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# DYNAMIC SIMULATION AND ANALYSIS OF GAIT MODIFICATION FOR TREATING KNEE OSTEOARTHRITIS

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# DYNAMIC SIMULATION AND ANALYSIS OF GAIT MODIFICATION FOR TREATING KNEE OSTEOARTHRITIS

A Dissertation Presented for the

Doctor of Philosophy

Degree

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Taylor Elyse Schlotman

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# DEDICATION

*To my parents*

Tim and Carolynne Schlotman

*My sisters*

Alyssa Schlotman and Jordan Black

*And my grandparents*

MacArthur and Ruby “Granniebird” Martin

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# ABSTRACT

Roughly 47.5 million people in the US have a disability, with 8.6 million reporting arthritis as their main cause of disability, making arthritis the leading cause of physical disability. With decreased mortality rates and a large, aging baby boomer generation, there will be more adults living with chronic musculoskeletal conditions causing disabilities that limit walking. Since walking ability is directly related to an individual's independence at home and in the community, losing this ability is a major setback for patients with arthritis. Knee osteoarthritis (OA) is the most prevalent form of arthritis affecting approximately 27 million adults and accounts for over 55% of all arthritis-related hospital admissions. OA is a highly painful disease with treatments limited to pain management. However, gait modification has recently shown promise as an early intervention treatment strategy to slow disease progression. Thus, the objective of this dissertation is to investigate subject-specific gait modifications to minimize joint loads for treating patients with knee OA.

The first study in this dissertation relies heavily on the development of subject-specific musculoskeletal models to analyze muscle forces and joint contact loads during toe-in gait modification for subjects with knee OA. This study will generate muscle-actuated, dynamic simulations to estimate muscle forces and internal joint contact loads during gait. The results of this study will aid in the advancement of gait modification as a treatment strategy for knee OA. The last two studies will employ machine learning and optimization techniques— specifically, forward sequential feature selection and surrogate-based optimization— to evaluate toe-in gait modification and improve its efficacy for use as a treatment strategy for knee OA. The goal will be to develop testable subject-specific gait modification patterns that reduce joint loads.

The use of both dynamic simulations and data mining techniques provides a unique approach to investigating the relationship between joint biomechanics and muscle function and joint contact loads with respect to gait modification. This approach has the potential to gain much needed insight into the underlying mechanism of gait modification and help advance research to create subject-specific gait modification patterns for treating knee OA in the future.

# PREFACE

This dissertation presents three studies conducted using dynamic simulations, machine learning, and optimization to develop more effective gait modification strategies for treating knee osteoarthritis (OA). Each chapter is written as a separate technical paper, and an overview of the goals and methods employed in each study are provided. Note, the first specific aim of this dissertation was conducted as two separate studies, thus this chapter is written as two technical papers. Additionally, each chapter provides an in-depth discussion of the study findings and how these findings were used to answer the questions posed. Chapter 6 provides a summary of the results and conclusions of the three studies in the dissertation and delineates how they were applied to develop better gait modification strategies for advancing the treatment of knee OA.

# TABLE OF CONTENTS


Chapter One: Introduction ..... 1
1.1 Project Summary ..... 1
1.2 Research Significance ..... 2
1.3 Research Innovation ..... 3
1.4 Research Methods ..... 3
1.4.1 Specific AIM 1: Determine muscle forces and corresponding joint loads before and after gait modification. ..... 4
1.4.2 Specific AIM 2: Identify the significant features of gait that have the potential to decrease joint loads. ..... 4
1.4.3 Specific AIM 3: Design testable subject-specific gait modifications to minimize knee joint loads using surrogate-based optimization. ..... 5
Chapter Two: Literature Review ..... 6
2.1 Background and Foundation ..... 6
2.1.1 Knee Osteoarthritis: A Significant Clinical Problem ..... 6
2.1.2 Gait Modification: A Promising Solution ..... 9
2.1.3 Musculoskeletal Modeling and Analysis of Human Movement ..... 10
2.1.4 OpenSim: Musculoskeletal Modeling Software ..... 12
Chapter Three: Specific AIM 1- ..... 14
Toe-in gait uniformly reduces harmful joint contact loads while muscle force modifications are not consistent for patients with knee OA ..... 14
3.1 Developing subject-specific musculoskeletal models and simulations ..... 14
3.1.1 Preparing the Model ..... 14
3.1.2 Scaling the Model ..... 15
3.1.3 Inverse Kinematics ..... 17
3.1.4 Inverse Dynamics ..... 18
3.1.5 Static Optimization ..... 18
3.2 Muscle force modification strategies are not consistent for gait retraining to reduce the knee adduction moment in individuals with knee osteoarthritis ..... 20
3.2.1 Introduction ..... 20
3.2.2 Methods ..... 21
3.2.3 Results ..... 24
3.2.4 Discussion ..... 24
3.3 Toe-in gait reduces the varus-valgus contact moment in individuals with knee osteoarthritis ..... 27
3.3.1 Introduction ..... 27
3.3.2 Methods ..... 29
3.3.3 Results ..... 32
3.3.4 Discussion ..... 33

Chapter Four: Specific AIM 2- .......... 37
Selected significant features of gait with the greatest potential to decrease joint loads for patients with knee OA .......... 37
4.1 Significant Features of Toe-in Gait with Potential to Lower Knee Joint Contact Loads of Individuals with Knee Osteoarthritis: Implications for Improving Gait Modifications .......... 37
4.1.1 Introduction .......... 37
4.1.2 Methods .......... 39
4.1.3 Results .......... 43
4.1.4 Discussion .......... 44
Chapter Five: Specific AIM 3- .......... 48
Testable gait modifications to minimize knee joint loads designed using surrogate-based optimization .......... 48
5.1 Using surrogate-based optimization to design testable gait modification strategies with potential to minimize varus-valgus contact moment .......... 48
5.1.1 Introduction .......... 48
5.1.2 Methods .......... 50
5.1.3 Results .......... 55
5.1.4 Discussion .......... 55
Chapter Six: Final Conclusions and Recommendations .......... 59
6.1 Significance of Research .......... 59
6.2 Research Innovation .......... 60
6.3 Fundamental Contributions .......... 61
6.4 Summary .......... 63
6.5 Glossary .......... 64
6.5 List of Acronyms .......... 69
List of References .......... 70
Appendix .......... 80
Vita .......... 109

# LIST OF TABLES

**Table 1:** Subject Demographics. ........................................................................................81

**Table 2:** Percent change in mean muscle force between baseline and toe-in gait for all subjects. Though muscle forces changed within subjects, there were no muscle force modifications across all subjects. ........................................................................................................84

