POSTURAL CONTROL IN PERSONS WITH MULTIPLE SCLEROSIS: AN INVESTIGATION OF DUAL TASK COST AND PHYSICAL MODELING

BY

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THESIS

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Abstract

Postural control is an essential activity of everyday life. There is ongoing debate concerning the contribution of central and peripheral control processes to the control of upright stance. Multiple sclerosis is known to negatively influence both central and peripheral control processes. This work investigates how human postural control is affected in persons with multiple sclerosis (MS).

The first study investigated the cognitive component of postural control in persons with MS. An experimental study was conducted to measure sway parameters during quiet standing and sway parameters during standing while performing a cognitive task. This study included persons with MS with varying levels of disability. It was hypothesized that the persons with higher disability would show a greater difference between the two testing conditions (quiet and dual task) than the persons with lower disability. Although significant differences were found in the traditional sway parameters between the quiet and dual task conditions, the hypothesized interaction between disability and dual task cost was not found. There are many possibilities for why this interaction did not exist. The most likely possibility is a difference in the way the persons with varying levels of disability allocate neurological cognitive resources to the different tasks. Understanding the influence of a cognitive task on postural control will help to further elucidate the factors that contribute to postural control, especially in persons with decreased postural control due to illness where improved postural control is a therapeutic goal.

The second study investigates a bi-planar inverted pendulum model of postural control for persons with MS with high and low spasticity. The inverted pendulum model was used to determine the underlying differences in the control strategies of a group of healthy adults compared to a group of persons with MS who have symptomatic spasticity. The model was modified from previous work [1, 2] to incorporate components that could account for the spasticity seen in persons with MS. The MS and controls models were able to create realistic center of pressure (COP) data that had similar traditional COP parameter values to that of experimental data [3]. The model gains used to achieve the realistic COP measures were compared between the controls and MS models. The gains indicated an increased stiffness (proportional gain) in neurological controller the ML direction, and an increased input noise gain in the ML direction for the MS model with high spasticity compared to the controls. These significant differences in the gains that drive the models suggest that there are different control strategies used for persons with MS and controls to maintain postural control. Relating these model gains to physiological components of postural control can help to gain insight into the changes that take place in the postural control system with disease.

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Nomenclature

AP	anterioposterior
B_{pass}	passive damping model gain
COP	center of pressure
DTC	dual task cost
EDSS	expanded disability status scale
EMG	electromyography
FP95	95% power frequency
K_i	integral gain of neural controller in model
K_N	input disturbance noise gain in model
K_p	proportional gain of neural controller in model
K_{pass}	passive stiffness model gain
Max	maximum sway value of center of pressure
MD	mean distance of center of pressure sway
ML	mediolateral
M_p	measure from participant data
MS	multiple Sclerosis
M_S	measure from simulation model
MV	mean Velocity
N	number of measures
PwMS	persons with MS
RMS	root mean square distances
SA	sway area
WLG	word list generation
τ_d	neurological transmission time delay in model
τ_N	time constant in low pass filter of input disturbance noise in model

Chapter 1: Introduction

Standing upright while maintaining one's balance, is one of the most basic activities of everyday life. In motor control this ability to control one's upright posture is referred to as postural control. A loss or decrease in postural control, can lead to a depreciated quality of life that is accented with injuries due to falls [4]. Decreased postural control is seen in populations such as older adults, persons with Multiple Sclerosis, and persons with Parkinson's disease [4-10]. As the general population ages, it is essential to study the mechanisms that contribute to this decrease in postural control so that possibilities for interventions and rehabilitation can be investigated. Understanding these mechanisms can lead to interventions aimed at slowing the loss of postural control or rehabilitating those that have decreased postural control. Restoring postural control can lead to fewer injurious falls, more independent activity, and an overall increased quality of life [5, 11, 12].

1.1 Postural Control Mechanisms

One of the most basic activities that the majority of people unconsciously participate in is maintaining an upright stance. This behavior is learned at an early age and becomes vital to everyday movement and function. Although maintaining one's balance is an unconscious task, it is not a trivial one, especially in regards to the physiological resources required for controlling upright posture. Even in a controlled environment without external perturbations or distractions of any sort, the body still must compensate for external gravitational forces and

internal forces from breathing, heart beating, and other physiological functions in order to maintain an upright stance.

There are many theories of motor control concerning how humans are able to control their motor output. Two of these theories are examined below in the context of postural control. The first of these theories is the reflex theory. The reflex theory is based on the idea that all of one's motions are rooted in reflexes (e.g. [13, 14]). For simple movements, the reflex theory states that a sensory stimulus activates a reflex loop resulting in a movement. For more complex movements, reflexes are chained together, one reflex activating or stimulating the next reflex, activating the next reflex to result in a total complex movement [13]. For example in postural control, the reflexes that keep a person upright would be initiated by a stretch in the soleus muscle that is activated when one's center of mass shifts forward from the ideal upright position. This reflex would then activate the muscles to counteract the forward movement. The reflex-controlled theory is also referred to as the peripheral control theory, as it implies that the control of the motor system lies in the peripheral components of the nervous system.

The second theory relevant in postural control is hierarchical or central control. The general idea behind the hierarchical theory is that there is an organizational structure that is top down, i.e., each higher level exerts control over the level below it. There are traditionally three levels: the higher association areas such as personality and cognitive function, which are above the motor cortex, which is in turn above the spinal levels of motor function. This theory is congruent with the understanding that higher centers can inhibit motor reflexes [13]. In

postural control, this theory suggests that higher centers such as cognition may impact postural control, even though it is a primarily unconscious activity.

There are three main physiological systems involved in postural control: the sensory system, the musculoskeletal system, and the central nervous system. The sensory system components are the how information is taken into the system, the musculoskeletal system components are the effectors, and the central nervous system is where the integration and processing of these signals takes place [14]. These systems are briefly described below along with the role each plays in each of the motor control theories.

1.1.1 Sensory Systems

The sensory system includes components from the visual, vestibular, and somatosensory systems. Research has shown that all three of these subsystems play an important role in postural control [15]. Studies on postural control have shown that normally sighted persons have an increased postural sway when their vision is reduced by partial blocking of vision, or distorting focus [15-17]. The decrease in postural control due to changing visual conditions demonstrates that the visual system is relied upon for input to maintain postural control both in quiet and perturbed stance. When comparing blind persons to sighted persons, this increased postural sway is not seen in any of the traditional measures of posturography indicating the existences of compensatory mechanisms from other sensory systems that allow normal control of upright stance [18].

Another subsystem that is used to maintain posture is the vestibular subsystem. The vestibular system is mainly the inner ear components that sense one's position in space from gravitational and inertial forces [19]. Many studies have been done to show the impact of the vestibular subsystem by eliminating or distorting visual input and manipulating the position of the feet. Many studies have shown vestibular function loss impairs postural control, especially when looking at balance under the effect of an external perturbation (e.g., [15, 20, 21]). Spontaneous displacements of the force platform are used to distort visual and somatosensory information such that the vestibular system is required to maintain balance [22].

The last of the sensory subsystems contributing to maintaining upright stance is the somatosensory system. The somatosensory system includes proprioceptive and tactile sensors. The proprioceptive sensors relay messages regarding the position of one's body in space, and the tactile sensors relay information about the feel of the environment [19]. Proprioception has been shown to be a factor in maintaining postural control, especially in clinical populations such as persons with Parkinson's disease or persons with cases of Multiple Sclerosis (MS) where proprioception is impaired [7, 23]. Tactile inputs, especially in the sole of the foot have been shown also to impact postural control. For example, decreased tactile and vibration sense in the sole of the foot, as seen in many pathologies such as diabetic neuropathy and multiple sclerosis, leads to decreased postural control [24, 25].

The two theories of motor control discussed above include the sensory system in different ways. In the reflex theory of motor control, the sensory system is the receptor of the stimulus.

The sensory components are what initiate the reflex, such as the sense of stretch in the soleus muscle which causes the center of balance to shift. In the hierarchical theory, the sensory system is the middle, at the cortex. The sensory inputs are processed at the somatosensory cortex where they are transferred into movement at the motor cortex, creating control over the lower processes of spinal motor function.

1.1.2. Musculoskeletal System

All sensory signals that influence musculoskeletal movement must be connected to an output in order for them to be useful in maintaining upright stance. The output or effectors of these signals is the musculoskeletal system. The musculoskeletal system has multiple components – muscles, bones, ligaments, and tendons – that work in tandem to create a sufficient structural support system. Traditionally, the only one of these components that is considered to have any intentional movement ability is the muscles. However, while this intentionally active component is important for locomotion, it is maintained that the passive stiffness and automatic reflexive nature of the musculoskeletal system that is important for postural control. The normal muscle tone and natural elasticity of tendons, ligaments, and other tissues is the bodies first response to an external perturbation of postural control [14]. Varying levels of resting muscle tension or muscle tone, strength and fatigue are all shown to impact postural control especially in persons with MS [24, 26, 27].

The two theories of motor control discussed here in regards to postural control incorporate the musculoskeletal system in different ways. The musculoskeletal system is the lowest level of

control in the hierarchical theory. Interacting with the musculoskeletal system is where spinal control is active. The nerves that innervate the peripheral muscles are lower motor neurons that synapse at the spinal cord. In the reflex theory, the musculoskeletal system and the nerves that innervate it are the basis for movement. The reflex is passed to the muscles through the lower motor neurons from sensory afferent neurons or other lower motor neurons.

1.1.3 Central Nervous System

The central nervous system, the spinal cord and brain, is where the sensory input signals are translated to the musculoskeletal output signals. In this context, the central nervous system is viewed primarily as the higher functions of the brain, where sensory signals are interpreted, and decisions are made in how to react to the inputs. From here on out, this combination of steps will be referred to as signal processing. The spinal cord is involved in transmitting the signals, but the higher level signal processing takes places in the brain. Current research has proposed different theories for how the various signals from the visual, vestibular, and somatosensory subsystems are combined and translated to an output signal that aims to maintain upright stance [15].

Research looking at altering multiple sensory inputs has shown that the sensory inputs do not all contribute equally and that there may be compensation mechanisms when each is varied [24]. There is also evidence that the processing of these sensory inputs is affected when a cognitive task is performed [28]. This suggests a cognitive component to postural control. In various populations, performance of a cognitive task during postural control measurements

shows a decrease in postural control [6, 28-30]. The decrease in postural control while performing a cognitive task is more pronounced in persons with an impaired postural control compared to controls [6, 30]. This change, whether negative or positive, in performance due to simultaneous performance of a cognitive task is referred to as the dual task cost (DTC).

In the hierarchical motor control theory, the higher centers of the brain are the top–most level of control. These higher centers control everything that falls beneath them. Therefore a cognitive component to postural control is plausible in this theory. The reflex control theory does not account for these higher association areas or processing in the brain. It maintains that all control is from the spinal level, and based on reflexive movement.

One way to research these motor control theories and physiological systems is to study a specific population that has deficits in one or more aspects of motor control. Studying various populations has been done many times, especially in populations with physical and/or neurological deficits. By studying how persons with physical and neurological deficits are able to maintain postural control, one can better understand which of these systems are essential for postural control. Determining how these systems interact in persons with deficits can lead to understanding of how these systems interact in healthy persons as well as how persons with deficits are able to compensate for their specific deficit.

1.2 Clinical Relevance of Multiple Sclerosis

One clinical population that experiences deficits in postural control is persons with multiple sclerosis (MS). Multiple sclerosis is a neurological disease affecting the myelin sheaths of nerves. Myelination serves to protect the nerve and improve the conduction of signals to and from the target tissue. In MS, the myelin sheath is subjected to an inflammatory response from the immune system that destroys myelin, therefore eliminating its protective properties. The sclerotic plaques from the myelin sheath destruction are located throughout the nervous system. The majority of the myelinated nerves are located in the brain, optic tract, and spinal cord [19]. A unique aspect of MS is the presence of stages that include asymptomatic and symptomatic periods (known as relapse) and periods of constantly worsening symptoms. The demyelination of major nerves causes a variety of symptoms including impaired vision and proprioception, decreased vibration sense and muscle strength, and spasticity [31]. These symptoms impact the everyday mobility demands.

