In Silico Techniques to Improve Understanding of Gait in Cerebral Palsy

Elijah C. Kuska

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Reading Committee:

Katherine M. Steele, Chair

Xu Chen

Krithika Manohar

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ABSTRACT

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Elijah C. Kuska

Chair of the Supervisory Committee:
Katherine M. Steele
Albert S. Kobayashi Endowed Professor
Department of Mechanical Engineering

In this dissertation we focus on utilizing computer-aided engineering techniques to improve our understanding of gait in cerebral palsy (CP). CP is the most common motor disability in children and arises from a non-progressive brain injury at or near the time of birth which alters control (i.e., poor coordination and increased muscle co-contraction). Additionally, individuals with CP often develop secondary, progressive impairments like weakness and contracture. Current treatments to improve mobility in CP primarily target secondary impairments but functional outcomes are inconsistent, leaving treatment efficacy at around 50%. To improve treatment efficacy, clinicians need a better understanding of the complex interactions between, and relative effects of, multi-modal neuromuscular impairments on gait. However, eliciting interactions between, and relative effects of, neuromuscular impairments on gait is difficult or even impossible to do clinically and

experimentally. Thus, the goal of this dissertation was to utilize *in silico* techniques to improve the understanding of gait in CP. Specifically, we use physics-based (i.e., musculoskeletal) modeling, optimal control (i.e., neuromuscular simulation), and data-driven modeling (i.e., machine learning) to investigate the interactions between, and relative effects of, altered control, muscle weakness, and contracture on gait and predict and understand gait energetics in CP which can be used to improve treatment efficacy.

The effects of altered motor control on gait are poorly understood because altered control persists post-intervention and its relative effects are difficult to discern amidst secondary impairments, like weakness and contracture. Prior studies have investigated the impacts of weakness, contracture, and altered control on gait, but they have yet to be investigated together. Thus, in this dissertation we sought to understand the effects of, and interactions between, neuromuscular impairments during gait by utilizing a musculoskeletal model and neuromuscular simulation framework. We simulated nondisabled (ND) gait and then perturbed each simulation with altered control, weakness, and contracture of varying severities. We found that altered control exacerbated the restrictions imposed by secondary impairments: ND gait was less robust to, and required more muscle activation to adapt to, weakness and contracture with altered control when compared to unaltered control (Chapter 3). These findings highlight the inimical effects of altered control on gait and emphasize the advantages of *in silico* techniques to identify specific impairments, such as altered control, that should take treatment precedence (*in silico*-informed interventions). However, it is unclear if these conclusions extend to different gait patterns like those in CP.

Abnormal gait patterns are common for individuals with CP; the most inimical and common of which is crouch gait. Crouch gait is characterized by excessive knee flexion, which

increases knee extensor demand while reducing the knee extensor's ability to extend the knee making it inefficient and disadvantageous. In Chapter 4, we extended our prior computational methods to simulate crouch gait of varying severities. By simulating both crouch and ND gait, and incorporating machine learning (ML), we investigated if the interactions between, and relative effects of, neuromuscular impairments are gait pattern-specific. We determined that the interactions between, and relative effects of, neuromuscular impairments are gait pattern-specific highlighting advantages and disadvantages of walking in crouch. Thus, by combining computational techniques like modeling, simulation, and machine learning we elicited rationale for why individuals may select non-normative gait patterns and emphasized the utility of *in silico* techniques to parse and identify impairments primarily affecting function in CP which could then be used to inform treatment.

Individuals with CP consume on average 2x the energy of their ND peers while walking; the origin of which remains unknown. Elevated energy consumption persists post-intervention making it a primary complaint among patients and objective of research in the CP community. We sought to accurately predict and understand energetics in CP with modeling, simulation, and machine learning to reduce clinical collection burden on patients and caregivers and improve identification of effective treatment methods for reducing energetics in CP. In the final study of this dissertation, we first used our modeling and simulation framework to generate and perturb walking simulations from gait data from the largest database of walking data for individuals with CP. Generated simulations then acted as synthetic data within a machine learning algorithm to complement existing clinical data and attempt to improve predictions of energetics in CP. Using simulations generated for 240 children with cerebral palsy we analyzed the energetic discrepancy—difference between measured and predicted—to identify primary mechanisms

elevating energetics in CP (Chapter 5). Synthetic data generated from gait simulations marginally improve prediction accuracy of energetics in CP, but augmented discrepancy models—energetic predictions with the reconstructed discrepancy—improved modeling of CP energetics, identifying kinematics at initial contact and contracture as primary mechanisms elevating walking energy in CP. Utilizing *in silico* techniques can provide additional synthetic data (i.e., data augmentation) to reduce data collection burdens on patients, caregivers, and clinicians while eliciting additional insight in causal mechanisms affecting gait and function.

This dissertation supports *in silico* informed interventions by improving our understanding of gait in CP. By utilizing modeling, simulation, and machine learning we examined the interactions between, and effects of, neuromuscular impairments on gait in both ND and CP individuals and how that information could better predict and understand energetics in CP. This work provides a foundation to utilize modeling, simulation, and machine learning to rapidly evaluate causal mechanisms impacting gait, probe and parse complex relationships between neuromuscular impairments, and incorporate synthetic data to better inform machine learning algorithms and clinical decision making. In conclusion, the work we have completed over the last 4 years highlights the benefits of *in silico* techniques to understand gait in CP, seeking to support the creation and implementation of *in silico* informed interventions for individuals with CP.

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Yea, this dissertation is dedicated to all the teachers who told me I'd never amount to nothin'

To all the Reviewer 2s who said my stats weren't good enough when I was just trying to publish to get my h-index up

And all the other grad students in the struggle

You know what I'm sayin'? It's all good, baby baby…

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Chapter 1. INTRODUCTION

Mobility enables exploration and interaction with one's world, which is pivotal for development and health. Among the many modes of mobility, walking is perhaps the most common, but its complexity is often overlooked. Walking requires precise neuromuscular coordination to efficiently and accurately actuate the musculoskeletal system to propel one forward. For individuals with neuromuscular impairments, altered coordination and changes to musculoskeletal morphology inhibit walking which affects development. Understanding the restrictions imposed by an individual's unique motor control and morphology has the potential to inform interventions to improve their mobility.

Individuals with cerebral palsy (CP) represent a large population of children with limited mobility; in fact, CP is one of the most common motor disability in childhood. Specifically, CP is a neurologic disorder resulting from a brain injury at or near the time of birth that occurs in 3 in every 1000 live births and currently affects nearly 800,000 people in the US. CP is then a movement disorder that primarily arises from altered motor control (*i.e.*, altered coordination) but is further complicated by secondary musculoskeletal impairments: individuals with CP often develop secondary, progressive impairments like weakness and contracture. A multitude of invasive and non-invasive interventions exists that attempt to improve mobility in CP, however functional improvements post-intervention are a "coinflip": only 50% of individuals with CP have significant improvements in function post-intervention.

Neuromuscular impairments, like the combination of altered control, weakness, and contracture, impose complex restrictions on mobility that are difficult to understand. Our limited understanding of these complex restrictions likely underlies "coin-flip" treatment efficacy in CP.

It remains difficult to bolster our understanding of gait in CP, because we cannot elicit relative effects of, or interactions between, neuromuscular impairments during gait. For example, we don't understand the effects of altered control on gait or the primary causal mechanisms driving elevated energetics—children with CP consume on average 2x more energy during walking than their nondisabled (ND) peers—because they are difficult to modulate and persists post-intervention. Understanding the impacts of altered control, and parsing the relative effects of neuromuscular impairments on gait and energetics, could improve our understanding of gait in CP, enabling clinicians to make more informed decisions on how to reliably improve mobility in CP.

In silico techniques offer an ideal testbed for improving treatment efficacy in CP. For example, modeling and simulation enable rapid causal investigations which could be used to evaluate hypotheses about the impacts of altered control on gait. Additionally, methods like machine learning (ML) enable parsing of complex relationships between neuromuscular impairments and gait while combatting population heterogeneity, another issue confounding treatment efficacy in CP. However, ML is a data hungry methodology and additional collections would exacerbate existing burdens on patients, caregivers, and clinicians. Modeling and simulation offer a non-resource intensive way to rapidly generate informative, synthetic data to complement existing clinical data and improve estimations and predictions of ML. Thus, *in silico* techniques could improve treatment efficacy in CP by enhancing our understanding of gait in CP.

This dissertation harnesses computer-aided engineering techniques—physics-based (*i.e.*, musculoskeletal) modeling, optimal control (i.e., neuromuscular simulation), and data-driven modeling (*i.e.*, machine learning)—to improve our understanding of gait in CP. Specifically, we

use modeling and simulation to understand the effects of altered control and its interactions with secondary neuromuscular impairments like weakness and contracture. Whereafter, we utilize synthetic data to improve modeling and understanding of gait energetics in CP. Thus, this dissertation evaluates clinical hypotheses via *in silico* techniques to improve the understanding of gait in CP which can be used to motivate and create *in silico* informed interventions, possibly improving treatment efficacy.

1.1 Focus of the Dissertation

The goal of this dissertation was to improve the understanding of gait in CP by utilizing *in silico* techniques. We utilized a 2D sagittal-plane musculoskeletal model and neuromuscular simulation framework to generate and perturb gait. We sought to understand how *in silico* techniques could improve understanding of gait in CP by first quantifying how neuromuscular impairments interact and affect gait, and then investigating if synthetic data could improve predictions of energetics in CP. We found that altered control exacerbates the restrictions imposed by weakness and contracture and increases the energetic cost of walking which could partially explain elevated energetics during walking in CP. By then investigating neuromuscular impairment interactions and their relative effects during CP and ND gait, we found that the interactions between, and effects of, altered control, weakness, and contracture were gait-pattern specific. Thus, we identified possible advantages and disadvantages of walking patterns in CP—typically thought to be inefficient and disadvantageous—first, highlighting rationale for why individuals with CP may select their gait pattern and then identifying neuromuscular impairments to target to more effectively improve mobility in CP. Additionally, we found that synthetic data generated from modeling and simulation marginally improved predictions of energy consumption in CP. However, synthetic data, specifically an energetic discrepancy

generated from data-driven modeling, improved modeling of energetics in CP highlighting that contracture may be a primary mechanism elevating energetics in CP. Thus, *in silico* methods and the synthetic data they generate can complement clinical data, simultaneously reducing clinical collection burdens and improving understanding of gait and biomechanical responses. These computational techniques and analyses improve our understanding of gait in CP and provide support for *in silico* informed interventions aimed to improve treatment efficacy for individuals with CP.

1.2 SIGNIFICANCE

The investigations in this dissertation make significant ($p < 0.05$) contributions to the field of computer-aided engineering, dynamics, biomechanics, and clinical research. To improve our understanding of gait in CP we need to understand the effects of, and interactions between, neuromuscular impairments and gait. Findings could then be used to inform treatment precedence: predicting and identifying the most effective intervention. However, to do so, we require methods to perturb and predict the effects of neuromuscular impairments which are not currently possible experimentally and clinically. This dissertation sought to emphasize the utility of *in silico* techniques to improve our understanding of gait in CP by rapidly evaluating clinical hypotheses about neuromuscular impairments and gait via mechanical engineering principles and computer-aided engineering techniques like modeling, simulation, and machine learning. The primary contributions of these investigations and their findings in the dissertation are presented below:

- **Eliciting the effects of altered control and its interactions with weakness and contracture during gait.** Individuals with neurologic injuries, like CP, often develop secondary, progressive musculoskeletal impairments like weakness and contracture in

addition to altered control. These multi-modal neuromuscular impairments impose complex restrictions on gait that are poorly understood, inhibiting treatment efficacy. We sought to elicit the interactions between altered control, weakness, contracture and gait by altering a musculoskeletal modeling and neuromuscular simulation framework to simulate ND gait with neuromuscular impairments of increasing severity. We investigated 1) the points at which the neuromuscular impairments became too severe and ND gait was irreplicable, and 2) the cost of maintaining ND gait in the presence of neuromuscular impairments, finding that altered control exacerbated the restrictions imposed by weakness and contracture.

- **Identifying gait-specific interactions between, and effects of, neuromuscular impairments.** Our prior investigation quantified how neuromuscular impairments interact and impose complex gait restrictions, but it remains unclear if that is gait-pattern specific which limits translation to CP where individuals often walk in abnormal gait patterns (e.g., crouch). To investigate if our prior findings were gait-specific, we simulated altered control, weakness, and contracture during crouch and ND gait and examined how the interactions between neuromuscular impairments changed with gait pattern. We found that the complex interactions between, and restrictions imposed by, neuromuscular impairments were gait pattern-specific. Understanding the gait pattern-specific interactions between neuromuscular impairments can highlight rationale underlying an individual's choice to select an abnormal gait pattern, e.g., walking in crouch was more advantageous than ND gait in the presence of altered control and plantarflexor weakness.

- **Parsing the individual effects of multi-modal impairments.** Our prior findings highlight how altered control can exacerbate the restrictions imposed by weakness and contracture but to improve treatment efficacy, it's important to be able to parse the relative effects of each neuromuscular impairment. We constructed a Bayesian additive regression trees (BART)—a machine learning (ML) algorithm—model and input our prior gait simulations to parse the relative effects of altered control, weakness, and contracture (predictors) on cost of walking (response). We found that crouch gait reduced the relative effects of almost all simulated neuromuscular impairments on cost of walking, but secondary impairments like vasti weakness had larger relative effects than altered control. These findings highlight advantages of utilizing machine learning to parse complex heterogenous relationships (e.g., neuromuscular impairments, gait, and energetics in CP) and emphasize how similar analyses could be used to inform treatment precedence by identifying primary mechanisms elevating energetics.
- **Quantifying the advantages of utilizing synthetic data to improve predictions of energetics in CP.** Individuals with CP consume on average 2x more energy than their ND peers; the cause of which remains unknown, limiting our ability to effectively intervene. To better treat elevated energy in CP, we need to identify the causal mechanisms elevating energy which remains difficult for several reasons: 1) complex interactions between neuromuscular impairments and gait muddy causal mechanisms elevating energy, 2) many individuals with CP are unable to complete the required energy analyses limiting the translation of findings to the broader CP population, and 3) CP population heterogeneity. Manipulating our musculoskeletal model and neuromuscular simulation framework, we simulated gait for each individual with CP within our clinical

collaborator's—Gillette Children's Specialty Healthcare— database and perturbed each simulation with neuromuscular impairments. Resultant simulations were then used to predict energy consumption in CP, finding that simulated synthetic data, specifically simulation results pertaining to tracking errors and objective function values, marginally improved accuracy of energetics in CP. Thus, simulated synthetic data offers a non-resource intensive data augmentation technique that has the potential to improve data-driven modeling accuracy but requires additional investigations to better understand its usage and utility in predicting biomechanical responses.

- **Eliciting primary causal mechanisms elevating energetics in CP with discrepancy modeling.** Prior studies investigating causal mechanisms elevating energetics in CP found conflicting findings around the role of kinematics, specifically, crouch and its effect on energetics. One study utilizing linear regression found little to no correlation between crouch severity and energetic cost while two other studies utilizing data-driven modeling identified kinematics as a primary driver of elevated energetics, and specifically, landing in crouch was a driver of elevated energetics in CP. Conflicting findings of mechanisms contributing to elevated energetics in CP likely arise from different methodologies and highlight the need for improved understanding of elevated energetics in CP. We trained a model on the discrepancy between measured and predicted CP utilizing clinical measures and gait features. Our augmented model— age, weight, and speed predictions + reconstructed discrepancy—accurately modeled CP energetics and identified contracture as a primary mechanism elevating energetics in CP; only behind that of hip and knee flexion at initial contact (*i.e.*, crouch). Thus, our data-driven approach for non-dimensionalizing energetics by analyzing the discrepancy from a model

trained on age, weight, and speed, may benefit future studies by minimizing assumptions inherent in normalization techniques and highlighted how synthetic data can improve modeling and understanding of biomechanical responses.

1.3 THESIS OVERVIEW

This dissertation is focused on three research studies that are presented as self-contained journal articles. After this general introduction, Chapter 2 presents necessary background material in 'Gait and Mobility', 'Cerebral Palsy', and '*In Silico* Techniques For Analyzing Gait' to understand the presented articles, and their motivation and impact. Chapter 3 quantifies the interactions between altered control, weakness, contracture, and gait during nondisabled gait (Kuska et al., 2022, published in the Journal of Biomechanics). Chapter 4 extends the work of Chapter 3 by conducting similar analyses but includes crouch gait—common in individuals with CP—and investigates how the individual effects of, and interactions between, neuromuscular impairments are gait pattern-specific (Kuska et al., 2023, *In Review* at the Journal of Biomechanics). Chapter 5 then generates synthetic data by 1) feeding clinical CP gait data through our modeling and simulation framework and 2) utilizing discrepancy modeling to improve predictions and understanding of energetics in CP (Kuska et al., 2023, *In Preparation*). Finally, Chapter 6 summarizes the significance of these investigations and their implications for future research. "We" is used throughout this dissertation to acknowledge all those who supported me throughout this dissertation: it was a team-process, and I could not have done it alone. I acknowledge these individuals in the acknowledgements and at the beginning and end of each respective chapter.

Chapter 2. BACKGROUND

2.1 GAIT AND MOBILITY

Mobility enables us to complete activities of daily living, explore, and interact with the world. The most common form of mobility is walking. For adults, walking is often the form of mobility used for work and leisure; for children, walking supports exploration-based development[1]. Quantitatively, the importance of walking is further emphasized, as its spatio-temporal parameters (e.g., speed, step-length, and cadence) have significant correlations with mortality, disability, and quality of life[2–4]. It has even been that walking, specifically walking speed, is considered a 'functional' and the '6th' vital sign. Because it encapsulates an individual's function and health[5]. To improve general health and well-being, we must then understand walking.

To understand walking, we have traditionally evaluated kinematics (motion) and spatio-temporal parameters from quantitative gait analyses. Clinicians use standardized measures from gait analyses like the gait deviation index (GDI)—a summary metric that quantifies the severity with which a gait pattern's kinematics deviates from an average nondisabled (ND) gait pattern—to assess function and pathology[6,7]. In the field of biomechanics, we further traditional gait analyses by applying mechanical engineering principles to increase our understanding of gait. We analyze kinetics (*e.g.*, ground reaction forces and joint moments) and muscle activity via electromyography (EMG) recordings; which encapsulates motor control. To aid in interpretation, we often segment a gait cycle into stance (0-60% of the gait cycle) and swing phase (60-100% of the gait cycle)[8,9]. By applying mechanical engineering principles and quantitatively analyzing gait, we improve our understanding of function which can provide insight for clinicians to improve mobility and health. In this dissertation, we leverage these biomechanical tools to better understand gait in cerebral palsy.

2.2 CEREBRAL PALSY

Cerebral palsy (CP) is a movement disorder that originates from a brain injury at or near the time of birth[10]. CP occurs in every 3 in 1000 live births and currently affects nearly 800,000 people in the US; making it one of the most common childhood motor disorders in the US[11,12]. Clinically, CP is diagnosed by identified delays in motor milestones and changes in muscle morphology and movement[13]. Traditionally CP diagnoses are binned by characterizing functional level[14], the number of limbs affected (*Figure 1*)[15], and movement patterns, *e.g.*, spastic (*i.e.*, stiff muscles), dyskinetic (*i.e.*, uncontrollable movements), and ataxic (*i.e.*, poor balance and coordination)[10,16]. Among individuals with CP, 59% can walk independently, 8% can walk using hand-held mobility devices, and 33% require wheeled mobility[17]. However, binned diagnoses and functional classifications like GMCFS are summary metrics which oversimplify population heterogeneity[18] in CP blurring each individual's unique neurologic injury and muscle morphology.

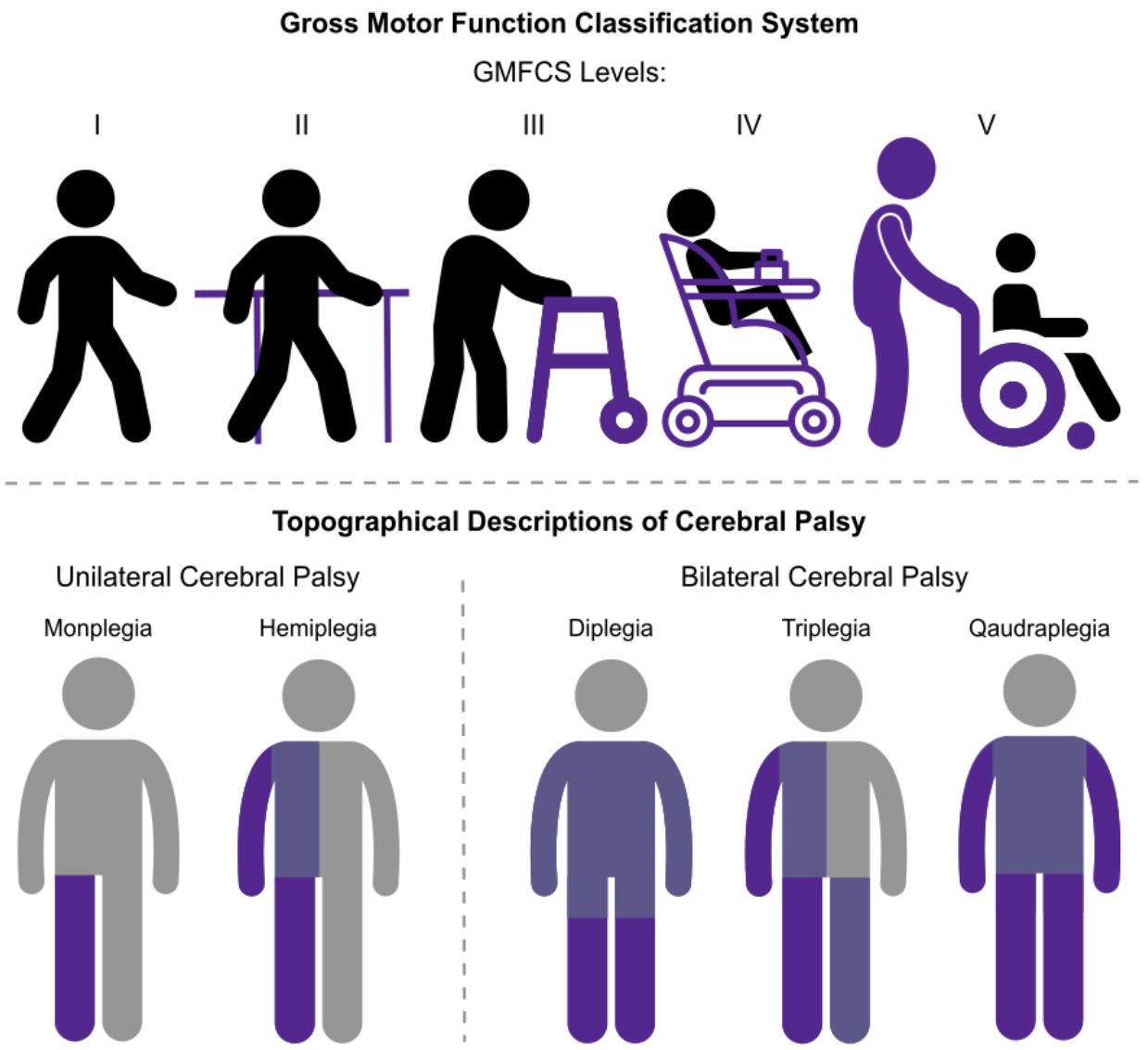

Figure 1: Diagnoses of Cerebral Palsy involve functional (top), number and severity of limbs affected (bottom), and movement pattern (not depicted) classification. (Top) The gross motor function classification system (GMFCS) is considered the gold standard for motor function classification in CP. GMFCS classification is an ordinal classification system based on an individuals age and function. The above depicted GMFCS levels are for children with CP, 6-12 years of age, and range from "Children walk and climb stairs without the use of a railing but are limited in balance and coordination (GMFCS I)" to "Children are transported in a wheelchair in all settings and have limited ability to control their head, trunk, and limbs (GMFCS V)." (Bottom) Topographical description in CP of additional diagnoses classified by side(s) affected—unilateral or bilateral—and the number and severity of limbs affected: darker purple indicating a more severely affected limb.

