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Motor control-based assessment of therapy effects in individuals post-stroke: implications for prediction of response and subject-specific modifications

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Motor control-based assessment of therapy effects in individuals post-stroke: implications for prediction of response and subject-specific modifications

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Sometimes I'll start a sentence, and I don't even know where it's going. I just hope I find it along the way. -Michael Scott

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Abstract

Producing a coordinated motion such as walking is, at its root, the result of healthy communication pathways between the central nervous system and the musculoskeletal system. The central nervous system produces an electrical signal responsible for the excitation of a muscle, and the musculoskeletal system contains the necessary equipment for producing a movement-driving force to achieve a desired motion. Motor control refers to the ability an individual has to produce a desired motion, and the complexity of motor control is a mathematical concept stemming from how the electrical signals from the central nervous system translate to muscle activations. Exercising a high-level complexity of motor control is critical to producing a smooth motion. However, the occurrence of a sudden, detrimental neurological event like a stroke damages these connecting pathways between these two systems, and the result is a motion that is uncoordinated and energy-inefficient due to diminished motor control complexity.

Stroke is a leading cause of disability with nearly 800,000 stroke victims each year in the U.S. alone, amounting to an estimated cost of $45.5B. Impaired mobility following a stroke is a widespread effect, with more than half of survivors over the age of 65 affected in this way, and up to 80% of survivors at some point experiencing hemiparesis during post-stroke recovery. As such, given the importance of independent mobility for quality of life, improving gait mechanics and mobility of stroke survivors has been the goal of rehabilitation efforts for decades.

In this work, we mold together the forefronts of statistics and computational physics-based modeling to obtain insight and information about post-stroke hemiparetic gait mechanics and what drives them that would otherwise be unavailable. We expand upon previous work to quantify motor control complexity as it relates to the health of the

neuromuscular system and analyze the effect of a specific therapy on motor control of individuals post-stroke. Secondly, we aim to develop a predictive model to conclude whether an individual will respond to the therapy based on kinematic and dynamic features from pre-therapy recordings. Lastly, we will determine how to individually tailor this therapy in order to achieve maximum improvement in motor control complexity in order to improve gait mechanics in individuals post-stroke.

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Chapter 1

Introduction

Biological problems, such as those studied in this work, are complex in nature. There are nearly boundless ways to begin an approach to finding a solution, and no two disciplines will take the exact same one. Consider post-stroke rehabilitation, and more precisely, gait rehabilitation. There are the seemingly obvious places to target an interventions, such as gait speed, joint angles, and timing. These targets are mechanics-based, and improvements in these features can be seen with a variety of treatments and therapies. In a clinical setting, these impairments may be addressed through treadmill training and orthotic devices, and changes are assessed with mechanics-based measures. However, these observable impairments arise from problems within the nervous system, wherein an assistive device could not be used to target a neurological problem.

Following a stroke, gait impairments, such as decreased knee bend are often observed. The stroke event, though, did nothing to the knee joint itself. There is not anything physically preventing the knee from bending through its full range. What the stroke did affect was the Central Nervous System's (CNS) ability to control this motion. As a result of the stroke, neural pathways are damaged, and communication between the nervous and musculoskeletal system is compromised. When these two systems cannot communicate effectively, the resulting motion is not as intended. Unlike assistive devices and other mechanical solutions, Functional Electrical Stimulation (FES) operates by providing a current directly to the muscle on an impaired limb, mimicking an excitation signal from the CNS to appropriately time the muscle activation and help produce more coordinated movement. With FES, it is believed that the electrical stimulation could repair the damaged portions of the nervous system and allowing the mechanics-based observable impairments to follow later, once the nervous system is able to accurately time the muscle activations. To recap, while the impairments we notice about post-stroke mobility are certainly problematic, these mechanical problems result from neural damage. There are therapies in place to address both sets of issues, broadly classified into two categories: 1. Top Down and 2. Bottom Up. Top Down therapy targets observable mechanics, with the idea that the neural framework will repair to facilitate the new, improved motion. Bottom Up therapy targets neurological damage, allowing the neural framework to be repaired first and the mechanics to improve as a result. In these studies, the treatment at hand is FastFES, and is a combination of Fast

Treadmill Walking (a bottom up therapy) and Functional Electrical Stimulation (a top down therapy) for hopefully a simultaneous and faster recovery of both neurological and physical impairments. However, this raises a new question: If the true problem is neural in origin, and we are studying the effects of a therapy that can target the neural problem, then should we not also consider performance measures that quantify neural recovery? This question is exactly the crux of the work that we have done. Ordinary performance measures that quantify speeds, angles, etc. are insufficient for drawing conclusions about neural recovery.

In this work, we seek to 1.) Investigate the effects of FastFES therapy on neural recovery, measured in terms of motor control complexity; 2.) Develop a predictive model of how much neural recovery an individual with certain baseline (pre-FastFES) features could expect with this therapy, and what this could mean for mechanical improvements; 3.) Determine how we can optimize FastFES for maximum neural recovery.

1.1 Research Methods

This work aims to combine the powerful fields of physics-based dynamic simulations with applied statistics, data science, and machine learning. We make use of OpenSim, an open-source musculoskeletal modeling software, and its API through Matlab to perform subject-specific simulations of individuals with post-stroke gait. These simulations are then used to gather information about the individuals' motor control and the impact of FastFES therapy.

1.1.1 Aim I: Quantifying dynamic motor control changes in individuals with post-stroke gait impairments following FastFES therapy

This aim is comprised of two goals. The first of which is to simply address the effectiveness of FastFES therapy at improving motor control complexity in individuals post-stroke. The second is more exploratory in nature and stems from a previous study that showed this therapy lead to increased walking speed, increased propulsive force, and increased trailing limb angle (Fig. 1) at toe-off. Due to the recent development of Statistical Parametric

Mapping (SPM) for use in biomechanics, we chose to revisit the significance of the trailing limb angle (TLA).

SPM preserves the time-dependent characteristics of statistical significance that traditional methods do not. Unlike these methods, SPM does not require *a priori* knowledge of where one would expect significance to lie and therefore does not require the extraction of one instance from the entire time series for statistical evaluation. SPM allows us to detect more regions of significance in the TLA other than toe-off.

To quantify the effects of FastFES at improving motor control complexity, we used the Walk-Dynamic Motor Control (Walk-DMC) Index, which has previously only been used in studies with children with cerebral palsy.

1.1.2 Aim II: Predicting response to FastFES therapy in individuals with post-stroke gait impairments

Based on results of Aim I, we classify individuals as a responder if they increased their Walk-DMC Index values following FastFES therapy, and we classify them as a nonresponder if they did not increase their Walk-DMC Index values following this therapy. Equipped with this information, we aim to develop a predictive model to determine whether an individual will increase their motor control complexity as a result of FastFES. We employ SPM again to identify distinguishing pre-therapy features between the responder and non-responder groups. Functional data analysis (FDA) is used to verify the findings of SPM and the validity of its parametric assumptions. The goal of this study is to generate a tool in which the clinician could know ahead of time whether this therapy could be beneficial to their patient.

1.1.3 Aim III: Optimization of FastFES therapy for maximum improvement in motor control complexity

For the last study in this project, we build upon the previous two and answer the new question of "How do we modify this treatment to maximize improvement in motor control

complexity?" This is particularly relevant to individuals that are predicted to be non-responders, but it is relevant to every participant in this therapy program. We want to contribute to the progressive field of subject-specific medicine, in which we do not prescribe a blanket therapy to all individuals that display a similar impairment.

In this study, we used the simulated activations from Aim I to identify which groups of muscles contribute to the largest changes in the Walk-DMC. We then used OpenSim Moco to track the activations of these muscles to simulate muscle activity that corresponds to different Walk-DMC values. From here, we grouped the simulations into mildly, moderately, and severely impaired groups based on the motor control complexity. We used SPM to evaluate the time-dependent differences in these activations to determine which muscles should be stimulated at what instance to move an individual from the moderately and severely impaired groupings to the mildly impaired grouping.

1.2 Looking Ahead

From this point forward, the next chapter will be a literature review detailing previous work and how these studies motivated this current project. Following the literature review, there will be three separate chapters for each of the three aims that comprise this dissertation. In these chapters, we will discuss the methods and findings of each study. Lastly, a final chapter will discuss how this work paves the way for future studies and the implications of this work.

Chapter 2

Literature Review

This section will explore the previous work done in the area of impaired gait analysis and motor control. Beginning with a discussion on popular measures of performance and common rehabilitation strategies, we lay the framework for why motor control is an important facet of stroke and other musculoskeletal disorders.

2.1 How does hemiparetic post-stroke gait differ from healthy gait?

Gait is divided into a series of phases and sub-phases. Broadly, one limb is tracked throughout a stride, and this limb undergoes a stance phase for roughly 60% of the stride and a swing phase for the remaining 40%. As the names might imply, stance phase occurs when the foot of the tracking limb is in contact with the ground, and swing phase is when the foot of this limb is off of the ground. These phases are then divided into sub-phases, each with a distinct function (Fig. 2), [1].

Healthy gait is marked by the ability to support one's body weight, properly balance, propel forward the center of mass, and adapt to changes in terrain [2]. However, this is only possible when the lower limb joints exercise proper ranges of motion. Just after heel-strike, the hip extends as the center of mass begins to move forward over the stationary limb in order to stabilize the torso. Just after heel-off, the hip flexes to assist in swinging the limb forward. During the stance phase, the knee provides most of the support and aids in keeping the body upright as it approaches full extension. During swing, enough knee flexion (bend) is critical to bringing the limb forward. The ankle is important for stability during stance, but also during swing the ankle must flex to ensure clearance of the toe of the ground [1].

However, during hemiparetic post-stroke gait, these motions are compromised due to reduced joint range of motion. Though we see varying levels of impairment at each phase of gait, there are shared commonalities in what joints are affected, and how so. During stance, hip extension is reduced such that there is not sufficient separation of the limbs during mid-stance. There is often decreased knee extension during mid-stance and late swing as the limb prepares for second heel-strike, coupled with decreased knee flexion during late stance as the

limb prepares for toe-off. At the ankle, propulsive force production is significantly reduced due to the ankle's limited ability to plantarflex (push into the floor) during late stance just before toe-off, but contrarily during swing we usually see some type of *foot drop* in individuals post-stroke, where the ankle cannot properly dorsiflex (pull upwards) to ensure foot-ground clearance [3]. A comparison of a healthy and impaired toe-off phase can be found in Fig. 3.

2.2 Developed rehabilitation strategies

There have been studies that have shown mental health care is important for bettering physical therapy outcomes following a stroke, with the understanding that a healthy mental status is necessary to encourage the individuals to both attend their suggested therapies and to put forth an effort during these sessions [4]. The discussion here will primarily revolve around physical rehabilitation strategies, though we do not neglect the importance of the mental health of these individuals.

Following a stroke, individuals often avoid using the affected limb. Constraint-Induced Movement Therapy (CIMT) is a specific strategy designed to overcome the habit of relying on the unaffected limb. In this therapy, the healthy limb is restrained and forces the individual to use their impaired side more than normal. Though the results of this are promising, with one study indicating that participants in CIMT maintain the benefits for two years post-therapy, this program is intense and requires a lot of trained individuals to be present [5, 6]. However, this form of therapy is only feasible for tasks that may be performed with one limb or the other and is likely not easily translated to tasks that simultaneously require the use of both limbs, such as walking.

Along the same lines as CIMT, Body Weight Support (BWS) therapy is designed to encourage proper usage of limbs, and is particularly useful for gait training. BWS therapy uses a harness or a handrail that offers support so that the individual is able to practice a healthy gait pattern and hitting each phase during stride without compromised balance or muscle weakness acting as a limiting factor. Slightly more advanced than traditional BWS therapies, robotic assistance can be used for both upper and lower limb impairments. The robotic device is placed on the individual, and in the case of lower limb usage, may still

provide body weight support. These devices are useful for helping the individual perform a specific motion either by simply assisting with the motion, or driving the motion entirely [5].

One of the most technologically advanced yet well-established methods is Functional Electrical Stimulation (FES) therapy. Unlike the other methods, this therapy targets recovery through a method that is not directly related to the physical impairments. When used during gait rehabilitation post-stroke, FES therapy uses electrodes to deliver a small electrical shock to the ankle muscles to promote dorsiflexion during swing and counteract the common problem of foot-drop. A study performed by Hausdorff et al. has found that after using an FES device for eight weeks, the average walking speed of 24 individuals post-stroke increased by 34% and their gait symmetry improved by 28% [7]. When FES is combined with treadmill gait training, other studies have identified improvement in the trailing limb angle of the paretic limb, as well as increased walking speed and activation of the ankle plantarflexors [8, 9].

Beyond these common treatment methods, more complex strategies that involve Transcranial Magnetic Stimulation (TMS) therapy and Virtual Reality (VR) therapy have been studied. TMS is useful for not only mapping changes in the brain that are a result of other therapies like CIMT and making inferences about the related motor control, but when TMS is used to stimulate the motor cortex located in the opposite side of the brain from the lesion caused by the stroke, motor improvements are noted [5, 10]. VR therapy is used to simulate environments and encourage movement, and while the true effectiveness of this therapy on post-stroke recovery is unclear, this strategy may offer more support for physical fitness improvement, which in turn facilitates performance and movement ability [5].

2.3 Common measures of performance

Probably one of the most critical parts of a study on a specific therapy, for any problem, including those not related to musculoskeletal disorders, is the bottom line of *does it work?* In order to answer this question, there must be some value that is measured and some significant change in this value that is believed to be a result of the therapy. Walking speed is arguably

the most common measure of performance following a therapy. An individual is considered community ambulatory if his/her walking speed is $\geq$ 0.8 m/s, and thus this is the target of many rehabilitation therapies post-stroke [11]. However, despite walking speed being an important factor and its association with a healthy neuromuscular system, it can be swayed through compensatory mechanisms. In other words, an increase in walking speed does not necessarily correlate to a neurological improvement because the individual could simply be utilizing his/her stronger limb [12]. Importantly, walking speed is not well-correlated with severity of impairment, reinforcing the idea that walking speed does not provide the full picture, and thus to quantify the effect of the therapy neurologically, walking speed alone is an insufficient measurement [13, 11, 14].

Another variable that may be used to measure motor performance is step length asymmetry [13]. It can be calculated two way, either by simply the ratio of the paretic step length to the non-paretic step-length (or *Step Length Ratio*, SLR), where a value of 1 would indicate perfect symmetry, or by the ratio of the paretic step length to the sum of the paretic and non-paretic (healthy) limb step lengths (more accurately known as the *Paretic Step Ratio*, PSR), where a value of 0.5 would indicate perfect symmetry [14, 15]. However, step length asymmetry is too widely variable alone from which to draw many conclusions, with some individuals post-stroke walking with a longer paretic step, some walking with a shorter paretic step, and even some that are symmetrical in lengths [13, 14]. Walking speed is only loosely related to step length asymmetry, and while this may seem discouraging at first, in fact it further indicates that walking speed alone may not being providing enough information about a person's recovery status [13, 16, 17].

Since step length asymmetry is a bit limited and overall implications of it are unclear, another metric known as *Paretic Propulsion* has been developed in an effort to assess neurological recovery as a result of a prescribed therapy. This metric is designed to quantify the percentage of propulsion generated by the paretic limb, and similar to PSR, a value of 50% indicates perfect symmetry, and ¡ 50% indicates that the non-paretic limb is compensating [11]. Propulsion in general is critical to walking speed and is primarily governed by the trailing limb angle (Fig. 1) [18, 19]. Paretic propulsion is a bit more related to walking speed than is step length asymmetry, but more important is how paretic propulsion and step

length symmetry are related to each other. There is a negative correlation, where a higher paretic propulsion ratio indicates a shorter step taken with the paretic limb [11, 14, 20]. Particularly because of the strong association of paretic propulsion with impairment severity (Fig. 4), this metric in particular has become popular for assessing and predicting treatment outcomes [21, 22, 23, 24].

Paretic propulsion as a measure of performance seems to provide additional information that walking speed does not about post-stroke recovery. There seems to have been a gradual progression in recognizing the need for a metric that quantified neurological improvement, and then relating this improvement to physical improvements in a top-down manner. Perhaps the most intriguing of these relationships is paretic propulsion and muscle modules. Muscle modules will be discussed more thoroughly in the following section, but briefly muscle modules are groups of co-activated muscles, meaning that rather than each muscle being independently activated by an individual electric signal generated by the central nervous system, one electric signal can actually activate multiple muscles at once. The number of muscle modules an individual utilizes is a function of their muscle activation patterns, and a larger number of modules indicates a more complex motor control scheme that is typical of healthy individual, whereas a smaller number of modules is indicative of impaired motor control. Paretic propulsion has been shown to be related to the complexity of motor control as defined in terms of these muscle modules [25, 26].

Paretic propulsion as it relates to motor control complexity is interesting because it begins to address this need to quantify neurological impairment, and it comes with clear intuition that *less paretic propulsion means more severely impaired motor control.* Because of this relationship, improving paretic propulsion has been the target of rehabilitation programs in the past [19]. Paretic propulsion as a metric is a combination of top-down and bottom-up assessments, where it is still a measure of physical capabilities but with implications to a problem at the neural level. Bottom-up assessments alone, such as walking speed or other motor function descriptives that are calculated based on only physical capabilities may leave out valuable information about post-stroke neurological recovery, or lack there of, as a result of a therapy. In fact, it has even been shown that mobility may improve independently of changes in muscle activation patterns, further indicating that bottom-up rehabilitation

programs do not target the neurological source of impairment [27]. The concept of modular control of movement paves the way for a deeper understanding of motor control complexity and how it is affected by a stroke, and therefore in the next section we provide a clear discussion of muscle modules and why the Walk-Dynamic Motor Control Index is the most direct measurement of motor control complexity and should be used as a performance metric in post-stroke rehabilitation assessment.

2.4 Previous work on motor control

The musculoskeletal system is redundant in nature, such that there are nearly infinite combinations of muscle forces that will ultimately lead to the same mechanical output generation. Underlying muscle force production, there is the black box of the central nervous system, in which somehow it selects from an exceedingly large set of muscle excitations to produce the desired mechanical output. Muscle modules may hold the key to understanding the control scheme that implemented by the central nervous system and how motion is produced.