**Table 3:** Summary of knee joint contact load means and standard deviations (SD) for normal and toe-in gait at the location in stance of the first peak net external knee adduction moment (KAM). The most relevant second-order approximation to the actual medial and lateral contact forces associated with knee OA is the positive varus-valgus contact moment (VVCM), responsible for unbalanced compression of the medial compartment of the knee joint with respect to the lateral compartment. At the post-training session, the VVCM significantly decreased ($p<0.01$) during toe-in gait, while all other knee joint contact loads showed no significant change ($p>0.09$). These results were retained at the follow-up session. The VCCM significantly decreased ($p<0.01$) during toe-in gait, while all other knee joint contact loads showed no significant change ($p>0.06$).......................................90

**Table 4:** Subject demographics for 10 subjects with medial compartment knee OA. Subjects were trained to walk with a 7° decrease in foot progression angle to achieve toe-in gait modification. With toe-in gait, subjects decreased knee adduction moment (KAM) by 20%, varus-valgus contact moment (VVCM) by 14.7% at post-training, VVCM by 16.7% at follow-up, and improved their visual analog pain score......................................................93

**Table 5:** Summary of the grouping parameters used to create each group for comparing the effects of the number of groups on the feature selection process. .......................................95

**Table 6:** Summary of average and standard deviation (SD) normalized values over stance of each selected significant feature of gait for all subject performance groupings at for toe-in gait at the *post-training* session. Forces were normalized by %BW and moments by %BW*HT. We used 10-fold cross-validation to estimate the ability of the regression model to make predictions for a new group with 98.8% of features correctly classified on average across the 10 cross-validation folds ($R^2$ = 0.97). The significant features included ground reactions (vertical reaction force), motion (pelvis list, rotation, tilt, height, and mediolateral position, hip flexion, adduction, and rotation), joint moments (knee adduction moment),

muscle force estimates (biceps femoris short head, gluteus maximus anterior, and gluteus maximus middle), and joint contact loads (hip compression and anterior shear force, and metatarsophalangeal flexion-extension contact moment). Group 1 (n=2), the worst group, included subjects with a slight increase in varus-valgus contact moment (VVCM). Group 2 (n=3) included subjects with a 0-6.99%, or well below average, decrease in VVCM. Group 3 (n=2) included subjects with a 7-13.99%, below average, decrease in VVCM. It is important to note that there were no subjects in group 4, or those subjects with a 14-20.99% (average) decrease in VVCM, at post-training, thus there are no results for this group. Group 5 (n=2) included subjects with a 21-27.99% (above average) decrease in VVCM. Group 6 (n=1), the best group, included subjects with a 28% or greater (well above average) decrease in VVCM..........................................................................................96

**Table 7:** Summary of average and standard deviation (SD) normalized values over stance of each selected significant feature of gait for all subject performance groupings at for toe-in gait at the *follow-up* session with 98.8% of features correctly classified on average across the 10 cross-validation folds ($R^2$ = 0.97). Forces were normalized by %BW and moments by %BW*HT. The significant features included ground reactions (vertical reaction force), motion (pelvis list, rotation, tilt, height, and mediolateral position, hip flexion, adduction, and rotation), joint moments (knee adduction moment), muscle force estimates (biceps femoris short head, gluteus maximus anterior, and gluteus maximus middle), and joint contact loads (hip compression and anterior shear force, and metatarsophalangeal flexion-extension contact moment). The baseline (*normal gait*) gait data has only one group for all subjects as this is the starting point for all subjects. The subject groupings for the follow-up (*toe-in* gait) data contain different subjects than the groupings for the post-training (*toe-in gait*, Table 2) data as some subjects improved to a new, better grouping at follow-up as compared to post-training. To improve to a better grouping, subjects saw a greater change in varus-valgus contact moment (VVCM) and moved to a different subject grouping based on the amount of change in VVCM, such that group 1 was the worst with a slight increase in VVCM and group 6 was the best with the most decrease in VVCM. Group 1 (n=3), the worst group, included subjects with a slight increase in VVCM. Group 2 (n=1) included subjects with a 0-6.99%, or well below average, decrease in VVCM. Group 3 (n=1) included subjects with a 7-13.99%, below average, decrease in VVCM. Group 4 (n=2)

included subjects with a 14-20.99% (average) decrease in VVCM. Group 5 (n=1) included subjects with a 21-27.99% (above average) decrease in VVCM. Group 6 (n=2), the best group, included subjects with a 28% or greater (well above average) decrease in VVCM..........................................................................................................................98

**Table 8:** Summary of average and standard deviation (SD) normalized values over stance of each selected significant feature of gait for the top performing subjects at all gait sessions with 100% of features correctly classified on average across the 10 cross-validation folds ($R^2$=0.98). Forces were normalized by %BW and moments by %BW*HT. The selected features from ground reaction force (GRF) readings were the mediolateral reaction force and ground free torque. The selected features from inverse kinematics (IK) include pelvis list, tilt, height, and mediolateral position, and hip adduction and rotation. The selected features from inverse dynamics (ID) include the joint moment, hip adduction moment. Finally, the selected features from joint contact load analysis (JRA) were the superior compression contact force at the hip joints and the knee flexion-extension contact moment........................................................................................................................100

**Table 9:** Comparison of the effects of varying the number of groups during feature selection, highlighting which of the selected features with 6 groups from this study also appear in 5, 4, 3, and 2 groups, respectively. 14 out of the 16 selected features with 6 groups appear as significant features in two or more groupings, with the last two selected, metatarsophalangeal flexion-extension moment and gluteus maximus anterior force, being those that were not similar to any of the other groupings. This suggests that these last two features may not have a large impact on decreasing VVCM. Additionally, hip rotation was the top selected feature for 6, 5, and 4 groups, and was in the top 6 selected features for 3 and 2 groups, highlighting this feature to most significant for decreasing VVCM during toe-in gait. Finally, hip rotation, pelvis tilt, pelvis height, biceps femoris short head force, and hip adduction were significant features in all groupings, indicating these may be the most important features to be targeted in future gait retraining studies to decrease harmful joint loading in patients with medial knee OA. In the end, these results validate the use of 6 groups during feature selection in this study, as 88% of these selected features appeared in the other groupings as well..........................................................................................101

**Table 10:** Comparison of the predictive power and percentage of similar selected features between 6 groups as used in this study and varied numbers of groups during feature selection. Predictive power decreases and the number of groups decreases, such that using 6, 5, or 4 groups had 99% correct predictions across the 10 cross-validation folds, using 3 groups had 98% correct predictions, and using 2 groups had 91% correct predictions. These results indicate that using fewer groupings may not be able to correctly classify the significant features as accurately and using more groups. Using more groupings helps highlight the smaller, unique differences between each subject during toe-in gait, utilizing more information about gait on a subject-specific basis to select features more efficiently, while using fewer groups yields more generalized results that may be significant on average but not on an individual basis. Importantly, using different numbers of groups yielded different sets of significant features. However, each of the groupings had many of the same selected features, for example 5 groups had 57% of the same features as using 6 groups, while 4, 3, and 2 groups had 34%, 41%, and 53% respectively. These results validate the use of 6 groups in the same set of features appear to be significant, regardless of the number of groups used during feature selection......................................................102