Multiple sclerosis is most commonly diagnosed in persons aged 20-40 years of age, making it the most prevalent debilitating neurological disease found in young adults [32]. There is currently no single accepted cause for the disease, and symptoms appear at different times and in different places in every person. Typically the diagnosis of MS is a diagnosis of last resort after all other potential diagnoses have been eliminated. Research in quantifying and comparing specific symptomologies in persons with MS to control subjects helps to create a larger and more specific database of symptoms for guiding MS diagnosis, a further

understanding of the physiological aspects affected by MS, and a more complete picture of areas for potential rehabilitation and treatment.

Symptom inventories have shown difficulty maintaining balance as a concern of persons with MS [33]. The concern of loss of postural control in persons with MS is not surprising given that the vestibular, visual, somatosensory, and motor systems are involved in maintaining appropriate postural control and these systems are all affected by multiple sclerosis [3, 25, 34, 35]. Previous research has also shown that persons with MS have an elevated dual task cost compared to controls in balance tasks [36-38]. This suggests that the cognitive component of postural control is also altered in persons with MS. However, this research has been based on persons with MS whom have mild disability based on the Expanded Disability Status Score (EDSS), the standard for evaluating disabilty in MS [39]. The effect of a cognitive task on postural control has not been investigated in persons with MS with higher levels of disability.

The postural behavior seen under dual task conditions can be best explained by the hierarchical or central control theory in motor control. Since the higher assocation areas control all motor movement along with all cognition, then these functions are related and can influence the effectiveness of the other task. The reflex or peripheral theory does not account for the behavior that is seen in dual task research, as the theory maintains that all motor movement is controlled at the spinal level, without influence from higher association areas that involve cognitive function. Even though the dual task research has shown that the reflex theory cannot

be the only control mechanism in maintaining balance, there are still factors related to reflexes that influence balance, such as spasticity.

Spasticity is a motor dysfunction described as a velocity-dependent increase in the stretch reflex [40]. Spasticity can present as increased muscle tone, such that there is a noticeable tightness in the muscle. Previous work on spasticity in persons with MS has shown that those with higher spasticity, as measured by the H-reflex amplitude, have greater postural sway than those without spasticity. This sway increase is especially signifcant in the mediolateral direction [3]. The postural behavior of a person with spasticity can be accounted mainly in the peripheral or reflex theory. Since spasticity causes the motor reflexes to be hyperreactive, in the reflex theory it stands that the reflexes will be evoked more often by movement, resulting in more sway. In the hieracrchical theory, spasticity would mainly affect the spinal levels of motor control, i.e., the lowest level. Based on the top down control paradigm, changes at this level should still be overriden by the higher centers.

Although it has yet to be fully investigated, it is thought that improvements in spasticity can lead to improvements in postural control in persons with MS. Previous research has shown that improvements in the postural control of persons with cerebral palsy have been achieved with a reduction of spasticity [41]. In Sosnoff *et al.*[3] spasticity is measured in the soleus muscle, which is one of the muscles that contributes to control of the ankle. Since control at the ankle is one of the strategies used to maintain postural control, it is easy to see how the spasticity in the soleus muscle could directly impact postural control [42].

1.3 Modeling

A postural control model can help us gain understanding as to the neurological and physiological factors affecting postural control. An inverted single link pendulum in the anterioposterior (AP) direction is traditionally the model of choice (e.g., [1, 43]). Some work has also been done looking at an inverted single link pendulum to represent sway in the mediolateral (ML) direction [2, 44]. Investigation of the mediolateral and anterioposterior models has been done for normal adults, children with scoliosis, and children with Cerebral Palsy (CP) [2, 45, 46].

The various models have led to insights about postural control. In previous works, inverted pendulum models in the AP plane have shown that model – specific parameters such as stiffness, damping, and noise level all increase due to aging [1, 47]. The scoliosis based model showed an increased stiffness in the AP plane compared to healthy children [46]. In children with CP the model has confirmed that the postural stability in both planes (AP and ML) is similar as opposed to healthy young adults where stability is greater in the AP direction. The model studies of children with CP also indicate that sensory deficits are detected, but the compensatory mechanisms to correct for the deficits are not available [45].

Many models start with a small disturbance torque that represents the natural noise in the human body from internal forces, such as circulation and respiration. The disturbance torque causes movement of the pendulum, or the human system. In order to maintain upright stance, the disturbance torque is controlled for by a proportional-integral-derivative (PID) controller

with a neutral set point. This PID controller roughly represents the sensory systems and the neural processing of the central nervous system to the output musculoskeletal system. Most models include a time delay between the motion of the pendulum and the feedback to the controller to represent the time for signal conduction from the cortex to the distal parts of the body.

There is some debate over the necessity of the inclusion of the integral part of the controller [1, 43]. Masani *et al.* [43] do not include an integral component of the controller, as they note that during quiet standing, the center of pressure oscillates around a set point. This behavior of oscillating around a set point is more characteristic of a proportional-derivative system as opposed to a proportional-integral-derivative system [43]. Maurer and Peterka [1] include the integral component in their work based on the previous work of Johansson *et al.* [48] who showed that the experimental data was best explained by the three component controller. Supporting the reasoning of Masani *et al.* [43], the integral component in Maurer and Peterka's [1] model was found to be a much smaller gain than the derivative and proportional components indicating overall behavior consistent with a proportional-derivative controller.

Another debated aspect is one of passive torque components. The passive components are passive stiffness and passive damping that represent the intrinsic mechanical properties of the musculoskeletal system. These components are not affected by the signal transduction time delay. The passive torque components have been left out of the study by Masani *et al.* [43], which assumed that balance was regulated by active torque alone. This assumption was made

to search for the simplest and most robust model, such that the active torque components would be able to compensate for the noise disturbances. It was reasoned that adding the passive torque components to the already sufficient purely active torque model would assist the active torque model to produce even more reliable and realistic results. In the Maurer and Peterka [1] study that optimized a PID controlled model with the passive components to match healthy adult traditional posturography measures, the best fit was found when the passive components converged to zero.

Creating a model that represents persons with MS is an intriguing task as many of the components represented in the traditional model are altered by disease, such that the disease's impact will hypothetically show up numerically in the model results. As the myelin sheathes are degraded in the central nervous system, the speed of signal transduction slows. The PID controller may be affected by changes in vision and cognitive performance that comes with the disease progression in persons with MS, although these aspects are not being directly investigated. The passive stiffness and damping components may be affected by the change in spasticity and strength that has been seen throughout the course of MS [49].

1.4 Research Questions in Thesis

The research questions addressed in this thesis stem from understanding factors that affect the postural control system. The first part of this work focuses on the impact that the simultaneous performance of a cognitive task has on postural control. Postural control was measured in persons with MS both during quiet standing and while performing a cognitive task. It was hypothesized that the postural control of persons with MS would be more negatively affected

by the cognitive task than the control subjects. The results of this simple test can help to indicate the importance of cognitive load to generally automatic motor tasks such as postural control.

The second part of this work focuses on the affects of spasticity on postural control. Previously collected postural control data from persons with MS and spasticity were used to test an existing inverted pendulum model. The inverted pendulum model was used to investigate possible explanations for the differences seen in postural control measures between persons with MS with high and low spasticity and controls. The model parameters that were expected to vary significantly from the model based from controls data to the model based from the MS data were the parameters of passive stiffness and passive damping. These passive components are independent from the model parameters that represent the neural control of postural control. The passive components were hypothesized to be different, as it is plausible that the effects of spasticity will be represented in these parameters, since spasticity is not necessarily dependent on higher level neural processes.

Chapter 2: Postural Control in Multiple Sclerosis: Effects of Disability Status and Dual Task

Abstract

Persons with Multiple Sclerosis (PwMS) have postural control impairments. The simultaneous performance of a cognitive task while maintaining an upright posture (i.e., dual task) negatively influences postural control in PwMS with mild disability. This investigation compares the effect of simultaneous cognitive task performance on postural control in PwMS with mild and moderate disability. Forty-five PwMS were divided into groups based on their Expanded Disability Status Scale (EDSS) scores: mild (EDSS: 2.0-3.5) and moderate (EDSS: 4.0-6.5) disability. Each participant underwent posturography testing during a quiet baseline condition and a cognitive task condition. The cognitive task was a word list generation. Median sway velocity, root mean square displacement, and sway area were calculated for each condition. The moderate disability group had significantly worse postural control than the mild disability group. There was a decrease in postural control in the dual task condition. There were no significant task-by-group interactions on postural control. The results suggest that postural control declines with disability status and is negatively affected by a concurrent cognitive task in PwMS. These results further suggest that, unlike findings of a detrimental effect of dual tasking during walking in PwMS, the dual task cost during a balance task is not different between disability levels.

2.1 Introduction

Multiple sclerosis (MS) is a central nervous system disease mainly diagnosed in young and middle-aged people [32]. The pathologic process presumably leads to inflammation and demyelination [50] resulting in heterogeneous clinical manifestations including visual impairment, vertigo, impaired proprioception and vibration sense, muscle weakness, and spasticity [32].

Balance impairment is common in MS [3, 33, 34]. This is not surprising given that maintaining an upright posture (e.g., postural control) requires integration of vestibular, visual, and somatosensory information and appropriate motor output. Balance impairment likely worsens with increased disability given that processes contributing to balance decline with disability progression. However, there is minimal research testing the effect of disability status on balance using posturography.

Balance impairment in MS might be accentuated when simultaneously performing a cognitive task (e.g., dual task). This notion is based on several factors including cognition impairment being common in MS [51, 52] and growing evidence that cognition contributes to postural control [53]. For instance, the simultaneous performance of a cognitive task during a postural task decreases postural control [30, 54, 55]. This effect termed dual task cost (DTC) is elevated in persons with impaired postural control compared to healthy controls [6, 53].
There are data supporting elevated DTC in balance tasks in MS compared to controls [37, 56, 57], but this has only been examined in those with minimal disability. Consequently, the

influence of disability progression in PwMS on dual task cost during postural control remains to be addressed.

This investigation compared DTC during standing in persons with MS with mild and moderate disability. We expected that, in general, the postural control of persons with moderate disability will be decreased and DTC will be increased when compared to persons with mild disability [58].

2.2. Methods

2.2.1 Participants

Forty-five community dwelling persons with a neurologist – confirmed diagnosis of MS participated. Each participant was ambulatory without or with an assistive device such as a cane or walker and had an Expanded Disability Status Scale (EDSS) score between 2.0-6.5 with a median of 4.0. Participants were divided into two groups based on disability status (mild and moderate). The mild disability (n = 19) group had an EDSS score between 2.0-3.5, and the moderate disability group (n = 26) had an EDSS score between 4.0-6.5.

2.2.2 Procedures

All experimental procedures were approved by the local institutional review board. Upon arrival, participants were informed of the research procedures and asked to provide informed consent. Participants next provided demographic and disease history information. All participants then underwent a neurological examination by a Neurostat certified examiner that yielded the EDSS score. Lastly, participants completed postural control testing. Postural control

was quantified with a 3-axis force platform (AMTI, Watertown, MA) in two separate conditions: 1) a baseline quiet standing condition and, 2) simultaneous performance of a cognitive task during standing condition. Each condition consisted of two 30 s trials. The cognitive task was a modified word list generation (WLG) task. The WLG task has been used previously in persons with MS as a cognitive test during neurophysiological testing [59] and dual task research [56, 58]. During the WLG task each participant was asked to name items in a given category. To minimize potential for learning, a semantic WLG task was used (i.e., list animals) in the first cognitive trial and in the second trial a phonetic WLG task was used (i.e., list words that start with the letter "H"). To quantify postural control, median sway velocity along the anterioposterior and mediolateral axes, root mean square displacement along the anterioposterior and mediolateral axes, and sway area (the area of the ellipse that encloses 95% of postural sway) were calculated based on established procedures [3].

