEn	1.35	1.44	0.442
pGRFTO	ApEn	1.48	1.45	0.111
	FuzzyEn	1.35	1.30	0.388
mlCOP	ApEn	1.25	1.20	0.127
	FuzzyEn	1.50	1.37	0.236
ROMhip	ApEn	1.46	1.27	0.279
	FuzzyEn	1.33	1.15	0.573
ROMknee	ApEn	*1.44	1.29	0.022
	FuzzyEn	*1.27	1.04	0.043
ROMankle	ApEn	1.42	1.35	0.310
	FuzzyEn	1.20	1.10	0.351

APPENDIX B

Rizzoli Lower Body Protocol. A 26 marker lower body tracking system based on the work of Leardini et al. (Leardini, Sawacha, & Paolini, 2007). The red markers are calibration markers that are removed prior to data collection. Figure obtained from OptiTrack documentation [NaturalPoint, Inc, USA].

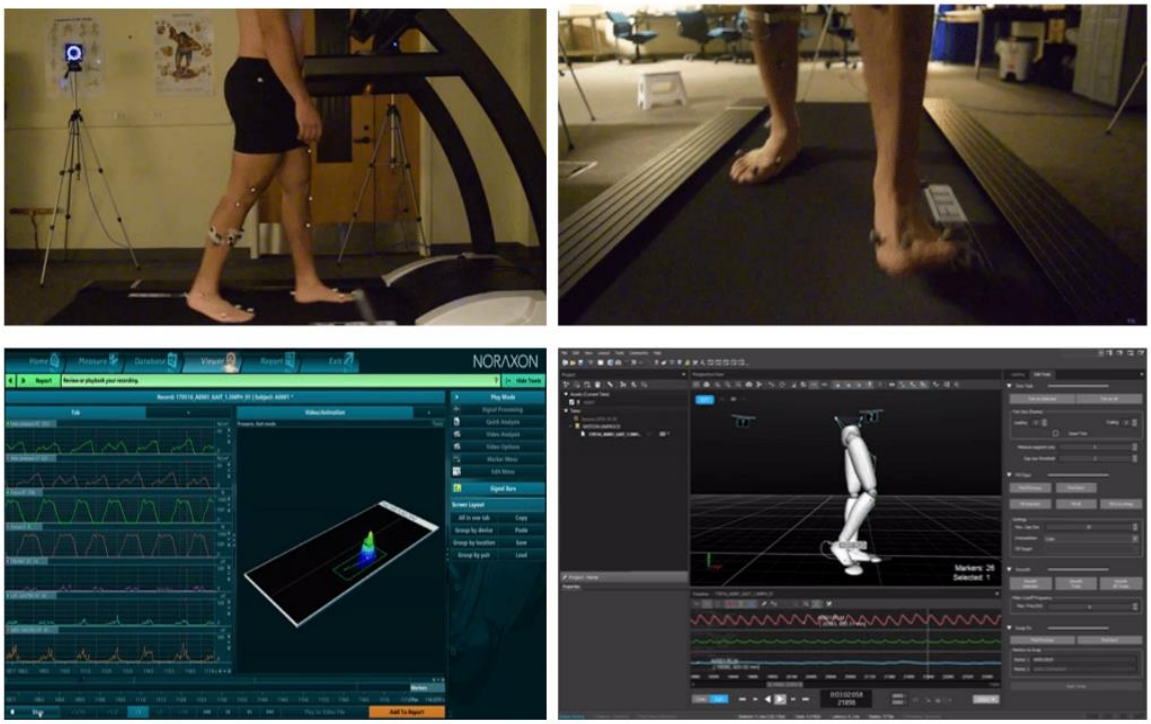


Coronal front and coronal back (left and right) images of a subject, displaying how Rizzoli 26 was implemented.



APPENDIX C

Data collection screen. Top left and top right show force and pressure sensitive treadmill in addition to motion capture cameras. Bottom left depicts real time data collection of force and pressure data via Noraxon software. Bottom right shows real time tracking of markers and a 3D skeleton.



APPENDIX D

Subject intake form: exclusion criteria (1-4) and auxiliary information (5-10).

Document: 005_Rev_B Subject Intake Form Released: EE 05/16/17

SUBJECT ID:		DATE:	
SEX: M F	AGE:	HEIGHT:	WEIGHT:

Please answer the following questions:

1) Have you ever been diagnosed with osteoarthritis? YES NO

> If YES, please indicate for which joints:

2) Have you ever had surgery performed on the hip or lower extremities? YES NO

> if YES, please explain:

3) Have you ever been diagnosed with a cardiac condition? YES NO

4) Are you capable of walking on a treadmill, at your desired pace, for 10 minutes? YES NO

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5) Have you sustained any injury to the hip or lower extremity within the last year? YES NO

6) Do you have a history of, or have been diagnosed with any neurological disorders (ex. Alzheimer's disease, Parkinson's disease, Stroke or Multiple Sclerosis)? YES NO

7) Have you been diagnosed with diabetes? YES NO

8) If female, are you currently pregnant? YES NO

9) Have you exercised at a moderate intensity for 2.5hrs or more per week, in the past year? YES NO

10) Have you been administered or consumed any analgesics, sedatives or illegal substances in the past 24hrs? YES NO

VITA

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EDUCATION

Master of Science in Mechanical Engineering at Oklahoma State University, January 2017 – present. Thesis title: "Entropy Analysis of Kinetic and Kinematic Gait Parameters as a Potential Tool to Predict Osteoarthritis Onset."

Bachelor of Science (May 2014) in Biomedical Engineering, University of Central Oklahoma, Edmond, Oklahoma.

ACADEMIC EMPLOYMENT

Research Assistant to Dr. Jerome Hausselle, Department of Mechanical and Aerospace Engineering, Oklahoma State University, Spring 2017 – Fall 2018. Research activities included setting up protocol for new research projects, conducting trials involving human subjects and writing code to process data.

Research Assistant to Dr. Yuhao Jiang, Department of Engineering and Physics, University of Central Oklahoma, Fall 2012 – Spring 2014. Research activities included tuning an unsharp masking filter and testing filter performance on medical x-rays.

PUBLICATIONS

Ekanayake, E., and Jiang, Y. 2014. Stent enhancement using a locally adaptive unsharp masking filter in digital X-ray fluoroscopy. Proceedings of SPIE Medical Imaging 2014, Image Processing.

PRESENTATIONS

Ekanayake, E., Estep, W., Ramadan, O., Hausselle, J., Age-Related Kinetic Imbalances During Gait. American Society of Biomechanics, Rochester, Minnesota, 8 August, 2018.

AWARDS

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Second place, Three Minute Thesis Competition, Mechanical and Aerospace Engineering – Oklahoma State University, March 2017.