# LIST OF FIGURES

**Figure 1:** A comparison of a healthy knee joint (far left) and different severities of knee osteoarthritis (OA) (moderate OA, middle; severe OA far right). Knee OA causes the joint space to narrow, articular cartilage deterioration, bone spur formation, loss of synovial fluid, and more, making it a highly painful disease..............................................................7

**Figure 2:** Schematic showing the calculation of the knee adduction moment (KAM), such that KAM is equal to the ground reaction force (GRF) multiplied by the moment arm to the knee joint center of rotation (LA). ...........................................................................................8

**Figure 3:** Diagram of individual elements between neural command and movement. Modified gait rehabilitation strategies alter many elements and the effects are not easily measured.........................................................................................................................11

**Figure 4:** Examples of recent model advancements in OpenSim software. The open-source feature of this software allows users to develop more complex models, such as these pictured, in order to address the ever-evolving scientific questions relating to human movement.........................................................................................................................13

**Figure 5:** Diagram showing the multi-step, forward dynamic simulation process to generate a muscle-actuated simulation of a subject's motion. The inputs are a dynamic musculoskeletal model, experimental kinematics, and experimental reaction forces and moments obtain from a subject. In step 1, experimental kinematics is used to scale the model. In step 2, an inverse kinematics (IK) problem is solved to find model joint angles. In step 3, inverse dynamics (ID) determines the generalized forces for the given movement. In step 4, a static optimization (SO) algorithm is used to determine a set of muscle excitations to track the motion of the subject. ....................................................................15

**Figure 6:** Example showing how to determine net joint moment from muscle forces for the ankle during static optimization (SO).............................................................................19

**Figure 7:** A representative subject walking with (left) normal gait and (right) toe-in gait. The subject internally rotated the foot by 6° which reduced the first peak knee adduction moment by 20%.............................................................................................................82

**Figure 8:** Averaged (top) foot progression angle and (bottom) knee adduction moment for all subjects for normal and toe-in gait............................................................................83

**Figure 9:** Example muscle force profiles from the representative subject shown in Figure 7 showing muscle force tradeoffs to perform toe-in gait. Solues and gluteus medius forces decreased, while vastus lateralis and rectus femoris forces increased. Muscle forces are averaged over ten steps of stance and shading represents one standard deviation. Significant muscle force modifications were evidenced in individuals like this representative subject, though no consistent muscle force modifications emerged for the gait modification across all subjects. ..........................................................................................................…...85

**Figure 10:** Illustrations showing the differing orders of approximations made through analyses of joint kinetics for an example planar knee joint. The net external knee adduction moment (KAM) (a, blue curved arrows) about the joint center results from a traditional inverse dynamics analysis determining the net generalized forces responsible for the movement. Very importantly for our case, the net KAM is determined without regard for the effects of internal muscle forces, which may be different following gait modification. The varus-valgus contact moment (VVCM) (b, green curved arrows) about the joint center results from a joint reaction analysis, taking into account the same forces and moments used for inverse dynamics but also includes the internal muscle force estimates (b and c, red straight arrows). This contact moment is directly related to the unbalanced bone-on-bone forces experienced by the medial and lateral knee joint compartments. As illustrated in this example of the knee modeled as a revolute joint, the VVCM is necessary to carry loads of the joint structure maintaining the joint motion of the two-piece hinge rotating about a common pin (gray shaded). The bone and joint contact loads (c, black straight arrows) may be obtained from higher-order analyses or measurements with an instrumented knee implant. Ultimately, the net external KAM (a) is a rough first-order approximation and the VVCM (b) is a second-order approximation with additional details related to the muscle forces affecting joint contact loads (c)......................................................................................86

**Figure 11:** All subjects showed, on average, (a) a reduction in the first peak external knee adduction moment located at 27% stance during the post-training session at the end of 6 weeks of training from normal gait (green, solid), (b) a 14.7% decrease ($p<0.01$) in the varus-valgus contact moment (VVCM), the load directly related to the unbalanced contact forces on the medial and lateral knee joint compartments during gait, at this same point in stance during the post-training session at the end of 6 weeks of training (red, dashed), and

(c) a 16.7% decrease ($p<0.01$) in the VVCM at this same point in stance during the follow-up session 1-month after the end of 6 weeks of training (blue, dashed)..............................87

**Figure 12:** Validation of varus-valgus contact moment (VVCM) using normal and medial thrust gait data collected from an instrumented knee implant (eKnee) available from the 4th Knee Grand Challenge competition. The (a) eKnee medial force measured from an instrumented knee decreases following medial thrust gait modification. Similarly, the (b) VVCM computed from joint reaction analysis follows this same trend, showing a decrease following medial thrust gait modification...........................................................................91

**Figure 13:** The correlation between the experimentally measured eKnee medial force and the model estimated varus-valgus contact moments (VVCM) for (a) normal gait and (b) medial thrust gait from 0-100% stance yields high coefficients of determination, R2= 0.934 and R2=0.942, respectively. This correlation shows the relationship between eKnee medial force and VVCM, such that the variation in VVCM is strongly related to the experimentally measured eKnee medial force before and after gait modification..............92

**Figure 14:** Schematic showing the forward sequential feature selection process from beginning to end. First, OpenSim modeling and simulation determines the initial inputs (a) or the various features of gait. These inputs include ground reaction forces (GRF), inverse kinematics (IK), inverse dynamics moments (ID), static optimization muscle forces (SO), and joint reaction analysis joint contact loads (JRA). Second, subjects are grouped based on performance (b) following toe-in gait analysis. These groupings are based on the amount of change in the varus-valgus contact moment (VVCM) following toe-in gait at both the *post-training* and *follow-up* sessions. Third, machine learning in Matlab (c) is used to carry out forward sequential feature selection to determine the significant features of gait with the potential to reduce joint loads during toe-in gait. To begin, the OpenSim input data is divided into testing and training groups using 10-fold cross validation. The data is separated into 10 folds, where 9 are used for training and 1 used for testing. Using the forward sequential feature selection (fSFS) algorithm, the training data is fit with a pseudo-quadratic discriminant analysis (pQDA) model to select features. Each possible subset of features is evaluated and compared before being validated with the testing data. The test data evaluates the final selected feature set. This will continue until a local minimum of the misclassification error (MCE) is found. The fSFS algorithm process repeats 10 times, going

through each of the 10 cross validation folds until each observation is used for testing and training. Then a final average of the results of each fold repetition determines the final set of selected features. The final average contains the selected significant features of gait, or the target outputs (d)..........................................................................................................94

