

THE INFLUENCE OF PERIPHERAL NEUROPATHY  
ON WALKING KINEMATICS AND PHYSICAL FUNCTION

A Dissertation

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## TABLE OF CONTENTS

ACKNOWLEDGMENTS.....	ii
LIST OF TABLES.....	v
LIST OF FIGURES.....	vi
ABSTRACT.....	vii
CHAPTER 1 – INTRODUCTION.....	1
Peripheral Neuropathy.....	1
Markers of Locomotor System Health.....	2
Walking Speed, Variability, and Local Instability.....	5
Walking with Peripheral Neuropathy.....	6
Dissertation Outline.....	8
References.....	9
CHAPTER 2: DIFFERENTIAL EFFECTS OF PLANTAR DESENSITIZATION ON LOCOMOTION DYNAMICS.....	13
Introduction.....	13
Methods.....	16
Participants.....	16
Procedures.....	16
Plantar Pressure Detection Threshold (PPDT).....	18
Outcome Measures.....	18
Data Analysis.....	22
Results.....	23
Discussion.....	25
References.....	30
CHAPTER 3: FASTER WALKING SPEEDS INCREASE LOCAL INSTABILITY AMONG PEOPLE WITH PERIPHERAL NEUROPATHY.....	34
Introduction.....	34
Methods.....	36
Data Acquisition.....	37
Data Analysis.....	41
Results.....	41
Discussion.....	45
References.....	48
CHAPTER 4: KINEMATICS, STRENGTH AND BALANCE DIFFERENTIALLY PREDICT PHYSICAL FUNCTION IN OLD AGE AND PERIPHERAL NEUROPATHY.....	51
Introduction.....	51
Methods.....	53
Participants and Protocol.....	53
Locomotion-Based Physical Function.....	54

Leg Strength.....	55
Standing Balance.....	55
Locomotor Kinematics.....	56
Data Analysis.....	57
Results.....	58
Discussion.....	62
References.....	67
CHAPTER 5 – DISCUSSION.....	70
Key Results.....	70
Implications of Key Results.....	71
Acute Versus Chronic Loss of Plantar Sensation.....	71
Peripheral Neuropathy and Challenging the Locomotor System.....	74
Physical Function and Peripheral Neuropathy.....	76
Limitations.....	77
Future Directions.....	79
Compensatory Walking Strategies in Peripheral Neuropathy.....	79
Peripheral Neuropathy and Walking Reflexes.....	80
Gait and Balance Training in Peripheral Neuropathy.....	81
References.....	83
MASTER REFERENCE LIST.....	86
APPENDIX A – COMPANY ADDRESSES FOR INCLUDED INSTRUMENTATION.....	94
APPENDIX B – REVIEW OF RELEVANT LITERATURE.....	95
VITA.....	190

## LIST OF TABLES

TABLE 3.1. Group characteristics.....	42
TABLE 3.2. Speed and joint effects on selected kinematic variables of treadmill walking.....	43
TABLE 4.1. Demographics, physical function, strength, balance, and kinematics.....	59
TABLE 4.2. Correlates (R, p) between physical function and selected measures.....	60
TABLE 4.3. Stepwise linear regression for predictors of physical function.....	62
TABLE 5.1. Differential effects of acute and chronic plantar pressure sensory loss.....	73

## LIST OF FIGURES

FIGURE 1.1. Stride times during six minutes of continuous overground walking.....	4
FIGURE 1.2. Variability (Mean SD) and local instability ( $\lambda^*_s$ ) of trunk accelerations.....	6
FIGURE 2.1. A schematic of the testing protocol.....	18
FIGURE 2.2. A 2-dimensional state space reconstruction and divergence analysis.....	21
FIGURE 2.3. Desensitization induced by exposure of the foot soles to shaved ice.....	23
FIGURE 2.4. The effects of desensitization on short-term and long-term local instability.....	24
FIGURE 2.5. The effects of walking speed on short- and long-term local instability.....	25
FIGURE 3.1. Representation of lower-extremity joint angle variability computation.....	38
FIGURE 3.2. A 3-dimensional state-space reconstruction and divergence analysis.....	40
FIGURE 3.3. Group effects on stride duration variability.....	42
FIGURE 3.4. The effects of PN on the short-term local instability.....	44
FIGURE 4.1. Relationships between physical function and selected dependent variables.....	61

## ABSTRACT

The 108th Congress (2005) has reported that 20 million U.S. citizens suffer from Peripheral Neuropathy (PN). Characterized by sensory nerve deterioration, PN reduces somatosensation (Padua et al., 2005) and increases the risk of fall-related injury (Richardson et al., 1992). The purpose of this dissertation was to provide insight into 1) the effects of acute loss of foot sole sensation on locomotor system health, 2) the effects of PN on locomotor system health, and 3) the underlying impairments associated with reduced physical function within the older adult and PN populations.

Locomotor system health was assessed by the magnitude of stride-to-stride variability and local instability contained in the kinematics of treadmill walking. In healthy young adults, ice-induced reduction of foot sole sensation did not alter the magnitude of stride-to-stride variability during treadmill walking. It did, however, increase lower-extremity joint local instability, or the sensitivity to small scale perturbations. Compared to controls, individuals with PN walked with similar local instability yet increased variability, at relatively slow speeds. When walking at relatively fast speeds, individuals with PN exhibited exaggerated increases in local instability.

In healthy older adults, locomotion-based physical function (LBPF), as defined by 6-minute walk and Timed Up-and-Go performance, was correlated to leg strength and measures of locomotor system health. However, only measures of locomotor system health provided independent predictive information of LBPF. The PN group exhibited reduced LBPF. As opposed to healthy old adults, correlates of LBPF were not leg strength but instead standing balance variables. Multiple variables of leg strength, standing balance, and locomotor system health provided independently predictive information regarding each test of LBPF.

The opposing effects of ice-induced reduction in foot sole sensation and PN on locomotor system health suggest that the chronic nature of PN allows for the implementation of partially effective compensatory strategies. Yet, the inability to adapt to relatively fast speeds suggests that falls likely occur during challenging situations. The fundamentally different correlates and predictors of LBPF between older adults and those with PN highlight the uniqueness of the movement disorder associated with PN.

## CHAPTER 1 – INTRODUCTION

### Peripheral Neuropathy

The 108th Congress (2005) has reported that 20 million citizens suffer from peripheral neuropathy. The disease thus outnumbers the incidence of more well-known diseases including diabetes mellitus (17-18 million), coronary heart disease (13.2 million), and asthma (15 million) (Thrall 2005). Nearly 85% of all diagnosed cases of peripheral neuropathy target the somatosensory system in a diffuse, symmetrical, and progressive fashion. These cases are categorized as “chronic diffuse polyneuropathy” (PN) (Padua et al., 2005). PN most commonly develops as a co-morbid condition associated with Diabetes Mellitus, which constitutes 27% of diagnosed cases (Mold et al., 2004). Clinical examination of PN reveals *sensory* nerve damage originating in the plantar aspects of both feet. Over time this nerve deterioration advances proximally to involve the entire foot, ankle, lower leg, and in some cases, the upper extremities (Boulton et al., 2004).

Menz et al (2004) reported that individuals with PN were not affected in either the visual or motor domains. Instead, they exhibited marked decline in lower-extremity somatosensation. Of these modalities, plantar cutaneous sensation is particularly impaired. Dingwell and Cavanagh (2001) reported that plantar pressure detection thresholds (PPDT) were 35 times greater at the heel, and over 400 times greater at the hallux in individuals with PN as compared to age-matched controls.

The loss of somatosensation, especially that of plantar cutaneous sensation, is believed to be primarily responsible for a host of specific PN-related movement disturbances observed during weight-bearing situations (Meyer et al., 2004a). Individuals with PN report reduced physical activity, standing balance, mobility, and independence (Albright et al., 2000; Meyer et

al., 2004b; Padua et al., 2005). Independent of other comorbidities, these individuals are also at increased risk of suffering falls (Richardson et al., 1992).

Walking is a critical component of physical function. Moreover, the majority of falls suffered by the PN population occur during situations in which the individual is walking (Richardson, 2002). It is therefore apparent that PN negatively impacts one's ability to generate safe and effective walking patterns.

### **Markers of Locomotor System Health**

The human locomotor system consists of all controlling elements and musculoskeletal components that contribute to the generation of the movements needed to displace the body from one point to another (i.e., walk) (Winter, 1995; Li, 1999). Alteration to any part of this system due to disease such as PN may impair locomotor system health, thus reducing one's ability to successfully walk throughout the environment.

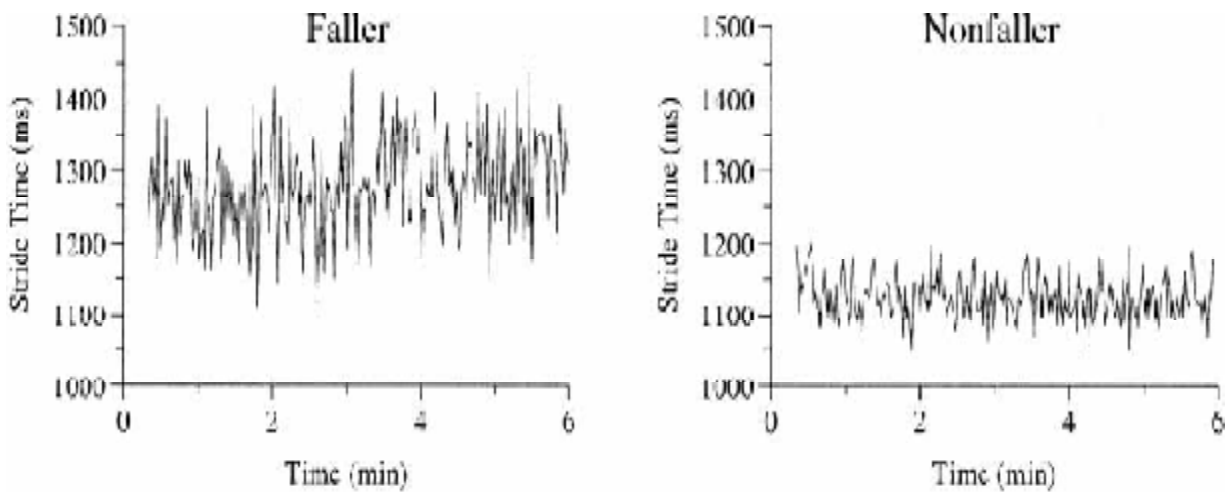
One critical aspect of pathological rehabilitation research is therefore the identification of markers that accurately reflect locomotor system health. Traditional practice has utilized markers reflecting *average* values of specific kinematic walking parameters such as preferred walking speed (PWS) or average stride duration (Lundgren-Lindquist et al., 1983). However, mounting evidence suggests that the nature of stride-to-to stride *variability* contained within these parameters offers additional, perhaps more accurate, insight into locomotor system health (Hausdorff et al., 2001b).

Both normal biological aging and disease may lead to reduction in average maximal and preferred walking speeds (PWS) (Jylhä et al., 2001; Samson et al., 2001). Reduced speed is also associated with decreased average stride duration and stride length, as well as increased double-support time. Although average values may differentiate between groups, the efficacy of using

these measures as markers of locomotor system health has been questioned. For instance, Fitzpatrick et al (2007) reported that PWS in community-dwelling ambulatory older adults does not correlate to several tasks of physical function or self-reported difficulty in completing activities of daily living. Maki et al (1997) further demonstrated that in a similar sample, average gait speed, stride length, and double support time were *not* associated with fall risk.

In the search for more sensitive markers, researchers have examined the stride-to-stride variability about these average values (Hausdorff et al., 2004). Although the movements of walking are repetitive, they are not exactly repeated. Instead they contain small fluctuation from stride to stride. This variability is in fact an inherent property of all human movement and arises as a result of the enormous complexities or “degrees of freedom” within the human body (Bernstein, 1967). Mounting evidence suggests that the nature of this stride-to-stride variability, both in discrete and continuous walking parameters, may provide additional information regarding the health of the locomotor system (Hausdorff et al., 2001b).

The most commonly assessed aspect of variability has been the *average magnitude* of fluctuation from stride to stride. It is quantified by computing the standard deviation away from the mean value of a particular walking parameter. In healthy older adults, the average magnitude of variability is small, with coefficients of variation for most parameters being only a few percent (Hausdorff et al., 1997). Individuals suffering from clinically relevant syndromes and diseases such as frailty, Parkinson’s disease, and Alzheimer’s disease demonstrate *increased* magnitudes of variability across many walking parameters (Blin et al., 1990; Hausdorff et al., 2001a). Furthermore, increased baseline magnitudes of stride-to-stride duration variability can prospectively predict falls within the older adult population (Figure 1.1) (Hausdorff et al., 2001b).



**Figure 1.1** Stride times during six minutes of continuous overground walking from a typical older adult “Faller” and “Non-Faller.” The magnitude of stride duration variability present from stride to stride was noticeably greater in the older adult that experienced a fall within the subsequent year. Figure adapted from Hausdorff et al., 2001.

Yet, despite its sensitivity to disease and clinically relevant syndromes such as falling, quantifying the magnitude of variability to assess the locomotor system is not without limitation. Determining the standard deviation away from a mean value of a walking parameter entails *averaging* these fluctuations over multiple strides. This practice assumes that stride-to-stride fluctuations are randomly generated independently from one another. Logically, however, fluctuation in one stride may affect several subsequent strides. Mounting evidence has in fact suggested that variability is *not* a randomly occurring phenomenon. Instead, it contains a degree of fractal-like structure and long-range correlation such that it is predictable over many different timescales (Hausdorff et al., 2001a).

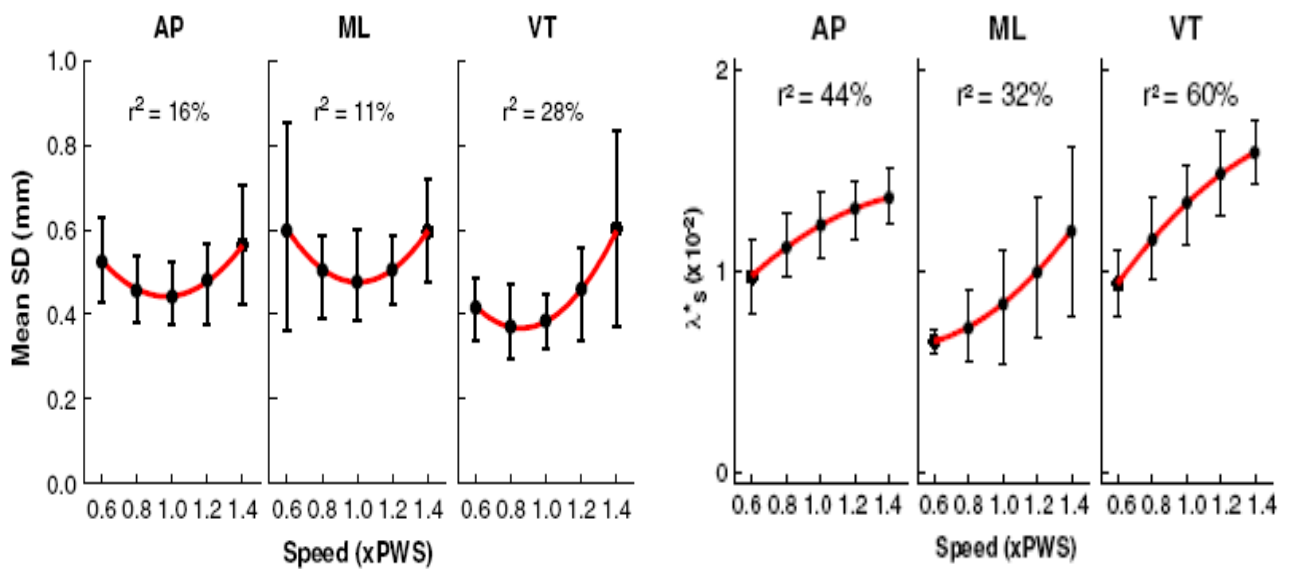
This structure, often referred to as dynamics, appears to offer still further insight into locomotor system health. Many different metrics have been developed and or applied from other disciplines to examine this structure. Once such metric is based on nonlinear Lyapunov exponent techniques adapted for relatively short time-series such as those obtained during human walking (Rosenstein et al., 1993). This metric assumes that even during unimpeded walking, “small-scale” or “infinitesimal” perturbations continuously disturb the locomotor system. “Finite-time”

Lyapunov exponents ( $\lambda^*$ ) estimate the average *rate* of kinematic divergence caused by these small perturbations. Dingwell and Cusumano (2000) suggested that  $\lambda^*$  is a measure of “local instability” because it estimates the “sensitivity” of the locomotor system to small-scale perturbation. England and Granata (2007) further suggested that this property may reflect the capacity of the locomotor system to “fine-tune” its movements in an on-going manner.

Whereas healthy biological aging does not affect the magnitude of variability, it results in increased local instability associated with trunk and lower extremity movement when walking (Buzzi et al., 2003). Similar results have been reported with respect to diseased populations. For instance, Buzzi et al (2004) reported that individuals with Down syndrome exhibit increased local instability as compared to their age-matched counterparts. Thus, just as the magnitude of variability provides information beyond that of average values, the structure of variability (i.e., local instability) appears to offer further insight into locomotor system health.

### **Walking Speed, Variability, and Local Instability**

Both variability and local instability are influenced by walking speed. With all other variables constant, a U-shaped relationship exists between speed and the magnitude of variability, with minimal variability generally occurring at one’s PWS (Winter, 1983; Oberg et al., 1993; Li et al., 2005) (i.e., “Mean SD” in Figure 1.2). Local instability, on the other hand, reacts differently. Dingwell and Marin (2006) demonstrated that this property is inversely correlated to walking speed in healthy young adults. Walking progressively faster resulted in *increased* local instability (i.e., “ $\lambda^*_s$ ” in Figure 1.2). As a result of these relationships, it is important to account for the possibility that experimental differences in variability and local instability may be simply a result of walking speed discrepancy, and not a consequence of physiological dissimilarities.



**Figure 1.2** Variability (Mean SD) and local instability ( $\lambda^*_s$ ) of trunk accelerations as a function of walking speed. Whereas variability exhibits a U-shaped trend about PWS, local stability generally decreases (i.e., increased  $\lambda^*_s$  values) with increased speeds. Figure adapted from Dingwell et al (2006).

### Walking with Peripheral Neuropathy

Diminished physical function and heightened fall risk suggests that the symptoms and impairments of PN negatively affect one's ability to walk. Multiple studies have demonstrated that average PWS is between 20-30% slower in those with PN as compared to aged-matched controls (Dingwell and Cavanagh, 2001; Menz et al., 2004; Richardson et al., 2004). As a result of slowed PWS, the average values of step length, ankle moments, and ground reaction forces are also decreased (Mueller et al., 1994; Richardson et al., 2004), whereas double support time and mean step width are increased (Courtemanche et al., 1996; Richardson et al., 2004).

Slowed PWS is directly linked to the degree of distal lower-extremity somatosensory involvement. Menz et al (2004) assessed PWS and conducted multiple tests of vision, peripheral sensation, muscle strength, reaction time and proprioception in a sample of diabetic PN patients. Plantar cutaneous vibration and pressure detection thresholds were the *only* independent

predictors of walking speed. The researchers thus concluded that *reduced PWS may be a primary compensatory mechanism employed to offset conditions of reduced plantar sensation.*

Despite slowing down, individuals with PN nevertheless fall at severely elevated rates and continue to report difficulty in completing activities of daily living. Studies have thus begun to explore the characteristics of stride-to-stride variability for additional insight into the influence of PN on locomotor system health. Richardson et al (2004) and Menz et al (2004) reported “normal” stride duration and step width variability in diabetic PN patients when walking over regular surfaces at PWS. Conversely, Dingwell et al (2000) reported elevated stride-duration, upper body acceleration, and lower extremity joint angle variability in these individuals. Furthermore, while decreased plantar pressure sensation predicted slower walking speeds, only slowed walking speed predicted increased magnitude of variability. This suggests that individuals with PN slow their walking speed *and as a result*, walk with increased magnitude of variability.

With the close relationship between variability and falls in mind, slowing PWS as strategy to compensate for the symptoms of PN may then be counterproductive. However, by examining the property of local instability, Dingwell and Cusumano (2000a) offered a potential explanation for this apparent paradox. It was reported that although walking at reduced PWS directly increases the magnitude of variability, individuals with PN may nevertheless do so because it effectively maintains “normal” local instability of trunk and lower-extremity movements.

Although this research has outlined a potential benefit to slowing down, it has not accounted for the predisposition to falls within the PN population. One possibility may be that although these individuals have little problem walking in unchallenging situations, they have

difficulty adapting to situations that challenge their locomotor system. Initial evidence in support of this theory has been provided by Richardson et al (2004) and Menz et al (2004). These researchers reported exaggerated decreases in walking speed and increases in both stride duration and step width variability when PN patients walked over irregular surfaces. It was thus concluded that falls and related injuries are likely the result of an inability to successfully adapt to challenging conditions.

### **Dissertation Outline**

**Chapter 1** has provided relevant background information regarding PN and its effects on established markers of locomotor system health. Available research suggests that the loss of plantar pressure detection threshold (PPDT) associated with PN may have deleterious effects on walking. However, individuals with PN suffer additional ailments such as Diabetes Mellitus, and additional impairments such as reduced lower-extremity range of motion and proprioception (Menz et al., 2004). As these complications may also affect the locomotor system, the direct influence of reduced PPDT on variability and local instability are unknown. **Chapter 2** presents a study in which PPDT was *selectively* reduced by ice-exposure in a homogeneous sample of healthy young adults. This technique reduces PPDT, yet leaves range of motion, strength, and proprioception of the feet unaffected. Its resulting effects on walking provide direct insight into the specific locomotor system disturbances created under conditions of *acute* reduction in plantar sensation.

PN is progressive and results in *chronic* loss of lower-extremity somatosensation. Despite reduced speeds and increased magnitudes of variability, individuals with PN are capable of generating largely normal walking patterns and have “normal” local instability in unchallenging conditions (Dingwell and Cusumano 2000a; Richardson et al. 2004). Predisposition to falls may

therefore result from an inability to successfully adapt to challenging conditions. Furthermore, the notion that individuals with PN slow PWS as a compensatory mechanism *inherently* suggests that faster than normal speeds are particularly challenging. **Chapter 3** presents a study examining the ability of individuals with PN to adapt their walking patterns to different walking speeds. The results provide insight into slowed PWS as a compensatory strategy as well as a mechanism through which falls may occur within this population.

Variability and local instability are believed to reflect health of the locomotor system. While *increased* variability and local instability are associated with decreased locomotor system health, little direct evidence exists to support this claim. **Chapter 4** presents a study in which markers of locomotor system health, leg strength, and standing balance are tested in their ability to predict performance in widely-used clinical tests of locomotion-based physical function. The results of this final study provide key insight into our understanding of variability and local instability as well as the uniqueness of the movement disorder associated with PN.

The studies outlined in chapters 2, 3, and 4 have increased our knowledge of the control of human walking and the debilitating effects of PN on this behavior. They also provide a foundation for future research within these areas. **Chapter 5** concludes this dissertation by providing a focused discussion related to key results, limitations, and future directions of related research.

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## **CHAPTER 2 – DIFFERENTIAL EFFECTS OF PLANTAR DESENSITIZATION ON LOCOMOTION DYNAMICS**

### **Introduction**

In order to walk successfully and avoid falls, the repetitive movement patterns of this behavior must be continuously modified in order to adapt to changing environmental and task constraints. Common examples include walking faster or slower than preferred (Li et al., 2005; Jordan et al., 2007), or over irregular support surfaces (Richardson et al., 2004). While less intuitive, movement patterns may also need to be modified when constraints are controlled such as walking on a motorized treadmill at constant speed (Dingwell et al., 2001). This is because the repetitive movements of walking are not exactly repeated, but instead contain fluctuations, or stride-to-stride variability (Winter, 1983). While these fluctuations are relatively small in magnitude, they nevertheless create constantly changing spatial and temporal organizational patterns that influence several future steps and strides (Dingwell and Cusumano, 2000; Su and Dingwell, 2007).

Dingwell and Cusumano (2000) have adapted a nonlinear time-series analytical technique that may provide insight into the sensitivity of the locomotor system to these small fluctuations. This technique is based on Lyapunov exponents, which for continuous-time systems with known equations of motion quantify the degree of chaos, or “sensitive dependence upon initial conditions” (Strogatz, 1998). While true Lyapunov exponents cannot be calculated from discrete time-series of biological system behavior (i.e., human walking), the largest exponent, which dominates system stability, can be estimated (Rosenstein et al., 1993; Kantz and Schreiber, 1997). Although this exponent may lead to spurious conclusions of chaos for “noisy” biological systems (Tanaka et al., 1998), it nevertheless provides an estimate of the exponential rate of separation of initially close trajectories in state space (Wolf et al., 1985). Dingwell and

Cusumano (2000) referred to this estimate as the “*Finite-time*” Lyapunov exponent ( $\lambda^*$ ). This quantity was given the name “local instability,” such that greater  $\lambda^*$  values indicate increases sensitivity to small-scale perturbations. This property was suggested to reflect the time-dependent sensitivity of the locomotor system to the temporospatial fluctuations, or “small-scale” perturbations, inherent to unimpeded walking. In this light, it may reflect the capacity of the system to modify its movements in an ongoing fashion.

The mechanisms through which small scale perturbations may be attenuated by the locomotor system are relatively unknown. However, it likely utilizes both passive and active components. Passive components might include mechanical properties such as the anatomical structure of the ankle joint (Siegler et al., 1984) or the elastic nature of muscles and ligaments (Cavanagh et al., 1997; Gefen, 2003). Active components may be consciously or subconsciously driven, and include the generation of reactive muscle contractions serving to alter preprogrammed movement patterns (Nielsen and Sinkjaer, 2002).

Critical to the latter is the acquisition of peripheral sensory information that provides the central nervous system with details of the ever-changing interaction between the individual and environment. The foot soles are the only points of contact with the environment when walking. Cutaneous mechanoreceptors in the glabrous skin of the foot soles are optimally positioned to provide the CNS with information related to the organism-environment interaction. They provide detailed load pattern characteristics during the stance phase with enough sensitivity to detect stride to stride changes induced by variability (Kavounoudias et al., 1998; Kavounoudias et al., 2001). Mazzaro et al (2005) demonstrated that load receptors are involved in reflexive lower-extremity muscular activity in response to small ankle joint perturbations induced during the stance phase of treadmill walking. Although the movement response to these perturbations was

not measured, this observation suggests that reduced plantar sensation may alter local instability, as defined by the capacity of the locomotor system to attenuate the small-scale perturbations of regular walking.

Experimental insight into the influence of reduced plantar sensation may be of relevance to our understanding of the movement disorder caused by chronic diffuse polyneuropathy, or peripheral neuropathy (PN). This prevalent disease is marked by deterioration of peripheral sensory nerves (Boulton et al., 2004) that results in reduced plantar pressure and vibration sensation (Dingwell and Cavanagh, 2001). This loss of plantar sensation is believed to underlie increased fall risk (DeMott et al., 2007) and the 15-fold increase in the number of walking-related injuries within this population (Cavanagh et al., 1992). Individuals with PN walk slower and as a result demonstrate increased magnitudes of stride-to-stride variability (Dingwell and Cavanagh, 2001). Yet, at these slower speeds, they demonstrate similar local instability of trunk and lower-extremity movement as compared to age-matched controls (Dingwell et al., 2000).

The authors therefore concluded that although slowed walking speed in individuals with PN increased variability, which is related to heightened risk of falls (Hausdorff et al., 2001), it may nevertheless be beneficial as a compensatory mechanism because it preserves “normal” local instability associated with walking movements. However, individuals with PN often suffer from co-morbidities such as diabetes mellitus and additional symptoms such as reduced ankle ROM, proprioception, and strength (Dingwell and Cusumano, 2000; Gutierrez et al., 2001). As each may influence the locomotor system independently, the direct influence of reduced plantar sensation on the sensitivity of the locomotor system to small-scale perturbations is unclear.

Nurse and Nigg (2001) have utilized an ice-exposure technique that selectively and temporarily reduces plantar pressure sensation while unaffected mechanical properties of the

exposed tissue, ROM, proprioception, and strength of the ankle and toes. Additional work has demonstrated that ice-induced plantar sensory loss induces a slowed or “cautious” gait pattern similar to that exhibited by individuals with chronic sensory loss due to PN (Eils et al., 2004). The primary purpose of the present investigation was therefore to provide insight into the control of locomotion by investigating the effects of experimentally reduced plantar sensation on kinematic variability and local instability of treadmill walking at different speeds in healthy young adults. It was hypothesized that sensory loss associated with ice exposure would increase local instability associated with lower-extremity walking movements. Additionally, as individuals with PN are believed to slow their walking speed to offset the negative effects of reduced plantar sensation, we hypothesized that the effects of ice-induced sensory loss would be exaggerated at relatively fast speeds.

## **Methods**

### **Participants**

Thirteen healthy participants were recruited for the study (6 women, 7 men, mean,  $\pm$  SD, age =  $21.3 \pm 1.4$  years, height =  $166.7 \pm 13.8$  cm, body mass =  $67.9 \pm 9.0$  kg). Exclusion criteria included self-reported presence of cardiovascular, respiratory, or metabolic disease, history of musculoskeletal disorder, trauma, or surgery, or any other health issue that may have influenced the ability to walk on a treadmill at different speeds. All participants provided written informed consent as approved by the Institutional Review Board.

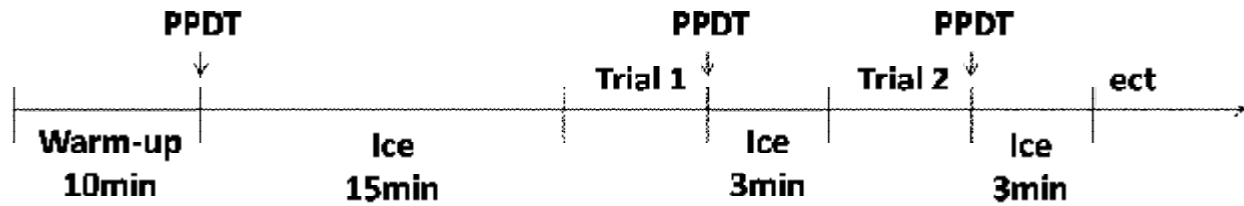
### **Procedures**

On the initial visit, demographic data of age, height, and body mass were recorded. To record over-ground preferred walking speed (PWS), two cones were placed 14m apart on the floor of a well-lit hallway, with the middle ten meters marked with tape. Participants walked

from cone to cone so as to ensure a constant walking speed over the middle ten meters. The participant was instructed to “walk to the far cone at your normal pace.” The time taken to walk the middle ten meters was recorded and averaged over three trials. PWS was then calculated by dividing 10m by the average time taken to walk this distance.

Participants then completed either a “Normal” or “Desensitized” protocol, in random order. The remaining protocol was completed one week later at the same time of day. All testing was performed barefoot, and each protocol was initiated with a warm-up consisting of treadmill walking at PWS for 10 min. On the first day, the participant was allowed to adjust the treadmill speed if desired to account for possible differences between overground and treadmill PWS. However, no adjustments were made by any participant. Following warm-up, plantar pressure detection threshold (PPDT) was assessed using procedures described below.

During the Desensitized protocol, participants placed their bare feet on shaved ice for 15 min. This procedure has been demonstrated to significantly and selectively reduce cutaneous PPDT while unaffected strength, position sense, or tissue properties of the ankle, feet, and toes (Perry et al., 2000; Nurse and Nigg, 2001). Participants then completed a two min bout of treadmill walking at PWS and three predetermined speeds (0.8m/s, 1.0m/s, 1.2m/s, PWS) in random order. For the purposes of this study, non-preferred walking speeds were considered “challenging” to the participant. PPDT was assessed immediately following each trial so as to ensure that desensitization persisted throughout the duration of each trial. Furthermore, as ice-induced desensitization is relatively short-lasting, participants placed their feet on ice for an additional three min in between each trial (Figure 2.1). During the Normal protocol, participants repeated the protocol with trials completed in the same order. However, ice immersion was replaced with seated rest of similar duration.



**Figure 2.1.** A schematic of the testing protocol. The Desensitized protocol is illustrated here. During the Normal protocol, times during which ice was administered were replaced with seated rest of similar duration. Plantar pressure detection threshold (PPDT) was assessed immediately following each walking trial.

### Plantar Pressure Detection Threshold (PPDT)

Due to time constraints associated with ice-induced sensation loss, a single 5.07 gauge Semmes-Weinstein monofilament (North Coast Medical, Inc) was used to assess PPDT. It has been widely employed in both clinical and research settings to diagnose the presence of PN (Kamei et al., 2005). The participant was seated with right leg supported and eyes closed. Five sites on the plantar aspect of the foot were tested, including the heel, mid-sole, bases of the first and fifth metatarsals, and hallux (Eils et al., 2002). At each site, the monofilament was pressed to the skin at a 90 deg angle with sufficient force to produce bowing for at least 1 second. Any callused or scarred areas were avoided by applying the monofilament to the perimeter of the test area. Each site was tested in random order with 2-5sec pauses between sites. Individuals were instructed to respond with a “yes” when pressure was detected. The number of correct responses was totaled to produce a PPDT score ranging from 0 to 5.

### Outcome Measures

Due to the inherent nonlinear coupling between body segments, single-plane motion of one segment influences the motion of that segment in all directions, and the motion of all other segments of the system (Zajac, 1993). By examining single-plane dynamics, the complexity of the whole system can be theoretically captured (Kantz and Schreiber, 1997). Thus, lower

extremity joint kinematics were recorded during the final 60s of each treadmill walking trial with a single camera motion analysis system (Motion Analysis, Santa Monica, CA) at 60 Hz.

Reflective markers, 2.0 cm in diameter, were placed on the right pelvis (ASIS), hip (greater trochanter), knee (lateral femoral condyle), ankle (lateral malleolus), and foot (5<sup>th</sup> metatarsal head). A standard cubic spline interpolation technique was employed to fill data gaps created by arm swing occlusion of the hip and pelvis markers. Sagittal plane hip, knee, and ankle angles were then derived from position data and used for further analysis. Temporal variability (i.e., stride duration variability, SDvar), spatial variability (i.e., hip, knee, and ankle joint angle variability, JTvar), and Finite-time Lyapunov exponents ( $\lambda^*$ ) related to hip, knee and ankle joint angle time-series were computed.

To calculate variability outcomes, one stride was defined as the consecutive occurrence of maximum knee joint flexion angles (Li et al., 2005). Thirty consecutive strides were then extracted from each time-series. SDvar was determined by computing the standard deviation about the mean stride duration of each trial. To determine JTvar of the hip, knee, and ankle joint angle time-series, the same 30 strides were time-normalized to 100 points (i.e., 100%) using linear interpolation. For each joint, the mean and standard deviation of each time point was then calculated across the 30 selected strides. JTvar was finally calculated by averaging the standard deviations across all 100 time points (Li et al., 2005)

A customized Matlab (MathWorks, Natick, MA) program was used to calculate Finite-time Lyapunov exponents ( $\lambda^*$ ) from 45 continuous strides. To appropriately compare  $\lambda^*$  values across different walking speeds, linear interpolation was used to normalize each time-series to the one of shortest duration (England and Granata, 2007). Normalized time-series contained 1930 data points, which is minimal yet sufficient for this analysis (Buzzi et al., 2003; England

and Granata, 2007). Time-series were reconstructed into state space using the method of delays (Takens, 1981; Abarbanel, 1996). Vectors in n-dimensional space were created using joint angle time-series, along with their time-delayed copies:

$$X(t) = [x(t), x(t + T), \dots, x(t + (n - 1)T)], \quad (1)$$

where  $X(t)$  is the n-dimensional state vector,  $x(t)$  is the original time-series data,  $T$  is the time delay (here,  $T$  is an integer representing the number of data points), and  $n$  is the embedding dimension. As an example, Figure 2.2 contains an exemplar knee joint angle time series (A), and its reconstructed 2-dimensional attractor, given by  $X(t) = [x(t), x(t + T)]$ , with an arbitrarily chosen  $T$  (B).