The primary result of the nonprogressive neurologic injury in CP is altered motor control: altered coordination and increased co-contraction (*i.e.*, simultaneous activation of agonist and antagonist muscles)[10]. In this dissertation we sought to evaluate the effects of altered control which require methodologies to quantify and analyze control. In a traditional engineering sense, control is the merging of engineering and applied mathematics to control dynamical systems where one develops an algorithm or model that governs the system's input-to-output to drive the system to a desired state. In this dissertation, we discuss control from a neural standpoint: a muscle's response to a nerve's stimulation of that muscle generated by volitional (feed-forward) control or reflexes (closed-loop control). To analyze neural control and when it is impaired (*i.e.*, altered control), we utilize muscle synergies: grouped patterns of muscle activations theorized to reflect modular control. In short, muscle synergies are low-dimensional representations of an individual's neuromuscular control extracted from EMG recordings during gait analysis. We selected muscle synergies to understand altered control because 1) they allow us to rapidly generate more accurate, patient-specific representations of control and 2) are clinically meaningful in CP: individuals with CP typically require fewer synergies to explain their EMG activity during walking than their ND peers, indicating less complex control strategies[19,20]. Less complex control strategies in CP correlate with impairment severity and poor treatment outcomes[21,22]. However, even with synergies, we have a limited understanding of the effects of altered control on gait because in CP it remains unchanged after intervention[23], meaning we remain unable to perturb and modulate control.

In addition to their non-progressive brain injury, individuals with CP often develop secondary, progressive impairments, such as weakness and contracture[24]. In CP, weakness can occur in many muscles, but in the lower-extremity, it is most prevalent in more distal muscles like

the dorsi- and plantar-flexors whose strength highly correlates with gait speed and function[18,25,26]. Contracture is defined as a limited joint movement that results from high passive muscle forces: either from a stiffening or shortening of the muscle or tendon[10]. In CP, contracture most commonly affects the hamstrings, plantarflexors, and hip flexors, and is thought to underlie common gait deviations in CP like crouch and equinus (*e.g.*, toe-walking)[27]. The amalgamation of altered control and altered morphology create complex neuromuscular restrictions on function and mobility which many interventions attempt to alleviate. The complexity of these interactions motivated my dissertation to investigate the interactions between multi-modal neuromuscular impairments and their effects on gait.

Most interventions (*e.g.*, strength training and muscle lengthening) in CP attempt to improve gait and function by addressing altered morphology like weakness and contracture. For example, treating contracture often involves serial casting or orthopedic muscle-tendon lengthening[28]. Serial casting involves the application of plaster casts at an affected joint to increase passive range of motion by maintaining a passive stretch in the affected muscle[29]. On the other hand, lengthening surgeries invasively alter the length of the musculotendinous junction in an attempt to improve range of motion while maximizing strength preservation[30]. Both serial casting and orthopedic surgery target and successfully improve altered morphology but often fail to create long-term functional improvements. Similarly, strength training interventions in CP successfully reduce weakness but improvements fail to translate to activities of daily life, having limited effect on gait speed and function[31–34]. Thus, we require more complex methods to better understand gait in CP and identify primary mechanisms affecting function to improve treatment efficacy in CP.

2.3 IN SILICO TECHNIQUES

In silico, or computational, techniques are used to rapidly evaluate hypotheses. In traditional engineering this often takes the form of design and testing of prototypes prior to fabrication which refines the design and testing process and minimizes resources. In gait biomechanics, *in silico* methods have been historically used to improve our foundational understanding of gait. Techniques like modeling, simulation, and machine learning enable us to rapidly elicit causal relationships between gait mechanics and impairments, analyze *in vivo* (within the living) quantities, and predict changes in gait prior to intervention; all of which are difficult or impossible to do experimentally[35–37]. For example, previous investigations using *in silico* techniques have highlighted how altered control increases sensitivity to assistive device tuning[38], analyzed how different walking patterns can reduce knee contact forces[39], and predict how orthopedic surgery can restore function in CP[40]. Note that a myriad of *in silico* methods exist in gait biomechanics, however their methods and application are beyond the scope of this dissertation. Rather, a summary of the most prevalent methods, and the ones utilized in this dissertation are presented below, along with their pros and cons and prior use in CP gait research.

2.3.1 *Physics-based Modeling*

Physics-based modeling spans a range of methods that utilize mathematical models defined by physiologically-consistent equations-of-motion to replicate, analyze, estimate, and predict dynamic behavior. In their simplest form, physiological models in biomechanics often represent gait by utilizing or combining simple dynamic systems: pendula, mass, springs, and dampers. For example, we can model and understand how the center of mass moves during gait with an inverted pendulum[41] or alter the stiffness of a spring attached to a pendulum to understand how contracture can alter swing phase gait dynamics (*e.g.*, increase step frequency)[42]. Simple physics-based models

have been informative for analyzing and understanding gait but lack morphology and control limiting their translation.

More complex physics-based models, specifically musculoskeletal models, have become more common in gait biomechanics over the past three decades. Musculoskeletal models are physics-based models that incorporate musculoskeletal anatomy (geometry of bones, mathematical descriptions of joint movement, and muscle path geometries) to better represent and understand function[35,38]. These models range from simple 2D-saggital plane models[43] to complex 3D models ranging upwards of 37 degrees-of-freedom[44]. OpenSim, is a fantastic opensource software that enables individuals to create and share biomechanical physics-based models and without it our understanding of gait and the utility of *in silico* techniques would not be where it is today[45]. It is important to note, that however complex a model is, that model is still a simplified representation of the musculoskeletal system and understanding the assumptions inherent in a model, and the model complexity required to test a hypothesis are necessary prior to application. That being said, musculoskeletal models have made great strides (badum tsss) in our understanding of gait. For example, musculoskeletal models enabled us to understand altered mechanics of crouch gait[46–48] and analyze muscle lengths during gait which can be used to inform orthopedic surgery[49,50]. However, musculoskeletal models alone do not improve our understanding of function: we require optimization techniques *(i.e.,* simulation) to investigate muscle function and control.

2.3.2 *Simulation*

Simulations can generate gait with a musculoskeletal model by identifying the joint moments (torques) required to generate the desired motion. By assuming an optimal control strategy, we can cacluate the muscle forces required to generate those torque profiles, and consequently the muscle

activations (control pattern) required to generate those muscle forces. In gait biomechanics, optimal control often uses the assumption that human movement, specifically its control patterns like muscle activations, are selected by optimizing some performance criterion (*i.e.*, objective function). The optimal control assumption is required because the musculoskeletal system is underdetermined: it has more muscles (variables) than degrees of freedom (unknowns) and thus, has an infinite number of non-unique solutions[51]. Gait simulations therefore use an objective function—a summation of optimality criteria that are minimized or maximized during the gait cycle—to simulate gait[52]. It is important to note the assumption of optimal control and the optimization of a selected objective function allow our simulations to converge, but also then represent an assumption about what an individual is prioritizing during gait. Thus, objective function choice is extremely important and can be used to represent *in vivo* neuromuscular control strategies supported by experimentation (*e.g.*, minimizing energy consumption or fatigue)[53,54]. However, they also represent a large limitation as they dictate the resultant gait pattern and its control strategy, making optimal control results extremely sensitive to objective function choice. The limitations of our optimal control assumption are still poorly understood during non-habitual gait patterns, exploration, adaptation, and gait in non-disabled populations, as it remains unclear what is optimized during these conditions and for these individuals[39,54]. With the optimal control assumption and within gait biomechanics, many methods of simulation exist and have been used to better understand gait and its dysfunction.

Static optimization is perhaps the simplest and most prevalent form of simulation used to evaluate human walking with a musculoskeletal model. Static optimization utilizes an already defined motion (*i.e.*, states like positions, velocities, and accelerations), and optimizes for the unknown muscle forces and activations separately and sequentially at each point in time (*i.e.*, time-

marching). Because static optimization utilizes an already known motion, we often refer to these methods as 'inverse simulations'. Inverse simulations are typically either tracking or prescribed simulations, meaning we force the simulation to match kinematics or kinetics, respectively. The simplicity of static optimization's formulation results in low computation time making it 1) an excellent tool for quickly generating a desired motion and predicting and analyzing *in vivo* quantities and 2) applicable to real-time analyses[55]. In CP, static optimization has improved our understanding of gait and interventions by eliciting how assistive devices can reduce energy consumption and fatigue[56] and predicting improvements in function post-intervention[40]. While informative and computationally efficient, static optimization is not appropriate for all gait patterns and individuals. Instantaneous optimization at each time-step ignores important dynamics (e.g., muscle activation and contraction dynamics) which may cause physiologically-unrealistic results. These limitations have minimal impact during ND walking but create much larger discrepancies during rapid motions like running, and for muscles that have more compliant tendons such as the soleus and gastrocnemii[57].

Dynamic optimizations offer a way to account for muscle activation and contraction dynamics, thus decreasing assumptions and generating more physiologically-realistic results[58]. However, the increased complexity of dynamic optimizations drastically increases computation time, decreasing their prevalence because they are subboptimal for real-time applications and nested algorithms[59]. More common in gait biomechanics are mixed methods approaches like computed muscle control (CMC)[60]. Mixed methods approaches join multiple methods of simulation to minimize their respective limitations. For example, CMC utilizes static optimization to rapidly generate muscle activations, and then utilizes those activations to drive a forward dynamic simulation. Forward dynamic simulations, inverse to inverse methods, generate gait by

integrating equations of motion forward in time from initial states, while applying predefined muscle forces. Mixed method approaches can then be used to generate less constrained or even novel gait patterns. Mixed methods like CMC have been used in CP to understand how tendon-transfer surgeries may alter balance recovery[61], predict efficacy of exoskeletons during swing phase[62], and how crouch gait alters demands and torque generating capabilities of muscles[46,47].

Additional methods of optimal control have emerged as promising techniques to simulate gait. These methods are divided into two categories, direct and indirect, which can then further be subdivided into forward, inverse, and implicit approaches[63]. In this dissertation, we mainly focus on and utilize direct collocation (DC) optimal control. DC optimal control is a trajectory optimization that 1) does not solve for boundary constraints but rather parameterizes the control and states (*i.e.*, direct) and solves the optimization with a non-linear program, 2) converts the trajectory constraints, boundary constraints, and objective function into algebraic equations (*i.e.*, implicit), 3) solves for each time-step simultaneously, and 4) then ties each time-step together (*i.e.*, collocation)[64]. In short, DC optimal control discretizes a trajectory and optimizes the entire trajectory by simultaneously solving for each discretized state and control while enforcing boundary and trajectory constraints via simple algebraic equations for computational efficiency. One limitation of DC optimal control is that it is a local search optimization, meaning it does not solve for the entire solution space but instead searches for an optimum locally. While local search optimizations may better represent *in vivo* control[65], they are very sensitive to initializations[66]. Thus, rigorous initialization testing must be done to ensure that results are not sensitive to initial guess, *i.e.*, one must confirm that the DC optimal control problem did not converge to a local, rather than a global, optimum. Because of its ability to rapidly generate gait simulations while accounting for muscle and activation dynamics, DC has become a prevalent methodology in

simulating gait. However, the complexity of setting up a DC optimal control problem and its sensitivity to initial guess made it less enticing to non-experts[57] until recently, with the release of OpenSim MOCO: an open-source, easy to use, and customizable, direct collocation software to rapidly optimize the motion and control of musculoskeletal models[67].

In gait biomechanics, DC optimal control has become increasingly prevalent but has seen limited application in clinical populations like CP. Several studies findings have implications to CP[43,68,69], but currently, only a single study has used DC optimal control to simulated gait in CP[70]. Falisse et al [2019], generated predictive simulations of gait for a single child with CP—rather than an inverse method where we track kinematics or prescribe kinetics, they generate a completely novel motion by applying constraints and minimizing a complex objective function that encompasses many subtasks within walking. They found that altered control can create gait deviations similar to those in CP and elevate the energetic cost of walking. They also found that to simulate a child's unique gait pattern predictively, complex and precise MTU tuning was required. Additionally, they found that for a single child with CP, altered MTU properties played a larger role in kinematic deviations but did not prevent normative gaitl. This study lays excellent groundwork for our understanding of gait in CP and highlights the applicability of DC optimal control to improve that understanding.

2.3.3 *Data-driven Modeling*

Data-driven models, *i.e.*, machine learning (ML), unlike physiological models, do not encode assumptions about the underlying dynamics of a system. In fact, they require very few assumptions to learn a system's underlying 'dynamics'. Once trained, data-driven models are often used for classification and prediction and enable the parsing of complex, heterogenous data like gait data[71] for individuals with CP which motivated this dissertation to utilize data-driven modeling to parse

the relative effects of multi-modal neuromuscular impairments on gait in CP. It should be noted that data-driven modeling is an emerging field in understanding dynamical systems including gait, but even outside of gait biomechanics, data-driven modeling is in its infancy.

Thus far, in human movement biomechanics, data-driven models have been used to primarily classify movement patterns[71]. For example, within CP, k-means clustering identified common gait patterns amongst a retrospective dataset of 2159 children with CP[72]. Additionally, data-driven modeling has emerged as a predictive, prognostic, and diagnostic tool in human health[71]. Within biomechanics, data-driven modeling has predicted pathologic gait incidents (*e.g.*, freezing gait in individuals with Parkison's Disease)[73], and responder and non-responders of interventions. Within CP, machine learning has been used as a diagnostic and prognostic tool for detecting CP via video or motion capture and as a prognosis tool. More recently, a few studies in CP began utilizing Bayesian Additive Regression Trees (BART) models to attempt to understand primary causal mechanisms underlying elevating energetics and heterogenous outcomes in CP.

BART is a sum-of-trees machine learning algorithm that estimates a function. Similar to other ensemble methods, each tree is a weak learner: a decision tree that explains a small portion of the function. However, BART is unique in that it utilizes Bayesian probability to prevent overfitting, *i.e.*, a regularization prior enables BART to autonomously hyper-parameterize itself[74]. In addition, BART has demonstrated similar and even superior predictive capabilities to other common machine learning algorithms (e.g., neural networks) with and without missing data[74,75]. Thus, BART's tuning automaticity, predictive capabilities, and prior success in CP research[76–79], make it an appealing tool for gait biomechanics and motivated this dissertation to utilize it for parsing, estimating, and predicting gait biomechanics in CP.

While useful, data-driven models are not without limitations. First, they require large amounts of data which can be difficult to collect, especially for disabled populations[71,80]. They also assume that the model inputs contain sufficient information to enable the data-driven model to learn the relationship (*e.g.*, linear or non-linear) between input and output; which in gait applications remains unclear[81]. Additionally, many uses of data-driven models ignore prior knowledge, *i.e.*, system dynamics, assuming they are learned and ignoring prior knowledge. Lastly, they require extensive parameter tuning and lack interpretability limiting clinical translation[71].

Physics-based musculoskeletal modeling, neuromuscular simulations, and machine learning offer a unique way to rapidly evaluate gait in the extremely complex and heterogenous population that is CP while generating informative data in a non-resource intensive or burdening way motivating our use of synthetic data to improve data-driven models' abilities to estimate and predict energetics in CP. The following chapters document our process for utilizing these *in silico* techniques to better understand gait in CP. This dissertation applies computer-aided engineering to biomechanics to build a foundation for research to better understand gait in CP with the long-term goal of improving treatment efficacy for individuals with CP.

Chapter 3. NUMBER OF SYNERGIES IMPACTS SENSITIVITY OF GAIT TO WEAKNESS AND CONTRACTURE

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Elijah C. Kuska
Department of Mechanical Engineering, University of Washington

Naser Mehrabi
Department of Mechanical Engineering, University of Washington

Michael H. Schwartz
Center for Gait & Motional Analysis, Gillette Children's Specialty Healthcare

Katherine M. Steele
Department of Mechanical Engineering, University of Washington

ABSTRACT

Muscle activity during gait can be described by a small set of synergies, weighted groups of muscles, that are theorized to reflect underlying neural control. For people with neurologic injuries, like cerebral palsy or stroke, even fewer synergies are required to explain muscle activity during gait. This reduction in synergies is thought to reflect altered control and is associated with impairment severity and treatment outcomes. Individuals with neurologic injuries also develop secondary musculoskeletal impairments, like weakness or contracture, that can impact gait. Yet, the combined impacts of altered control and musculoskeletal impairments on gait remains unclear. In this study, we use a two-dimensional musculoskeletal model constrained to synergy control to simulate unimpaired gait. We vary the number of synergies, while simulating muscle weakness and contracture to examine how altered control impacts sensitivity to musculoskeletal impairment while tracking unimpaired gait. Results demonstrate that reducing the number of synergies increases sensitivity to weakness and contracture for specific muscle groups. For example, simulations using five-synergy control tolerated 40% and 51% more knee extensor weakness than those using four- or three-synergy control, respectively. Furthermore, when constrained to four- or three-synergy control, the model was increasingly sensitive to contracture and weakness of proximal muscles, such as the hamstring and hip flexors. Contrastingly, neither the amount of generalized nor plantarflexor weakness tolerated was affected by the number of synergies. These findings highlight the interactions between altered control and musculoskeletal impairments, emphasizing the importance of measuring and incorporating both in future simulation and experimental studies.

3.1 INTRODUCTION

Muscle synergy analysis decomposes measurements of muscle excitations into common patterns of co-activation during dynamic activities. These patterns are theorized to reflect modular spinal and supraspinal networks that are used to control movement[82,83] and reduce the dimensionality of neuromuscular control[84]. Although the origins and neurophysiology of synergies remain a topic of debate[85], synergies provide a useful tool, clinically and scientifically, to evaluate and model control[21,86,87]. For example, muscle activity during walking can be explained by fewer synergies for individuals with neurological injuries than unimpaired peers, and has been associated with impaired function[22] and treatment outcomes[21,88,89]. Further, individuals with neurologic injuries commonly develop secondary musculoskeletal impairments like contracture and weakness[90,91]. The interactions between altered control and musculoskeletal impairments make identifying the causal mechanisms underlying gait pathologies challenging and limit our ability to effectively intervene.

Computational models of the neuromusculoskeletal system enable evaluation of hypothetical relationships between impairment mechanisms. Previous studies using modeling and simulation examined how weakness[92], contracture[93], and fixed numbers of synergies[69] impact gait. Weakness, contracture, and reliance on fewer synergies make achieving unimpaired gait more difficult. However, these impairments were imposed in isolation and did not address interactions between altered control and musculoskeletal impairments. One case study of a child with cerebral palsy (CP) used simulation to evaluate the combined effects of altered synergies and musculoskeletal impairments, suggesting that altered muscle-tendon properties, rather than impaired control, were the primary cause of the child's altered gait[70]. Understanding the

interactions and impacts of musculoskeletal impairments and altered control is important to understand function.

The purpose of this study was to examine the interactions and impacts of altered control (number of synergies) and musculoskeletal impairments (weakness and contracture) on unimpaired gait. Specifically, we used musculoskeletal simulation to examine how the number of synergies alters the sensitivity of unimpaired gait to weakness and contracture. We used a direct collocation framework[69] to generate tracking simulations while varying the number of synergies and simulating progressive weakness and contracture. We hypothesized that control constrained to fewer synergies would (1) reduce the amount of weakness and contracture the simulation can tolerate before unimpaired gait is irreplicable, and (2) increase the amount of muscle activity required to replicate unimpaired gait with weakness and contracture.

3.2 METHODS

3.2.1 *Musculoskeletal Model*

We built a sagittal-plane, musculoskeletal model in MapleSim (Maplesoft, Inc) based on Geyer and Herr[94] with an added rectus femoris[95]. The model consisted of seven rigid body segments – one combined head, arms, and torso (HAT) and three segments per leg (thigh, shank, and foot) – linked by hinge joints (Figure 1). Eight Hill-type musculotendinous units per leg actuated the model's nine kinematic degrees of freedom: biarticular hamstring (HAM), gluteus maximus (GLU), iliopsoas (IP), rectus femoris (RF), vasti (VAS), gastrocnemius (GAS), soleus (SOL), and tibialis anterior (TA)[69]. Ten continuous Coulomb friction contact spheres were placed in-line and equidistantly along each foot to simulate ground contact[96]. Sphere contact stiffness was hand-tuned to a value of 848500 N/m to prevent unrealistic foot movements and spikes in ground reaction forces[69].

3.2.2 *Optimization*

Dynamic equations of motion were exported from MapleSim to a direct collocation (DC) optimal control framework (*Figure 2*) within MATLAB (Mathworks, Inc) to generate tracking simulations [69]. DC converts a trajectory tracking problem into a non-linear program by discretizing states, inputs, and dynamics, and transcribing the equations of motion into algebraic constraints. In general, DC has become popular because of its ability to accurately and rapidly simulate motion [57,97].