**Figure 15**: Example surrogate response surfaces. While the approximate surface for the optimization in this study had 16 design variables, or features of gait, these surfaces are visual representations of how the simulated gait data fits with the surrogate response surface for two features at a time. The surfaces shown represent the response surface approximation for combinations of the top 3 selected significant features of gait including (a) hip rotation and knee adduction moment ($R^2$=0.83), (b) hip rotation and pelvis list ($R^2$=0.55), and (c) knee adduction moment and pelvis list ($R^2$=0.78). To visualize the fit of the simulated gait data to the response surface, the gait data were plotted over the surface (pink, open circles). Because the response surface moves and changes through stance, these visuals represent only 1% of stance, specifically showing 27% of stance of the average location of the first peak knee adduction moment (KAM) for the subjects in this study. Note, the fit of two features at 27% stance is different than the fit of all 16 features over full stance (0-100%) used for the surrogate-based optimization in this study and serves as a visual example of how a surface can be fit to gait data.....................................................103

**Figure 16:** By varying significant features of gait, the optimizer was able to minimize the varus-valgus contact moment (VVCM) (*blue*, solid) in comparison to the mean and standard deviation of the subject data (*red, dashed*) for individuals with medial knee OA. The VVCM was minimized to be less than the mean of the subject data for most of the stance phase of gait. The few time steps where the VVCM was slightly larger than the mean were still within 1 standard deviation...........................................................................................105

**Figure 17:** Target design variables (*blue, solid*) for the sixteen significant features of gait over stance as determined from a surrogate-based optimization compared to the mean and standard deviation of the subjects' simulation data (*red, dashed*). The sixteen features include ground reactions (vertical reaction force), motion (pelvis list, rotation, tilt, height, and mediolateral position, hip flexion, adduction, and rotation), joint moments (knee adduction moment), muscle force estimates (biceps femoris short head, gluteus maximus anterior, and gluteus maximus middle), and joint contact loads (hip compression and

anterior shear force, and metatarsophalangeal flexion-extension contact moment). The top 3 selected features were hip rotation, knee adduction moment, and pelvis list. These results serve as recommendations to minimize VVCM by incorporating the kinematic changes in future gait retraining studies. For example, hip rotation should be increased, or further rotate the ipsilateral limb internally, and pelvis list should be decreased to increase obliquity on the contralateral limb for minimized VVCM with toe-in gait.........................................................................................................................106

# CHAPTER ONE: INTRODUCTION

## 1.1 Project Summary

Millions of people around the globe suffer from a physical disability that lowers their quality of life. Arthritis is currently the leading cause of disability in the United States, with osteoarthritis (OA), especially of the knee, being the most prevalent form. Knee OA is characterized by decreased neuromuscular control, weakened knee musculature, and knee joint instability— with limited and ineffective treatment options to combat the pain and functional limitation associated with the disease. Gait modification has recently been proposed as a noninvasive, early intervention method to treat knee OA and has been shown to reduce the knee adduction moment (KAM), a key factor in knee OA disease progression. Many modification strategies have been studied, but one, a decreased foot progression angle, or toe-in gait, has been studied far less, despite having been shown to reduce KAM and improve knee joint function for patients with knee OA.

Gait retraining paradigms typically focus on modifying kinematics, though the underlying muscle force modifications responsible for the kinematic changes remain unknown. By ignoring muscle forces, many studies are ignoring the potentially critical role the changes in muscle forces play in achieving gait modifications. Toe-in gait has been shown to reduce KAM, but the full effect of muscle forces and the corresponding knee loads is not known. Investigating knee joint contact loads, specifically the forces and moments corresponding to the internal loads the joint structure carries, under toe-in gait conditions, may better characterize this gait modification in terms of creating targeted intervention strategies. It may be that optimal gait patterns combine a number of previously reported modification strategies to reduce the net external KAM and joint loading to improve knee function and slow progression of knee OA.

The ultimate ***goal*** of this research was to maximize the potential of a gait modification by investigating subject-specific gait modifications to minimize joint loads and improve overall joint function for treating patients with knee OA. The overall ***hypothesis*** was that several gait modification factors— foot progression angle, trunk lean, step width, etc.— contribute to changes in muscle forces and joint loads during gait for individuals with knee OA. Due to a lack of knowledge about how gait modifications assessed by clinical movement analysis correlate to muscle forces and joint loads that need treatment, currently gait rehabilitation treatments stand to be improved. A new treatment strategy using simulation-based medicine will lead to an enhanced and diverse understanding of rehabilitation. Patients' treatment outcomes are more likely to be favorable when interventions are performed that systematically correct the underlying biomechanical sources causing harmful joint loads as identified from the proposed simulations.

## 1.2 Research Significance

Arthritis is the leading cause of physical disability in the US and patients are commonly left with disabling pain leading to loss of mobility [1]. Currently, there are 47.5 million adults in the US who have a disability [2] and roughly 8.6 million report arthritis as the main cause of their disability [1]. Additionally, arthritis accounts for more than 23% of incident disability in daily living activities among older adults [3]. In coming years, with decreased mortality rates and a large, aging population of the baby boomer generation, there will be more adults than ever before living with chronic musculoskeletal conditions that cause disabilities that may limit walking; it is projected that over 67 million people will be affected by arthritis by the year 2030 [1]. Since walking ability is directly related to an individual's independence at home and in the community, losing this ability is a major setback for patients with arthritis.

OA, especially in the knee, is the most prevalent form of arthritis affecting approximately 27 million adults overall or over 13.9% of adults aged 25 and older [4] and accounts for over 55% of all arthritis-related hospital admissions [5] in the US. Job-related costs due to OA are estimated to be nearly $13.2 billion annually in the US alone [6]; moreover, indirect costs of missing work as a result OA adds another $10.3 billion to the total US costs [7]. This issue is not limited to the US, as worldwide, OA in the US, Canada, UK, France, and Australia accounts 1–2.5% of each country's gross national product [8].

***Osteoarthritis affects approximately 27 million adults, or nearly 13.9% of all adults over age 25 in the United States.***

Repetitive motions such as walking can be modified to achieve beneficial changes in joint loads linked to OA severity and progression, but how they can be modified to achieve the most favorable outcomes is an open question. In the past, experimental approaches have greatly advanced our understanding of the human body in relation to neuromuscular control, joint motion, muscle strength, and functional capacity. However, progress has been limited by three factors: 1) key variables, such as muscle forces, are not measured, 2) cause-and-effect relationships, such as the contribution of motion to joint loads, are not established [9], and 3) in the cases of patients currently suffering from a musculoskeletal disease, such as OA, important parameters cannot be directly measured. Determining just how individual muscles contribute to observed motions and joint loading, though, is very difficult because a muscle can accelerate joints it does not cross and body segments to which it is not attached [9]. A detailed scientific framework is needed, in combination with experimental approaches, to uncover those principles that govern muscle forces and joint loads during abnormal movement in individuals with musculoskeletal disorders, such as OA. By utilizing muscle-actuated dynamic simulations, such a framework can be established. Additionally, these simulations complement experimental approaches by allowing important variables to be estimated and cause-and-effect relationships identified. The use of musculoskeletal modeling and simulations in combination with experimental approaches has the potential to greatly improve patient care [10].