2.2.3 Statistical Analysis

Multiple statistical analyses were performed to understand the relationship between disability level and postural control. Differences in the demographic characteristics and word counts between groups were determined by an independent-samples χ^2 test for categorical variables and an independent samples *t*-test for continuous variables. The main analysis of the posturography measures consisted of mixed model ANOVA with task (baseline or dual) as a within-subject factor and group (mild or moderate) as the between-subject factor. Significance was noted when $p < 0.05$. The magnitude of the task and group effect were expressed using partial eta-squared (η^2) and Cohen's guidelines of 0.01, 0.06, and 0.14 were used for judging

the η^2 as small, moderate, and large, respectively [19]. Statistical analyses were completed using SPSS version 17.0 (SPSS, Inc, Chicago, IL).

2.3 Results

Demographic characteristics of the sample population are reported in Table 2.1. The demographic characteristics of this sample are in line with the general MS population [60]. Per design, the mild disability group had a lower EDSS score than the moderate disability group. The mild disability group further had lower assistive device use, was younger, and had fewer cases of progressive MS. The mild disability group listed a greater number of words (13.4 ± 2.8) than the moderate disability group (10.8 ± 2.8; $p = 0.003$).

Group and cognitive task influenced postural control (Figure 2.1). There generally were significant main effects for group and task but no interactions (Table 2.2). The moderate disability group had worse postural control as quantified by a larger sway area (295.5 vs. 182.4 mm^2), and anterioposterior root mean square displacement (6.5 vs. 4.5 mm). Effect sizes for the group effect on the postural control parameters were moderate for both sway area ($\eta^2 = 0.11$) and root mean square displacement in the anterioposterior direction ($\eta^2 = 0.10$).

The cognitive task decreased postural control compared to the baseline condition as indexed by greater sway area (277.3 vs. 200.6 mm^2), median velocity in the anterioposterior direction (8.6 vs. 6.8 mm/s) and the mediolateral direction (11.9 vs. 8.5 mm/s), and root mean square displacement in the mediolateral direction (6.8 vs. 5.7 mm). Effect sizes (η^2) for the task effect

on the postural control parameters were large, ranging from 0.145 for sway area to 0.334 for median velocity in the mediolateral direction (Table 2.2).

2.4 Discussion

This investigation examined the effect of disability status and cognitive task on postural control performance in persons with MS. This investigation yielded two novel observations: 1) PwMS with greater disability had decreased postural control; and 2) the effect of the cognitive task on postural control did not differ by disability status.

It has been previously reported that persons with MS have impaired postural control compared to controls [3, 33, 61]. Fjeldstad and colleagues [8] found significant impairment in PwMS compared to controls using clinical measures and posturography. The current observations extend these reports by documenting that postural control in static balance continues to decline with advances in disability status in MS.

Due to the behavioral nature of this investigation the mechanisms underlying the decline in postural control were not elucidated. Deficits in postural control in MS are most likely multifaceted. Sosnoff and colleagues[3, 62] demonstrated that spasticity contributes to postural dysfunction in PwMS. Rougier and colleagues[23] found that proprioception deficits contribute to postural dysfunction in this population. Indeed there have been several reports that proprioception deficits contribute to altered postural control in PwMS [33, 63]. In addition to spasticity and proprioception, other factors including muscle strength and fatigue [64] have been implicated in postural control deficits in PwMS. Recently, elevated lesion load in the brain

stem and motor cortex have been associated with postural impairments in PwMS[65]. It is possible that any or all of these factors could worsen with disability progression in PwMS and result in deficits in postural control. Further research is necessary to understand the factors contributing to elevated postural deficits with disability progression in PwMS.

2.4.1 Dual Task

The impact of the cognitive task on postural control in PwMS with minimal disability has been demonstrated previously. Kalron *et al.* [56] demonstrated persons with clinically isolated syndrome suggestive of MS had elevated postural sway (43% increase from baseline quiet standing) in a dual task condition. Porosinka *et al.* [37] and Negahban *et al.* [57] also showed decreased postural control in PwMS with mild disability with a concurrent cognitive task. These findings are congruent with our results of increased median velocity in both the AP and ML axis with a cognitive task (27% and 40%, respectively).

There are two main theoretical explanations for the observed dual task effect: the bottleneck model and the capacity model [53]. The bottleneck model suggests decreases in performance arise because both tasks are attempting to utilize the same neurological pathway. Although it is logical to assume that the neural pathway(s) required for word generation do not overlap with that of postural control, it has been suggested that verbal fluency tasks, such as the task used here, share complex neural pathways connecting different brain regions which are interlinked with those controlling gait and posture [66]. The capacity model suggests that there exists a set capacity limit on the amount of cognitive resources available, and that the tasks at hand are completed within the limits of those resources. In the capacity model, the postural control

performance would potentially have to be decreased to allow for performance of the WLG task. Due to neurological damage caused by MS, PwMS could potentially have less neurological capacity. Further research is needed to examine these competing theories of dual task effect in MS.

One might expect that PwMS with greater disability would have less cognitive capacity or more difficulty using the same neurological pathway simultaneously, but surprisingly, there was no task by disability group interaction within the current investigation. It was hypothesized that persons with greater disability would demonstrate a greater DTC. This hypothesis was based on extant data [58] demonstrating an elevated DTC during walking in PwMS with greater disability compared to those with lower disability.

The lack of a task by group interaction may be due to several factors. The most likely explanation is that neither group was able to exceed the physical boundary of their postural control. Essentially, the static postural control task employed here demonstrates a floor effect. It is also possible that the groups allocated resources to the dual task condition differently. When presented with a dual task individuals intuitively pick a given task as the primary task. It has been argued that postural control is the *de facto* primary task [53]. It is possible that the moderate disability group sacrificed their performance on the cognitive task in an effort to maintain their upright posture, while the mild disability group did not have to sacrifice performance of the cognitive task to maintain a postural control. In support of this notion, the mild disability group had greater number of word utterances than the moderate disability

group. Unfortunately, baseline cognitive performance was not collected here. Consequently, this possibility cannot be directly tested with the current data. Further work is necessary to determine why disability was not related to dual task performance in postural control.

Investigating the dual task cost during postural control is relevant because of its association with falls in MS [67] and other clinical populations[68]. Specifically, poor concentration has been shown to a contributing factor to falls in PwMS [69]. Although there is evidence that dual task performance can be improved in older adults without MS [5], it is not clear that it can be improved in PwMS. There is evidence that postural control can be improved in PwMS [70, 71] and there is some limited evidence that cognitive function can be improved with target interventions [71, 72]. Indirectly, the benefits of rehabilitation on postural control and cognition suggest that dual task cost in PwMS during postural control can be minimized with targeted interventions. However, this possibility requires additional scientific scrutiny.

A limitation of this study is its cross-sectional design. Also, there were no controls included in this study, so it is not clear that the dual task effects seen in persons with MS are distinct from age and gender matched controls. However, given that previous reports have documented that dual task effects are elevated in MS compared to controls [37, 56, 57], this is of minimal concern.

In the current study, persons with MS who had moderate disability showed worse postural control than those with mild disability. The execution of a concurrent cognitive task decreased

the performance of postural control in persons with both mild and moderate disability. However, this dual task cost did not increase with a higher disability level. Further work examining the functional consequences and predictors of dual task cost in persons with MS is needed.

2.5 Figures

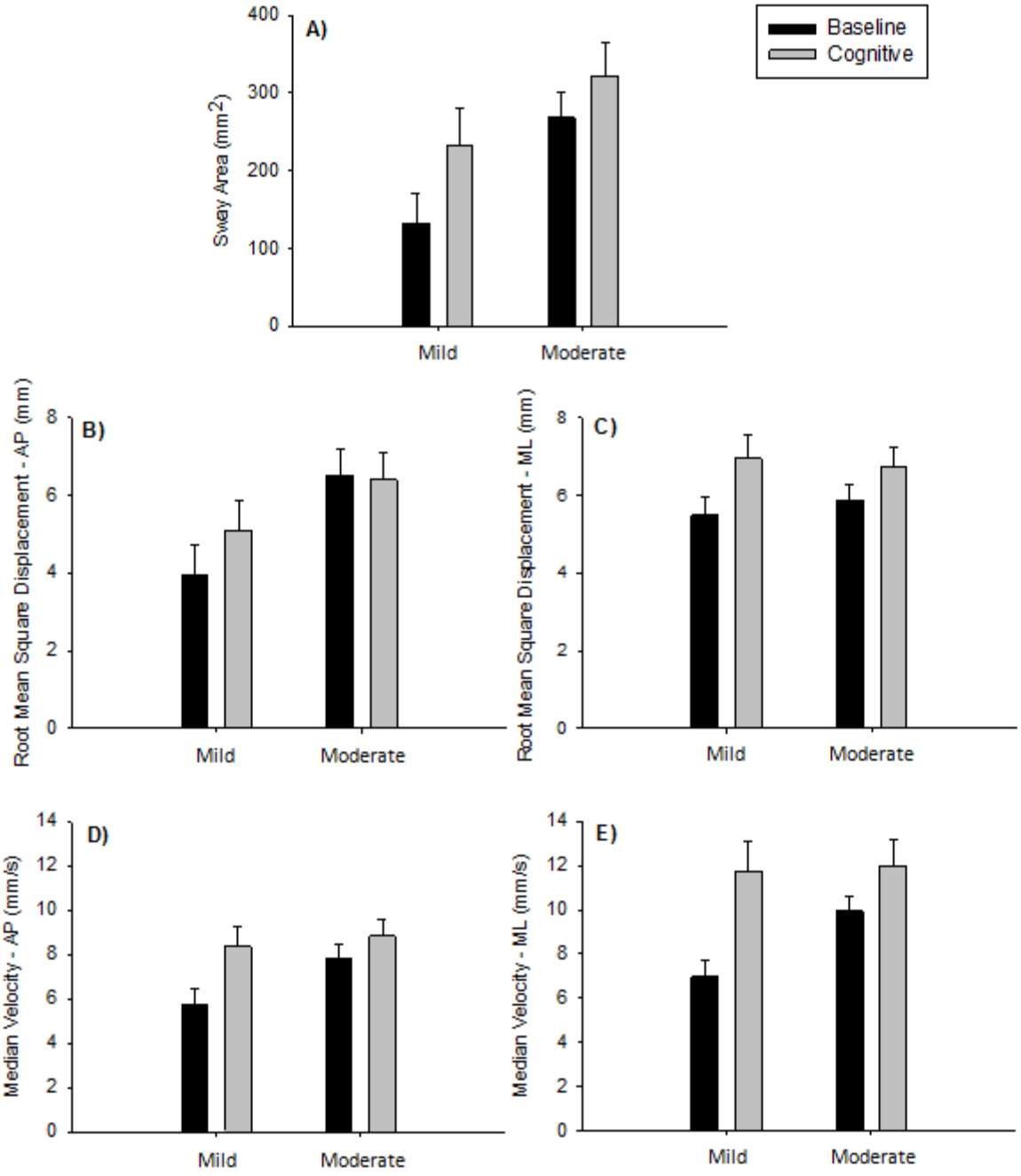

Figure 2.1: **Postural Control metrics as a function of group and task**. Values are means ± SE. **A)** Sway Area; **B)** Root Mean Square Displacement (anterioposterior); **C)** Root Mean Square Displacement (mediolateral); **D)** Median Velocity (anteriorposterior); and **E)** Median Velocity (mediolateral).

2.6 Tables

Table 2.1: Participant Demographics.