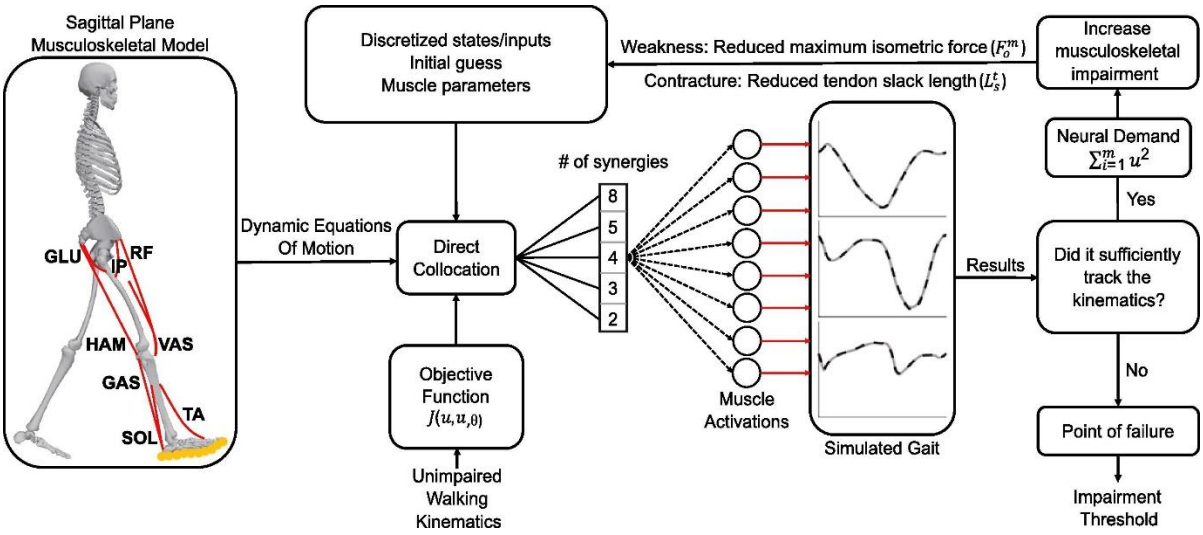

Figure 2: A two-dimensional sagittal plane musculoskeletal model and synergy simulation framework tracked unimpaired gait kinematics. The model had nine degrees of freedom, including right and left leg hip, knee, and ankle flexion, actuated by eight muscles per leg. Fixed sets of synergies constrained control, forcing the direct collocation algorithm to solve for synergy activations. The objective function minimized deviations from unimpaired kinematics and the sum of muscle activations (u) squared (neural demand). Weakness, simulated by a reduction in maximum isometric force (F_o^m), and contracture, simulated by a reduction in tendon slack length (L_s^t), were progressively increased for each muscle or muscle group until the simulation failed to replicate unimpaired gait. Kinematic deviations and convergence determined the success of the simulation. The primary outcomes were (1) musculoskeletal impairment thresholds, defined by the amount of weakness or contracture before failure, and (2) neural demand of each gait cycle.

Within our framework, an implicit Euler collocation scheme[52,98] transcribed the dynamic equations of motion using a 51-point temporal grid representing a half gait cycle[69]. ADiGator[99]

assisted with autonomic differentiation and MATLAB's interior-point optimizer (IPOPT) [100] solved each optimization. The framework generated tracking simulations that minimized deviations from desired kinematics, the amount of muscle activation required – which we termed "neural demand"[52,69] – and a smoothing term for neural control:

$$J = \int_{t=0}^{t=t_f} \left(w_1 \sum_{j=1}^{9} (\Theta - \Theta_{tracked})^2 + w_2 \sum_{m=1}^{16} u_m^2 + w_3 \sum_{m=1}^{16} \dot{u}_m^2 \right) dt \quad (1)$$

where Θ - $\Theta_{tracked}$ represents deviations from tracked kinematics, and u represents muscle activations with $\dot{u}$ derivatives. In lieu of a metabolic model, neural demand acted as an energetic estimator that has previously been shown to replicate gait[52]. Weighting factors (w_1, w_2, and w_3) applied to the tracking, neural demand, and neural derivative terms were set to 5000, 35, and 0.05, respectively[69]. Gait replication was the primary goal, thus tracking error was heavily weighted. Average unimpaired walking kinematics[101] were tracked ($\Theta_{tracked}$) and symmetry was assumed to reduce computation time[102].

A null guess – tracked kinematics, muscle lengths estimated from tracked kinematics, and zeroed controls – was used for simulation validation[69] and to provide the initial guess (i.e., hot start to improve convergence time) for all subsequent simulations. To test sensitivity to initial guess, simulations were run with four scenarios: a null guess, two constant control guesses, and a hot start. Constant control guesses were initialized with the tracked kinematics, muscle lengths estimated from the tracked kinematics, and an arbitrary constant (0-1) applied to all controls. Analysis of initial guess sensitivity demonstrated that kinematic variance from different initial guesses was within a single standard deviation of experimentally reported sagittal-plane waveforms[103] and that there was no significant difference between null guess and hot start results.

3.2.3 *Neuromuscular Control*

We implemented a neuromuscular controller within the DC framework (Figure 1) that varied the number of synergies controlling each leg[69]. Nonnegative matrix factorization (NNMF)[104] generated synergies from an initial simulation that controlled each muscle individually (i.e., not constrained by synergies). Briefly, NNMF decomposes control signals into weights and activations by a multiplicative update algorithm that minimizes deviations from the original signal. Thus, the chosen sets of 3-5 synergies represented the groups of muscles that would explain the greatest variance in simulated muscle activity.

For each number of synergies, synergy weights were imposed to constrain muscle activation patterns during the tracking simulations. Fewer synergies simulated more severe neuromuscular impairments[19,22]. We selected 5 synergies to reflect unimpaired control[105,106] and 3-4 to reflect the altered control observed in CP[19,20,87,89] and stroke[107]. Two synergy control, sometimes reported in stroke[107] and CP[87,89], could not track unimpaired gait and was excluded[69].

3.2.4 *Musculoskeletal Impairments*

We simulated weakness by reducing maximum isometric force (F_o^m)[43,92,93]. Each muscle was weakened individually, along with both plantarflexors (PFlex = GAS + SOL), knee extensors (KExt = RF + VAS), knee flexors (KFlex = GAS + HAM), hip extensors (HExt = GLU + HAM), and hip flexors (HFlex = IP + RF). To examine generalized weakness, all muscles were weakened simultaneously (ALL).

We simulated contracture for SOL, GAS, HAM, and PFlex; muscles that commonly exhibit contracture in CP[18,108] and stroke[109,110]. The original MTU model, based on Geyer & Herr[94], is mathematically constructed (i.e., no muscle paths) such that reductions in tendon slack length (L_s^t) had no effect on tendon elongation. To simulate contracture, we added altered L_s^t values to

the musculotendon dynamics such that reductions in L_s^t increased tendon elongation and passive force generation (Appendix A). We chose to model contracture by reducing L_s^t because of heterogeneity reported in CP muscle fiber and tendon lengths, this method's prior use in literature, and greater interpretability[93,111–114].

3.2.5 *Analyses*

We progressively increased weakness or contracture, using 1% increments for weakness and 0.1% increments for contracture, until the simulation failed to replicate unimpaired gait. Weakness and contracture thresholds were defined when there was >1° average root-mean-squared error for a degree of freedom or the simulation did not converge after 2500 iterations. Thresholds demonstrate robustness to weakness or contracture with differences in thresholds across controls highlight how altering the number of synergies can impact robustness to weakness and contracture. Additionally, for muscle weakness, we labelled muscle groups "control sensitive" if the average difference in weakness thresholds with varying number of synergies exceeded 7.7%, representing one standard deviation in lower limb muscle volume and strength for unimpaired children[18,115].

To further examine interactions between neuromuscular and musculoskeletal impairments, we analyzed the neural demand required to replicate unimpaired gait (*Figure 5*a). The neural demand of five-synergy control was subtracted from four- and three-synergy control. Specifically, we plotted the amount of weakness or contracture versus the relative difference in neural demand for four- and -three-synergy control. We fit a quadratic to characterize the compounding effects of impairments on muscle activity required for unimpaired gait (*Figure 5*b). Quadratic curves were selected because they provided the best fits and the second order coefficient (i.e., steepness of the curve) could be used to evaluate sensitivity of neural demand to

weakness or contracture. Greater second-order coefficients indicate larger increases and more rapid deviations in neural demand relative to five-synergy control (*Figure 5*c). The second-order coefficients were normalized to the maximum observed for weakness and contracture.

3.3 RESULTS

3.3.1 *Weakness*

Tolerance to weakness decreased as fewer synergies were used to track unimpaired gait (Figure 2). Averaged across all weakness scenarios, five-, four-, and three- synergy control tolerated 80%, 62%, and 59% reductions in F_o^m, respectively. Weakness thresholds for specific muscle groups varied. The VAS, KExt, HAM, HExt, KFlex, HFlex, IP, and TA were all control sensitive (*Figure 3*). For these muscles, five-synergy control could replicate unimpaired gait with, on average, 82% weakness while four- and three-synergy control could only tolerate 53% and 47% weakness, respectively. Four- and three-synergy control were least robust to TA, IP, and HFlex weakness. The muscles and muscle groups that were not sensitive to the number of synergies (i.e., control insensitive) included the GAS, GLU, RF, ALL, SOL, and PFlex. The GAS, GLU, and RF, could be fully weakened (i.e., completely removed from the simulation with a weakness threshold of 100%) without preventing unimpaired gait for all synergy-based controls.

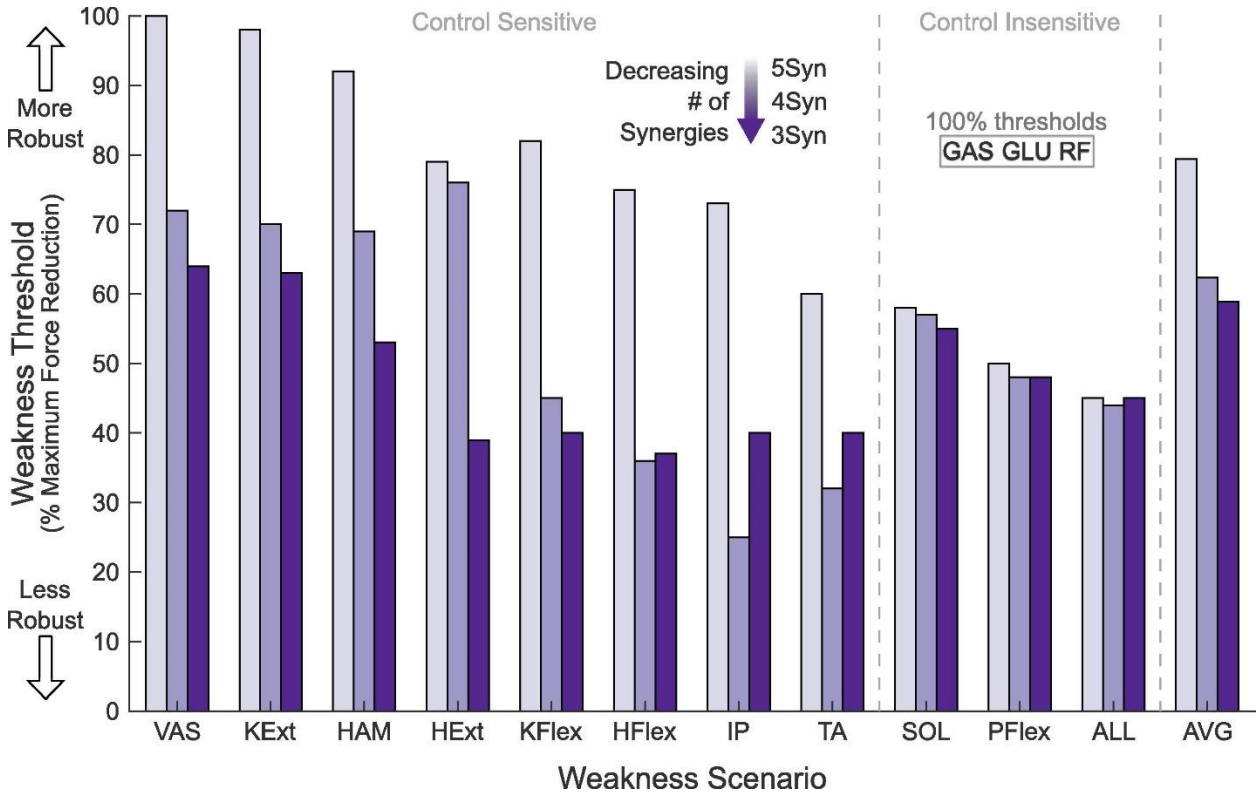

Figure 3: Weakness thresholds for five-, four-, and three-synergy control. A greater weakness threshold indicates muscle groups that are more robust to weakness while tracking unimpaired gait. Three muscles (GAS, GLU, and RF) had a weakness threshold of 100% (i.e., could be removed entirely from the simulation without impairing gait) for all synergy controls. Muscles were considered control sensitive or control insensitive based on the average threshold differences between five-, four-, and three-synergy control. If the average difference in weakness thresholds between five-, four-, and three-synergy control exceeded 7.7%, it was considered control sensitive. Control sensitivity indicated that changes in the number of synergies used by the control strategy altered weakness thresholds.

When ALL muscles were weakened, the simulations had similar tolerances to weakness regardless of number of synergies. Five-synergy control tolerated a 45% reduction in strength (i.e., simulation failed to track when all muscles were weakened by 45%), while four- and three-synergy control tolerated 44% and 45% reductions in strength, respectively. Similarly, SOL and PFlex weakness had minimal differences in thresholds with fewer synergies.

3.3.2 *Contracture*

The tolerance to contracture decreased as fewer synergies were used to track unimpaired gait (*Figure 4*). On average, five-synergy control tolerated a 6.8% reduction in L_s^t while four- and three- synergy control only tolerated 4.8% and 3.9% reductions, respectively. However, contracture thresholds varied between muscle groups. All three plantarflexor scenarios (SOL, GAS, PFlex) showed similar robustness to contracture: five-synergy control tolerated 3.4-4.4% reductions in L_s^t while both four- and three-synergy control only tolerated 2.1-3.0% reductions. Additionally, five-synergy control tolerated a 13.8% reduction in L_s^t for the HAM, compared to a 12.2% and 3.6% reduction for four- and three-synergy control, respectively.

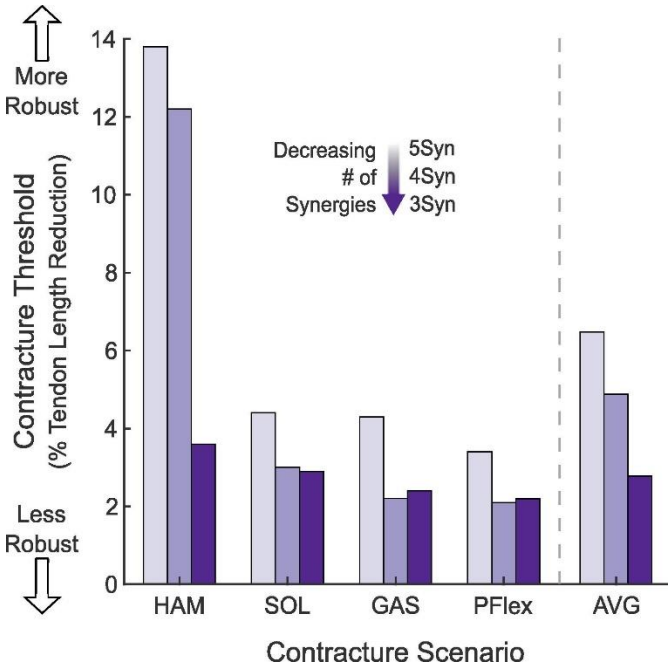

Figure 4: Contracture thresholds with five-, four-, and three-synergy control. A greater contracture threshold indicates muscle groups that are more robust to contracture while tracking unimpaired gait.

3.3.3 *Neural Demand*

Weakness, contracture, and the number of synergies used by the control strategy impacted neural demand (sum of squared muscle activations) during gait. Weakness of ALL muscles, as well as weakness of the PFlex and SOL had the largest impacts on neural demand with five-synergies. With five synergies, contracture of the plantarflexors (SOL, GAS, and PFlex) increased neural demand more than HAM contracture. Without weakness or contracture, neural demand increased by 16.7% with four-synergy control compared to five-synergy control, with a further increase of 3.7% with three-synergy control (*Figure 5*a, y-axis intercept).

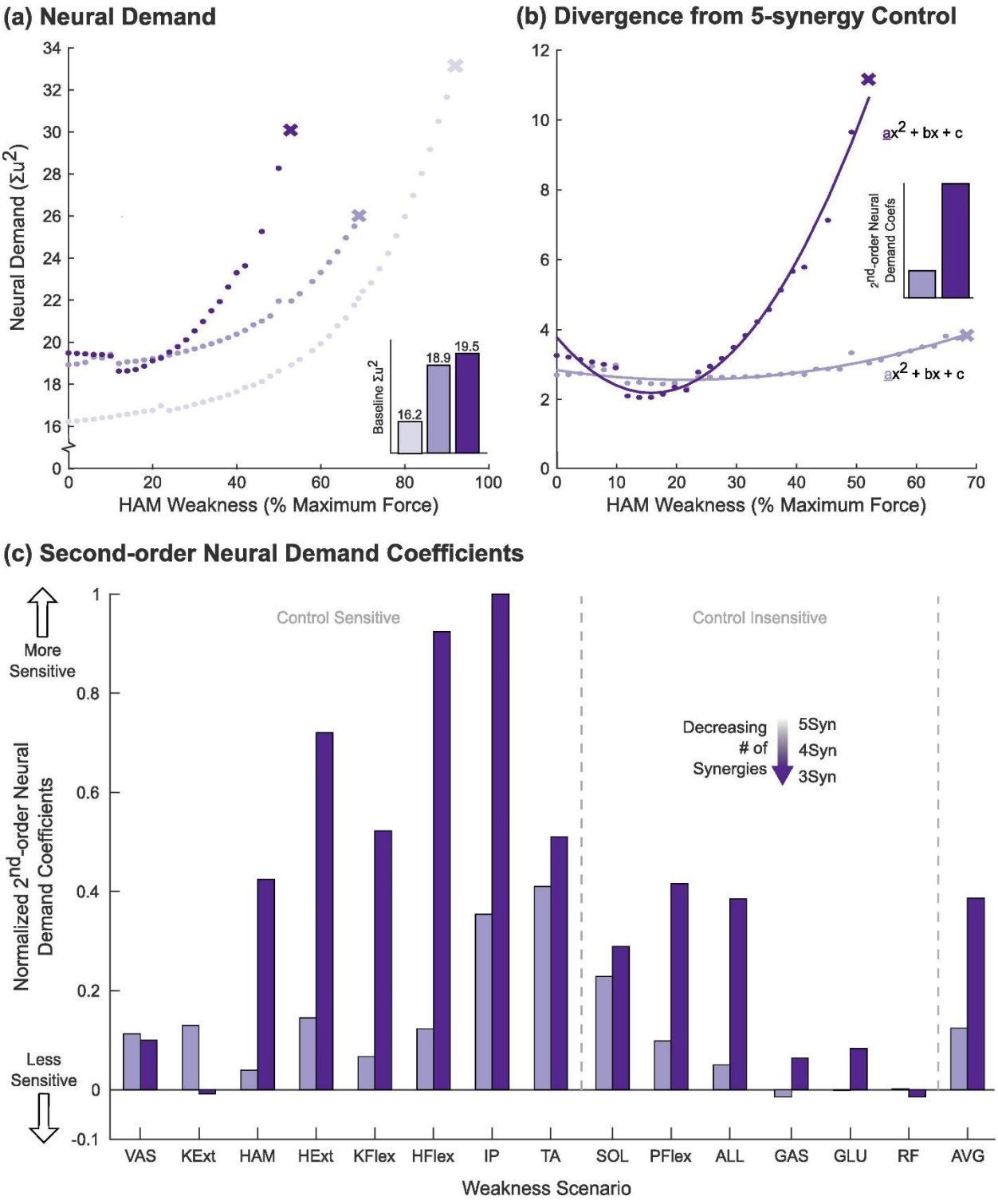

Figure 5: Neural demand – the summation of muscle activations squared - results for weakness simulations. (a) Neural demand values for five-, four-, and three-synergy control as hamstring (HAM) weakness, used as an example, was progressively increased. Weakness thresholds (X) indicate when simulations could no longer track unimpaired gait. Baseline neural demand (no weakness or contracture) was higher when control was constrained to fewer

synergies (y-axis intercept). (b) Points represent neural demand differences relative to five-synergy control, i.e., five-synergy control's neural demand subtracted from four- and three-synergy neural demand. Differences from five-synergy control's neural demand were fit with quadratic polynomials where second-order coefficients indicate neural demand's sensitivity to weakness (i.e., how, as weakness progressed, neural demand increased and deviated from five-synergy control when control strategies were constrained to use fewer synergies). (c) Weakness second-order neural demand coefficients, normalized to the maximum (0.02) of four- and three-synergy control. Greater second-order coefficients indicate greater sensitivity and larger increases in neural demand relative to five-synergy control with increasing weakness.

The sensitivity of neural demand to weakness increased as the control strategy used fewer synergies for most muscles (*Figure 5*c). Averaged across weakness scenarios, the second-order coefficient for three synergies (*i.e.*, neural demand with three synergies – five synergies) was 3.5x that of four synergies, indicating that neural demand increased and deviated more rapidly relative to five-synergy control. For example, when ALL muscles were weakened, the second-order coefficient increased from 0.05 for four synergies to 0.39 for three synergies. Deviations from five-synergy control were greatest for the control sensitive muscles, especially weakness of the IP and TA. In contrast, the number of synergies had less impact on neural demand for the control insensitive muscles, with GAS, GLU, and RF second-order coefficients close to zero.

The sensitivity of neural demand to contracture increased as the control strategy used fewer synergies (Figure 5). When averaged across contracture scenarios, the second-order coefficient was 2.5x larger for three than four synergies. The second-order coefficients were greatest for contracture of the plantarflexors (SOL, GAS, and PFlex) and smallest for HAM contracture.