For each time-series,  $T$  was chosen as the value that maximized the volume of the reconstructed attractor (Rosenstein et al., 1993). Average  $T$  values were similar to those reported in the literature ( $10.3 \pm 1.4\%$  of the average stride duration) (England and Granata, 2007). The embedding dimension ( $n$ ) of each state space was defined as the number of orthogonal dimensions needed to unequivocally define the reconstructed trajectory at any point in time. It was determined by “global false nearest-neighbors” (GFNNs) analysis (Kennel, 1992). This procedure determined the minimal number of orthogonal coordinates needed to minimize the number of ambiguous vectors, or “false neighbors,” on the reconstructed trajectory. False neighbors occur when vectors arbitrarily close in dimension  $n_i$  are distinguished in dimension  $n_{i+1}$ . The value of  $n$  was chosen as the dimension where the percentage of false neighbors approached zero. GFNN analysis revealed  $n=5$  was sufficient for all time-series, which is in agreement with existing reports (Dingwell and Cusumano, 2000).

Within reconstructed state space,  $\lambda^*$  estimates the average exponential rate of divergence of initially near-by trajectories (Dingwell and Cusumano, 2000). It was estimated from an

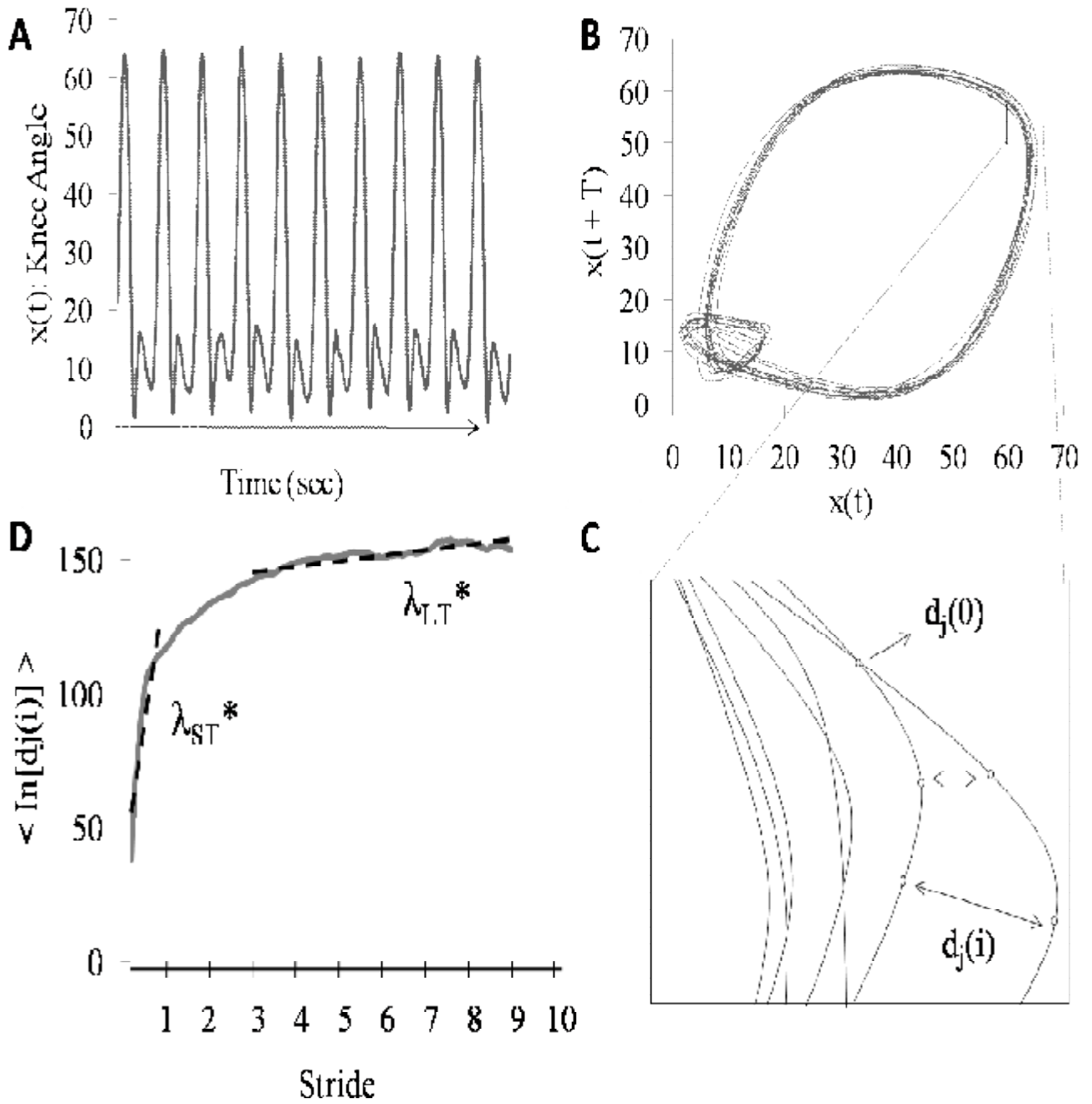


Figure 2.2. A 2-dimensional state space reconstruction and divergence analysis. The original time series of knee joint angle (degree) plotted as a function of time (A) was reconstructed into a 2-dimensional state space (Equation 1:  $n = 2$ ,  $T = 10$ ) (B). It is of note that while  $n = 2$  was used for graphic purposes,  $n = 5$  was computed and used for all analyses. Within state space, all pairs of nearest neighbors,  $d_j(0)$ , were found and the Euclidean distance between points at all subsequent time steps,  $d_j(i)$  were tracked and averaged (Equation 2) (C). These average distances were graphed on a log scale and normalized to stride number (D). Short term ( $\lambda_{ST}^*$ ) and long term ( $\lambda_{LT}^*$ ) Lyapunov exponents were calculated as the slope of linear best-fit lines drawn from 0-1 strides and 4-10 strides, respectively.

algorithm introduced by Rosenstein et al (1993):

$$y(i) = \Delta_t^{-1} \langle \ln[d_j(i)] \rangle, \quad (2)$$

where  $\Delta_t$  is the sampling frequency, and  $\ln[d_j(i)]$  is the logarithmic distance between the  $j^{\text{th}}$  pair of nearest neighbors at each time step,  $i$ . The symbol  $\langle - \rangle$  denotes average of the contents.

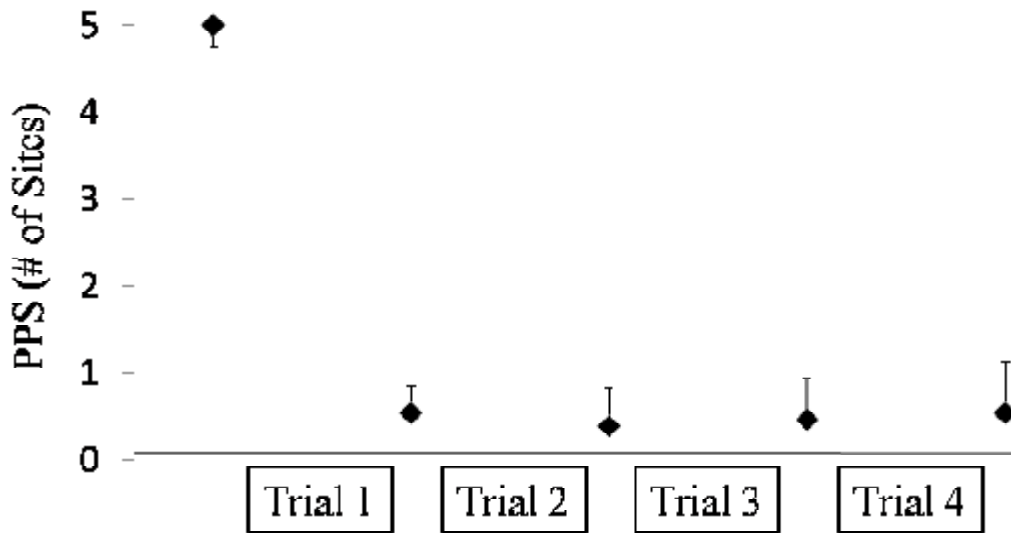
Graphic illustration of this process is provided in Figure 2.2C, in which a nearest neighbor,  $d_j(0)$ , and subsequent  $d_j(i)$ 's are highlighted in a 2-dimensional reconstructed attractor. This process produces a logarithmic curve,  $y(i)$ , demonstrating the average, exponential divergence of all pairs of nearest neighbors at  $t = 0$  and at each subsequent time step (i.e., data point) thereafter (Figure 2.2D). As stride duration is not constant across individuals, the x-axis was rescaled for each curve to represent the average stride number. The rate of exponential divergence,  $\lambda^*$ , was estimated by calculating the slope of  $y(i)$  over predetermined linear scaling regions. The selected linear scaling region corresponding to the “short-term” Lyapunov exponent ( $\lambda_{ST}^*$ ) was chosen to be between 0-1 strides, and the “long-term” Lyapunov exponent ( $\lambda_{LT}^*$ ) was chosen to be between 4-10 strides (Dingwell et al., 2001) (Figure 2.2D). Both  $\lambda_{ST}^*$  and  $\lambda_{LT}^*$  values were multiplied by 100 to ease data presentation.

### Data Analysis

Statistical analyses were performed using Statistix software (Analytical Software Student Edition, V1.0, Boston, MA). Each dependent variable was analyzed using a 3-way repeated measures ANOVA using condition (Normal versus Iced), walking speed, and joint as within subject factors. Tukey's post-hoc analysis was used to examine differences in factor means where appropriate. Significance for all statistical tests was set to  $p < .05$ . All results are presented as means  $\pm$  standard error of the mean (SEM).

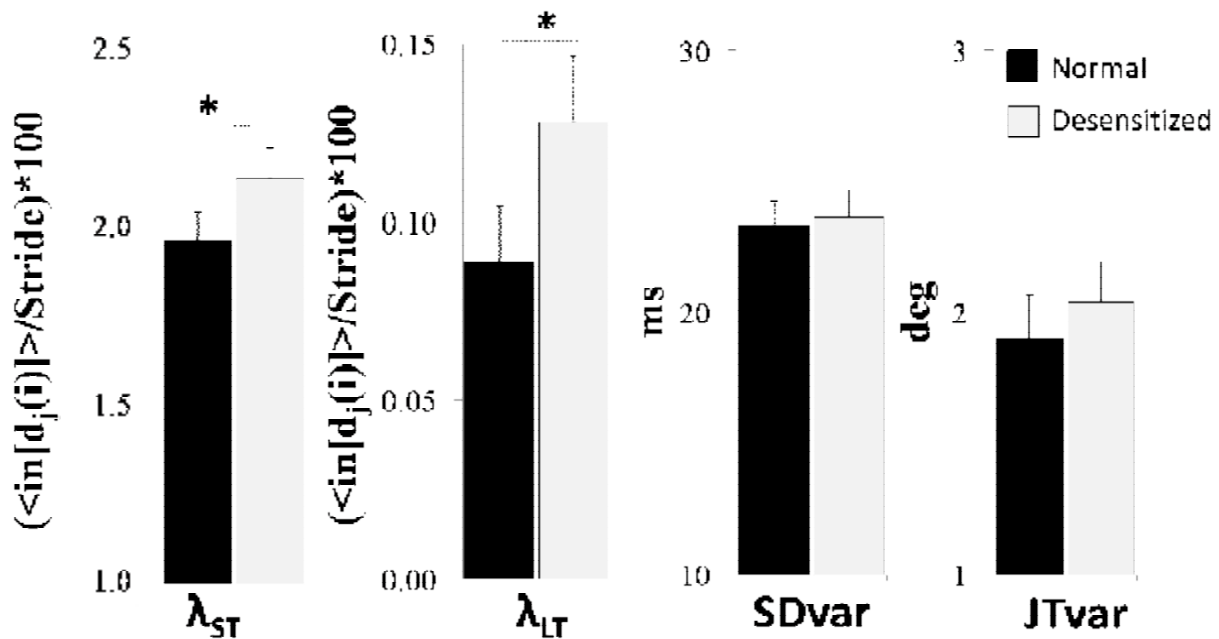
## Results

Ice exposure was effective and provided the expected desensitization for the experiment. Prior to ice immersion, all participants were able to detect the 5.07 gauge monofilament on all five tested sites, e.g. PPDT = 5. The ice immersion procedure significantly decreased PPDT scores to less than one site throughout all four Desensitized trials ( $p < .001$ ) (Figure 2.3).



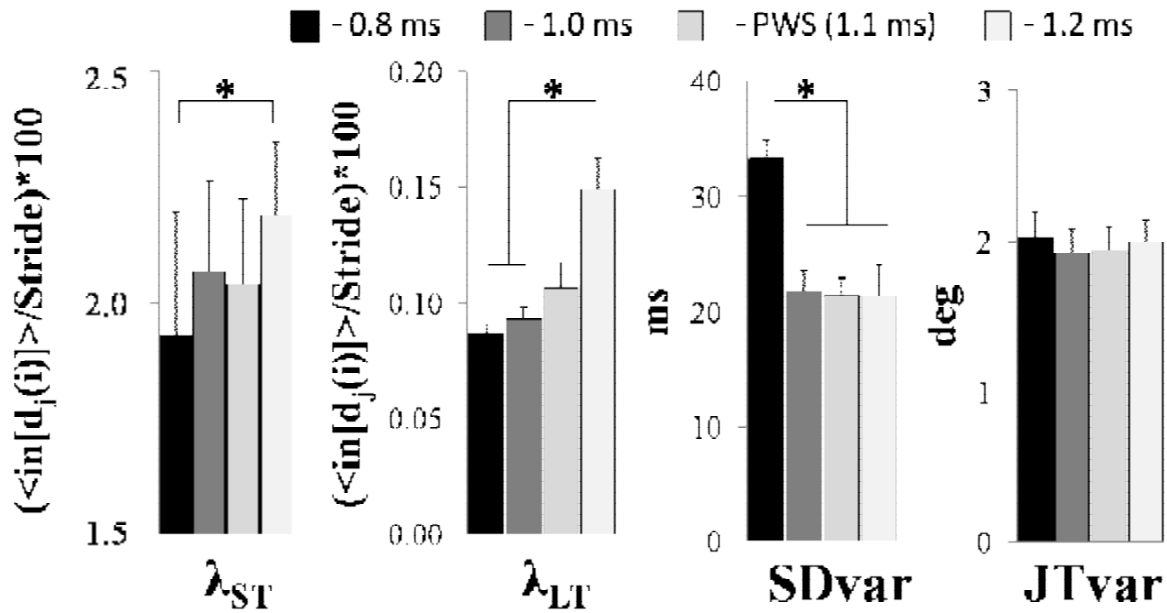
**Figure 2.3** Desensitization induced by exposure of the foot soles to shaved ice. All participants were able to detect the 5.07 gauge monofilament at all 5 sites before exposure. PPS-plantar pressure sensitivity, which was tested by number of detectable sites immediately following each trial, was significantly reduced ( $p < 0.001$ ) in each test thereafter.

Ice-induced desensitization significantly increased the calculated short- and long-term Finite-time Lyapunov exponents.  $\lambda_{ST}^*$  increased from  $1.9 \pm 0.07$  to  $2.2 \pm 0.08$  units ( $F_{1,12} = 30.2$ ,  $p = .0001$ ) and  $\lambda_{LT}^*$  increased from  $0.09 \pm 0.02$  to  $0.13 \pm 0.02$  units ( $F_{1,12} = 7.0$ ,  $p = .02$ ) across all treadmill speeds and joint angles (Figure 2.4). This procedure did not, however, lead to any detectable change in SDvar ( $23.5 \pm 0.9$  ms) or JTvar collapsed across joints ( $1.97 \pm 0.16$  deg).



**Figure 2.4** The effects of desensitization on short-term and long-term local instability collapsed across joints, stride duration variability (SDvar) and joint angle variability (JTvar) collapsed across joints (means $\pm$ SEM). Desensitization led to increased  $\lambda_{ST}^*$  and  $\lambda_{LT}^*$  while having no effect on SDvar or JTvar (\* indicates significance at  $p < 0.05$ ).

The average PWS was  $1.1 \pm 0.04$  m/s. The PWS for each individual participant fell between the two fastest predetermined speeds (1.0 and 1.2 m/s). Average PWS has therefore been presented between these two predetermined speeds in relevant analyses and figures. A significant main effect of speed was present with respect to  $\lambda_{ST}^*$  ( $F_{3,36} = 4.0$ ,  $p = .01$ ),  $\lambda_{LT}^*$  ( $F_{3,36} = 4.1$ ,  $p = .01$ ), and SDvar ( $F_{3,36} = 35.2$ ,  $p < .0001$ ) (Figure 2.5). In general, post hoc analysis revealed increased  $\lambda_{ST}^*$  and  $\lambda_{LT}^*$  with increased walking speed. For both variables, the fastest speed (1.2 m/s) resulted in significantly greater finite time Lyapunov exponent values as compared to the slowest speed, and slowest two speeds (average PWS was  $1.1 \pm 0.04$  m/s.), for  $\lambda_{ST}^*$  and  $\lambda_{LT}^*$  respectively. On the other hand, the slowest treadmill walking speed led to SDvar values significantly greater than all other walking speeds. There was no effect of treadmill speed on JTvar of the hip, knee, or ankle joints.



**Figure 2.5.** The effects of walking speed on short- and long-term local instability collapsed across joints, stride duration variability (SDvar), and joint angle variability (JTvar) collapsed across joints (means $\pm$ SEM). In general, Lyapunov exponents  $\lambda^*$  increased with increased speed, with the fastest and slowest speeds significantly different. Conversely, SDvar was greater at the slowest walking speed as compared to the other three speeds. No differences were observed in JTvar (\* indicates significance at  $p < 0.05$ ).

A significant joint effect was observed for  $\lambda_{ST}^*$  ( $F_{2,24} = 44.8$ ,  $p < .001$ ),  $\lambda_{LT}^*$  ( $F_{2,24} = 7.8$ ,  $p = .002$ ), and JTvar ( $F_{2,24} = 13.15$ ,  $p < .0001$ ). For  $\lambda_{ST}^*$ , values for the knee joint ( $2.5 \pm 0.2$ ) were significantly greater than both the hip ( $1.8 \pm 0.1$ ) and ankle ( $1.9 \pm 0.001$ ).  $\lambda_{LT}^*$  associated with both knee ( $0.13 \pm 0.005$ ) and ankle ( $0.12 \pm 0.003$ ) were greater than those derived from hip joint ( $0.078 \pm 0.004$ ). JTvar associated with the both the knee ( $2.05 \pm 0.03$ ) and ankle ( $2.13 \pm 0.03$ ) were greater than that of the hip ( $1.74 \pm 0.02$ ). No significant interactions were observed between condition (normal vs. ice) and walking speed for any outcome variable.

### Discussion

This study investigated the effects of ice-induced plantar desensitization on the variability and local instability of treadmill walking in healthy young adults. We failed to observe any effect

of plantar sensory loss on the magnitude of stride duration or lower-extremity joint angle variability. However, plantar desensitization increased both  $\lambda_{ST}^*$  and  $\lambda_{LT}^*$  associated with lower-extremity joint movement. Although walking faster also increased  $\lambda_{ST}^*$  and  $\lambda_{LT}^*$ , the effects of ice-induced sensory loss were not exaggerated at these speeds. The results nevertheless demonstrate that acute reduction of plantar sensation affects the ability to accommodate the unavoidable small-scale perturbations that arise during unimpeded treadmill walking.

Dingwell and Cusumano (2000) interpreted  $\lambda^*$  to indicate local instability associated with walking kinematics. Relatively decreased local instability has been viewed as an indication of a healthy locomotor system. This notion is intuitively reasonable and indirectly supported by the effects of both speed (Dingwell and Marin, 2006; England and Granata, 2007) and pathology (Dingwell and Cusumano, 2000; Buzzi et al., 2003). However, little direct empirical evidence exists as grounds for this belief. The present results, that local instability values increased across all lower-extremity joints and walking speeds following plantar desensitization, supports the notion that less lower-extremity local instability is in fact advantageous to locomotion.

Existing research has utilized local instability to examine between-group differences in locomotion kinematics. However, as a linear relationship exists between walking speed and local instability (Dingwell and Marin, 2006; England and Granata, 2007), group differences may have been a result of different PWS and not a *direct* consequence of physiological group dissimilarities. The sensitivity of this metric to ice-induced plantar sensory loss *while controlling for walking speed* provides evidence suggesting that this kinematic property is in fact influenced by altered sensation levels.

The present observations appear to suggest that the locomotor system at least partially relies on intact plantar sensation to make on-going adjustments to unintended irregularities in

stride trajectories. Mechanoreceptors located in the foot soles are capable of detecting pressure distribution patterns during weight-bearing situations (Kavounoudias et al., 1998). Nurse et al (1999) reported a negative correlation between the degree of plantar sensitivity and peak plantar pressures experienced during walking and running in healthy young adults. In more recent work, ice-induced plantar desensitization resulted in a shift of foot sole center of pressure away from areas of decreased sensitivity (Nurse and Nigg, 2001). Our observations suggest that reduced plantar mechanoreceptor functioning may also lessen the capacity of the locomotor system to detect stride-to-stride fluctuations experienced during unimpeded walking. While additional research is needed to better understand this relationship, our results offer novel insight into the neuromuscular control of walking, as well as a potential mechanism through which the locomotion of specific populations may become impaired.

Dingwell and Cusumano reported that when allowed to walk at preferred speed, individuals with PN and related loss of plantar sensation walked with similar local instability associated with trunk and lower-extremity movements. Based on the current observation that ice-induced plantar desensitization increased local instability, one may speculate that the chronic nature of PN leads to the employment of compensatory mechanisms that effectively offset the influence of plantar sensory loss on the sensitivity of the system to small-scale perturbations.

One potential compensatory mechanism may be reducing one's preferred walking speed. In the current sample of healthy young adults, although plantar desensitization increased  $\lambda^*$  values *in general*, its effects were not influenced by walking at non-preferred speeds. This result was somewhat surprising. First, when an individual stands, the effects of reduced plantar sensation on measures of postural sway are more deleterious to the system under challenging conditions, such as when the base of support is reduced (Hong S.L., 2007). Second, people with

PN exhibit pronounced increases in spatial and temporal variability when walking in challenging environments (Menz et al., 2004; Richardson et al., 2004). People with PN often present with additional disturbances, such as reduced position sense and or lower-extremity range of motion (Dingwell et al., 1999), that may prevent successful adaptation to challenging walking speeds. In the present investigation challenging speeds were defined as speeds away from one's PWS and chosen to correspond to speeds observed in the PN population for future comparison. This range, however, may not have challenged the locomotor system past some needed threshold to observe the hypothesized results.

The presence of lower-extremity joint differences across all outcome measures suggests joint-specific control by the locomotor system. England & Granata (2007) reported that " $\lambda_{max}$ " values (i.e., the exponential rate of divergence from 0-1 strides) were smallest (i.e., the divergence rate was slowest) at the ankle joint. The authors took this result to suggest "greater neuromuscular stabilizing control" at this joint as compared to the hip and or knee. The  $\lambda_{ST}^*$  values acquired in the present study, which correspond to the aforementioned " $\lambda_{max}$ " values, generally agree with this statement. In the present study, however,  $\lambda_{LT}^*$  values (i.e., the exponential divergence rate from 4-10 strides) were statistically smallest at the hip joint. Additional research is needed to determine the optimal scaling-region to examine locomotor kinematics, as well as the mechanisms through which lower extremity joints differ in their capacity to accommodate variability-induced fluctuations.

A potential limitation of the present study was the use of a mechanical treadmill. While employed to control walking speed both pre and post ice exposure, Dingwell et al (2001) reported that treadmill walking leads to small yet significant reductions in both the magnitude of joint variability and  $\lambda^*$  values as compared to overground walking. The failure to observe

desensitization-related changes in the magnitude of stride-to-stride variability may have therefore been masked by externally-imposed treadmill constraints. An additional limitation was the determination of SDvar from acquired time-series because a relatively low sampling frequency was employed. While significant speed effects were observed for this variable, average differences in SDvar magnitude at the lowest walking speed as compared to the faster speeds were comparable to the sampling interval. While results are in accordance with existing research (Dingwell and Marin, 2006), the reader should nonetheless exercise caution when forming conclusions related to the observation that plantar desensitization did not alter the magnitude of variability.

The glabrous portions of the foot soles contain receptors sensitive to several environmental stimuli in addition to mechanical pressure, such as vibration, heat, and pain. Regional variation exists with respect to the distribution and sensitivity of these receptors (Wells et al., 2003). While not assessed, the ice-exposure employed in the current study likely did not selectively impair pressure specific receptors. Furthermore, pressure detection thresholds were assessed in non-weight-bearing situations, which may be different from those during weight-bearing situations such as walking. Thus, while changes in pressure sensation were most likely the cause of the observed kinematic changes following ice-exposure, further experimentation is needed to fully explore these issues.

In conclusion, ice-induced loss of normal plantar sensation did not affect the magnitude of stride-to-stride spatial or temporal variability during treadmill walking. It did, however, alter locomotion dynamics by reducing the capacity to attenuate the variability-induced state-space trajectory divergence of lower extremity joint kinematics. While exaggerated effects of desensitization were not observed at non-preferred speeds, the results nevertheless provide

potential mechanisms through which locomotor stability may be negatively affected by diseases resulting in loss of plantar sensation. Additional research examining the differences between acute sensory loss as studied in the current experiment and chronic sensory loss caused by PN is warranted. Furthermore, as  $\lambda^*$  can be acquired safely, research is needed to determine its relationship to “global” stability in the traditional sense (i.e., the ability of the locomotor system to respond to finite perturbations such as slips or trips), its association to falls, and its responsiveness to intervention.

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## CHAPTER 3 - FASTER WALKING SPEEDS INCREASE LOCAL INSTABILITY AMONG PEOPLE WITH PERIPHERAL NEUROPATHY

### Introduction

Chronic diffuse polyneuropathy, or peripheral neuropathy (PN), is marked primarily by symmetrical deterioration to the peripheral sensory nerves (Boulton et al., 2004). This deterioration results in progressive loss of somatosensation within the distal extremities. Individuals with PN are predisposed to falls (Richardson et al., 1992) and are 15 times more likely to suffer walking-related injury (Cavanagh et al., 1992). As the majority of these falls occur when walking (Demott et al., 2007), research has begun to examine the effects of PN on this essential human behavior.

Individuals with PN walk 20-30% slower than age-matched healthy controls (Dingwell and Cavanagh, 2001; Menz et al., 2004; Richardson et al., 2004). Dingwell et al (2001) and Menz et al (2004) demonstrated that those with greater PN-related loss of plantar cutaneous sensation tended to walk with slower preferred walking speed (PWS). This “cautious” gait strategy has therefore been argued as the primary compensatory mechanism employed to maintain safe walking patterns under conditions of reduced sensation (Menz et al., 2004).

In addition to walking slower, individuals with PN may exhibit increased stride-to-stride variability (Dingwell and Cavanagh 2001). The magnitude of variability is defined as the average fluctuation about the mean value of a specific walking parameter. Increased baseline levels of variability predict future falls within the older adult population (Hausdorff et al., 2001). From this point of view, a compensatory reduction in PWS would be counterproductive because it directly increases variability in those with PN (Dingwell and Cavanagh, 2001).

On the other hand, it is unknown if increased variability *causes* falls. In fact, the relationship between variability and “stability” has been questioned (Dingwell et al., 2001; Li et

al., 2005). Stability, defined as the sensitivity or responsiveness of a system to perturbation (Full, 2002), is closely related to fall risk (Grabiner et al., 2008). Statistically averaging deviations from stride to stride may not provide a direct account of this property. In fact, the magnitude of stride-to-stride variability did not predict either the sensitivity to small perturbation (Dingwell and Cusumano, 2000) or the responsiveness to large perturbation (Li et al., 2005) during treadmill walking in healthy young adults.

While of the capacity to respond to large-scale perturbations has not been examined in the PN population, a property termed “local instability” has been quantified (Dingwell and Cusumano, 2000). This research assumed that during unimpeded walking, “small-scale” perturbations continuously disturb the locomotor system. A nonlinear technique using “Finite-time Lyapunov Exponents” ( $\lambda^*$ ) was adapted to estimate the average rate of kinematic divergence caused by these perturbations. It is believed that increased rates of divergence reflect increased sensitivity to small scale perturbation, or increased local instability. Individuals with PN exhibit *similar* local instability of lower body and trunk movement during walking as their healthy counterparts (Dingwell and Cusumano, 2000). As participants walked at PWS, and those with PN walked slower than controls, it was concluded that although slowing down increases variability, it may nevertheless be employed as a compensatory mechanism because it maintains “normal” local instability.

Although this research has outlined a potential benefit of walking slower, it does not allow conclusion regarding the influence of PN on variability and local instability directly. Observed group differences may have resulted solely from dissimilar walking speeds. In healthy young adults, a U-shaped relationship exists between speed and the magnitude of variability, with minimal variability occurring at PWS (Winter, 1983; Oberg et al., 1993; Li et al., 2005). In

contrast, faster speeds led to increased local instability (Dingwell and Marin, 2006; England and Granata, 2007). Elucidation of the direct effects of PN therefore requires acquisition of these measures under speed-controlled conditions

Furthermore, the notion that slowed PWS is compensatory in nature *inherently* suggests that faster walking speeds are particularly challenging to the PN population. This issue has not been explored. Investigation of the effects of PN on faster walking speeds would provide more direct evidence that reduced walking speed is in fact compensatory. It may also outline a mechanism for the predisposition to falls within this population.

The purpose of this study was to examine the effects of PN on the magnitude of variability and local instability over a range of walking speeds. It was hypothesized that individuals with PN would demonstrate increased variability and increased local instability *over and above* that caused solely by walking slower. It was further hypothesized that individuals with PN would demonstrate a relative inability to adapt their walking patterns to faster walking speeds.

## **Methods**

Twelve individuals with all-cause PN and 12 age-, body mass-, and height-matched healthy controls gave consent as approved by university IRB. All individuals presenting with PN had been previously diagnosed by a neurologist. As diagnostic criteria for PN are poorly defined and often vary across physicians (Boulton et al., 2004), the presence of PN was confirmed by the assessment of plantar pressure detection threshold (PPDT). PPDT assessed with a 5.07 gauge Semmes-Weinstein monofilament (North Coast Medical, Inc) has high diagnostic specificity and is useful for detecting advanced cases of PN (Kamei et al., 2005). Five plantar sites were tested three times: the heel, mid-sole, bases of the first and fifth metatarsals, and hallux (Eils et al.,

2002). The monofilament was pressed to each site at a 90 deg angle with sufficient force to produce bowing for at least 1sec. Each site was tested in random order with a 2-5sec pause between sites. Individuals were instructed to respond with a “yes” when pressure was detected. Intact sensation at each site was defined by at least two of three correct responses. The number of sites with intact sensation was totaled to produce a PPDT score ranging from 0 to 5.

In addition to physician diagnosis, criteria for inclusion into the PN group were a PPDT < 3, the absence of any other cardiovascular, respiratory, or musculoskeletal disease or injury that might have influenced gait, and the ability to walk 6-min unassisted. Inclusion criteria for the Control group were a PPDT = 5, the absence of any disease or injury that may have affected gait, and the ability to walk 6-min unassisted.

Age, height, body mass, duration of PN from diagnosis, and the cause of PN were recorded. An overground 6-min walk test determined fast walking speed (FWS) (i.e., distance covered in meters/360sec). Cones were placed 30m apart along a hallway, and participants were instructed to “walk as far as possible in 6-min by walking back and forth around the cones.”

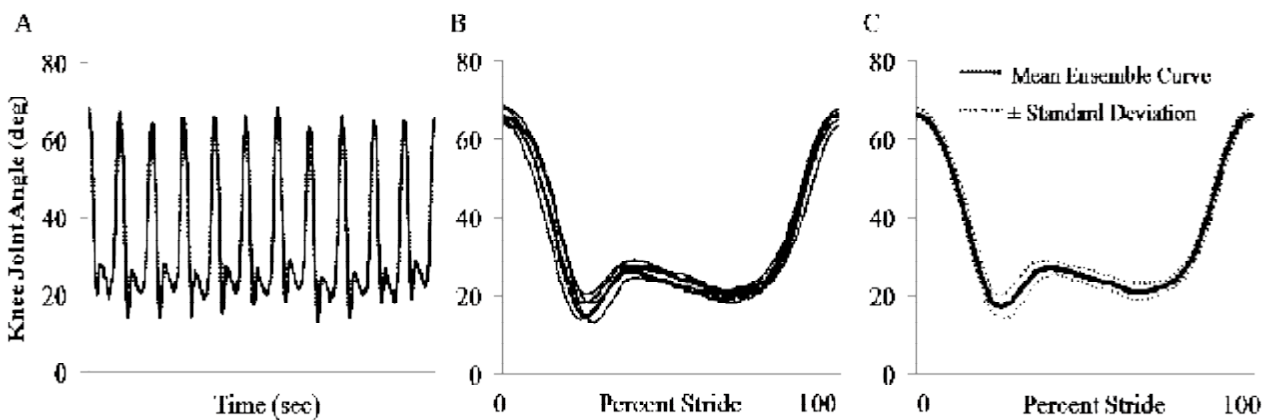
Following 15-min rest, a 3-min treadmill familiarization trial at FWS was completed. While treadmill habituation takes longer (2002), this duration was chosen to limit fatigue. Participants wore a custom-built harness that prevented falls without altering locomotion. Three, 3-min trials were completed in random order at 60, 80 and 100% FWS. At least 5-min rest was given between trials.

#### Data Acquisition

Two-dimensional sagittal plane kinematics were acquired (60 Hz) using single camera motion capture (Motion Analysis Corp, Santa Rosa, CA). Joint movement was tracked with reflective markers placed on the right ASIS, greater trochanter, lateral femoral condyle, lateral

malleolus, and 5<sup>th</sup> metatarsal head. A standard cubic spline interpolation technique was employed to fill data gaps created by normal arm swing occlusion of the hip and pelvis markers. Hip, knee, and ankle angles were computed from the final 2min of each trial. Joint angle time-series were used to compute stride duration variability (SDvar), joint angle variability (JTvar), and both short- and long-term Finite-time Lyapunov Exponents ( $\lambda_{ST}^*$ ,  $\lambda_{LT}^*$ ).

To calculate variability, time-series were filtered using a 6Hz, low-pass second-order Butterworth filter. SDvar was defined as the standard deviation from the mean stride duration over thirty strides. Stride duration was computed by calculating the elapsed time between consecutive, maximum knee joint angles (Van de Putte et al., 2006). JTvar for each joint was determined from the same thirty strides. Individual strides were time-normalized to 100 points and then averaged to produce an ensemble curve for each trial (Figure 3.1). The standard deviation from the mean value at each point was determined, and JTvar was defined by the average standard deviation across all 100 points (Dingwell and Marin, 2006; Li et al., 2005).



**Figure 3.1** Representation of lower-extremity joint variability computation. An exemplar knee joint angle (deg) time-series (A) was divided into individual strides by determining consecutive knee joint flexion maxima. Linear interpolation was employed to normalize each stride to 100 points (B). Using 30 consecutive curves, the mean  $\pm$  standard deviation about each point was determined (C). JTvar was calculated by averaging standard deviations across all 100 points.