As mentioned previously, muscle modules are a group of co-activated muscles, but how exactly are these modules determined? For this purpose, a decomposition method is implemented on an array of muscle activations. Take for example, a set of 5 lower limb muscles. At each percent of gait, which has been normalized to 100% from heel-strike to heel-strike, these muscles have an activation value ranging between 0 (entirely inactive) and 1 (entirely active). These values are arranged in an array of 101×5, where the rows represent activation values at each frame of gait, and the columns represent each muscle. This large array is then decomposed, most recently by Non-negative Matrix Factorization (NMF), into a product of two smaller, lower-dimension matrices [28, 25, 29, 26]. NMF, as it sounds, is only suitable for data in which the values never fall below zero. The first matrix in the decomposition product is similar to the original array, but instead of it being a 101×5 array of muscle activations over stride, it is a $101 \times \alpha$ array of module activations, where α is the number of modules. The second product is a $5 \times \alpha$ array, indicating the weight of each muscle within each module.

We refer to the 101 $\times$ 5 array of muscle activations as the *original array* and the decomposition product as the *reconstructed array*. Similarities between these two arrays are quantified by the *Variance Accounted For (VAF, Eqn. 1)*.

$$VAF = \left(1 - \frac{||Orignal - Reconstructed||^2}{||Original||^2}\right) \times 100 \tag{2.1}$$

In general, a number of modules is said to describe a motion if roughly 95% VAF is reached. Less VAF indicates more modules are needed because the reconstruction is poor and the modular decomposition does not describe the motion well. At around 95% VAF, the reconstructed array is very similar to the original array and the motion generated by modular control is very similar to the motion generated by individual muscle activations.

Modular control would certainly serve as a feasible dimensionality reduction technique, wherein the central nervous system would only be responsible for control of a handful of muscle modules rather than hundreds of musculotendon units [30, 31, 29, 32]. To be clear, modular control of movement is is a *theory* that has held up well when being tested against many different movements, but it is not something that is known for certain that the central nervous system does. For example, one proposed mechanism behind modular control theory is that muscles are grouped (and activated) by their biomechanical function, such as body weight support, leg swing during gait, etc. This would indicate a hierarchical control structure such that muscles that govern part of a motion, like leg swing, will not be activated if a more important task, such as balance, is compromised [33, 34]. However, in a study investigating the force production by the seven muscles on the index finger, researchers found that the motion was best controlled by individual muscles, and evidence that the muscles were activated based on function was not found [35]. All of the proposed mechanisms behind modular control in some way result in reduced dimensions of the solution set, regardless of whether these mechanisms involve grouping muscles by biomechanical functions [33, 34], identifying which muscles are important for a specific tasks and disregarding those deemed irrelevant [36, 37, 38, 39], or learning the most efficient recruitment of muscles to perform a tasks [37, 40, 41]. However, it is unknown if the redundancy of musculoskeletal system and the exceedingly large set of muscle excitations is a burden at all on the central nervous

system, and whether reducing this dimensionality is a goal it has. Work by Valero-Cuevas et al. [35] is indicative that modular control is not strictly necessary as a control scheme, and supports the *uncontrolled manifold hypothesis*, wherein the extra degrees of freedom allow for flexibility of control patterns [42].

Despite modular control of movement perhaps not well-describing all movements, particularly for simple motions like finger flexion and extension, this control scheme has proven effective in multiple cases such as frog swimming [43], cycling [44], cat postural response to surface perturbations [29], and human locomotion [28, 45]. In a study by Neptune et. al [28], four muscle modules, or groups of muscles, were found- each with a distinct function and phase of stride that they are activated (Table 1.) Importantly, when these modules were used as the controls for a forward dynamic simulation, the simulated kinematics agreed well with experimental kinematics, lending credibility to a modular control scheme. Therefore, solving the redundancy of the musculoskeletal system and reducing the size of the feasible solution set of muscle excitations may not be a primary goal of the central nervous system, but rather an effect of the control mechanism and solution selection process that the central nervous system is implemented.

When these four modules are activated appropriately, i.e. at the correct time during stride, gait is smooth. However, this is not the case with post-stroke hemiparetic gait, as previously mentioned. Recall that at each phase of gait, some deviation can typically be observed in individuals post-stroke. Superficial, mechanics-based, bottom-up measurements leave out a great deal of information with regard to neurological recovery, and therefore, eventually the modular control theory was applied to impaired motion as well. Clark et. al [25] found not only are less than four modules needed to described hemiparetic gait, but the modules that are present, are actually the same modules that are observed in healthy gait, just merged together. In other words, the same muscles are present in each individual module, meaning that the same muscles are co-activated by one neural signal, but for example, the modules that are typically only active during stance may extend activation into later gait phases, and overlap in activation with other modules. This merging means that each modules cannot perform its designated function as defined in Table 1, such that the ability to generate forward propulsion is compromised due to reduced function of the ankle plantarflexors [26].

However, using only muscle modules to determine motor control complexity can be misleading. In a population of individuals post-stroke, some percentage may only need two modules to describe their motion, some may need three, and still some may require four. First, this requires separation of the individuals into groups by the number of modules that were determined necessary for their motion. Within these groups themselves though exist a further ranking that must take place- i.e. not every individual with the same number of modules will exhibit the same level of impairment. Mathematically, this is represented by the VAF. An individual with two modules that account for 88% variance has a more complex control scheme and are "closer" to utilizing a third module than an individual with 2 modules that account for 92% variance (Fig. 5).

While this "group and rank" method has been used as a predictor of post-therapy locomotor performance [25], the inherent assumption that no matter the VAF, individuals with two modules are *always* using a less complex control scheme than individuals with three modules (and similarly individuals with three modules always use a less complex control scheme than those with four modules), may not be true and is difficult to support in some case. It is challenging to say if an individual with three modules that account for 95% variance is truly exhibiting less motor control complexity than an individual with four modules and 99% VAF. Therefore, not only is the "group and rank" method a bit cumbersome, but it also runs the risk of misclassification. The Walk-Dynamic Motor Control (DMC) Index provides a way around this potential problem.

The Walk-DMC Index is a single value that compares impaired individuals with healthy individuals on a scale. This computation (Eqn. 2) is designed such that the average Walk-DMC Index value of a healthy individual is equal to 100, and values less than this indicate some level of impairment in motor control.

$$Walk - DMC = 100 + 10 \times \left(\frac{VAF_{1_{avg}} - VAF_1}{VAF_{1_\sigma}} \right) \tag{2.2}$$

Rather than finding how many modules are necessary to fully describe an individual's gait motion, the Walk-DMC only assumes a single module, and it is a function of the VAF by that one module. In the equation, VAF_1 is the VAF by one module of the individual's

motion that is currently being analyzed, $VAF_{1_{avg}}$ is the variance accounted for in the average *unimpaired* individual, and $VAF_{1_{\sigma}}$ is the standard deviation of variance accounted for by the average unimpaired individual [46, 47]. While the Walk-DMC Index may seem very abstract with no other implications outside of its mathematical basis, the Walk-DMC Index is strongly correlated to improvements in walking speed following a therapy, along with improvements in the Gait Deviation Index (another mechanics-based metric meant to quantify the impairment severity of an individual) [46].

In the following three studies, the Walk-DMC Index will be used as the performance measure for the individuals post-stroke, as we feel that it is the best metric available that directly quantifies neurological impairment. The groundwork for the fundamentals of this project have been laid with the introduction of and reasoning behind the Walk-DMC Index, but before moving into greater detail about the three studies in this project, this section will conclude with a brief discussion on the statistical methods used for gait analysis, since they differ from traditional methods.

2.5 Statistical Methods

2.5.1 Statistical Parametric Mapping (SPM)

SPM was originally developed for analysis of brain images [48], but has since gained traction in biomechanics due to its ability to detect time-dependent differences between trajectories [49, 50, 51, 52, 53, 54]. Traditional statistical methods are problematic for time series analyses for a few reasons. Firstly, more often than not they require *a priori* knowledge of where one expects to find a significant difference. For example, picking discrete points (known as the *scalar extraction approach*) to compare can read to regional focus bias, where other points of significance remain undetected because they were not tested. Secondly, if one wanted to test multiple points in a trajecotry for significance, repeated hypothesis testing results in an increased likelihood of incorrectly identifying a signficant difference. In this way, traditional hypothesis testing is biased to expand the scope of the null hypothesis [55].

SPM is hinged on a *non-directed hypothesis*. This simply is a hypothesis that states "I believe there are statistical differences between these two trajectories," rather than traditional *directed hypotheses* that state something like "I believe there are statistical differences in the [peak, minimum, average, etc.] values of these trajectories at X%." The trajectories are compared all at once, rather than extracting specific time points for analysis. Then, the broader analysis will points or regions in the trajectories that are significantly different, allowing one to zero in on important parts of the trajectory. Thus, SPM is designed to restrict the scope of the null hypothesis [55].

Most biomechanical data, be it electromyography signals, ground reaction forces, joint angles/moments, etc., is represented as a curve comprised of hundreds of individual observations. This curve is usually normalized over a particular event, say 0-100% of the stance phase, or 0-100% of the entire stride. Not only is it computationally costly, but it is also statistically invalid to compare mulitple discrete time points across two trajectories to find instances that are statistically different (Fig. 6). So how then is it possible to get a comprehensive picture of where all the statistical differences between two trajectories lie, without performing multiple tests? SPM circumvents this by considering each trajectory, not as a collection of many observations, but as a single observation represented as a vector field.

For example, a typical joint angle series, θ, would normally be represented as $\theta_i(t)$, where i is the observation number. However, represented as a vector field, this becomes $\boldsymbol{\theta}(t)$, where $\boldsymbol{\theta}$ is comprised of multiple components that vary throughout time. Under vector field considerations, the t-statistic and critical t-statistics are functions over time, rather than discrete values. The critical t-statistic is calculated based on Random Field Theory, which is used to assess the smoothness of the field. When the t-statistic breaches the critical value, what we are actually interpreting is the probability that this would have occurred due to chance by random fields of the same smoothness [55]. The results of SPM are easy to interpret as they are presented directly in the sampling space, and there is directionality associated with the t-statistic such that it is clear in what way the groups are statistically different [56, 55, 57]. For SPM, the t-statistic trajectory is determined by

$$T(t) = \frac{\overline{x_1(t)} - \overline{x_2(t)}}{\sqrt{\frac{1}{n_1}Var[x_1(t)] + \frac{1}{n_2}Var[x_2(t)]}} \tag{2.3}$$

where the numerator represents the difference in the means of the respective populations; n_1, n_2 are the population sizes, and $Var[x_1(t)]$, $Var[x_2(t)]$ are the variances [49].

with the critical threshold, $t_{critical}$, being derived from [49]

$$1 - \exp(\int_{t_{critical}}^{\infty} f_{pdf}(x)dx - ED) = \alpha \tag{2.4}$$

where f_{pdf} is the probably density function of the t-statistic, ED is Euler density function, and α is the error rate, normally set to 0.05.

2.5.2 Functional Data Analysis (FDA)

Along the same lines as SPM, FDA is another method that allows for continuous trajectory analysis. It, too, is suitable for time-series analysis as it does not require prior discretization. FDA has been implemented in studies involving biomechanics, including knee effusion [58], gait in individuals with Parkinson's Disease [59], and post-stroke gait [60]. Unlike SPM, FDA does not invoke vector fields or Random Field Theory, but rather it operates by expressing the data as a linear combination of basis functions, typically B-splines or Fourier functions [61]. This provides a lot of information about the curve behavior and its derivatives that would otherwise be unavailable. FDA is flexible and the user is left with a lot of freedom in how he/she chooses to perform the analysis, but this also means that the user is left with a lot of decisions regarding the order of the spline functions, how many functions to use, how to determine the coefficients of the linear combination, and what to do about overfitting.

There is a bit of vocabulary that accompanies FDA that is worth addressing, and we will do so in the context of our project. For our analysis of post-stroke hemiparetic gait, our data is always normalized with 101 frames, from 0-100% of gait or 0-100% of stance phase (see Fig. 2), depending on the parameter. This means that our *range* is [0, 100], and we have 99 *interior knots* with 101 total *break points*. The knots and break points are where the spline

function changes, and we chose the number of spline functions for the linear combination based on Eqn. 4, from Ramsey et. al [61]:

$$n_{functions} = n_{knots} + n_{order} - 2 \tag{2.5}$$

Coefficients for the linear combination may be obtained via linear regression, but more suitable for this project where so many basis functions are used is to a method that imposes a roughness penalty on the total curvature of the curves to avoid overfitting from using so many basis functions [61]. We are particularly concerned with the smoothness of the second derivative (acceleration) of these curve, so we define the roughness measure (which we are penalizing) as the curvature of acceleration, given by Ramsey et. al [61] as

$$Rough = \int [D^4 x(t)]^2 dt \tag{2.6}$$

which is this included in the fitting criterion from which the coefficients are determined

$$F(\mathbf{c}) = \sum_j [y_j(t) - x(t_j)]^2 + \lambda \times Rough \tag{2.7}$$

where $y_j(t) = x(t_j) + \epsilon_j$, $x(t) = \mathbf{c}\phi$, ϵ_j is the error, $\mathbf{c}$ is the array of coefficients and ϕ is the array of basis functions, and λ is the smoothing parameter where large values penalize the curvature so much that only small amounts are present at knots and break points, and very small values do not penalize the curvature much at all, meaning that overfitting is not accounted for very much and the user is trying to get as close of a fit as possible to the data [61].

Once the data is expressed as a linear combination, statistical analyses can be performed on this functional representation of the data. The critical t-statistic is found by randomizing the group labels and computing the t-statistic value, storing the maximum of these values, and repeating for the maximum number of permutations of the labels. This is the *t-max distribution*, and the critical t-statistic is taken as the $100 \times (1-\alpha)^{th}$ percentile, where α is the specified error rate [49].

The t-statistic trajectory itself is given exactly the same as SPM, minus the ability to provide information about directionality of significance

$$T(t) = \frac{|\overline{x_1(t)} - \overline{x_2(t)}|}{\sqrt{\frac{1}{n_1}Var[x_1(t)] + \frac{1}{n_2}Var[x_2(t)]}} \tag{2.8}$$

SPM and FDA are different methods that serve a similar purpose, and even though SPM is a parametric method and FDA is a nonparametric method, generally good agreement is found between the two in terms of what features over what regions are determined as significant, and slight differences between the two can be attributed to 1. Differences between the parametric/nonparametric approaches; 2. Sensitivity and insensitivity of SPM and FDA to changes in field smoothness, respectively; and/or 3. Inconsistencies in the calculation of the FDA critical t-statistic, since it is dependent on number of permutations [49].

The statistical methods are what we believe to be the most sound approaches to analyzing differences between time-varying biomechanical data. Now that we have introduced motor control, the concept of modular control, and the Walk-DMC Index, along with these statistical methods, we are now ready to begin the discussion of the three studies.

Chapter 3

Aim I: Dynamic motor control changes in individuals with post-stroke gait following functional electrical stimulation therapy

Abstract

Motor control complexity is impaired in individuals suffering strokes due to detrimental neural changes, leading to uncoordinated motions and difficulty performing motor tasks, including walking. Functional Electrical Stimulation (FES) therapy has been shown to be superior to conventional therapies at improving physical post-stroke gait performance measures, but it remains unclear if similar improvements take place in motor control complexity, which has been shown to be diminished in individuals post-stroke. We generated subject-specific simulations and quantified the effects of FES therapy to improve motor control complexity of eight individuals with post-stroke gait using the Walk-Dynamic Motor Control Index (DMC-Index). We found the 12-week FES-intervention combined with fast treadmill walking increased control complexity in 4 out 8 of the participants. We used Statistical Parametric Mapping (SPM) for two purposes: 1. to determine relationships between increasing the motor control complexity and changes in observable gait mechanics; and 2. to expand upon previous work wherein the trailing limb angle (TLA) was shown to be important for paretic propulsion, specifically the value of TLA at toe-off. However, our work shows that as a result of FES-combination therapy, the TLA increased, on average, over the first 20-40% of gait during mid-stance. This indicates that outside of toe-off, initializing increases in TLA earlier is also important for propulsion improvements.

3.1 Introduction

The ability to control muscles to perform a desired task is crucial for navigating the surrounding environment and this delicate control system can be severely damaged when a stroke occurs, restricting oxygen from reaching certain areas of the brain. A stroke can often have lasting negative impact on motor control ability and severely decrease overall quality of life for individuals suffering strokes. For several decades, improving motor control and resulting gait mechanics in these individuals has been the focus of rehabilitation protocols [62]. Despite the scientific research and rehabilitation, only about 25% of stroke survivors recover to their pre-stroke functional levels [63]. Furthermore, nearly 800,000 people experience a stroke each year, costing upwards of $34B annually in stroke-related healthcare costs and missed work days in the U.S. alone. Thus, the related financial burden of the initial stroke event only compounds the problems related to physical impairments that follow.

Treatments targeting post-stroke gait can be categorized into two broad approaches [64]: 1. *Bottom-up* and 2. *Top-down*. Bottom-up approaches target mechanical repair, in which neural plasticity is thought to improve as a result of improvements to the observable, physical deficits. Commonly, physical metrics such as walking speed, step length symmetry, or paretic propulsion determine performance [13]. However, these metrics are only tangentially related to recovery at the neural level or motor control complexity, in the sense that these higher-level improvements will follow as a result of mechanical changes, and any conclusions drawn about neural recovery will be indirect. Furthermore, the most common performance metric, walking speed, can be increased by the use of compensatory mechanisms (Nadeau et al. 1999), which can also lead to secondary complications, such as arthritis, even in the non-paretic limb [65]. Other metrics, like step-length symmetry, are rather variable and inconsistent in trends amongst individuals suffering from post-stroke gait. Overall, metrics typically associated with bottom-up approaches that are aimed at observable gait mechanics in terms of angles, speeds, etc. are not particularly enlightening in terms of neural recovery.

Contrarily, top-down approaches target neural repair and allow the physical improvements to follow as a result [64]. One common type of top-down treatment is functional

electrical stimulation (FES), wherein the electrical stimulation directly impacts the muscle activity, something that is very closely related to and governed by the nervous system. When FES is combined with gait-retraining programs, there is strong evidence that hemiparetic post-stroke gait mechanics improve [66, 8]. Gait improvements following FES and fast treadmill walking combination therapy include increased walking speeds, peak propulsive force, and paretic trailing limb angles (TLA), or the angle the limb makes with vertical prior to toe-off [8]. However, whether these observed gait improvements can be associated with and indicate similar improvements in motor control complexity, a quantity related to the variability in the muscle activation pattens and has been shown to be lower in individuals with neural impairments, remains unknown.