## 1.3 Research Innovation

At this time, there is a gap between the experimental approaches used by physicians, physical therapists, and rehabilitation scientists and the computer simulation approaches used by engineers, mathematicians, and computer scientists. The researched detailed in this dissertation combines these two different approaches and builds a relationship that allows each field to benefit from the strengths of the others. This is the first study of its kind, to look into the specific muscle contributions and joint loads of gait modification. The research in this dissertation is novel because 1) simulations were based on optimal, subject-specific models rather than generic, one-size-fits-all models, allowing the best possible results for individual subjects (similar to simulating aircraft-performance in the aerospace field or vehicle-performance in the automotive field) to be produced and 2) a quantitative basis to discover effective movement modifications has been fully enabled, providing evidence-based knowledge about which movement prescriptions work best in which patients with musculoskeletal disabilities. Although this research focuses on movement modification, this research may also impact other areas, including ergonomics, sports performance, and injury related to high joint loads.

***The research described helps bridge gaps between disciplines and enhances studying and teaching of movement modification.***

## 1.4 Research Methods

To complete this research, we utilized OpenSim in connection with Matlab software to create subject-specific simulations. Simulations have been used in biomechanics for a wide variety of applications, such as analyzing athletic performance, designing ergonomically safe environments such as cars, and they have been extremely advantageous in helping to understand and treat movement disorders. They are also popular in the entertainment industry to create human and animal characters for movies and video games. While OpenSim provides the musculoskeletal simulation software with a powerful graphical user interface (GUI) and open-source plug-in capabilities, it has limited recourses for rapid design and control of dynamics systems. On the other hand, Matlab provides powerful math software with rapid design and control of dynamic systems, but is limited in modeling musculoskeletal systems. Combining the strengths of both OpenSim and Matlab allows a unique way to answer scientific questions relating to human movement. Using the combination of OpenSim and Matlab, we completed the following three studies:

### *1.4.1 Specific AIM 1: Determine muscle forces and corresponding joint loads before and after gait modification.*

**Goal:** The purpose of specific aim 1 was to answer the following questions:

1) What are the individual muscle forces generated during toe-in gait?
2) What are the internal joint contact loads at the knee during toe-in gait?

**Methods:** To accomplish this study, subject-specific simulations reproduced experimentally measured kinematics of 10 subjects with medial compartment knee OA. For each simulation, individual muscle forces and joint loads were estimated using static optimization and joint reaction analysis.

**Significance**: This investigation will clarify how muscles generate force to compensate for gait modification and how this affects the joint contact loads that characterize knee OA.

### *1.4.2 Specific AIM 2: Identify the significant features of gait that have the potential to decrease joint loads.*

**Goal:** The purpose of specific aim 2 was to answer the following questions:

1) What are the features of gait with the potential to decrease harmful joint loads during toe-in gait?
2) What are the features of gait that the top performing subjects use during toe-in gait to decrease joint loads?

**Methods:** To accomplish this study, simulation data for all patients was divided into groups based on amount of decrease in joint loads following gait modification. Forward Sequential Feature Selection will be used with 10-fold cross-validation and pseudo-quadratic discriminant analysis to select a subset of features with the most potential to decrease joint loads.

**Significance**: This investigation clarified the potential of toe-in gait modification to decrease joint loads.

### *1.4.3 Specific AIM 3: Design testable subject-specific gait modifications to minimize knee joint loads using surrogate-based optimization.*

**Goal:** The purpose of specific aim 3 was to answer the following questions:

1) How can significant features of gait be used to create optimal gait modification strategies to minimize joint loads?
2) What do optimal subject-specific gait modifications look like to minimize joint loads?

**Methods:** To accomplish this study, joint loads were fit as a multidimensional quadratic function of the most significant features of gait modifications. Optimizations varied gait modifications to determine optimal patient-specific gait modification.

**Significance**: This investigation created targeted training methods to use gait modification to decrease knee joint loads for patients with knee OA.

*This dissertation combines original ideas and comprehensive research strategies. These results advance our understanding of the efficacy of gait modification strategies to reduce knee joint loads for patients with knee OA. These methodologies advance core medical technology and clinical techniques, enable new discoveries for gait rehabilitation, and lay the framework for future studies on/applications to subject-specific simulation-based treatment options for knee OA.*

# CHAPTER TWO: LITERATURE REVIEW

## 2.1 Background and Foundation

Experiments alone have a limited understanding of the dynamics of human movement. Although some variables responsible for movement (e.g., ground reaction forces (GRF) and electromyography (EMG) muscle activity) can be measured experimentally, it is extremely difficult to measure variables such as individual muscle forces and joint loading. It is even more difficult to establish cause-and-effect relationships that convey an understanding of muscle function. Similar to an observed movement, a simulated movement results from many individual elements. Models and simulations based on experiments can generate the muscle-tendon dynamics, musculoskeletal geometry, and multi-joint dynamics during a simulated movement that are not able to be evaluated using experimental observation alone. These simulations enable important cause-and-effect relationships to be identified and allow "what if" studies to be performed to test different hypotheses, predict outcomes, and identify behaviors [9]. For example, insights into the potential treatment for knee pain and functional limitation from OA can be investigated. In most patients, OA pain is felt in the medial compartment, causing the patient to adopt new gait abnormalities to deal with the pain. However, to prescribe a gait retraining strategy simply by clinical evaluation proves to be difficult with limited success. Subject-specific simulations have the ability to determine the potential utility of a gait retraining treatment strategy. The simulated movement can also provide estimates of important variables involved in generating the movement. The simulations can provide necessary information about the movement to develop a new treatment recommendation for knee OA. Clinicians often use intuitive models based on clinical experience or general approaches based on population studies to plan treatments for knee OA. However, because such models are constructed using data from other patients, the predicted clinical outcome for a particular patient is unreliable.

***Simulations complement experiments and give estimates of generally immeasurable variables providing insights into movement modification.***

### *2.1.1 Knee Osteoarthritis: A Significant Clinical Problem*

Knee OA (Figure 1), the most common type of OA, is a top ten cause of disability impacting quality of life, has a high incidence of pain, and carries high socio-economic costs [45]. Knee OA is a chronic condition that occurs when the joint cartilage deteriorates, resulting in decreased neuromuscular control, weakened knee musculature, and joint instability [11]. The symptoms of this disease include pain, tenderness, stiffness, loss of flexibility, bone spurs, and more. These symptoms develop slowly and worsen over time over time with limited treatment options available. Treatment is mainly focused on pain management and improving functionality [12], until pain becomes too severe and impacts daily living to the point where a joint replacement is needed.