Finite-time Lyapunov exponents were computed from 100 consecutive strides of unfiltered data for each continuous joint angle time-series. This metric is sensitive to sampling frequency (England and Granata, 2007). To compare across speeds, time-series were time-normalized to the one 100-stride series of shortest duration (~81 seconds, or 4905 data points).

Exponents were computed using a custom Matlab® program (v7.4, Mathworks Inc, Natick, MA). Time-series were reconstructed into a valid state-space (Figure 3.2) using the “method of delays” (Takens, 1981). Vectors in n-dimensional state-space were created from each time-series and its time-delayed copies such that:

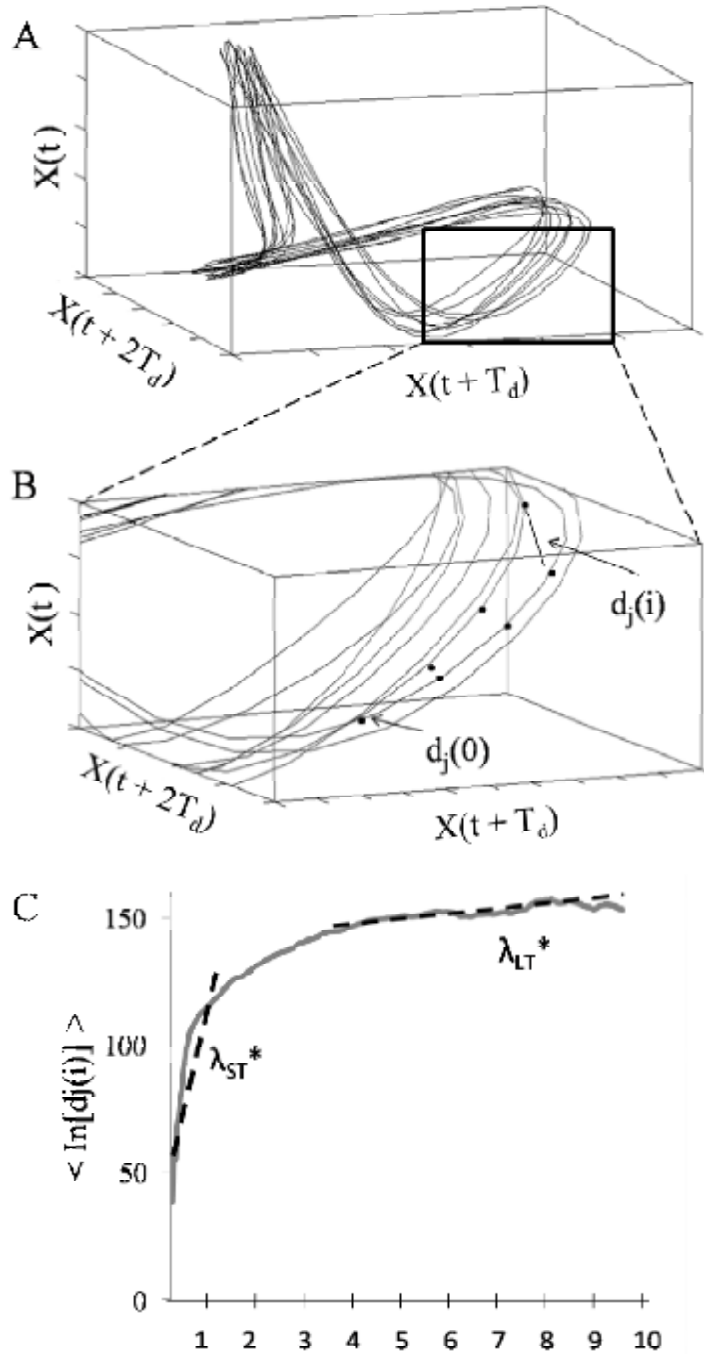
$$X(t) = [x(t), x(t + T), \dots, x(t+(n-1)T)], \quad (1)$$

where  $X(t)$  is the reconstructed n-dimensional state vector,  $x(t)$  is the original time-series data, and  $T$  is the time delay. The time delay was chosen as the value that maximized the geometric volume of the reconstructed time-series (Abarbanel, 1996). The appropriate embedding dimension,  $n$ , was determined using global-false-nearest-neighbor analysis (Kennel et al., 1992). The method ensured that reconstructed time-series had sufficient dimension to minimize the number of vectors falsely overlapping solely as a result of the embedding dimension being too small.

Within reconstructed state-space,  $\lambda^*$  estimates average exponential rate of divergence of initially near-by trajectories (Rosenstein et al., 1993). Divergence is assumed to be caused by small-scale perturbations inherent to unimpeded walking. It estimated from an algorithm introduced by Rosenstein et al (1993),

$$y(i) = \Delta_t^{-1} \langle \ln d_{j(i)} \rangle, \quad (2)$$

where  $\Delta_t^{-1}$  is the sampling frequency,  $\langle \cdot \rangle$  denotes the average of the contents, and  $d_j(i)$  is the distance between the  $j^{\text{th}}$  pair of nearest neighbor vectors at time  $i$ .



**Figure 3.2** A 3-dimensional state-space reconstruction and divergence analysis. An exemplar knee joint angle (deg) time-series was reconstructed into a 3-dimensional state-space (Equation 1:  $n = 3$ ,  $T = 10$ ) (A). It is of note that while  $n = 3$  was used for graphic purposes,  $n = 5$  was computed and subsequently used for all analyses. Within state-space, all pairs of nearest neighbors,  $d_j(0)$ , were found and the Euclidean distance between points at all subsequent time steps,  $d_j(i)$  were tracked and averaged (Equation 2) (B). Average distances were graphed on a log scale and normalized to stride number (C). Short term ( $\lambda_{ST}^*$ ) and long term ( $\lambda_{LT}^*$ ) Lyapunov exponents were calculated as the slope of linear best-fit lines drawn from 0-1 strides and 4-10 strides, respectively.

This algorithm produces a logarithmic curve,  $y(i)$ , representing the average divergence of all pairs of nearest neighbor vectors at  $t = 0$  and at each subsequent time step (i.e., data point) thereafter (Figure 3.2B). As stride duration varies across individuals, the x-axis was rescaled to the average stride number. The exponential *rate* of divergence,  $\lambda^*$ , was estimated by calculating the slope of a least-squares best fit line to  $y(i)$  over predetermined linear scaling regions. The “short-term” Lyapunov exponent ( $\lambda_{ST}^*$ ) corresponded to the slope between 0-1 strides, and the “long-term” Lyapunov exponent ( $\lambda_{LT}^*$ ) 4-10 strides (Figure 3.2C) (Dingwell and Cusumano, 2000). All computed values were multiplied by 100 to ease data presentation.

#### Data Analysis

Statistical analyses were performed using Statistix software (V1.0, Boston, MA). The effects of Group (PN, Control) and Speed (60, 80, 100 FWS) on SDvar were analyzed using a 2-factor ANCOVA. The effects of Group, Speed, and Joint (Hip, Knee, Ankle) on JTvar,  $\lambda_{ST}^*$ , and  $\lambda_{LT}^*$  were analyzed using 3-factor ANCOVAs. Effects of individual variance in FWS were controlled by including each individual’s FWS value as a covariate in all models. Tukey’s post-hoc analysis was used when needed. R-square values were used to represent shared variation between concerned variables. Significance for all statistical tests was set to  $p < .05$ .

### Results

Participant characteristics, PPDT scores and FWS are presented in Table 3.1. Groups did not differ in age, height, or body mass. The PN group demonstrated reduced PPDT ( $p < .001$ ) and slower FWS ( $p < .001$ ) as compared to the Control group.

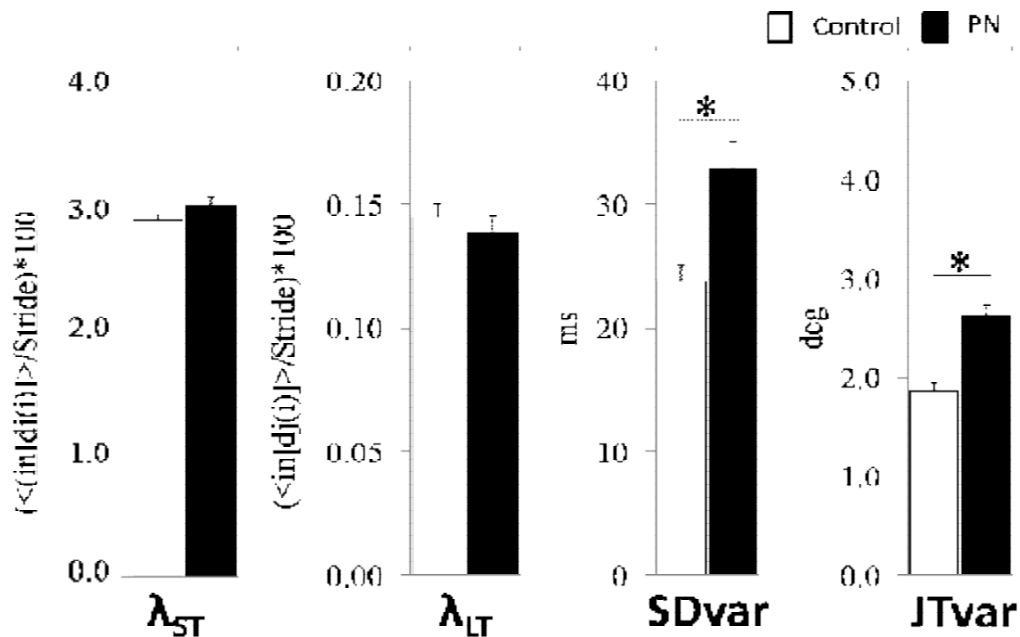
A Group effect ( $F_{1,22} = 11.68$ ,  $p < .001$ ) was observed for SDvar. With data collapsed across Speed, SDvar of the PN group ( $34 \pm 2$  ms) was greater than that of the Control Group ( $24 \pm 2$  ms). A Group effect ( $F_{1,22} = 10.42$ ,  $p = .004$ ) was also observed for JTvar. With data

**Table 3.1** – Group Characteristics (mean  $\pm$  SEM)

	PN group	Control group
Age (years)	66 $\pm$ 3	68 $\pm$ 3
Height (cm)	172 $\pm$ 3	169 $\pm$ 2
Body Mass (kg)	84 $\pm$ 5	78 $\pm$ 6
PN duration (years)	5.4 $\pm$ 2.1	-
PPDT (# of sites)	1.9 $\pm$ 0.3*	5
FWS (m/s)	1.1 $\pm$ 0.1*	1.5 $\pm$ 0.1

Abbreviations: PPDT – Plantar Pressure Detection Threshold, FWS – Fast Walking Speed. \* denotes significance at  $p < .001$ .

collapsed across Speed and Joint, this measure was greater in the PN group ( $2.7 \pm 0.2$  deg) as compared to the Control group ( $1.9 \pm 0.2$  deg;). No Group effects were observed for either  $\lambda_{ST}^*$  or  $\lambda_{LT}^*$  (Figure 3.3).



**Figure 3.3** Group effects on stride duration variability (SDvar) and the joint angle variability (JTvar), short-term Lyapunov exponents ( $\lambda_{ST}^*$ ), and long-term Lyapunov exponents ( $\lambda_{LT}^*$ ) collapsed across joints (means  $\pm$  SEM). With data collapsed across Speed and Joint, the PN group demonstrated increased SDvar and JTvar yet similar  $\lambda_{ST}^*$  and  $\lambda_{LT}^*$  values (\* indicates significance at  $p < 0.05$ ).

A Speed effect ( $F_{2,22} = 8.52, p < .001$ ) was observed for SDvar. With data from both groups combined, the slowest speed (60% FWS) was associated with greater SDvar than the fastest speed (100% FWS). A Speed effect was also observed for both  $\lambda_{ST}^*$  ( $F_{2,44} = 3.46, p = .04$ ) and  $\lambda_{LT}^*$  ( $F_{2,44} = 18.57, p < .001$ ). With data collapsed across Group and Joint, 100% FWS elicited greater  $\lambda_{ST}^*$  and  $\lambda_{LT}^*$  values as compared to either 60% or 80% FWS (Table 3.2).

**Table 3.2 Speed and Joint Effects on Selected Kinematic Variables of Treadmill Walking**  
Speed (% FWS)

	60	80	100
SDvar (m/s)	33.2 ± 1.4 <sup>A</sup>	29.7 ± 2.5 <sup>AB</sup>	24.5 ± 3.0 <sup>B</sup>
JTvar (deg)	2.38 ± 0.11	2.22 ± 0.10	2.20 ± 0.12
$\lambda_{ST}^*$ ( $\mu$ )	2.86 ± 0.07 <sup>A</sup>	2.92 ± 0.07 <sup>A</sup>	3.08 ± 0.07 <sup>B</sup>
$\lambda_{LT}^*$ ( $\mu$ )	0.12 ± 0.01 <sup>A</sup>	0.13 ± 0.01 <sup>A</sup>	0.17 ± 0.01 <sup>B</sup>

	<u>Joint</u>		
	Hip	Knee	Ankle
SDvar (m/s)	-	-	-
JTvar (deg)	2.13 ± 0.10	2.35 ± 0.09	2.32 ± 0.13
$\lambda_{ST}^*$ ( $\mu$ )	2.99 ± 0.07 <sup>B</sup>	3.38 ± 0.06 <sup>C</sup>	2.48 ± 0.05 <sup>A</sup>
$\lambda_{LT}^*$ ( $\mu$ )	0.14 ± 0.01 <sup>B</sup>	0.17 ± 0.01 <sup>C</sup>	0.11 ± 0.01 <sup>A</sup>

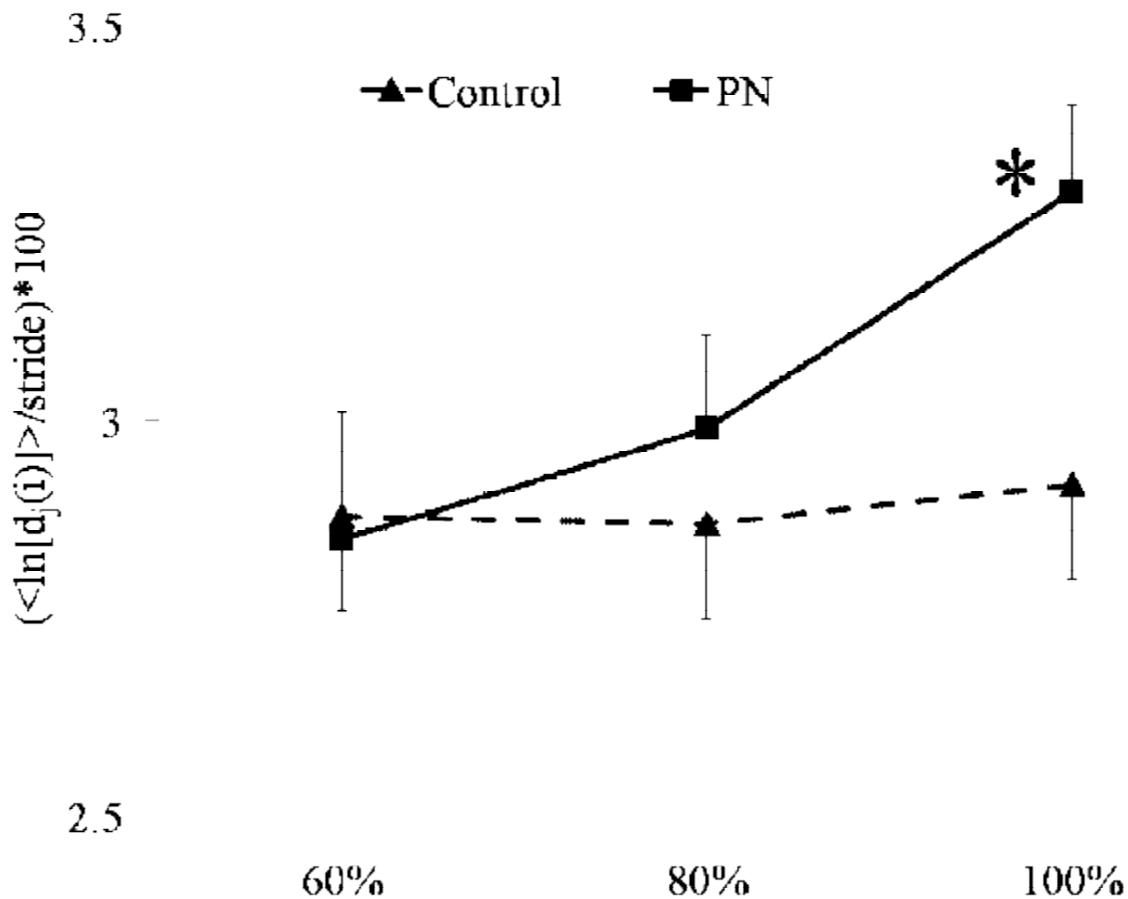
The symbol  $\mu$  denotes units = ( $\langle \ln[dj(i)] \rangle / \text{Stride}$ )\*100.

Values demonstrating effects of speed have been collapsed across group, and joint where applicable. Values demonstrating effects of joint have been collapsed across group and speed. A, B, and C subscripts denote homogeneous groups within each row. Means with different letters are significantly different from each other ( $p < .05$ ).

A significant Joint effect was observed for both  $\lambda_{ST}^*$  ( $F_{2,44} = 3.6, p = .04$ ) and  $\lambda_{LT}^*$  ( $F_{2,44} = 76.7, p < .001$ ). With data collapsed across Group and Speed, the magnitudes of both  $\lambda_{ST}^*$  and

$\lambda_{LT}^*$  were greatest at the knee joint and smallest at the ankle joint (Table 3.2). A Joint effect was not observed for JTvar.

A Group by Speed interaction ( $F_{2,44} = 3.6, p = .03$ ) was observed for  $\lambda_{ST}^*$ . With data collapsed across Joint, the PN group demonstrated greatest  $\lambda_{ST}^*$  values at 100% FWS as compared to the two slower speeds *as well as* the control group at all three speeds (Figure 3.4). No other interactions between Group, Speed, and Joint were observed.



**Figure 3.4** The effects of PN on short-term Lyapunov exponents ( $\lambda_{ST}^*$ ) associated with lower-extremity joint kinematics as a function of walking speed. Values represent averages across the three measured joint angles. The PN group demonstrated greater  $\lambda_{ST}^*$  at 100%FWS as compared to all other means at any speed for either group.

## Discussion

Individuals with PN walked slower than age-matched controls. Despite controlling for individual variance in walking speed, the PN group demonstrated greater magnitudes of variability during treadmill walking. This variability was present in both temporal (i.e., SDvar) and spatial (JTvar) walking parameters. The PN group and Control group exhibited similar variability and both short- and long-term local instability at slower walking speed. However, the PN group walked with exaggerated short-term local instability at 100% FWS. While JTvar did not differ across joints, both measures of local instability were greatest at the knee and smallest at the ankle.

We observed a nearly 18% reduction in FWS with PN. Those individuals with more severe loss of plantar sensation tended to walk slower. Several studies have reported that individuals with PN exhibit 20-30% slower PWS compared to controls (Dingwell and Cavanagh, 2001; Menz et al., 2004; Richardson et al., 2004). Slowed PWS has also been linked to the degree of somatosensory involvement. Menz et al (2004) assessed PWS and conducted multiple tests of vision, somatosensation, muscle strength, reaction time and proprioception in a sample of diabetic PN patients. Plantar cutaneous vibration and pressure detection thresholds were the *only* independent predictors of PWS.

The effects of walking speed on variability and local instability ( $\lambda^*$ ) were generally consistent with existing research (England and Granata, 2007). Greatest variability occurred at the slowest speed, whereas the greatest local instability was observed at the fastest speed. The observation that stride duration variability was smallest at 100% FWS was inconsistent with related literature. Although this inconsistency does not interfere with conclusions, it was possibly elicited because FWS was estimated by walking as fast as possible for 6-min. Therefore,

estimated FWS may have been relatively close to PWS for some participants.

Existing reports of the effects of PN on the magnitude of stride-to-stride variability have been inconsistent. When walking overground at PWS, similar (Menz et al., 2004), trends towards increased (Dingwell et al, 1999), and increased variability (Dingwell and Cavanagh, 2001) have all been reported. This inconsistency may have been caused by the known relationship between walking speed and this metric (Dingwell et al., 1999; Menz et al., 2004; Richardson et al., 2004). As individuals with PN commonly walk slower than controls, conclusions regarding the direct effect of PN has also been limited. In the current study, the effect of individual variance in walking speed was statistically controlled. The PN group nevertheless walked with increased magnitude of temporal and spatial stride-to-stride variability. As increased variability is predictive of future falls (Hausdorff et al., 2001), research is needed to elucidate the specific PN-related impairment(s) underlying this change.

A novel result of the current research is that individuals with PN exhibited exaggerated local instability *only* at 100% FWS. Both Richardson et al (2004) and Menz et al (2004) reported marked decreases in walking speed and increases in both stride duration and step width variability in PN patients when walking over irregular surfaces. Together these results suggest that those with PN have difficulty adapting their walking patterns to conditions that challenge the locomotor system, thus providing a potential mechanism for the increased number of falls suffered by this population.

Whether occurring consciously or subconsciously, walking slower is thought to be compensatory in nature. Benefits may include protecting the desensitized foot (Eils et al., 2002) and or reducing potentially destabilizing inertial effects across various portions of the body (Menz et al., 2004). We have provided more direct evidence that walking slower is in fact

compensatory within the PN population, as these individuals maintained “normal” local instability *when walking at relatively slow speeds*. One benefit of walking slower may therefore be to minimize the time-dependent sensitivity of the locomotor system to small-scale perturbations.

Both individuals with PN and age-matched controls exhibited smallest local instability values at the ankle joint. This suggests minimal sensitivity to small-scale perturbations at this joint. This result is supported by England & Granata (2007), who reported that “ $\lambda_{\max}$ ” values, which correspond to  $\lambda_{ST}^*$ , were smallest at the ankle as compared to the knee and hip. Although these authors concluded “greater neuromuscular stabilizing control” at this joint, additional research is needed to determine the mechanisms through which joints may differ in their capacity to accommodate small-scale perturbations. However, the fact that both groups exhibited similar local instability at any given joint suggests that fully intact plantar sensation may not be critical for this type of joint control.

Generalization of conclusions to the entire PN population may be limited. The protocol required participants to complete several treadmill walking trials without assistance. Although this possibly created a relatively high functioning sample, the authors believe that the influence of PN would have been further exacerbated if lower-functioning individuals were included. The use of treadmill may be another limitation. While the treadmill allowed data collection of many consecutive strides, it may have led to small yet significant decreases in both variability and local instability (Dingwell and Cusumano, 2000). However, as both groups were subjected to the same protocol, treadmill-induced constraints did not likely interfere with conclusions.

Local instability reflects average rates of kinematic divergence in reconstructed state-space. This property has been viewed as a measure of the sensitivity of the locomotor system to

small-scale perturbations inherent to unimpeded walking. Future work is needed to outline potential control issues related to this metric, the nature of these perturbations, and their relationship to stability as defined by the time-dependent responsiveness of the locomotor system to a large-scale perturbation such as a push or slip. Nevertheless, this study demonstrated that PN disrupts the ability of the locomotor system to adapt to relatively fast walking speeds. This supports the notion of compensatory reduction in walking speed. As rehabilitation management of PN calls for maximization of function, minimization of injury and deformity risk, and full integration into society (Carter, 2005), the current results provide insight that should be considered in the design of such programs.

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## **CHAPTER 4 – KINEMATICS, STRENGTH AND BALANCE DIFFERENTIALLY PREDICT PHYSICAL FUNCTION IN OLD AGE AND PERIPHERAL NEUROPATHY**

### **Introduction**

Physical function refers to the ability to perform normal activities of daily living without substantial risk of injury (Guralnik and Simonsick, 1993). Locomotion is a fundamental component of many activities that are critical to the maintenance of an independent lifestyle. Determination of specific physiological impairments that underlie decline in locomotion-based physical function (LBPF) is therefore clinically relevant, especially when designing patient education and exercise intervention programs. For example, Misic et al (2007) reported that compared to aerobic fitness and adiposity, impaired leg strength best predicted LBPF decline in community-dwelling older adults. The authors logically emphasized the importance of strength training for the maintenance of physical function in this population.

In addition to reduced leg strength, it is likely that other impairments also contribute to LBPF decline. One such impairment may be poor standing balance, which is often reported with advancing age and specific disease (Simoneau et al., 1994). While reports such as these have led to the incorporation of balance training components in many rehabilitation programs (Pollock et al., 2007), the direct link between standing balance and LBPF in community dwelling older adults has been questioned. For instance, Hughes et al (1996) reported that performance in several standing balance tests did *not* predict LBPF level in this population.

LBPF may also decline secondary to impairment of the locomotor system itself. In recent years, multiple kinematic properties have been quantified that are believed to assess the health of the locomotor system. The magnitude of stride-to-stride variability has been the most widely assessed property to date. As an individual walks, the involved cyclical movements are not exactly repeated, but instead contain small fluctuation across strides. When walking at preferred

speed, a relative increase in the average magnitude of variability, whether examining discrete (e.g., stride duration) or continuous (joint angle) variables, is generally believed to reflect impairment. This belief has stemmed from reports of increased variability in old versus young adults (Grabiner et al., 2001) and in older adults with specific pathology versus age-matched controls (Dingwell and Cavanagh, 2001). However, despite these group differences it is currently unknown if increased variability within an individual's walking patterns is in fact predictive of LBPF decline.

Recently, Dingwell et al (2000) employed nonlinear time-series analysis to examine an alternate property of locomotor system kinematics. For this analysis, it is assumed that even during unimpeded walking, “small-scale” perturbations are present within the locomotor system. The average time-dependent kinematic divergence caused by these perturbations can be estimated by “Finite-Time” Lyapunov exponents ( $\lambda_{ST}^*$  and  $\lambda_{LT}^*$ ). Dingwell and colleagues termed this metric “local instability.” Increased values reflect increased divergence within the state space, which may be related to impaired control of the locomotor system (Buzzi et al., 2003). Due to its time-dependent properties, local instability may more accurately reflect locomotor system impairment as compared to traditional measures of variability. Yet, similar to measures of variability, the relationship between this metric and LBPF is unknown.

Determining those impairments that predict LBPF decline is of particular importance in populations suffering from debilitating movement disorders. Furthermore, due to the specific nature of certain disorders, fundamentally different impairments may underlie LBPF decline. Peripheral neuropathy (PN) is one such movement disorder resulting from the progressive deterioration of sensory nerves and a related loss of somatosensation in the distal extremities (Boulton et al., 2004). PN is associated with reduced independence (Padua et al., 2005) and a 15-

fold increase in walking-related injury due to falls (Cavanagh et al., 1992).

Despite these setbacks, individuals with PN exhibit only minimal lower-extremity strength decline (Menz et al., 2004). Furthermore, they walk with similar or only slight increases (Dingwell and Cavanagh, 2001) in stride-to-stride variability and approximately “normal” local instability of their walking movements in unchallenging environments (Dingwell et al., 2000). On the other hand, individuals with PN present with severe loss of standing balance (Menz et al., 2004). Thus, it is of interest to determine whether strength, balance, and or locomotion-related impairments related to LBPF decline suffered by these individuals. With this knowledge in hand, intervention programs could then be tailored to focus on those impairments most important in preventing and or reversing loss of LBPF and independence.

The primary purpose of this study was to determine potential impairments resulting in diminished LBPF in healthy older adults and those suffering from PN. It was hypothesized that the property of local instability would better predict LBPF as compared to traditional measures related to the magnitude of stride-to-stride variability. It was additionally hypothesized that fundamentally different factors would predict LBPF in those with PN as compared to controls. Specifically, while leg strength would more closely predict LBPF in healthy older adults, standing balance impairment would more closely predict LBPF in individuals with PN.

## **Methods**

### **Participants and Protocol**

Twelve individuals with PN and 12 age-matched healthy older (HO) adults gave university-approved IRB consent. The presence of PN was first determined by past diagnosis of PN by a neurologist. As diagnostic criteria for PN often vary across physicians (Boulton et al., 2004), it was experimentally confirmed by plantar pressure detection threshold testing. This

diagnostic test has low incidence of false-positive results when compared to gold-standard electrodiagnostics, and is thus a conservative test for the presence of PN (Kamei et al., 2005). Participants were seated with eyes-closed and right leg supported. The 5.07 gauge Semmes-Weinstein monofilament (North Coast Medical, Inc) was employed using standard procedures. Testing sites included the heel, mid-sole, bases of first/fifth metatarsals and hallux (Nurse and Nigg, 2001). Each site was tested three times in random order. Individuals were instructed to say “Yes” if pressure was felt. Intact sensation at each site was defined by two or more correct (i.e., Yes) responses and was given a score of “1.” Reduced sensation, defined by two or more incorrect (i.e., absent) responses, was given a score of “0.” Assigned scores for each site were added to produce a score from 0-5.

Inclusion into the PN group was contingent upon 1) physician-diagnosed PN, 2) plantar pressure detection threshold score  $\leq 3$ , and 3) the ability to walk six minutes continuously and unassisted. Inclusion criteria for the HO group included 1) the absence of PN, 2) plantar pressure detection score of 5, and 3) the ability to walk six minutes unassisted. For both groups, potential participants were excluded if they presented with foot ulceration, any other movement disorder that may affect function, or any uncontrolled cardiovascular, respiratory, or metabolic disorder.

Testing took place at the same time of day on different days separated by one week. On the first visit, age, height, body mass, duration of PN from diagnosis, and the cause of PN were recorded. Two separate tests of LBPF were then completed, followed by tests of leg strength and standing balance. On the second visit, kinematic properties of treadmill walking were assessed.

#### Locomotion-Based Physical Function (LBPF)

The 6-minute walk test was administered using standard procedures. Two cones were placed on opposite ends of a 30m hallway. Participants were instructed to walk around the cones

and cover as much distance as possible in six minutes. The distance walked to the nearest meter was recorded. Specific protocol and participant instructions can be found in the American Thoracic Society statement (ATS, 2002). The timed up-and-go test was administered according to Podsiadla et al (1991). A chair with arm rests was placed in the middle of a well-lit, indoor hallway. In front of the chair, a distance of 3m was marked with a cone. The test began with the participant seated with their back against the chair and arms in lap. Instructions were to stand up using the arm rests if needed, walk safely around the cone and back to the chair, and sit back in the chair as fast as possible. The average time needed to complete each of two trials was used for analysis.

### Leg Strength

Knee extensor (KEPT) and flexor peak torque (KFPT) were measured at 60 deg/s with a Biodex dynamometer (Biodex Medical, Shirley, NY). Warm-up consisted of five reciprocal knee extension/flexion movements. Instructed were to increase force with each trial to generate maximal force during the fifth trial. Following rest, five maximal trials were completed with 10 sec rest between trials. Verbal encouragement was provided to facilitate maximal efforts. For the five movements, peak torque from the three best trials was recorded and averaged.

### Standing Balance

Standing balance was assessed using an AccuSway ® force platform and SWAYWIN 95 version 2.1 software (AMTI, Watertown, MA). Participants completed three 30-sec trials with normal stance (i.e. heels five cm apart, feet abducted laterally 10 degrees), arms by their side, and eyes closed. For each trial, the average velocity (VEL) of the body center of pressure, and the area of a bivariate confidence ellipse inclosing 95% of the center of pressure trajectory (A95) (Prieto et al., 1996) were calculated.

## Locomotor Kinematics

At the beginning of the second day of testing, an overground 6-minute walk test was completed using the aforementioned procedures. Average speed was calculated (i.e., distance covered / 360 seconds) and used for treadmill walking trials. Participants were outfitted with a commercial safety harness designed to prevent falls but not interfere with locomotion. A three minute familiarization trial of treadmill walking at each participant's calculated speed was completed. While complete habituation to the treadmill may take longer (Van de Putte et al., 2006), three minutes was chosen to limit possible fatigue. All participants comfortably walked at their calculated speed. Following a ten minute rest period, a second three minute trial was completed during which kinematic data were collected.

Two-dimensional sagittal plane joint motions were acquired (60 Hz) using a single camera motion analysis system (Motion Analysis Corp, Santa Rosa, CA). Joint movement was tracked with reflective markers placed on the right ASIS, greater trochanter, lateral femoral condyle, lateral malleolus, and 5<sup>th</sup> metatarsal head. Hip, knee, and ankle angles were computed from the final two minutes of each trial. Stride duration variability (SDvar, SDcov), joint angle variability (JTvar), and short- and long-term Finite-time Lyapunov Exponents ( $\lambda_{ST}^*$ ,  $\lambda_{LT}^*$ ) related to state space divergence or local instability were computed from each acquired time-series.

Variability measures were quantified by filtering each time-series with 6Hz, digital low-pass second-order Butterworth filter. SDvar was defined as the standard deviation from the mean stride duration over thirty consecutive strides. Stride duration was computed by determining the elapsed time between consecutive, maximum *knee* joint angles (Li et al., 2005). To account for potential individual variance in stride duration, the coefficient of variation (SDcov) was also

computed by dividing SDvar by stride duration. JTvar for the hip, knee, and ankle joints was determined from the same thirty strides. Ensemble curves of each stride were created using a linear interpolation technique (Figure 2, Li et al., 2005). This technique normalized each stride to 101 points (i.e., 0-100%). The standard deviation from the mean value at each point was determined and the average standard deviation across all 101 points was computed. JTvar was determined by averaging variability scores across the hip, knee, and ankle joints.

Finite-time Lyapunov exponents were computed from 100 consecutive strides using maximum knee joint flexion angles as cut off points. Time-series were filtered using a 10Hz low-pass, fourth-order Butterworth filter (England and Granata, 2007). Algorithms published by Rosenstein et al (1993) were employed. Briefly, “global false nearest neighbors” analysis and the “method of delays” were used to reconstruct valid, 5-dimensional state spaces for each time-series. The distance between all possible pairs of nearest neighbor trajectories were tracked as the system moved forward in time, averaged, and subsequently graphed on a logarithmic scale normalized to the average stride duration for each participant. The *rate* of exponential divergence,  $\lambda^*$ , was estimated by calculating the slope of a least-squares best fit line to the produced curves over predetermined linear scaling regions. The “short-term” Lyapunov exponent ( $\lambda_{ST}^*$ ) corresponded to the slope between 0-1 strides, and the “long-term” Lyapunov exponent ( $\lambda_{LT}^*$ ) between 4-10 strides (Dingwell et al., 2001). Final  $\lambda_{ST}^*$  and  $\lambda_{LT}^*$  scores were produced by averaging hip, knee, and ankle joint values.

## Data Analysis

For this analysis, dependent variables were measures of LBPF, which included 6-Minute Walk distance and Timed Up-and-Go time. Independent variables were chosen as potential predictors of physical function, and included plantar pressure detection threshold, knee extensor

and flexor peak torque (KEPT, KFPT), standing balance (AREA, VEL), and locomotor kinematics (SDvar, SDcov, JTvar,  $\lambda_{ST}^*$ ,  $\lambda_{LT}^*$ ). Statistical analyses were performed using Statistix software (V1.0, Boston, MA). Univariate statistics and Pearson product correlations were used to analyze dependent and independent variables. For each group, stepwise linear regression was employed to determine the ability of the independent variables to predict performance in each test of LBPF. Significance level was set to  $p < .05$  for all analyses.

## Results

Group means  $\pm$  standard deviation for participant characteristics, dependent and independent variables are presented in Table 4.1. Groups presented with similar age, height, and body mass. The average duration since diagnosis for individuals within the PN group was  $5 \pm 5$  years. While all HO participants had intact plantar sensation as measured in the current study, sensation in those with PN was significantly reduced (i.e., plantar pressure detection threshold score =  $2.1 \pm 0.3$  sites). The PN group demonstrated significantly impaired LBPF, as evidenced by decreased 6-Minute Walk distance ( $p = .01$ ) and increased Timed Up-and-Go time ( $p = .02$ ). Additionally, the PN group exhibited significantly ( $p < .01$ ) greater sway AREA during eyes-closed standing balance as compared to HO group. Despite these declines, no group differences were observed for either measure of leg strength.