An approach to replace bottom-up metrics in evaluating the FES-combination therapy outcomes with a top-down metric directly is aimed at determining control complexity of the central nervous system, known as the Walk-Dynamic Motor Control (DMC) Index. The Walk-DMC index operates under the assumption that motor control complexity is lower in individuals with neurological impairments than in unimpaired individuals, and this complexity is assessed by the presence of muscle modules, or synergies, present in muscle activation patterns. Rather than individual muscles being activated by specifically directed excitations, modular control of movement instead allows for co-activated muscles where a single excitation signal can activate multiple muscles [30, 31, 29, 32, 42, 36, 37, 38, 39]. A simulation study from Neptune et al. demonstrated that healthy gait could be controlled by four modules, indicating the use of high-complexity control [28]. However, in individuals post-stroke, these four modules become merged (not independently activated) and therefore the gait is described by fewer than four modules, which indicates the use of lower-complexity control [26]. Synergistic control of movement in terms of muscle modules has been previously used to draw conclusions about the complexity of motor control, but this approach, aimed at classifying individuals as mildly, moderately, or severely impaired based on the number of modules necessary to describe their gait, can be challenging to implement without misclassifying individuals [25, 26]. At its core, the Walk-DMC Index normalizes motor control complexity to only consider a single module and the variance it accounts for. Furthermore, the Walk-DMC Index is a metric specifically designed to estimate motor

control complexity as it relates to the nervous system itself, and aids in drawing strong conclusions about neural recovery as a result of a therapy for post-stroke gait. This is important information regarding how an individual is recovering post-stroke and is more insightful than reporting the effects only in terms of gait mechanics.

This study used a combination of gait analysis, computer simulation, and statistical approaches to evaluate improvements following FES-combination therapy. Because of the improvements in gait metrics that have been previously identified, we hypothesize that this therapy will increase the motor control complexity in these individuals. We tested this hypothesis by computing the Walk-DMC Index values changes before and after therapy. In addition, we determined the effects that this therapy has on traditional gait measures through Statistical Parametric Mapping to identify any different effects that may not have been found with conventional statistical methods used in other studies [57, 56, 67, 55, 49]. Determining the beneficial effects of gait therapy on post-stroke motor control is critical to better understand and improve treatment for this movement disorder. The approaches used here extend beyond this study population, leading to the development of better treatment planning and furthering the emergent field of patient-specific medicine.

3.2 Methods

3.2.1 Study population and data collection

Eight individuals recovering from stroke (61.8 ± 8.4 y, 3 male, >6 months post-stroke) (Table 2) agreed to participate in a 12-week FES gait retraining program to stimulate both the paretic ankle plantarflexors and dorsiflexors. Minimum physical fitness to walk consistently for five minutes without an assistive device was required to participate in this study. Individuals with any co-morbidities were excluded. The gait retraining was divided into four six-minute rounds, where individuals walked at their fastest comfortable speed on an instrumented treadmill, and during the first, third, and fifth minute of each round, the paretic ankle plantarflexors were electrically stimulated with an FES device during paretic pre-swing, and paretic dorsiflexors were stimulated during paretic swing. After all four

rounds were completed, a fifth round served as a transition from treadmill to overground walking. During this round, minutes 1-3 took place on the treadmill with FES, and the last three minutes involved overground walking without FES. The individuals participated in this gait retraining program three times per week over 12 weeks for a total of 36 training sessions. Kinematic and dynamic gait data, including three-dimensional marker trajectories, ground reaction forces, as well as each individual's self-selected walking speed, were recorded. Further information on the experimental setup and gait data collected can be found in Knarr et al.[9]; moreover, further FES-combination therapy details can be found in Kesar et al. [8].

3.2.2 Musculoskeletal Modeling

We generated three-dimensional musculoskeletal models with 23 degrees of freedom and 92 muscles using OpenSim 3.3 to match each subject's height and weight. Initially, we used Computed Muscle Control (CMC, Fig. 7) to determine muscle activations required to produce pre- and post-therapy gait motions. CMC implements an optimizer that is designed to identify a set of muscle activations that drive the model kinematics to a set of kinematics at the expense of a two-part cost function: sum of squared activation and sum of errors in accelerations. First, it uses PD control to compute a desired acceleration trajectory based on experimentally determined values, and then static optimization is applied to find a set of controls that produces these accelerations. However, further investigation revealed that the muscle activity from CMC was noisy, despite efforts made to rectify this by decreasing the convergence tolerance, locking specific joints that seemed to contribute to high reserve forces (forces applied when a simulation "asks" a muscle or torque actuator to generate infeasible forces), or simulating smaller lengths of time. Because future analyses performed on these muscle activations, we needed to make sure that our results reflected true relationships or underlying mechanisms in the data, rather than be dependent on the noise of the inputs. For this reason, we eventually chose to explore our options outside of OpenSim CMC and regenerated these results with OpenSim Moco's Inverse tool, which resulted in much smoother solutions for muscle activations.

Moco uses direct collocation, an optimal control method to optimize the states (joint positions) and controls (muscle activity) of the musculoskeletal system simultaneously.

Unlike CMC, where static optimization calculates the controls for a set of desired accelerations at small intervals of forward-stepping time, direct collocation instead uses a mesh of time points, where between the knot points of the mesh the states and controls are approximated with splines. At each point of the mesh constraints are enforced to ensure that the derivatives of the splines are consistant with the derivative of the differential ewuations describing the system dynamics at that time point [68]. With this approach, fictitious residual forces that are normally required by CMC to maintain dynamic consistency between the model and experimentally collected ground reaction forces are not required by direct collection, since the system dynamics are used as constraints. For our studies with OpenSim Moco, the motion has been prescribed, which means that the simulated motion matches exactly the experimentally-derived motion and is not allowed to vary at all, whereas CMC allows small adjustments to be made to the kinematics.

3.2.3 Determination of muscle modules and quantification of motor control complexity

As previously mentioned, using muscle modules to gain information about motor control has been studied before. However, the critical difference between the approach presented here and previous work is the use of the Walk-DMC index. Unlike prior studies involving modular control in which the number of muscle modules necessary to describe a given motion is critical to how an individual's motor control capabilities are estimated, Walk-DMC only considers the presence of a single muscle module. We found this single muscle module using a decomposition algorithm known as *non-negative matrix factorization (NMF)* [26, 25, 29, 28]. Muscle activations for a set of 38 lower limb muscles were decomposed into the product of two smaller, lower dimension matrices. The first consists of the activation of each module over the complete gait cycle (i.e., the modular activation profile), and the second represents the muscle weights within each module. The resulting product of these lower dimensional matrices is referred to as the reconstructed signal (Fig. 8), which is an approximation of the original muscle activation inputs based on the modular decomposition, and the accuracy of this approximation is calculated by the variance accounted for (VAF, Eqn. 2.1).

The Walk-DMC Index is a powerful parameter as it provides an intuitive notion about the extensiveness of the impairment with respect to neural control, relative to an unimpaired population, where the Walk-DMC Index (Eqn. 2.2) of a healthy individual averages 100. Here, it is worth mentioning that the average and standard deviation of VAF_1 in the Walk-DMC Index equation are simply scale factors. These factors may change the value of the Walk-DMC Index, but will not change the relationship between subjects, or the change in Walk-DMC Index from pre- to post-therapy, due to linear relationship between VAF_1 and the Walk-DMC Index (Fig. 10).

As such, due to lack of data from a healthy population, we were not able to get the appropriate factors for the average and standard deviation to scale the Walk-DMC Index. Thus, while we can report on how much the Walk-DMC Index *changed* for the individuals in this study, any actual value of the Walk-DMC Index that we report pre-therapy or post-therapy would be inaccurate. Going forward then, we leverage the relationship in Fig. 10, and talk about changes in motor control complexity with regard to Variance Not Accounted For (VnAF) by one module, since this quantity scales directly, rather than inversely with Walk-DMC Index. Therefore, an increase in VnAF_1 correlates to an increase in Walk-DMC Index and an increase in motor control complexity, whereas a decrease in VnAF_1 correlates to a decrease in Walk-DMC Index and a decrease in motor control complexity.

For each of the eight individuals in this study, we obtained an average VnAF from pre-FastFES therapy and again after the therapy was completed. Each subject completed between 5-14 strides during data collection. For each stride, we used CMC to determine the muscle activity that could have produced the individual's gait motion. To obtain the average VnaF, we averaged the activations across all gait cycles for the individual, and used this averaged signal for decomposition with NMF.

3.2.4 Statistical Analysis of Trailing Limb Angle and Propulsive Force

Gait differences between pre-therapy and post-therapy were analyzed with Statistical Parametric Mapping (SPM, see section 2.5.1) to determine if more information could be

obtained through continuous, rather than discrete, evaluation of the trajectories. Previous work has concluded that the TLA increased at paretic toe-off following therapy [8, 9]. However, we'll refer to this as the *paretic limb angle* (Fig. 9), since whether it is a trailing limb or leading limb will depend oon where the individual is in the gait cycle. We will then analyze the entire paretic limb trajectory (and its angle relative to the lab vertical axis) throughout all of gait, eliminating the first step of discretization.

When invesetigating propulsive force with SPM, we narrow the region of interest here to be only the stance phase. In both cases, we use an error rate of 0.05, and we observe in the t-statistic trajectory where breaches of the critical t-statistic occur. While SPM does not require *a priori* knowledge of where statistical significance resides between two trajectories, it does help to know the general region. Giving SPM too wide of a region to search for decreases the sensitivity of its ability to detect differences. With a larger region, the critical t-statistic is higher, indicating that SPM will only be able to detect exceptionally large field fluctuations and will likely overlook smaller fluctuations. In some ways, it becomes somewhat of a balancing act given the inverse relationship between statistical power and size of the region of interest [69].

3.3 Results

The 12-week FES-combination therapy increased dynamic motor control complexity, reported in terms of the $VnaF_1$ in 4 of the 8 individuals in this study from $10.4 \pm 2.0\%$ pre-therapy to $15.0 \pm 3.1\%$ post-therapy (Fig. 11, green). For the remaining 4 individuals (red), no significant changes in pre- and post-therapy were detected.

These dynamic motor control changes resulting from the therapy effects did not appear to make statistically significant time-varying differences, determined by SPM, in the paretic limb angle (Fig. 12, right) and the propulsive force (Fig. 12, left). However, we note a region of very near significance around 60-70% gait, where toe-off is occuring. Even though there is not a statistical difference here, we note that there likely would be had we condensed our region of interest to be perhaps, double support, or stance phase. At its current trajectory, it does read that the pre-therapy paretic limb angle at toe-off is lower

than the post-therapy paretic limb at toe-off, and the lack of statistical difference can be attributed to the large region of interest, and the variance within this entire region. Thus, for the most part, our analysis of the paretic limb angle is consistent (or nearly so) with previous studies. SPM did not detect any significant differences in the propulsive force between the pre- and post-therapy gait data, contrary to the findings of traditional statistical analyses of peak propulsive force. However, we again note the trend in the t-statistic, where it is at a minimum near toe-off and where peak propulsive force is generally produced. Similar to our interpretation of the paretic limb angle, this implies that, even though there are no significant differences identified, the pre-therapy propulsive force at this instance was lower than the post-therapy propulsive force. And similarly, we may have found true significant differences had we limited our region of interest. Furthermore, it is important to consider the timing of the peak propulsive force, especially in traditional analyses. In healthy gait motion, peak propulsive force is produced at or very near toe-off, just before the limb enters the swing phase. Definitionally, propulsive force is the anterior (forward) component of the ground reaction force, and peak propulsive force is then the maximum value of this vector. However, we found that in some cases, the "peak propulsive force" happens very early, sometimes while in single support. This magnitude is greatly reduced from typical peak propulsive forces produced at true toe-off. In addition, we found that in these cases, at toe-off, the orientation is such that a propulsive force is not produced here at all, but instead a braking force, as seen in Fig. 3b. As such, this could be a reason for the discrepancy between SPM and traditional analyses of propulsive force, and it would be worth investigating the changes in the "forces produced at toe-off", rather than the anterior ground reaction force, as they may not occur at the same instance.

3.4 Discussion

To treat movement impairments in individuals with post-stroke gait, FES therapy combined with fast treadmill walking shows promise at improving not only surface-level gait mechanics, but also the governing motor control. Previous work found this top-down therapy improves traditional gait performance measurements, such as paretic TLA at toe-off and peak

propulsive force, but these physical measures do not shed light on potential improvements in the nervous system itself. Furthermore, these conclusions were drawn from traditional statistical analyses that are not well-suited for application to time-varying data due to the need for discretization prior to any statistical testing. Our results evaluating the $VnaF_1$ suggest that this FES combination therapy has positive effects on the motor control complexity of some individuals post-stroke, but like most other performance mechanics-based performance measures, there is a wide variation in response.

We recognize there are limitations of this work and our findings should be interpreted in the context of our research challenges. First, the number of participants was relatively small compared with other post-stroke gait studies, and the eight individuals may not represent the general population of stroke survivors before and after FES combination therapy. However, this study involved a 12-week therapy, which may be too long for some individuals to participate in the research. Second, the muscle-driven simulations of post-stroke gait and quantification of motor control in this study did not explicitly model individual motor impairments. When analyzing impaired gait, the cost function used in our simulations and may not be appropriate and it could potentially overestimate the experimental motor control complexity for some subjects. However, the simulated activations were compared with EMG patterns of other individuals post-stroke in a study conducted by [70]. We observe an increase in plantarflexor activity and an improvement in the timing of these muscles, particularly gastrocnemius, following therapy. Furthermore, the magnitude of the $VnAF_1$ changes observed here may be different if we made different simulation and motor control assumptions, but the conclusions regarding the direction of these control complexity changes would be unlikely to change because these same assumptions would be made across both pre- and post-therapy gait simulations.

Despite the limitations, we found that our hypothesis is partially supported regarding whether functional electrical stimulation of the paretic ankle muscles combined with fast treadmill walking would increase the Walk-DMC Index of subjects with post-stroke gait. We then aimed to analyze time-varying gait data using SPM, a statistical tool used to mitigate the effects of bias associated with discretization, to expand upon previous findings relating to TLA and propulsive force by Kesar et al. Our results are consistent with Kesar

et al. in that the TLA does increase as a result of this therapy; however, since SPM does not discretize time-varying data, we found that TLA increases over the entire stance phase, rather than a single point in gait. Concerning propulsive force, our SPM results are not consistent with those Kesar et al. found and do not support an increase in propulsive force, though we do observe an approach towards significance during late stance. The significance found by Kesar et al. in peak propulsive force could be due to the inconsistency of timing when this force is produced.

This study is the first to analyze the motor control complexity of individuals post-stroke in terms of only a single module, and how motor control may increase following FES-combination therapy. The approach could easily be extended to other populations undergoing therapy for movement disorders to investigate the improvements in dynamic motor control complexity. This study identified a distinct variation in response, quantified by the variance *not* accounted for by a single module, amongst the subjects that is commonly seen with many musculoskeletal disorders and their treatments. We identify four individuals that increased their post-therapy Walk-DMC index values, and four individuals who did not. This result indicates the FES-combination treatment may have a limited effect on some subjects, particularly if their motor control is not severely impaired prior to therapy. Future work will focus on determining the contributing factors that underly an individual's outcome to develop a model for predicting a person's response to this therapy. In addition, should an individual fall in the "does not improve" group, defined by no change or a decrease in the Walk-DMC index values then it will be necessary to identify areas to target or ways to modify current therapies to improve the outcome for these individuals.

3.5 Aim I Plain Language Summary

Until now, the evaluation of post-stroke rehabilitation has been primarily centered around mechanics-based measures like walking speed, step-length symmetry, paretic propulsion, etc. However, because stroke is a problem with a neurological origin, we suggest that a truer measure of recovery is one that relates to neurological recovery. We use a modified version of the Walk-DMC Index to quantify the motor control complexity of individuals post-stroke.

We find that like other studies on post-stroke gait that discussed rehabilitation outcomes in terms of mechanics-based measures, we also found there was quite a lot of variability in the response when we quantified performance with a measure designed to target neurological function. There were some people that increased their motor control complexity, and some people who did not. Even within these categories, there was a wide range. Some people increased their motor control complexity by a considerable amount, while others saw a much smaller improvement.

Chapter 4

Aim II: Predicting response to FastFES therapy in individuals with post-stroke gait impairments

Abstract

Predicting outcomes of rehabilitation is an important aspect of treatment design and prescription. Unfortunately, it can be a "toss-up" regarding whether an individual will benefit from a therapy. This is likely due to complex origins of impairment, where individuals that display similar disabilities do not necessarily have the same set of causes for these problems and require different therapies. However, there exist some well-established rehabilitation protocols that are commonly followed based on post-stroke motor assessments. In this study, we seek to build a predictive model to determine whether a patient is a good candidate for FastFES therapy based on pre-therapy baseline measurements alone. We employ a Support Vector Machine (SVM) and compared the performance of this at classifying gait motions as belonging to a responder/nonresponder with a k-Nearest Neighbors (kNN) algorithm. Features used in these classifiers were determined through Statistical Parametric Mapping (SPM) and Functional Data Analysis (FDA), which identified regions in the trajectories that were significantly different between the two groups. Averages over these regions were taken and used as the predictor variables for SVM and kNN.

4.1 Introduction

Prescribing rehabilitation outcomes for individuals post-stroke can be a challenging process. Most importantly, the clinician must advise for a treatment that he/she believes will provide the patient with the best opportunity for success in recovery of motor function. However, the best a clinician can do is consider a long term prognosis based on current assessments, and this prognosis will impact his/her recommendation for discharge from an acute care unit following a stroke. Should the clinician believe that the individual will be largely unaffected by therapy and will remain severely disabled, the patient will be placed in a long-term care facility rather than being released to his/her residence. Contrarily, if the clinician believes that the individual can regain substantial motor function, the patient will likely be released to his/her home, or possibly to a relative [71, 72]. This may be problematic, however, if in fact the person does not make expected gains with therapy and is unable to function independently at home.

Furthermore, there is the issue of possibly placing an individual in a therapy from which they will not benefit, and the effects that this may have on the patient's mental status. This will almost certainly damage the patient's self-confidence, a strong motivating factor behind rehabilitation outcomes [73, 74, 75]. This may discourage patients from further rehabilitation, leading them to remain disabled, even though they may benefit from other treatment and therapies. Thus, the clincian has a heavy duty of prescribing a therapy as accurately as possible.