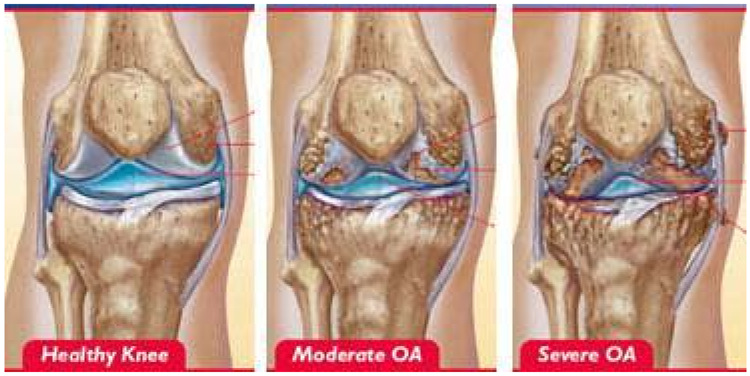


**Figure 1:** A comparison of a healthy knee joint (far left) and different severities of knee osteoarthritis (OA) (moderate OA, middle; severe OA far right). Knee OA causes the joint space to narrow, articular cartilage deterioration, bone spur formation, loss of synovial fluid, and more, making it a highly painful disease [13].

Most patients with OA suffer medial compartment pain, nearly 10 times more often than lateral compartment, likely due to greater medial loading during walking and daily activities [46]. Knee OA affects both knee kinematics and kinetics, leading to abnormal coordination to maintain stability. This abnormal bracing can lead to a significant increase in KAM and knee flexion moment that together force the knee joint toward a greater varus alignment, or an inward angulation of the distal part of the knee joint (Figure 2) [14]. This forces the weight of the body to be localized to the medial aspect of the knee, such that the GRF trajectory passes medial and posterior to the knee joint itself. The magnitude of the KAM directly correlates to joint space narrowing, medial joint capsule loosening, pain levels, and functional limitations [15]. These biomechanical changes are the primary source of pain and functional limitation, and, therefore, preventing the progression of these changes is critical in managing and treating knee OA [16].

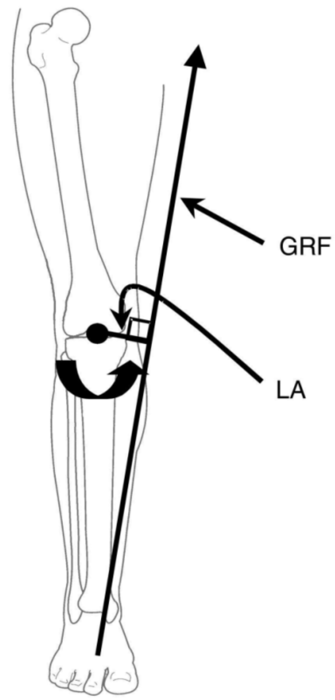


**Figure 2:** Schematic showing the calculation of the knee adduction moment (KAM), such that KAM is equal to the ground reaction force (GRF) multiplied by the moment arm to the knee joint center of rotation (LA) [14].

Presence, severity, and even progression of medial knee OA has been correlated with the first peak external KAM, which is commonly used to assess medial knee loading [15] due to high correlation with measured medial knee contact force [17]. However, this approach does not account for muscle forces when estimating joint contact loads. Determining internal joint contact loads gives a better understanding of joint mechanics and overall musculoskeletal function as this analysis includes muscle forces which change following gait modification [18, 19]. To better treat patients with knee OA, it is necessary to understand these internal knee joint contact loads (i.e., forces and moments). Computational models and experimental gait analysis provide a way to determine these internal musculoskeletal loads *in silico* because non-invasive *in vivo* measurements are not possible for patients currently suffering from knee OA [18].

In the future, a new approach using computational models based on engineering mechanics and optimization may be used to discover a new movement as a treatment. This method may also be used to predict post-treatment outcomes using pre-treatment data on an individual patient basis. Simulations are a vital tool for multidisciplinary study of human movement because they can provide a fundamental understanding about the causes of movement in order to better determine optimal treatment recommendations.

Currently, treatment recommendations are based on a physical examination and movement analysis, both of which characterize the movement without describing the underlying sources. Typically, clinicians use prior experience to combine observations, kinematic and kinetic measurements, and EMG data. Clinical examination of a single passive joint motion does not fully address coordinated multi-joint movements. Movement analysis describes the motion of limb segments but not the individual muscle contributions causing this motion. A new treatment strategy combining physical examination, movement analysis, and simulation-based approaches may lead to a better understanding of movement modification and, ultimately, a better treatment option for patients with knee OA.

***Combining experiments and simulation-based approaches leads to a better understanding of movement modification.***

### *2.1.2 Gait Modification: A Promising Solution*

Gait modification is a nonsurgical approach to reducing the KAM and can be a noninvasive alternative to a total knee replacement or a high tibial osteotomy, where a wedge of bone is added or removed from the proximal tibia to change the leg alignment. Currently, early treatment options are limited to pain management until the disease progresses to a point where pain is no longer manageable and a joint replacement surgery is needed. With more research and better understanding, gait modification will be better able treat patients with knee OA in the future.

Gait modification has recently been proposed as an early intervention strategy to better treat knee OA by mitigating harmful knee joint contact loads. These loads are considered major contributors to articular cartilage degeneration associated with OA progression [20] as patients with knee OA exhibit increased joint loads during gait [21]. It has recently been hypothesized that gait modification can reduce the first peak external KAM and subsequently reduce pain and discomfort associated with knee OA while slowing the progression of the disease itself [15, 22].

Recently, many studies have investigated different modification strategies that reduce the first, and generally larger, peak KAM, including slowed walking speed, decreased stride length, increased medial-lateral trunk sway, and lateral heel wedges [15, 23, 24], and these modifications subsequently reduce pain associated with knee OA and slow disease progression [15, 22]. One way these modifications are designed to train subjects to adopt a gait pattern with increased hip adduction and internal rotation to reduce KAM [25]. It is common in these studies to find that while the first peak KAM is reduced, the knee flexion moment increases. This increase in knee flexion may increase overall knee contact force and counteract the potential benefits of a reduced KAM [26]. In comparison, toe-in gait, or internally rotating the feet to decrease the foot progression angle, does not constrain the hip angles and has been shown reduce the first peak KAM while not impacting the knee flexion moment in patients with medial knee OA [27, 28]. However, there are far fewer studies on toe-in gait, and the use of toe-in gait in current research has shown inconsistent results, showing the need for the development of optimal gait retraining paradigms [45].

***Gait modification shows promise as an early intervention treatment strategy for patients suffering from knee OA.***

Though many studies have investigated gait modification strategies, few focus on toe-in gait and far fewer on internal joint contact loads that contribute to knee OA disease progression. Because most gait modification studies only focus on reducing KAM, which ignores the contributions of muscle forces, it will be important in the future to include the internal joint contact loads that account for the muscle forces in gait studies. It has recently been found that patients with medial knee OA alter their muscle force activations to achieve a desired gait modification in a subject-specific manner [19]. This finding highlights the need to include the internal joint contact loads in gait modification studies, especially those studying patients with knee OA. A better understanding of the effects of gait modifications on muscle forces and internal joint contact loads is necessary to incorporate gait modification as a treatment strategy for patients with knee OA.