The mean walking speed of the PN group, computed by the average speed during the 6-Minute Walk, was slower than that of the HO group ( $1.09 \pm 0.08$  vs.  $1.47 \pm 0.07$  m/s,  $p = .01$ ). During treadmill trials, the PN group walked with increased magnitude of stride duration variability in both absolute (SDvar,  $p = .01$ , JTvar,  $p = .01$ ) and relative terms (SDcov,  $p = .02$ ). In spite of increased variability, no group differences were observed for either  $\lambda_{ST}^*$  or  $\lambda_{LT}^*$  (Table 4.1).

**Table 4.1 Demographics, physical function, strength, balance, and kinematics (\* denotes units =  $\{<\ln[dj(i)]>/\text{stride}\} * 100$ ).**

	<u>Group (Mean ± SEM)</u>		p value
	HO	PN	
<b>Participant Demographics</b>			
Age (years)	68 ± 10	66 ± 11	.65
Height (cm)	169 ± 6	172 ± 11	.32
Body Mass (kg)	78 ± 20	84 ± 18	.45
PN Duration (years)	-	5 ± 5	-
PPDT (# of intact sites)	5 ± 0	2 ± 1	<b>.001</b>
<b>Physical Function</b>			
6MW Distance (m)	530 ± 25	391 ± 27	<b>.01</b>
TUG Time (sec)	7.1 ± 0.5	9.5 ± 0.6	<b>.02</b>
<b>Strength</b>			
KEPT (Nm)	146 ± 14	121 ± 17	.25
KFPT (Nm)	65 ± 9	63 ± 9	.51
<b>Standing balance</b>			
VEL (cm/s)	2.4 ± 0.2	3.0 ± 0.4	.25
AREA (cm <sup>2</sup> )	3.8 ± 0.4	11.8 ± 2.4	<b>.01</b>
<b>Locomotor Kinematics</b>			
Stride Duration (ms)	933 ± 28	936 ± 32	.93
SDvar (ms)	19.9 ± 1.6	27.2 ± 1.9	<b>.01</b>
SDcov	2.1 ± 0.2	3.0 ± 0.3	<b>.02</b>
JTvar (deg)	1.7 ± 0.1	2.6 ± 0.2	<b>.01</b>
$\lambda_{LT}^*$ (*)	0.17 ± 0.01	0.17 ± 0.01	.93
$\lambda_{ST}^*$ (*)	2.92 ± 0.12	3.08 ± 0.09	.33

The correlations between each independent variable and dependent variables for each group are presented in Table 4.2. Scatter plots of selected relationships are presented in Figure 4.1. Within the PN group, those with lower plantar pressure detection threshold scores (i.e., increased plantar sensory loss) tended to walk shorter distances in the 6-Minute Walk test. In the remaining correlations, the types of independent variables that correlated to the dependent variables were considerably different across groups. Knee extensor leg strength was correlated to

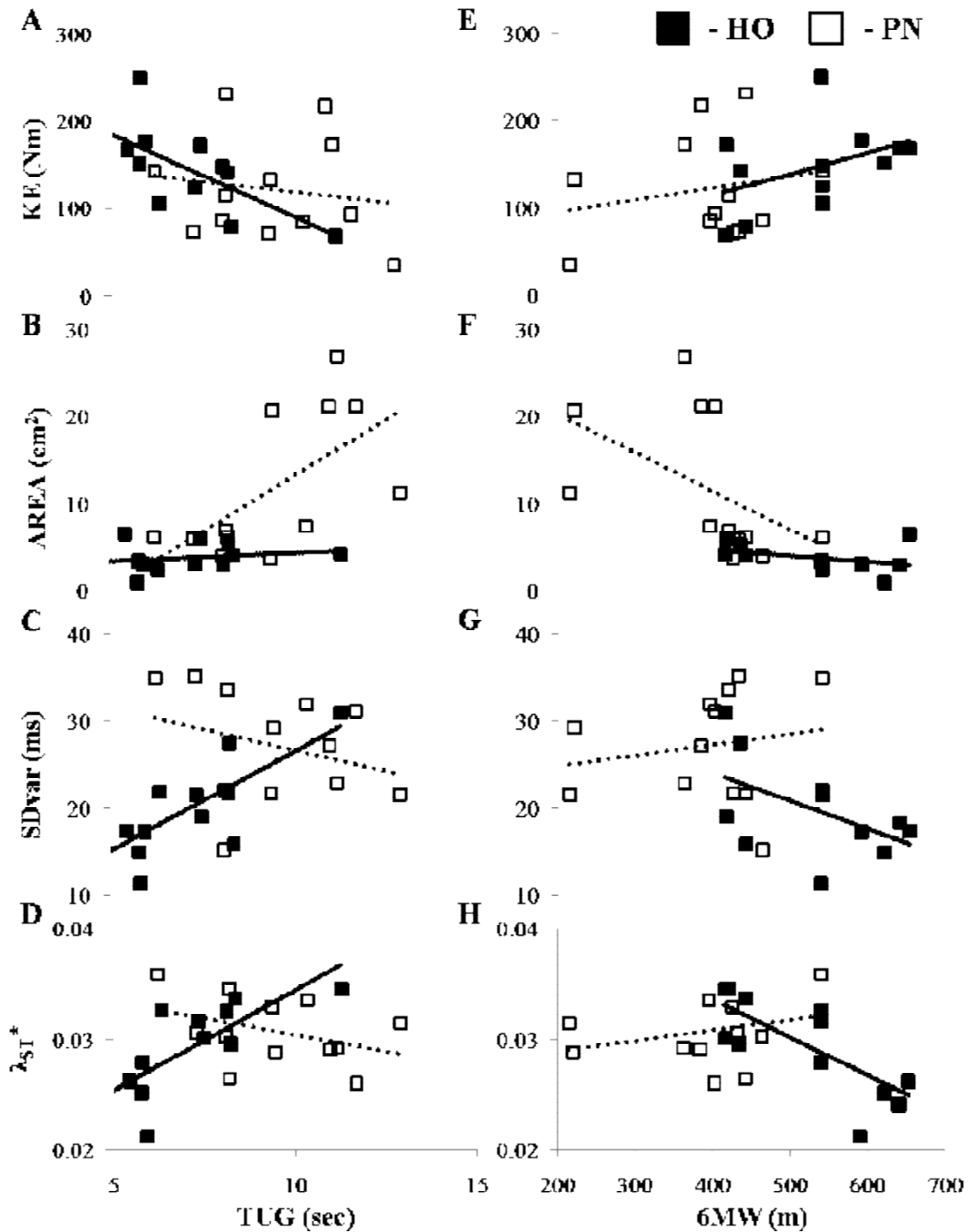
**Table 4.2 – Correlation (R, p) between physical function and selected measures of sensitivity, leg strength, standing balance, and locomotor kinematics.**

	<u>6MW</u>		<u>TUG</u>	
	HO	PN	HO	PN
<b>Sensitivity</b>				
PPDT	-	<b>.58, .05</b>	-	-.43, .16
<b>Leg Strength</b>				
KEPT	<b>.63, .04</b>	.21, .51	<b>-.67, .02</b>	-.15, .63
KFPT	.04, .90	.09, .77	-.41, .19	.00, .99
<b>Standing Balance</b>				
AREA	-.37, .24	<b>-.78, .003</b>	.22, .48	<b>.62, .03</b>
VEL	-.02, .94	-.49, .10	.27, .39	.23, .47
<b>Locomotor Kinematics</b>				
SDvar	-.51, .09	.18, .58	<b>.75, .005</b>	-.29, .36
SDcov	-.41, .19	.22, .49	<b>.66, .02</b>	-.27, .39
JTvar	.07, .81	.10, .75	.49, .10	-.01, .97
$\lambda_{LT}^*$	.44, .15	.38, .22	-.05, .87	-.13, .68
$\lambda_{ST}^*$	<b>-.71, .01</b>	.28, .37	<b>.76, .004</b>	-.38, .22

Significant correlations have been bolded. When examining positive and negative correlations, it is of note that walking *further* in the 6MW test indicates increased performance, where as completing the TUG test in *less* time indicates increased performance.

physical function (6-Minute Walk) in the HO group only. Conversely, AREA during eyes-closed standing balance was associated with performance in both the 6-Minute Walk and Timed Up-and-Go in the PN group only.

Within the HO group, several kinematic measures of locomotion were associated with LBPF. The nonlinear measure of  $\lambda_{ST}^*$  was highly correlated to performance in both LBPF tests. Those exhibiting greater  $\lambda_{ST}^*$  values tended to cover less distance in the 6-Minute Walk and take more time to complete the Timed Up-and-Go. Furthermore, HO participants with increased magnitude of stride duration variability, both in absolute (SDvar) and relative (SDcov) terms,



**Figure 4.1** Relationships between physical function and selected dependent variables. The TUG (A, B, C, D) and the 6MW (E, F, G, H) have been plotted against KE, AREA, SDvar, and  $\lambda_{ST}^*$ , respectively. Presented dependent variables were chosen based on significant Pearson product correlation in at least one group (see Table 4.2). The solid (HO) and dashed (PN) lines were placed using the method of least squares. It is of note that completing the TUG in *less* time and covering *more* distance in the 6MW indicate better performance.

**Table 4.3 Stepwise linear regression for predictors of physical function**

	<b>6MW</b>			<b>TUG</b>		
	<b>Variable</b>	<b>Coefficients (<math>\beta</math>)</b>	<b>P value</b>	<b>Variable</b>	<b>Coefficients (<math>\beta</math>)</b>	<b>P value</b>
<b>HO &amp; PN Combined</b>	KF	1.72	.004	KE	-0.02	.001
	AREA	-7.36	.02	AREA	0.22	.000
	$\lambda_{LT}^*$	16500	.002			
	PPDT	15.1	.05			
<b>HO</b>	$\lambda_{ST}^*$	-14600	.01	$\lambda_{ST}^*$	218	.02
				SDvar	0.16	.03
<b>PN</b>	KF	3.62	.002	KE	-0.025	.000
	AREA	-7.58	.01	AREA	0.125	.000
	SDvar	-31.8	.01	VEL	-0.430	.000
	SDcov	204.9	.01	SDvar	0.300	.003
	$\lambda_{ST}^*$	17300	.04	SDcov	-3.83	.000
	$\lambda_{LT}^*$	21200	.006	JTvar	2.37	.000
				$\lambda_{ST}^*$	-482	.000
				$\lambda_{LT}^*$	457	.005
			PPS	-.070	.001	

tended to take more time to complete the Timed Up-and-Go. Within the PN group, no kinematic variable was significantly correlated to either measure of LBPF (Table 4.2, Figure 4.1).

In addition to correlation analysis, stepwise linear regression was employed to determine independent predictors of performance in LBPF for each group (Table 4.3). Within the HO group,  $\lambda_{ST}^*$  and SDvar significantly predicted performance in one or both tests of LBPF. Interestingly, no other variables provided additional independent predictive information of performance within this group. When analyzing the PN group, multiple variables independently predicted performance in both LBPF tests, including nearly all acquired locomotor properties.

### **Discussion**

This study set out to determine if leg strength, standing balance, and kinematic properties of the locomotor system are associated with locomotion-based physical function (LBPF). It was

hypothesized that local instability would better predict LBPF as compared to the average magnitude of variability present from stride to stride. This hypothesis was partially supported as local instability was the only significant independent predictor of HO group performance in the 6-Minute Walk. However, additional kinematic variables provided independently predictive information regarding performance in the Timed Up-and-Go, as well as both LBPF tests within the PN group. It was also hypothesized that fundamentally different impairments would underlie LBPF decline in each group. This hypothesis was supported as HO adults with less leg strength demonstrated reduced LBPF, while those PN individuals with diminished standing balance demonstrated reduced LBPF. Furthermore, although multiple kinematic locomotor properties correlated with LBPF within the HO group, none of these measures were significantly correlated within the PN group.

The kinematics of locomotion is often investigated to assess the integrity of the locomotor system. Relatively increased magnitude of stride-to-stride variability and decreased magnitude of local instability is viewed as impairment because of association with aging and disease (Buzzi et al., 2003; Dingwell and Cavanagh 2001). Aside from reported group differences, however, little direct empirical evidence exists to support these claims. Results of the current study demonstrated that increased magnitude of variability *and* increased (short-term) local instability are both associated with reduced LBPF within healthy older adults. This observation supports the notion that relative increases in these variables reflect impairment of the locomotor system.

With all variables examined together, stepwise linear regression revealed that short-term local instability,  $\lambda_{ST}^*$ , was the only independent predictor of 6-Minute Walk distance in the HO group. Local instability, which does not correlate to the magnitude of variability (Dingwell and

Cusumano, 2000), estimates the sensitivity of the locomotor system to the small-scale perturbations inherent to normal walking. It has been suggested to indicate the capacity of the locomotor system to “fine-tune” its movements in an ongoing manner (England and Granata, 2007). Our observations suggest that as compared to the magnitude of variability, and even leg strength and standing balance, this property may be better suited to investigate impairment leading to LBPF decline.

Both the magnitude of variability *and* local instability predicted performance in the Timed Up-and-Go test for HO adults. Each property also provided independently predictive information regarding Timed Up-and-Go and 6-Minute Walk performance for individuals with PN. This highlights the importance of quantifying both properties to more fully evaluate the locomotor system. Future work should focus on determining the cause of these relationships, such as potential active and or passive nervous, muscular, and mechanical factors that mediate the control of these properties.

Individuals with PN demonstrated severely reduced LBPF. On average, the PN group walked 140 meters less in the 6-Minute Walk and took almost 2.5 seconds longer to complete the Timed Up-and-Go. In the 6-Minute Walk, those with decreased plantar pressure detection thresholds tended to cover less distance. This observation is supported by Menz (2004) and Dingwell (2001) who both reported that the degree of sensory involvement predicted preferred walking speeds within this population.

The PN group exhibited increased magnitude of stride-to-stride variability, yet maintained similar local instability as compared to the HO group. Dingwell and Cusumano (2000) recently reported similar results, which may be explained by known relationships between each variable and walking speed. Walking slower than preferred leads to *increased*

magnitude of stride-to-stride variability, and *decreased* local instability in young adults (Dingwell and Marin, 2006; England and Granata, 2007). These researchers suggested that slowed walking speeds under conditions of reduced plantar sensation may be beneficial, despite leading to increased variability, as they reduce local instability. However, correlation analysis in the current study also revealed that no kinematic locomotor property was significantly related to performance in either test of LBPF. This may speak to the heterogeneity of the PN population and suggests that other factors, such as reduced postural control, likely contribute to LBPF decline.

Those HO group participants with greater leg strength tended to perform better in both tests of LBPF. This result was expected as lower-extremity strength has been correlated to 6-Minute Walk distance in similar populations (Bean et al., 2002). Interestingly, individuals with PN demonstrated similar leg strength as compared to their age-matched counterparts. However, neither measure of leg strength was related to LBPF within this group. Instead, impaired standing balance closely correlated to reduced performance in both the 6-Minute Walk and Timed Up-and-Go. This observation speaks to the severity of standing balance impairment in the PN group (i.e., AREA increase of 215%) as compared to the HO group. Similar standing balance impairments have been reported elsewhere (Simoneau et al., 1994), and the severity of impairment has been linked to the amount of plantar pressure sensation loss (Ducic, 2004). Together, these group differences suggest that leg strength is an important factor of performance, *provided that one does not experience severely impaired standing balance control.*

Generalization of the observations from this study may be limited. A treadmill was utilized to acquire kinematic locomotor variables. While this was done to allow data collection over an extended duration, Dingwell et al (2001) reported small reductions in both the magnitude

of stride-to-stride variability and  $\lambda^*$  of specific trunk and lower extremity movements when walking on a treadmill as opposed to over ground. As both groups were subjected to the same protocol, we believe that treadmill walking does not influence the interpretation of our results.

The choice of dependent variables within each physical domain was based on published relationships to LBPF as well as commonness of use in clinical and research settings. Other variables, such as joint power acting at the knee or ankle joint have also shown correlation to LBPF in older adult populations (Richardson, 2002). Especially within the PN group, psychological parameters such as lower-extremity pain and or fear of falling likely further influenced performance. Although acquisition of these variables may have strengthened our analyses, the present correlations and predictive ability of obtained variables allowed appropriate tests of our hypotheses.

In conclusion, the relationship between LBPF and both the magnitude of variability *and* local instability indicates the importance of examining each measure to more fully explore potential locomotor system impairment. Future investigation should attempt to elucidate potential thresholds for LBPF within these variables, as well as their sensitivity to intervention. The negative impact of PN on LBPF highlights the need for exercise intervention with this population. White et al (2004) has concluded that inadequate evidence was available to evaluate the effectiveness of exercise programs. Richardson et al (2001) has, however, reported that a three week exercise program focusing on strengthening “balance specific” lower-extremity musculature improved functional reach, unipedal and tandem stance times for this population. The results of the current study indicate that the effectiveness of such programs might be augmented by the inclusion of specific training designed to improve standing balance control in the absence of normal plantar sensation.

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## CHAPTER 5 – DISCUSSION

### Key Results

The relationship between PN, physical disability, and falls has warranted investigation into the effects of this prevalent and debilitating disorder on walking. As individuals with PN often present with many additional ailments and alterations, **Chapter 2** examined the influence of acute, selective loss of plantar sensation on kinematic markers of locomotor system health in young healthy adults. The variability and local instability associated with lower-extremity kinematics were computed as participants walked on a motorized treadmill. With these results in hand, a similar protocol was utilized in **Chapter 3** to determine the influence of PN on the same kinematic markers obtained from treadmill walking at relatively slow and fast speeds. **Chapter 4** then explored the clinical usefulness of these markers of locomotor system health by examining their relationship to widely-employed tests of locomotion-based physical function (LBPF). The following discussion will reiterate the key results from these studies and explore several insights by examining the combined results of this dissertation. It will conclude with the limitations of this work and directions of future research.

In healthy young adults, ice-exposure of the foot soles significantly reduced plantar pressure sensation during each subsequent treadmill walking trial. This acute reduction in sensation did *not* alter the magnitude of stride duration or lower-extremity joint angle variability. It did, however, increase short- and long-term local instability associated with lower-extremity joint kinematics.

Individuals with PN demonstrated reduced “faster walking speeds” (FWS) over six minutes as compared to healthy age-matched controls. After controlling for variance in FWS, individuals with PN demonstrated greater magnitudes of variability during treadmill walking at

all speeds. At relatively slow treadmill speeds, no group differences were observed in either indicator of local instability. However, individuals with PN exhibited significantly elevated short-term local instability of lower-extremity joint kinematics *at the fastest walking speed*.

In healthy older adults, LBPF was correlated to leg strength, short-term local instability, and the magnitude of stride duration variability. With all independent variables analyzed together, only those measures of locomotor system health (short-term local instability, stride duration variability) provided independent predictive information regarding LBPF.

The PN group exhibited reduced performance in both tests of LBPF. They also demonstrated reduced plantar sensation, poor standing balance, and increased magnitude of stride duration and joint angle variability during treadmill walking. No leg strength differences were observed. As opposed to healthy old adults, correlates of LBPF were not leg strength but instead standing balance variables. When examined together, multiple variables related to leg strength, standing balance, and locomotor system health all provided independently predictive information regarding performance in each test of LBPF.

### **Implications of Key Results**

#### Acute versus Chronic Loss of Plantar Sensation

In healthy young adults, selective loss of plantar cutaneous sensation by exposure of the foot soles to ice did not alter the magnitude of stride-to-stride timing or joint angular variability during treadmill walking. However, it did result in increased local instability, or in other words, *increased* the sensitivity of the locomotor system to small-scale perturbations. It may be speculated that 1) intact plantar sensation plays a *direct* role in actively dampening the effects of this type of perturbation, or alternately, 2) ice-induced sensory loss *indirectly* caused the observed increases in this property.

Reduced plantar sensation may have directly influenced local instability. While specific pathways are unknown, it may have done so by altering normal reflexive muscular activity. Stride-to-stride variability is present in the plantar pressure distribution patterns of each subsequent stance phase of walking (Cavanagh et al., 1997). Properly functioning cutaneous mechanoreceptors in the glabrous skin of the foot soles are responsive to loading, with sufficient sensitivity to detect these small, variability-induced changes (Nielsen and Sinkjaer, 2002; Mazzaro et al., 2005). Intact plantar sensation may therefore detect these subtle load fluctuations, and through A $\beta$  reflexive activity, produce “on-going” corrective muscular activity (Christensen et al., 1999; van Wezel et al., 2000). Ice-induced reduction of plantar sensation may have therefore diminished the capacity of the locomotor system to detect, and subsequently correct these irregularities. This would have in turn created the observed increases in local instability.

The activeness of the above reflex pathway during unimpeded walking is unknown. Certainly, reflexive muscular activity is most commonly observed under conditions of abrupt departures from normal levels of sensation (Christensen et al., 1999). This was not the case in the current research, as individuals were allowed to walk unimpeded for several minutes. It is therefore possible that under normal conditions, plantar sensation does not actively contribute to the degree of local instability associated with walking kinematics.

Instead, ice-induced sensory loss may have indirectly increased local instability. Eils et al (2002) demonstrated that in healthy young adults, ice-exposure of specific portions of the plantar surface of the foot led to modified plantar pressure distribution patterns *away* from the desensitized areas. Whether resulting from a conscious or subconscious adaptation, modified foot strikes may have altered the *nature* of small-scale perturbations. Increased local instability

may have thus occurred not by hindering the ability to actively respond to small-scale perturbations, but instead by changing the characteristics of the perturbations themselves.

Although possible, this latter mechanism is improbable. In the current research, the entire weight-bearing surface of the foot was exposed to ice. Uniform reduction in plantar sensation did not likely alter foot strike characteristics to the same degree as reported in Eils et al (2002). Furthermore, Dingwell et al (2000) suggested that the magnitude of variability reflects precisely the average size of small-scale perturbations inherent to normal walking. As ice-exposure did not alter the magnitude of stride duration or joint angle variability, it is more likely that acute loss of plantar sensation increased local instability by directly decreasing the capacity to detect small-scale perturbations.

PN results in decreased protective sensation across all sensory modalities in the distal extremities (Boulton et al., 2004). The loss of plantar pressure sensation can be severe (Dingwell and Cavanagh, 2001), and is often more apparent than other modalities such as proprioception (Meyer et al., 2004). As ice exposure increased local instability in healthy young adults, it logically follows that those individuals with PN-related plantar sensory loss would also walk with increased local instability. On the contrary, individuals with PN walked with increased magnitude of variability yet *similar* local instability of lower-extremity joint motion as compared to age-matched controls (Table 5.1).

**Table 5.1 – Differential Effects of Acute and Chronic Plantar Pressure Sensory Loss on Markers of Locomotor System Health**

<b>Plantar Sensory Loss</b>	<b>Magnitude of Variability</b>	<b>Local Instability</b>
<b>Acute: Ice-Exposure</b>	No change	Increased
<b>Chronic: PN</b>	Increased	No Change

The fundamentally different effects of acute ice-exposure and chronic PN suggest that individuals with PN consciously or unconsciously compensate, at least in part, for reduced lower-extremity somatosensation. Due to known relationships between walking speed and both variability (Li et al., 2005) and local instability (Dingwell and Marin, 2006; England and Granata, 2007), the current research statistically controlled for individual variance in walking speed. The persistent, opposing effects of ice-induced plantar sensory loss and PN therefore suggest that compensatory actions are employed in addition to slowing one's PWS.

The exact compensations employed are unknown. One possibility may be an increase in lower-extremity joint stiffness. Joint stiffness is defined by the joint's angular resistance to torque (Stefanyshyn and Nigg, 1998). Although the cause of increased stiffness was not investigated, Williams et al (2007) demonstrated that when walking at similar speeds, individuals with PN exhibit increased ankle joint stiffness during the second half of the stance phase. Increased joint stiffness results in decreased joint angle displacement following an applied perturbation (i.e., torque) of known magnitude (Gottlieb and Agarwal, 1988). Increased stiffness would then theoretically decrease the time-dependent sensitivity of that joint to the inherent small-scale perturbation of unimpeded walking. As a result, it may reduce, or nullify, potential increases in local instability secondary to the PN.

#### Peripheral Neuropathy and Challenging the Locomotor System

When walking over regular surfaces at relatively slow or preferred speed, individuals with PN demonstrate largely similar walking patterns as their aged-matched healthy counterparts. Chronic loss of lower-extremity somatosensation therefore does not appear to drastically effect walking under relatively unchallenging situations. The current research instead suggests that the PN-related predisposition to falls more likely occurs during situations in which

the locomotor system is challenged (Dingwell et al., 2000; Richardson et al., 2004). This appears to be the case whether the system is challenged by walking at relatively fast speeds, or by walking over irregular support surfaces (Menz et al., 2004, Richardson et al., 2004b). While these conditions represent fundamentally different challenges, these observations nevertheless provide important insight into PN-related impairment of the locomotor system.

First, it has been suggested that individuals with PN slow their walking speed to compensate for loss of somatosensation. This conclusion has been extrapolated through reports of 1) reduced walking speed in unchallenging situations (Courtemanche et al., 1996; Dingwell et al., 2000), 2) correlation between walking speed and the degree of lower-extremity sensory involvement (Menz et al., 2004), 3) evidence of decreased local instability as a result of walking slower (Dingwell et al., 2000), and 4) exaggerated reduction in walking speed when on irregular surfaces (Menz et al., 2004; Richardson et al., 2004). The current observation, that walking relatively faster exacerbates local instability within the PN population, provides direct evidence that reduced speed as compensatory. One benefit to this compensation may be the preservation of “normal” local instability levels.

The pronounced differences in walking speed, variability, and local instability when the system is challenged suggests that markers of locomotor system health may be more sensitive when obtained during these situations. Moreover, it is speculated that falls more likely occur during these situations. Walking faster than normal increases the inertial effects of walking and reduces the time spent in double support (Winter, 1983). Walking over irregular surfaces alters the foot-ground interaction thus inducing unexpected perturbations to the locomotor system. Timely and accurate feedback stemming from lower-extremity somatosensation is more critical to successful movement in these situations (Grabiner et al., 1993). Chronic loss of

somatosensation is thus a likely mechanism through which individuals with PN have difficulty meeting these challenges.

### Physical Function in Peripheral Neuropathy

Individuals with PN exhibited decreased performance in both clinical tests of LBPF. Of the obtained predictor variables, the strongest correlates to LBPF within this population were variables related to eyes-closed standing balance (i.e., VEL, AREA). When examining all predictor variables together, VEL and AREA each provided independent predictive information regarding LBPF within the PN group.

The correlation between standing balance and LBPF within the PN group opposes that of existing literature. Within the healthy older adult populations, little correlation exists between the capacity to stand quietly and perform tasks in which walking is a significant component (Owings et al., 2000; Hrysomallis et al., 2006). Indeed, this dissociation was also observed in Chapter 4, as neither measure of standing balance predicted LBPF within the healthy old group. The lack of correlation between standing and walking in *healthy* populations is not surprising as the tasks are quite different. Standing requires maintenance of the body's center of mass (COM) within its base of support (BOS). When walking, on the other hand, the COM must be displaced outside the BOS and subsequently "caught" with each proceeding step to avoid falling (Winter, 1995).

The cause of correlation between standing balance and LBPF in the PN group is unclear. However, it likely stems from the characteristics of the employed field tests that defined LBPF. Both the TUG and 6MW required the participant to not only walk under steady-state conditions, but also rise from a chair, initiate and terminate gait, and turn 180 degrees. It is speculated that timely and accurate completion of several of these tasks requires precise control of the body's COM while standing. Deteriorated standing balance may have therefore reduced performance in

the TUG, and to a lesser extent the 6MW, by increasing the time needed to safely complete one or more of these additional tasks.

The initiation of walking (i.e., taking a step from a standing position) is thought to rely heavily on standing balance control. In the healthy adult population, kinetic and kinematic analyses of this task have been completed (Brunt et al., 1991). Distinct shifts in plantar pressure and body center of mass are observed, with only slight intra-subject variation from trial to trial. Although not examined to date, it is likely that PN-related reductions in standing balance control hinders the ability to quickly and safely unload one limb, load the other, and subsequently place the swing limb in its intended position.

Research has examined the influence of PN on the termination of walking, which involves plantar pressure and body center of mass shifts that are virtually mirror images of those made during initiation (Brunt et al., 1991). Meier et al (2001) reported that older adults with PN took longer to terminate walking at PWS than healthy old adults. Increased duration of termination was independent of group differences in PWS. It was instead caused by delayed onset and decreased magnitude of braking forces during the stance phase. The authors suggested that this observation reflected intolerance to rapidly changing task conditions. The required tasks of the 6MW and TUG tests in addition to steady state walking (i.e., walking initiation, termination, turning) reflect precisely such rapidly changing conditions. Intolerance to these tasks may therefore underlie, at least in part, the close correlation observed between standing balance and LBPF in this population.

### **Limitations**

The research outlined in this dissertation contained several methodological issues that potentially limit generalization of conclusions. Two major issues relate to 1) sampling bias, and

2) the use of a motorized treadmill. A sampling bias may have occurred such that the PN sample was relatively high functioning. This may limit generalization of results to the entire PN population. Individuals with PN were recruited and included pending 1) physician diagnosis of PN, 2) severe loss of plantar pressure sensation, 3) the lack of any complication that may have influenced gait, and 4) the ability to walk six minutes continuously and unassisted. These criteria were implemented to ensure the presence of significant PN-related sensory involvement and yet, safe completion of overground and treadmill walking trials.

Although multiple complications associated with PN would have led to exclusion from participation, volunteering participants did not present with any such complications. In fact, all met the first three inclusion criteria. Only two potential participants were unable to walk on the treadmill unassisted and were thus excluded from participation. The relative homogeneity of included participants was sought after as it enabled insight into the specific movement disorder associated with PN. On the other hand, it limited extrapolation of conclusions to those individuals with PN also suffering from one or more the above-mentioned confounding factors.

A second limitation of this dissertation was the utilization of a motorized treadmill to acquire the kinematic time-series from which markers of locomotor system health were calculated. These markers, which included variability and local instability, require a relatively large sample of consecutive strides. While a treadmill was required to allow data collection using existing motion capture instrumentation, the validity of comparing treadmill walking to the more clinically relevant overground walking has been debated.

Provided that the belt moves at a constant speed, there are no theoretical mechanical differences between overground and treadmill walking (van Ingen Schenau, 1980). Riley et al (2007) reported that treadmill walking is both “quantitatively and qualitatively similar” to

overground walking. Yet, treadmill walking has been associated with kinematic and kinetic differences. It results in shorter stride length and increased cadence (Arsenault et al., 1986), and reduced vertical ground reaction forces during mid- and late-stance (White et al., 1998). The speed constraints induced by the treadmill belt also result in decreased variability and local instability associated with both lower-extremity and trunk movements (Dingwell et al., 2001).

The present observations obtained from treadmill walking may therefore not hold to overground walking. However, limitation did not likely interfere with related conclusions. All participants were subjected to the same protocol, and the included kinematic measures closely correlated to performance in overground tests of physical function. Furthermore, healthy young adults demonstrated increased local instability following ice exposure, and those with PN exhibited exaggerated local instability at relatively fast walking speeds. As external treadmill-related constraints reduce the value of calculated measures, it is speculated that observed differences would have only been exacerbated if obtained from overground walking.

### **Future Directions**

The results of this dissertation provided insight into the control of human walking, the effects of PN on this behavior, and specific predictors of performance in LBPF in both the healthy older adult and PN populations. Based on these initial observations, several directions of future research are warranted. This research should be designed to 1) elucidate the walking-related compensatory mechanisms implemented by those with PN, 2) examine the effects of PN on speed-related reflexes, and 3) determine optimal exercise interventions for this population.

#### **Compensatory Walking Strategies in PN**

Ice-induced reduction of plantar sensation did not alter the magnitude of stride-to-stride variability, yet increased local instability during treadmill walking. Conversely, individuals with

PN walked with increased magnitude of variability, yet similar local instability (at slower walking speeds) compared to controls. As the influence of individual variance in walking speed was statistically controlled in the latter study, the chronic and progressive nature of PN appears to afford development of specific compensatory mechanisms that effectively offset the often severe loss of lower-extremity somatosensation.

In Section 5.2.1., it was speculated that one mechanism of compensation may be increased joint stiffness. Williams et al (2007) reported that individuals with PN walk with increased ankle joint stiffness during the latter half of the stance phase. Increased stiffness would theoretically reduce the sensitivity of the locomotor system to small-scale perturbation. While the cause of increased stiffness was not investigated in that study, it may be actively increased via elevated amounts of lower-extremity joint co-activation. Kwon et al (2003) reported that individuals with diabetic PN demonstrated increased co-activation of antagonist muscles at both the knee and ankle joints during the stance phase. It was concluded that this co-activation was related to “an adaptive walking strategy that compensates for the diminished sensory information from the ankle and foot.” A potential benefit may therefore be an increase stiffness and as a result, maintenance of “normal” local instability levels. Future research is needed to better understand this potential compensatory mechanism by examining the relationships between joint co-activation, stiffness, and markers of locomotor system health, in both healthy adults following ice exposure of the foot soles as well as those suffering from PN.

#### Peripheral Neuropathy and Walking Reflexes

Walking relatively fast resulted in exaggerated local instability associated with walking in the PN population. This condition may be particularly challenging for individuals with PN due to disruption of recently discovered *speed-related* spinal reflex pathways during walking. The

“Common Peroneal Quadriceps (CPQ)” reflex links vastus medialis and lateralis muscle activity to polysynaptic reflexive action spurred by active lengthening of the tibialis anterior during the beginning of the stance phase (Marchand-Pauvert and Nielsen, 2002) Iglesias et al (2008) recently demonstrated that the CPQ reflex is modulated by walking speed. The EMG response amplitude in the quadriceps is nonexistent at very slow speeds, but increasingly greater at successively faster speeds. This speed-dependent reflex was argued to be one mechanism “involved in knee joint control to ensure upright posture during walking.”

It is unknown if PN alters the CPQ reflex; yet, it is possible as advanced cases of PN may involve the large fibers of the common peroneal nerve (Boulton et al., 2004). In these cases, CPQ reflexive action may be reduced, delayed, or absent *when walking at relatively fast speeds*.

Section 5.2 highlighted a potential link between lower-extremity reflex action and the sensitivity of the locomotor system to small-scale perturbations, or local instability. If this relationship does in fact exist, PN-related alteration in the functioning of speed-dependent reflexes such as the CPQ reflex may be in part responsible for exaggerated local instability at relatively fast speeds.

#### Gait and Balance Training in Peripheral Neuropathy

Individuals with PN present with reduced quality of life (Padua et al., 2005), increased risk of falls (DeMott et al., 2007), and diminished LBPF. The goals of rehabilitation management are therefore to “maximize functional capacities, prolong or maintain independent function and locomotion, inhibit or prevent physical deformity and injury, and provide access to full integration into society” (Carter, 2005). The unique set of movement disorders associated with PN calls for multidisciplinary intervention programs that are specifically tailored to the needs of this population. Based on the results of this dissertation and those of currently published research, future clinical-based research should examine the capacity of exercise programs and

other interventions to improve 1) the ability to walk in challenging environments, and 2) standing balance control in the PN population.