As such, there has been substantial research involving predicting rehabilitation outcomes. A study involving 878 individuals post-stroke concluded that the patient's age does not have any impact on response to a multidisciplinary rehabilitation program involving therapy for neurologic dysfunction, traumatic brain injury, nono-traumatic spinal cord injury, traumatic spinal cord injury, stroke, amputation, and arthritis [76]. In another analysis of nearly 30,000 individuals, the Functional Independence Measure (FIM) upon admission explained 60% of the variance in the FIM at discharge. This study found weaker, but still worth mentioning, relationships between cognitive function at admission with functional measures at discharge, along with age of the patient, and disruptions during rehabilitation [77]. Yet another study

found that a model with four predictors could explain 40% of the variance in functional outcomes of post-stroke rehabilitation: neurological impairment, cognitive function, pre-stroke Activities of Daily Living (ADL) value, and age [78].

There are many more models, ranging from regression to simple variance analysis, that have been proposed as methods to predict functional outcomes of a wide variety of disorders. However, just in the few that we have mentioned here, we notice that there is conflicting information regarding what factors are actually important. This becomes a central problem in creating models- *How do I know what is important?*. In this study, we continue with the same kinematic and dynamic data recorded from the eight individuals' post-stroke gait motions in the first study, which is available from the pre-FastFES case and the post-FastFES case.

We then group the subjects into one of two groups: *responders* and *non-responders*, depending on whether their post-FastFES Walk-DMC Index was greater than their pre-FastFES Walk-DMC Index. Statistical Parametric Mapping (SPM) and Functional Data Analysis (FDA) were used to identify differences in the gait data between the two groups. A total of 20 time-varying trajectories were analyzed with SPM and FDA. If SPM and FDA identified a region of a trajectory that was statistically different, then an average value was taken over that region in the trajectory. The averaged values were used as inputs to SVM and kNN for classification of the gait motion.

4.2 Methods

The same individuals from Aim I are used in this study. Please refer to section 3.2.1 for more details on FastFES therapy, and Table 3.1 for more information on subject parameters.

Briefly, machine learning is the process of training machines (computers) to make decisions in the way that a human would. In our case, we will be talking about decisions in terms of *classification*. For example, given a bouquet of flowers, a human could readily classify each flower as a rose, daisy, or tulip. In this way, there are three *classes* of flowers. To decide what type of flower it was, we may consider the color of the flower, the number of petals, and/or the shape of the petals. Each of these is considered a *feature* or *predictor*

variable. Furthermore, we want to be able to distinguish these flowers not only in the bouquet we have, but perhaps in the wild as well. Similarly, with machine learning, we want the algorithm to perform well on not only data that it has "seen" before, or been exposed to/trained on, but the real test of performance is how generalizable it is. Can it adequately classify data that it has not been trained on? In our case, we have two classes: responders and non-responders, and we seek to classify gait motions of these individuals post-stroke as belonging to one of these two classes with two algorithms: SVM and kNN. SVM was chosen because of its ability to handle outliers, and this was compared with kNN, a non-parametric method that is suitable for our project due to the small dataset and low number of features that we using for predictor variables. To ensure thorough testing, data from 6 subjects was used for training, and the remaining 2 subjects' data was used for testing. In this way, the algorithms were not both trained and tested on data from the same individual.

4.2.1 Support Vector Machine (SVM)

SVM is a supervised technique, meaning that we have prior knowledge of what gait motions belong to a responder and which ones belong to a non-responder. In other words, we know the *labels* of the data we are classifying. If a gait motion belongs to a responder, we assign it a label of '1'. Otherwise, we assign it a label of '0' to relay that it belongs to a non-responder.

The goal of SVM is to find a decision boundary in the form of a hyperplane. A decision boundary, as the name implies, is the "dividing line" between two classes, such that (hopefully) all of one class will exist on one side of the boundary, which the other class primarily exists on the other side of the decision boundary. In a two-dimensional problem, or classification with two predictor variables, the decision boundary hyperplane is a line. It is a plane with three predictor variables, a surface with four features, etc. The decision boundary is of $n-1$ dimension, where n is the number of features or predictor variables.

If we consider a two-dimensional problem with two classes that are very easily separated, there are a near infinite number of boundary lines that we could draw between the classes, so how does SVM select the best one? In Fig. 13, we show how the optimal hyperplane is selected. Support vectors pass through the most extreme data points in each of the classes- or the points in class 1 that are nearest to points in class 2, and vice versa. By centering

the boundary hyperplane within this margin, we maximize the width of the margin, which makes the SVM robust against outliers.

Below, we provide a brief mathematical explanation of the optimal hyperplane. Let $\vec{n}$ be the normal vector to our boundary hyperplane. Assign labels of '1' to be in class 1, and labels of '-1' to be in class 2. Then, the upper "edge" of the margin will be defined by

$$\vec{n}^T\vec{x} - b = 1 \tag{4.1}$$

and the lower edge of the margin will be defined by

$$\vec{n}^T\vec{x} - b = -1 \tag{4.2}$$

The width of the margin is then defined as $2/||\vec{n}||$, and we want to maximize the width of the margin. For each label, y_i, we maximize $2/||\vec{n}||$ such that $y_i(\vec{n}^T x_i - b) \geq 1$. Maximizing the margin width under this constraint prevents any data point from falling inside the margin. In our case, we projected our data to a higher dimension using a radial basis function, since it is not linearly separable in its original state.

4.2.2 k-Nearest Neighbors (kNN)

Mathematically, kNN is much simpler in terms of implementation that SVM. We provide kNN with training data, and then for each point in the testing data, we calculate the distance from this test point to each training data point. We then sort by the distances, and assign the test point the label of its k nearest neighbors. If $k = 1$, then we assign the test point of its single closest neighbor. If $k = 2$, we assign it the label of its two closest neighbors. It is likely, especially for a large number of neighbors, that all training points will not have the same label. In this case, we assign the majority label to the test point.

In our case, we are classifying pre-therapy gait motions as belonging to a responder or non-responder. In total, there are 69 gait motions that we are classifying. We used the elbow method Fig. 14 to determine the appropriate number of neighbors. We found

that 11 neighbors was the optimal number, where adding additional neighbors decreased performance of the kNN classifier.

4.2.3 Feature Extraction

In total, we have 22 time-varying features in forms of their trajectories over all of gait.

- Angles, Moments, Velocities, Powers for Hip Ad-/Abduction, Flexion
- Angles, Moments, Velocities, Powers for Knee Flexion
- Angles, Moments, Velocities, Powers for Ankle Flexion
- Paretic limb angle
- Angle between lab vertical and vector joining the center of mass with the center of pressure

Neither SVM or kNN are equipped to classify data with time-series as predictor variables, so we need to isolate specific regions of these trajectories that we can extract and use as features. For this, we employ SPM. Given our responder/non-responder groups Fig. 11, we use SPM to identify differences between the two groups. However, with our current exploration of features, we do not find any statistical differences between these groups.

We note that Subject #5 experienced a very small decrease, or a rather minimal change at all, in VnAF. As such, we chose to remove this subject, and search for differences between the remaining seven. When we do this, we find that the responders have a smaller support moment between 40-50% of stance (Fig. 15a), and they also have a larger knee flexion angle 20-40% of gait (Fig. 15b.) We note in Fig. 16 the similarities in the significant features found by FDA. For our features then, we considered only pre-therapy gait motions for a total of 69 cycles. For each cyle, we averaged over the regions deemed signficant by SPM. It is worth noting that a non-parametric method, FDA, was used for comparison. The critical t-statistic threshold defined by FDA was slightly varied from SPM, allowing for an additional feature (Hip Flexion Moment) to have a very slight region of significance. We note that the shape of the t-statistic trajectory between SPM and FDA are the same, but FDA reports the magnitude without the direction.

4.3 Results

We compare the performance of a SVM with a radial basis function kernel to the performance of kNN with 11 neighbors (Fig. 17). We find that the models perform similarly, with SVM operating at roughly a 74% accuracy and kNN at nearly 75% on average. Therefore, with reasonable accuracy we are able to predict from an individual's baseline gait motion whether he/she is a good candidate for FastFES therapy. We would like to note that for the two individuals with the most minimal change, we can predict their gait motions as belonging to a responder or non-responder with only about 50% accuracy. Thus, individuals that are on the edge of being a responder vs. non-responder are most difficult to predict, and our overall average accuracy does increase if we take these subjects out of classification. However, it is useful information in and of itself to know about this "toss-up" prediction, because that likely means this therapy will not have much effect on them at all, and it may not be advised that the patient undergo this therapy. These methods can be extended beyond post-stroke gait impairments and FastFES therapy, and it may be possible to develop a reliable predictive model based on data that is recorded before the individual undergoes any sort of treatment to determine if the therapy in question is one that will be useful to the individual.

4.4 Discussion

A prominent issue when designing any sort of model is identifying the appropriate features or predictive variables that will optimize the performance of the model and ensure the highest accuracy. A tempting solution might just be to throw all the data we have at the models and see what happens, but this likely will not result in good performance, especially if this is an exceptionally large feature set. Models are somewhat susceptible to irrelevant information, and not only will providing the model with more information than necessary almost certainly result in more computational expense, but providing too much information that is not important can also lead to a decreased accuracy. In this way, some pre-modeling steps are necessary to determine which bits are data are going to make for the most successful predictor variables.

To identify features in our data, which consisted of 22 time-varying trajectories that evolve as the gait cycle progresses, we used SPM to identify regions of significant differences in these pre-therapy trajectories between two groups that we defined as responders and non-responders based on the effect (or lack there of) that FastFES therapy had on their motor control complexity, as measured by the VnAF changes from pre-therapy to post-therapy. Ultimately, we found there were differences in the support moment, knee flexion angle, and trailing limb angle. To obtain the predictor variables used in our models, we then averaged over the signficant regions determined by SPM in these trajectories. For both models, we were able to achieve accuracies in excess of 75% at predicting whether a gait motion that was recorded before any intervention is generated by a responder or a non-responder.

Limitations of this work certainly involve the limited dataset. We were classifying only 69 pre-therapy gait motions, generated from a total of 8 individuals. In order to further assess the performance of our models, we did verify, that given the three features we were using, there were in fact two distinct clusters in our data. Furthermore, while the predictive power of these models does exceed current methods, where accepting that some people will get better and some people will not is commonplace in rehabilitation, there is still room for improvement and ideally we could increase predictive power upwards of 85% or even 90%+. Some suggested methods are to attempt some hyperparameter optimization of these models, interestingly, treat the data as similar to the MNIST handwritten digit dataset, and convert the trajectories into grayscale images for classification. This would eliminate the possibility of perhaps discarding information through averaging that could improve the performance of these models [79]. In addtion, it may be possible to use these features to not only predict responder or non-responder groupings post-therapy, but rather to predict values of motor control complexity following therapy. This would be particularly useful, because currently we consider anyone that had a positive increase in motor control complexity to be a responder to FastFES therapy, no matter how marginal this increase was. Therefore, knowing ahead of time *how much* improvement a person can expect to experience as a result of therapy is more powerful than predicting that they will have some undetermined amount of improvement, and may contribute to a clincian's recommendation of therapy.

Until this point, we have shown the variation in subject response to FastFES therapy, and we have shown that it is possible to predict, based on pre-therapy data alone, a person's response to this therapy. The final study will stem directly from these previous two, and focus on modifying this current therapy to maximize rehabilitation outcomes for individuals based on their pre-therapy motor control impairments.

4.5 Aim II Plain Language Summary

A large problem of various treatments for a wide array of diseases and disorders revolves around the inconsistency in response. It is difficult to predict with great accuracy that effect that a therapy will have on improving an individual's condition. For some therapies, this is fairly low-risk, and not much is sacrificed outside the the time spent undergoing the treatment (which is not necessarily negligible!). However, for some more invasive therapies like surgeries, it becomes more problematic to subject an individual to it without having confidence that he/she will benefit substantially. Though FastFES is not an especially risky therapy, we still wanted to explore patient pre-therapy baseline kinematic and kinetic gait data (joint angles, moments, powers, velocities) to see if would be possible to predict ahead of time with any sort of accuracy whether a person would respond, or increase their value of motor control complexity, as a result of FastFES. We used SVM with an rbf kernel and a kNN with 11 neighbors for this, after extracting some relevant features from pre-therapy data with statistical parametric mapping and functional data analysis. We found that both SVM and kNN could predict with roughly 75% accuracy whether a given gait motion was generated by a responder, someone that improved their motor control complexity, or a non-responder, someone that did not.

Chapter 5

Aim III: Optimization of FastFES therapy for maximum improvement in motor control complexity

Abstract

In this study, we aim to show that subjects with similar impairments in observable gait mechanics can have vastly different motor control complexities. In this way, the variation in response that a top-down therapy such as FastFES has in a population is justified. Targeting the same two muscles at the same instance in time for everyone in a study, simply because their impairments appear to be superficially similar, is insufficient at ensuring that each individual maximally benefits. Instead, we propose that motor control complexity should be evaluated, and the therapy should be tailored depending on the severity of the neurological impairment. For this investigation, we generated a total of 800 simulations in total, and evaluated the motor control complexities of the control strategies behind each simulation. Each of the 800 simulations was then grouped into one of three categories: Mildly, Moderately, or Severely Impaired. Then, we employ SPM to evaluate time-varying differences in muscle activity between the Mildly Impaired and Moderately Impaired groups, as well as the Mildly Impaired and the Severely Impaired groups. In this way, we can determine not only *which* muscles are important to electrically stimulate, but also *when* those muscles should be stimulated to maximize outcomes from this therapy.

5.1 Introduction

The idea of subject-specific medicine is not new, but was set in motion roughly 70 years ago when it was noted what a wide range of responses individuals had to various medications. Since, it has been discovered that a large part of patient drug response is rooted in genetics, and that factors such as age and general health should be accounted for to anticipate outcomes. Though the concept of subject-specific medicine took hold with drug therapy, or prescription medications, this concept has expanded to many types of therapy for many diseases and disorders with the goal of treating them with higher and more consistent accuracy [80].

Patient-specific medicine has begun emerging in rehabilitation settings as well. With technology such as 3D printing that allow for ease of production in terms of both time and cost, efforts have been made in generating subject-specific ankle-foot orthotic devices, as well as orthopedic casts, that are designed with individual patient needs and anatomical data accounted for [81, 82]. And, extending beyond physical devices or internal therapies in the form of medication, further application of patient-specific medicine has been employed in a non-surgical treatment of knee osteoarthritis. Subject-specific modifications to their gait were recommended in such a way that the knee adduction moment was reduced. This is a minimally invasive method for the treatment of knee osteoarthritis, and furthermore, to avoid asking the patient to change their gait pattern in an extreme manner that would be difficult to learn and maintain, part of the cost function for reducing the knee adduction moment was that the recommended gait pattern must deviate as little as possible from their current gait pattern. In this way, the new gait pattern can reduce knee loads that contribute to osteoarthritis but is not uncomfortable for the patient [83].

In this study, we follow similar trajectories of previous work, and we aim to modify an exisiting therapy from a "one-size-fits-all" format that has rather unpredictable outcomes into a therapy that is flexible depending on needs of an individual with outcomes that are not only predictable, but that ensure each an individual maximally benefits. The power of computer simulation allows us to perform this study in a low-risk envrionment without subjecting individuals to test therapies. We generate 800 simulations of post-stroke gait

motions and use OpenSim Moco to determine the muscle activity, which we then use to evaluate the motor control complexity. Each of the 800 is categorized based on the severity of the motor control impairment, and finally, vector-field statistical methods are applied to determine how to best modify the stimulation pattern to achieve improved motor control complexity.

5.2 Methods

Perhaps the question at this point is- *why not just group the simulations from the first two studys in to the impairment categories and evaluate differences in muscle activity? What is the need for these extra simulations?* And, as it turns out, the very reason that the former simulations are insufficient is exactly what we exploit to generate the hundreds of simulations for this study.

What we find is that even though suface-level gait impairments may seem similar between individuals, they may have vastly different control patterns in terms of which muscles are active at what time or phase in gait. Because FastFES, particularly the electrical stimulation component, is a top-down therapy, the neural control is what is being targeted, and is arguably more important in this context of this therapy than the observable mechanics. Thus, because we know that there are differences in control patterns, we suggest that the therapy should be applied differently based on a person's neurological capacity, rather than a blanket therapy used to treat people of similar physical capacity. Because we had such a limited amount of data in the previous studies, we used this notion to generate hundreds simulations of similar motions but that varied widely in terms of their motor control complexity. Since this study is attempting to make treatment modifications, more data is better for statistical analysis.

5.2.1 Generating variability

When we consider variability in motor complexity, we have to consider what *causes* this to happen, in order to simulate it. We know the variation in motor control complexity is determined by the muscle activity, represented as activation patterns as they evolve over

the gait cycle. Thus, it follows that we need to somehow introduce variation into these muscle activations. Initially, we intended to develop a cost function for determining the muscle activations that would be depend on the level of motor control complexity that we were trying to achieve. However, because we are using OpenSim Moco for these simulations, the cost function was not able to be altered due to continuity constraints imposed by its use of direct collocation. Therefore, we needed to come up with another way to introduce variability into the muscle activations to achieve our desired variability in motor control complexity. For this, we employed OpenSim Moco's *EMG Tracking Goal*.

The simulations in Moco are similar to performing simulations with OpenSim's CMC algorithm in terms of what inputs are required. We give Moco a model, motion (consisting of coordinate trajectories over gait), and ground reaction forces. With the EMG tracking goal, we can also supply Moco with muscle activity that we desire the simulated controls to "track", or be similar to. While we do not have EMG, we do have previously simulated activations from post-stroke gait. We also have a single set of activations from a previously simulated healthy, unimpaired gait cycle. To achieve variation in muscle activity (and thus in motor control complexity), we can mix the healthy activations with the stroke activations in various combinations to form multiple sets of *hybrid activations*. We have limited models and motions, but with Moco's ability to track given muscle acitivity, we can simulate the same motion with multiple different control patterns.