### *2.1.3 Musculoskeletal Modeling and Analysis of Human Movement*

Human movement requires the coordination of many muscles across multiple joints, and the transformations between neural control signal and purposeful movement are highly complex and involve many different elements (Figure 3) [9]. First, a neural command signal is given to excite certain muscles, of which the electrical potential can be recorded with EMG, to achieve a desired movement. Second, the muscle-tendon dynamics based on length and velocity properties of the muscle and tendon produce individual muscle forces. Third, musculoskeletal geometry defines the location of joints, the direction of muscle forces, and the muscle moment arms that produce joint moments. Fourth, given these moments, multi-joint dynamics determines accelerations and ground reactions which produce the observed movement. The way the human body moves affects subsequent neural commands to adjust the movement and affects the length and velocity of each muscle-tendon, the direction of muscle forces and moment arms, and the resulting dynamics of the multi-body system.

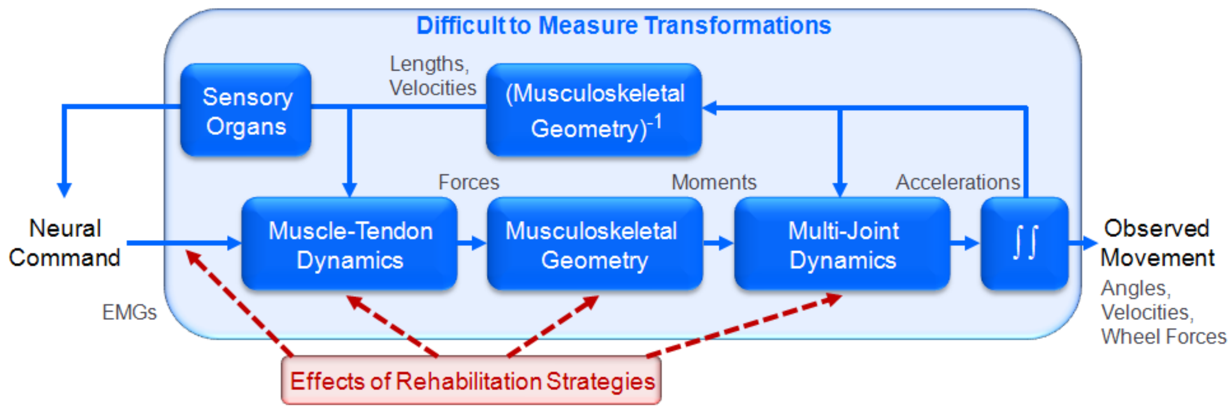


**Figure 3:** Diagram of the individual elements between a neural command and movement. Modified gait rehabilitation strategies alter many elements and the effects are not easily measured.

Computational models and simulation-based approaches have emerged as powerful tools for investigating muscle coordination and function during human movement. Computational modeling of human movement relates different aspects of the human biological system to purposeful movement. In the past, biomechanical models were more simplistic, with only 1- or 2-dimensional models containing much fewer body segments, degrees of freedom, and muscles than those used today [29-32]. Thanks to immense advancements in computer technology, today's biomechanical models are much more comprehensive and computationally efficient [33].

Today, biomechanical models have been developed to estimate muscular forces in the lower extremity during walking [34-40], running [41, 42], cycling [43-47], jumping [48-52], kicking [53, 54], and other physical activities [55-59]. Sophisticated muscle-actuated, forward dynamic simulations have been developed to address specific clinical questions. For example, studies have been conducted to assess electrical stimulation systems to restore unsupported gait to paraplegics [60], to evaluate exercise for persons with spinal cord injury [61, 62] and patients with patellofemoral pain [63], to examine the influence of foot positioning and joint compliance on ankle sprains [64, 65], and to investigate causes of stiff-knee gait [66-68]. These studies have demonstrated the potential utility of models for analyzing causes of gait abnormalities and the effects of treatments.

Using computational modeling, researchers can now develop subject-specific models and simulations to relate joint kinematics and kinetics to muscle force production and overall function. Simulations can account for many musculotendon properties— such as muscle activation and contraction dynamics, force-length and force-velocity relationships, and moment arms— in their analyses to more accurately model the non-linear relationship between muscle activation and force production. This is a major advancement over using EMG, in which muscle activations are linearly related to muscle force. This allows simulations to be used in cause-and-effect relationship studies between muscle function and joint movement [69-73].

***Patient-specific models and simulations are necessary to realize the potential of simulation-based medicine in identifying new treatments.***

Given that the accuracy of a simulation is affected by its underlying model, an optimal model providing the best possible representation of the experiment will produce the best possible variable estimations and relationship identifications. It is also important that simulations be tested to determine limitations because approximations and assumptions are made in developing musculoskeletal models and simulations [10]. There is a rapidly growing community of engineers, therapists, and scientists eager to address clinically motivated questions on medical rehabilitation. For example, the excitation pattern of a muscle can be changed and the resulting motion can be observed through simulation. Subject-specific modeling and simulation allows for higher accuracy when investigating human movement to address the many questions on medical rehabilitation. If a one-size-fits-all model is used rather than a patient-specific one, then the simulation will not accurately represent the subject. Implementing subject-specific modeling and simulation has the potential to change the future of patient care, allowing maximum treatment efficacy, limited undesirable consequences, and reduced costs [10]. Thus, the research presented here promises to significantly impact more than one field.

### *2.1.4 OpenSim: Musculoskeletal Modeling Software*

Musculoskeletal modeling software provides users with generic models to use in creating subject-specific simulations to explore a wide variety of research questions. One such software, OpenSim, provides the framework to build musculoskeletal models, simulate movement, and analyze resulting behaviors. OpenSim enables the creation of musculoskeletal models and provides a set of tools to visualize the motion of the models and extract meaningful information. The mathematical and computational modeling framework of this software allows users to analyze anything from assessing the outcomes of surgical procedures like tendon lengthening in cerebral palsy patients to designing prosthetic devices and studying how they function in the body. Moreover, OpenSim allows for the study of cause-and-effect relationships and has the tools needed to extract meaningful information and predict outcomes.

An important feature of OpenSim is that it is open-source, creating a unique scientific community and environment with plug-in capabilities to allow users to develop customized controllers, analyses, and models. Some recent model advancements (Figure 4) include a model of the scapulothoracic joint [74], the lower-limb [75], and the lumbar-spine [76]. This software is unique in that it is user friendly and that the open-source feature and plug-in capabilities allow users to increase model complexity to answer many difficult problems. This feature also encourages collaboration throughout the biomechanics and modeling community worldwide. A major benefit of using OpenSim in developing subject-specific models is that the discovery can be shared, investigated, and discussed to help advance the field.