Very limited research suggests that individuals with PN can in fact improve walking performance under challenging conditions. Richardson et al (2004) reported that those with PN exhibited pronounced decreases in PWS and exaggerated increases in stride time and step width variability when walking over irregular surfaces. However, by the end of the testing session, which included approximately 50 trials of walking over a 10m irregular surface, those with PN significantly increased walking speed during the trial. While promising, additional research is needed to elucidate the effectiveness of such practice at alleviating fall risk, as well as the mechanisms through which practice might augment the capacity of these individuals to walk in challenging conditions.

As mentioned above, the severe declines in standing balance and its relationship to physical function also highlights the need for standing balance-related intervention. To date, the capacity to improve balance in this population is largely unknown. As of 2004, White and colleagues concluded that inadequate evidence was available to evaluate the effectiveness of such exercise programs. In fact, they reported that the only well-controlled program implemented in the PN population was conducted by Richardson et al 2001. This program focused on *strengthening* lower-extremity muscles deemed important for weight-bearing balance. In only three weeks, individuals with PN significantly improved standing balance as indicated by enhanced functional reach, and both unipedal and tandem stance. Chapter 4 indicated that the effectiveness of such programs might be augmented by the inclusion of training designed specific to improve standing balance control in the absence of normal plantar sensation. Future work should investigate optimal design of such programs as well as the underlying mechanisms

responsible for improved standing balance control under conditions of reduced lower-extremity somatosensation.

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## **APPENDIX A – COMPANY ADDRESSES FOR INCLUDED INSTRUMENTATION**

### **North Coast Medical, Inc.**

18305 Sutter Boulevard  
Morgan Hill, CA 95037-2845 USA

### **Motion Analysis, Inc.**

3617 Westwind Blvd  
Santa Rosa, CA 95403

### **MathWorks**

3 Apple Hill Drive  
Natick, MA 01760-2098

### **Biodex Medical**

20 Ramsay Road,  
Shirley, New York, 11967-4704

### **AMTI**

176 Waltham St  
Watertown, MA 02472

**APPENDIX B – REVIEW OF RELEVANT LITERATURE**

**THE LOCAL STABILITY AND VARIABILITY OF WALKING KINEMATICS IN  
PERIPHERAL NEUROPATHY**

A General Exam

Submitted to the Graduate Faculty of the  
Louisiana State University and  
Agricultural and Mechanical College  
in partial fulfillment of the  
requirements for the degree of  
Doctor of Philosophy

in

The Department of Kinesiology

by

Brad Manor

B.S., University of Toledo, 2002

M.S., University of Toledo, 2004

# CHAPTER 1

## INTRODUCTION

The human being is a biological system capable of producing a wide range of dynamic behaviors. Walking is one such behavior essential to survival as it allows for interaction with the surrounding environment. Healthy individuals can successfully walk under a seemingly countless number of ever changing system, task, and environmental conditions. Unfortunately, over the course of the aging process, or in response to specific disease, deleterious alterations may occur that compromise this ability. These alterations in turn lead to reduced mobility and independence, along with an increased risk of suffering injury related to falls. It is these disturbances, and resulting decrease in quality of life, that warrant investigation aimed at increasing our understanding of human walking.

One of the most frequently investigated movement properties associated with human walking has been stability. Intuitively, stability may be viewed as the ability to successfully maintain a particular behavior over time. With respect to walking, therefore, stability has often been operationally defined as the ability to maintain balance (i.e., avoid falls) under a variety of conditions (Winter, 1995). Unfortunately, the ambiguity associated with this definition has led to a range of methods used to quantify walking stability, which has in turn led to confusion in related literature. The technique traditionally used to quantify stability has involved the measure of walking variability (Corriveau et al., 2004; Menz et al., 2003). This is performed by collecting walking data for a number of isolated strides, and subsequently calculating the statistical mean of a particular kinematic variable, such as stride duration. This approach therefore determines the “typical” stride, as well as the average deviation (i.e., standard deviation) away from this stride.

Using this method, individuals exhibiting greater stride-to-stride deviation are believed to exhibit “less stable” walking patterns, and visa versa (Menz et al., 2004; Richardson et al., 2004).

The clinical relevancy of this technique is justified by the large body of evidence linking increased walking variability to aged and or diseased populations, as well as those populations at increased risk of suffering a fall (Hausdorff et al., 2001a; Hausdorff et al., 2004; Hausdorff et al., 1997). Despite this evidence, however, drawing conclusions about walking stability based on walking variability is problematic. First, considerable evidence exists suggesting that variability may have a beneficial role in purposeful movements (Davids et al., 2003; Goldberger et al., 1990). Second, and most importantly, this practice ignores the physical definition of stability as the time-dependent responsiveness of a system to perturbation (Full, 2002). Certainly, the quantification of the standard deviation away from the mean behavior provides only the average magnitude of variability, and thus offers no insight into the capacity of a system to respond to perturbations.

Unfortunately, subjecting individuals to large-scale perturbations during walking, especially those in aged and or diseased populations, is potentially hazardous. In response to this and the above issues, several researchers have recently applied nonlinear analysis techniques to human walking (Abarbanel, 1996; Dingwell and Marin, 2006; Rosenstein et al., 1993). These techniques have afforded the measurement of a specific type of stability, termed “local stability,” which quantifies the sensitivity of a system to small-scale or “infinitesimal” perturbations. Importantly, these perturbations are precisely those arising from fluctuations caused by movement variability (Dingwell and Cusumano, 2000). This sophisticated mathematical technique has thus provided a framework through which stability as it relates to variability can be directly investigated. Preliminary research in this area has produced several intriguing results,

and has suggested a dissociation between the two movement properties. This in turn suggests that local stability and variability should not necessarily be equated, as they may reflect fundamentally different aspects of the neuromuscular control strategies employed to produce the dynamic behavior of walking.

In order to discuss these issues in depth, however, knowledge of motor control theory as it relates to human walking is first needed. This review will therefore begin by providing a brief outline of concepts related to the neuromuscular strategies employed to generate and control normal walking patterns. With this knowledge in hand, the review will then discuss variability and stability as they pertain to walking. This discussion will be developed primarily from the perspective of dynamical systems theory, which provides a theoretical construct through which clear, distinct descriptions of each property can be made.

Together, these initial discussions will serve as a foundation for a subsequent exploration of the movement-related disorders associated with peripheral neuropathy (PN). This surprisingly prevalent neurological disease is characterized by peripheral nerve deterioration and related alterations in lower extremity somatosensory function (Boulton et al., 2004). Investigations of walking in this population have reported a severely elevated risk of both suffering falls (Oka et al., 2005), and injuries related to falls (Cavanagh et al., 1992). Interestingly, however, Dingwell et al (2000) demonstrated that despite exhibiting increased variability, the slower speeds with which PN patients walked effectively increased local stability. This and related research will therefore be explored as a necessary first step in better understanding the specific movement disturbances present within this population.

## CHAPTER 2

### THE CONTROL OF HUMAN WALKING

Walking is a unique and characteristic behavior produced by humans that allows for navigation through one's surrounding environment. While an extremely complex task requiring coordination of many joints, and even more muscles, the walking patterns of humans are surprisingly effective. In terms of energy consumption, humans are comparably efficient to quadrupedal animals, and far more efficient than bipedal walking in our primate relatives (Abitbol, 1988). This efficiency has been theorized to stem largely from a number of musculoskeletal adaptations that have taken place during evolution. For example, re-alignment of the pelvis, spine, and head has enabled weight-bearing and created optimal attachments for muscles. Similarly, modification of knee, ankle, and foot anatomy has promoted the required range of motion within lower extremity joints as well as the attenuation of forces arising from interaction with the ground (Nielsen, 2003)

Walking is also highly effective in terms of its cognitive planning. For many complex or continuous movements, humans must only consciously determine an overall goal, or intention, to activate the appropriate motor program required to accomplish the task (Georgopoulos et al., 1986). Humans thus need not "think" about controlling individual joint movements, nor the underlying patterns of muscle activation leading to these movements. For movements involving the entire body in weight-bearing situations, such as walking, this phenomenon is imperative as it would likely be impossible to direct the seemingly countless number of degrees of freedom required for successful walking (Bernstein, 1967).

Thus, despite the apparent ease with which (healthy) humans walk, this behavior presents a rather difficult underlying challenge to the neuromuscular system. In the most general sense,

the goal of walking is to propel the body forward while maintaining an upright position. Much of the challenge of walking has thus been suggested to arise from the fact that nearly two-thirds of the body's mass is located two-thirds of the body's height above the ground (Winter, 1995). As a result, the movement patterns of the extremities must be produced in such a way as to continually control the large inertial load of the upper body. Interestingly, Kavanagh et al (2005) demonstrated that oscillations of the head are smoother, and more tightly controlled (i.e., contain less average acceleration), than those of the lower trunk and especially, the lower extremities. These researchers have consequently concluded that the involved body movements of walking are together organized with the ultimate goal of moving the body while minimizing the motion of the head, presumably to regulate input to the visual and vestibular sensory systems.

The ability to limit the motion, and in particular accelerations, experienced by the head is impressive in lieu of the dynamic movements observed in the extremities. During normal, unimpeded conditions, the purpose of lower extremity movement in walking is to first propel the body forward. Thus, during each toe-off portion of the stance phase, the body's center of mass (COM) is projected forward and outside of the individual's base of support (BOS). These movements then function to "catch" the COM with each subsequent heel-strike. In this light, Winter (1983) succinctly described the COM/BOS relationship by stating that "only by safe placement of the swing foot do we avert a fall once every step."

Further complicating the task of walking is the fact that, in addition to generating precise muscle activation patterns and the related movements necessary to maintain an upright position while walking, the neuromuscular system must also do so with the flexibility required to adapt to ever changing environmental and task conditions. Certainly, individuals rarely walk in a straight line, at a constant speed, and over even ground. Instead, we must constantly navigate around

objects, change speeds, and walk over irregular surfaces. Further, the upper extremities must often neglect their normal, oscillating movements in order to interact with various objects in the environment. It is therefore evident that multiple intricate and complex control mechanisms are at hand that must function together to ultimately give rise to the phenomenal capacity of humans to walk.

While a vast amount of research has been conducted on human walking, it is nevertheless likely that relatively little is currently known regarding its neuromuscular control. To date, however, it is accepted that walking arises from the integrated function of several neuronal circuitries at different levels of the CNS (Nielsen, 2003). Further, these circuits are facilitated at multiple levels by somatosensory, vestibular, and visual sensory feedback (FB) containing information related to both the sensory consequences of produced movements, and their interaction with the surrounding environment (Buschges and Manira, 1998). Figure 2.1 provides a simplified schematic of these processes, illustrating the involvement of supraspinal, spinal, and peripheral control. As a lengthy discussion could be developed in regards to any one pathway under just one of many possible conditions, the purposes of this review will be satisfied by limiting the discussion to 1) the generation of the characteristic patterns observed in normal, unimpeded walking, and 2) the role of somatosensory information in the modification of these patterns in response to perturbations. The current understanding of each of these phenomena will be discussed specifically in terms of central versus peripheral control of human walking.

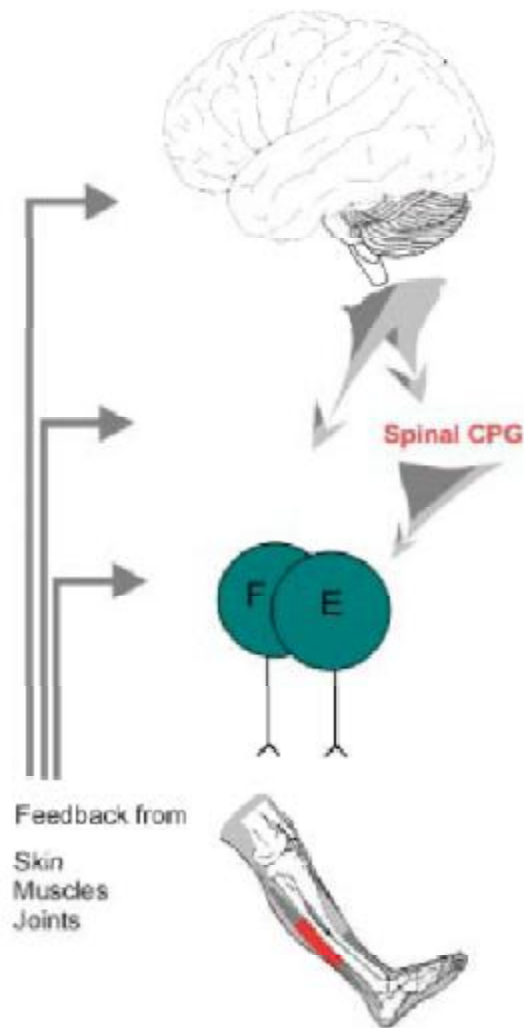


Figure 2.1: An overview of the control centers of human walking. Both supraspinal and spinal circuits are involved in the generation of muscle activation patterns, with multiple forms of sensory FB facilitating these circuits on multiple levels. From (Nielsen, 2003)

## 2.1. Central Control of Walking

The stepping movements of humans are believed to arise largely in response to muscle activation patterns produced by a combination of supraspinal and spinal output. With respect to the latter, much attention has been paid to the potential existence of “spinal” or “central pattern generators” (CPGs) located within the spinal cord. CPGs are defined as “neuronal circuits that produce coordinated motor patterns in the absence of sensory feedback and in response to brief

or tonic inputs (Enoka, 2002). A walking-related CPG would therefore produce the alternating, agonist/antagonist muscle activity patterns of lower extremity muscles, thereby minimizing the cognitive demands of the task. Our current knowledge of CPGs has primarily arisen from research on reduced animal models. In this research it has been repeatedly demonstrated that the isolated spinal cord of non-mammalian vertebrates (Grillner, 1981), as well as quadrupedal mammals such as rats and cats (Fedirchuk et al., 1998), is capable of producing spontaneous EMG bursts responsible for the generation of walking patterns in the complete absence of supraspinal control and peripheral feedback.

With respect to humans, the emergent kinematic, kinetic, and electromyographic activities of walking have been far more extensively studied than its underlying neural control (Capaday, 2002). Further, explicit proof of CPG involvement, as well as their exact location within the spinal cord, has not been produced to date. As a result, neural control theories related to CPG involvement in human walking have had to rely mainly on extrapolations from those simpler animal models. Certainly, however, the evolution of bipedal walking in humans has imposed different, and perhaps greater, demands on the system as compared to quadrupedal mammals that have likely been met by evolutionary changes to the spinal control of walking. Thus, while it is likely that human CPGs do exist and have retained some or many of the characteristics found in other animals, it is not a foregone conclusion. Caution must therefore be exercised when discussing the role of CPGs in human walking (Capaday, 2002).

Despite these limitations, continually mounting evidence exists that supports at least a contributing role of CPGs in the control of human walking. The majority of this evidence stems from one of two lines of research involving either 1) spinal cord injury (SCI) patients or 2) healthy infants and adults walking on split-belt treadmills. First, SCI patients have disrupted

neural pathways that limit or completely negate communication between the “higher” CNS (i.e., the brainstem and cortical areas) and the spinal cord. Despite this disruption, muscle activation patterns and even stepping movements have been reported in this population. For example, Brussel et al (1996) reported a case study in which alternating flexion-extension patterns of lower extremity muscle activity were elicited following excitation of the flexor reflexes. More recently, both Dietz et al (1998) and Dobkin et al (1995) reported that lower-extremity muscle activity patterns reflecting those of normal walking could be elicited in incomplete as well as complete SCI patients when a therapist passively generated stepping-like movements in the patient’s lower extremities (Dobkin et al., 1995).

Perhaps the most convincing research supporting the existence of CPG control in human walking, however, was recently conducted by Dimitrijevic and colleagues (1998) on patients with long-standing, complete SCI. Specifically, these researchers investigated the capacity of the lumbosacral spinal cord, with a trauma-induced separation from supraspinal control, to produce stepping movements in response to an externally generated, sustained electrical train of stimuli delivered via segmental input. First, this research determined that with patients in a supine position, application of a stimulus to the posterior structures of the L2 vertebra elicited “rhythmic, step-like EMG discharges with flexion/extension movements in the lower limbs.” Stimulation away from this site produced either tonic activity, or weaker rhythmic activity, with no corresponding locomotor (i.e., walking) movements. With the optimal site of application found, the researchers then demonstrated that tonic EMG activity was elicited in various lower limb muscles with stimuli of strength up to 4.5 V. With a 5 V stimulus, however, the tonic EMG activity was replaced with rhythmic muscle activity accompanied by flexion/extension movements in the lower limbs. This phenomenon was reliably elicited within the same session,

across different sessions, and in different subjects. These results led the researchers to conclude that there exists in the lumbosacral spinal cord a neuronal network mechanism that determines the “temporal pattern of rhythm generation and motor output shaping” that can be initiated and maintained by “non-patterned, segmental stimulation of a particular site, with specific strength and frequency.”

The second line of research on the spinal control of human walking has come about through the invention of the split-belt treadmill, and has provided intriguing insights into the general organization of CPGs. The split-belt treadmill consists of two belts laid side-by-side that are each controlled by a separate motor, giving each belt the capacity to run at the same speed (i.e., tied-belt), different speeds, or even in opposite directions. Considerable research has been conducted examining walking on this treadmill in a variety of animals (Forssberg et al., 1980; Foth and Bassler, 1985). With respect to humans, very recent research has produced the theory that two CPGs exist within the human spinal cord, often termed “coupled oscillators” (von Holst, 1973), with each controlling a respective lower extremity. To this end, Yang et al (2005) examined the stepping movements of infants aged 7-12 months while supported over the split-belt treadmill. In this case, infants were studied as the possibility of volitional control overriding true, CPG produced movements was deemed less likely in this population as compared to adults (Yang et al., 1998).

Yang and colleagues demonstrated that infants could step in a coordinated manner on the treadmill with the belts running at significantly different speeds, as well as in opposite directions. More specifically, when both belts were moving forward but with differing speeds, low speed differentials led to the adoption of step cycle durations intermediate between that observed during stepping during tied-belt conditions at each of the two belt speeds. This demonstrated that

the adaptation to split-belt walking was made cooperatively by both legs, with “the leg on the fast belt taking a slower step than it normally would at the speed under tied-belt conditions while the leg on the slow belt did the opposite.” When one leg was stopped (by placing a piece of cardboard under the foot and holding it stationary), the free foot immediately reverted back to its normal step cycle. Interesting, during conditions of high speed differentials, the infants neglected the “normal” walking pattern (i.e., right and left steps alternating in a one-to-one manner), and routinely took more steps with the limb on the fast belt. Further, when the belts moved in opposite directions, the infants were able to effectively produce forward stepping in one limb while backward stepping in the other. Importantly, however, despite the effective adaptation to these several situations, all lower-extremity muscle activity patterns and resulting movements maintained a fairly fixed, reciprocal relationship throughout the experiment. Collectively, these findings support the notion that the stepping patterns of each leg are produced by separate CPGs that possess both a degree of independence, and interdependence, in their functional role in human walking.

Therefore, while the specifics in terms of location, neural organization, and function are still largely unknown, it is now generally accepted that the human spinal cord does possess a rhythm-generating CPG network that is largely responsible for the production of the characteristic patterns of movement observed in human walking. Certainly, however, this does not rule out a contributory role of supraspinal centers in the production of walking. On the contrary, this level of control is critical to the behavior, and likely far more so in humans than in other, more widely researched bipeds and quadrupeds. For example, cats are capable of walking over flat ground following a complete lesion of the motor cortex (thereby negating any supraspinal control), and only during walking under more difficult conditions such as on a

horizontal ladder do they encounter difficulties (Drew et al., 1996). In contrast, the poor recovery from motor cortex and/or pyramidal tract lesions in humans, along with limited empirical evidence (Nathan, 1994) has led to the conclusion that an intact motor cortex is a critical prerequisite for even normal walking to occur.

The limited evidence existing in this area suggests there are at least two major pathways of supraspinal control employed during human walking. First, in the previously reported study by Dimitrijevic and colleagues it was demonstrated that a train of non-patterned electrical stimuli to the lumbosacral spinal cord effectively produced walking-related muscle activation and lower extremity movement patterns. Thus, the authors concluded that one role of supraspinal control may be to provide the input needed to activate the CPG that subsequently governs walking. Second, technological advances including single photon emission tomography (SPECT) and transcranial magnetic stimulation had allowed for detailed investigation of brain activity during dynamic movements such as walking. Together, this research (Christensen et al., 1999; Petersen et al., 1998; Schubert et al., 1997) has led to the conclusion that the motor cortex “makes a significant contribution to the activation of the muscles through direct monosynaptic projections to the spinal motoneurons even during locomotion on a treadmill or on a flat surface” (Nielsen, 2003).

## **2.2. Peripheral Control of Walking**

If a CPG responsible for human walking does in fact exist, which current research strongly suggests, it is apparent that it is much less robust than those of other mammals such as rats and cats. Unquestionably, considerably more work is required to elicit walking patterns in humans with central lesions as opposed to these other animals. As a result, in addition to the

need for supraspinal control, it is also believed that a relatively large amount of peripheral control is required for the successful production, and flexibility, of human walking.

At the foundation of this control are sensory receptors located throughout the body. These specialized receptors function to convert one form of energy, such as pressure, light, and sound, into electrochemical action potentials that are sent to the CNS with timely information regarding the system's state as well that of its surroundings (Umpherd, 1995). This type of information flow, from peripheral sensory receptors to the CNS, is referred to as sensory feedback (FB). There are two main types of receptors that produce sensory FB in humans. These include proprioceptors responsible for the detection of stimuli generated by the system itself, and exteroceptors responsible for the detection of external stimuli (Gandevia, 1996). While it is well established that sensory FB from both the proprioceptors located within the muscles and joints, and the exteroceptors located within the eyes, ears, and skin, contribute to the motor output that ultimately gives rise to walking patterns, the current review will primarily focus on those receptors located within the somatosensory system. Referring back to figure 2.1, the contributions of these receptors are thought to arise through both spinal and supraspinal connections, and include primarily the facilitation of "preprogrammed motoneuronal drive," as well as the modification of ongoing movement patterns (Nielsen and Sinkjaer, 2002).

First, there is convincing evidence that peripheral sensory FB is involved in "preprogrammed motoneuronal drive" and therefore crucial for the generation of "normal" muscle activity patterns that produce human walking under unperturbed, steady-state conditions. In other words, it is believed that less central input to the motoneurons, whether spinal or supraspinal, is needed if sensory FB is present than if it was absent (Nielsen and Sinkjaer, 2002). Available research on humans related to this fact has stemmed from earlier research in cats. For

example, sensory FB arising from hip muscle and joint receptors of spinalized cats was demonstrated to contribute to the relative timing of different phases of the gait cycle (Grillner, 1975). More recently, Pearson et al (1998) reported that the characteristic decrease in sensory FB arising from receptors in the lower extremity extensor muscles of spinalized cats, which is caused by the unloading of the ankle joint late in the stance phase, was responsible for the initiation of the swing phase of that limb. Much additional, related research in cats has led to the general acceptance that during normal, unimpeded walking, sensory FB is involved in (at least) sculpting observed movement patterns, regulating step frequency, and quite possibly controlling ipsilateral and contralateral limb coordination (Giuliani and Smith, 1987).

Considerably less is known regarding the contribution of sensory FB to motoneuron drive in humans. However, both Sinkjaer et al (2000) and Mazzaro et al (2005b) recently published elegant studies related to this possibility by investigating the muscle activity patterns of the lower extremity during treadmill walking. Before testing, however, a custom built mechanical device was attached to the participant's right ankle joint. This device did not impede normal walking patterns, and yet was capable of inducing controlled sagittal-plane movements about the joint. The researchers subsequently imposed low amplitude, slow plantarflexor and or dorsiflexor movements during the stance phase of the walking cycle. These movements forced either a loading or unloading of the plantarflexor muscles, which in turn caused an increase or decrease, respectively, in the amount of normal sensory FB arising from "load" receptors (i.e., muscle spindles) located within the soleus muscle. Interestingly, loading the ankle joint with small dorsiflexor movements of systematically increasing velocity (in steps of two degrees/sec) incrementally increased EMG activity recorded from the active ankle plantar flexors at a latency of 60ms. Conversely, unloading the ankle joint by inducing plantarflexion movements in a

similar fashion led to an incremental decrease in EMG activity. Further, to rule out the possibility of reflexive responses arising from the related stretching of the dorsiflexor muscles, the experimental procedure was repeated following anesthetization of these muscles (Sinkjaer et al., 2000). Even under these conditions, significant alterations in EMG activity persisted. Together, these results demonstrated that FB arising from the extensor muscles during the stance phase significantly contributes to “motoneuronal drive” during normal walking, much the same way as has been shown in the cat.

In addition to contributing to motoneuronal drive, peripheral sensory FB is also involved in the generation of corrective responses that serve to modify the ongoing cyclical pattern of lower extremity movement. To date, however, this research has been largely biased towards the ability of healthy adults to produce corrective movements in response to large-scale perturbations that produce finite alterations to the intended movements of walking. Thus, relatively little is known regarding special populations, or the control of corrective responses secondary to small-scale perturbations, such as those arising from stride-to-stride spatiotemporal variations in walking (which will be discussed thoroughly in chapter 3). Nevertheless, the primary findings of research involving large-scale perturbations is noteworthy as this type of perturbation mimics situations that humans commonly encounter during walking, such as when suffering a slip or trip.

Specifically, this research has demonstrated that the pathways through which corrective responses are generated following perturbation begin with peripheral sensory receptors (Dietz et al., 1987; Nielsen and Sinkjaer, 2002; Sinkjaer et al., 1996; Yang et al., 1991). These receptors, located within the visual, vestibular, and somatosensory systems, serve to signal the perturbation, or its resulting effects on the body, through abrupt changes in their afferent output. These signal

changes are therefore not anticipated by the CNS, but instead serve as “error” signals that are employed in well-defined reflex pathways, likely at both spinal (Christensen et al., 1999) and supraspinal levels (Duysens et al., 1990; Yang and Stein, 1990) that ultimately give rise to compensatory muscle activation. At the same time, the error signals also serve to notify higher centers of the brain about the perturbation, whereby non-reflex (i.e., volitional) adjustments may quickly follow after the initial reflex evoked activities (Umphred, 1995).

## CHAPTER 3

### VARIABILITY AND LOCAL STABILITY OF HUMAN WALKING

A vast amount of research exists regarding the variability and stability of human walking. This chapter will initially provide the relevant dynamical systems background information needed to properly discuss this research. Through this discussion, unambiguous and accurate definitions of both variability and stability will be provided, and the common misconceptions regarding each property will be resolved. Finally, the chapter will attempt to explore the origins and control of variability and local stability, keeping in mind the central and peripheral neuromuscular strategies employed to control walking as discussed in chapter 2.

#### 3.1. A Dynamical Systems View of Walking

A dynamical system is simply any process or collection of processes that change with respect to time (Hirsch et al., 2004). From a mathematical viewpoint a dynamical system can be more precisely defined as possessing two elements. The first element is a dynamic “rule” that governs how the system evolves in time. For known examples, this rule takes the form of one or more differential equations (Hirsch et al., 2004). The second element is a set of initial conditions from which the system starts. A classic physical example of a dynamical system is a single-segment, undamped pendulum (Figure 3.1). Ignoring air resistance, once set in motion this type of pendulum will continue its oscillatory behavior for all time. The specific laws controlling this motion, in terms of its position and velocity, are known. The values of these two “state variables” at any point in time therefore fully describe the system, and are together called the system’s “state.” The collection of all possible states of a system is referred to as its “phase

space,” or “state space.” Finally, the evolution of a system in phase-space, given by a string of successive states, is called a trajectory (Abarbanel, 1996).

To illustrate these concepts, the trajectory within phase-space of the single-segment pendulum is presented in Figure 3.1. This dynamic system can be graphically represented in two dimensions by plotting all possible combinations of its state variables (i.e., position along one axis and angular velocity along the other). From this illustration, it becomes apparent that a particular state in a system’s phase-space *completely* describes the system at that moment. Further, by knowing only the pendulum’s current state it is possible to determine all future states with accuracy. A major importance of dynamical systems theory, therefore, lies in the ability to precisely describe behavior, which in turn allows accurate prediction of future states given only the system’s initial conditions or current state.

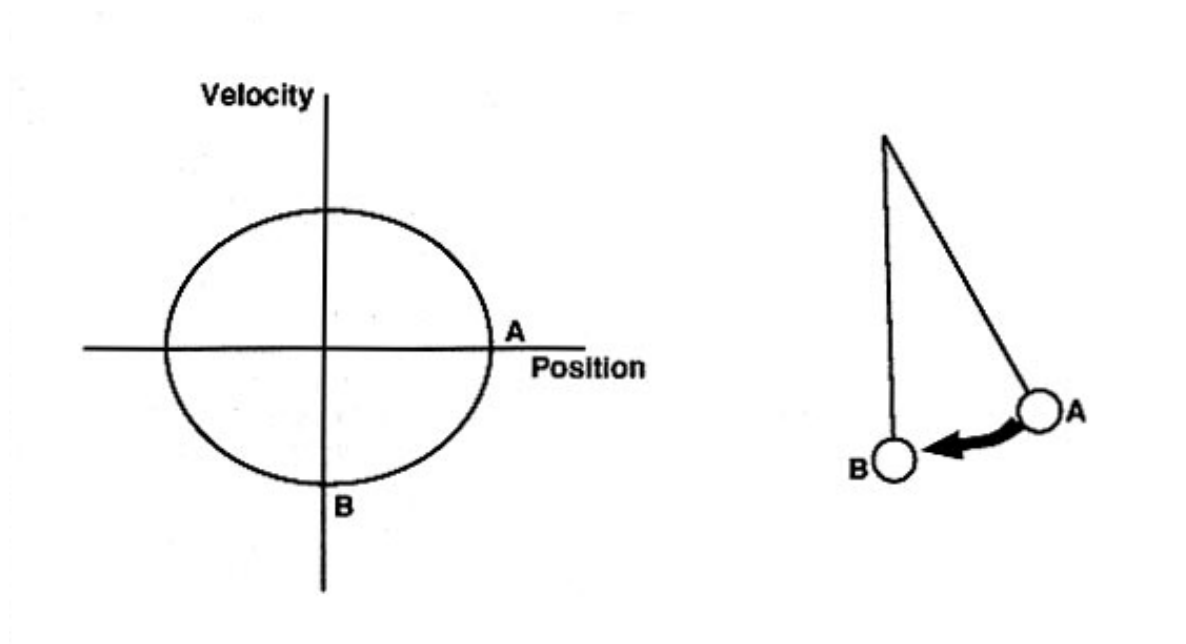


Figure 3.1. Illustration of the phase-space of a single segment, undamped pendulum. From: <http://www.airpower.maxwell.af.mil/airchronicles/apj/apj94/nichols.html>.

The capacity of humans to produce continuous movements permits the application of dynamical systems theory to human movement. In this context the human is viewed as a dynamical system, with walking as just one of the numerous behaviors it is capable of producing. Walking has therefore been specifically defined as the collective functioning of all controlling elements of the system, together with the produced movements that characterize the behavior (Full, 2002; Hamill et al., 1999; Li, 1999). Additionally, it is important to note that both environmental (i.e., walking surface, lighting, etc...) and task (i.e., walking at different velocities) constraints also contribute to shaping walking-related movements (Li, 1999). Thus, in contrast to the simple pendulum, the “controlling elements” that give rise to successful walking patterns are extremely *complex* as they must control and coordinate numerous muscles across multiple joints while at the same time allowing for adaptation to a seemingly countless number of ever-changing environmental and task demands.

This “complexity” of the human system is in fact a property of all biological systems (Abarbanel, 1996). By definition, complex dynamical systems are comprised of many controlling elements that are together coordinated to produce a single, collective behavior (Matthews et al., 1991). Unfortunately, for complex systems no a priori knowledge exists regarding the set of dynamic rules governing their behaviors (Hirsch et al., 2004). Further, even if these rules were by chance uncovered, they would likely not act in simple linear fashions, but instead follow intricate nonlinear laws for which solutions would be impossible to formulate (Abarbanel, 1996).

Together, these limitations make accurate predictions of the unfolding behavior of complex systems unattainable. However, it is still worthwhile to approach human walking from a dynamical systems point of view because it allows for accurate description of the involved

movements (Hamill et al., 1999; Li, 1999). This has been made possible in large part by technological advances that have enabled researchers to capture both kinematic and kinetic aspects of human walking at discrete time points in rapid succession. While the true behavior is continuous, investigating these isolated “pictures” as time progresses produces a close approximation of walking over some finite period of time. The experimentally-generated time-series data can therefore serve as an accurate representation of certain aspects of the involved movements. Application of dynamical systems theory then allows for the precise description of multiple temporospatial properties of walking. Variability and stability are two such properties that, when described in this light, have proven highly beneficial in advancing our understanding of human walking.

### *3.1.1. Phase-Space Reconstruction*

A necessary first step in investigating variability and stability of walking within the dynamical systems approach is determining the appropriate phase-space for the behavior. Abarbanel (1996) has stated that a proper phase-space allows the system to be fully described at any point, and therefore can be defined by an  $n$ -dimensional graph of the system’s  $n$  state variables. Thus, for the simple pendulum, a two-dimensional graph is needed as the behavior of the system can be uniquely described by two state variables (i.e., position and angular velocity). As previously stated, however, no a priori knowledge of the number of state variables exists for human walking. Further, the investigator has at his or her disposal only a 2- or 3-dimensional time-series of some measured signal, serving only as an approximation of the holistic behavior of the system. Together, these hurdles make representation of the *true* phase-space of human walking exceedingly difficult, and perhaps impossible.

However, multiple attempts have been made to *approximate* the phase-space of walking. The majority of traditional attempts have utilized acquired joint position data along with its time derivatives (i.e., velocity and acceleration) to serve as state variables of the system. This method therefore plots the original (angular) position data along one axis, and (angular) velocity along the second axis (Hamill et al., 1999; Li, 1999). Figure 3.2 provides an example of this method of phase-space reconstruction for a healthy individual's knee joint movement over a single stride of treadmill walking at preferred speed (Li et al., 1999). Certainly, a degree of structure is revealed in phase-space that is difficult to observe in the original time-series. Specifically, the periodic nature of the original time-series gives rise to a closed orbit in the reconstructed phase-space. One revolution of the system's trajectory around this orbit therefore represents one complete walking cycle (i.e., from right heel strike to right heel strike). Importantly, it is the subsequent analysis of time-series structure within phase-space that serves as the backbone of human movement research operating within dynamical systems theory.

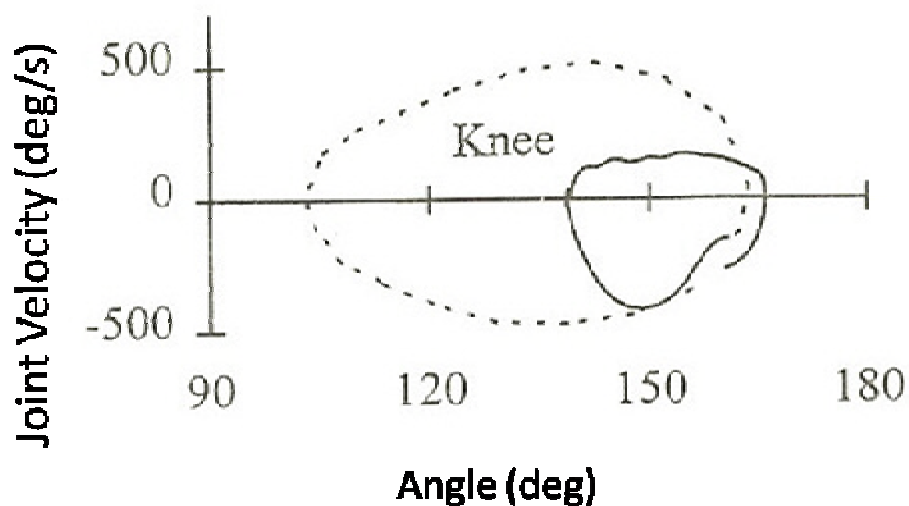


Figure 3.2. The time-derivative method of phase-space reconstruction from a time-series of knee joint position over a single stride of treadmill walking for a healthy individual. Stance phase is indicated by a solid line, whereas the swing phase is indicated by a dashed line. Adapted from Li et al., 1999

However, while the time derivative approach to phase-space reconstruction has been applied to walking (Buzzi et al., 2003; Diedrich and Warren, 1995; Hamill et al., 1999; Li et al., 2005; Li, 1999), several problems are associated with this practice. First, it is impossible to objectively determine the number of dimensions (in this case time-derivatives) that are sufficient to fully describe the dynamics of the system. For example, although a degree of structure is uncovered in the two-dimensional phase-space of knee joint kinematics of human walking (Figure 3.2), it is possible that the addition of a third dimension (i.e., angular acceleration) would reveal additional structure not seen when graphing only position versus velocity. To this end, it is therefore possible that the addition of a fourth dimension, or any n-dimensions, will further unfold the true structure of the original time-series.