5.2.2 Creation of healthy-stroke hybrid muscle activations

We consider a single set of healthy activations and a single set of stroke activations. Each set consists of 38 muscles. We group the muscles by function, forming 12 groups of healthy muscles and 12 groups of stroke. Note that in each group, because they are grouped by function, there is a different number of muscles. We calculate an initial value of the motor control complexity, measured by the VnAF, for the set of stroke activations. Then we replace 6 groups of the stroke muscles with the same 6 groups of the healthy muscles to create a set of hybrid muscle activations. For these new hybrid activations, we again evaluate the VnAF, and note the ΔVnAF that this switch had from the original value. Given 12 groups and we are changing 6 at a time, this is a total of 924 possible permutations. Because is not feasible

to use all 924 permutations, we arrange the values of ΔVnAF from each permutation into a histogram, and we select the permutation that lies nearest the midpoint of each bin. This allows us to main the same spread, but we can achieve the same variability with only 10 permutations, rather than 900+ (Fig. 18).

In total, we have 16 models of individuals post-stroke (8 subjects, but models were regenerated for pre- vs. post-therapy simulations to account for change in mass ove the 12 weeks between recording a gait data). Recall that for each individual, we have 5-14 gait cycles during their pre-therapy and post-therapy data collection sessions. As such, we considered 5 gait motions from each individual to avoid any one individual's motion from being overrepresented. For each of the 5 gait motions, we gave OpenSim Moco 10 different sets of controls (muscle activitations) that it should track during the simulation. A general workflow of Aim III can be seen in Fig. 19. Once all the simulations have been generated, we evaluate the motor control complexity of each and group into one of the three impairment categories.

5.3 Results

In Fig. 20, we see how the 800 simulations are divided in terms of motor control complexity. In this analysis, because the green group of mildly impaired motor control strategies were the top perfromers in terms of VnAF, we consider this as the healthy population and thus as the goal for therapy. We want to know then what changes in muscle activity are necessary to bring individuals from the yellow group of moderately impaired simulations and from the red group of severely impaired motor control strategies into the green group, that we are calling the healthiest or most complex motor control strategies. We note that the distribution is skewed towards severely impaired motor control complexity, however, for our purposes of identifying differences in muscle activity this distribution is sufficient. If one desired a more even distribution, strategic selection of which muscle permutations strictly increased the VnAF could be used to ensure that more simulations will fall in the "healthy" category.

Each of our models has 38 muscles, however, we need to narrow down our search for significant differences in muscles between groups to involve only muscles that are actually

important. To narrow our search, we consider the average weights of the muscles present in the single module of the healthy group. A muscle is only said to be important or contributing to the module if its weight ≥ 0.4. Because we are trying to improve the motor control complexity from the moderately and severely impaired groups to be more similar to the healthy group, we only consider for our analysis the muscles that contribute to the module used by the healthy group. Larger muscle weights indicate that the activity from that muscle explains more of the variance in the overall activation of the module. The average weights in the module for the healthy group are observed in Fig. 21.

We identify a few muscles that seem to have the key differences in the transition from the moderately impaired (Fig. 22) and the severely impaired (Fig. 23) groups into the healthy group. In both transitions, a gluteus maximus muscle was identified to have a larger activation in the healthy group, as well as vastus lateralis. In the latter transition, we observe a larger activation of soleus at the beginning and end of the gait cycle of the healthy group. We note some slight differences in timing where the statistical signficance begins in vastus lateralis and gluteus maximus, but in general we observe similar trends in both transitions. We note that because SPM takes into account variance from the data, that sometimes where we would assume there to be statistical significance, because this a region of high variability SPM does not necessarily detect any statistical significance. This is particularly noticeable in vastus lateralis, where SPM detects difference in the later region around 65-70% of gait, even though there is very near statistical difference earlier in stance.

There are a few things worth considering while interpreting these results. First, we must remember that our "healthy" (green group) population is not actually data acquired from true, unimpaired individuals. The motions analyzed here and used to generate the simulations for all group were motions generated by stroke individuals, but the "healthy" population had the highest VnAF, our measure of motor control complexity. A principle of this study is that similar motions can have widely varying control patterns. Thus, although we are studying the transitions required from moderate and severe impairment groups to the "healthy" group, we have to recognize that the control patterns we are considering to be healthy or the targets, are not actually reflective of healthy individuals. Therefore, when we observe changes in soleus, for example, we may note that SPM picks up that the

"healthy" group has a higher activation of soleus near swing phase. In order to obtain a control pattern that more closely resembles our healthy group, we should conclude from this that we should stimulate the soleus near swing phase. However, as biomechanists, we know that soleus *should not* be active in swing phase of gait, as this would cause what is known as "foot-drop" and likely lead to tripping due to lacking clearance of the toe as the limb moves forward. We suggest that these results merely be used as a proof of concept, that transitioning from lower to higher motor control complexity largely depends on the severity of motor control impairment to begin with.

5.4 Discussion

In this study, we perform 800 simulations with OpenSim Moco. The prescribed motions for each simulation are from individuals post-stroke, and we use Moco's EMG tracking goal to track a set of previously determined muscle activations. In this way, the same motion could be produced with different control patterns. For each simulation where we obtained muscle activity, we analyzed the motor control complexity and then classified the control scheme as mildly, moderately, or severely impaired. We then used SPM to identify time-varying differences in the muscle activity for comparisons of two groups: Mildly vs. moderately impaired, and mildly vs. severely impaired. In our study, because the mildly impaired group was our top performers in terms of motor control complexity, we made their control scheme the target for which we wanted to determine what muscles to stimulate at what time were necessary for transitioning an individual from the moderately and severely impaired groups into the mildly impaired group. We found a few overlapping muscles (gluteus maximus and vastus lateralis) that required stimulation at similar times, but when also some distinct muscles (soleus) that were only important for the transition of a severely impaired individual.

A limitation of this study is the lack of healthy data. As such, our "healthy" target control scheme is not from a healthy population, but rather from post-stroke simulations that had a high motor control complexity. This, in part, explains why the simulated healthy group was so much smaller than the other two groups. It would be possible to generate more simulations in this group with strategic picking of permutations that were shown to

increase VnAF, but even so this data would still be from only post-stroke individuals. To really understand what muscles and stimulation times could be helpful for transitioning between motor control complexity impairment groups to a higher motor control complexity that resembles a healthy, unimpaired motion, the target control schemes should be derived from data by a healthy population. However, this study does show that it is possible to identify the appropriate muscles along with the appropriate stimulation timing to initiate a higher motor control complexity. Identifying these differences in an impaired individual from a target before beginning a therapy could help improve rehabilitation outcomes because the therapy has specifically been modified to treat an individual's unique differences. Because of the top-down nature of electrical stimulation, we would expect mechanics-based performance measures to improve as result of improved control patterns.

Future work should focus on acquiring data from healthy individuals in order to understand what their control schemes look like, and how these differ from our "healthy" individuals. This could mean that we could identify how to modify the treatment to give *everyone* the best outcomes, rather than only the most severely impaired. We know that the motions across these groups look similar, and their differences lie largely in their motor control complexity, which is determined by the muscle activity. Thus, even though we have classified 37 as "healthy", the fact is that there is still room to improve their motor control complexity, and subsequently their post-stroke gait mechanics over time. The idea of modifying the electrical stimulation component of this therapy to be specific to the individual is to ensure that everyone maximally benefits from this therapy. In order to do this, it is necessary to identify specific differences in each person's control scheme so that we know what muscle to target and when. This study provides a framework to do so, by combining modern statistics with motor control analysis methods.

5.5 Aim III Plain Language Summary

We set out with the goal of determining how to modify an existing therapy, FastFES, to maximally benefit individuals post-stroke in terms of improving the complexity of their motor control patterns. Specific modifications to FastFES revolve around the FES, or the

function electrical stimulation, component, which involves (at this time) supplying an electric stimulation to a couple ankle muscles at times during the walking cycle where appropriate ankle motion is important. We suggest that even though individuals post-stroke walk similarly, they do not necessarily have similar control patterns, or muscle activity. Thus, therapy that is designed without individual differences in mind means that some people will get better, and some people will not, which is what we found from Aim I. In fact, this problem of variable responses extends far and beyond post-stroke and FastFES therapy. In our study here, we used a newer statistical method, known as Statistical Parametric Mapping, to identify differences in muscle activity of individuals with high motor control complexity and lower motor control complexity. We generated hundreds of simulations and grouped them into three groups, depending on how low (impaired) their motor control complexity is. We showed that transitioning to a high motor control complexity group from a moderate motor control impairment group requires different muscles stimulated at different times than does transitioning from a severe motor control impairment group.

Chapter 6

Moving forward

In these studies, we have a powerful framework consisting of near equal parts modeling/simulation and statistics. Simulations provide a low-risk environment to ask big *what if* questions. They give us information that is impossible to obtain with only experimentation, though that is not to say that simulations are not without limitations. When performing simulations, there will always been factors that are unaccounted for and it is impossible to model everything. Thus, there will always be error in the model, and even though there are some general guidelines, it is somewhat up to the user to decide what is an acceptable error tolerance. However, generally these errors can be sufficiently minimized to generate reliable results, allowing researchers to gain new insight, make discoveries and predictions, draw impactful conclusions, and suggest new, better methods for solving a problem. When we apply this framework to a real-world system, we can make progress on persistent problems that have been affecting human quality of life for decades.

An important aspect of research is staying up to date with current methods and technology, and constantly thinking of how to apply estabilished methods to new problems. In this project, we use modern statistics in the form of statistical parametric mapping and functional data analysis to solve a problem involving hypothesis testing of time-series data. Although traditional statistical methods can be insightful, they certainly run the risk of important differences not being identified. Furthermore, extending machine learning methods into biomechanics is useful for identifying trends or finding relationships in data that would otherwise go undetected. We can leverage these two areas to make predictions regarding the effect of a given therapy on a patient, and furthermore to make suggestions of ways to improve a therapy to give a patient the best chance at a favorable outcome.

In our work, we focused on a single problem of post-stroke gait rehabilitation and a single therapy, known as FastFES. In three studies, we showed variability in subject response in terms of effect on motor control complexity, built two reliable models for predicting response, and suggested a new method for modifying this therapy for maximal benefit. Even though the scope of this project was limited to one condition and therapy, these methods are easily extended to a wide array of movement disorders. For a majority of this project, we were limited to an very small data set, with only eight individuals, due to the restrictions on physical capabilties required to participate in this study. Thus, it is difficult to say whether

our findings pertain to the post-stroke population as a whole, and additional work should be performed regarding the generalizability of these results to a larger sample and including individuals post-stroke with physical comorbidities.

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Appendices

A Tables

Table 1: Four modules are neccessary to describe healthy gait.

Module	**Phase of Activation**	**Recruited Muscles**	**Biomechanical Function**
1	Early stance	Hip abductors, knee extensors	Body weight support
2	Late stance	Plantarflexors	Body weight support
3	Early swing	Dorsiflexors, biarticular knee extensors	Leg swing
4	Late swing	Hamstrings	Leg swing

Table 2: Summary of subject data.

Subject	Gender	Age (y)	Effected Side	Time Since Stroke (months)	Δ(Walking Speed (m/s))	Pre-Therapy Walk-DMC Index	Post-Therapy Walk-DMC Index	Δ TLA (∘)	Fugl-Meyer
1	M	66	R	19	0.10	73.92	82.83	5.1	21
2	M	70	L	21	0.10	86.03	91.65	-0.7	13
3	F	65	R	15	0.60	71.46	77.44	17.8	18
4	F	65	R	18	0.20	78.72	77.46	1.2	18
5	F	54	R	55	0.30	74.23	83.26	10.1	17
6	F	58	R	12	0.20	73.59	76.87	7.2	13
7	M	46	R	8	0.10	75.94	74.60	1.5	15
8	F	70	L	9	0.20	85.50	78.86	4.8	22

B Figures

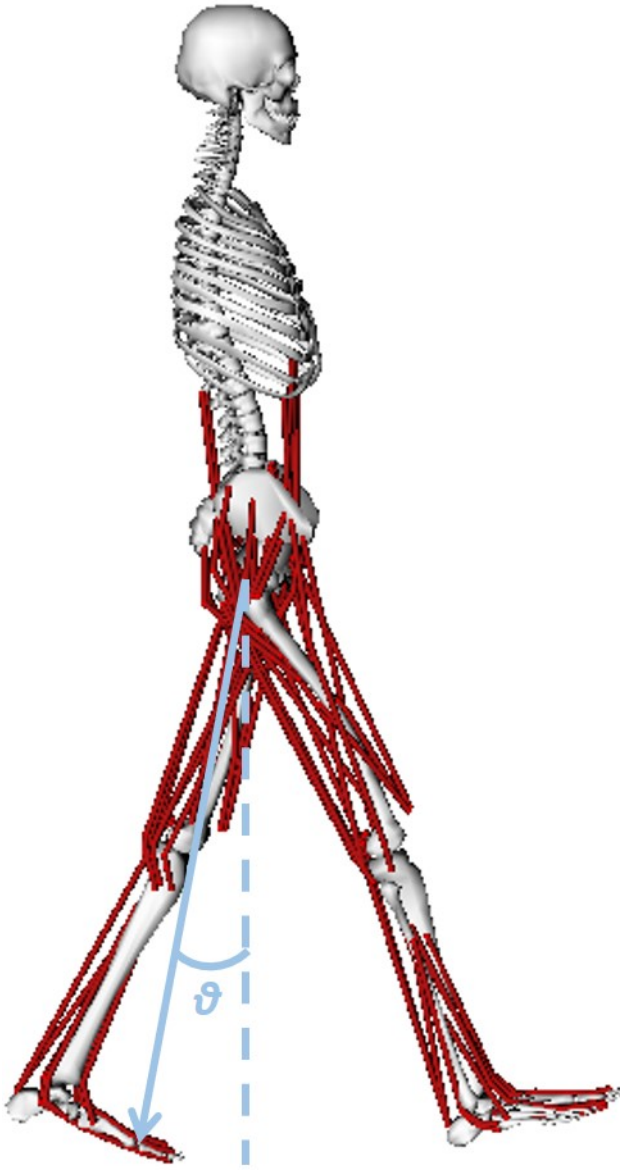

Figure 1: The trailing limb angle (TLA). It is measured as the angle between the lab vertical axis and the vector joining the greater trochanter with the toes.

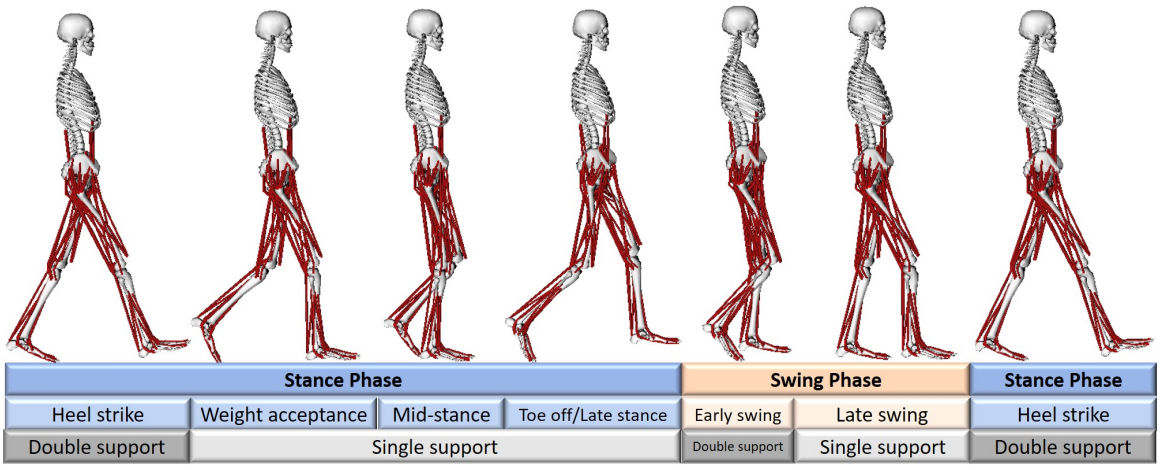

Figure 2: Bipedal gait cycle phases. Stance phase is a combination of double and single support, depending on how many limbs are making contact with the ground. Swing phase is responsible for limb advancement.

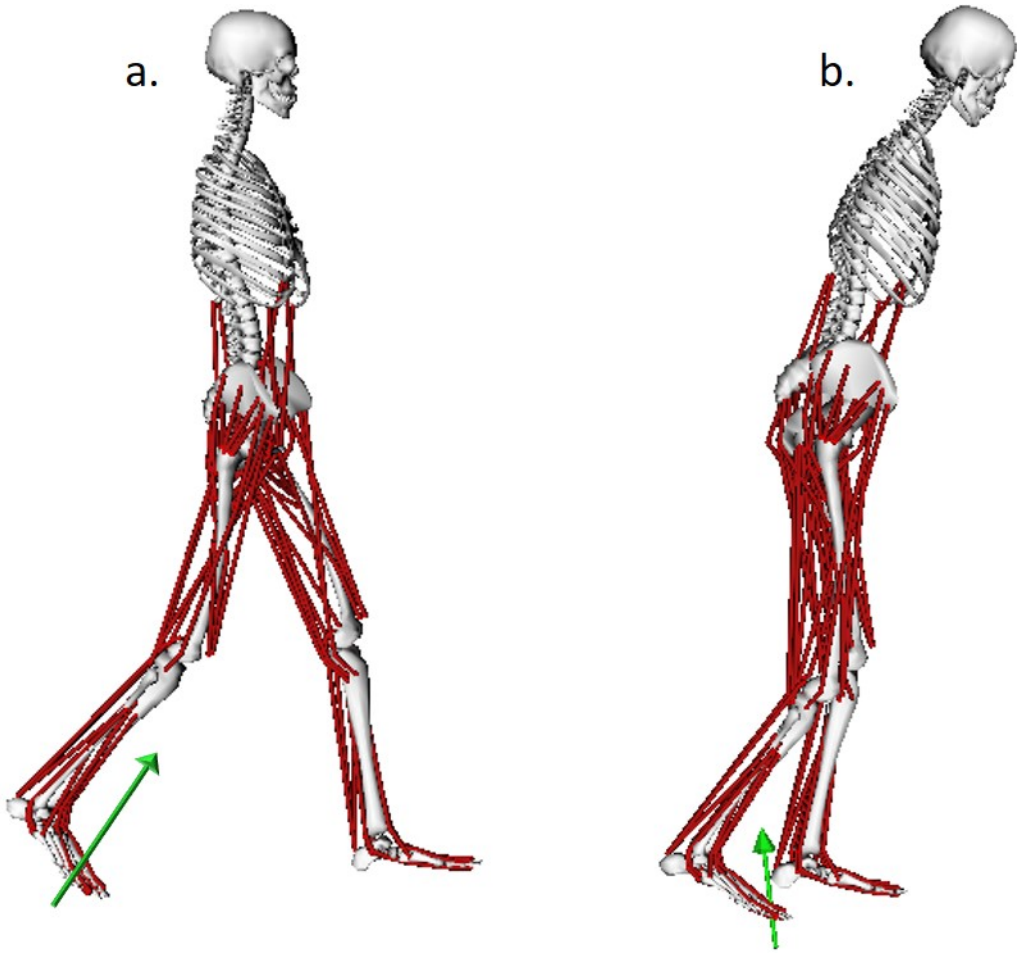

Figure 3: Comparison of toe off between healthy motion (a) and post-stroke motion (b). Note that during the healthy motion, the anterior component of the ground reaction force (green arrow) is directed forwards, indicating it is producing a propulsive force. At the same instance in the post-stroke motion, the ground reaction force is directed posteriorly, producing a braking force.