Demographic Characteristic	Mild n = 19	Moderate n = 26	p-value
MS Type (Relapsing-remitting/ Progressive)	19/0	23/3	0.045*
Age [years], mean(std)	46.4 (13.1)	58.2 (7.5)	0.002^{+}
Gender (female/male)	17/2	24/2	0.744*
MS Duration [years], mean(std)	10.3 (9.1)	15.65 (9.7)	0.062^{+}
EDSS, median (IQR)	3.0 (0.5)	6.0 (2.0)	0.000*
Use of Assistive Device (% use)	0%	54%	0.001*

*significance determined by an Independent-Samples χ^2 test

$^{+}$significance determined by an Independent Samples t-Test

Table 2.2: Repeated Measures ANOVA results of center of pressure measures.

Parameter		F (1, 43)	p-value	η^2
Sway Area	Task (Baseline/Cognitive)	7.31	0.010	0.145
	Task*Group	0.65	0.426	0.015
	Group (mild/moderate)	5.02	0.030	0.105
Mean Velocity (AP)	Task	9.56	0.004	0.182
	Task*Group	1.85	0.180	0.041
	Group	1.83	0.183	0.041
Mean Velocity (ML)	Task	21.54	0.000	0.334
	Task*Group	3.45	0.070	0.074
	Group	1.75	0.192	0.039
Root Mean Square (AP)	Task	1.03	0.317	0.023
	Task*Group	1.52	0.224	0.034
	Group	4.51	0.039	0.095
Root Mean Square (ML)	Task	8.03	0.007	0.157
	Task*Group	0.61	0.439	0.014
	Group	0.022	0.883	0.001

Chapter 3: Effects of Spasticity in Persons with Multiple Sclerosis: A Bi-planar Modeling Approach

Abstract

Single link inverted pendulum models have been developed to further understand postural control. Some of these models, including the one in this study, use variations of a proportional-integral-derivative controller to control the pendulum. Persons with multiple sclerosis (MS) are known to have decreased postural control, with spasticity contributing to the decline. A bi-planar inverted pendulum postural control model was modified from previous models to represent populations of persons with MS with high and low spasticity, and a population of healthy controls. The experimental data used to inform the model were previously published. The model successfully recreated differences in traditional sway parameters between the two MS groups (low and high spasticity) and control group as noted experimentally. The model gains used to achieve the center of pressure measures were analyzed for significant differences between the MS and controls models. Significant differences were found between the group model gains of neurological controller stiffness and input noise gain in the mediolateral direction. A linear regression analysis revealed that a combination of the passive stiffness in the anterioposterior direction, and the neurological controller stiffness in both directions best accounted for the variance in the H-M reflex level, a measure of spasticity. These significant differences in gains suggest that persons with MS use different control strategies than healthy persons to maintain postural control.

3.1 Introduction

Multiple sclerosis (MS) is a neurological disease affecting the myelin sheaths of nerves. This myelin serves to protect the nerve and improve the conduction of signals to and from the target tissue. In MS, the myelin sheath is subjected to an inflammatory response from the immune system that destroys the protective property of the myelin. This response causes the destruction of myelin sheaths and the creation of sclerotic plaques that are located throughout the nervous system, especially in the brain, optic tract, and spinal cord [19]. The demyelination of major nerves causes varied symptoms including impaired vision and proprioception, decreased vibration sense and muscle strength, and spasticity [31].

Symptom inventories have shown that loss of balance and difficulty maintaining balance are concerns of persons with MS. The concern of loss of postural control in persons with MS is not surprising given that the vestibular, visual, somatosensory, and motor systems are involved in maintaining appropriate postural control and these systems are all affected by multiple sclerosis [3, 25, 34, 35]. One of these symptoms of interest in this report is spasticity. Spasticity is a motor dysfunction described as a velocity-dependent increase in the stretch reflex that presents as an unusual tightness of the muscle [40]. The tightness or resistance to stretch of the muscle impacts balance. Previous work by Sosnoff *et al.* found that in persons with MS and higher spasticity had greater postural sway than those without spasticity [3, 49]. The results from the Sosnoff *et al*. [3] study indicated that COP measures of 95% confidence elliptical area sway, ML sway range, radial sway velocity, and ML 95% power frequency were significantly different between persons with spasticity and controls ($p<0.05$). Specifically, these values were

larger for persons with spasticity than for controls. It is unclear how spasticity may affect the psotrual control mechanism. Mathematical models of the postural control system may help to facilitate identifying features that represent spasticity.

A postural control model can help us gain understanding as to the neurological and physiological factors affecting postural control. A closed-loop inverted single link pendulum model with time delayed proportional-integral-derivative or proportional-derivative control in the anterioposterior (AP) direction is traditionally the model of choice (e.g., [1, 43]). Some work has also been done assessing an inverted single link pendulum to represent sway in the mediolateral (ML) direction [2, 44]. Investigation of the mediolateral and anterioposterior models has been done for normal healthy adults, children with scoliosis, and children with Cerebral Palsy (CP) [2, 45, 46].

The various models have led to insights about postural control. In previous work, inverted pendulum models in the AP plane have shown that parameters, such as stiffness and damping in the neurological controller and noise level, all increase due to aging [1, 47]. The scoliosis based model showed an increased stiffness of the neurological controller in the AP plane compared to healthy children [46]. In children with CP, the model confirmed that postural stability in both planes (AP and ML) is similar, as opposed to healthy young adults where stability is greater in the AP direction. Model studies of children with CP also indicate that sensory deficits are detected, but the compensatory mechanisms to correct for the deficits are not available to the child due to the symptoms of cerebral palsy [45].

In this study, the model created by Maurer and Peterka [1] was expanded to explore possible changes in the AP and ML postural control system in a population of persons with multiple sclerosis and spasticity (Figure 3.1). This model uses a time-delayed proportional-integral-derivative (PID) controller to represent active neural control. It also includes components to represent the passive stiffness and damping properties of the musculotendon structure. In this study, we hypothesized that the physiological changes in postural control due to spasticity will result in changes to these passive components, but not active components since spasticity is expected to only affect the stretch reflex. We further hypothesized that the passive components in the ML direction will be especially affected since experimental data found greater postural sway in the same direction [3].

3.2 Methods

3.2.1 Participant Data Collection

The postural control data of sixteen subjects with MS (9 with high spasticity and 7 with low spasticity) and sixteen age- and sex-matched controls were used in the current study and have been previously presented in [3]. All participants provided written informed consent and the protocol was approved by the university's institutional review board. The procedures used to collect and analyze the data are described in detail in [3] and are briefly summarized below.

All participants with MS underwent H-reflex testing with standard electromyography (EMG) equipment. The H-reflex was used as an electrophysiological indicator of spasticity as the

excitability of the motor neuron pool [73]. The outcome measure of this test was a maximal H wave/maximal M wave ratio (H-M ratio) [73]. The H wave occurs after the alpha motor neuron has been activated by the stimulated 1a afferent sensory neuron from the reflex loop. The M wave occurs when the alpha motor neuron is directly stimulated. In spasticity, the H-M ratio is increased, mainly by a hyperactive stretch reflex which increases the H wave. Based on the H-M ratio, the MS participants were divided into two groups, high spasticity, and low spasticity. The two spasticity groups did not show any significant differences in the demographic variables of age, expanded disability status score (EDSS), and duration of MS [3].

All participants with MS and control participants underwent postural control testing, using dual force platforms (OR-6-3A, AMTI, Watertown, MA). One foot was placed on each platform. The participant was then asked to stand quietly. A total of four 30 second postural sway trials were collected from each participant. The forces and moments from each force platform were then combined to calculate the total body center of pressure (COP) in the anterioposterior (AP) and mediolateral (ML) directions. From these COP measures, traditional postural sway measures were calculated for each direction [74]. These measures included sway range, velocity, and 95% power frequency. 95% confidence elliptical area was also determined.

3.2.2 Model Description

An inverted pendulum model of postural control for the anterioposterior direction has been previously created by Maurer and Peterka [1]. The model created by Maurer and Peterka was expanded by Bustamente Valles *et al.* [2] to predict sway in both the anterioposterior and

mediolateral directions [2]. This previous research was the basis of the model used in this study, which was developed to account for variation seen in postural control of persons with MS as a function of spasticity (Figure 3.1).

The inverted pendulum model assumes a neural controller that senses the deviation from the ideal upright position and corrects for the deviation by creating a corrective torque. This model assumes no external disturbance torque to the body, and all deviations are caused by an internal disturbance such as respiratory, circulatory, and digestive functions. These internal disturbances are represented in the model by a band-limited white noise [1, 43]. The white noise was sent through a low pass filter before entering the system as the disturbance torque [1, 43] (Figure 3.1).

As per the previous modeling work [1, 2, 43], the inverted pendulum represents the human body with the parameters set to represent the average adult human male that sways only at the ankle joint (moment of inertia = 66 kg/m^2, mass = 76 kg, height of center of mass = 0.87m). The neural controller is represented by a proportional-integral-derivative (PID) controller with a neutral set point. This PID controller roughly represents the sensory systems and the neural processing of the central nervous system to the output musculoskeletal system. The input to the PID controller is the body sway with a time delay for signal transduction and processing. Additional control components are included which account for the passive components of body, intrinsic stiffness and damping at the ankle, which contribute to postural sway. The passive components from Maurer and Peterka's [1] model investigation were included for this

study on spasticity in persons with MS, as spasticity affects the reflexive stiffness of the muscles, especially in the lower leg. These components of the inverted pendulum model use in this study are expressed in a block diagram shown in Figure 3.1.

There are eight parameters that influence the behavior of the model (Figure 3.1). The neural controller contains three of these gains: the proportional, derivative, and integral gains (K_p, K_d, and K_i, respectively). The passive components incorporate two of these gains: the passive stiffness K_{pass}, and passive damping B_{pass} of the system. The input noise characteristics are determined by two gains, K_N and τ_N. K_N is the gain of the low pass filter on the input noise, and τ_N is $1/f_c$, where f_c is the cutoff frequency of the low pass filter. The last parameter is the time delay in the feedback control concerning the transmission and processing time of neurological signals, τ_d. The control equations for the model are in Appendix A. The Simulink block diagram is in Appendix B.

Simulations were performed to estimate either AP or ML center of pressure (COP) data. Simulations were performed using Simulink version 7.3 of MATLAB 7.8.0 (The MathWorks, Natick, MA). The simulation was solved with the Dormand-Prince algorithm (ode5) with a fixed step size of 0.01 seconds. The simulation was run for 20 seconds to match the length of the participant data trials. An example stabilogram from the simulation can be seen in Figure 3.1F.

3.2.3 Model Optimization

The model parameters were optimized (Figure 3.2) to match the participant data for the two test groups (controls and persons with MS). The model gains (K_N, K_p, K_d, K_{pass}, and B_{pass}) were

optimized using the function “fmincon” from the optimization toolbox in MATLAB. Traditional COP measures were then calculated from the output of the model simulation. These traditional measures were then compared to traditional measure computed from the participant COP data from [3]. A total error was then calculated as the difference between the model simulation values and the experimental participant values. This error value was then minimized by the optimization function by altering the gain values of the simulation. The error function was

$$E = \sum_{i=1}^{N} abs\left(\frac{M_p - M_s}{M_p + M_s}\right) \tag{3.1}$$

where M_p is the measure calculated from the participant data, M_s is the measure calculated from the simulation data, and N is 6, the total number of traditional measures calculated and compared. Equation 3.1 is the same error function used by Maurer and Peterka [1].