This limitation, along with the recent development of non-linear techniques and improved computational power, has driven researchers to develop alternative methods of phase-space reconstruction for time-series data acquired from complex biological systems.. The most popular of these methods, termed the method of delays (Dingwell, 2006; Packard, 1980; Rosenstein et al., 1993; Takens, 1981), has proven robust for finite time series, and contains an mathematically proven, objective method for determining the appropriate dimension of a system's phase-space.

To understand this method, first recall that the number of state variables, which determines the number of phase-space dimensions, is unknown for biological systems. The method of delays therefore begins by choosing an “embedding dimension”,  $n$ , that serves as an approximation for the number of state variables in a system. The value of  $n$  is found by limiting the number of arbitrary points on the reconstructed attractor, which are created by the intersections of overlapping trajectories (recall that a true phase-space must allow for unambiguous description of a system at any point in time). The amount of overlap is minimized

through a Global False Nearest Neighbors (GFNN) analysis. Briefly, false nearest neighbors (FNN) are defined by points that are very close to each other in dimension  $n = k$ , but not in the dimension  $n = k + 1$  (Kennel, 1992). As demonstrated in figure 3.3, FNNs cause the appearance of an overlap in two-dimensions, when in reality (i.e., three-dimensions) the trajectory does not cross over itself. Within walking-related research, an embedding dimension of five has proven sufficient to significantly limit the number of FNN and allow accurate analysis of the time-series data (Rosenstein et al., 1993).<sup>1</sup>

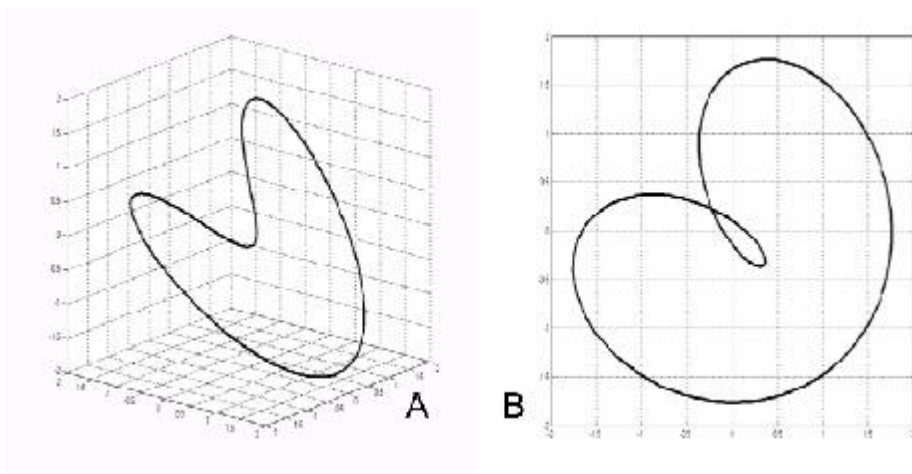


Figure 3.3: A plot of  $x(t) = \sin(2\pi t) + \cos(\pi t)$  with embedding dimensions of 2 (A) and 3 (B). From (England and Granata, 2006).

The method of delays is then employed to unfold the time-series into a five-dimensional phase-space (Packard, 1980). Specifically, the process reconstructs the original time-series into a matrix where each row is a time-vector of a single point and each column is an incrementally delayed version of that vector. The time-series (to be described below) is therefore represented by:

$$S(t) = [x(t), x(t + \tau), x(t + 2\tau), x(t + 3\tau), x(t + 4\tau)]$$

<sup>1</sup> It is of note that a phase-space of five dimensions is beyond the limits of visualization. Consequently, two- and three-dimensional phase-spaces will be used as examples.

where  $x(t)$  is the original time series and  $\tau$  is the time delay. The magnitude of  $\tau$  is chosen to maximize the information gain by the addition of subsequent copies of the original time-series (Abarbanel, 1996). While multiple methods of computing  $\tau$  have been used, the value of  $\tau$  most typically represents approximately 10% of the walking cycle. These concepts are illustrated in Figure 3.4, which consists of a schematic representation of three-dimensional phase-space reconstruction using this method.

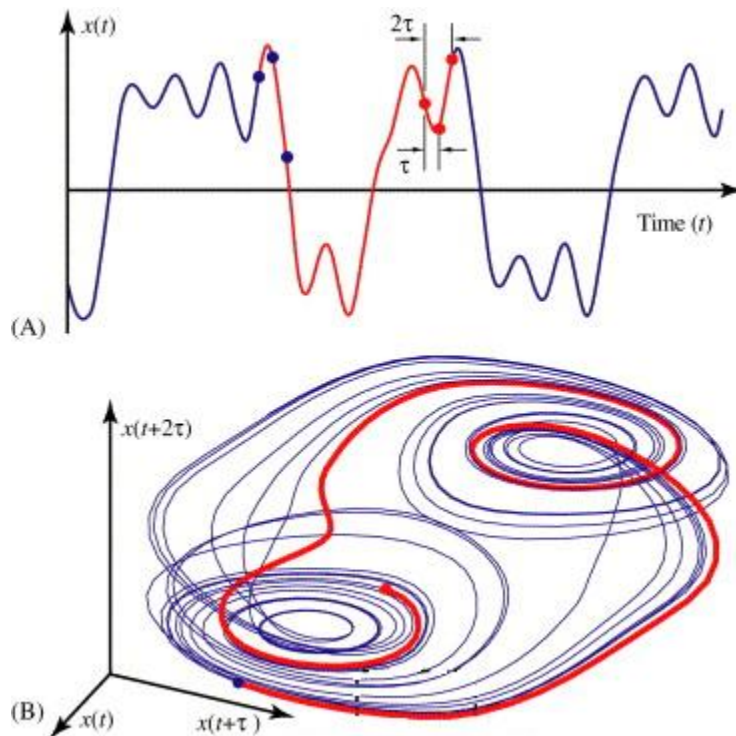


Figure 3.4: A schematic representation of phase-space reconstruction using the method of delays. (A) An arbitrary time-series,  $x(t)$ , plotted against time. (B) A three-dimensional reconstruction of  $x(t)$  such that  $S(t) = [x(t), x(t + \tau), x(t + 2\tau)]$ . Adapted from (Dingwell and Marin, 2006).

### 3.1.2. Attractors

Within phase-space, all biological systems are thought to possess one or more “steady” or “preferred” states. That is, if left unperturbed, the system evolving in time from some set of initial conditions will have a tendency to evolve towards its steady state. If slightly perturbed, the

system is spontaneously attracted back towards this state, or set of states. The behavioral steady states of dynamical systems are therefore known as attractors (Strogatz, 1998). An attractor can be precisely defined by a minimal, invariant set to which any neighboring trajectory will be drawn. An attractor is minimal in that it cannot be broken down into multiple “smaller” attractors, and invariant such that if unperturbed the behavior of the system (i.e., trajectory) will remain on, or close to, the attractor for all time (Strogatz, 1998). Further, the term “basin of attraction” is often used to describe the set(s) of all states in a system’s phase-space such that trajectories with initial conditions located within this set lead to evolution towards a particular attractor (Giesl and Wagner, 2006).

Attractors most commonly exist as mathematically defined set points, limit cycles, or strange attractors (Figure 3.5)<sup>2</sup>. The simplest are point attractors, which consist of a single, unique state to which the system is drawn over time. Limit cycles, on the other hand, do not consist of a single point, but instead are comprised of a series of points that together form a closed loop in phase-space (Strogatz, 1998). Finally, strange attractors are similar to limit cycles in that system behavior evolves in an apparently periodic fashion, but dissimilar in that the attractor never absolutely closes in on itself. This suggests that the behavior of the system never exactly repeats itself. Strange attractors are therefore unique from other attractors in that it is impossible to precisely determine where on the attractor the system will be at any one point in time (Abarbanel, 1996).

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<sup>2</sup> A (limit) torus, illustrated in figure 5, is a special type of limit cycle attractor. It will not be discussed in the present review as likely does not apply to human movement.

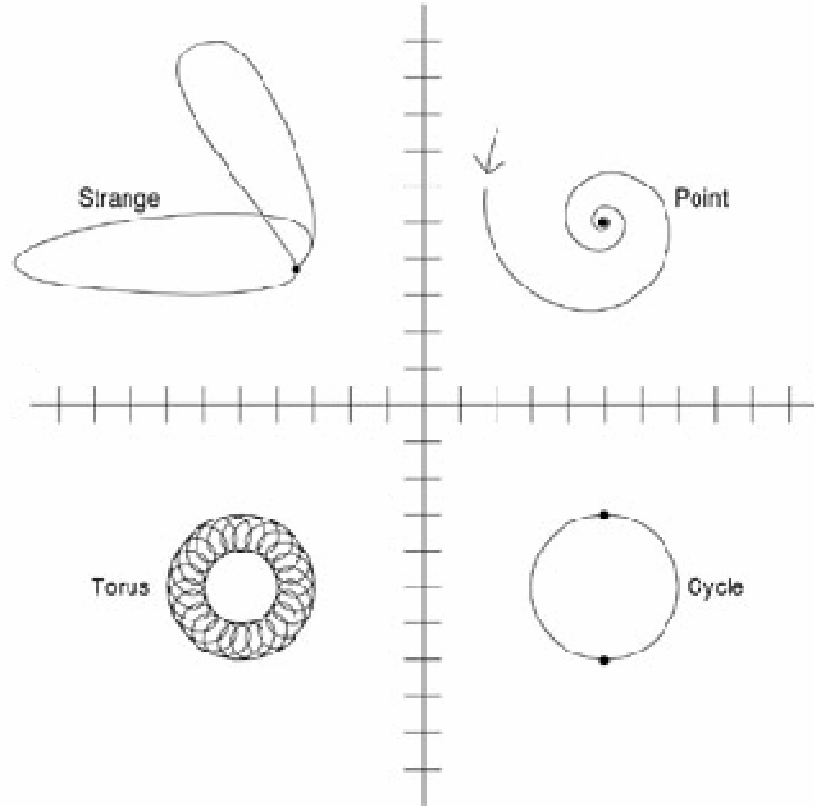


Figure 3.5: Typical attractors existing in phase-space of known dynamical systems. Adapted from: <http://www.chanceandchoice.com/ChanceandChoice/attractors.jpg>

With respect to human walking, attractors exist that may be comprised of one or more preferred states. However, the type of attractor that is unfolded is dependent upon the method used to analyze the acquired time-series. First, *despite representing a departure from the concept of phase-space*, kinematic parameters of walking are often viewed as possessing attractors from a statistical point of view. This is a common practice that is accomplished by simply determining the mean value of a particular behavior over some finite period of time. Logically, despite short-term fluctuations away from the mean, the system “tends” to operate about this value. For discrete variables such as stride duration, step width, etc., the behavior is attracted to a single

value, or point attractor. Graphic illustration of this method with respect to the walking is presented in figure 3.6A, which contains a graph of 30 consecutive stride durations during treadmill walking. While there exists stride-to-stride deviation from the mean, or “typical” stride represented by the dotted horizontal line, the behavior appears to be attracted to this point over time. Similarly, an analogous technique can be employed to analyze continuous variables such as joint angle. In this case, however, the behavior is not attracted to a singular point, but rather a *set* of “typical” points specific to each moment over the entire walking cycle. The use of this technique therefore models walking as being under the influence of a limit cycle attractor (Figure 3.6B).

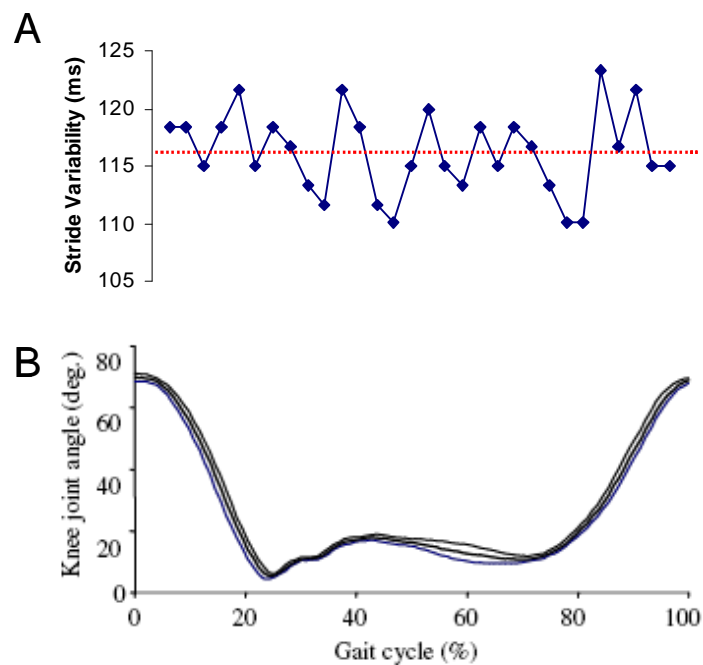


Figure 3.6: (A) A plot of 30 consecutive stride durations of treadmill walking (unpublished data).

Each individual stride duration deviates, but remains close to, a point attractor given by the average stride duration (red dotted line). (B) An ensemble curve of knee joint angle for several strides of treadmill walking, consisting of the mean (black line) and SD (blue lines) values across the entire gait cycle. Similar to (A), knee joint angle deviates, but remains close to the limit cycle (black line) Adapted from Li et al 2005.

The practice of modeling various walking-related variables as statistical point or limit cycle attractors is commonly employed (Hausdorff et al., 2001a; Hausdorff et al., 2004; Menz et al., 2003), easy to compute, and ultimately provides valuable information about the movement under investigation. However, the “typical” movement, formulated by averaging across multiple movements, should not be equated with the *true* attractor of the behavior as it is not computed from within an appropriate phase-space of the system. Thus, true attractors are only uncovered when using the previously mentioned phase-space reconstruction methods. Interestingly, the appropriate phase-space reconstruction of continuous kinematic walking variables reveals the existence of strange attractors (Abarbanel, 1996). For example, as previously illustrated in Figures 3.2 and 3.4, phase-space reconstruction, whether using the time-derivative method or the method of delays, reveals an irregularly shaped, *strange* attractor that never completely converges to one limit cycle over time. However, the trajectory does follow a fairly predictable path about a closed-loop, with only small deviations in each orbit.

### **3.2. Variability of Walking**

Human walking under steady state conditions will tend to operate about an attractor, again with the specific type being dependent upon the methods used to analyze the variable in question. Regardless of the type that is unfolded, however, the system will not operate unvaryingly about this attractor. Instead, it will continuously fluctuate as time evolves. These stride-to-stride, and within-stride fluctuations can be seen in Figures 3.4B and 3.6B, which used specific analyses to create a strange and point attractors, respectively. It is precisely these fluctuations that are described by the term variability. In this light, therefore, variability can be defined as *the average magnitude of deviation away from an attractor over a finite period of time.*

It has been argued that this intra-subject variability is an inherent property of all human movement (Newell, 1993). Certainly, the variability observed in the movement patterns of walking supports this statement. At the most general level, movement variability is believed to arise as a result of the enormous complexities, or “degrees of freedom,” of the human body that must be controlled for purposeful movement to emerge (Bernstein, 1967). Degrees of freedom exist across many levels of analysis and are both structural and functional in nature. Walking patterns, for example, can be produced through a seemingly infinite number of possible joint movement combinations. There also exists a countless number of muscle recruitment combinations that can potentially produce the torque underlying each possible joint movement. Indeed, this example can be continued across many levels of analysis, with an exponential increase in coordinative possibilities with the addition of each new level (Newell, 1993). Further, for walking to be successful, the seemingly limitless number of degrees of freedom must be precisely coordinated together in such a way as to allow successful interaction with the often changing environmental and task constraints (Gentile 2000). From this point of view, variability seems inevitable and accordingly, it is not surprising that variability has been a central issue in the study of human movement in general, and walking in particular. To date, the prevailing belief of walking variability is that it primarily arises subsequent to inconsistencies or variations in the *central control of motor output* (both spinal and supraspinal), which as stated in the previous chapter is largely responsible for the generation of the muscle activation patterns that give rise to characteristic walking-related movements in humans (Newell, 1993). Research into the nature of these variations, however, has produced two theories that operate under two distinct and opposing lines of thought.

### *3.2.1. Variability as Error*

The conventional belief of variability has been that it arises as an unavoidable consequence of random noise within the (central) planning and execution processes that give rise to volitional movement. Within this line of thought, therefore, one would argue that the intended output is purely deterministic (i.e., predictable) in origin, with variability arising as a result of stochastic (i.e., random) “noise” *superimposed* on top of the desired output (Newell, 1993). This suggests that, in the absence of noise, one should be able to produce repetitive or continuous movements with exact replication. Variability is therefore often viewed as unwanted or unfavorable “error” that alters the intended movement (Reynolds and Day, 2005).

While the driving force behind this theory has likely been its intuitive appeal, the traditional practice of employing descriptive statistics to quantify walking variability fits nicely within this construct. In this method, the statistical mean of a specific walking output variable, such as stride duration, is initially calculated. This mean therefore represents the “intended” output that would repeatedly occur within each stride in the absence of error. Then, whether examining discrete or continuous variables, measures such as the standard deviation (SD) or coefficient of variation (CV) are used to quantify the average magnitude of deviation (i.e., error) away from the truly intended output over all strides. This method therefore operates under the assumption that each stride occurs in complete isolation from all other strides. As a result, the average temporal or spatial variability over a specific time or number of strides appears to be randomly generated, as any possible structural trends within variability are effectively concealed.

Walking-related research utilizing these techniques has seemingly supported the idea that variability arises from error, or randomly-generated noise. Providing the majority of support for this notion is the often reported increase in variability in certain aged and or diseased populations (Corriveau et al., 2004; Herman et al., 2005; Menz et al., 2003), as well as in populations at

increased risk of suffering a fall (Hausdorff et al., 2001b). As previously mentioned, this relationship has also been the driving force behind practice of equating stability (as defined by avoiding falls) to variability. For instance, Herman et al (2005) investigated stride duration variability in healthy elderly adults as compared to elderly adults with “cautious gait,” as defined by mild to moderate reductions in speed, reduced stride length, and widening of the base of support (Nutt, 2001). Stride duration variability observed during two minutes of walking at preferred speed for a single, representative individual from each group is demonstrated in Figure 3.7. A qualitative increase in stride duration variability is clearly evidenced in the individual with cautious gait. Further, when group averages were determined, stride duration variability was nearly twice as large in the patient group ( $52 \pm 26$  ms) as compared to controls ( $27 \pm 9$  ms).

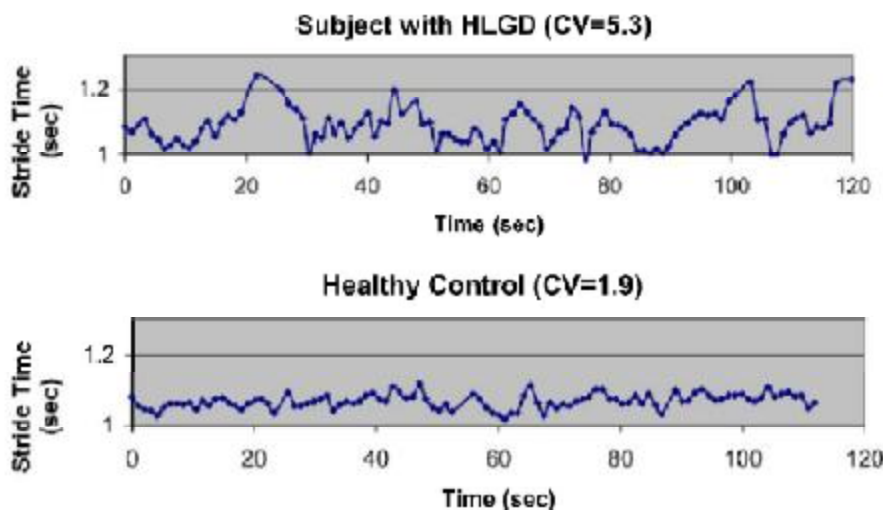


Fig. 3.7. Example of the stride time fluctuations in an older adult with “cautious” gait and a control subject. Note the increased variability in stride-to-stride duration in the patient compared to the control subject. From (Nutt, 2001)

Increased walking variability has also been associated with an increased risk of suffering falls. Hausdorff and colleagues have provided the majority of research regarding this association. For example, Hausdorff et al (2004; 1997) investigated the variability of stride duration, stance

and swing phase duration, and percent stance time during six minutes of walking at preferred speed in 53 community-dwelling elderly adults. The researchers subsequently kept track of falls over a one-year follow up period. Startlingly, nearly 40% of the participants experienced at least one fall within this time frame. Further, when data was averaged across these individuals, all measures of walking variability were elevated compared to those individuals who did not experience a fall. For example, stride duration variability was over two times greater for the group of fallers ( $106 \pm 30$  ms) compared to non-fallers ( $40 \pm 4$  ms), providing strong prospective evidence that walking variability is a significant predictor of falls.

Specific populations suffering from certain neurological disorders in which severe gait disturbances are reported, such as Parkinson's disease and Huntington's disease, also exhibit elevated variability when walking. Blin et al (1990) demonstrated that Parkinson patients present with significantly increased variability of multiple temporal and spatial gait cycle parameters compared with age-matched controls. Similar findings have been reported in those suffering from peripheral neuropathy (Dingwell et al., 2000; Dingwell et al., 1999) as well as Huntington's disease (Hausdorff et al., 2004). Further, more recent research has also established that when individuals with Huntington's disease are grouped according to fall status, stride time variability is over two times greater in "fallers" versus "non-fallers" (Schaafsma et al., 2003). Collectively, the evidence presented in this section certainly suggests that the walking patterns of healthy individuals are ordered and regular, with increased amounts of variability indicative of walking impairment. This in turn supports the notion that variability arises as unwanted error superimposed on top of the intended, or desired output of the system.

### *3.2.2. Variability as Part of the Dynamic*

The conception that variability reflects random error, however, has recently been challenged. This argument has primarily arisen from the application of dynamical systems theory to the description of human movement. In this light, variability is not viewed merely as a “superimposed” component of motor output that contributes only to the *quantitative* properties of the measured movement variable. Instead, variability is envisioned as a critical part of the inherent set of dynamic rules that govern system behavior (Newell, 1993). Thus, regardless of its source of origin, proponents of this view argue that variability should not be equated with error as it directly contributes to the *qualitative* aspects of the behavior.

A relatively large body of research exists in support of this theory. First, the belief that variability arises as an emergent property of the system is backed by the discovery of chaos in human movement. The term chaos simply refers to a particular type of dynamical system behavior. Specifically, Kelso and Ding (1993) provided a working definition of chaos as “mathematically predictable behavior when the initial conditions are known, but qualitatively appearing random.” Importantly, this definition proposes that the seemingly irregular and unpredictable nature of variability, such as that seen across all aspects of human walking, may not be a sole consequence of stochastically-generated (i.e., random) noise. Instead, at least a portion of the variable component may be “deterministic” in origin and therefore predictable over relatively short time periods (Abarbanel, 1996).

If variability is in fact deterministic in nature, it follows that it should possess a certain degree of structure over time. Hausdorff et al (1995) and Goldberger et al (1990) have in fact uncovered structure in walking variability by examining the long-range correlations of an individual’s stride duration variability. Through this research it was revealed that the stride-to-stride temporal variations in healthy walking, over thousands of strides, demonstrate chaotic,

fractal-like behavior. A fractal form, most commonly exemplified by complex geometric objects, displays “self-similar” organization such that the object is composed of sub-units, and sub-sub-units, etc..., with structure resembling that of the whole unit (Goldberger, 1996). The existence of this structure in walking variability therefore provides direct evidence that system variability does not arise from randomly-generated error superimposed on the “true” behavior of the system.

One of the most common methods used to examine the structure of walking variability is called “detrended fluctuation analysis (DFA) (Hausdorff et al., 1995). While not the focus of this review, this method computes a “fractal scaling factor,” given by  $\alpha$ , that reflects the degree of structure within a measured signal.<sup>3</sup> For a system in which the present state, given by the value of the current stride duration, is uncorrelated with any previous values,  $\alpha = 0.5$ , which demonstrates completely random noise. In contrast, if long-range correlations are present,  $\alpha$  will fall between 0.5 and 1.0, with higher values indicating an increased amount of structure in the signal.

Subsequent research using DFA has demonstrated that fractal scaling factor values ( $\alpha$ ) for healthy gait most commonly fall between 0.8 and 1.0. Further, values falling below this window have been reported to significantly distinguish between the healthy individuals and those with specific gait disturbances (Hausdorff et al., 2004; Hausdorff et al., 1997; Herman et al., 2005). For example, Herman et al (2005) reported that  $\alpha$  was significantly lower in a “cautious gait” group ( $0.75 \pm 0.18$ ) compared to a “healthy gait” group ( $0.88 \pm 0.22$ ). Further, in this study the amount of structure within the variable component of the signal also differentiated between past

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<sup>3</sup> Specifically, DFA is a modified random walk analysis that makes use of the fact that long range correlations in time series data can be uncovered by integrating the acquired signal over all possible observation window sizes,  $n$ . (the number of strides in the window of observation). The time series is determined to be self-similar (i.e., fractal-like) if the observation windows ( $F(n)$ ) scale as a power-law with respect to  $n$ . Typically,  $F(n)$  increases with  $n$ , and “a linear relationship on a double log graph indicates that  $F(n) \approx n^\alpha$ , where the scaling index,  $\alpha$ , is determined by calculating the slope of the line relating  $\log F(n)$  to  $\log n$ ”

“fallers” and “non-fallers” within the cautious gait group, with average scaling factors approaching 0.6 in those reporting a history of falls.

Again, the structural trends in walking variability provide support to the argument that variability cannot necessarily be equated with error. Therefore, whether or not variability is stochastically or deterministically generated (or some combination of the two), it likely serves some meaningful, operational purpose with respect to the spatio-temporal evolution of the movement in question. While difficult to empirically demonstrate, several potential functional roles of variability have been suggested. Briefly, these roles may include serving as “critical fluctuations” or “exploratory behavior” that provide the system with the flexibility needed to adapt to ever-changing constraints (Diedrich and Warren, 1995), and effectively reducing the amount of repetitive stress acting on certain parts of the body (James et al., 2000). However, to date only limited evidence exists for these possibilities in human walking. Nevertheless, the existence of structure in the variable component of human walking, together with these possibilities, is cause enough to exercise caution when discussing the nature of variability within this behavior.

### **3.3. Stability**

In general, stability can be defined by the time-dependent ability of a system to accommodate or respond to perturbation (Full, 2002). From a dynamical systems perspective, the behavior of a system under steady-state conditions will tend to operate about an attractor in its appropriate phase-space. In this light, stability can be more specifically defined as *the time-dependent ability of a system to return to its attractor following perturbation* (Full, 2002). Therefore, as opposed to variability, stability during walking is a reactive process that requires the employment of *peripheral control mechanisms*. As mentioned in section 2.3, sensory

receptors must therefore first detect the perturbation and relay sensory FB to the CNS regarding its characteristics as well as its effects on the system. This FB is then utilized by the CNS to produce corrective reactions that may be reflexive and or volitional in nature.

While seemingly straightforward, there are two important concepts of stability that warrant discussion. The first relates to the meaning of “perturbation.” A perturbation is any “force” that causes the trajectory of a system to deviate away from its attractor. In physical systems, perturbations most often take the form of finite or “large-scale,” externally-generated disturbances imposed on the system. With respect to behaviors arising from biological systems, in this case human walking, perturbations may similarly take the form of externally-generated disturbances such as those imposed from a slip, trip, or push. Further, they may also take the form of *internally*-generated disturbances. This type of perturbation occurs in response to intentional, or volitional, movements that significantly alter steady-state conditions, such as stepping over an obstacle in one’s path (Enoka, 2002).

Finally, although traditionally overlooked, perturbations may also arise from internally-generated, infinitesimally-small disturbances (Dingwell and Cusumano, 2000). As an example, the reader is again directed to figure 2, which provides an illustration of the two-dimensional attractor of knee joint movement during normal walking that was unfolded using the time-derivative method. As previously stated, this is an example of a strange attractor in that it is comprised fairly predictable, irregularly-shaped trajectories that never exactly repeat in time. Thus it is apparent that even during steady-state conditions, knee joint movement does not occur with exact repetition. Rather, the system’s trajectory appears to be constantly perturbed away from its attractor on a small-scale level. Importantly, these continuous, small-scale perturbations

are precisely those arising as a result of intra- and inter-stride variability (England and Granata, 2006).

With these distinctions in mind, stability can therefore be divided based on the relative size of the perturbation that the system must endure. In this light, the ability to respond to large scale perturbation has been termed “global stability.” Alternately, the sensitivity of a system to small-scale perturbations has been termed “local stability” (Dingwell and Cusumano, 2000). The former is by far the most commonly studied of the two types, whereas the latter is an innovative concept that has only recently been applied to human walking. While this review will primarily focus on local stability, both have proven beneficial in our understanding of the control of walking (Dingwell et al., 2001; England and Granata, 2006), as well as our appreciation of specific walking disturbances (Buzzi and Ulrich, 2004; Buzzi et al., 2003; Dingwell et al., 2000).

Before discussing each type, however, the other concept of stability in need of clarification is the idea that it is a “time-dependent” measure. Therefore, if two identical systems are disturbed away from their attractors by a similar perturbation, the system that returns to its attractor in the least amount of time is considered to possess a relatively greater amount of stability (Full, 2002). However, intuitive logic would suggest that the *magnitude* of deviation away from the attractor is similarly important. This may well be the case in walking, especially when considering large-scale perturbations. Certainly, a perturbation causing a deviation greater than some intrinsically-defined threshold would cause the trajectory of a system to pass outside the attractor’s basin of attraction, and ultimately cause the individual to fall. Nevertheless, based on the aforementioned definition, the magnitude of deviation away from the attractor following a perturbation is not *directly* related to stability by definition.

### 3.3.1. Global Stability

Global stability can be defined as the time-dependent responsiveness of a system to *large-scale* perturbations (Dingwell and Cusumano, 2000). As previously mentioned, large-scale perturbations are finite and may come in the form of externally-generated forces (i.e., a slip or trip) and or internally-generated forces (i.e., volitional movement).<sup>4</sup> Regardless of the type, however, these perturbations present a disturbance that must be corrected in a timely manner in order to prevent a fall. This direct relationship to falls has resulted in a large amount of research conducted in this area. While not the focus of this review, the majority of these attempts have created experimental environments in which external perturbations are imposed on the individual, thereby attempting to mimic those unexpected perturbations that may occur during normal daily activities.

Within this construct, individuals are most commonly exposed to mechanical perturbations, such as those produced from moving support surfaces (Oddsson et al., 2004) or even direct impact of some external object (Grabiner et al., 1993). While this research has increased our knowledge of walking, it has been limited by at least two issues. First, the most frequently analyzed variable is the magnitude of deviation from the intended movement following the perturbation. As suggested above, this research therefore neglects the time-dependence of the response, which is a critical component of stability. Second, exposure to large-scale perturbations while walking is potentially hazardous, and often contraindicated in elderly and diseased populations. Available research is therefore biased towards healthy, young adults.

Recently, however, Li et al (2005) directly examined global stability during treadmill

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<sup>4</sup> If the perturbation is expected, specific neuromuscular strategies are employed *prior* to the disturbance. These “anticipatory postural adjustments” are consistently observed and are characterized by coordinated patterns of postural muscle activation that occur just prior to voluntary limb movement. While not the focus of this review, APAs serve to offset the upcoming, potentially destabilizing shifts in the body’s COM (Xu et al, 2004)

walking, as well as its relationship to kinematic variability. In this study, participants walked on a treadmill at six different speeds. Before testing, participants were instructed to maintain a constant distance relative to a poster hung roughly 50 cm in front their visual field. During each trial, a randomly-induced, visual perturbation was imposed by moving the poster approximately 50 cm towards the participant. This procedure thus created a large-scale perturbation as the participant voluntarily moved backward relative to the treadmill. Participants then tried to recover their “normal” walking pattern as quickly as possible following the perturbation.

To examine global stability and variability, an ensemble curve was first created by determining the mean joint angle and SD over five strides of steady-state walking, each normalized to 100 points. Variability of knee joint angle was then found by determining the average SD across these five strides. Global stability was subsequently calculated by determining the cross-correlation coefficients between steady state walking and all possible windows of similar size (i.e., five strides). This coefficient value thus decreased at the onset of perturbation, and subsequently increased as the participant recovered their normal walking pattern. The “recovery time” following perturbation therefore provided a direct measure of the *time-dependent* response to large-scale perturbation. Average recovery time across all speeds was  $1.20 \pm 0.6$  s, and interestingly, remained unchanged across all walking speeds. Variability, on the other hand, decreased as walking speed increased. Further, very low correlations were observed (from -0.193 to 0.230) between global stability and variability for all participants tested. These results therefore suggest little association between variability and global stability when correctly defining global stability as the time to recover from large-scale perturbations.

### 3.3.2. Local Stability

As previously mentioned, during unimpeded walking the cyclical movements of the trunk and lower extremities do not unerringly repeat in time. This inter-stride variability gives rise to the characteristic strange attractors to which the system is bound in its appropriate phase-space (Abarbanel, 1996). The fluctuation from orbit to orbit in phase-space can be viewed as occurring in response to small-scale or “infinitesimal” perturbations. Local stability is thus a measure of the time-dependent sensitivity of a system to these perturbations. Figure 3.8 provides a schematic of this concept in an attractor created from an artificially-produced, cyclical time series using the method of delays. The distance between a pair of nearest neighbors (3.8B), as given by points on neighboring trajectories that are initially close together, tends to increase as time evolves.