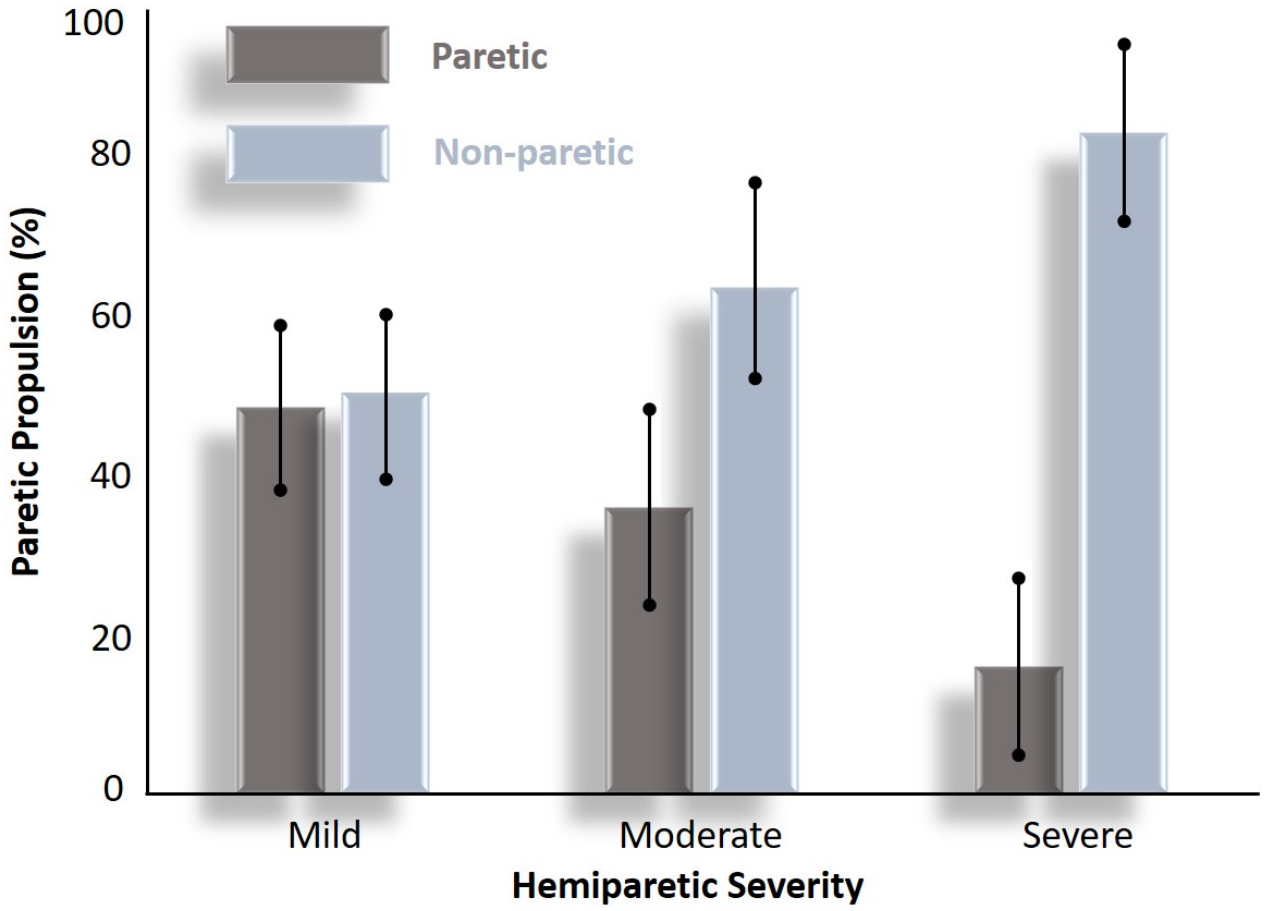

Figure 4: A strong relationship between paretic propulsion and impairment severity. Paretic propulsion agrees well with impairment severity in terms of paretic propulsion, where a less symmetric propulsion ratio indicates more compensation by the non-paretic limb. cite Awad

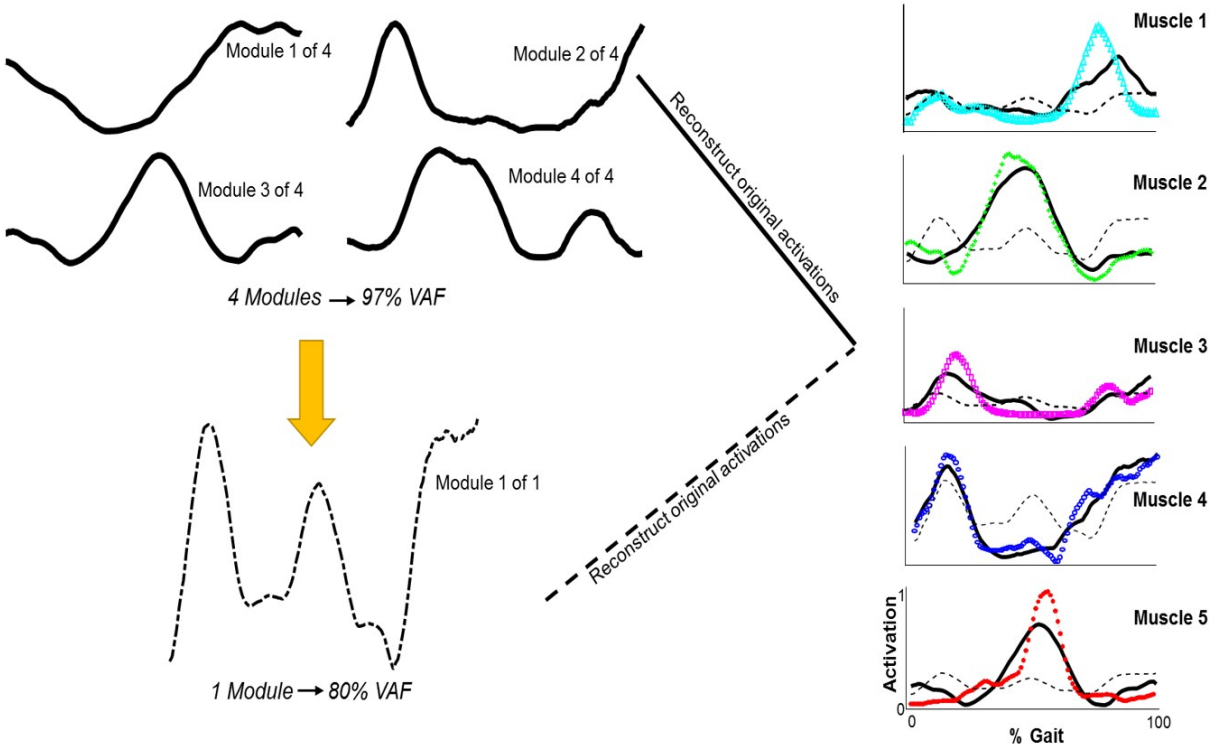

Figure 5: Muscle activity is better reconstructed when more modules are used in the decomposition.

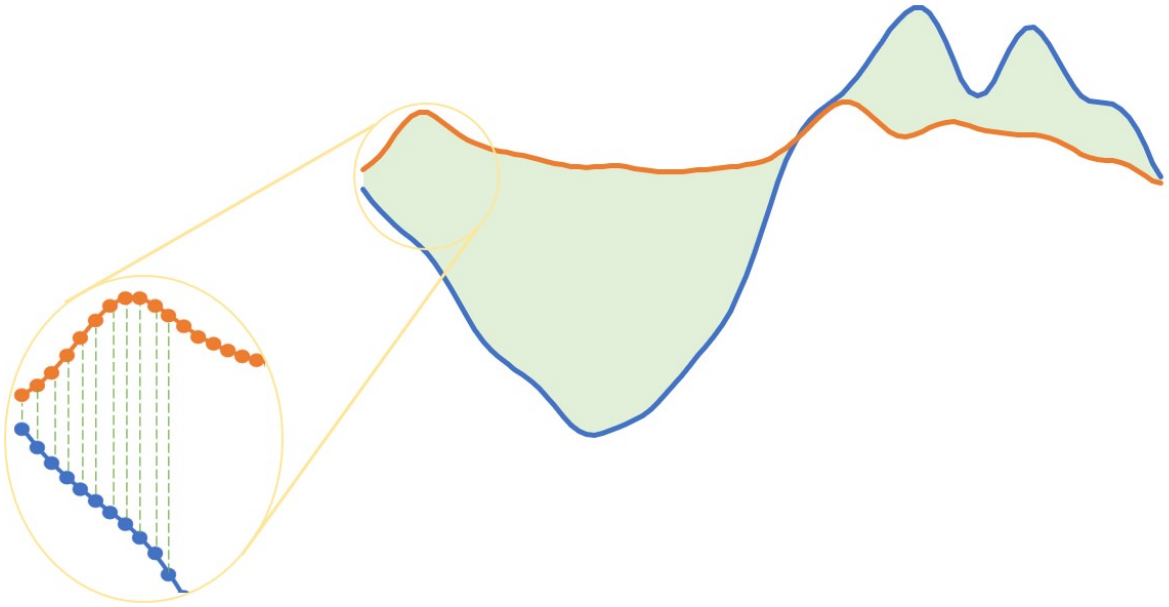

Figure 6: Testing multiple discrete points from two random trajectories. Testing only instance runs the risk of missing other points of interest where two trajectories are significantly different, but repeated statistical testing risks incorrectly identifying significant differences between two points, where in fact there is none.

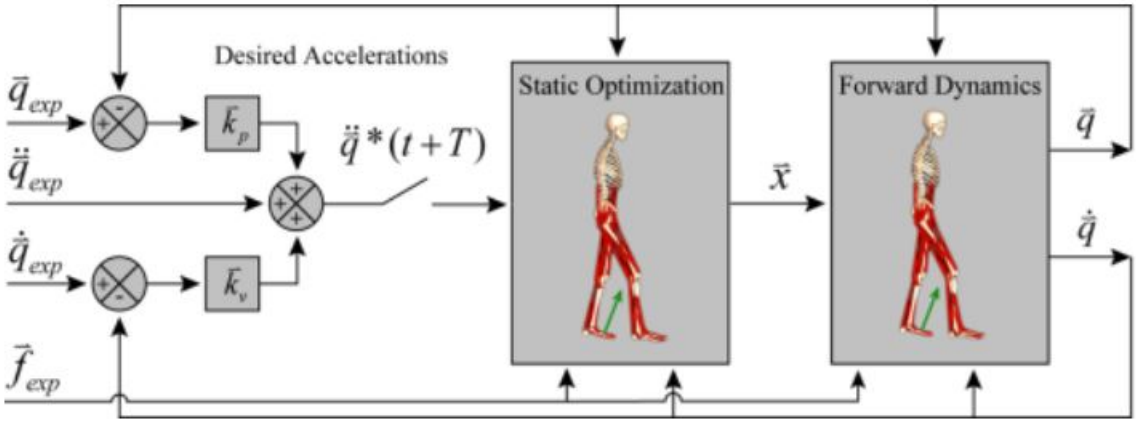

Figure 7: Block diagram of the computed muscle control algorithm.

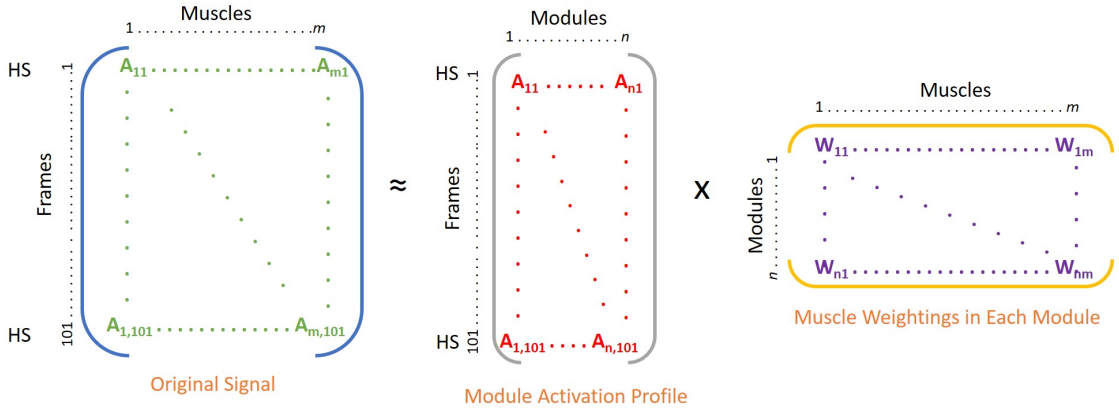

Figure 8: Non-negative matrix factorization. The entire array of muscle activations (left) are decomposed into the product of a modules matrix, consisting of the activation of a pre-specified number of modules, and a weightings matrix, detailing the importance of each muscle within each module. HS: heel strike, $m = 38$.

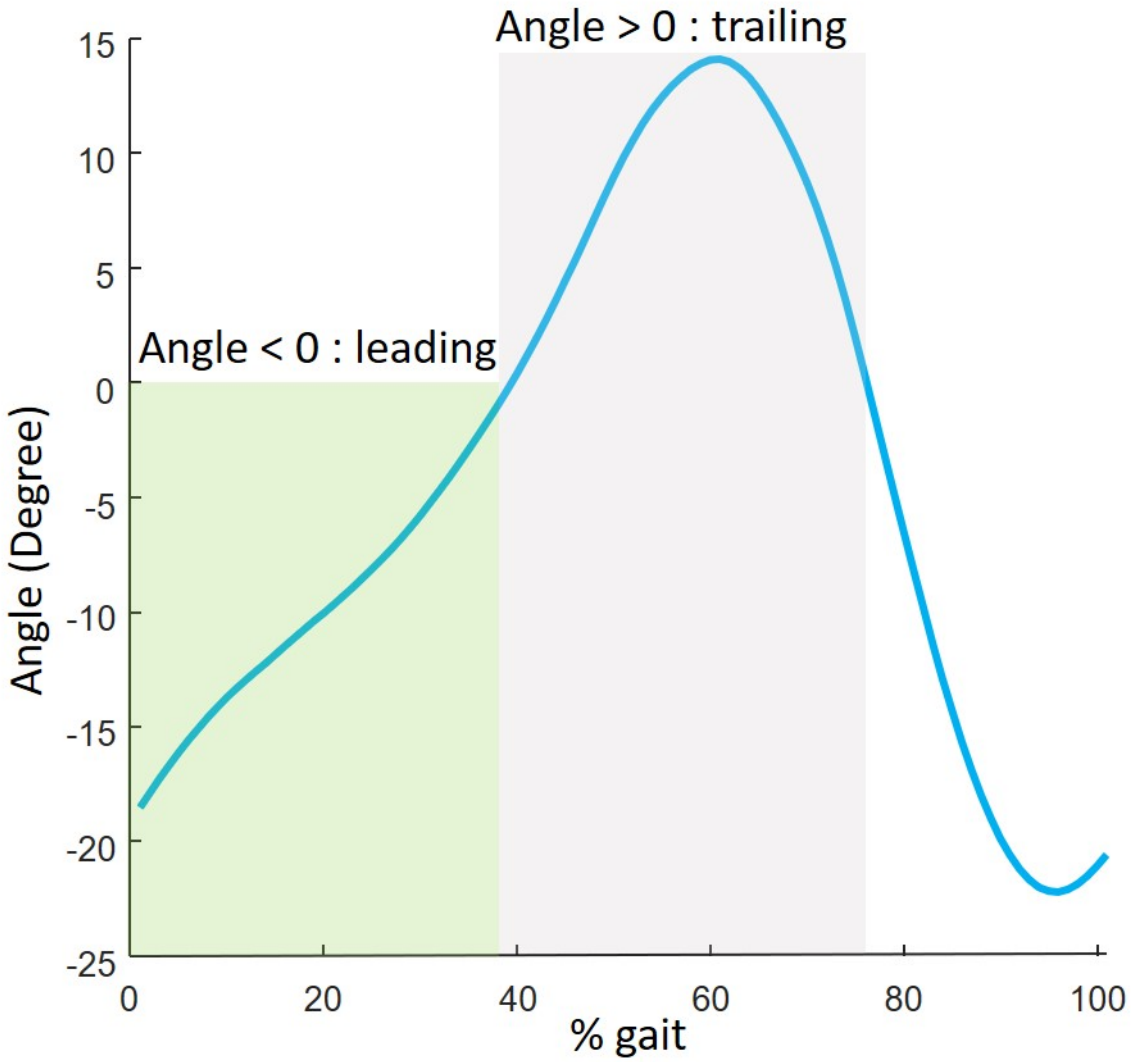

Figure 9: The paretic limb angle is negative when the paretic limb is the leading limb, and it is positive when the paretic limb is the trailing limb