A few of the model parameters were set to constant values. In previous modeling work [1, 2, 45, 46], τ_d was allowed to vary, but those works did not include the passive components of the model. Also since the primary focus of the current investigation was the effect of spasticity, allowing the cortex-motor delay (τ_d) to vary was not essential. When τ_d was allowed to vary to match previous data sets [2, 45, 75], the change was minimal (τ_d = 0.171, 0.175, 0.165). Further, preliminary simulations found that the values of K_i, τ_N, and τ_d, were unchanged between the mediolateral (ML) and anterioposterior (AP) models. Therefore in order to minimize the number of parameters for optimization, K_i, τ_N, and τ_d were held to constant values consistent with the previous literature [1, 2]. Based on previous modeling work, K_i was set to 0.6 Nm·s^{-}

^{1}·deg^{-1}[1]. The cutoff frequency of the low pass filter on the input noise was set to 0.5 Hz, such that τ_N was set to 0.32 Hz^{-1}, similar to other previous work [43]. τ_d was held constant at 0.171 s.

The gains that were allowed to vary during the optimization procedure were K_N, K_p, K_d, K_{pass}, and B_{pass}. The initial guess for the gains during the optimization were set to the gains found by Maurer and Peterka [1] in their model that included passive stiffness and damping, with the exception of K_N which was set to start at the value used by Masani *et al* [43]. These values were K_N = 2 Nm, K_p = 10.0 Nm·deg^{-1}, K_d =0.34 Nm·s·deg^{-1}, K_{pass} = 10.2 Nm·deg^{-1}, and B_{pass} = 3.0 Nm·s·deg^{-1}. Within fmincon, the lower bound was used such that no gains were allowed to vary below zero, and the upper bound was set to 100 for each gain to confine the optimization space. The upper bound was determined by investigating the gain values of previous modeling work and allowing for generous movement on those values. The default criterion of fmincon was used to determine minimization of the error function (Eq. 3.1).

Optimizing to experimental data

The model was optimized to the individual characteristic behaviors of each test subject (16 control subjects and 16 MS subjects (7 with low spasticity and 9 with high spasticity)). The AP and ML simulations were run independently, such that they did not have information nor feedback from the other directional model. Therefore a total of 32 model optimizations were run. To compare the model simulation results with the experimental data, the characteristic behavior of each subject was determined by averaging the traditional parameters calculated from the COP of four independent 20 second experimental trials. The optimized models were then used to create estimated AP and ML center of pressure (COP) data which were then used

to calculate traditional measures of sway. These measures were mean distance, root mean square distance, maximum distance, range, mean velocity, and 95% power frequency. 95% confidence ellipse could not be included since the two directional models were not informed of the position of each other.

3.2.4 Statistical Analysis

A number of statistical analyses were performed. To determine if the COP parameters produced by the models were similar to the experimental COP parameters, independent samples *t*-tests were run between each experimental group COP parameters and the corresponding model COP parameters. For these tests a lack of significance showed that it was possible for the COP parameters to come from the same underlying distribution. To determine whether gains for the control and MS subject models were different, a univariate ANOVA with group as between – subject factor was performed for each gain. The gain values analyzed were the mean values of the model gains calculated for each participant per test groups. The gains were separated by AP and ML directions. Another univariate ANOVA with group as between subject factor compared whether the simulation-derived COP measures from the controls and MS models showed similar group differences as the experimental traditional parameters of control and MS subjects as noted in Sosnoff *et al*. [3]. Finally, a step-wise linear regression analysis of MS subject model data was used to determine if there were any model gains that were related to the spasticity index of H-M ratio. Statistical analyses were completed using SPSS version 17.0 (SPSS, Inc, Chicago, IL). Significance for all statistical tests was noted when $p < 0.05$.

3.3 Results

The optimization procedure produced gains that allowed the model to produce realistic COP trajectories (**Error! Reference source not found.**3), such that simulation-estimated traditional COP measures were within one standard deviation of the control and MS experimental subject data. There were no significant differences between the experimental subject traditional parameters and the corresponding model simulation traditional parameters for either test group (3.6 Tables **Table** 3.1, 3.2 and 3.3).

In comparing the MS with high spasticity and MS with low spasticity model simulations to the control model simulation results, main group effects were found in ML mean distance (MD-ML), ML maximum distance (Max-ML), ML mean sway velocity (MV-ML), ML range (Range-ML), and ML root mean square distance (RMS-ML). Post hoc analysis revealed that the MS model with high spasticity had significantly greater MV-ML ($p = 0.05$) and Range-ML ($p = 0.04$) than the controls, which is consistent with Sosnoff *et al.*[3]. The MS model with high spasticity also had significantly higher MD-ML ($p < 0.01$) and RMS-ML ($p=0.01$) than the model simulations of the control population. Post hoc analysis revealed that the MS model with low spasticity was significantly different from the control model in RMS-ML ($p<0.01$), Range-ML ($p = 0.01$), Max-ML ($p = 0.01$), and MD-ML ($p<0.01$). There were no significant differences between model results in the low and high spasticity groups.

Significant differences were also found in the gain values between the model simulations of the control and MS populations (low and high spasticity) (Tables 3.4 and 3.5). In the AP direction,

the gains were not significantly different between any of the three models. In the ML direction, a main group effect was seen in the noise gain (K_N-ML) ($p = 0.04$). Post hoc analysis revealed that the high spasticity model had a significantly higher K_N-ML than the controls model ($p = 0.02$) as well as a significantly higher K_p-ML than the controls model. The linear regression analysis revealed that K_p-ML, K_{pass}-AP, and K_p-AP created a model to predict the H-M ratio ($R^2 = 0.702$, $p = 0.02$).

3.4 Discussion

3.4.1 MS and Control Model Comparison

The goal of this study was to determine if the difference in experimental COP measures between controls and persons with MS would be recreated in a bi-planar inverted pendulum model by differences in the gains of passive components. It was expected that modifications to existing models of postural control [1, 2] would be successful in representing the postural control of a population of persons with MS. The parameters that define the differences in the model, K_N, K_p, K_d, K_{pass}, and B_{pass}, were expected to vary significantly between the controls model and the model of persons with MS. Due to spasticity in the persons with MS, K_{pass} and B_{pass} were especially suspect in predictions of the significant differences in the controls and MS models. The differences in the model provide insight into the differences in postural control mechanisms between the three populations.

The optimal gains from the model produced sway measures that accurately represented postural sway of populations of MS and control subjects. There were no significant differences

between the values produced by the model simulations and experimental data (Tables 3.1, 3.2, and 3.3). The model simulations were also able to recreate the significant differences in MS and control populations found by Sosnoff *et al.* [3] in ML sway range and radial sway velocity (Figures 3.3 and 3.4).

The comparison of model parameters between groups provides insight into the differences between the postural control systems of healthy normal controls and people with MS with high and low spasticity. One could speculate that the increased noise gain (in the ML direction) physiologically represents the degradation of the neural signal transduction in persons with MS [1, 45]. The main group effect seen with K_N-ML was significant between the controls model and the model of persons with MS and high spasticity, but not between the models of persons with high spasticity and persons with low spasticity, or persons with low spasticity and controls. Since it was only significant in the model of persons with high spasticity, it is likely that this noise represents a higher level of spasticity as opposed to indicating an aspect of MS common between the two spasticity groups. The differences seen in K_p-ML, the stiffness of the neurological controller, between the high spasticity group and the controls are similar to those seen in previous AP models between controls and elderly subjects [1]. Once again, there were no significant difference between the low spasticity model and either of the other two models. This suggests that the increased K_p-ML is directly related to spasticity level, as opposed to being associated with MS.

Since the two directional models were not integrated, it is difficult to gain a full perspective of the interaction between the AP and ML components. It has previously been proposed that the different COP parameter changes in the AP and ML direction in persons with MS may be due to compensatory mechanisms used to cope with the increased "stiffness" at the ankles due to spasticity [3]. Since differences in gains were only seen in the ML direction, the differences may be a representation of some compensatory mechanisms to try to control overall sway.

The linear regression analysis found that the H-M ratio was strongly predicted by the passive stiffness in the AP direction (K_{pass}-AP), and the neurological stiffness (K_p-AP and K_p-ML) in both directions. Larger H-M ratio values suggest more severe spasticity. This correlation of the H-M ratio and model gains support the idea that spasticity is represented in the stiffness of the model. The AP direction of K_{pass} is not surprising given that the AP direction is the general plane of motion of the soleus muscle, which was measured for spasticity [3].

3.4.2 Model Comparison to Previous Models

There is some debate over the necessity of the inclusion of the passive torque components [1]. The passive components are passive stiffness and passive damping that represent the intrinsic mechanical properties of the musculoskeletal system. These components are not affected by the signal transduction time delay. The passive torque components have been left out of a previous study, because it was assumed that balance was regulated by active torque alone [43]. This assumption was made such that the most robust model with the fewest components would be found. Eliminating the passive components allowed the active torque components to compensate for the noise disturbances. It was reasoned that adding the passive torque

components to the already sufficient purely active torque model would assist the active torque model to produce even more reliable and realistic results [43]. In the Maurer and Peterka study which optimized a PID controlled model with the passive components to match healthy adult traditional posturography measures, the best fit was found when the passive components converged to zero [1]. According to Maurer and Peterka [1] since the passive components converged to zero, the passive components are not an essential part of postural control for healthy persons. Given that persons with MS have impairments in postural control, it was relevant to leave the passive components in the model. Based on the observation that the passive components did not converge to zero in the optimization of the MS or controls models, these passive components aid in representing postural control.

3.4.3 Future Directions and Limitations

Although this model produced results that are realistic and significant, there could be improvements. One improvement could be to include more subjects with MS with high and low spasticity to inform the model or data from a separate test group. Using more subjects to determine appropriate gains for the different groups would give more power in the statistical analysis, and solidify the differences in gains that were seen in this study. More test subjects would also help with the validation of the model.

Improvements could also be made specifically to the ML model. Many versions of the inverted pendulum model for AP sway simulation have been accepted for investigation, as humans typically use an ankle control strategy for small sway [13]. In the ML direction, the mechanism of sway is not as simple, as the sway is typically controlled at an action at the hip rather than

completely at the ankle [2]. The simplification to a single inverted pendulum also overlooks the aspect of having two legs in the ML direction, so a parallelogram would be a better approximation of the actual physiological system. Yet, even with the gross approximation of ML sway as an inverted pendulum with sway at an "ankle", significant differences were seen as expected in the MS model. A more accurate model might even further investigate these differences.

3.4.4 Conclusions

In summary, this modeling study demonstrated a significant difference in the mediolateral noise gain (K_N-ML) and neurological stiffness (K_p-ML) of the model between MS with high spasticity and control models. Since the differences were only seen between the controls group and the group of persons with MS with high spasticity, it is likely that these differences are directly related to high spasticity as opposed to MS. Persons with MS and high spasticity potentially use different compensatory mechanisms than those with low spasticity or controls to help control the instability in their posture caused by high levels of spasticity, demonstrated by the difference in model gains. Results from this study can be used to inform future research on postural control and the role of spasticity in persons with MS, as well as rehabilitation programs to regain normal postural control.

3.5 Figures

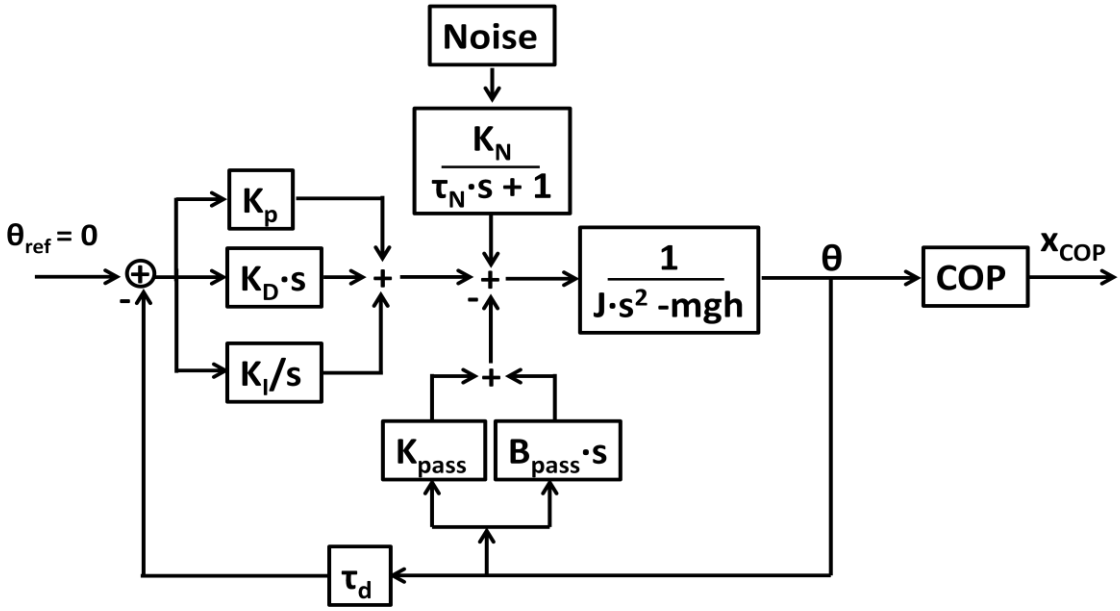

Figure 3.1: Diagram of inverted pendulum model. The same model setup was used for both the AP and ML simulations [1].