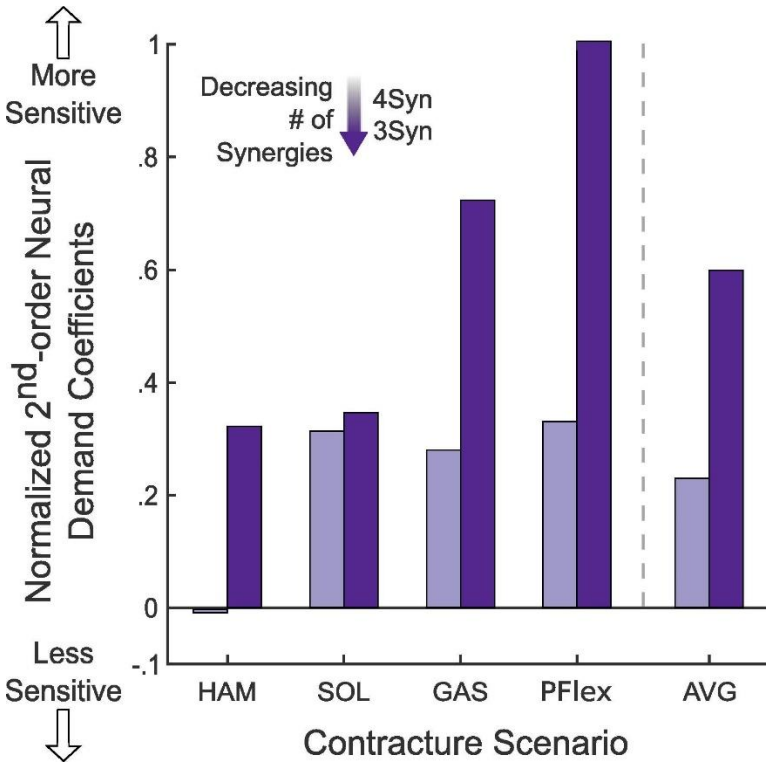

Figure 6: Contracture second-order neural demand – summation of muscle activations squared - coefficients, normalized to the maximum (1.46) of four- and three-synergy control. Greater second-order coefficients indicate increased sensitivity and larger increases in neural demand relative to five-synergy control as contracture progressed.

3.4 DISCUSSION

This study found that altered motor control (e.g., a control strategy constrained to fewer synergies) impacts sensitivity of unimpaired gait to musculoskeletal impairments. This supports our hypotheses that control strategies constrained to fewer synergies (1) tolerate less weakness and contracture and (2) exacerbate increases in neural demand with weakness and contracture for unimpaired gait. Prior analyses have excluded altered control when analyzing the impact of weakness or contracture on gait[92,93,116]. Our results highlight that interactions between altered control and musculoskeletal impairments influence the sensitivity of gait and should be factored into future analyses, especially for populations with neuromuscular impairments.

Most muscles and muscle groups were sensitive to the number of synergies used to track unimpaired gait. Weakness of proximal muscles and contracture of the hamstrings and plantarflexors were most sensitive to changes in the number of synergies. Previous studies examining muscle weakness found that unimpaired gait was generally robust to weakness when control was not constrained to synergies[92,93], but could only tolerate up to 3% reductions in tendon slack length[93]. Our findings indicate similar trends: five-synergy control was robust to the removal of several muscles and tolerated up to 3% reductions in tendon slack length for the plantarflexors. However, with four or three synergies, simulations were less robust to weakness and contracture. Thus, the ability for the simulation to track unimpaired gait with weakness and contracture quickly diminished as the control strategy was constrained to use fewer synergies.

Our simulations of unimpaired gait were least robust to weakness of ALL muscles and plantarflexor (SOL and PFlex) weakness (*Figure 3*), similar to prior literature that did not use synergy-based control[92,93]. Since, the plantarflexors always appear in a single synergy activated in late stance for propulsion, the simulations had similar weakness thresholds for ALL and plantarflexor weakness, regardless of number of synergies. These findings highlight the importance of plantarflexor strength for unimpaired gait and the lack of compensatory techniques, irrespective of control, for plantarflexor weakness[92,101,117].

Our sagittal-plane simulations of unimpaired gait were most robust to the weakness of redundant and bi-articular muscles. Independent of the number of synergies, our simulations could track unimpaired gait with the removal of the gluteus maximus, rectus femoris, and gastrocnemius, which may be surprising due to the low redundancy measure (# of muscles divided by # of degrees of freedom +1[118]) of our model compared to previous studies: 1.5 vs. 3.8[92] and 4.8[93]. This may be most surprising for the gluteus maximus because of its ability to

generate hip extensor moments[119]. However, our model and other previous studies found that redundant hip and knee extensors could compensate for gluteus maximus weakness[92]. Robustness to rectus femoris and gastrocnemius weakness were previously reported[92] and stem from lower maximum isometric forces and lower joint accelerations induced per unit force[119]. In contrast, Jason J. Kutch and Valero-Cuevas[120] found that removing the gastrocnemius and rectus femoris had the greatest impact on endpoint force generation, emphasizing a lack of redundancy in the musculoskeletal system. However, comparing to our results from gait, highlights that redundancy can be task-specific.

From a clinical perspective, it is surprising that our results indicate that gluteus maximus, rectus femoris, and gastrocnemius weakness would not prevent unimpaired gait as these are common suspects of gait deviations in CP[43,46]. However, an individual would likely alter their gait pattern, adapting to contracture and weakness to reduce energetic costs or improve stability[70]. Our investigation and prior studies analyze unimpaired gait kinematics; applying similar methods to altered gait patterns could highlight how kinematic adaptation can alter sensitivity to weakness and contracture. Additionally, impairments in CP rarely occur in isolation. Children with CP typically have weakness and contracture impacting multiple muscle groups[18] and can also develop bone deformities[10]. Additionally, model simplifications may also affect sensitivity to altered muscle-tendon properties but are likely not the sole cause as prior studies using more complex models found similar robustness to GAS, GLU, and RF weakness[92]. Lastly, our investigation and prior studies analyzed the impact of weakness during only unimpaired gait. GAS, GLU, and RF weakness may have a greater impact during gait patterns that rely more on flexors, such as crouch gait in CP[46].

The neural demand of unimpaired gait was most sensitive to weakness of ALL muscles and plantarflexor weakness and contracture, aligning with previous results indicating that impairments in these muscle groups lead to large increases in neural demand[92]. In addition, our study and previous findings highlight that knee extensor, gastrocnemius, gluteus maximus, and rectus femoris weakness have little to no effect on neural demand for unimpaired gait[92]. Using fewer synergies exacerbated the increases in neural demand required to adapt to weakness and contracture. The second-order coefficients from the quadratic fit comparing neural demand relative to five-synergy control highlight the magnitude of the exacerbating effect. Second-order coefficients were largest for the weakness and contracture scenarios that four- and three-synergy control were least robust to. These findings indicate that an individual's neural demand 1) increases most when adapting to the to the musculoskeletal impairments they tolerate the least and 2) increases more rapidly in response to weakness and contracture when using fewer synergies.

There are several important limitations of this study. Simulations provide a simplified representation of human gait, with simplified muscle paths that neglect active stability and control in the mediolateral direction. Simplified muscle paths likely reduced sensitivity to hamstring contracture. Without mediolateral movement we could not investigate sensitivity to hip abductor weakness[92]. Nonetheless, our simplified simulations had similar robustness to weakness and contracture as three-dimensional analyses of unimpaired gait[92,93] and highlight how, even in a simple model, fewer synergies increased sensitivity to weakness and contracture. We also assumed bilateral symmetry which can be a poor assumption for pathologic gait. Similarly, the specified synergy weights may not reflect neurologic disorders. Synergy weights were fixed and defined from a simulation with individual muscle control (Appendix A). Using

these synergy weights maximized the amount of variance in muscle activity a given number of synergies could explain for unimpaired gait. Post-hoc analyses examining different synergy weights verified these synergies were the most robust to weakness and contracture, representing a best-case for replicating unimpaired gait. Our objective function minimized a metabolic estimator – neural demand – rather than metabolic cost during tracking of unimpaired gait. Future studies that examine different objective functions or altered gait patterns will provide further insight into the complex interactions and impacts of neuromuscular and musculoskeletal impairments, especially for individuals with neurological injuries.

This study investigated the interactions between neuromuscular and musculoskeletal impairments on unimpaired gait. We found that when control strategies were constrained to use fewer synergies, the likelihood of achieving an unimpaired gait pattern with weakness and contracture was reduced supporting our hypotheses that control constrained to fewer synergies 1) increases the sensitivity of unimpaired gait to musculoskeletal impairments and 2) exacerbates the increased muscle activation required to replicate unimpaired gait with musculoskeletal impairments. These results could be used to develop hypotheses for designing future interventions. For example, targeting plantarflexor weakness may be advantageous for an individual who uses fewer synergies because of its control insensitivity and importance in gait[92,101,117]. In conclusion, the severity with which musculoskeletal impairments influence unimpaired gait is affected by altered control. Incorporating these factors into patient-specific models is pivotal for understanding functional limitations imposed by multifactorial impairments.

ACKNOWLEDGEMENTS

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Chapter 4. DOES CROUCH ALTER THE EFFECTS OF NEUROMUSCULAR IMPAIRMENTS ON GAIT?

Publication in review

Elijah C. Kuska
Department of Mechanical Engineering, University of Washington

Katherine M. Steele
Department of Mechanical Engineering, University of Washington

ABSTRACT

Cerebral palsy (CP) is a neurologic injury that impacts control of movement. Individuals with CP also often develop secondary impairments like weakness and contracture. Both altered motor control and secondary impairments influence how an individual walks after neurologic injury. However, understanding the complex interactions between and relative effects of these impairments makes analyzing and improving walking capacity in CP challenging. We used a sagittal-plane musculoskeletal model and neuromuscular control framework to simulate crouch and nondisabled gait. We perturbed each simulation by varying the number of synergies controlling each leg (altered control), and imposed weakness and contracture. A Bayesian Additive Regression Trees (BART) model was also used to parse the relative effects of each impairment on the muscle activations required for each gait pattern. By using these simulations to evaluate gait-pattern specific effects of neuromuscular impairments, we identified some advantages of crouch gait. For example, crouch tolerated 13% and 22% more plantarflexor weakness than nondisabled gait without and with altered control, respectively. Furthermore, BART demonstrated that plantarflexor weakness had twice the effect on total muscle activity required during nondisabled gait than crouch gait. However, crouch gait was also disadvantageous in the presence of vasti weakness: crouch gait increased the effects of vasti weakness on gait without and with altered control. These simulations highlight gait-pattern specific effects and interactions between neuromuscular impairments. Utilizing computational techniques to understand these effects can elicit advantages of gait deviations, providing insight into why individuals may select their gait pattern and possible interventions to improve energetics.

4.1 INTRODUCTION

Cerebral Palsy (CP) is a motor disorder caused by a brain injury at or near the time of birth[10]. This primary neurologic injury alters control (*i.e.*, increased co-activation and reduced capacity to selectively activate individual muscles), resulting in less complex control strategies during walking for individuals with CP than nondisabled (ND) peers[19,20]. Less complex control has been shown to be associated with worse function and treatment outcomes[21,22]. Additionally, individuals with CP often develop secondary, progressive impairments like weakness and contracture[24,90]. Interactions between neuromuscular impairments impart complex restrictions on gait that are difficult to elicit and understand experimentally[121], inhibiting treatment efficacy.

In silico techniques, like modeling, simulation, and machine learning (ML), offer a means to investigate interactions between neuromuscular impairments and parse their individual effects on gait[36,71]. Prior research primarily focused on identifying gait deviations caused by altered control [69] *or* weakness and contracture[43,93,122,123]. The few studies that investigated the effects of altered control *and* muscle morphology highlight how the two combinatorially impose greater restrictions on gait than either alone[70,121]. Investigating the interactions between neuromuscular impairments and their effects on gait could improve our understanding of the mechanisms inhibiting function in individuals with CP and bolster treatment efficacy.

The purpose of this study was to investigate the interactions between neuromuscular impairments and gait in CP. Specifically, we used modeling, simulation, and ML to examine how altered control, weakness, and contracture interact and impact crouch gait. We then compared our findings to those from ND gait to elicit how crouch gait can alter the effects of neuromuscular impairments, determining whether there are advantages to walking in crouch. We hypothesized that 1) similar to ND gait, altered control would exacerbate the effects of weakness

and contracture and increase the muscle activations required to walk in crouch but, 2) when compared to ND gait, crouch gait would reduce the effects of neuromuscular impairments, making crouch potentially advantageous with altered control *and* muscle morphology.

4.2 METHODS

To evaluate how altered control and neuromuscular impairments interact with crouch gait, we utilized a sagittal-plane musculoskeletal model[69,121] built in MapleSim (Maplesoft, Inc) (*Figure 7*). The model consisted of seven rigid body segments and nine kinematic degrees of freedom actuated by eight Hill-type musculotendinous units per leg: biarticular hamstring (HAM), gluteus maximus (GLU), iliopsoas (IP), rectus femoris (RF), vasti (VAS), gastrocnemius (GAS), soleus (SOL), and tibialis anterior (TA). Ground contact was simulated by modeling ten continuous Coulomb friction contact spheres placed in-line and equidistantly along each foot[124]. Dynamic equations of motion were exported from MapleSim into a direct collocation (DC) optimal control framework in MATLAB (Mathworks, Inc). Within this framework, we used an implicit Euler collocation scheme with a 51-point temporal grid[52] to optimize and simulate a half gait cycle; symmetry was assumed[69,125]. ADiGator[99] assisted with autonomic differentiation and MATLAB's interior-point optimizer (IPOPT)[100] solved each optimization. This model and framework were chosen because of their ability to rapidly elicit the effects of altered control[69,121].

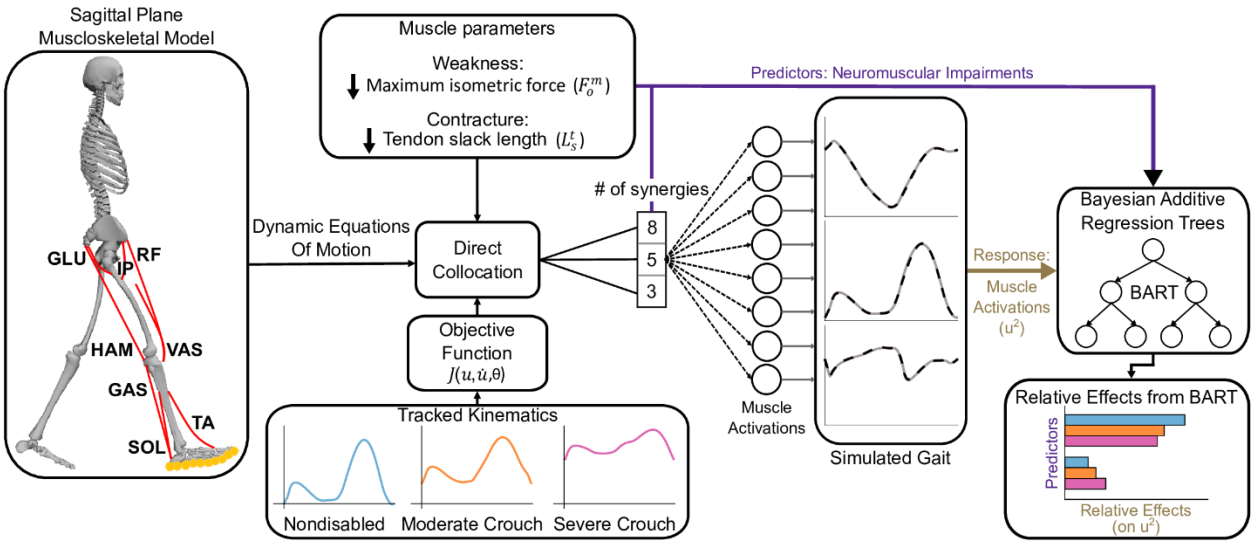

Figure 7: A sagittal-plane musculoskeletal model and neuromuscular simulation framework that tracked average nondisabled (ND) kinematics and moderate and severe crouch gait. The model contains nine degrees-of-freedom (pelvic tilt and translation, and right and left hip, knee, and ankle flexion) actuated by eight Hill-type musculotendinous units per leg. The objective function minimized deviations from tracked kinematics and the sum of muscle activations squared (u2). We perturbed each gait simulation with multi-modal neuromuscular impairments—altered control, weakness, and contracture—of varying severities. Altered control was simulated by reducing the number of fixed synergies controlling each leg, and weakness and contracture were simulated by reducing a muscle's maximum isometric force (F_o^m) and tendon slack length (L_s^t), respectively. A Bayesian Additive Regression Trees (BART) model then predicted resultant u2 from the simulated neuromuscular impairments for crouch and ND gait to evaluate the relative effects of each simulated neuromuscular impairment on the muscle activations required to maintain each gait pattern.

As direct collocation is sensitive to initial guesses, we analyzed variance in simulations from different initializations. We tested initial guess sensitivity with a null guess (*i.e.*, perfect state matching and zeroed controls) and a hot start (*i.e.*, a prior simulation used as the initial guess). Analyses revealed that kinematic variance from the different initial guesses were within a single standard deviation of experimentally reported ND sagittal-plane waveforms[103]. Thus, all reported results were generated by simulations initialized with a hot start to reduce convergence time.

Tracking simulations (minimizing deviations from desired kinematics) generated gait while minimizing muscle activations—the summation of all muscle activations squared (u^2)[52] —and an activation smoothing term:

$$J = \int_{t=0}^{t=t_f} \left(w_1 \sum_{j=1}^{9} (\Theta - \Theta_{tracked})^2 + w_2 \sum_{m=1}^{16} u_m^2 + w_3 \sum_{m=1}^{16} \dot{u}_m^2 \right) dt \quad (1)$$

Heavy weighting was placed on the tracking term (w_1 = 5000) to force the model to remain in the desired gait pattern. The additional u^2 (w_2) and derivative (w_3) weightings were set at 35 and 0.05, respectively[69]. To analyze crouch gait, we tracked average moderate and severe crouch patterns previously identified by k-means clustering from a database of 2000 children with CP[72]. Additionally, average ND kinematics were tracked [101] for comparison. To minimize the effects of walking speed, both CP and ND gait patterns were fixed to the same gait speed, whereafter, corresponding cadence and step-length were selected based on non-dimensional values in CP and ND age-matched individuals[126].

A modular neuromuscular controller simulated altered control. To alter control, we varied the number of muscle synergies—grouped patterns of muscle weightings theorized to reflect modular control—controlling each leg[69]. During walking, fewer synergies are required to explain the muscle excitations of individuals with CP than their ND peers[19,20]. We used sets of eight, five, and three synergies to simulate each gait cycle. Eight synergies, or individual muscle control (IMC), is commonly used in simulation studies[56,70]. Five and three synergies were selected to represent control of ND children and adults and children with CP, respectively[20,127–129]. Muscle excitations from each gait patterns' IMC simulation were decomposed using non-negative matrix factorization (NNMF)[104] to determine the synergy weights—fixed ratios of muscle activations—for five and three synergies. Synergy weights were fixed, thereby

constraining the controller to modulate only synergy activations. Synergy weights can vary when task demand is altered[130]; however, we chose to fix synergies, assuming gait-specific task demand did not change. Imposing neuromuscular impairments may change task demand, but our gait-specific sets of synergies represented the groups of muscles that would explain the greatest variance in simulated muscle activity and were the most robust to a broad range of neuromuscular impairments[121].

We simulated two secondary, progressive impairments common in individuals with CP: weakness and contracture[10]. Muscle weakness was simulated by reducing maximum isometric force (F_o^m)[43,122,131]. Contracture was simulated by reducing tendon slack length (L_s^t)[113,114,131] of the muscles commonly impacted in CP: HAM, GAS, SOL, and PFlex (GAS + SOL)[18,132].

Weakness and contracture were incrementally increased in severity from the original value, by 1% for weakness and 0.1% for contracture, until the simulation failed to generate each gait pattern. Weakness and contracture failure thresholds were defined when RMSE between the simulated and any tracked lower-extremity kinematic exceeded 2.5°, or the simulation did not converge after 2500 iterations; 2.5° reflects intra-gait cycle variance for children with CP[133]. Weakness and contracture thresholds demonstrate how robust a gait pattern is to weakness and contracture and, by varying the number of synergies, we elicit how control complexity alters those thresholds[121].

To evaluate the relative effect of each neuromuscular impairment on u^2, we developed a Bayesian Additive Regression Trees (BART) model[74]. BART is a sum-of-trees machine learning algorithm that uses Bayesian probability to prevent overfitting. We chose BART because of its predictive capabilities and ability to parse complex, nonlinear relationships like those between altered control, weakness, contracture, and gait[75,134,135]. We built a BART model for each gait

pattern where simulated neuromuscular impairment severities were input and BART predicted u^2. Hyperparameters for each BART model were tuned using 10-fold cross-validation[77] and we used pseudo-R^2 as measure of model quality. Accumulated local effect (ALE) plots were used to determine the relative effects of each simulated neuromuscular impairment on u^2 while accounting for all other variables in the model. BART model development and ALE plot generation were performed in R[136] using the 'bartMachineCV'[137] and 'ALEPlot' packages[138].

4.3 RESULTS

Simulations closely tracked ND and crouch kinematics but tracking errors and muscle activations (u^2) increased with crouch severity and fewer synergies (*Figure 8*). Average lower-extremity RMSE for ND, and moderate, and severe crouch gait with IMC were 0.15°, 0.28°, and 0.57°, respectively. With three synergy-control, average lower-extremity RMSE values increased to 0.32° for ND gait, 0.51° for moderate crouch, and 1.17° for severe crouch. With IMC, u^2 was 20% and 190% greater than ND gait, for moderate and severe crouch gait, respectively. Decreasing control complexity from IMC to three synergies, increased u^2 by 38% for ND gait, 32% for moderate crouch, and 19% for severe crouch.