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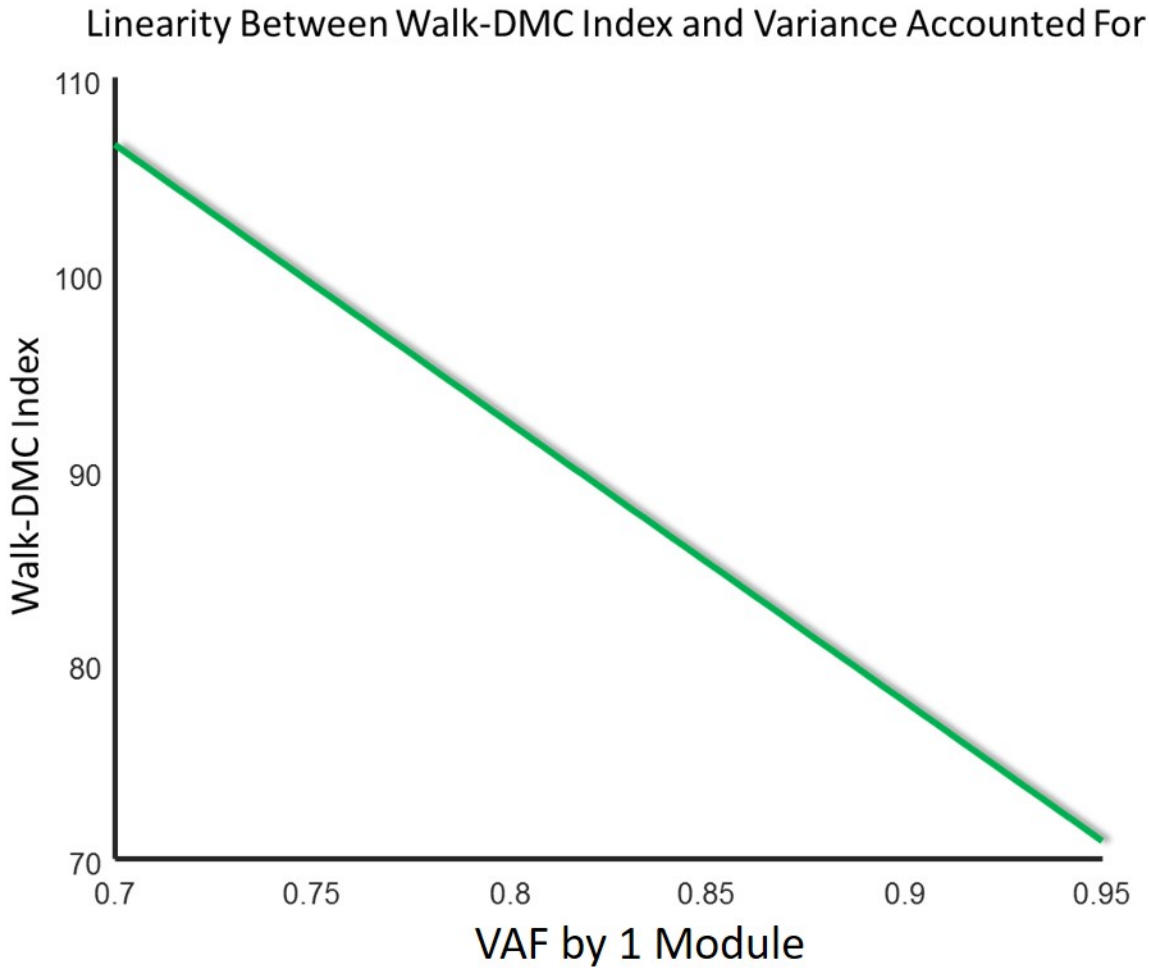

Figure 10: There is a linear relationship between the Walk-DMC Index and VAF_1. During the computation, the factors of the average and standard deviation for the unimpaired population only scale the values of the Walk-DMC Index

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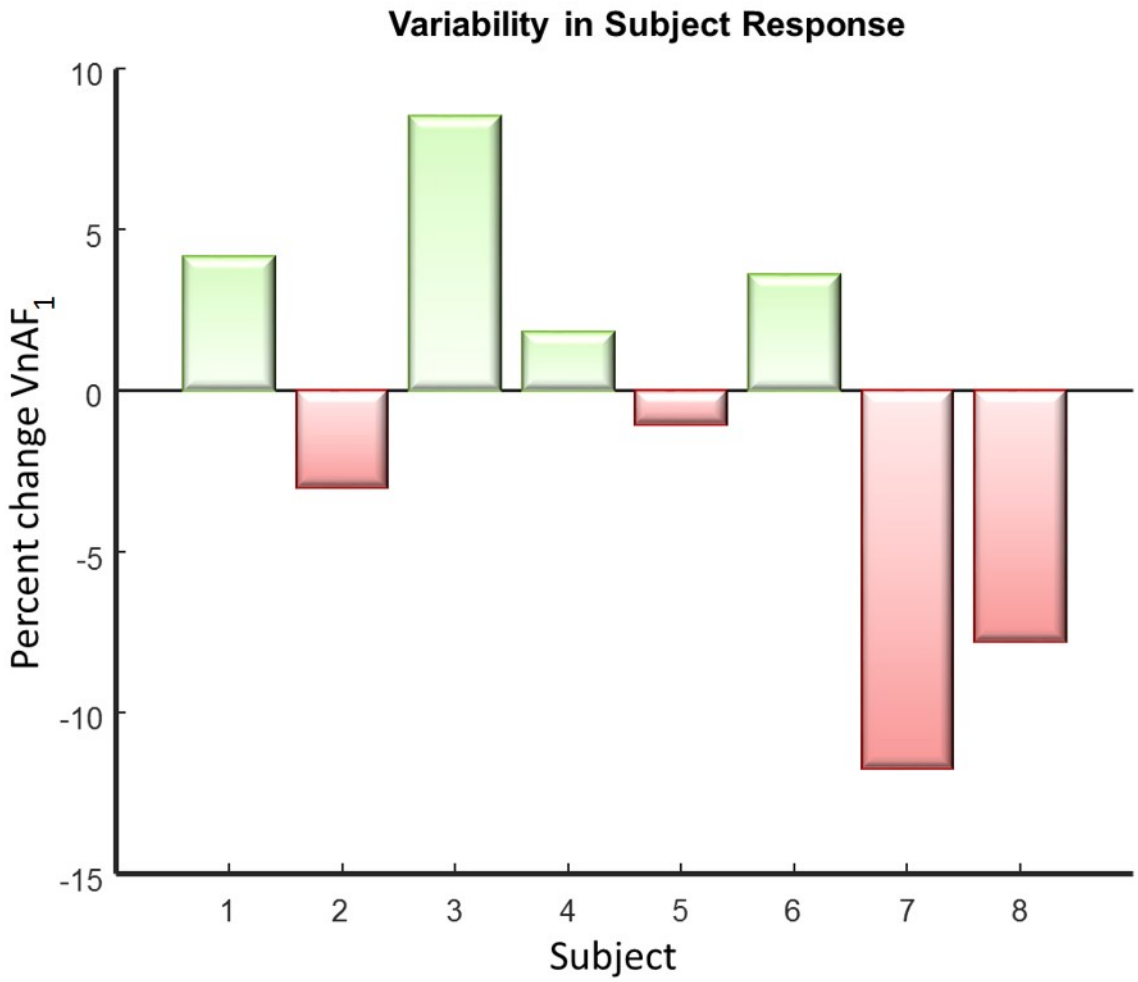

Figure 11: Similar to what is commonly found in traditional performance measures, we also find that motor control complexity varies between individuals of the same treatment

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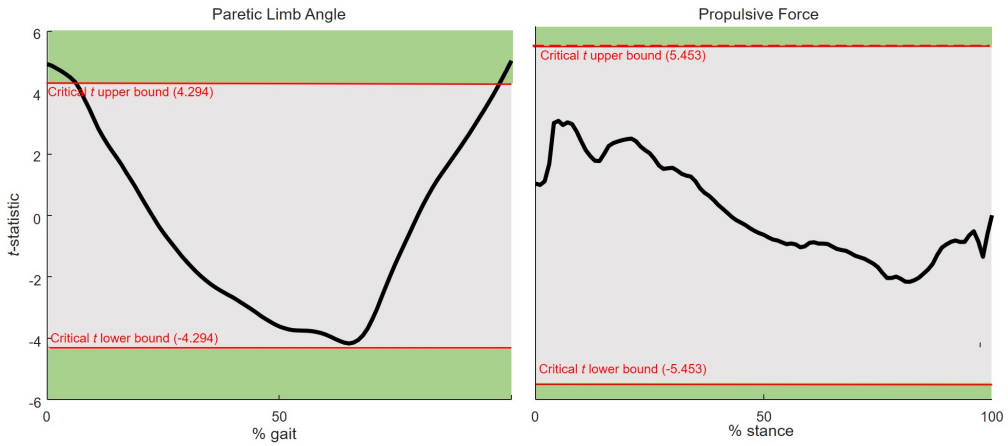

Figure 12: We observe near significance in the paretic limb angle, around toe-off, which is consistent with previous findings. While we also do not observe significant differences in the propulsive force, we note that it is trending downwards around toe-off, where peak propulsive force is likely produced, implying that although not significant, it does appear that the pre-therapy peak propulsive force was lower than post-therapy peak propulsive force.

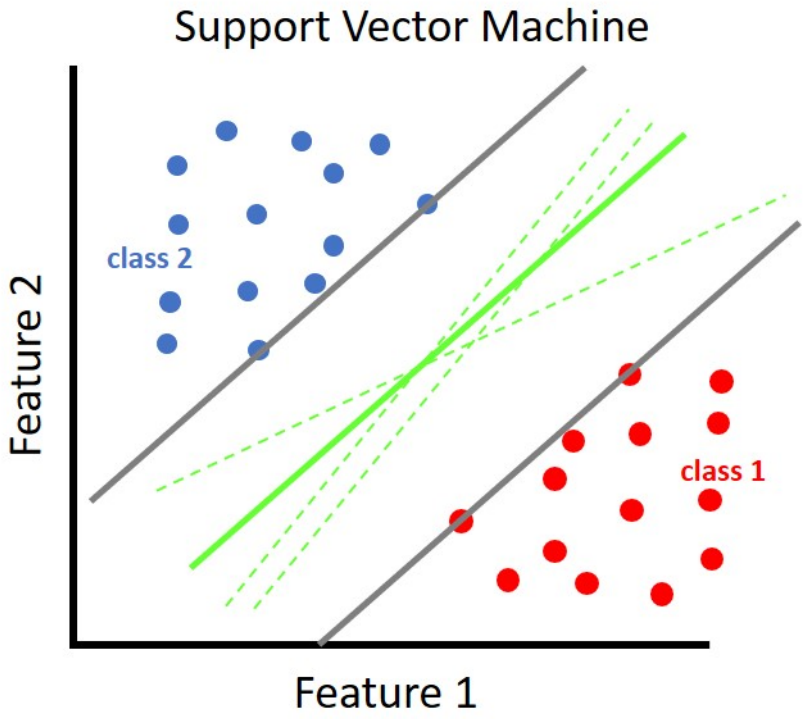

Figure 13: A simple depiction of SVM with two classes. The support vectors (black solid lines) form a margin in which the boundary hyperplane (solid green) line is directly centered between. The dashed green lines represent other lines that also separate the classes, though the solid green boundary line determined by SVM is the line that will minimize classification error

.

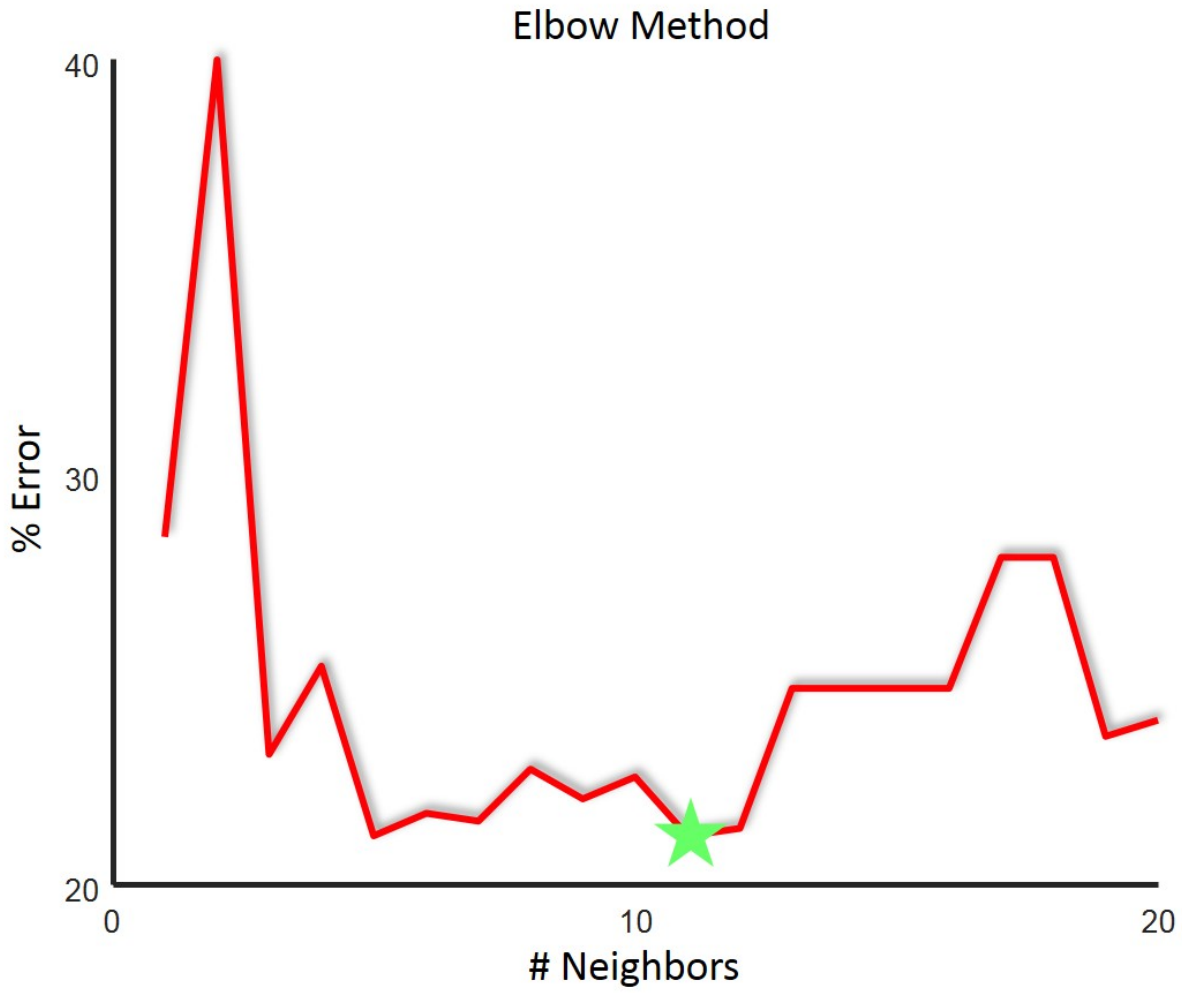

Figure 14: 11 neighbors appears to have the minimum classification error, where adding additional neighbors seems to only decrease model performance.

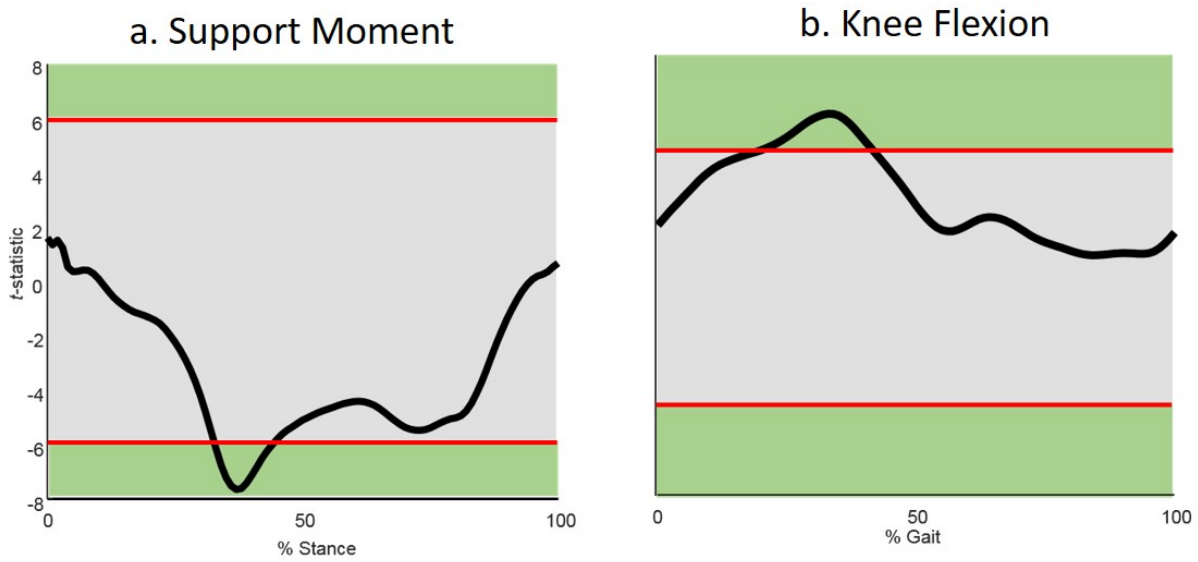

Figure 15: SPM identifies that the responders have a smaller support moment during early-mid stance than the non-responders .SPM identifies that the responders have a larger knee flexion angle during 20-40% of gait than the non-responders.

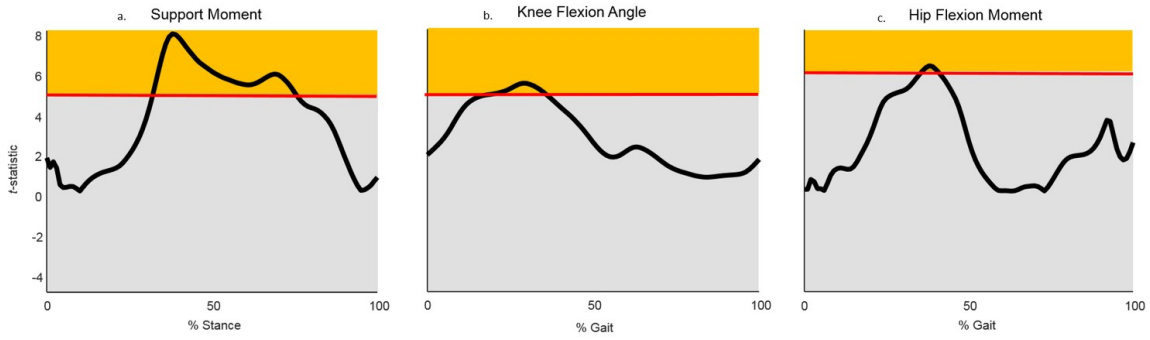

Figure 16: FDA does not have the directionality that SPM does, in which we only know that there *is* a significant difference, but we do not know in what direction.