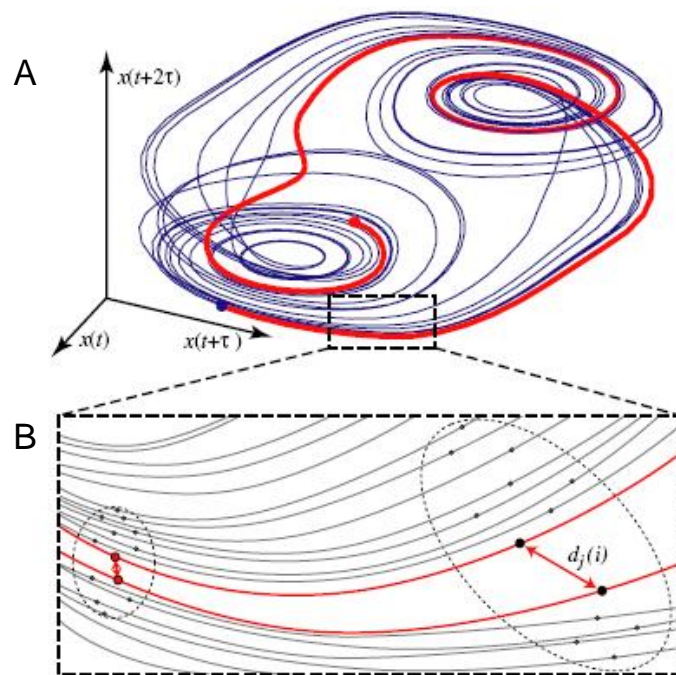


Figure 3.8: A representation of small-scale perturbations leading to divergence of nearest neighbors. Recreated from (Dingwell and Marin, 2006)

More specifically, therefore, local stability is a measurement of the average exponential rate of divergence of all possible pairs of nearest neighbors as the system is tracked forward in time (Dingwell, 2006). This average rate of divergence is quantified by Lyapunov exponents ( $\lambda$ )

(Rosenstein et al., 1993). Mathematically, one  $\lambda$  exists for every dimension of the phase-space within which the reconstructed attractor lies. Positive  $\lambda$ 's suggest that the trajectories are expanding, whereas negative  $\lambda$ 's suggest that the trajectories are converging. Thus, an n-dimensional sphere of initially close trajectories will evolve over time into an ellipsoid with principal axes that expand or contract at rates determined by each respective  $\lambda$ .

In order for an attractor to exist, the full Lyapunov spectrum of the system must sum to a value less than or equal to zero (i.e., globally converging) (Rosenstein et al., 1993). However, for biologically complex systems, determination of the Lyapunov spectrum is impossible as no a priori knowledge of the equations governing its motion exists. However, Rosenstein et al (1993) realized that *locally*, the average rate of divergence of initially nearby trajectories will be dominated by the largest exponent,  $\lambda_{\max}$ , due to the exponential growth in that direction. Further, these researchers utilized the method of delays to reconstruct time-series data and subsequently demonstrated that  $\lambda_{\max}$  can be estimated empirically by the formula:

$$y(i) = \Delta_t^{-1} \langle \ln d_{j(i)} \rangle$$

where  $\Delta_t$  is the sampling frequency,  $\langle \rangle$  denotes the average of the contents, and  $d_{j(i)}$  is the distance between the  $j^{\text{th}}$  pair of nearest neighbors at time  $i$ . This process thus produces a curve demonstrating the average logarithmic divergence of all pairs of nearest neighbors at  $t = 0$  and at each subsequent time step thereafter. An example of a typical curve is illustrated in Figure 3.9. In this case the time axis has been normalized to the average stride time and presented as the number of strides.  $\lambda_{\max}$  is then ultimately calculated by determining the slope of this average logarithmic divergence curve. A curve with relatively greater slope indicates a higher rate of divergence, or in other words, an increased sensitivity to small-scale perturbations (often referred to as increased local instability, or decreased local stability). It is of note, however, that there is

no standard “linear scaling region” from which this slope is calculated, and caution must therefore be taken when attempting to compare results between studies. However,  $\lambda_{\max}$  has been most commonly computed over a “short-term” region ( $\lambda_S$ ) and a “long-term” region ( $\lambda_L$ ), from 0 to 1 strides and from 4 to 10 strides, respectively (Dingwell et al., 2000).

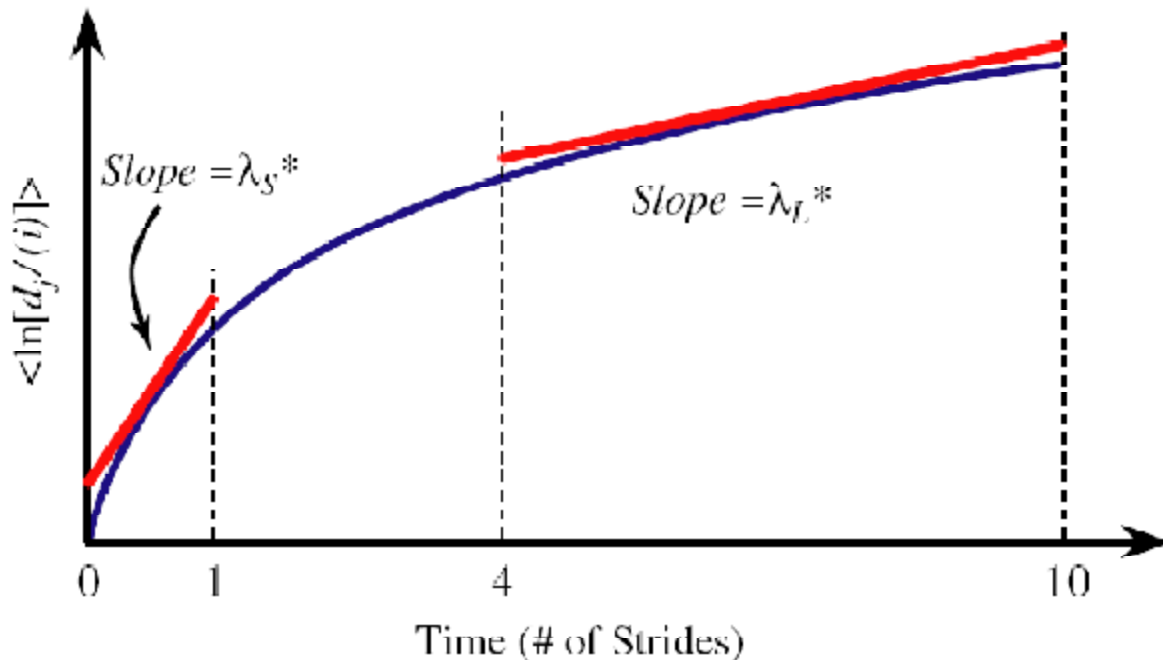


Figure 3.9: A representation of the typical average logarithmic divergence of all pairs of nearest neighbors over time, which has been normalized to stride time.  $\lambda_S$  and  $\lambda_L$  are calculated as the slope of the best fit line of their respective linear scaling regions (Dingwell and Marin, 2006).

At this point it is important to re-emphasize that  $\lambda_{\max}$  is a measure of the *sensitivity* of the system to infinitesimal perturbations. Thus, while intuitively related to stability, it should not be viewed as a pure measure of stability as physically defined by the time-dependent *response* to perturbations. Further, to date little is known regarding its underlying physiological meaning, such as the potential benefits of having higher local stability, or its relationship to global

stability. Nevertheless, while these issues present a challenge to future research, promising evidence exists that suggests local stability is a meaningful property of human walking and thus worthy of further investigation.

The first line of evidence arises from comparisons of  $\lambda_{\max}$  calculated from time-series of human walking and those of known equations of motion. For instance, graphing  $f(x) = \sin(x)$  on the xy-coordinate plane produces completely periodic oscillations. The periodicity of this function subsequently gives rise to a closed-loop orbit in reconstructed phase-space, on which the trajectory of the system unerringly travels. There is thus no divergence between trajectories on neighboring orbits as time evolves, which results in a  $\lambda_{\max} = 0$  (i.e., a completely horizontal logarithmic divergence curve). A completely randomized time-series, on the other hand, such as those produced by surrogation methods (Rosenstein et al., 1993), produces rapidly diverging trajectories in phase-space.  $\lambda_{\max}$  values for these time-series approach 0.50.  $\lambda_{\max}$  can therefore be thought of as a continuum between complete periodicity and complete randomness (Stergiou et al., 2004). Kinematic time-series of human walking should therefore, and do in fact produce  $\lambda_{\max}$  values between, and significantly different from, these two extremes (Rosenstein et al., 1993).

The other line of evidence supporting the meaningfulness of this measure has stemmed from preliminary research examining the local stability of walking under different conditions and within different populations. First, local stability has been demonstrated to be inversely correlated with walking speed. Dingwell and Marin (Dingwell and Marin, 2006) recently investigated healthy adults while walking on a treadmill across a range of speeds representing 60, 80, 100, 120, and 140% of their preferred walking speed (PWS). Trunk accelerations were recorded for three minutes using three-dimensional infrared motion analysis, and  $\lambda_S$  and  $\lambda_L$  were computed for trunk movement in the sagittal, frontal, and transverse planes. For all measures,

with the exception of  $\lambda_L$  in the sagittal plane, highly significant differences were demonstrated in local stability across walking speed. Specifically, decreased speeds consistently elicited lower values of  $\lambda_S$  and  $\lambda_L$  (i.e., increased local stability). Similar results have more recently been reported by England and Granata (2006). In this study, however, the researchers accounted for the potential influence of differing numbers of data points sampled within each stride, as a consequence of walking at different speeds, by re-sampling all time-series to the same total number of points. Despite this manipulation, however, results consistently demonstrated an increase in local stability with a decrease in walking speed.

Local stability during walking has also been reported to be affected by aging and disease. With respect to aging, Buzzi et al (2003) investigated the walking patterns of 10 younger (20-37) and 10 older (71-79) adults free of major illness during 30 consecutive strides of walking on a treadmill at preferred speed. Hip, knee, and ankle joint positions were acquired using two-dimensional videography. The specifics of the computational procedures used to compute local stability, as well as potential differences in preferred walking speed were not given. However, the older group demonstrated decreased local stability of hip, knee, and ankle displacements, as well as knee angle, by an average of 22%, 12%, 20%, and 44%, respectively, as compared to younger counterparts.

Similar findings have been reported with respect to diseased populations. For instance, Buzzi et al (2004) reported that individuals with Down syndrome exhibit significantly reduced hip, knee, and ankle local stability as compared to their age-matched counterparts. Further, while the previously mentioned inverse correlation between stability and walking speed was again confirmed, the Down syndrome group exhibited significantly greater changes in the magnitude

of  $\lambda_{\max}$  as the treadmill speed was systematically increased from 40% to 100%, and finally to 110%, of PWS.

The findings of reduced local stability in impaired populations, however, do not universally hold. To this end, Dingwell and colleagues (Dingwell and Cusumano, 2000; Dingwell et al., 2000) have published seemingly counter-intuitive reports with respect to local stability of walking in those suffering from peripheral neuropathy (PN). This prevalent neurological disease (discussed in chapter 4) is characterized by peripheral nerve deterioration and a related reduction in lower extremity somatosensory functioning. These alterations are in turn believed to be related to reductions in mobility, as well as an increased risk of suffering an injury while walking. Interestingly, however, it was demonstrated that despite these disturbances PN patients walked with significantly increased  $\lambda_{\max}$  (i.e., greater local stability) at PWS than did age-matched controls. In an attempt to explain this finding, the researchers utilized a path analysis (Hair, 1998), which confirmed their hypothesis that PN patients slow their walking speed specifically to maintain, and even increase, local dynamic stability. Certainly, this conclusion has since been supported by the previously outlined, inverse-relationship between local stability and walking speed.

Collectively, this research has provided preliminary evidence that local stability is a physiologically meaningful property of walking. However, as previously suggested, little is currently known regarding the structural and or physiological mechanisms underlying its control. For instance, Buzzi et al (2004) attributed the decreased local stability with increasing age to a “decrease in motor control.” They further stated that “deficiencies in the ability to actively control joint motion may manifest itself in increased noise and more local instability at these given joints.” Similarly, the findings of reduced local stability in Down syndrome (Buzzi and

Ulrich, 2004) were credited, albeit ambiguously, to “structural and neuromuscular alterations as a result of the impairment.” Certainly, therefore, future research designed to directly investigate the neural, muscular, and structural mechanisms that control local stability within multiple populations is warranted.

### *3.3.3. The Relationship between Variability and Local Stability*

Again, variability quantifies the average magnitude of variation in specific walking variables away from their attractor, whereas local stability quantifies the time-dependent sensitivity of the system to the small-scale perturbations that arise from movement variability. Thus, the development of local stability analysis has provided a means through which variability and stability can be investigated in a new light. Research in this area has provided several intriguing results. First, upon examination of the divergence curve featured in Figure 10 (which, while a reproduced graphic resembles those produced by actual data), it is apparent that the slope of the curve remains positive for at least 10 strides. If the small-scale perturbations leading to divergence of neighboring trajectories were in fact isolated to a single stride, the curves would have saturated, or leveled off (Dingwell et al., 2001). This characteristic therefore demonstrates that these perturbations endured during normal walking continue to affect kinematic trajectories for at least this many strides. This in turn suggests that kinematic variability, which produces a quantification of the average magnitude of variations across strides, is insufficient to characterize the property of local stability.

To this end, multiple researchers have reported a dissociation between local stability and variability of walking. First, it is generally accepted that walking at speeds either fast or slower than one’s PWS will result in increased variability of nearly all kinematic walking variables (Li et al., 2005; Oberg et al., 1993; Winter, 1983). Conversely, local stability is inversely correlated

to walking speed. Dingwell and Marin (Dingwell and Marin, 2006) clearly demonstrated the relationship between these two dynamic properties in healthy young adults (Figure 3.10). During treadmill walking at different speeds, highly significant quadratic trends were observed for multiple measures of kinematic variability, with the least amount of variability occurring in trials at PWS.  $\lambda_S$  and  $\lambda_L$  values (only  $\lambda_S$  values are shown), on the other hand, were consistently lower with decreasing speed, indicating increased local stability during these conditions. Dingwell and colleagues (2000) produced similar results in their investigations of PN patients. Specifically, these patients walked slower than their age-matched counterparts and with significantly greater kinematic variability. However, they concurrently exhibited significantly greater local stability of multiple measures of both upper and lower body movements.

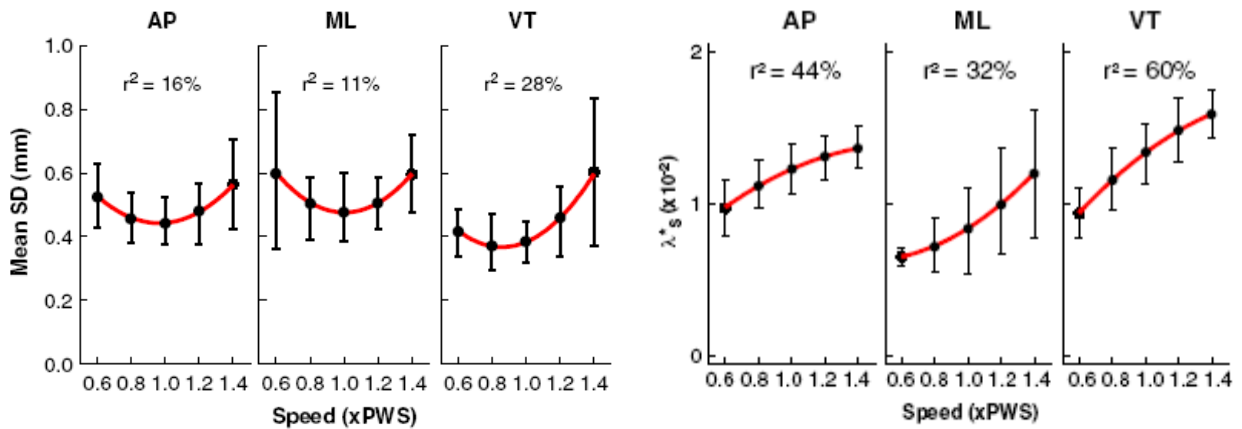


Figure 3.10: Graphic depictions of variability and  $\lambda_S$  in the three cardinal planes across a range of treadmill speeds.

From this research it is evident that statistical measures of variability do not alone sufficiently account for the entire spatiotemporal structure of walking patterns. Thus, whether variability arises from error or as part of the dynamics governing system behavior, it should not automatically be equated with either global or local stability of human walking. Further, and of

importance to this review, the evident dissociation between variability and local stability suggests that these two seemingly related properties in fact reflect fundamentally different aspects of the neuromuscular control strategies employed to produce human walking. This independence is not entirely surprising, however, if one accepts the previously stated notions that variability arises largely as a consequence of variations in centrally-generated motor output, whereas stability is largely dependent upon peripheral mechanisms involved in the detection of perturbations. As a result of these differences, future research on the variability and local stability of walking may potentially provide additional insights into the underlying mechanisms involved in the control of human walking, as well as the specific walking disturbances commonly seen in diseased populations.

## CHAPTER 4

### VARIABILITY AND LOCAL STABILITY IN PERIPHERAL NEUROPATHY

Peripheral neuropathy is a general term for the family of severely debilitating, progressive diseases that target the peripheral nervous system (PNS) (Boulton et al., 2004). Obviously, the PNS is responsible for a multitude of highly specialized sensory, motor, and autonomic functions. As a result, more than 100 types of peripheral neuropathy have been identified (Boulton, 1998) giving rise to a wide array of signs, symptoms, and complications. By far the most common form of peripheral neuropathy, however, is termed “chronic diffuse polyneuropathy” (PN), which primarily targets the peripheral sensory system. Clinical examination of individuals suffering from PN habitually reveals symmetrical sensory nerve damage originating in the plantar aspects of both feet. Over time this nerve deterioration may progress proximally to include the entire foot, ankle, lower leg, and in some cases, the upper extremities (Boulton et al., 2004).

The prevalence of all-cause PN is staggering. The Neuropathy Association (2003) has stated that over 20 million U.S. citizens suffer from the disease, outnumbering the incidence of more well-known diseases including diabetes mellitus (17-18 million), coronary heart disease (13.2 million), and asthma (15 million) (Thrall, 2005). When broken down into population segments, it becomes apparent that PN risk increases with advancing age. For example, Martyn and Hughes (1997) estimated the prevalence of all-cause PN to be 2.4% in the entire adult population, whereas over 8-10% in the population segment over the age of 55. Unfortunately, the incidence of this disease across all populations segments is expected to rise, especially as the prevalence of its most frequent cause, Diabetic Mellitus (DM), is increasing at an alarming rate

(Harris et al., 1997). Despite its prevalence, PN has received little public attention to date and related research is severely deficient as compared to other major chronic diseases. This may be principally due to the fact that PN is often over-looked as a treatable or perhaps preventable disease (Boulton et al., 2004). As an unfortunate result, current healthcare practice is palliative, treating only the symptoms of the disease. As this form of treatment is long-term, it is extremely resource intensive and U.S. healthcare expenditure related to all-cause PN was estimated to be over 43 billion dollars in 2003 (The Neuropathy Association, 2003; Gordios et al., 2004).

In addition to its economic cost, the host of unique symptoms and complications elicited by PN are extremely costly in terms of the individual's physical and psychological well-being. For example, as compared to age-matched controls, PN patients exhibit significantly reduced mobility (Richardson, 2002), independence, and ultimately, quality of life (Resnick et al., 2002). Additionally, associated movement disturbances greatly increase the risk of suffering falls in this population (Cavanagh et al., 1992; Richardson, 2002). To this end, however, while the link between PN and falls is well established, the underlying mechanisms responsible for these falls remain poorly understood. This fact, together with reports that the majority of falls occur while walking (Donoghue et al., 2003), has recently driven researchers to begin examining the effects of PN on this behavior. Within this research, results related to both the variability and local stability of walking have provided intriguing preliminary insights that have increased our knowledge of the walking-related complications of PN.

#### **4.1. A Brief Overview of PN**

Nearly 85% of all diagnosed cases of PN target the somatosensory system in a diffuse and symmetrical fashion. These cases are categorized as “chronic diffuse polyneuropathy” (Padua et al., 2005), or similarly, “chronic symmetrical polyneuropathy,” “chronic sensorimotor

neuropathy,” “distal symmetrical sensory polyneuropathy”, and “painful symmetrical polyneuropathy.” To avoid confusion the abbreviation PN will refer to this type of peripheral neuropathy. The remaining, less common forms of peripheral neuropathy may be focal or multifocal in nature, and may additionally or separately affect the peripheral nerves related to the motor and or autonomic systems.

While the general medical definition of PN is straightforward, diagnosis of the disease is complicated for several reasons. First, guidelines remain poorly defined, and criteria for what constitutes PN are highly variable throughout the healthcare and research industries. In fact, diagnostic guidelines frequently differ both from physician to physician in clinical settings, as well as from study to study in research settings (Boulton et al., 2004). Second, patients often have difficulty reporting their symptoms, which are plentiful and diverse both within and between patients. Finally, similar peripheral neurological deficits are commonly found during examination of older patients. In fact, common deteriorations detected from PN diagnostic techniques are often listed in geriatric textbooks as normal findings in very old people (Jordan, 1999). Unfortunately, while these age-related changes in the structure and function of the PNS usually relatively minor, inconsistent diagnostic guidelines frequently lead to both mis- and undiagnosed cases (Mold et al., 2004).

Nevertheless, of those cases that are diagnosed, the majority are acquired secondary to pre-existing illness. The most common of these “co-morbidities” include systemic disease, infections, and or autoimmune disorders (Boulton et al., 2004). As taken from Mold et al (2004), specific causes of PN include “diabetes mellitus, alcoholism, nutritional deficiencies (e.g., thiamine, B12), infections (e.g. HIV, Lyme disease), malignancies (e.g., bronchogenic carcinoma, renal cell carcinoma, lymphoma, multiple myeloma), trauma from external agents or

injury, and autoimmune diseases (e.g., systemic lupus erythematosus, Sjogren’s syndrome, Rheumatoid arthritis).”

Of the above listed causes, PN most frequently occurs as a co-morbid condition associated with both type I and type II DM. In fact, “diabetic peripheral neuropathy” (DPN) constitutes 27% of all diagnosed cases (Mold et al., 2004). More specifically, Harris et al (1993) reported that 30% of type I diabetics, and 36% of type II diabetics, develop DPN. Despite these high rates, however, they likely underestimate actual incidence rates as many cases of DPN are asymptomatic and likely go undiagnosed (Nicolucci et al., 1996). With respect to type II DM, Carter (2005) reported an age-related increase in DPN, as over 50% of individuals over the age of 60 contract this co-morbid condition. Further, evidence also exists linking early markers of type II diabetes, such as impaired glucose tolerance and/or abnormal fasting glucose levels, to an increased risk of developing DPN (Smith et al., 2001). As a result of these correlations, the vast amount of available research related to PN has been conducted on this form of the disease.

The second largest sub-group of PN cases are those of indeterminant cause and are often termed “idiopathic.” In fact, Mold et al (2004) reported that among older adults referred for subspecialty evaluation, a specific cause was identified in only 74% of cases. Failure to find a cause despite ample evaluation therefore occurred in roughly one fourth of individuals with diagnosed PN. Further, the authors commented that referred patients, comprising the majority of participants recruited for epidemiological research, were more likely to have “severe or unusual symptoms and syndromes,” and therefore do not likely represent of the majority of patients seen by primary care physicians. The percentage of idiopathic PN cases is therefore likely much higher in the actual population than demonstrated in current research (Mold et al., 2004).

It is of note at this point that a relatively extensive amount of research has been completed to date on the pathogenic pathways involved in the development and progression of peripheral neuropathy with known cause. Thus, current knowledge in this area is heavily skewed towards DPN. As a result, while several pathways of peripheral nerve deterioration have been outlined, the exact pathogenic processes remains controversial, are likely multifactorial, and may possibly differ with each cause as well as between individuals with similar co-morbid conditions (Boulton et al., 2004). This review will therefore not provide an in depth discussion on this topic. However, very briefly with respect to DPN, the current presiding belief is that chronically impaired blood glucose control results in numerous molecular alterations. These alterations in turn lead to reduced blood flow to both small and large-fiber peripheral nerves, related ischemia and oxidative stress, and demyelination of involved nerves (Boulton et al., 2004).

#### *4.1.1. Clinical Presentation*

While the presentation of PN is highly inconsistent, general clinical diagnostic guidelines are fairly straightforward and are defined by “the presence of symptoms and/or signs of peripheral sensory nerve dysfunction” (Boulton, 1998). With respect to specific sensory nerve impairment, several consensus panels have recommended that sensory nerve conduction testing be the “gold standard” diagnostic technique in both clinical and epidemiological studies (American Diabetes Association, 1988; Peripheral Nerve Society, 1995). This is largely because this techniques provides an objective and accurate measure of large-diameter, myelinated nerve function in terms of both the velocity (NCV) and amplitude of conducting action potentials. To this end, the standard nerve assessed by nerve conduction tests has been the sural, or short saphenous nerve, as it supplies innervation to much of the skin along the posterior aspect of the lower legs, ankles, and feet (Umpherd, 1995).

The vast majority of available research employing sural nerve conduction testing has examined the extent and progression of DPN in DM. In these patients, NCV along the sural nerve diminishes approximately 0.5 m/s each year (Claus et al., 1993). For example, Jarmuzewska and Ghidoni (2000) analyzed NCV of the sural nerve over a ten year period in individuals with newly diagnosed type II DM, and reported that average NCV declined from 48.3 to 44.4 m/s, or 3.9 m/s during this timeframe. Much additional research with similar results has been published (1995; Arezzo, 1997), and additionally, reduced NCV of the sural nerve has been linked to impaired glycemic control (Tkac and Bril, 1998), abnormal sensation (Loseth et al., 2006), and quality of life (Padua et al., 2002) in this population. However, while nerve conduction testing is considered a valuable method for detecting and monitoring DPN, additional research is needed to determine its effectiveness for identifying PN in other populations.

As mentioned above, nerve conduction testing is limited to large-diameter nerves. However, as previously stated PN develops distally, and as a result, deterioration to small, unmyelinated fibers ( $< 7 \mu\text{m}$ ) likely occurs prior to larger fiber involvement in the earliest stages of the disorder. To this end, Lacomis (1997) hypothesized that many early-stage symptomatic cases go undiagnosed when using electro-diagnostic testing. Evidence supporting this theory has since been produced by Periquet et al (1999), who used a *skin* biopsy procedure to harvest a sample of skin containing small-diameter, unmyelinated intra-epidermal nerve fibers (IENF) associated with the sural nerve. While nerve conduction tests for this nerve were abnormal in only 50% of patients with PN-like symptoms, skin biopsy revealed reduced IENF density of 89% of these patients (Figure 4.1). This provides direct evidence that small-fiber involvement is at least to some degree independent of large-fiber involvement, and has led to the suggestion that PN be further divided into both “large fiber neuropathy,” and “small fiber neuropathy,”

according to the relative nerve size involved (Lacomis, 2002). This fact, together with the sensitivity of skin biopsy testing for diagnosing PN in its early stages has resulted in a rapid increase in its utilization. To date, however, its widespread employment is currently limited by the invasiveness of the procedure and requirement of expensive, highly specialized instrumentation as well as complex histological techniques (Lacomis, 2002).

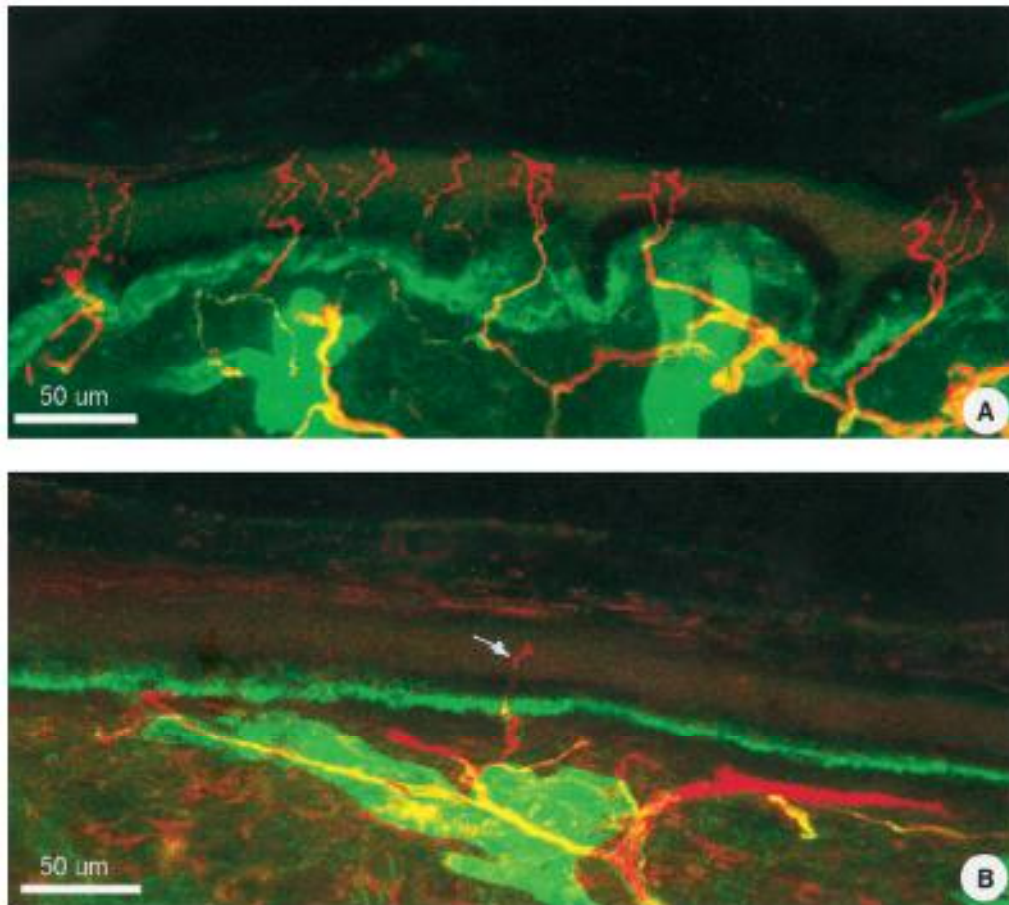


Figure 4.1: Examples of representative skin biopsies from a control participant without PN or DM (A) and a participant with DM and painful “small-fiber” PN. The reduction in IENF (stained red) density is clearly demonstrated as only a single fiber (white arrow) was present in patient biopsy. From (Periquet et al., 1999).

While primarily targeting peripheral sensory nerves, PN may also affect peripheral motor nerves. However, existing research of muscular involvement is sparse, has focused specifically

on the DPN population, and the results have been inconclusive to date. At the macroscopic level, Anderson et al (2004) reported significantly reduced maximal isokinetic muscle strength of the ankle extensors (17%), ankle flexors (14%), and knee flexors (14%) in neuropathic DM patients compared to non-neuropathic DM patients. Conversely, Resnick et al (2002) reported no lower extremity strength differences in similar groups of individuals. Further, Andreasson et al (2006) found maximal strength declines in symptomatic DPN patients, but not so in asymptomatic DPN patients, or non-neuropathic DM patients. The argument has therefore been raised that reported strength losses in DPN may be associated with indirect causes such as reduced physical activity (Boulton et al., 2004), rather than by a direct result of diminished peripheral motor nerve function. To this end, while motor nerve conduction testing is often recommended, it is most frequently utilized to diagnose, or similarly rule out, alternate forms of peripheral neuropathy.

In addition, and potentially in consequence, to isolated conduction impairments in peripheral sensory nerves, PN also gives rise to a host of related somatosensory deteriorations and associated symptoms. With respect to impairments, less sophisticated neurological evaluations, including qualitative sensory testing, vibration detection threshold testing, and cutaneous pressure detection threshold testing, commonly reveal deficits across all somatosensory modalities, the most significant of which occur in the distal lower extremities. For example, Menz et al (2004) assessed 30 patients with DPN and 30 age-matched controls in a variety of somatosensory, motor, and visual tests. While no significant between-group differences were observed in either the visual or motor domains, highly significant differences were reported with respect to somatosensory functioning. Specifically, PN patients exhibited increased plantar cutaneous pressure detection and vibration detection threshold, along with decreased lower-extremity proprioception as measured by a “lower-limb matching task.” The

most severe, and commonly reported of these impairments, however, is reduced plantar cutaneous pressure detection threshold. To illustrate, Dingwell and Cavanagh (2001) reported that the minimum detectable buckling force of diagnostic monofilaments, which apply a calibrated pressure to the plantar aspect of the foot, was 35 times greater at the heel, and over 400 times greater at the hallux, in PN patients as compared to age-matched controls.

In addition to sensory nerve and somatosensory-related impairments, the characteristic nerve damage of PN also gives rise to a host of often severe symptoms. Unfortunately, however, many patients have difficulty reporting symptoms and in fact, significant variation in the description of symptoms is common even among individuals with similar pathological lesions (Boulton et al., 2004). Further, there may also be marked differences depending upon the patient's age, the cause of PN, the time of day, and the duration of the underlying cause (if any detected). Nevertheless, PN is most often manifest by positive and/or negative symptoms of paraesthesia, or abnormal sensation. Positive symptoms arise spontaneously or as a response to stimuli, and both painful (i.e., prickling, tingling, burning, throbbing, allodynia, etc.) and non-painful (stiff, asleep, prickling, tingling, etc.) may be reported (Apfel et al., 2001). Positive symptoms are regularly worse at night and after prolonged periods of weight-bearing activity. Negative symptoms, on the other hand, represent a reduced response to stimuli and are most often described as numbness or "feet feel dead" (Boulton et al., 2004). In addition to these symptoms, a variety of lower extremity complaints such as leg cramps and restless legs syndrome are also reported (Holland et al., 1998).

Additionally, individuals may suffer from PN, as indicated by significant peripheral nerve dysfunction, without experiencing clinical symptoms. Despite the absence of symptoms, however, this form of PN is clinically relevant as these individuals often remain naïve to the

increased risk of developing common complications associated with PN (as discussed below). While the number of “asymptomatic” PN cases is difficult to estimate, several authors believe that its prevalence is quite high (Gordois et al., 2004; Resnick et al., 2002). For example, Resnick et al (2002) indirectly demonstrated the commonness of asymptomatic DPN in DM by assessing three groups of elderly adults, including DM patients with diagnosed DPN, DM patients without symptomatic DPN, and non-diabetic controls. The diabetic groups both with and without diagnosed DPN exhibited reduced peripheral nerve function (in terms of nerve conduction, vibration, and pressure detection testing) as compared to the non-diabetic control group. However, no differences in peripheral nerve function were reported between the two groups of diabetic patients, suggesting group-wide peripheral nerve damage in the diabetic patients without diagnosed PN, despite the absence of symptoms.

#### *4.1.2. Complications of PN*

PN is a chronic condition for which there exists no effective, long-standing cure. Yet, despite its numerous, often severe symptoms, isolated sensorimotor damage characteristic of the disease is in theory a non-life-threatening condition (Boulton et al., 2004). Nevertheless, PN has been associated with several life-altering and potentially life-threatening complications. First, the most common and perhaps most well known complication of PN, particularly with respect to DPN, is foot ulceration. In fact, foot ulceration and related complications associated with the “diabetic foot” remains one of the most prevalent and serious complications of both type I and type II DM. The International Diabetes Foundation reported that as many as 25% of this population develop a foot ulcer (IDFTA, 2005), far more than any other patient group. Foot ulceration frequently leads to amputation of part or all of the foot and lower limb, and as a consequence, nearly 70% of all amputations are carried out on DM patients (Boulton, 2000). The

unfortunate consequences of amputation in this population are startling. For example, Tentolouris et al (2004) followed 250 such amputees for five years post-surgery. Mean survival time for these patients was only six years, with the average patient passing away at 64.7 years of age. Further, in addition to causing pain, reducing mobility, and increasing mortality, diabetic foot has substantial economic consequences as diabetic foot ulceration and amputations were estimated to cost 10.9 billion health care dollars annually (Gordois et al., 2004).