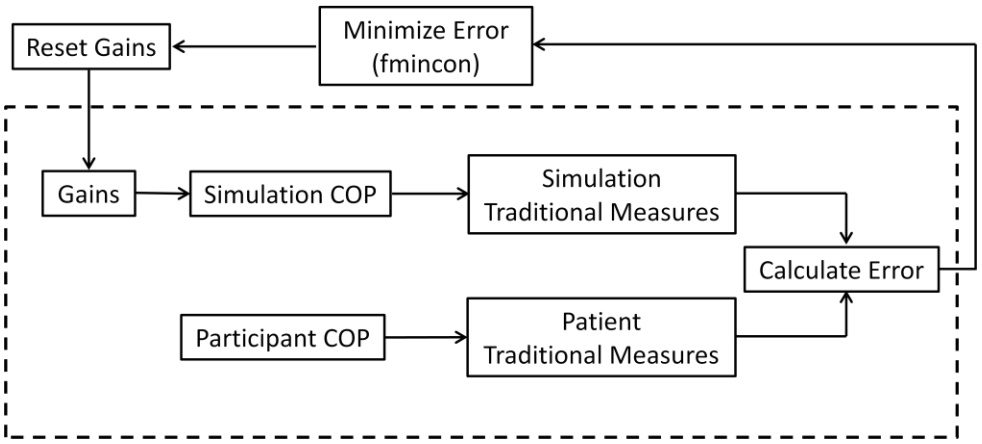

Figure 3.2: Optimization procedure flow chart. The components inside the dotted line are calculated for the optimization to progress from the input gains to the output error.

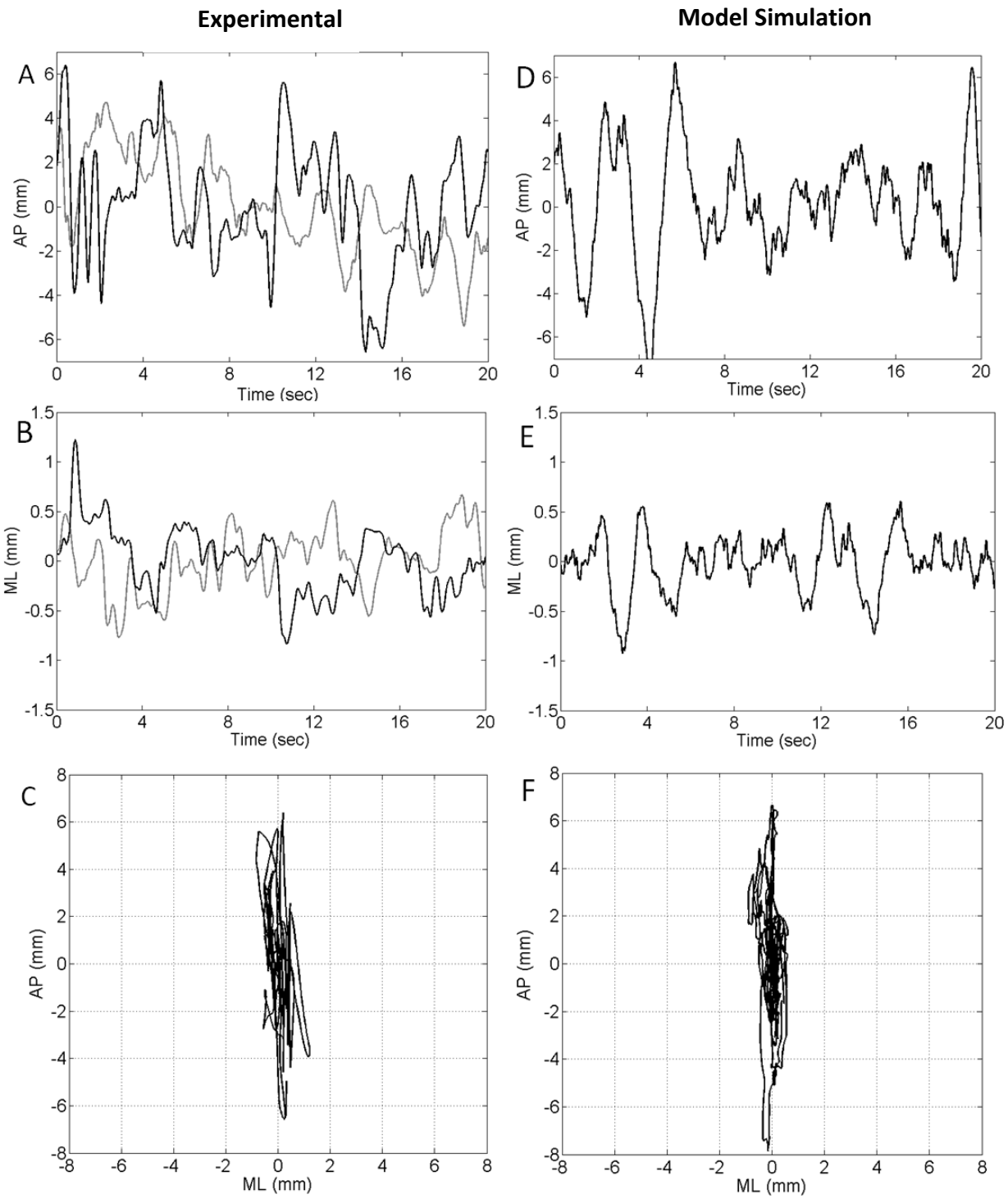

Figure 3.3: Control subject experimental and model simulated center of pressure traces. **A**. Time series of AP control subject data. **B**. Time seres of ML control subject data. Two trials are shown in each to give the overal behavior of the control subject. **C.** Stabilogram of AP and ML control subject sway. **D.** Time series of AP model data. **E**. Time series of ML model data. **F**. Stabilogram of AP and ML model sway. The model behavior on the right were optimized to match the average behavior (of 4 trials) of the control subject presented on the left.

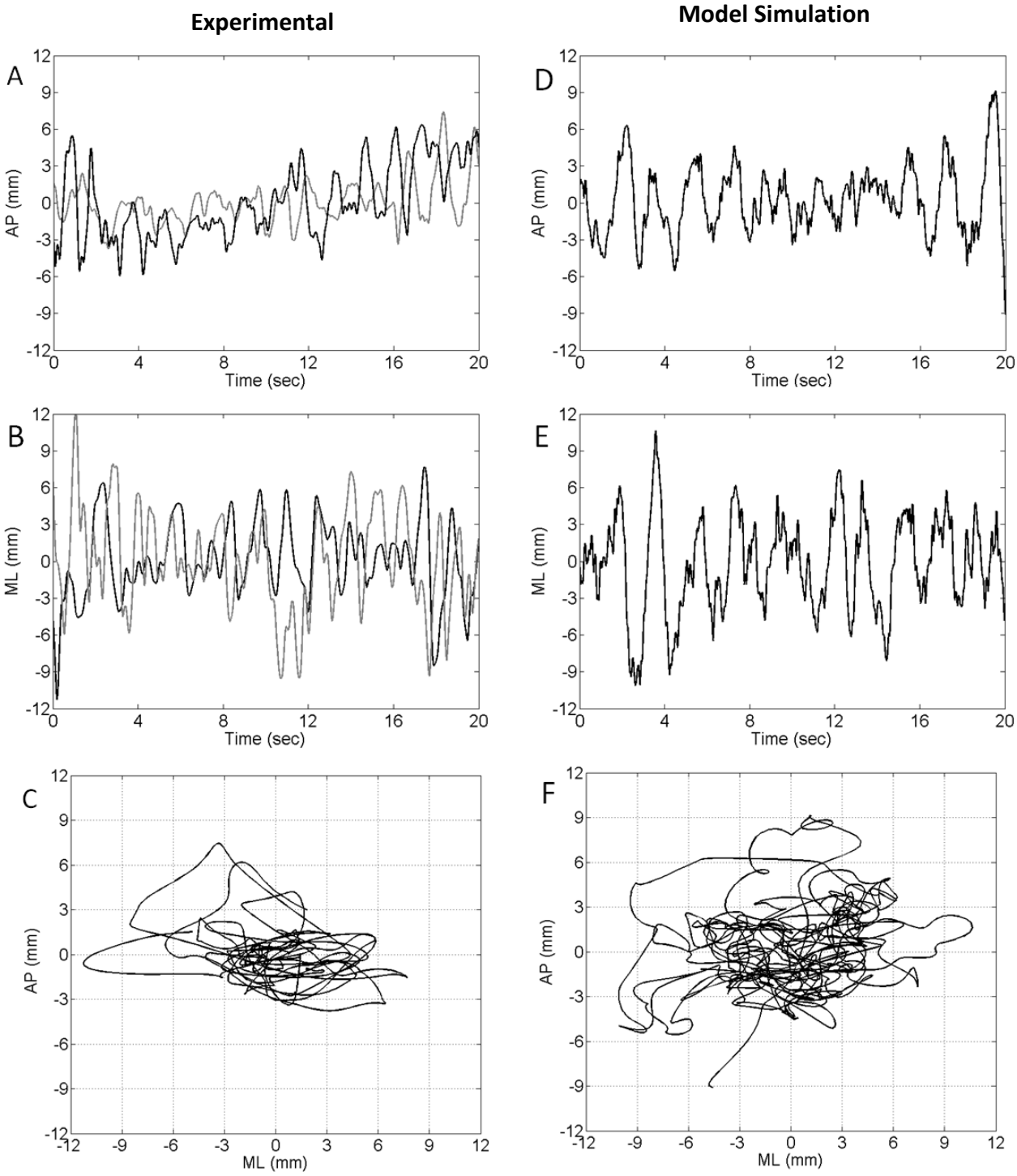

Figure 3.4: **MS subject with high spasticity experimental and model simulation center of pressure traces**. **A**. Time series of AP spastic subject experimental data. **B**. Time seres of ML spastic experimental subject data. Two trials are shown in each to give the overal behavior of the spastic subject. **C**. Stabilogram of AP and ML spastic subject experimental sway. **D**. Time series of AP model data. **E**. Time series of ML model data. **F**. Stabilogram of AP and ML model sway. The model behavior on the right were optimized to match the average behavior (of 4 trials) of the spastic subject presented on the left.