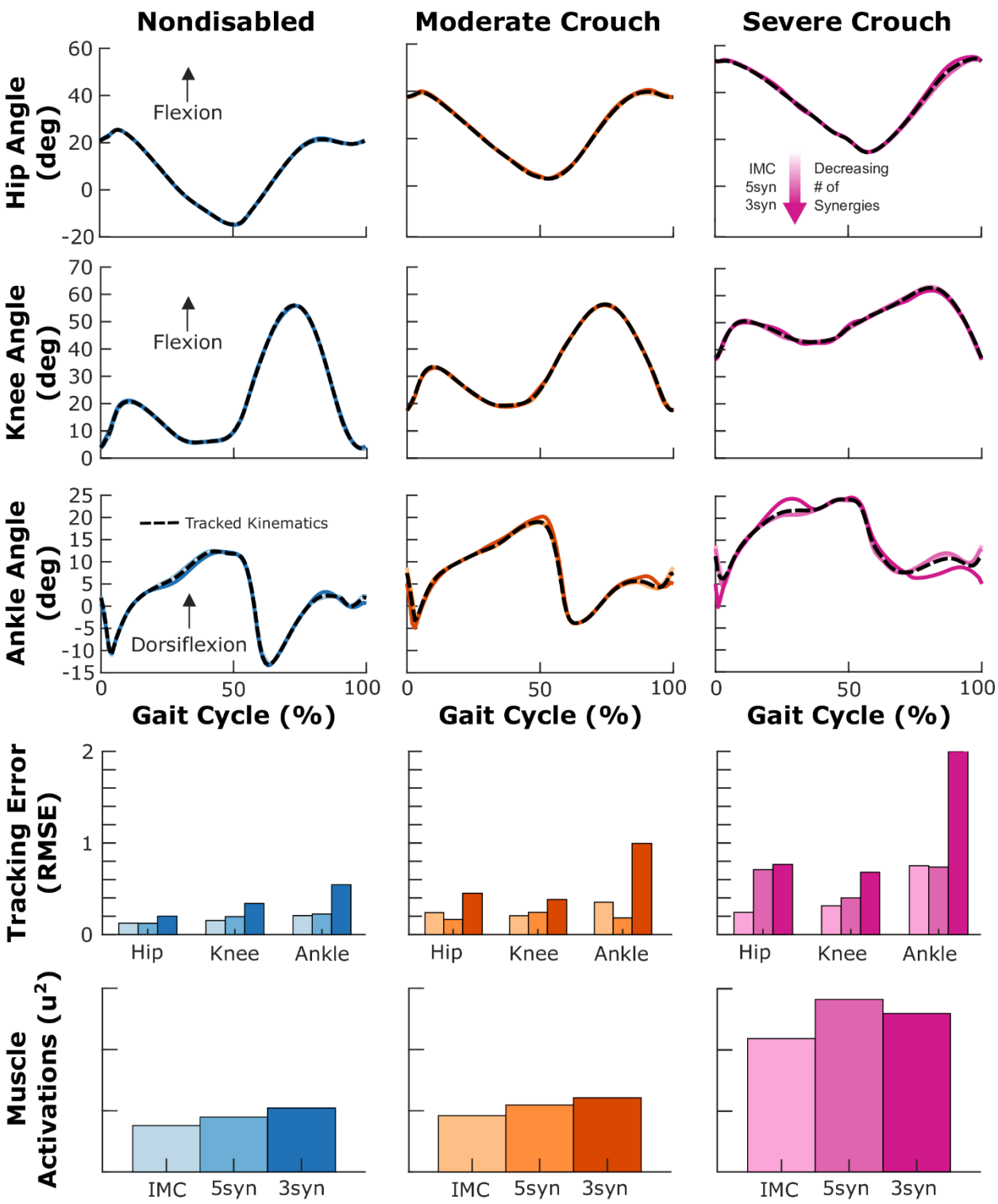

Figure 8: (Top) Simulated kinematics (right leg hip, knee, and ankle) for nondisabled gait and moderate and severe crouch with individual muscle control (IMC), five-synergy control, and three-synergy control. (Bottom) Root-mean squared errors (RMSE) between tracked kinematics and simulated gait at each lower-extremity joint and muscle activations (u^2) required to generate each gait pattern.

With IMC, ND and crouch gait tolerated nearly 100% reductions (*i.e.*, the muscle could be removed) in GLU, HAM, and GAS strength. ND gait tolerated the greatest reductions in VAS and HFL strength, but the least in PFlex strength. Moderate and severe crouch tolerated the most weakness in PFlex, and the least in the HFL and TA. As fewer synergies were used by the controller, muscles weakness thresholds decreased (*Figure 9 &Figure 10*). Average weakness threshold decreased from 92% (IMC) to 71% for ND gait when constrained to three-synergy control. Similarly, average weakness threshold for moderate and severe crouch decreased from 96% and 90% with IMC, to 68% and 49% with three-synergy control, respectively.

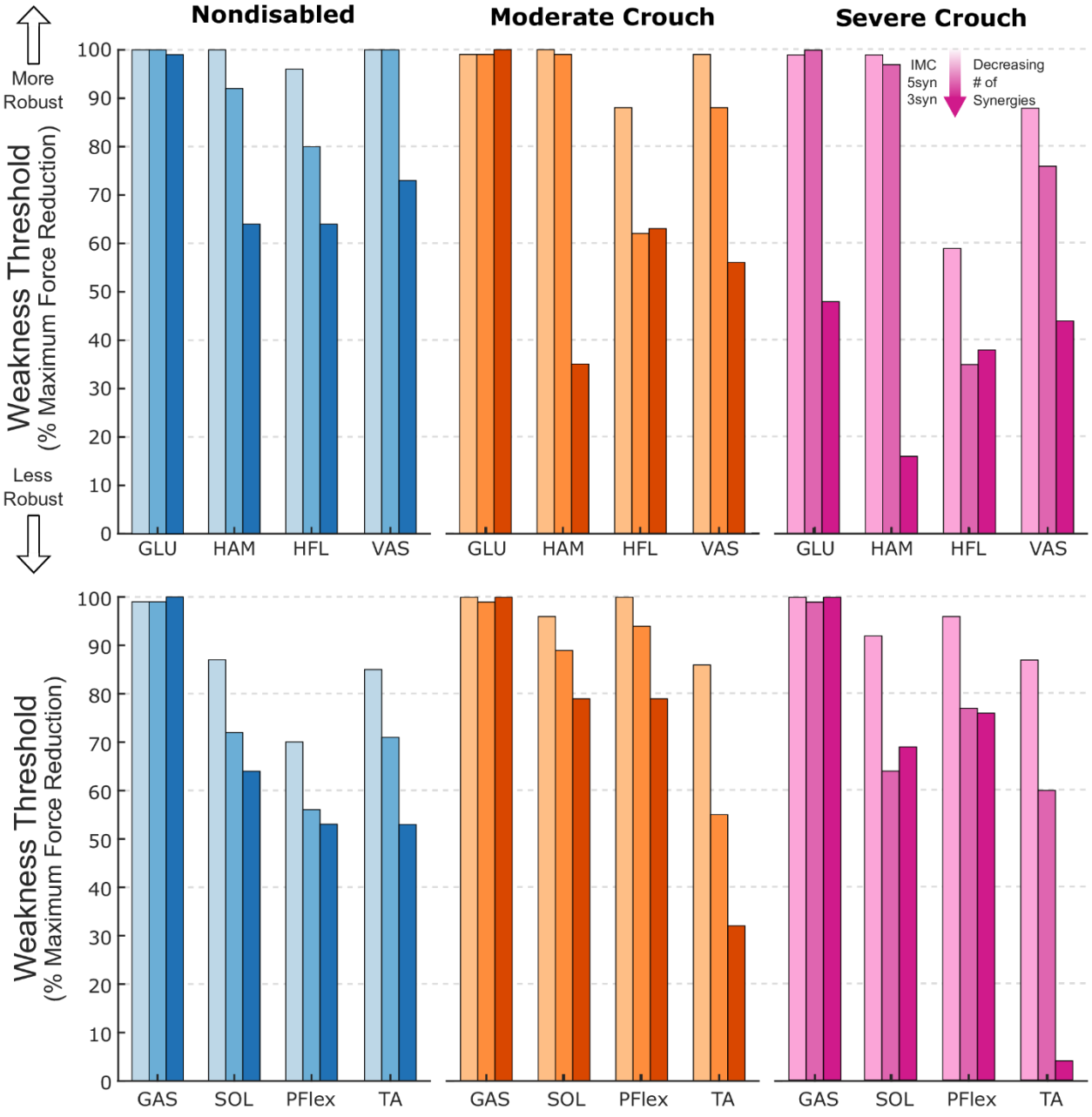

Figure 9: Weakness thresholds for nondisabled, moderate crouch, and severe crouch with individual muscle control (IMC), and five- and three-synergy control. A greater threshold indicates that the simulations were less sensitive, i.e., more robust, to weakness of that muscle. (Top) Hip and knee weakness thresholds. (Bottom) Ankle muscle weakness thresholds.

Crouch gait impacted the effect of altered control on weakness thresholds (*Figure 10*). Changing from IMC to five-synergy control only affected VAS weakness thresholds in moderate and severe crouch. Decreasing control complexity from IMC to five-synergy control did not

affect HAM weakness thresholds for moderate or severe crouch, but did for ND gait. Weakness thresholds (except GAS) decreased with altered control, but the magnitude was gait-pattern specific. For example, when changing from IMC to three-synergy control, VAS and HAM weakness thresholds decreased more for crouch than ND gait, but SOL weakness thresholds decreased more for ND than crouch gait.

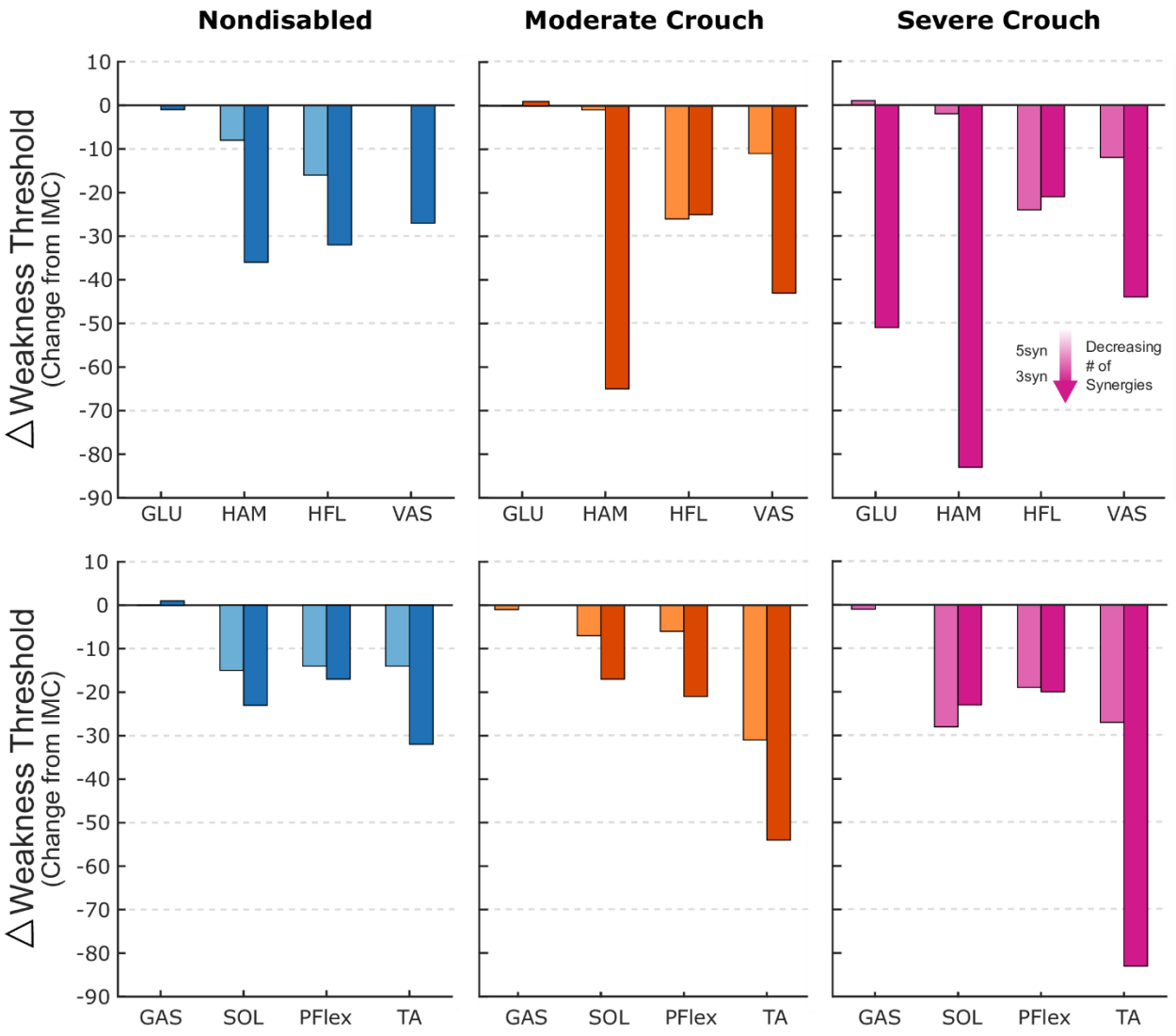

Figure 10: Change in weakness threshold when changing from IMC to five- and three-synergy control for nondisabled and moderate and severe crouch gait. Negative values indicate decreases in weakness threshold when decreasing control complexity (# of synergies) from IMC to five- or three-synergy control. Larger values indicate greater effects of altered control. (Top) Change in hip and knee muscle weakness thresholds. (Bottom) Change in ankle muscle weakness thresholds.

With IMC, HAM contracture threshold was greater for ND gait than crouch, but GAS contracture thresholds were greater for crouch than ND gait (*Figure 11*). Contracture thresholds decreased for all gait patterns when decreasing control complexity to five- and three-synergy control, but the magnitude was gait-pattern specific. For example, decreasing control complexity from IMC to three-synergy control had a larger effect on GAS contracture threshold in severe crouch. Contrastingly, the effect of altered control on HAM contracture threshold was smaller with more severe crouch, e.g., when changing from IMC to three-synergy control, HAM contracture threshold decreased more for ND than crouch gait.

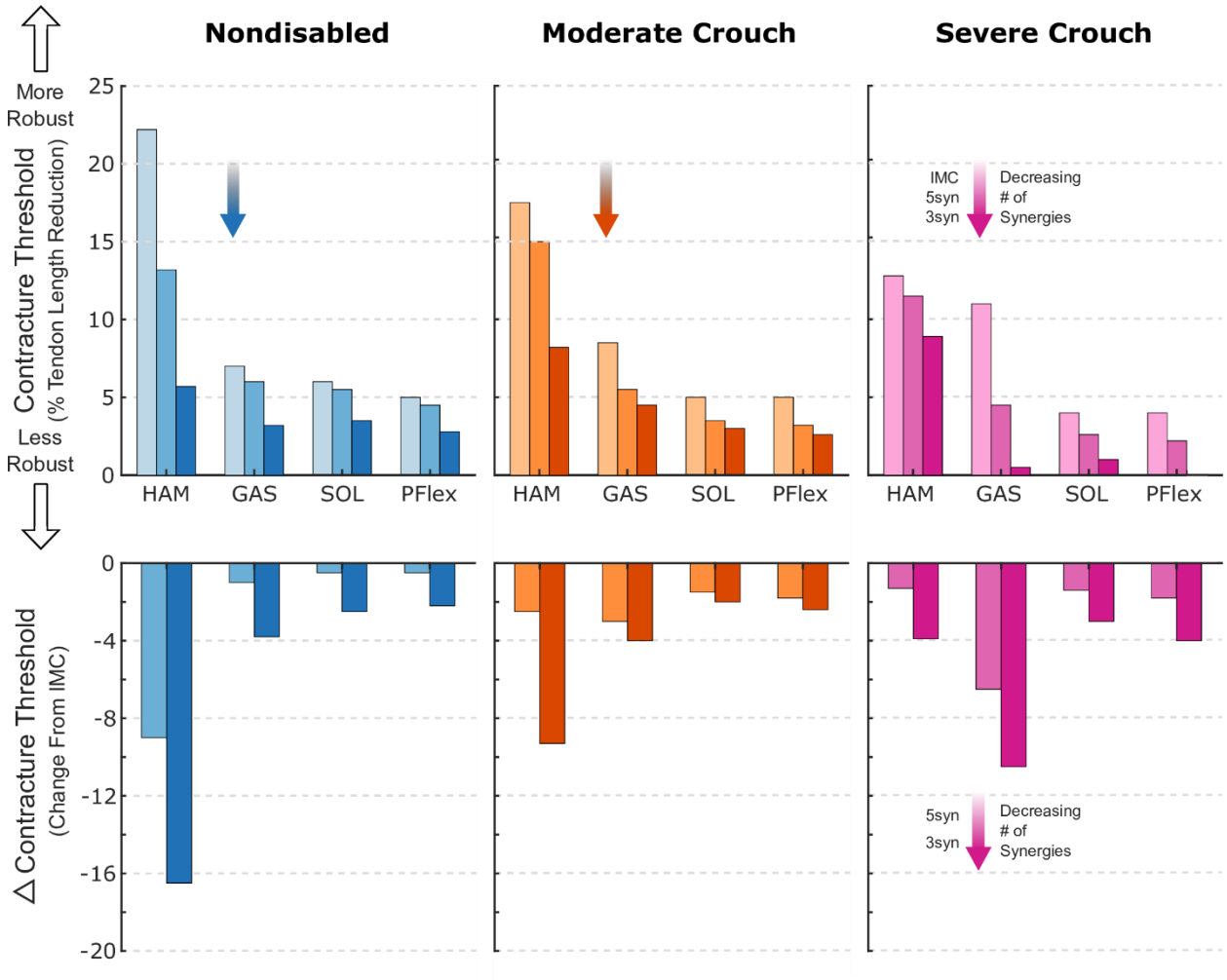

Figure 11: (Top) Contracture thresholds for nondisabled, and moderate and severe crouch with individual muscle control (IMC), and five- and three-synergy control. A greater contracture

threshold indicates that the simulations were less sensitive, i.e. more robust, to contracture of that muscle. (Bottom) Change in contracture threshold when changing from IMC to five- and three-synergy control for nondisabled and moderate and severe crouch gait. Negative values indicate decreases in contracture threshold when decreasing control complexity (# of synergies) from IMC to five- or three-synergy control. Larger values indicate greater effects of altered control.

Muscle activations required to generate gait (u^2) were accurately predicted by BART from the simulated neuromuscular impairments for all gait patterns (pseudo-R^2 > 0.97). Hamstring contracture had the largest effect on u^2 during ND gait and vasti weakness had the largest effect on u^2 during crouch (*Figure 12*). Plantarflexor contracture (except GAS) had a larger effect on u^2 during crouch when compared to ND gait and plantarflexor weakness had a larger effect on u^2 during ND gait when compared to crouch gait. The effect of control complexity (*i.e.*, number of synergies) on u^2 was larger with less severe crouch.

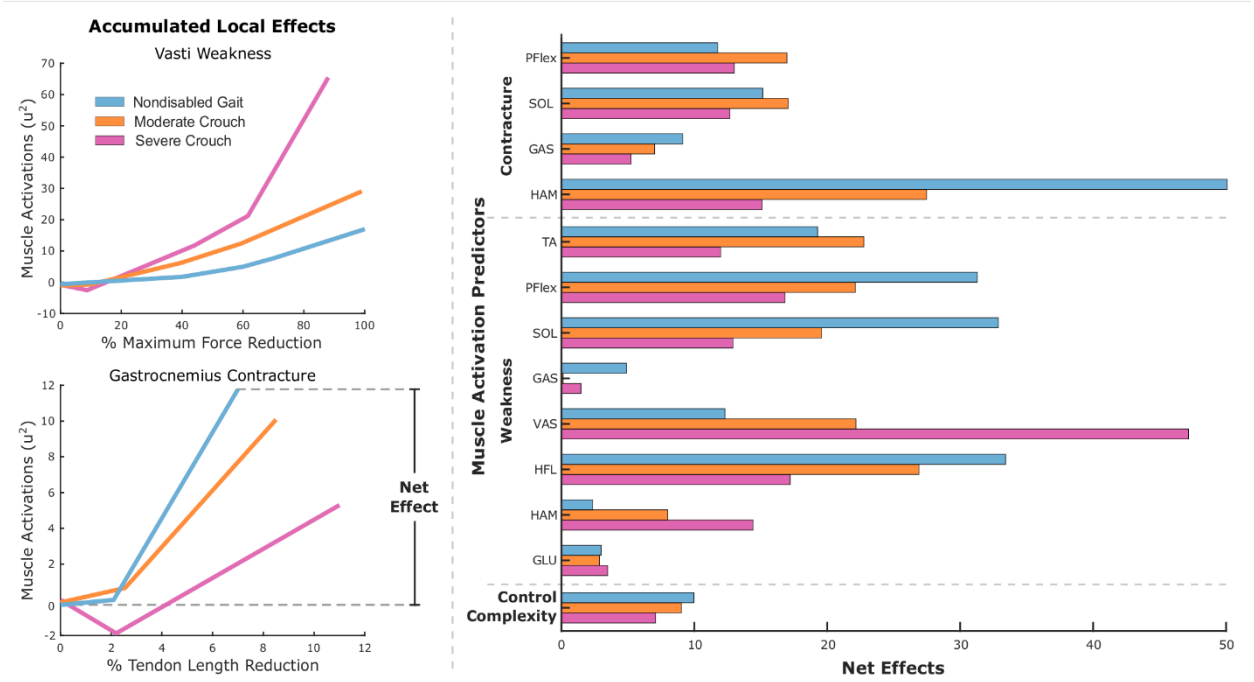

Figure 12: Accumulated local effect (ALE) plots (left) generated from Bayesian Additive Regression Trees (BART) models that predicted muscle activations required to generate each gait pattern (u^2) from simulated neuromuscular impairments. Relative, net effects of each neuromuscular impairment parsed by BART and estimated via ALE plots (right). Larger net

effects indicate neuromuscular impairments that had a larger effect on muscle activations during nondisabled and crouch gait.

4.4 DISCUSSION

Altered control made it more difficult to walk by 1) increasing the muscle activations required to generate gait and 2) decreasing the amount of weakness and contracture that could be tolerated. This supports our first hypothesis that altered control would make it more difficult to remain in crouch with and without secondary neuromuscular impairments. However, our second hypothesis that crouch gait, when compared to ND gait, would lessen the effect of neuromuscular impairments was only partially supported. We found that the effects of, and interactions between, neuromuscular impairments were gait-pattern specific, *i.e.*, the effects of neuromuscular impairments could be lessened *and* exacerbated by crouch gait, highlighting both advantages and disadvantages of walking in crouch. Thus, our results highlight 1) complex interactions between neuromuscular impairments and gait, emphasizing the importance of including altered control in future analyses of populations with neuromuscular impairments, and 2) the restricting effects of altered control on gait make it a promising, but not often addressed, target for interventions.