Diabetic foot disorder is most commonly caused by the “pathogenic triad” of trauma, neuropathy, and ischemia. Briefly, this type of ulcer develops in large part from trauma in the form of elevated, repetitive mechanical stresses applied to the plantar aspect of the foot during weight-bearing activities such as walking. In the healthy foot, these stresses are effectively dissipated over the relatively large areas to which they are applied (Abouaesha et al., 2001). The diabetic foot, however, may undergo several biomechanical alterations, including small muscle wasting, foot deformities such as clawing or hammering of the toes, distal migration of the fatty deposits located under the metatarsal heads, increased plantar tissue stiffness, and reduced ankle and foot joint mobility, that together disrupt the interaction between the foot and the ground while walking (Bus et al., 2002). The main consequence of these alterations is increased peak pressure experienced by the forefoot and toes during both the initial contact and propulsion phases of the walking cycle (van Schie, 2005). Certainly, similar disturbances in a healthy foot would trigger uncomfortable protective sensations, in turn causing the person to avoid the offending pressures. Neuropathy in the DPN foot, however, diminishes the effectiveness of these protective mechanisms (i.e., pain, vibration, pressure, and temperature sensations). In consequence there is no warning of excessive pressures or damage, and persistent localized stresses continue to advance the injury. In fact, many cases of diabetic foot go unnoticed and

medical attention is not sought until ulceration has developed into advanced stages (Boulton, 2000). Lastly, the healing of a wound requires “a well orchestrated integration of complex biological and molecular events” (Falanga, 2005). Chronic ischemia within these tissues, caused by both vascular and circulatory abnormalities (Dinh and Veves, 2005), certainly alters the microenvironment of the foot. Thus, while a model of chronic, non-healing wounds has not been established, it is believed that these changes contribute to diabetic foot by hindering the normal progression of wound healing.

The other major complication of PN can be collectively described by a host of specific movement-related disturbances during weight-bearing situations. These disturbances are highlighted by well-known correlations between PN patients and comparatively diminished amounts of physical activity (Albright et al., 2000), reduced self-reported mobility and independence (Padua et al., 2005), and receiving the most attention, increased risk of falling (Richardson et al., 1992). With respect to the latter, falls and related injuries certainly negatively affect the nation’s entire elderly population, as up to 40% of individuals within this segment experience at least one fall each year (Tinetti et al., 1988). In the sub-segment comprised of PN patients, the risk of suffering a fall is severely elevated. PN patients are much more likely to suffer a fall and multiple falls as compared to those in the non-PN population (Richardson et al., 1992). Further, these patients are also 15 times more likely to suffer an injury while walking (Cavanagh et al., 1992), and their increased risk of falling is independent of other comorbidities (Richardson et al., 1992). In any population the personal consequences of suffering a fall are severe and multifaceted, and include hospitalization, loss of mobility and independence, and increased mortality (Richardson et al., 1992). These facts, together with extremely costly

economic consequences, make falls one of the biggest healthcare concerns currently facing the elderly, and undoubtedly the PN population.

As the majority of falls occur while walking (Cavanagh et al., 1992), an increased amount of research has been published related to the effects of PN on walking under various conditions. The results of this research have collectively demonstrated several distinct movement-related disturbances that may individually or collectively contribute to the increased risk of suffering falls. However, PN is a chronic, progressive, and often comorbid condition. Respectively, these facts suggest that significant inter-individual variation exists with regards to the extent of sensory involvement, individuals likely develop compensatory strategies in an attempt to counteract their specific sensory disturbances, and multiple complicating factors may contribute to the clinical presentation of those affected. The collective result of these issues leads to an extremely non-homogeneous population. As a result, it is extremely difficult and perhaps impossible to isolate the effects of the direct, PN-related somatosensory disturbances on walking. Thus, while the effects of PN on walking are of ultimate importance, it is worthwhile to first explore the results of research in which experimentally-induced peripheral sensory alteration or loss has been imposed on otherwise healthy individuals. For the purposes of this review, this discussion will be limited primarily to research examining the effects of plantar cutaneous desensitization of the foot soles on unperturbed walking in healthy individuals, as this form of somatosensory FB can be selectively targeted and directly relates to the impairments of PN.

#### **4.2. The Role of Plantar Cutaneous Feedback in Walking**

The plantar surfaces of the feet are the exclusive points of contact with the environment during walking. Cutaneous exteroceptors located in these areas are therefore optimally positioned to provide the CNS with pressure distribution characteristics throughout the stance

phase of the walking cycle. Specifically, Ruffini, Merkel, and Meissner terminations, which are slowly or moderately fast adapting with relatively small receptive fields (Macefield, 2005), give rise to detailed non-nociceptive spatial and temporal information regarding ground reaction forces arising from ground contact (Kavounoudias et al., 2001). Transmission of FB arising from these exteroceptors to the CNS is believed to be transmitted largely through large-myelinated and low-threshold afferent fibers (i.e., A $\beta$  fibers) of lower extremity afferent nerves such as the sural nerve. Additionally, however, smaller-myelinated fibers (i.e., A $\delta$  fibers) that mostly transmit nociceptive information have also been reported to transmit non-nociceptive signals (van Wezel et al., 2000).

From section 2.2., once arriving at the CNS, all peripheral sensory FB may contribute to both spinal reflex and supraspinal pathways and is likely involved in the drive of pre-programmed motoneuronal output leading to the movements of walking, as well as the correction of unintended movement disturbances. Available evidence suggests that these pathways indeed hold with respect to FB related to plantar cutaneous pressures. To this end, a large amount of research has been conducted in which electrical stimulation is employed to momentarily increase plantar cutaneous FB over and above typical levels at specific points of the walking cycle. The collective results of this research have greatly increased our knowledge of the pathways in which this FB is involved in human walking.

First, for example, Van Wezel (2000) demonstrated that plantar cutaneous FB can modify motor output during walking through polysynaptic spinal reflex pathways. Specifically, in healthy adults, electrical stimulation of the sural nerve, thus mimicking abrupt changes in plantar cutaneous FB, during the swing phase of the walking cycle significantly modified ipsilateral EMG activity of the biceps femoris and the tibialis anterior muscles from normal levels at a

latency of 70-110 ms. Interestingly, it was also reported in this study that electrical stimulation early in the swing phase produced a significant increase in EMG activity in each muscle, whereas similar stimulation during the late swing phase produced a significant decrease in EMG activity. These results, which have been reproduced numerous times both at different points in the swing phase and between the swing and stance phases (Yang and Stein, 1990; Zehr et al., 1997), reveal that the polysynaptic reflex pathways of plantar cutaneous FB are also modulated across different points in the walking cycle. The generally-accepted functional significance of this phenomenon is that these reflexes are involved in the “stumbling response,” such as following a trip, that must be specifically tuned to the demands of the body at that particular moment. Finally, in addition to pathways originating at the spinal level, plantar cutaneous FB has also been demonstrated to be involved in supraspinal pathways. For instance, Christensen et al (1999) employed combinations of both cutaneous electrical stimulation and motor evoked potentials arising from transcranial magnetic stimulation to demonstrate that plantar cutaneous FB is also involved in transcortical reflex pathways, likely involving the corticospinal tract. Through this pathway, the researchers concluded that plantar cutaneous FB likely contributes to both “basic rhythmic locomotor activity (i.e., preprogrammed motoneuronal drive) as well as the “adaptation of this rhythm to environmental and motivational influences.”

Electrical stimulation of cutaneous exteroceptors, or their related nerves, artificially increases FB levels above normal levels and therefore most closely represents the mechanisms through which this FB is utilized in response to large-scale, unexpected perturbations that may occur when walking. While this information is obviously relevant, caution must be taken when extrapolating results to form conclusions regarding the role of plantar cutaneous FB in the production of movement patterns related to steady-state, unperturbed walking (the primary focus

of this review). In order to examine this issue, it has been argued that one must alternatively investigate the effects of reducing, instead of increasing, normal amounts of somatosensory FB (Nielsen and Sinkjaer, 2002). Recently, and largely in response to the increased incidence and related awareness of PN, this type of research has mounted (Eils et al., 2002; Eils et al., 2004; Nurse and Nigg, 2001). With respect to walking, the most common protocol utilized to induce desensitization of the foot soles has been ice immersion, which selectively and significantly reduces plantar cutaneous pressure sensitivity while unaffected strength, position sense, or cutaneous tissue properties of the ankle, feet, and toes (Nurse and Nigg, 2001; Perry et al., 2000)

A reduction in plantar cutaneous pressure sensitivity using ice immersion causes individuals to adopt a “cautious gait” strategy that is evident during the both the initiation (Eils et al., 2004) and termination (Perry et al., 2001) of walking, as well as under steady-state conditions. In general, this strategy is characterized by significant reductions in walking speed and related ground reaction forces during both the heel-strike and toe-off portions of the stance phase. Further, ankle joint angles, and EMG activity of related muscles, are specifically modified (i.e., decreased dorsiflexion at heel contact and increased dorsiflexion at toe-off), so as to maximize the duration of foot contact with the ground during the stance phase. With this in mind, Eils et al (2002) additionally demonstrated that pressure distribution patterns during the stance phase are significantly altered following desensitization. Specifically, these changes reflect an overall reduction in peak pressures (directly related to reduced walking speed), a load shift to the forefoot at heel strike, a consistently larger contact area of the foot, and a push-off phase that takes place from the central and lateral foot as the load is not transferred to the toes.

Together these alterations suggest that normal sensory FB related to plantar cutaneous pressure information strongly facilitates the production of steady-state walking patterns.

However, the underlying reasons for the adoption of a cautious gait strategy are unclear at this point. Certainly, the employment of this strategy may occur consciously or subconsciously, and may hold several benefits that may include protecting the desensitized foot (Eils et al., 2002), reducing potentially destabilizing inertial effects across various portions of the body, and or maximizing the present capacity to respond to unexpected perturbations (Perry et al., 2000). To this end, however, no research has directly examined the effects of plantar cutaneous desensitization on the ability to respond to either large-scale or small-scale perturbations, nor its resulting effects on the variability of related movement variables. Nevertheless, available research is sufficient to conclude that sensory input from cutaneous receptors of the foot plays an essential role in both the production of normal walking patterns and the response to unexpected large-scale perturbations, and thus should be taken into careful consideration when investigating human walking in special populations.

#### **4.3. The Effects of PN on the Variability of Walking**

Despite the aforementioned peripheral nerve damage and related impairments suffered by PN patients, the vast majority of these individuals are capable of walking in well-lit and open spaces when on regular surfaces. For example, in Dingwell et al (2001) 12 patients with advanced PN each walked for ten continuous minutes overground with no reports of injury, falls, or adverse events. This suggests that somatosensory FB from the distal lower extremities is not *critical* to the generation of effective walking patterns in these situations. Thus, it appears that “along with pre-programmed and predictive control mechanisms, visual and proximal somatosensory feedback mechanisms are sufficient for maintaining stable locomotion” (Dingwell and Cavanagh, 2001). Nevertheless, PN patients do often present with severe disturbances to multiple kinematic and kinetic variables associated with walking. First, aside

from measures of variability, individuals with PN exhibit similar walking alterations to those demonstrated by individuals with experimentally-induced plantar cutaneous desensitization. Specifically, PN patients walk with a cautious gait with significantly decreased speeds (Dingwell and Cavanagh, 2001; Menz et al., 2004; Richardson et al., 2004), step lengths (Richardson et al., 2004), ankle moments, ankle powers, and ground reaction forces in the AP and vertical directions (Mueller et al., 1994). These patients also walk with significantly increased double support time (Courtemanche et al., 1996) and mean step width (Richardson et al., 2004). Setting PN patients apart from individuals with experimentally-induced desensitization, however, is that the above walking-related disturbances are consistently more pronounced in the patient population (Eils et al., 2004). Indeed, this finding is important as it speaks to the fact that PN does not selectively target plantar cutaneous pressure receptors alone, but rather impairs all peripheral sensory modalities and is accompanied by significant reductions in physical activity (Andersen et al., 2004).

While the above walking-related disturbances seem numerous, related decreases in joint moments, powers, and ground reaction forces are collectively the likely consequence of reduced walking speed. The 20 to 30% slower walking speeds in PN patients as compared to age-matched controls has therefore been targeted to be the primary compensatory strategy employed to offset the lower extremity somatosensory losses suffered by this population (Dingwell 2001). To this end, Menz et al (Menz et al., 2004) reported a direct relationship between the amount of sensory loss and walking speed. In fact, while multiple physiological tests of vision, peripheral sensation, muscle strength, reaction time and proprioception were measured in this study, lower extremity somatosensory assessments of vibration and plantar cutaneous pressure sensitivity were the only significant predictors of walking speed.

In the same study, Menz (2004) suggested that one potential benefit of reducing walking speed is that it ensures upper body accelerations remain at a tolerable level, inasmuch as large accelerations of the upper body may threaten the capacity to maintain balance (i.e., avoid falls). While this theory is in line with the notion that involved body movements of walking are organized with the ultimate goal of reducing the accelerations of the trunk and especially the head (Kavanagh et al., 2005), it is met with conflicting empirical evidence. For instance, both Menz et al (2004) and Dingwell et al (2001) reported that when compared to controls, DPN patients exhibit significantly reduced accelerations at the pelvis in both the vertical and horizontal directions when walking both overground and on a treadmill. Conversely, however, Menz et al also reported that PN patients continue to have difficulty minimizing accelerations at the head despite slowing down, as even though the patients walked with 20% slower speeds, head accelerations remained comparable between groups.

In addition to these more commonly investigated variables, PN may also affect the variability of walking. In fact, the link between walking variability and falls in other populations, together with the increased risk of suffering falls in the PN population, has led to a considerable amount of research in this area. However, if one recalls that variability is widely accepted to primarily reflect fluctuations in centrally-generated motor output, it logically follows that peripheral sensory loss should not directly affect the variability of walking. Nevertheless, this notion has not deterred researchers from developing hypotheses concerning the effects of peripheral sensory loss on walking variability. On one hand, for instance, PN has been theorized to increase variability due to a lack of related FB contributing to motoneuronal drive, or more specifically, “missing or incorrect information involved in the precise control of timing of the walking cycle” (Gandevia et al., 1992). On the other hand, it has also been suggested that PN

may actually decrease variability as these individuals have a reduced capacity to detect uncomfortable or painful stimuli that would normally lead to appropriate, on-going corrections in those individuals with intact somatosensory systems (Brand, 1988).

The results of related research have demonstrated inconclusive findings and have not consistently backed any one theory over another. For example, both Richardson et al (2004) and Menz et al (2004) reported that despite walking slower, DPN patients did not significantly differ from age-matched controls in terms of step width or step duration variability, respectively, when walking over regular surfaces. Interestingly, however, both studies reported group differences in these measures when participants walked in “challenging environments” consisting of an irregular walking surface. Similarly, Dingwell et al (1999) reported only trends of increased variability in this population across five measures of walking variability, including stride duration, sagittal plant displacement of the hip, minimum toe clearance, and knee and angle angles when walking on a motorized treadmill. Collectively, these results most strongly support the notion that, over regular surfaces, PN patients “are able to regulate their gait to a similar degree as healthy individuals, but at the cost of speed and efficiency” (Richardson et al., 2004).

Alternatively, however, Dingwell et al (2000) has also reported significant increases in walking variability in DPN patients compared to aged matched controls during overground walking. First, while no between-group differences were observed in terms of multiple joint ROM and lower extremity strength measures, large group differences were observed in both vibration and plantar cutaneous pressure sensitivity thresholds. With respect to walking, DPN patients walked with significantly reduced walking speeds, but additionally exhibited increased variability in both maximum and continuous measures of gait cycle timing, upper body accelerations, and lower extremity joint angles. Interestingly, and in support of Menz et al (2004)

the use of an exploratory path analysis (Hair, 1998) demonstrated that peripheral sensitivity was the only significant predictor of walking speed. Further, walking speed and lower extremity strength were the only significant predictors of walking variability. This finding provides convincing evidence that 1) the primary compensatory strategy employed by these individuals to offset their peripheral sensory loss is reduced walking speed, 2) increased variability likely arises as a secondary consequence of this compensatory strategy, and from a theoretical standpoint, 3) walking variability is generated in large part through centrally-mediated mechanisms as reduced peripheral sensation does not directly lead to increased variability.

With respect to the third point, all related research that has reported increased variability in PN patients has also reported significantly reduced walking speeds in this population. Further, as stated in section 3.3.3, increased variability is commonly reported in even healthy young adults when asked to walk at slower than preferred walking speeds (Winter, 1983). However, the possibility of increased variability being nothing more than a consequence of reduced walking speed is still somewhat speculative at this point as no published research has directly examined variability in PN patients when walking across a number of different speeds. Whether this relationship holds or not, however, the combined results of available research clearly demonstrate that the peripheral sensory loss suffered by PN patients does disturb walking patterns when compared to controls. However, as previously stated these patients can still generate effective walking patterns in non-challenging environments. It is thus probable that the majority of falls in this population occur during challenging environments in which these patients are required to continuously modify their normal walking patterns (Dingwell and Cavanagh, 2001; Menz et al., 2004; Richardson et al., 2004).

#### **4.4. The Effects of PN on the Local Stability of Walking**

Although PN patients appear to attempt to compensate for peripheral sensory loss through a reduction in walking speed, the fact that these individuals remain more likely to fall than age-matched controls implies that some aspect of their walking continues to predispose them to an increased risk of a loss of balance when walking. To this end, several researchers have intuitively theorized that these individuals continue to fall because PN considerably and deleteriously affects walking stability (Courtemanche et al., 1996). Furthermore, Menz et al (2004) concluded that the close association between the level of distal somatosensory loss and walking speed indicates that slowed walking or “conservative gait, with less potential for instability, is a protective adaptation to a perceived threat to stability when there is insufficient sensory information about the position and movement of the body and limbs.” Unfortunately, this theory has been based solely on the view that stability is defined by the ability to maintain balance during weight-bearing situations, and not on its physical definition. Furthermore, the traditional practice of equating stability with variability would directly contradict the notion that these individuals slow down to improve stability because, as stated in the previous section, this strategy directly related to increased variability.

Thus, until recently there has been a lack of empirical evidence regarding the affects of PN on walking stability. However, recall that the true physical definition of stability is given by the time-dependent ability of a system to return to its attractor following perturbation (Full, 2002). Further, the critical first step in responding to a perturbation is detecting the perturbation’s characteristics, as well as its ensuing effects on the body. This task is accomplished by the peripheral nervous system and in particular the somatosensory system pertaining to the lower extremities. As a result, the often times severe distal somatosensory loss suffered by PN patients should in theory significantly impair both global and local stability during walking. Despite the

logical appeal of this theory, however, no research has been published to date regarding the global stability of walking in the PN population. This unfortunately reality is likely due to potential hazards related to exposing these patients to large-scale perturbations during weight-bearing situations. Nevertheless, this limitation has also been the primary driving force behind the application of local stability quantification techniques to human walking. Certainly, examining the effects of small-scale perturbations, which are internally induced by inherent stride-to-stride spatiotemporal fluctuations, is much safer than inflicting external perturbations and nevertheless provides insight into a specific form of walking stability.

Both direct and indirect evidence is available regarding the effects of PN on the local stability of walking. With respect to the latter, Mazzaro et al (2005a) recently utilized a previously outlined technique (section 2.2) to examine the effects of PN with large sensory nerve fiber involvement on the ability to modify soleus muscle activity in response to relatively small ankle joint perturbations inflicted during the stance phase of walking. Briefly, both all-cause PN patients and age-matched controls walked on a treadmill with their right leg attached to a device that did not interfere with normal walking patterns, but was capable of producing low velocity and low amplitude perturbations to the ankle joint. Perturbations were inflicted between 200 and 400 ms following heel strike, with amplitudes sufficient to cause either enhanced or reduced dorsiflexion to the order of 2-4 deg at 15-17 deg/sec, thereby attempting to mimic the normal stride-to-stride fluctuations in unperturbed walking. While the researchers examined the subsequent electromyographic (EMG) response in the several lower extremity muscles, these perturbations only produced observable changes in the soleus muscle. Figure 4.1 illustrates the results of a typical PN patient and control subject with respect to slow-velocity, dorsiflexion enhancements and reductions. First, visual observation of ankle movement in response to each

type of perturbation (Figure 4.1A and D) reveals that this variable returned to its normal trajectory following perturbation. Interesting, however, it seems as though the PN patients took longer to do so than the control subjects. While this would directly demonstrate a reduction in stability in PN patients, these results were unfortunately not reported for both groups of participants. Nevertheless, it was reported that, with respect to soleus EMG activity (Figure 4.1B and E), PN patients responded with a significantly greater latency following each type of perturbation as compared to controls. Furthermore, with respect to the amplitude of EMG modification (Figure 4.1C and F), background levels did not differ between groups. However, whereas control subjects exhibited approximately 19% increases following perturbations causing dorsiflexion enhancement and 14% decreases following perturbations causing dorsiflexion reductions, EMG modification in PN patients was only 7% and 2.5% in response to perturbations of similar size and direction.

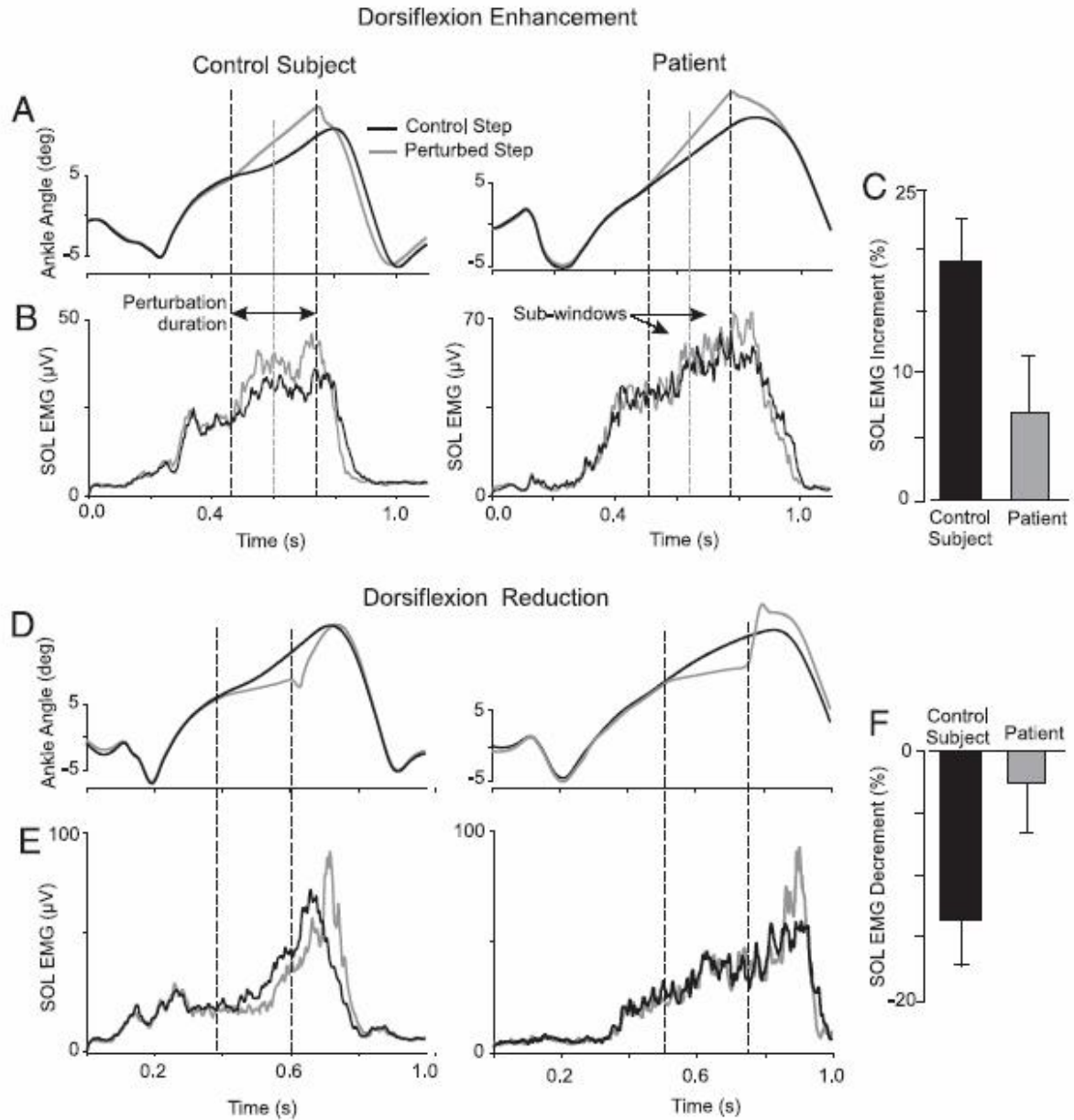


Figure 4.1: Characteristic response of both PN patients and controls subjects to relatively slow, low amplitude ankle joint perturbations causing dorsiflexion enhancement and reduction. Results are presented in terms of ankle joint movement (A and D), soleus EMG activity (B and E), and percent soleus EMG modification (C and F). Adapted from (Mazzaro et al., 2005a).

In contrast to large and or fast perturbations, the low amplitude, slow perturbations utilized in this study were deemed optimal for examining the role of sensory FB during normal walking. As a result, the researchers formulated the conclusion that large diameter sensory fibers

are likely responsible for transmitting sensory FB, largely from the distal somatosensory system, that directly contributes to the detection and subsequent muscular response to relatively small perturbations imposed while walking. This conclusion was strongly backed by the reduced ability of PN patients to modify soleus muscle activity in response to the same imposed ankle-trajectory modifications during the stance phase of walking. It is of note, however, that because the PN patients demonstrated on average significantly reduced large fiber sensory nerve (i.e., sural) conduction velocity and related impairments in the Achilles tendon tap response, and pain, vibration, and position sensitivity compared to controls, more detailed conclusions regarding the exact receptors and underlying pathways involved in the response to this type of perturbation were limited.

As previously stated, while the perturbations in the above study were *externally*-generated, their characteristics closely resemble those that are *internally*-generated giving rise to walking variability. As PN patients demonstrated a reduced capacity to modulate muscle activity following these perturbations, one might reasonably predict that the local stability of walking would in turn be significantly impaired in this population. However, Dingwell and Cusumano (2000) have provided evidence that directly contradicts this hypothesis. In this research, DPN patients demonstrated no lower extremity strength loss, but did present with significant reductions in both plantar cutaneous pressure sensitivity and ROM of the knee and the first metatarsal-phalangeal joint as compared to age matched controls.

Local stability ( $\lambda_{\max}$ ) and variability of three-dimensional accelerations of the trunk, as well as lower extremity joint angles (hip, knee, and ankle) in the sagittal plane, were computed as described in sections 3.1.1 and 3.3.2 for all participants from continuous kinematic data collected during several 10 min trials of overground walking. For upper body accelerations in the

ML and AP directions in the horizontal plane, as well as the majority of lower extremity joint angles, PN patients walked with significant increases in variability as compared to controls. Surprisingly, however, they also walked with significantly decreased  $\lambda_{\max}$ , indicating *increased* local stability. Furthermore, and similar to all previously presented research, DPN patients walked with significantly reduced walking speed and stride lengths as compared to controls. Thus, similar to the study published by the same authors on walking variability in this population, a statistical path analysis was employed to reveal the predictors of both walking speed and local stability. Similar to the first study, peripheral sensation was the only significant predictor of walking speed. Walking speed, and additionally ROM (of the knee, ankle, and first metatarsal-phalangeal joints) were the only significant predictors of  $\lambda_{\max}$ .

Together with the results of Dingwell (2000), the results of this study have therefore provided further evidence that variability and local stability are dissociated (as outlined in chapter 3.3.3). Furthermore, in a somewhat related proposal, the authors suggested that while reducing the speed of walking increases variability, this compensatory strategy is nevertheless implemented as it allows for the effective maintenance of local stability. This in turn suggests that PN patients can effectively compensate for their distal somatosensory impairments in terms of local stability, as this variable can be maintained during normal, unperturbed walking. As a result, while much additional research is needed, the elevated risk of falling in PN patients does not appear to arise from a disability in generating locally stable walking patterns in unchallenging environment. On the contrary, the authors suggested that falls are more likely occur within challenging environments and or due to an impaired ability to generate effective responses when faced with large-scale perturbations that occur during walking, such as those occurring from a slip or trip.

## **CHAPTER 5**

### **DEVELOPED HYPOTHESES**

#### **6.1. The Role of Plantar Cutaneous FB in the Variability and Local Stability of Walking**

Dingwell et al (2000, 2001) have demonstrated that within the PN population, only walking speed, and not plantar cutaneous pressure sensitivity, significantly predicts the local stability of walking. However, these results are potentially misleading as PN is a long-term disease and affected individuals employ numerous compensatory strategies to offset their sensory loss. Furthermore, it is likely that these strategies in turn lead to chronic alterations to both structural and functional aspects of the individual's skeletal, muscular, and nervous systems. It is therefore impossible to completely isolate plantar cutaneous pressure sensitivity in this population for direct comparison to the local stability, or likewise the variability, of walking. To this end, ice immersion of the foot soles is an effective method to selectively reduce plantar cutaneous pressure sensitivity. Future research investigating both the local stability and variability of various walking-related movements following ice immersion of the foot soles in otherwise healthy, young adults can therefore directly examine the role peripheral sensory FB plays in these variables, while simultaneously avoiding the limitations inherent to the PN population.

As this research has not been conducted to date, the formulation of related hypotheses requires the review of multiple concepts related to both the description of walking from a dynamical systems perspective and current theory related to its motor control. First, recall that variability is most accurately described as the average magnitude of deviation of a system away from its attractor over a finite period of time. Furthermore, whether occurring through unwanted

error or as part of the underlying movement dynamic, deviations away from the system's attractor are believed to primarily originate secondary to fluctuations in centrally-generated motor output. In this light, therefore, a consistent, albeit temporary reduction in peripheral FB during walking, as assumed by a decrease in plantar cutaneous pressure sensitivity, would not directly affect the variability of related movements.

Stability, on the other hand, is most accurately described as the time-dependent ability of a system to return to its attractor following perturbation. Given this definition, local stability can then be defined as the average rate of exponential divergence of initially neighboring trajectories in a system's phase-space. Thus, while not a true measure of stability in the physical sense, local stability does provide a quantitative measurement of the time-dependent sensitivity of the system to the same, small-scale perturbations that give rise to walking variability. With this in mind, recall that a major role of peripheral FB is the initial detection of perturbation characteristics and their ensuing effects on the body. A reduction in plantar cutaneous FB during walking, again assumed by a decrease in plantar cutaneous pressure sensitivity, which has been demonstrated to contain information critical to the modulation of on-going movements secondary to *externally*-generated small-scale perturbations (Mazzaro et al., 2005b), would therefore reduce the ability to detect small-scale perturbations and ultimately decrease the local stability of walking. It is important to note, however, that this hypothesis only holds for similar walking speeds before and after experimentally-induced desensitization, as reduced speeds have consistently led to increased local stability within related literature.

## **6.2. Physical Performance Measures in PN Patients**

The severity of symptoms and associated complications of PN, together with the current lack of research related to this prevalent disease, warrants further investigations regarding its

effects on those inflicted individuals. Particularly devastating to these individuals are the movement-related disturbances during weight-bearing situations that are evidenced by an increased fall risk (Richardson et al., 1992) and decreased mobility, independence, and quality of life in this population (Padua et al., 2005). However, perhaps due to the prevailing belief that PN is a non-treatable disease, negligible research has been conducted related to the effects of PN on physical performance. Thus, compared to other aged and or diseased populations, relatively little is known regarding performance in muscular strength testing, or in standardized physical performance field assessments such as the 6-min walk test and the timed up-and-go test. Certainly, this information would be beneficial in comparing PN to other diseased populations, as well as assessing the effectiveness of interventions designed for PN patients.

A necessary first step in conducting the above tests is the determination of test-retest reliability. Furthermore, while Dingwell and colleagues (2000, 2001) have produced several studies regarding both the local stability and variability of walking in the PN population, there is an additional need for reliability testing related to these measures in this population as well. Importantly, while reliability represents a necessary consideration in any population, the reliability of physical performance testing in all-cause PN patients spurs particular concern as this population is far from homogeneous. While not a comprehensive list, causes for this non-homogeneity include the progressive nature of the disease, the large number of identified causes and co-morbidities, the numerous and variable symptoms associated with the disease, and the lack of standardization in diagnostic guidelines in both medical and research settings. With these characteristics in mind, however, moderate to strong test-retest reliability has been reported in the above traditional assessments in multiple unstable and non-heterogeneous populations including those suffering from congestive heart failure (Selig et al., 2002) stroke (Tyson and

DeSouza, 2004), and severe respiratory disease (Hayes et al., 2000). Additionally, Kang and Dingwell (2006) recently reported that the quantification of local stability utilizing the methods outlined in this review are reliable for young adults. Thus, in spite of the unique characteristics of PN, it is hypothesized that this population will similarly demonstrate adequate test-retest reliability in all of the above-mentioned assessments.

With proof of reliability in hand, much needed research attempting to provide insight into the meaningfulness of local stability as a measurement variable can be conducted. Specifically, comparisons can be made between the local stability of walking in both PN and age-matched controls and related performance in standardized physical assessments. Again, however, physical performance norms within the PN population have not been sufficiently established to date. As a result, the formulation of hypotheses regarding correlations between local stability and measures of lower extremity strength, endurance, and mobility is difficult. Nevertheless, one intriguing prediction can be made with regards to local stability and the 6-min walk test. First, it is known that PN patients walk with significantly reduced walking speed, and these patients should therefore demonstrate reduced performance in the 6-min walk test as compared to controls. Furthermore, a strong negative correlation should exist between performance in the 6-min walk test and local stability. In other words, due to the previously illustrated relationship between local stability and walking speed, reduced performance in the 6-min walk test, which is directly related to decreased walking speed, should be highly linked to increased local stability. Future investigation supporting this prediction would thus further develop our knowledge regarding the relationship between walking speed and local stability, particularly as it pertains to populations of differing functional status.

### 6.3. Local Stability of Walking at Challenging Speeds in PN Patients

Preliminary research involving the quantification of the local stability of various walking-related movements has collectively demonstrated that it is a physiologically meaningful variable. The direct relationship of local stability to walking speed, along with its characteristic decrease in aged (Buzzi et al., 2003), and Down syndrome patients (Buzzi and Ulrich, 2004) speaks to this meaningfulness. Furthermore, Dingwell et al (2000, 2001) concluded that PN patients employ a cautious gait strategy and slow their walking speed *specifically* to preserve or even increase the local stability of involved movements as compared to aged-matched controls. Collectively, this research, together with the fact that local stability can be easily and safely measured in even high-risk populations, warrants additional research examining both its meaning and usefulness as a measurement variable. Interestingly, all available research related to the local stability of walking has operated under, and certainly supports, the assumption that movements with relatively greater  $\lambda_{\max}$  values, which indicate increased sensitivity to small-scale perturbations or similarly decreased local stability, are inherently detrimental to the individual. While intuitively logical, however, the theoretical grounds for this assumption have not been concretely established.

Future research extending Dingwell et al (2000, 2001) by comparing the local stability of walking in PN patients and aged-matched controls across different speeds may provide critical insights into this theoretical issue. Specifically, these researchers originally demonstrated that PN patients exhibit both decreased preferred walking speed and increased local stability of several trunk and lower extremity movement variables when walking in an unchallenging environment. Importantly, it was also revealed that walking speed was the only significant predictor of local stability. This finding has since been supported by Dingwell et al (2006) and England and

Granata (2006), which have both demonstrated an direct, inverse relationship between these two variables. Nevertheless, despite the relative increase in local stability, PN patients still present with an increased risk of suffering falls as compared to age-matched, healthy counterparts. This in turn has led researchers to conclude that the majority of falls suffered by this population occur when walking in more challenging environments (Menz et al., 2004, Richardson et al., 2004). With respect to the local stability of walking, this notion has been supported in Down syndrome patients. Specifically, Buzzi et al (2004) demonstrated that across all walking speeds, individuals with Down syndrome exhibit reduced local stability of lower extremity joint angles when compared to controls. Furthermore, significantly more pronounced decreases in local stability were observed in the patients as the environment was made more challenging by systematically increasing treadmill speed away from each participant's preferred speed. Therefore, if the notion holds that decreased local stability is detrimental to walking in PN patients, it is hypothesized that while these patients can preserve local stability at preferred walking speed, walking under progressively more challenging conditions will elicit related changes in local stability over an above those seen in age-matched controls.

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## VITA

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