3.6 Tables

Table 3.1: Traditional COP measures of control subject experimental data and related model simulation measures

		EXPERIMENTAL		SIMULATION		
		Mean	Std. Dev	Mean	Std.Dev	p-value*
95% Power Frequency (Hz)	FP95-AP	1.15	0.32	1.28	0.40	0.31
95% Power Frequency (Hz)	FP95-ML	0.94	0.25	1.06	0.33	0.26
Mean Distance (mm)	MD-AP	1.11	0.84	1.36	1.10	0.48
Mean Distance (mm)	MD-ML	0.24	0.13	0.28	0.16	0.45
Maximum distance (mm)	Max-AP	5.90	4.05	5.48	3.89	0.77
Maximum distance (mm)	Max-ML	1.15	0.56	1.06	0.53	0.62
Mean Velocity (mm/s)	MV-AP	4.05	1.67	4.10	1.71	0.94
Mean Velocity (mm/s)	MV-ML	0.71	0.32	0.83	0.37	0.33
Range (mm)	RANGE-AP	10.07	6.94	10.20	6.82	0.96
Range (mm)	RANGE-ML	2.00	1.01	2.00	1.00	0.99
Root Mean Square distance (mm)	RMS-AP	2.08	1.51	1.74	1.32	0.51
Root Mean Square distance (mm)	RMS-ML	0.44	0.23	0.36	0.19	0.29
*Independent-samples t-test						

Table 3.2: Traditional COP measures of MS subjects with low spasticity experimental data and related model simulation measures (n = 7)

		EXPERIMENTAL		SIMULATION		
		Mean	Std. Dev	Mean	Std.Dev	p-value*
95% Power Frequency (Hz)	FP95-AP	1.12	0.31	0.93	0.28	0.26
95% Power Frequency (Hz)	FP95-ML	0.90	0.32	0.93	0.37	0.89
Mean Distance (mm)	MD-AP	5.86	8.57	5.95	8.55	0.98
Mean Distance (mm)	MD-ML	2.03	2.09	1.72	1.52	0.76
Maximum distance (mm)	Max-AP	22.45	29.28	20.78	29.59	0.92
Maximum distance (mm)	Max-ML	6.99	8.00	6.90	8.05	0.98
Mean Velocity (mm/s)	MV-AP	15.03	24.70	17.25	29.61	0.88
Mean Velocity (mm/s)	MV-ML	4.33	5.76	4.94	6.99	0.86
Range (mm)	RANGE-AP	33.24	36.93	37.84	54.26	0.86
Range (mm)	RANGE-ML	10.37	9.88	12.54	14.05	0.74
Root Mean Square distance (mm)	RMS-AP	7.68	11.39	7.29	10.52	0.95
Root Mean Square distance (mm)	RMS-ML	2.54	2.73	2.17	2.00	0.78
*Independent-samples t-test						

Table 3.3: Traditional COP measures of MS subjects with High spasticity experimental data and related model simulation measures (n = 9)

		EXPERIMENTAL		SIMULATION		
		Mean	Std. Dev	Mean	Std. Dev	p-value*
95% Power Frequency (Hz)	FP95-AP	1.20	0.31	1.14	0.39	0.74
95% Power Frequency (Hz)	FP95-ML	1.12	0.35	1.03	0.35	0.57
Mean Distance (mm)	MD-AP	2.63	1.73	2.83	1.83	0.81
Mean Distance (mm)	MD-ML	1.51	1.08	1.53	1.08	0.98
Maximum distance (mm)	Max-AP	9.90	6.36	9.40	5.78	0.87
Maximum distance (mm)	Max-ML	5.49	3.70	5.46	3.90	0.99
Mean Velocity (mm/s)	MV-AP	7.44	4.00	7.82	4.40	0.85
Mean Velocity (mm/s)	MV-ML	4.78	4.45	5.01	4.41	0.91
Range (mm)	RANGE-AP	17.25	11.15	17.63	10.68	0.94
Range (mm)	RANGE-ML	9.72	6.72	10.11	7.24	0.91
Root Mean Square distance (mm)	RMS-AP	3.33	2.09	3.46	2.16	0.90
Root Mean Square distance (mm)	RMS-ML	1.89	1.30	1.88	1.30	0.98
*Independent-samples t-test						

Table 3.4: **Optimized model gains for MS subjects and control subjects.**

	Control		MS – low spasticity		MS – high spasticity		Main Group Effect
	Mean	Std. Dev	Mean	Std. Dev	Mean	Std. Dev	p – value*
K_d-AP	0.30	0.35	0.84	0.96	0.88	1.04	0.12
K_p-AP	9.44	1.36	10.54	5.33	10.87	1.11	0.40
K_N-AP	3.42	1.30	10.33	17.00	5.25	3.06	0.18
K_{pass}-AP	10.08	0.66	11.35	8.87	10.27	0.54	0.78
B_{pass}-AP	2.12	0.81	1.39	0.76	1.75	1.15	0.21
K_d-ML	0.69	0.81	1.41	1.82	0.73	0.67	0.29
K_p-ML	9.63	0.67	9.96	1.76	10.87	1.36	0.06
K_N-ML	0.68	0.35	3.16	5.02	4.06	4.29	**0.04**
K_{pass}-ML	9.45	1.09	10.38	0.99	10.03	1.12	0.08
B_{pass}-ML	1.50	1.04	0.94	0.92	1.67	1.11	0.36
*univariate ANOVA with group as the between-subject factor							

Table 3.5 Post Hoc Analysis for model gain differences between groups.

	Post Hoc Analysis p-values*		
	Control vs. Low	Control vs. High	Low vs. High
K_N-ML	0.09	**0.02**	0.50
K_p-ML	0.43	**0.02**	0.21
K_{pass}-ML	0.06	0.06	0.50
*one-sided analysis			

Chapter 4: Conclusions and Future Work

4.1 Dual Task Conclusions

The research questions addressed in this thesis stem from understanding factors that affect the postural control system. The first part of this work focused on the impact of a cognitive task on postural control. Postural control was measured in healthy control persons and persons with MS both during quiet standing and while performing a cognitive task. It was hypothesized that the postural control of persons with MS would be more negatively affected by the cognitive task than the postural control of the controls. The results of this simple test can help to indicate the importance of cognitive load to generally automatic motor tasks such as postural control.

The investigation into dual task and postural control yielded two novel observations: 1) persons with MS with greater disability had decreased postural control; and 2) the effect of the cognitive task on postural control did not differ by disability status of the participant. These observations extend previously reports by documenting that postural control in static balance continues to decline with advancing disability status in MS. Yet, due to the behavioral nature of this investigation, the mechanisms underlying the decline in postural control with disability status were not determined.

It was hypothesized that persons with greater disability would demonstrate a greater dual task cost in their postural control. This hypothesis was based on previous data demonstrating an elevated dual task cost during walking in persons with MS with greater disability compared to

those with lower disability [76]. The lack of a task by group interaction may be due to several factors. The most likely explanation is that neither group was able to exceed the physical boundary of their postural control. Essentially, the static postural control task employed here demonstrates a floor effect. A similar floor effect is likely not seen in the walking trials, as the participant is able to stop walking and maintain intermediate stationary poses in order to accomplish the cognitive task while still walking. It is also possible that the groups allocated neurological resources to the dual task condition differently.

4.1.1 Dual Task Implications on Motor Control Theories

The results of the dual task study lend some insight into the two different motor control theories addressed by this research. The reflex theory maintains that postural control is driven primarily by reflex loops and chains that are activated by the natural sway of the body. In contrast, the hierarchical theory defines levels of control, a top down approach, where movements are initiated at the spinal or reflex level and controlled by the motor cortex, which is then controlled by higher lever processing in the brain [13]. The significant decrease in some postural control performance parameters with the addition of a cognitive task indicate that there is likely a connection between the postural control mechanism and the higher level processing centers of the brain where cognition is located. Based on the dual task research, it is improbable for the reflex theory to be the sole component of a postural control theory, as the reflex theory indicates that there should be no change in postural control due to the cognitive task, as the processes are not related.

The dual task research completed here does not rule out a potential motor control scheme that involves some reflexive components. For instance, since a floor effect was demonstrated by the lack of interaction between disability and dual task performance, it is possible that a baseline reflexive component exists to maintain motor control that is essential for upright stance. This possible theory could be extended such that when the higher level processing resources are available, they add a level of control to the system that gives improved stability as seen in the quiet postural control tasks.

4.2 Dual Task Future Directions

Future research is necessary to understand the factors contributing to elevated postural deficits with disability progression in persons with MS. To determine how the demands of a simultaneous cognitive task and a postural task are divided between available neurological resources, future work is needed. It is possible that the cognitive task is a secondary priority to the postural control task. In order to test this theory, a baseline seated cognitive task performance would be needed, where the subject was not asked to maintain upright stance. If the cognitive task was made secondary to the postural control task, one could expect to see a decline in cognitive task performance from the seated to standing conditions, especially in persons with neurological decline.

There is also evidence that postural control can be improved in persons with MS and there is some limited evidence that cognitive function can be improved with target interventions [71, 72, 77]. Improving dual task ability will improve the quality of life of people, as many daily activities require consistent dual tasking, such as holding a conversation while walking or even

just standing. Also since an increased dual task cost has been associated with an increased risk of falling [68], improving dual task ability may decrease the number of injurious falls in at-risk populations. Indirectly, the benefits of rehabilitation on postural control and cognition suggest that dual task cost in persons with MS during postural control can be minimized with targeted interventions. However, this possibility requires additional scientific scrutiny.

4.3 Modeling Conclusions

The second part of this work focused on the affects of spasticity on postural control. Previously-collected postural control data from persons with MS and spasticity[3] were used to update an existing inverted pendulum model. The inverted pendulum model was used to investigate possible explanations for the differences seen in postural control measures between persons with MS, with high and low spasticity, and healthy controls. The model parameters that were expected to vary significantly from the model based on controls data to the models based on the MS data were the parameters of passive stiffness and passive damping, as it was predicted that these parameters would best represent the spasticity difference between the two groups. These passive components were independent from the model parameters that represent the neural control of postural control. The passive components were hypothesized to be different, as it is plausible that the effects of spasticity will be represented in these parameters, since spasticity is not dependent on higher level neural control.

The model simulations were able to recreate the differences in MS and control populations shown by Sosnoff *et al.* [3] in ML sway range and sway velocity. In the ML model, K_N-ML was significantly greater in the MS with high spasticity model than in the controls model. One could

speculate that the increased noise gain (in the ML direction) physiologically represents the degradation of the neural signal transduction in persons with MS [1, 45]. Or since K_N-ML was only significantly different in the persons with high spasticity, the increased gain could be due to an increased level of spasticity.

There is some evidence to support the idea that spasticity is represented in the passive components of the model in the correlation of the H-M ratio and model gains. The model components that were significant in the linear regression analysis against the H-M ratio were K_{pass}-AP, K_p-AP, and K_p-ML. The AP direction of K_{pass} is not surprising given that this is the primary direction of sway based on the activation of the soleus muscle. The regression analysis indicates that the larger the H-M ratio, which represents more severe spasticity, the larger the passive stiffness value (K_{pass}-AP).

Understanding the nature of spasticity from a modeling point of view is important as it may lead to insights concerning the functional outcomes of reducing spasticity. The reduction of spasticity is a therapeutic goal for populations such as persons with MS. Reduced spasticity could improve balance and mobility in affected populations. It has already been shown that exercise can help to decrease the H-M ratio, one physiological measure of spasticity [78].

4.3.1 Modeling Implications on Motor Control Theories

The bi-planar inverted pendulum model can help to inform where the control of upright stance potentially lies in the neurological system by investigating the differences between persons with MS and controls. The two motor control theories addressed in this work were the

hierarchical theory and the reflex theory. The model contained two major sections of control. The first aspect of control in the model was the neurological PID controller. The second aspect of control was the passive stiffness and passive damping components. The two motor control theories can be assessed by looking at the differences in the control parameters of each of these components between persons with MS and controls.

Generally, significant differences existed in aspects of the neurological controller and aspects of the passive components in the model between the two populations. These differences in both aspects indicate that it is not just the neural components or just the passive components that control upright stance. If either the passive controller or neural controller stayed constant between the two populations, then it could be hypothesized that the constant component might be an intrinsic property of the system, but does not influence any control over the differences in postural control parameters. Since this was not the case, once again there is evidence of some combined motor control where both reflexes and higher level neurological control play a significant role.