Walking in severe crouch necessitated a greater u^2 (*Figure 8*): a common proxy for energetic cost [52,53]. Thus, our findings align with the greater amounts of energy children with CP consume during walking when compared to ND peers[139,140]. The cause of increased energy consumption in CP still remains unclear[141], but our results suggest that crouch severity would correlate with elevated energetics. This contrasts with reported weak correlations between crouch severity and elevated energy consumption[142] but aligns with more recent studies that found that

altered gait kinematics, specifically landing in crouch, were associated with elevated walking in CP[76,79].

Fewer synergies (i.e., less complex control) made walking more difficult, creating larger deviations from tracked kinematics and increasing u^2 (*Figure 8*). Our prior studies found similar trends in ND gait[69,121], but we found a decrease in u^2 for severe crouch when changing from five- to three-synergy control (*Figure 8*). This was the result of our multi-term objective function: our three-synergy severe crouch simulation incurred a small decrease in u^2 for a large increase in ankle tracking error. However, the overall objective function value increased with decreasing control complexity, highlighting that less complex control increased the cost of walking[70]. Our findings, along with experimental improvements in walking energy with interventions that improved motor control[143,144], support that altered control contributes to elevated energy in CP[76].

Modeling and simulation enabled us to conduct these point-of-failure analyses, allowing us to highlight interactions between neuromuscular impairments and elicit advantages of different gait patterns. For example, without altered control, crouch gait was less robust to vasti weakness than ND gait (*Figure 9*). Thus, walking in crouch with vasti weakness would be disadvantageous, *i.e.*, "like driving with your parking brake on[145,146]." Then when reducing control complexity, we found that crouch gait increased the impact of altered control on vasti weakness, exacerbating the disadvantages of walking in crouch with knee extensor weakness (*Figure 10*). Conversely, crouch gait was more robust to plantarflexor weakness— the most prevalent secondary neuromuscular impairment in CP often targeted by interventions[18]—and decreased the effect of altered control on plantarflexor weakness. These results highlight 1) advantages of walking in crouch in the presence of neuromuscular impairments and 2) why

individuals may select to walk in crouch. Similar methods extended to patient-specific analyses could elicit potential advantages and causes of gait deviations for a given individual.

Using BART with synthetic data from simulation let us compare the relative effects of neuromuscular impairments on gait. BART results emphasized how the effects of neuromuscular impairments on gait are gait-pattern specific. Additionally, BART highlighted how vasti weakness in crouch, with or without altered control, is a primary driver of muscle activations (*Figure 12*). Targeting vasti weakness may be an effective intervention to reduce muscle demand, and perhaps energetics, for individuals with CP who walk in crouch. Conversely, GAS contracture had a relatively small effect on muscle activations during crouch gait, highlighting why corrective surgeries, like tendon lengthenings that impact the gastrocnemius, may not improve energetics[147]. Surprisingly, altered control had a small relative effect on u^2 compared to weakness and contracture. This contrasts the minimal changes in energetics in CP post-strength training and corrective surgeries[147–149], as well as retrospective causal analyses that identified selective and dynamic motor control as clinical measures associated with energetics in CP[76]. The relatively small net effect of control relative to weakness and contracture may be due to the range of values evaluated in this study. Weakness and contracture were simulated to failure, while only three levels of altered control were evaluated.

Interestingly, our simulations of ND and crouch gait did not reflect experimental observations of changes in control common in CP. Children with CP who walk in crouch typically demonstrate fewer synergies and a larger total variance accounted for by one synergy ($tVAF_1$) than ND peers[19,20,128,150]. In contrast, from our simulations, the $tVAF_1$ for ND gait and moderate and severe crouch were 0.63, 0.58, and 0.51 respectively. Thus, our simulations of crouch required more complex activation strategies when compared to ND gait. These findings

could stem from several causes: 1) our model is tuned to generate ND gait[69,121], 2) disabled individuals use different control strategies than their ND peers[54], 3) the altered demand of crouch dynamics are not enough to simplify control[151], and 4) constraints imposed by weakness and contracture force individuals with CP to operate in different, lower-dimensional control spaces. These all warrant further investigation but emphasize the importance of incorporating control complexity into simulations. Using muscle synergies to constrain simulations provides a method for 1) improving lower-dimensional control representation[152,153] typical in individuals with CP[20], 2) personalizing control based on an individual's EMG patterns[154], and 3) understanding the implications of altered control[69,70,121].

Our simulation were simplified representation of ND and crouch gait (*e.g.*, we used simplified muscle paths that likely influenced HAM contracture[121]). Additionally, we assumed symmetry because the added complexity of asymmetric gait was not necessary to investigate how crouch impacted the effect of altered control. We also only simulated average gait patterns meaning our results may not extend to patient-specific analyses. However, our results were gait-pattern specific and aligned with literature (e.g., landing in crouch increases cost of transport[79]), highlighting our methods potential applicability to patient-specific analyses. Additionally, our objective function minimized tracking errors and an energetic approximation—u^2 defined as the summation of all muscle activations squared[52,155]. However, what individuals with CP (and ND individuals) optimize during gait is still unknow and our results highlight advantages and possible rationale for why individuals with CP choose to walk in crouch.

By utilizing modeling and simulation with machine learning this study investigated interactions between altered control, weakness, and contracture and their complex effects on gait. We found that the interactions between, and the effects of, neuromuscular impairments were

gait-pattern specific. These results emphasize potential advantages of walking in gait patterns like crouch, but are dependent on an individual and their unique neuromuscular impairments. Additionally, the inclusion of altered control enabled us to find new and even greater advantages of crouch gait (*e.g.*, crouch was more robust than ND gait to hamstring contracture *only with* altered control). Thus, the inclusion of altered control can create quantitative *and even* qualitative differences in results. Future studies investigating populations with neurologic injuries should include altered control and consider utilizing *in silico* techniques to elicit advantages and possible rationale for gait deviations and to identify primary mechanisms affecting gait.

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Chapter 5. EVALUATE IMPROVEMNTS IN PREDICTIONS AND UNDERSTANDING OF ENERGETICS IN CP FROM SYNTHETIC DATA

Publication in review

Elijah C. Kuska
Department of Mechanical Engineering, University of Washington

Megan Ebers
Department of Mechanical Engineering, University of Washington

Michael H. Schwartz
Center for Gait & Motion Analysis, Gillette Children's Specialty Healthcare

Katherine M. Steele
Department of Mechanical Engineering, University of Washington

ABSTRACT

Individuals with cerebral palsy (CP) consume on average 2x more energy than their non-disabled peers during walking; the cause of elevated energetics in CP remains unknown inhibiting our ability to effectively intervene. Attempting to predict and understand biomechanical responses like energetics, even in non-disabled individuals, remains an ongoing challenge where prior success is limited by quality and quantity. Data is often noisy, erroneous, limited in quantity, and insufficient (*i.e.*, does not contain sufficient information to encode response). Addressing data limitations would necessitate greater amounts or more informative data, potentially exacerbating already existing burdens on patients, caregivers, and clinicians. Thus, the purpose of this study was to evaluate whether synthetic data can improve predictions and our understanding of elevated energetics in CP. We generated synthetic data by creating patient-specific simulations of walking using a database of 240 individuals with CP. Each individual's simulation were perturbed by simulated impairments, including altered motor control, weakness, and/or contracture, and simulation results were combined with clinical data to predict energetics in CP. To evaluate causal mechanisms influencing walking energetics, we also used a model augmented with an energetic discrepancy—the difference between predicted and measured energetics. Our energetic discrepancy was from a data-driven model utilizing age, weight, and speed, which allowed us to non-dimensionalize energetics and remove the influence of non-clinically addressable mechanisms contributing to energetics (e.g., anthropometrics). We then trained additional models on the discrepancy utilizing kinematics and clinical data. Models with simulated synthetic data, at best, marginally improved energetic predictions in CP when compared to models utilizing only clinical data. However, the augmented discrepancy models were able to accurately learn energetic discrepancies, improving modeling of energetics in CP.

Additionally, our discrepancy models elicited primary causal mechanisms elevating energetics in CP like kinematic positioning at initial contact and limited range of motion (*i.e.*, contracture). These findings emphasize the utility of *in silico* techniques to 1) better understand energetic in CP by creating data-driven methods to non-dimensionalize energetics that minimize assumptions about the effects of age, weight, and speed, and 2) generating synthetic data (e.g., gait simulations and discrepancies) that comes at little to no cost and can be used to elicit novel insights into primary causal mechanisms elevating energetics in CP.

5.1 INTRODUCTION

Cerebral palsy (CP) is one of the most common motor disabilities in childhood and is caused by a non-progressive brain injury at or near the time of birth[10–12]. The primary result of the non-progressive brain injury is altered coordination and control[10], however many individuals with CP often develop secondary impairments like weakness, contracture, and spasticity[24]. The complex interactions between these impairments make it difficult to understand their relative effects on gait limiting translation to treatment[121,156]; a challenge in CP further exacerbated by population heterogeneity[18]. For example, children with CP consume on average 2x more energy than their ND peers when walking[139,140,157,158]. Elevated energy consumption in CP persists post-intervention[147,149,159,160] making fatigue a common complaint among families and a top research priority identified by the CP community[161]. While impairments such as altered control and weakness have been suggested to affect energy consumption, we require new methodologies to identify the primary causal mechanisms elevating energy consumption in CP.

To analyze energy consumption, we commonly use indirect calorimetry which estimates energy consumption from measured respiratory gas exchange during a 6-minute walk test: an assumed standard time necessary for an individual to reach steadystate[162]. Previous studies

utilizing indirect calorimetry identified how quickly nondisabled (ND) individuals explore, optimize, and adapt during walking[65,163]. However, these findings, along with inherent assumptions within indirect calorimetry methodologies, may not translate to disabled populations limiting their applicability to CP. For example, 1) individuals with CP require additional time to reach steady-state energy consumption[164], 2) not all individuals with CP are able to complete the 6-minute walking bout necessary for energy consumption analyses and 3) individuals with CP have altered biology which may impact energy consumption processes[165–169]. If we could develop methods to accurately predict energetics for individuals with CP, this could not only help us understand the mechanisms contributing to increased energy consumption in CP, but also improve and expand access to energetic analyses to inform clinical care.

Accurately predicting physiological measures, like walking energy, remains an ongoing challenge in biomechanics. Even with robust methods like data-driven modeling—ideal for parsing non-linear, heterogeneous data[71] like that of energetics in CP—we remain unable to predict biomechanical responses in ND individuals[170]. Our inability to predict physiological measures likely stems from insufficient data: either in fidelity or volume. For example, previous studies analyzing ankle exoskeletons have shown that EMG and kinematic data do not fully predict, *i.e.*, encode, responses to exoskeletons for nondisabled adults[170], but the inclusion of *in vivo* muscle tendon dynamics can improve encoding of exoskeleton responses [171,172]. However, collecting additional data, especially that of *in vivo* measurements, increases already existent burdens on patients and caregivers. Thus, we require less resource intensive methods to gather sufficient data to better predict and understand physiological responses like walking energy.

Synthetic data—data that is artificially manufactured—is a less-resource intensive way to generate additional information to improve accuracy and robustness of data-driven models[173,174].

Two emergent methodologies in biomechanics for generating synthetic data are discrepancy modeling and simulation. A discrepancy is the difference between our modeled and measured (*i.e.*, true) response[175]. Historically, we minimize the discrepancy, report it in some form (*e.g.*, R^2 and RMSE), and then discard it. This is common practice in biomechanics with methods like inverse kinematics[45]—converting tracked markers to joint trajectories while minimizing the discrepancy between true and modeled marker trajectories—and prescribed motion simulations: minimizing the use of residual actuators (i.e., non-physiologically real forces and torques required to adjust for modelling discrepancies) while forcing a model to replicate kinematics and kinetics[39]. However, recently, discrepancies have been shown to be modellable and informative[170]. On the other hand, modeling and simulation enables rapid evaluation of causal relationships not possible experimentally. Thus far, synthetic data-generation from simulation is novel in biomechanical applications, but other synthetic data generation methods improved data-driven modeling of gait mechanics[80,173,174]. Thus, synthetic data has the potential to improve prediction and understanding of elevated energetics in CP which could then improve treatment efficacy of elevated energetics in CP.

The purpose of this study was to evaluate the ability of synthetic data to improve predictions and understanding of energetics in CP. We used a clinical database of walking energetics from children with CP and predicted energy consumption from solely clinical models utilizing only clinical data, including kinematics and clinical measures like strength, spasticity, and selective motor control, and models utilizing clinical and simulated synthetic data. To generate simulated synthetic data we perturbed simulations of each child's gait with multi-modal impairments. A Bayesian additive regression trees (BART) model was used to predict energetics (O^2 consumption) from clinical or clinical and synthetic data to evaluate the ability of simulated

synthetic data to improve predictions of energetics in CP. We also evaluated the energetic discrepancy between our measured energetics and predicted energetics from a BART model trained on age, weight, and speed (AWS). We then reconstruct that AWS energetic discrepancy with kinematics and clinical measures. The AWS discrepancy represents variance in energetics assumed to be mechanistic and clinically addressable. We hypothesized that synthetic data would improve prediction accuracy of energetics in CP and provide insight into causal mechanisms elevating energetics in CP, highlighting the utility of *in silico techniques (e.g.*, combining data-driven modeling, and physics-based modeling and simulation) and synthetic data to better understand biomechanical responses.

5.2 METHODS

We retrospectively analyzed de-identified data from children seen after the year 2000 at the Center for Gait and Motion Analysis at Gillette Children's Specialty Healthcare (*Figure 13*a). Only data from individuals meeting the following criteria were included: formally diagnosed with CP and classified as GMFCS I, II, or III[176], successfully completed 1) quantitative gait assessment containing bi-lateral lower-extremity kinematics during barefoot walking and 2) a 6-minute walk test with recorded oxygen consumption[162]. Individuals were excluded if they had a prior rectus femoris transfer, distal femoral extension osteotomy, or patellar tendon advance—surgical procedures that would alter the musculoskeletal physiology relative to our model. Additionally, we excluded any individuals with unilateral or bilateral equinus and whose gait assessment walking speed deviated by more than 10% from their 6-minute walk test speed during which oxygen consumption was recorded.

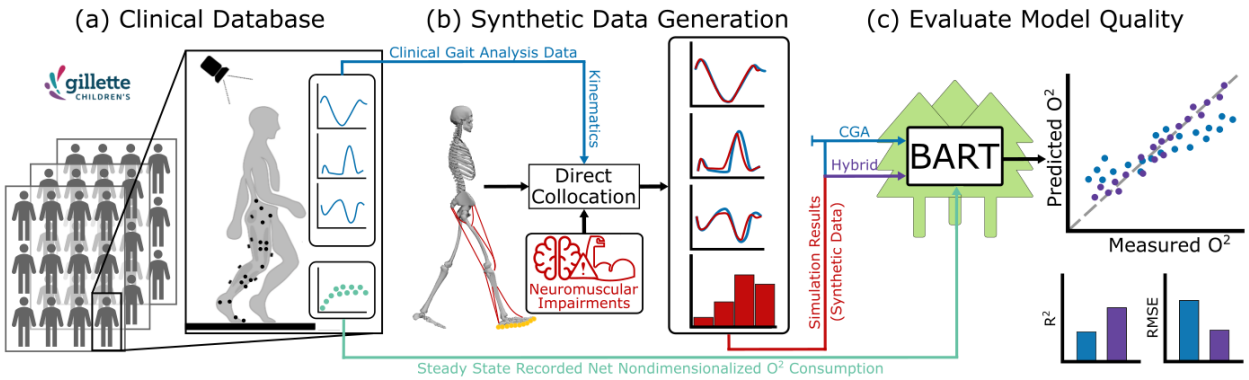

Figure 13: O^2 consumption prediction framework. a) a database of clinical gait analysis data for individuals with cerebral palsy (CP) was used to generate subject-specific simulations. Clinical data for each individual contained bi-lateral sagittal-plane kinematics during barefoot overground walking and clinical measures of strength, spasticity, selective motor control, and contracture. b) Each individual's left and right leg kinematics were tracked in a musculoskeletal simulation framework to generate subject-specific gait simulations. Subject-specific simulations were perturbed with impairments (altered control, weakness, and/or contracture) commonly reported in CP. c) Clinical data without and with (augmented) resultant simulated data were learned by a BART model to predict O^2 consumption in individuals with CP using 5-fold cross validation. Resultant clinical and augmented model quality were evaluated by pseudo-R^2 and RMSE and compared between models.

From each individual, we used anthropometrics (age, height, mass), kinematics, and clinical measures as predictors of steady-state oxygen consumption (O^2ml/s), herein referred to as O^2, extracted according to Schwartz (2007)[177]. For kinematics, gait speed and lower-extremity sagittal plane kinematic waveforms were condensed into 22 gait features—2 pelvis and 10 bi-laterally—identified to differentiate different gait patterns and influence energy consumption[79,178]. Clinical measures included an additional 38 predictors including bilateral range-of-motion at each lower extremity joint (e.g., hip internal and external rotation, and flexion, knee extension and flexion, and ankle plantarflexion), individual lower-extremity muscle strength and selective motor control (SMC[179]) for the hip and knee flexors and extensors, and ankle plantarflexors, and spasticity[180] for the hip flexors, rectus femoris, and plantarflexors; all clinical measures were measured by a trained physical therapist.

To investigate the utility of synthetic data for predicting and understanding elevated energetics in CP, we generated additional synthetic predictors for each individual from a previously developed physics-based modeling and neuromuscular simulation framework[69,121,156]. This framework was selected because of 1) its ability to rapidly evaluate the impacts of neuromuscular impairments on gait and 2) the minimal amount of data required to generate a gait simulation: only kinematics are required; ground contact is predicted. In short, the framework consists of a musculoskeletal model and neuromuscular simulation. The sagittal-plane musculoskeletal model consists of seven rigid body segments, totaling nine kinematics degrees-of-freedom, actuated by eight Hill-type musculotendinous units per leg[69]. Ground contact was simulated by ten continuous Coulomb friction[124] contact spheres placed equidistantly, in-line along each foot. This ground contact model does not work well for equinus gait patterns, which is why we excluded this gait pattern. To simulate gait, an implicit Euler direct collocation

optimal control framework generated a tracking simulation of a half gait cycle (*i.e.*, symmetry is assumed[69,125]) across a 51-node temporal where the model's equations of motion act as dynamic constraints[52]. The optimization identifies patterns of muscle excitations to minimize tracking errors and the summation of all muscle activations squared[52,69,121,156].

For each individual we generated a baseline—no simulated impairments—left and right leg gait simulation. We then generated subject-specific models of altered control with sets of five and three muscle synergies—grouped patterns of muscle activations thought to represent modular control[69]—from baseline simulations using NNMF[104]. Fewer synergies represent less complex control, *i.e.*, altered control, better representing control strategies of individuals with CP[19,20]. Sets of three and five synergies were selected and enforced because they represent ND and CP control complexities[20,127–129], and affect secondary impairments, gait, and energetics[121,156]. To generate the simulated synthetic data, we then perturbed each individual's left and right leg gait simulations by simulating impairments: altered control of varying severities with weakness and contracture (*Figure 13*b). Weakness and contracture were simulated by reducing a muscle's maximum isometric force and tendon slack length, respectively[43,114,122,131]. Weakness and contracture perturbations, *i.e.*, muscle(s) affected and severity of affect, were chosen based on 1) commonly affected muscles in CP[18,132] and 2) secondary impairments previously reported to affect gait simulation energetics[69,121,156]. In total, twelve different simulations—one baseline and eleven perturbed—were generated for each leg of each individual.

From each simulation, lower extremity tracking errors (RMEs) at each joint during stance and swing, total objective function value, total muscle activation squared, and resultant spatio-temporal parameters were extracted and used as synthetic predictors. Important to note, gait simulations were constrained to match the nondimensionalized spatio-temporal parameters of

each individual's gait pattern within 2% of reported values. By permitting slight variance in the simulations, we improve convergence while better representing intra-gait cycle variance in CP[133]. It should be noted that clinical and synthetic data were missing (not all simulations converged for every individual), thus we imputed missing data. Missing data was imputed in R[136] (2020) utilizing a Multivariate Imputation by Chained Equations (MICE[181]) package. Imputation was completed via predictive mean matching (PMM[182]) with five iterations, and three donors. PMM parameters were selected by holding out known data from a smaller non-missing dataset and selecting parameters that most accurately imputed missing data: best agreement between imputed and held-out data (R^2) and their distributions (Kolmogorov-Smirnov test).

We then constructed synthetic data features using principal component analyses (PCA). Feature engineering is a common practice in data-driven methods to reduce overfitting. It was necessary in this study to address an overfitting issue common in data-driven modeling where the number of predictors (m = 264) was greater than the number of datapoints for our response (n = 240)[71]. Specifically, we extracted the first three principal components and then projected each individual's simulated data into those PCA spaces reducing our simulated synthetic predictors from 264 to up to three per individual (PCA1-3). The first three principal components accounted for 43.4%, 55.2%, and 61.6% of the variance in the simulated synthetic data and were selected because they 1) optimized prediction accuracy while minimizing overfitting and 2) were minimally impacted by imputation methodological choices.

To predict elevated energetics in CP, we developed Bayesian additive regression trees (BART[74]) models (*Figure 13*c). In short, BART is an ensemble data-driven modeling method that utilizes Bayesian probability and a sum-of-trees to estimate non-parametric functions. BART was selected over other data-driven methods for several reasons: 1) ability to capture non-linear

direct, total, and interaction effects, 2) provides interpretability, 3) requires little-to-no tuning, 4) handles a large number of predictors of various types, and 5) outperforms other prediction methods without and with missing data[75,134,135]. To predict CP O^2, clinical and augmented BART models were built. Clinical BART models utilized 1) age, weight, and speed (AWS), 2) kinematics (Gait), clinical measures (CVars), or all three (Combined). Then three additional augmented BART models were built for each of the four clinical BART models where each model additionally included our synthetic data features PCA1, PCA1 and 2, or PCA1-3 as predictors. BART model development was performed in R[136] (2020) utilizing RStudio (RStudio, 2020) and the 'bartMachine' package[137]. Model quality was evaluated using 5-fold cross-validation where prediction accuracy was evaluated via pseudo-R^2 and RMSE between each model's predicted O^2 and true O^2.