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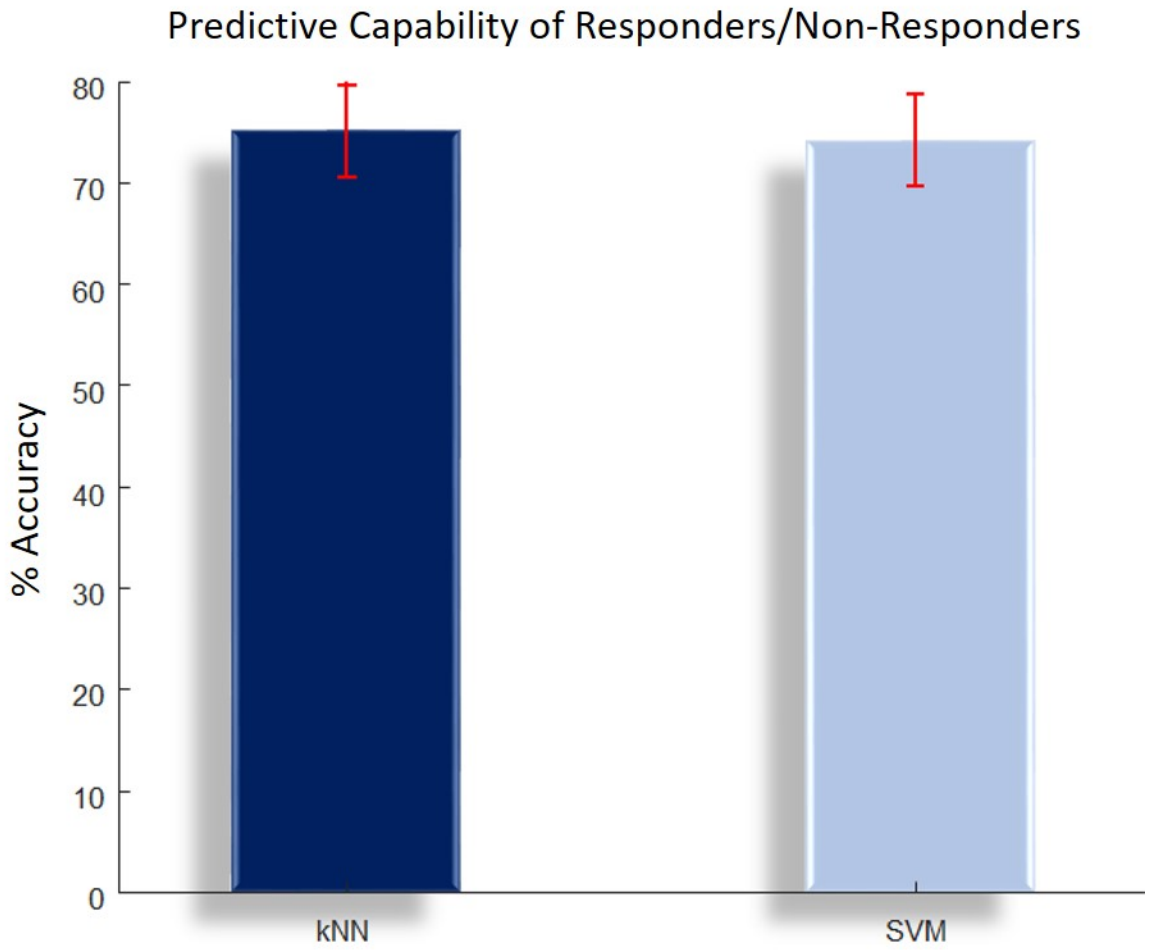

Figure 17: kNN and SVM perform similiarly, with average accuracies of 75.1% and 74.1% respectively.

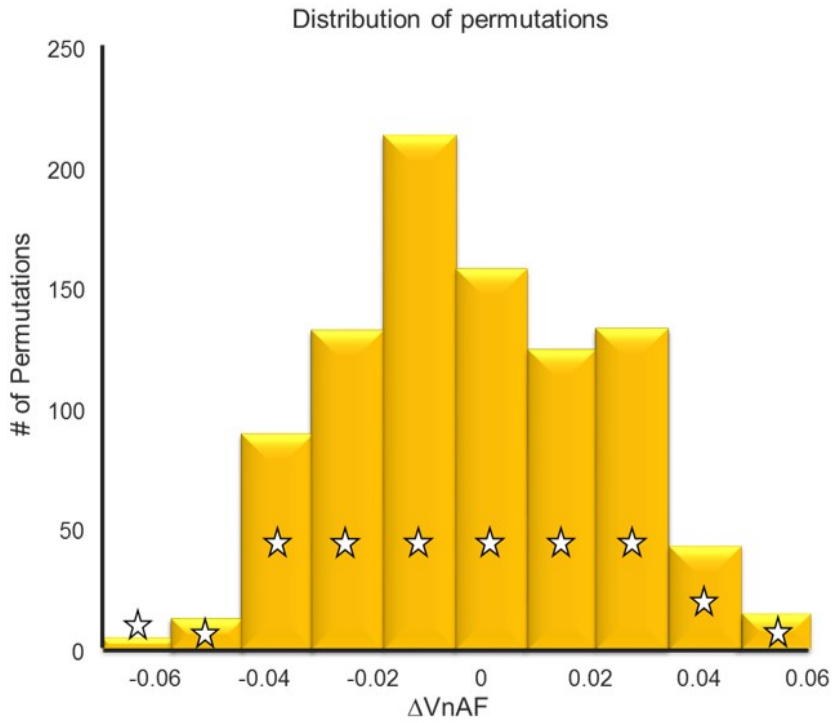

Figure 18: Histogram depicting distribution of hybrid activation permutations. Instead of using all 924, we selected one permutation, the one that lied closest to the midpoint, from each bin.

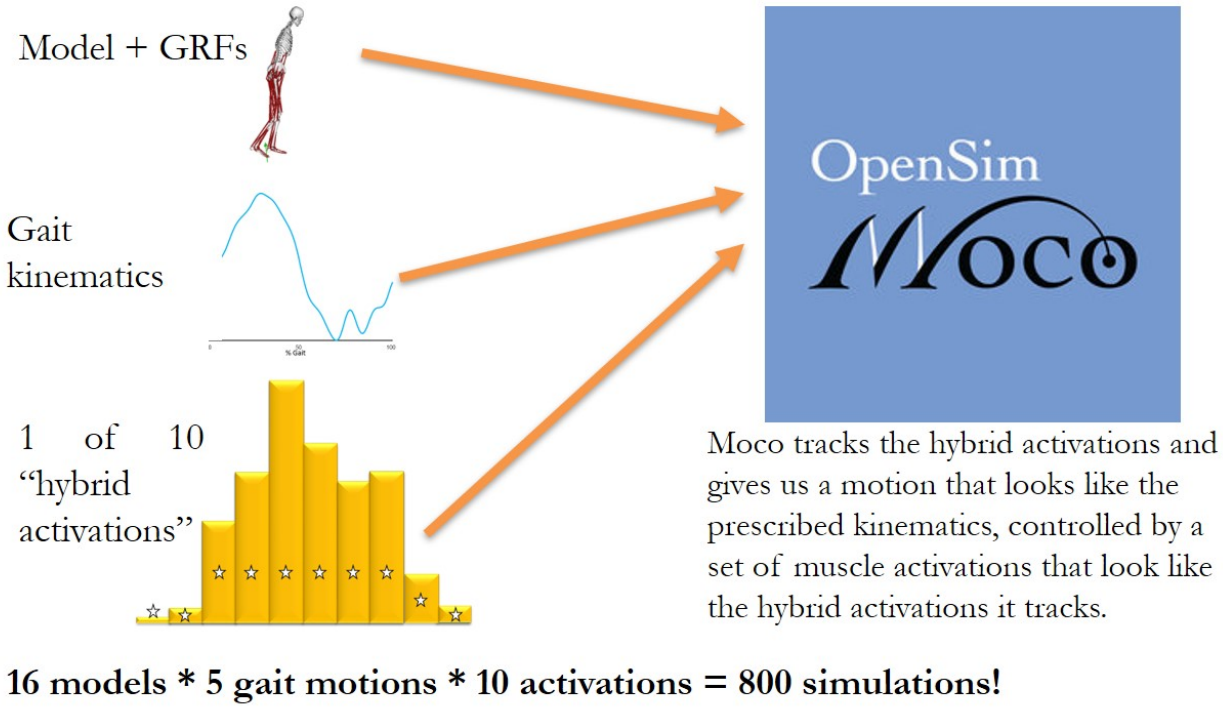

Figure 19: Generating 800 simulations in OpenSim Moco.

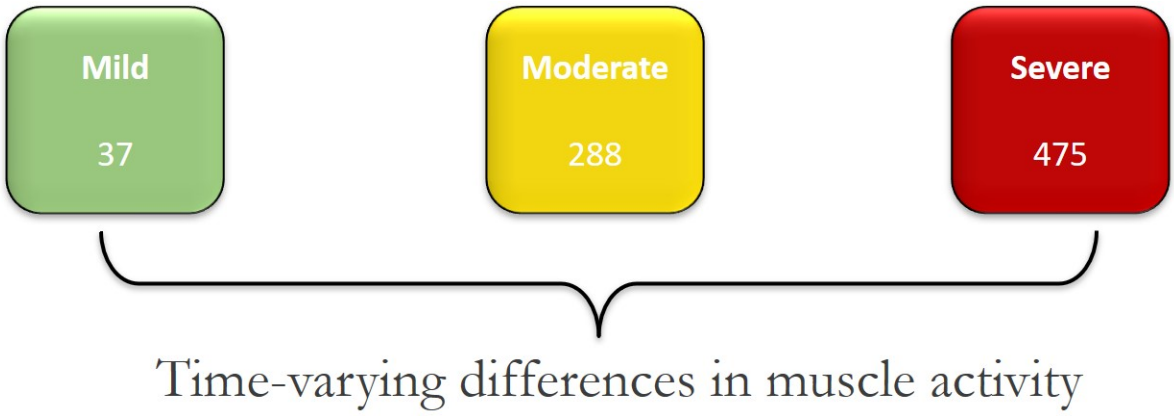

Figure 20: Distribution of motor control complexities in the Moco simulations.

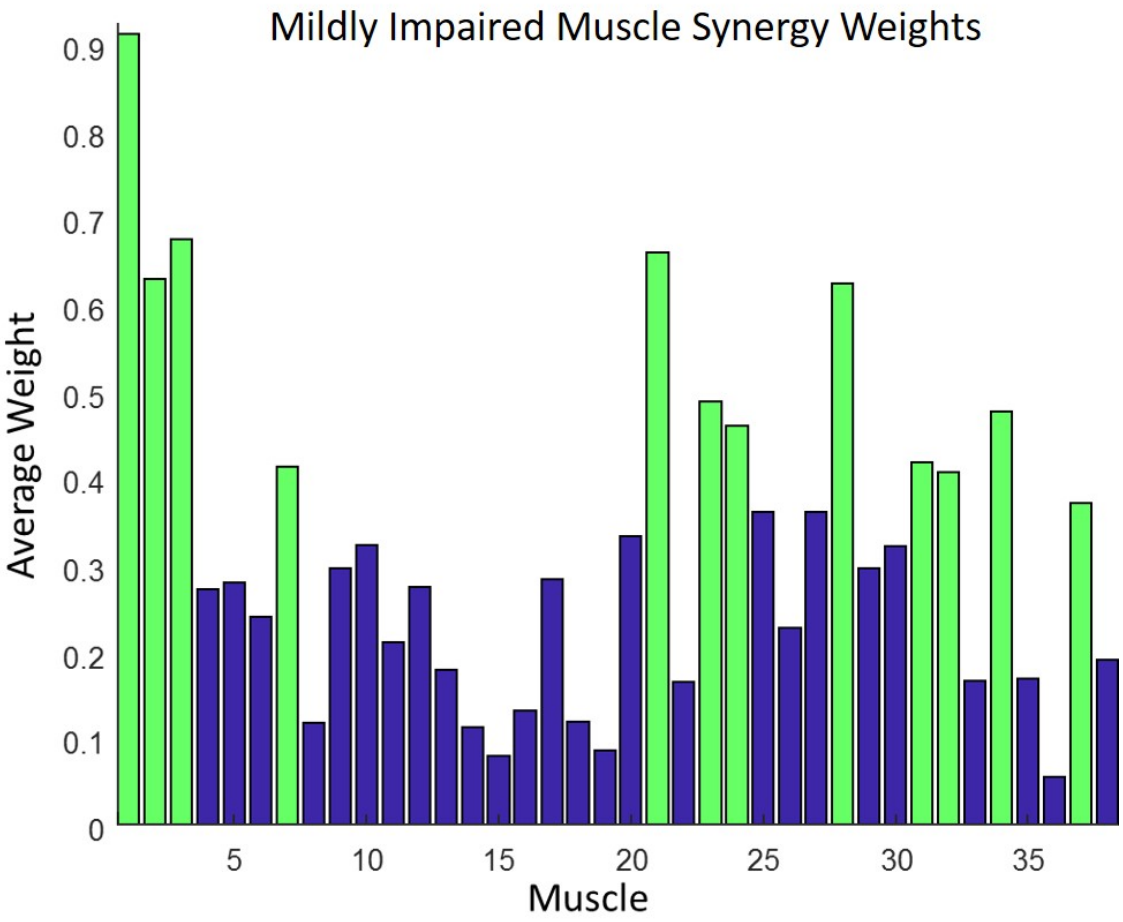

Figure 21: Average muscle weights in the single module of the healthy group. Green muscles indicate weights ≥ 0.4, and the only muscles that we will be comparing activity for between groups.

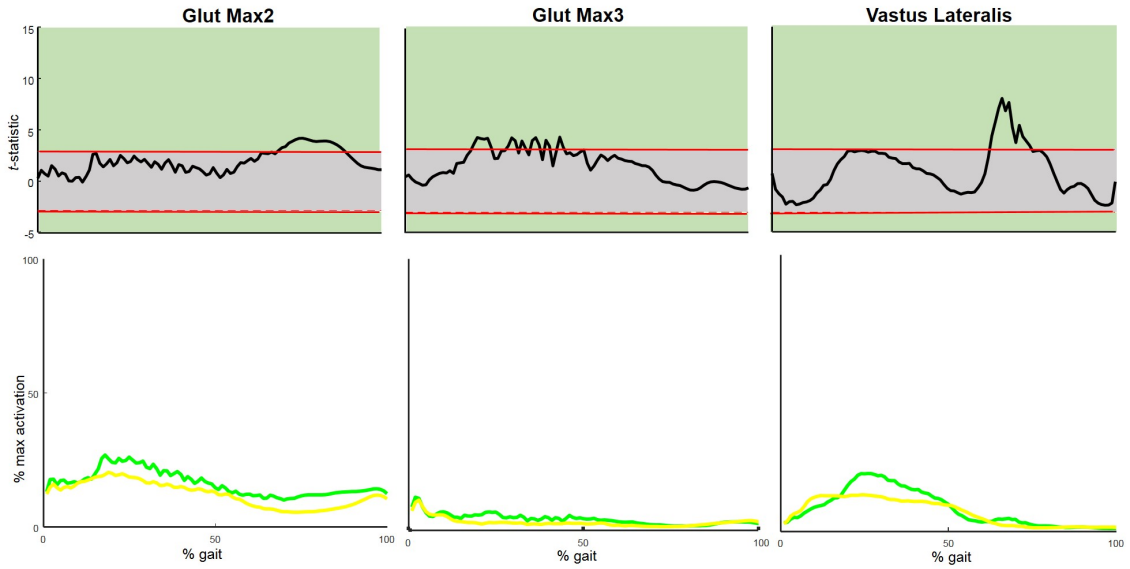

Figure 22: Time-varying differences in muscle activity between the healthy group (green) and the moderately impaired group (yellow).

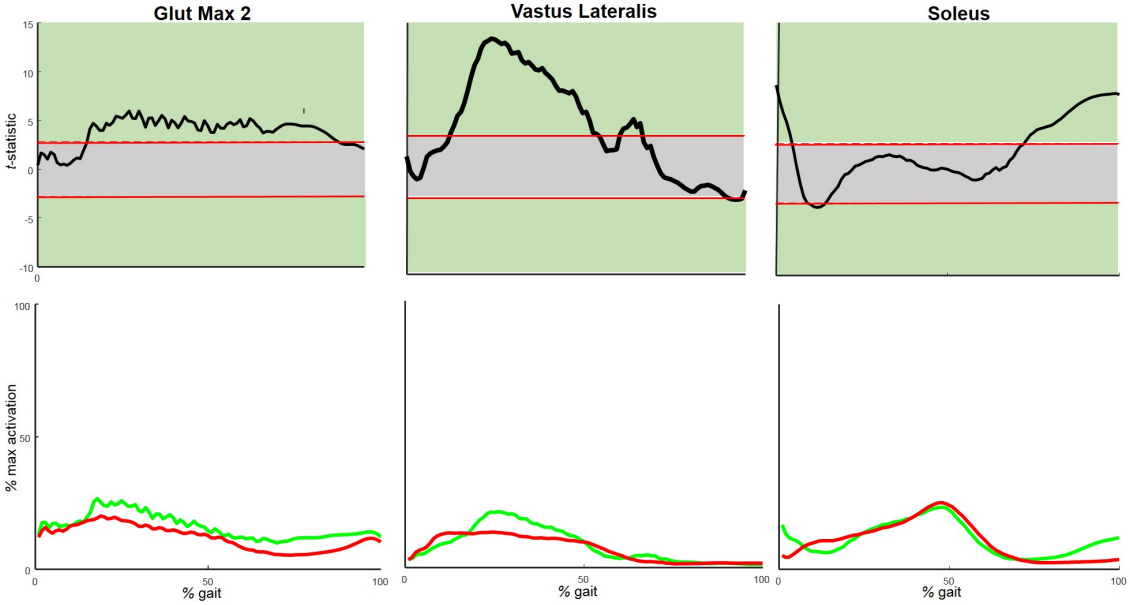

Figure 23: Time-varying differences in muscle activity between the healthy group (green) and the severely impaired group(red).

Vita

Ashley Rice was born February 26, 1994 in Asheville, NC. She grew up in Aiken, SC where she graduated from South Aiken High School in 2012. From August 2012-May 2017, Ashley was a student at College of Charleston (Charleston, SC), where she recevied her Bachelor of Science in Physics. For graduate school, she attended the University of Tennessee (Knoxville, TN) and joined the Neuromuscular Biomechanics Lab under the direction of Dr. Jeffrey Reinbolt. In May 2021, she earned her M.S. and Ph.D in Mechanical Engineering.