4.4 Modeling Future Work

Although this model produced results that are realistic and significant, there could be improvements. This is especially true in regards to the ML model. Many versions of the inverted pendulum model for AP sway simulation have been accepted for investigation, as humans typically use an ankle control strategy for small sway, allowing only sway at the ankle, which the single link inverted pendulum represents [13]. In the ML direction, the mechanism of sway is not as simple, as the sway is typically controlled as an action at the hip rather than at

the ankle [2]. Yet, even with the gross approximation of ML sway as an inverted pendulum with sway at an “ankle”, significant differences were seen as expected in the MS model. A more accurate model might even further investigate these differences.

Another improvement would be to match the physiological pendulum parameters such as height, weight, and center of mass location to each specific participant. In this study, the pendulum parameters were based on average male participants. This could especially be improved for the population studied here as the gender balance in the study included more females than males (88% females).

Another improvement on the model studied here would be to allow the neurological time delay to vary for each participant. This could be especially interesting when modeling persons with MS as the demyelination of the nerves due to the disease can cause delayed signal transduction. Allowing the neurological time delay to vary might also be able to distinguish between levels of severity of disease course in persons with MS, where a larger time delay could indicate more neuronal damage.

A final improvement that could be made would be to have a model that incorporates the work done on dual task cost along with the spasticity model created above. This model would be able to distinguish from reflexive components and higher level neurological components of postural control. Creating a model that can distinguish between these components would lead to understanding of how the components might interact and how the control is split between

the different systems. Insights could be gained for rehabilitation and interventions to help improve the postural control of persons with disabling deficits.

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Appendix A: Transfer Functions for Postural Control Model

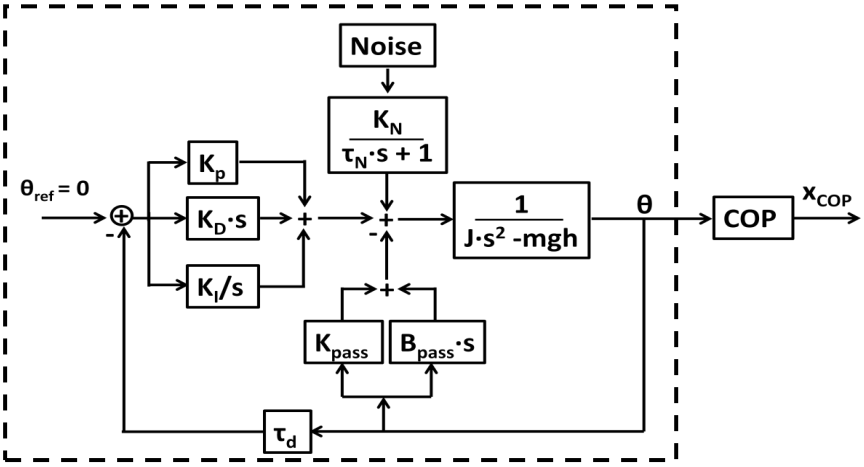

Figure A.1: Diagram of inverted pendulum model – from Figure 3.1. The same model setup was used for both the AP and ML simulations [1].

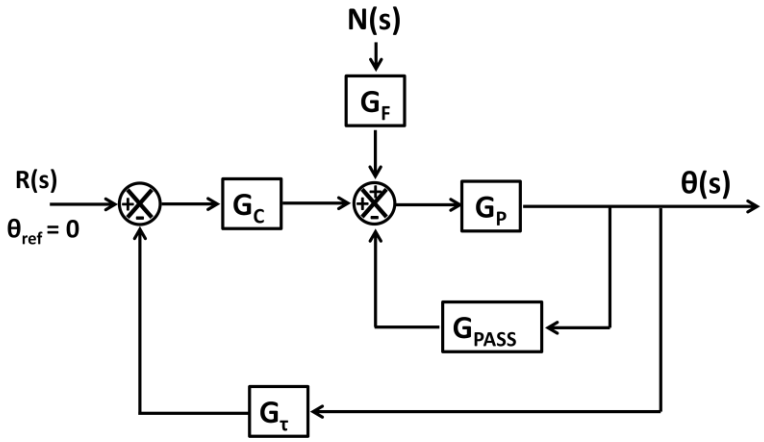

Figure A.2: Block Diagram representation of inverted pendulum model. Components are inside the dotted-border control volume in Figure A.1. The transfer functions for the model correspond to this diagram. The transfer function for the inverted pendulum control system is defined in Eq. A.1

The system block diagram (Figure A.2) was used to determine the transfer function for the system.

$$\boldsymbol{\theta(s)[1 + G_P G_{PASS} + G_C G_P G_\tau] = N(s) \cdot G_P G_F + R(s) \cdot G_P G_C} \qquad (A.1)$$

Since the input reference signal assumes upright equilibrium, $\theta_{ref} = R(s) = 0$, the complete transfer function can be simplified to Eq. A.2.

$$\frac{\boldsymbol{\theta(s)}}{\boldsymbol{N(s)}} = \frac{\boldsymbol{G_P G_F}}{\boldsymbol{1 + G_P G_{PASS} + G_C G_P G_\tau}}$$

(A.2)

where the individual transfer functions in Eq. A.2 are defined in Table A.1.

Table A.1: Transfer functions of postural control model. These equations can be substituted into Eq. A.2 for complete evaluation of the system. The values for each parameter are defined in the text.

G_P		$\frac{1}{Js^2 - mgh}$
G_F		$\frac{K_N}{\tau_N s + 1}$
G_{PASS}	=	$K_{PASS}(1 + B_{PASS} \cdot s)$
G_C		$\frac{K_p(1 + K_i \cdot s + K_i K_d \cdot s^2)}{K_i \cdot s}$
G_τ		$e^{-\tau_d s}$

Solving Eq. A.2 for $\theta(s)$ given a white noise input signal ($N(s)$) and then converting to the time domain, allows for the calculation of the translational center of pressure (COP). The COP is calculated in the given direction as a function of time, following the method in [1] and as expressed in Figure A.1 The same calculation was used for both the AP and ML simulations.

$$x_{COP} = \frac{(m_B d_B^2 - J_B)\ddot{\theta}_B + m_B x_B(g + \ddot{y}_B) - m_B y_B \ddot{x}_B - m_B h_F \ddot{x}_B + m_F d_f g}{m_B(g + \ddot{y}_B) + m_F g}$$

(A.3)

where $g = 9.81\ m/s^2$, J_B is the moment inertia of the body, m_B is the mass body excluding the feet, m_F is the mass of the feet, and all variables for Eq. A.2 are depicted in Figure A.3. The values used for each constant in Eq. A.3 can be found in Table A.2

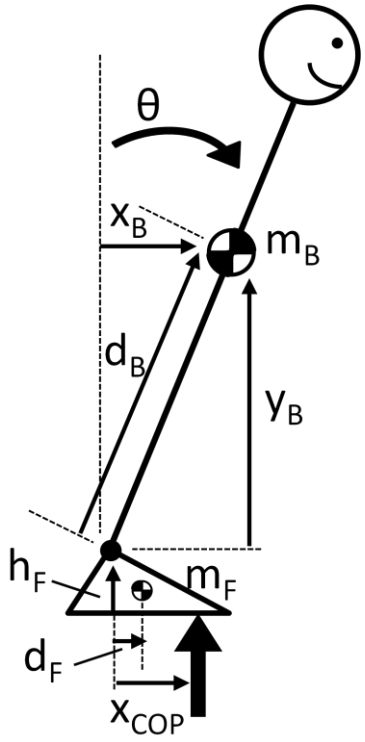

Figure A.3: Diagram of pendulum parameters for calculating COP. This figure is replicated from Figure 1 in [1]**.** The same model was used for both AP and ML directions. The parameters of x_B and y_B were calculated from the model from the motion of the center of mass.

Table A.2: Values used for pendulum body parameters. These values are the same as used by [1].

J_B	66 kg/m^2
m_B	76 kg
m_F	2.01 kg
d_B	0.87 m
h_F	0.085 m
d_F	0.052 m

Appendix B: Simulink Block Diagram for Model

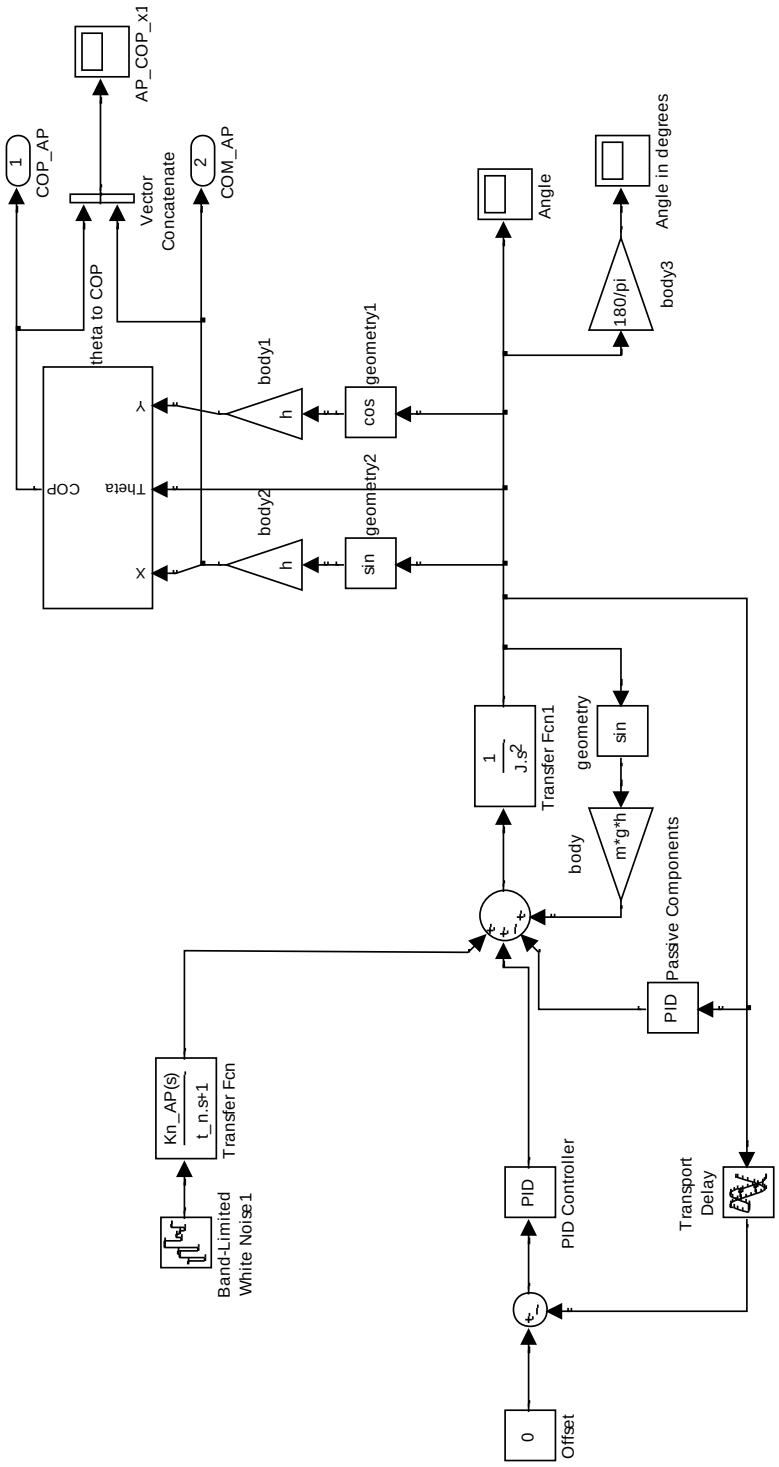

Figure B.1: Simulink "code" used in model simulations. The blocks displayed here are for the AP model. An identical system was used for the ML model.