To gain a better understanding of elevated energetics in CP, we analyzed the discrepancy (Δ)—the residuals or difference—between the predicted and held-out O^2 values during five-fold cross-validation from our AWS BART model. Discrepancies have been shown to be learnable and informative when predicting biomechanics responses[170,175]. The ΔO^2 from our AWS model is assumed to encapsulate the variance in CP O^2 consumption not attributed to anthropometrics (*i.e.*, non-clinically addressable), and thus, governed by clinically addressable mechanisms contributing to elevated energetics in CP (*Figure 14*). We reconstruct the discrepancy using three BART models: Gait, Cvars, and Gait+CVars. Discrepancy reconstruction accuracy will be compared between models via pseudo-R^2 and RMSE, whereafter, augmented discrepancy model predictions (AWS predictions + learned discrepancy from each BART model) will be compared via pseudo-R^2 and RMSE. Output from BART models reconstructing the AWS discrepancy were interpreted with Accumulated Local Effect (ALE) plots. ALE plots are used to visualize the

effect that each predictor had on the response while accounting for all other variables in the model[138]. Using ALE plots, we approximate the net effect of each variable as the difference between the max and mean of the response. ALE plot generation was completed in RStudio (RStudio, 2020) using the 'ALEPlot' package[138].

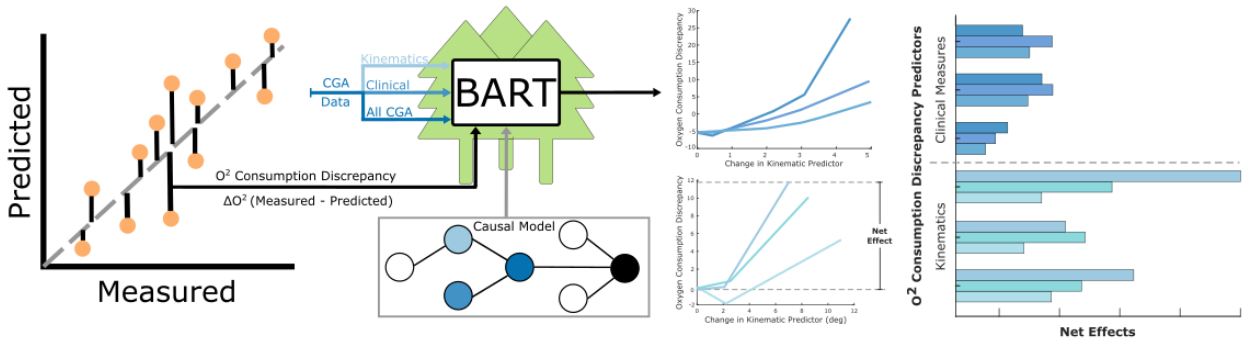

Figure 14: Framework for reconstructing O^2 consumption discrepancies (Δ) from our age, weight, and speed (AWS) BART model. ΔO^2 represent energetics in CP not attributed to anthropometrics and gait speed, i.e., mechanistic and clinically addressable measured driving elevated energetics in CP. ΔO^2 was reconstructed by three clinical data models: kinematics (Gait), clinical measures (CVars), and Gait + CVars. BART results were interpreted via local effect plots to visualize the change effect each change in each predictor had on the $\Delta O^2$and extract the net effect of each predictor (max – min of ALE plot). ALEs were plotted and analyzed and net effects were compared between all clinical predictors to identify the primary determinants of the ΔO^2.

5.3 RESULTS

Between our clinical models, AWS most accurately predicted CP O^2 consumption accounting for 64% (R^2) of the variance in the data (RMSE = 2.72 O^2ml/s). The combined model with kinematics, AWS, and clinical measures (Gait+AWS+Cvars) was the next most accurate accounting for 60% of the variance in the data (RMSE = 2.91 O^2ml/s) (*Figure 15*). CP O^2 consumption was most poorly predicted by Gait and Cvars. Cvars accounted for 9% of the variance in the O^2 data (RMSE = 4.43 O^2ml/s) and Gait accounted for only 2% of the variance in the O^2 consumption data (RMSE = 4.53 O^2ml/s).

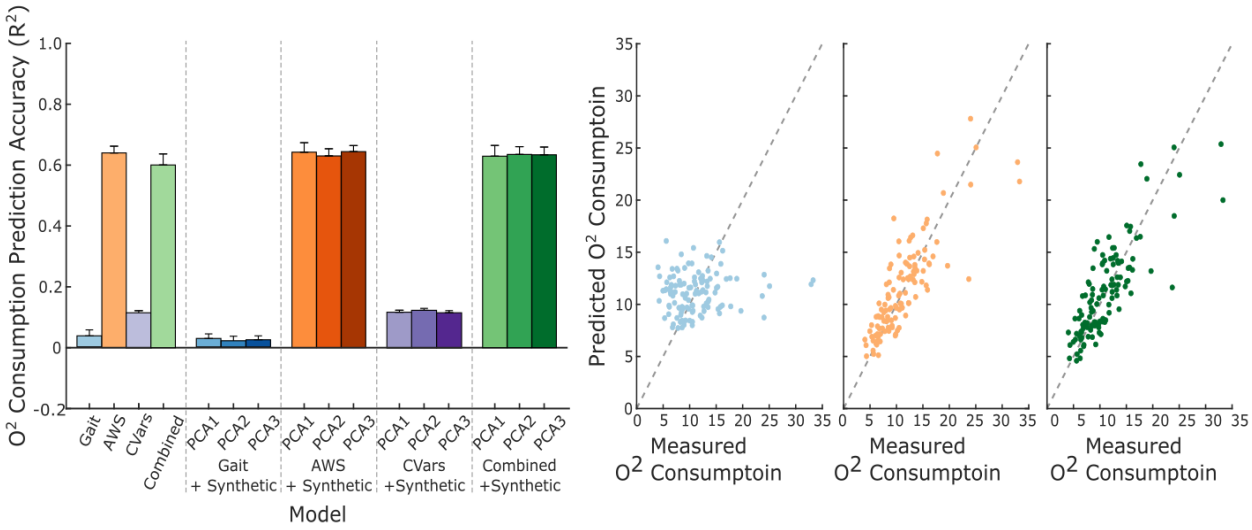

Figure 15: (Left) Prediction accuracy results (R2) from our 4 clinical models utilizing kinematics (Gait), age, weight, and speed (AWS), clinical measures (CVars), and the combination of all three (Combined). Three additional models were generated for each clinical model: PCA1, PCA1-2, and PCA1-3 which are hybrid models containing an additional one to three synthetic data features extracted from gait simulations generated for each individual. (Right) Depicts scatter plots of measured vs. predicted O2 consumption values predicted by Gait, AWS, or our 'kitchen sink' hybrid model containing all experimental, clinical, and synthetic data (Combined+PCA1-3). Gray dashed line indicates a perfect fit between measured and predicted data: predicted = measures.

Synthetic data from musculoskeletal simulations did not improve prediction accuracy compared to clinical models. Adding synthetic data to the Gait, AWS, and combined models resulted in a drop in R^2 and an increase in O^2 RMSE. The hybrid—containing both clinical and synthetic data—Cvars models were the only models to not see a change in prediction accuracy when including synthetic data features.

The O^2 consumption discrepancy—difference between true CP O^2 consumption and those predicted from the AWS model—was accurately reconstructed by all three models (*Figure 16*). The combined model (Gait + CVars) containing kinematic features and clinical measures most accurately reconstructed the discrepancy, accounting for 67% of the variance in the data (RMSE = 1.46 O^2ml/s). The CVars model least accurately reconstructed the ΔO^2 accounting for 52% of

the variance in the data (RMSE = 1.88 O^2ml/s). The Gait model accounted for 58% of the variance (RMSE = 1.81 O^2ml/s).

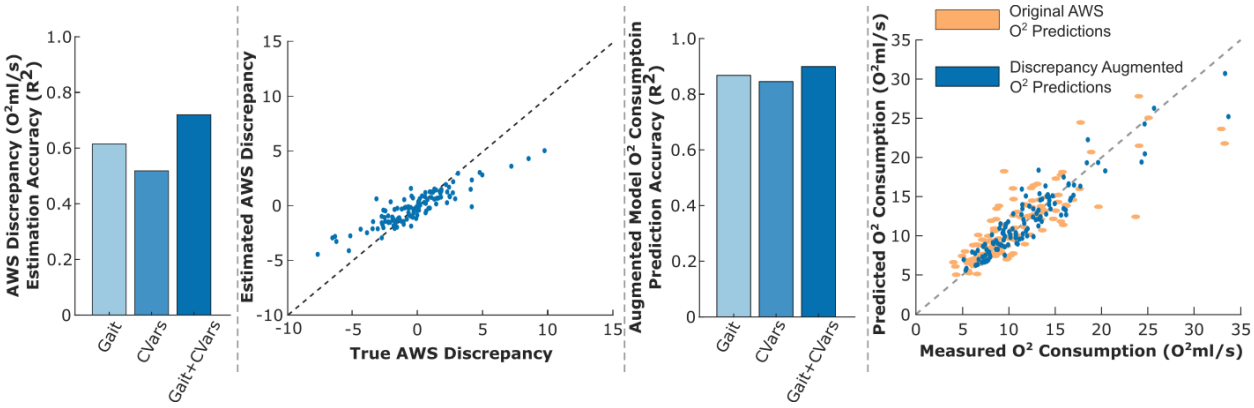

Figure 16: (Left) Reconstruction accuracy (R2) of the O2 discrepancy (Δ) between our age, weight, and speed (AWS) model and the true O2 consumption values. Δ between AWS model and true O2 consumption values represent the remaining variance in CP O2 data assumed to be caused by mechanisms that are clinically addressable. ΔO2 were reconstructed by models utilizing kinematic (Gait) features, clinical measures (CVars), or both (Gait+CVars). (Right) Reconstructed O2 consumption values by each augmented model. Rightmost scatter plot highlights Gait+Cvars reconstruction vs. the true AWS discrepancy. Gray dashed line indicates a perfect fit between measured and predicted data: predicted = measures.

All augmented discrepancy models (AWS prediction + Δ reconstruction) improved estimation of CP O^2 consumption (*Figure 16*). The combined model containing kinematic features and clinical measures (Gait + CVars) improved accuracy the most, with improvement in variance accounted for from 64% to 89% (RMSE = 1.52 O^2ml/s). The solely CVars augmented discrepancy model improved estimation the least accounting for an additional 19% of the variance in the data (RMSE = 1.89 O^2ml/s) while the Kinematic model improved estimation slightly more accounting for an additional 21% of the variance (RMSE = 1.79 O^2ml/s).

Of our kinematic and clinical variables, kinematic position at initial contact (IC) had the largest effect on the discrepancy (ΔO^2), with knee and hip flexion at IC being the largest effectors within that group (Figure 5). After kinematic position at IC, range of motion (*i.e.*, measures of contracture) had the largest effect on ΔO^2 with knee and hip flexion RoM being the

largest effectors within that group. Average effect size of spasticity and SMC predictors were similar, and larger than muscle strength. Within spasticity, spasticity of the rectus femoris and plantarflexors had the largest effect on ΔO^2. Within SMC, knee extensor and plantarflexor SMC had the largest effect on ΔO^2. Strength had the smallest effects size with knee flexor and extensor strength having the largest effect size within the strength group. Hip flexor and plantarflexor strength had the smallest effect sizes on ΔO^2 of any kinematic feature or clinical measures.

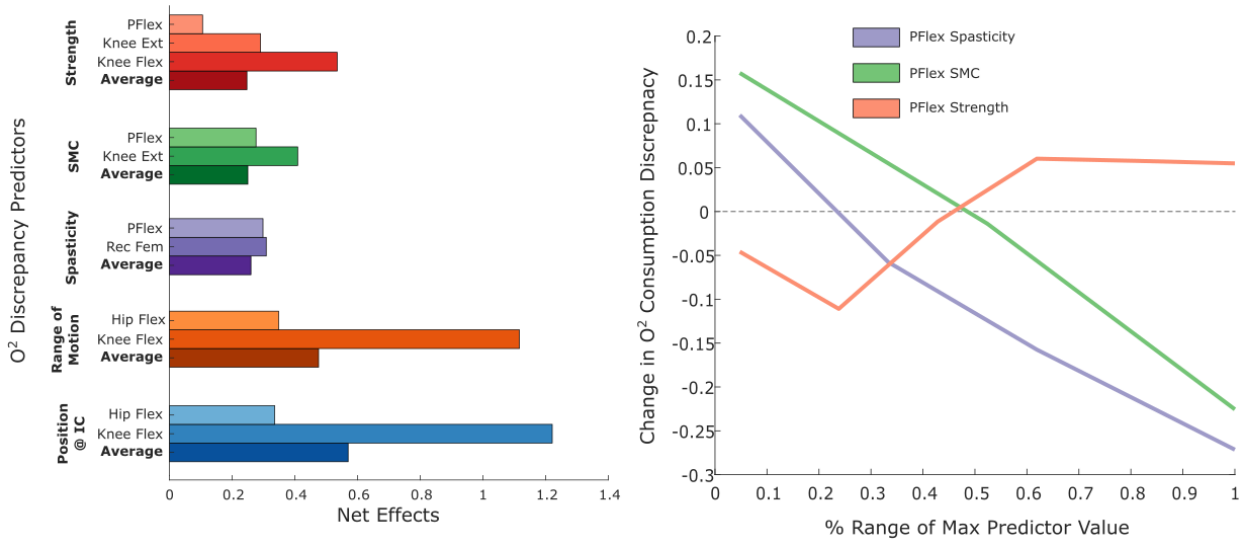

Figure 17: (Left) Grouped effect sizes of predictors of O2 consumption discrepancy (Δ) between age, weight, and speed (AWS) model predicting CP O2 consumption and true CP O2 consumption values. 42 predictors in total were grouped into kinematic position at initial contact (Position @ IC), range of motion measures—i.e., contracture—spasticity, selective motor control (SMC), and strength. Average values of each group are depicted in the darkest respective color with the two largest effectors in each group above them. (Right) Example of accumulated local effect (ALE) plot which depict change in predictor and its corresponding change in response. Negative values indicate where predictors accounted for overpredictions from the AWS model and positive values indicated where predictors accounted for underpredictions from the AWS model, thus, predictors that accounted for positive discrepancies (underpredictions by AWS) have positive values and would indicate kinematic features or clinical measures that are driving elevated energy consumption in CP.

5.4 DISCUSSION

In this study we investigated the ability of synthetic data—generated from gait simulations or discrepancies from data-driven modeling—to better predict and understand elevated energetics in CP. Our first hypothesis, that synthetic data generated from gait simulations would improve predictions of CP energetics was not supported as our hybrid models—data-driven models predicting energetics from clinical and synthetic data—did not outperform our purely clinical, data-driven models. However, by utilizing a discrepancy, specifically the difference between our experimentally measured CP O^2 consumption and that predicted from a data-driven model trained on AWS, we were able to elicit mechanisms elevating energetics in CP. Our results indicated that joint position at initial contact and measures of contracture were the largest predictors of ΔO^2. Thus, synthetic data, at least those pertaining to a discrepancy, have the ability to improve our understanding of biomechanical factors influencing gait energetics, highlighting the benefits of utilizing data-driven models for analyzing complex heterogenous data.

Within our clinical models containing either age, weight and mass (AWS), kinematic gait features, clinical measures, or all three combined, the AWS model best predicted CP O^2 consumption (*Figure 15*). While AWS are primarily correlates of energetics[183,184], it was surprising to find that combinatorial models containing additional kinematic and clinical variables performed worse than the AWS model. This is likely for two reason. First, all BART models had the same structure (*i.e.*, hyperparameters). This was to promote true comparisons between models. However, because the combinatorial models contained more observations, they were higher dimensional. This higher dimensionality was forcibly compressed, similar to neural nets with fewer nodes[185], when fed through the same dimensional space as the AWS model, limiting the additional data's expression. Second, prediction capacity of kinematic features and

clinical measures may be limited by inherent increased variance from noise, error, and inter-rater reliability[186,187]. To test this hypothesis, we reconstructed each model but allowed BART to optimize each models parameters ('bartMachineCV'). The combined model more accurately reconstructed the training data than the AWS model, but the AWS model still predicted held-out O^2 consumption values more accurately than any of the other clinical models indicating kinematic and clinical measures were overfitting the model.

The amount of variance accounted for by AWS in this small population of individuals with CP (64%) is similar to that from our entire clinical database of over 10,000 individuals with CP (70%). However, the amount of variance accounted for in energetics by age, weight, and speed in ND individuals is different: AWS can account for up to 88% of the data in ND individuals and up to 76-96% with just a linear regression model of weight[188]. A similar linear model accounts for much less in our CP data ($R^2 = 0.67$). Differences in prediction accuracy between CP and ND individuals with models of age, weight, and speed indicate that 1) normalization schemes typically used for analyzing energetics data may not be appropriate for CP[189–191] and 2) that the effects of age, weight, and speed may be more non-linear and complex in CP than ND. For example, mass may play a larger role in CP gait because of poor skeletal alignment, necessitating more active, *i.e.*, muscle driven, support[192] and thus energy to support their body weight. Future studies should investigate these ideas and consider normalization schemes that are more data-driven to limit assumptions while removing influences of non-mechanistic variables.

Clinical models utilizing synthetic data features from simulated gait cycles, at most, marginally improved prediction accuracy from their respective purely clinical models (*Figure 15*). The use of synthetic data and feature engineering is not new to data-driven modelling in

biomechanics [71], but the use of physics-based modeling and simulation to generate synthetic data to improve predictions of complex dynamic systems responses, is novel. Reduced prediction accuracy also likely stemmed from the same 'forced compression' and overfitting as are combined clinical model as BART models hypertuned to each synthetic dataset improved reconstruction but hindered prediction accuracy. Two prior studies using similar methods in biomechanics[49,80] were able to 1) identify responders and non-responders to gastrocnemius lengthening and 2) improve prediction of kinematics from simulated IMU data. Both methods used more complex models then our sagittal-plane musculoskeletal model[69]. Thus, increased model complexity and accuracy may improve encoding of information in synthetic simulated data and has been shown to improve simulation of metabolic cost in disabled populations[70,193]. However, the increased demand required to personalize models both in the clinic and computationally, limit their applicability to heterogenous populations like CP, especially when most analyses operate with large-scale retrospective data. Future studies should examine if other simulated data better compliments clinical data. For example, rather than tracking errors, predicted kinetics and MTU dynamics[194] may better encode information relative to energetics.

Models utilizing kinematics and clinical measures were able to accurately capture O^2 consumption discrepancies (ΔO^2), and more importantly, resultant augmented discrepancy models (AWS predictions + Δ reconstruction) more accurately modeled O^2 consumption in CP, demonstrating that energetic discrepancies in CP, when normalized by age, weight, and speed, are learnable and informative (*Figure 16*). Kinematics, specifically kinematic positions at IC, were better predictors of ΔO^2 than clinical measures which aligns with previous findings that summary gait metrics (GDI) and landing in crouch-increase hip, knee, and ankle dorsiflexion were primary predictors of energetics in CP[76,79]. However, from an optimal control standpoint,

we would assume that individual select their gait pattern and spatiotemporal parameters to minimize some objective function, meaning that kinematics may not represent the underlying causal mechanisms elevating energy consumption in CP. It remains unclear what individuals with CP optimize, but the influence of clinical measures on ΔO^2 may better represent mechanist causes of elevated energy consumption in CP.

Within the clinical measures, limited range of motion specifical at the hip and knee were the largest predictors of ΔO^2 (*Figure 17*). We are one of the first studies to discover that measures of contracture may be primarily driving elevated energetics in CP. The influence of contracture on energetics, and if ameliorating contracture would reduce energetics, is difficult to parse clinically. A common intervention to ameliorate contracture in CP are muscle lengthenings/tendon transfers. However, it is difficult to identify if these surgeries improve energetics because they are typically done within a single event multi-level surgery (SEMLs), require long recovery times, and are prone to overcorrection inducing complex changes[28] in gait and function like calcaneal gait, crouch, and recurrent equinus deformities[27,49,195,196]. Future studies should investigate if less invasive interventions, like serial casting, can effectively improve range of motion and energy.

Measures of motor control–spasticity and SMC–were the next largest predictor of ΔO^2. This finding similarly aligns with a prior retrospective investigation of mechanisms elevating energetics in CP[76] and with purported effects of altered motor control on gait and energetics[121]. However, it contrasts prior findings that reductions in spasticity did not improve energetics, but rather, aging was the primary effector reducing energetics in CP after selective dorsal rhizotomy[160]. Additionally, in line with prior findings, strength was the weakest prediction of energetics in CP. Within strength, strength of the knee extensors contributed the most to ΔO^2

likely stemming from individuals walking in crouch which increases demand on the knee extensors[46,47,156]. It is interesting to note that plantarflexor strength was one of the smallest predictors of the AWS O^2 consumption discrepancy. Plantarflexor weakness is the most prevalent secondary impairment in CP[18] and this may further indicate that altered gait patterns in CP are selected to reduce the necessity and energetic demand of the plantarflexors, i.e., advantageously or optimally[156].

It is important to note that our study looked at a small sample of individuals with CP, primarily excluding individuals who walk in equinus. This was because our framework struggled to simulate equinus gait likely because of high-contact stiffnesses, however, we wished to avoid tuning our model so that the true causal analyses could be used to inform data-driven modeling. Our small sample size likely hinders translation of findings to the larger, heterogenous CP population but this warrants further investigation. Additionally, we only analyzed CP individuals. If the difference between CP and ND individuals is desired, future investigations should include ND individuals as well, but be cautious, as predictors like weight and speed may have different influences between populations. Lastly, it should be noted that our augmented discrepancy models were not able to fully reconstruct O^2 consumption, *i.e.*, no augmented model was able to reach an $R^2 = 1$. This indicates data insufficiency[81]. This warrants future investigation but could indicate that the data required to predict energetics was not present in the model and that response data (i.e., O^2 consumption) may be erroneous or noisy.

This study utilized synthetic data generated from physics-based modeling and simulation and discrepancies to better predict and understand O2 consumption in CP. Data-driven models (BART) using synthetic data generated from perturbed gait simulations, at best, marginally improved prediction accuracy of O^2 consumption. However, synthetic data generated from

discrepancy modeling provided additional insight into mechanisms elevating energetics in CP: increased flexion at initial contact and limited range of motion were the two largest drivers of elevated O^2 consumption. Thus, augmented data-driven models trained on synthetic data provide a unique method, one novel in biomechanics applications, to better understand and probe walking energetics and biomechanical responses.

Chapter 6. CONCLUSION

6.1 SUMMARY

This dissertation presents foundational knowledge for understanding gait in CP that, without *in silico* techniques, would be extremely difficult or impossible to elicit, supporting the development and implementation of *in silico* informed interventions. We developed a unique musculoskeletal modeling and neuromuscular simulation framework that can be used to 1) understand the interactions between, and the relative effects of, multi-modal neuromuscular impairments on gait and 2) can rapidly and economically generate informative synthetic data that can be used train and improve data-driven models of gait. The modeling and simulation framework will be made freely-available for researchers and clinicians to download and use at SIMTK and GitHub.

The first objective of this dissertation was to elicit the effects of altered motor control and its interactions with secondary musculoskeletal impairments like weakness and contracture. In Chapter 3, we utilized a musculoskeletal model and neuromuscular simulation framework to simulate ND gait with multi-modal neuromuscular impairments (*i.e.*, altered control, weakness, and contracture) of varying severities. Results indicated that altered control—the primary impairment in CP—exacerbates restrictions and demands imposed by secondary impairments making it more difficult and energetically costly to maintain ND gait. Future investigations and clinical applications should consider incorporating modeling and simulation to better understand and elicit interactions between neuromuscular impairments which could inform treatment

precedence (e.g., our results highlighted that ameliorating altered control could create larger improvements in function than if weakness and contracture were treated).

The second objective of this dissertation was to investigate if the interactions between neuromuscular impairments were gait specific. In Chapter 4, we extended our prior modeling and simulation methods to also simulate crouch gait of varying severities and compared results between crouch and ND gait. Results indicated that interactions between neuromuscular impairments are gait-specific, highlighting advantages of walking in crouch—thought to be inefficient and disadvantageous—in the presence of neuromuscular impairments. Thus, *in silico* investigations can elicit underlying rationale for why an individual may select their gait pattern which is an important consideration to better understand patient-specific function and priorities.

The third objective of this dissertation, also presented in Chapter 4, was to elicit the relative effects of neuromuscular impairments on gait. We input our simulated gait patterns, neuromuscular impairments, and resultant energetics into a data-driven model (BART). Data-driven modeling successfully parsed and identified the individual effects of each simulated impairment on gait energetics and how they varied with gait pattern. Thus, data-driven modeling successfully identified neuromuscular impairments that would have the largest impact on energetics. Future investigations and clinical practice should consider utilizing data-driven modeling to parse the complex, heterogenous effects of neuromuscular impairments on gait and identify impairments that should take treatment precedence to effectively reduce energetics in CP.

The final objective of this dissertation was to investigate if and how synthetic data could improve predictions and understanding of energetic cost in CP; a mystery shrouded by population heterogeneity and a lack of understanding of the causal mechanisms that elevate energy

consumption in CP. In Chapter 5, we generated synthetic data in two ways: first, by simulating and perturbing gait simulations of a cohort of individuals with CP and second, by utilizing discrepancy modeling. We used clinical gait data with or without our simulated synthetic data to predict energy consumption during walking. The integration of synthetic data marginally improved prediction of CP walking energetics, however, with the use of discrepancy modeling, we improved data-driven modeling of CP walking energetics and elicited novel mechanisms elevating energetics in CP (e.g., contracture may be a primary mechanism elevating energetics). Thus, *in silico* techniques have the potential to increase data efficiency (*i.e.*, reduce data collection burdens on patients, caregivers, and clinicians) by bolstering the amount of information from each collection, while simultaneously enhancing our understanding of gait in CP. These techniques can work cooperatively to more rapidly and effectively identify causal mechanisms affecting gait in CP.

6.2 FUTURE WORK

The work completed and presented in this dissertation constructs a strong foundation for *in silico*-informed interventions by improving our understanding of gait in CP via novel and creative use of computational techniques. For example, the results of our studies provide rationale for how modeling, simulation, and machine learning can enable investigation and accurate prediction of poorly understood or difficult/impossible to measure quantities in CP. Thus, this dissertation improves our understanding of gait in CP through *in silico* investigations and catalyzes future investigations to better understand gait and poor treatment efficacy in CP, such as:

- What impact do patient-specific musculoskeletal parameters have on perturbed gait simulations, resultant interactions, and direct effects of neuromuscular impairments?

- How do additional secondary impairments common in CP (*e.g.*, spasticity, bone deformities) interact with altered control, weakness, and contracture?
- Do optimal control assumptions, specifically objective functions and their different forms, affect interactions and direct effects of neuromuscular impairments in gait simulations?
- How could our population-based perturbation methods be personalized for individual-specific gait and enable the identification of patient-specific mechanisms affecting gait, energetics, and limiting treatment efficacy?
- What synthetic data generated from modeling and simulation, if any, is pertinent to improving data-driven modeling of energetics in CP and ND individuals?
- What minimum set (*i.e.*, sparse sensing) of clinical and complementary synthetic data is needed for energy consumption predictions and how well does the sparse set generalize to other populations: within and outside of CP?

The findings in this dissertation and their implications open avenues for exciting future work utilizing *in silico* techniques to better understand gait and complement experimentation and clinical practice. The following section outlines additional areas of future research that can further support *in silico* informed interventions aiming to improve treatment efficacy for disabled individuals with gait pathologies:

- **Do predictive simulations reveal different interactions between, and direct effects of, multi-modal neuromuscular impairments?** Most investigations of gait are inverse methods, meaning by construction they utilize and reproduce previously defined kinematics and/or kinetics, which limits our ability to analyze how novel gait patterns are generated from multi-modal neuromuscular impairments. Future studies should utilize a

modeling and simulation framework (similar to ours presented in Chapters 3 and 4) within a predictive direct collocation optimal control framework to better understand 1) how novel gait patterns arise from multi-modal neuromuscular impairments and 2) if interactions between and direct effects of neuromuscular impairments are different if gait is permitted to adapt more readily.

- **How does altered control affect device interaction and optimization?** Device prescription efficacy for disabled individuals with neurologic injuries is highly variable; likely because current prescription methods do not fully consider an individual's control. A better understanding of how patient-specific control alters device interaction and adaptation could improve the consistency of prescription success. Future studies should simulate different gait patterns, neuromuscular impairments, and a multitude of assistive devices to investigate 1) how neuromuscular impairments interact with devices and their design parameters and 2) how altered control inhibits effective device prescription.
- **What do disabled individuals optimize during gait?** We currently do not understand what disabled individuals prioritize during gait. Future investigations should leverage modeling and simulation to elicit, like Chapter 4, advantages of gait deviations in disabled populations by 1) modeling, simulating, and perturbing gait with neuromuscular impairments and 2) utilizing inverse optimal control to identify primary optimality criteria that needs to be included in objective functions to better represent *in vivo* neuromuscular control. Whereafter, creative and novel experiments could perturb individuals to confirm *in silico* findings and understand how altered objective functions influence gait exploration and adaptation.

- **Do novel rehabilitation methods improve motor control in individuals with CP?** Current treatments in CP primarily target secondary impairments (e.g., weakness, contracture, and spasticity) and do not improve motor control despite it being the primary impairment in CP. Our findings from Chapters 3 and 4 indicate that altered control exacerbates restrictions imposed by secondary impairments indicating that treatments that target control are needed. Recent interventions combining multi-modal techniques (e.g., biofeedback, audio-visual feedback, and transcutaneous spinal cord stimulation) have indicated improvements in motor control in small cohorts of individuals with CP. These methodologies warrant further investigation to understand their capacity to improve altered motor control in CP.
- **What simulated synthetic data improves prediction accuracy of biomechanics responses?** Poor prediction accuracy of biomechanical responses like that of exoskeleton walking and energetics of disabled individuals remains an ongoing challenge. A single prior study highlighted the utility of modeling and simulation to better predict joint kinematics from IMU data, but it remains unclear if the utility of synthetic data extends beyond kinematics and IMUs. Future studies should investigate the utility of simulated *in vivo* data like kinetics, muscle-tendon dynamics, and individual muscle forces to complement existing experimental and clinical datasets and improve predictions and understanding of biomechanical responses.
- **Can synthetic data be used to improve the predictions of intervention outcomes?** Poor prediction accuracy of intervention outcomes remains difficult even in ND individuals (*e.g.*, it is challenging to predict exoskeleton response). Future studies should, similar to Chapter 5, investigate if the use of synthetic data (*e.g.*, simulated muscle-

tendon dynamics) can improve prediction accuracy of, or elicit why we remain unable to accurately predict, individual responses such as changes in gait with an exoskeleton or outcomes of a strength training program.

- **How can we better understand adaptation to novel devices? Does incomplete adaptation affect our ability to design, create, test, investigate, and implement effective assistive devices?** Methodologies for quantifying if, how, and when an individual has adapted to a device are limited which may underlie our ability to effectively prescribe assistive devices. Future investigations should consider utilizing muscle synergies as a way to model and investigate personalized control (Chapter 4) and adaptation, likely revealing that prior investigations of novel devices provided insufficient exploration, training, and adaptation time leading to suboptimal device usage and poor outcomes.

The goal of the presented work in this dissertation and the future investigations above aim to improve mobility for individuals with CP and has implications for individuals with neuromuscular disabilities. Walking is the most common form of mobility and enables exploration and interaction with one's world. Individuals with neurologic injuries and gait pathologies, like in CP, have altered mobility, limiting exploration and interaction which affects development. By utilizing *in silico* techniques like modeling, simulation, and machine learning we can rapidly investigate hypotheses that are either difficult or impossible to measure experimentally which can then inform experimentation and treatments, creating a greater understanding of gait in CP, all with the aim to improve mobility and quality of life for individuals with cerebral palsy.

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APPENDIX A

MUSCULOTENDINOUS UNIT (MTU) MODEL MODIFICATIONS TO PERMIT CONTRACTURE SIMULATIONS (CHAPTER 3)

Muscle contracture is defined as limited joint movement that results from high passive muscle force and is common in cerebral palsy (Graham et al., 2016).

Traditionally, a Hill-type muscle model consisting of a passive, contractile, ballistic, and series element is used for simulation of muscle-tendon dynamics. Within the Hill-type muscle model there are several ways to increase passive force generation (e.g., alter optimal fiber length, tendon slack length, tendon stiffness, and stiffness of the parallel elastic element). We wanted to simulate muscle contracture and chose to increase passive muscle forces through reductions in tendon slack length because of this methods prevalence in literature, experimental evidence, and greater interpretability.

Within the Hill-type muscle model, tendon slack length reductions simulate contracture by increasing tendon elongation ($L_{se} - \mathrm{L}_{\mathrm{s}}^{\mathrm{t}}$) and strain ($(L_{se} - \mathrm{L}_{\mathrm{s}}^{\mathrm{t}})/\mathrm{L}_{\mathrm{s}}^{\mathrm{t}}$), thus, increasing passive tendon force (F_{se}):

$$F_{se} = F_{max} * ((L_{se} - \mathrm{L}_{\mathrm{s}}^{\mathrm{t}})/\mathrm{L}_{\mathrm{s}}^{\mathrm{t}}). \quad (1)$$

However, the original musculotendinous unit (MTU) model used by Geyer & Herr (2010) did not permit simulation of contracture through reductions in tendon slack length. The text below outlines 1) why the original model could not be used for contracture simulations, and 2) the changes we made to correct this. For simplicity and uniformity, the original model will be denoted by ‘unalt’ (unaltered) and modeling changes will be denoted by ‘alt’ (altered).

The original MTU model used by Geyer & Herr (2010) is mathematically constructed (*i.e.*, not constrained to predefined muscle paths nor anchored by attachment points) such that changes in MTU length (ΔL_{MTU}^{unalt}) are defined as deviations from a reference joint angle (θ_{ref}^{unalt}):

$$\Delta L_{MTU}^{unalt} = \theta - \theta_{ref}^{unalt}, \quad (2)$$

where MTU length *at* the refence angle is equal to the sum of tendon slack length (L_{ts}^{unalt}) and optimal fiber length (L_{mo}^{unalt}):

$$L_{MTU}^{unalt}\left(\theta_{ref}^{unalt}\right) = L_{ts}^{unalt} + L_{mo}^{unalt}. \quad (3)$$

MTU length for any kinematic orientation (θ) can then be defined as the summation of tendon slack length, optimal fiber length, and change in MTU length:

$$L_{MTU}^{unalt}(\theta) = L_{ts}^{unalt} + L_{mo}^{unalt} + \Delta L_{MTU}^{unalt}(\theta). \quad (4)$$

Because the Geyer & Herr (2010) MTU model was mathematically constructed and tuned to simulate unimpaired gait, it is inappropriate for simulations of non-normative gait and some musculoskeletal impairments. For example, reductions in tendon slack length (i.e., muscle contracture, in the present work) have little to no effect on passive tendon force (a defining characteristic of contracture). To demonstrate this, we plug an altered tendon slack length (L_{ts}^{alt}) into equation (4) and obtain:

$$L_{MTU}^{alt}(\theta) = L_{ts}^{alt} + L_{mo}^{unalt} + \Delta L_{MTU}^{unalt}(\theta). \quad (5)$$

From (5), we see that altered tendon slack length alters MTU length. This is problematic in the Geyer & Herr (2010) model because the change in MTU length is proportional to the change in tendon slack length,

$$\mathrm{L}_{\mathrm{ts}}^{\mathrm{unalt}} - \mathrm{L}_{\mathrm{ts}}^{\mathrm{alt}} = \mathrm{L}_{\mathrm{MTU}}^{\mathrm{unalt}} - \mathrm{L}_{\mathrm{MTU}}^{\mathrm{alt}}, \quad (6)$$

And proportional to the change in tendon length (L_{se}),

$$\mathrm{L}_{se}^{\mathrm{unalt}} - \mathrm{L}_{se}^{\mathrm{alt}} = \mathrm{L}_{\mathrm{MTU}}^{\mathrm{unalt}} - \mathrm{L}_{\mathrm{MTU}}^{\mathrm{alt}}. \quad (7)$$

This prevents altered tendon slack length from changing tendon elongation:

$$\mathrm{L}_{se}^{\mathrm{alt}} - \mathrm{L}_{\mathrm{ts}}^{\mathrm{alt}} = \mathrm{L}_{se}^{\mathrm{unalt}} - \mathrm{L}_{\mathrm{ts}}^{\mathrm{unalt}}. \quad (8)$$

Thus, altered tendon slack length has little to no effect on passive tendon force:

$$\mathrm{F}_{se}^{alt} \approx \mathrm{F}_{se}^{unalt}. \quad (9)$$

To permit tendon elongation for contracture modeling, we constrain the MTU length to be a function of *unaltered parameters* (4) and plug the *altered* tendon slack lengths into (1) to calculate the new values for tendon elongation, strain, and passive force ($\mathrm{F}_{se}^{contracture}$):

$$\mathrm{F}_{se}^{contracture} = F_{max} * ((\mathrm{L}_{se}^{\mathrm{unalt}} - \mathrm{L}_{\mathrm{ts}}^{\mathrm{alt}})/\mathrm{L}_{\mathrm{ts}}^{\mathrm{alt}}). \quad (10)$$

This is similar to fixing a spring's length but altering its resting length. The original model would alter both the spring's length and its resting length.

In summary, we constrained MTU length to be a function of unaltered MTU properties and kinematics, preventing MTU length from scaling with reductions in tendon slack length, and

then use the reduced tendon slack length to increase tendon elongation and strain, thus, increasing passive tendon force (*Figure 18*). We were then able to be simulate contracture by reducing tendon slack length.

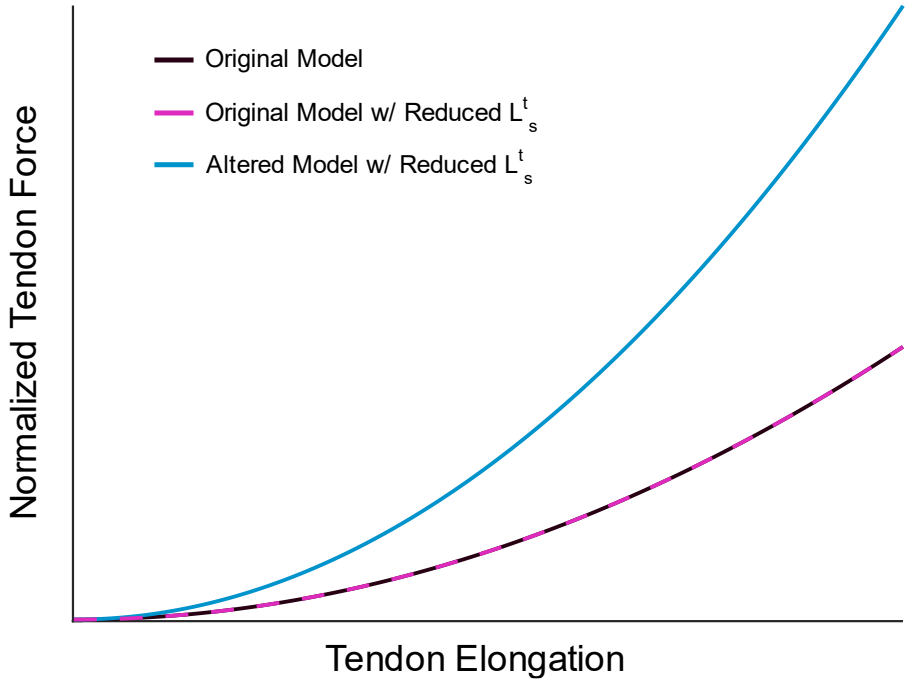

Figure 18: Tendon Elongation Versus Normalized Tendon Force for Three MTU Models. The original model's (black - Geyer and Herr 2010) MTU length scaled with changes in tendon slack length (L^t_s) preventing changes in tendon elongation. For the original model, altered tendon slack length had no impact on tendon elongation and little to no effect on passive tendon force (pink line). Muscle dynamics were modified to use both unaltered and altered tendon slack lengths. The altered model increased tendon elongation and passive tendon force (blue), enabling simulation of contracture with reductions in tendon slack length.

Baseline Simulation Kinetics and Muscle Activations

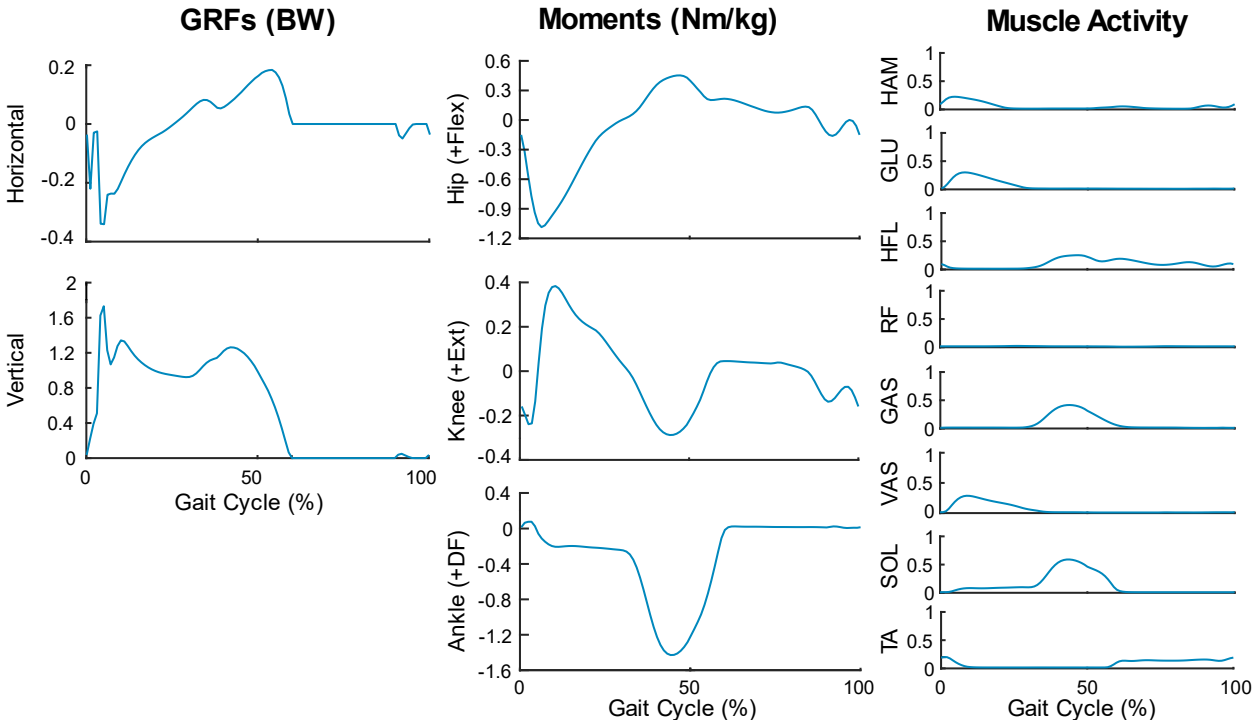

Figure 19: Ground reaction forces (GRFs), kinetics, and muscle activity of simulated walking. Baseline – no weakness or contracture and individual muscle control – walking simulation ground reaction forces (left), joint moments (middle), and muscle activity (right) from the right leg for a single gait cycle. Positive horizontal (top) ground reaction forces are anterior. Positive hip (top) moments are flexion, positive knee (middle) moments are extension, and positive ankle (bottom) moments are dorsiflexion. Muscle activity (from top to bottom) for the bi-articular hamstring (HAM), gluteus maximus (GLU), iliopsoas (HFL), rectus femoris (RF), gastrocnemius (GAS), vasti (VAS), soleus (SOL), and tibial anterior (TA). For additional reference data we refer the reader to Mehrabi et al (2019).

Methods to Create Accurate Tracking Simulations

To improve the accuracy of the tracking simulations we 1) tuned the tracked pelvic translations and 2) applied a large weight to the tracking term. Tracked kinematics were average kinematics from a previous study of nondisabled individuals (Liu et al., 2008). However, because of our model's anthropometrics, the averaged pelvic translations were inaccurate. Thus, an initial simulation's pelvic translations were appended to the tracked joint angles, creating accurate

nondisabled kinematics for our framework to track. Thereafter, the large tracking weight dissuaded the optimization from deviating from the desired gait pattern.