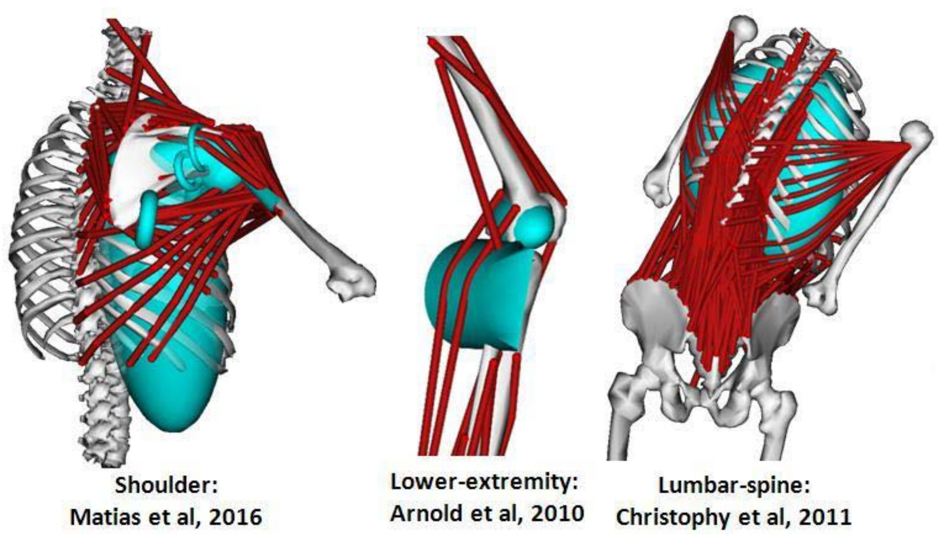


**Figure 4:** Examples of recent model advancements in OpenSim software. The open-source feature of this software allows users to develop more complex models, such as these pictured, in order to address the ever-evolving scientific questions relating to human movement [74-76].

# CHAPTER THREE: SPECIFIC AIM 1- TOE-IN GAIT UNIFORMLY REDUCES HARMFUL JOINT CONTACT LOADS WHILE MUSCLE FORCE MODIFICATIONS ARE NOT CONSISTENT FOR PATIENTS WITH KNEE OA

In aim 1, subject-specific, muscle-actuated, dynamic simulations of 10 individuals with symptomatic, medial compartment knee OA were developed and analyzed in a multi-part study. The goal of specific aim 1 was to create subject-specific models and simulations to understand the individual muscle forces generated during toe-in gait and the associated joint loads. This study was accomplished using subject-specific musculoskeletal simulations that reproduced previously collected, experimentally measured gait kinematics and kinetics of those same 10 subjects with knee OA. For each simulation, individual muscle forces and knee joint loads were estimated using static optimization (SO) and joint reaction analysis (JRA) in OpenSim. This investigation clarified how muscles generate force to compensate for gait modification and how the knee joint contact loads that characterize knee OA change with this modification.

## 3.1 Developing subject-specific musculoskeletal models and simulations

Three hundred subject-specific, muscle-actuated dynamic simulations were created to reproduce the gait dynamics during *normal* and *toe-in gait* trials of 10 subjects with radiographic evidence of medial compartment knee OA. The simulations were used to conduct subsequent analyses of muscle forces and knee joint contact loads and changes in these measures between different gait conditions as well as to determine significant features of gait and create an optimal subject-specific gait pattern.

### *3.1.1 Preparing the Model*

A three-dimensional, lower-limb musculoskeletal model with 12 degrees of freedom and 43 muscle–tendon actuators was created by modifying the generic Gait 2392 model in OpenSim to match experimental data of the ipsilateral limb and pelvis [77]. The contralateral lower extremity, head, upper extremities, and torso were removed and represented as external, or residual, forces and torques acting on the pelvis. The position and orientation of the pelvis relative to ground were defined with 6 degrees of freedom. The remaining lower extremity joints were modeled as follows: the hip as a ball-and-socket joint, the knee as a planar joint with tibiofemoral and patellofemoral translational constraints as a function of knee flexion [78], and the ankle and subtalar joints as revolute joints [79]. All inertial parameters for each of the body segments of the model are derived from Anderson and Pandy (1999) [48]. Each muscle–tendon actuator was modeled as a Hill-type muscle in series with a tendon based on musculotendon parameters from Thelen et al. (2003) [80]. Subject-specific musculoskeletal models were then created for each of the 10 subjects. In total, 30 muscle-actuated dynamic simulations (10 consecutive *normal gait* steps before *toe-in gait* training, 10 consecutive *post-training toe-in gait* steps following the 6-week toe-in gait training regimen, and 10 consecutive *follow-up toe-in gait* steps 1 month following the end of training) were created for each subject during the stance phase of gait using a multi-step dynamic simulation process (Figure 5) detailed below [77].

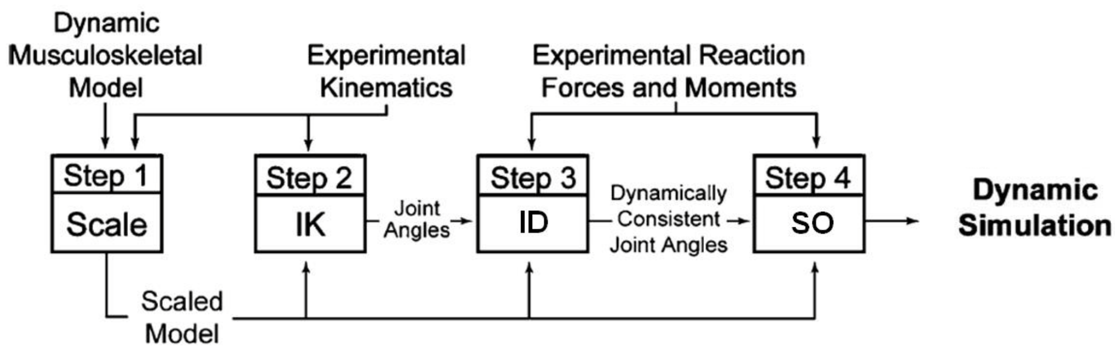


**Figure 5:** Diagram showing the multi-step, dynamic simulation process to generate a muscle-actuated simulation of a subject's motion. The inputs are a dynamic musculoskeletal model, experimental kinematics, and experimental reaction forces and moments obtained from a subject during motion capture. In step 1, experimental kinematics is used to scale the model. In step 2, an inverse kinematics (IK) problem is solved to find model joint angles. In step 3, inverse dynamics (ID) determines the generalized forces for the given movement. In step 4, a static optimization (SO) algorithm is used to determine a set of muscle excitations to track the motion of the subject.

### *3.1.2 Scaling the Model*

The generic Gait2392 musculoskeletal model in OpenSim [77] was scaled to represent each subjects' mass properties and segment dimensions obtained from experimental marker data using a novel scaling algorithm. When scaling by hand using the scale tool in the OpenSim GUI, it can be a tedious task of trial-and-error to fit the markers on the model as best as possible to the experimentally measured markers. The novel scaling algorithm was written to streamline and speed up the scaling process due to the large number of simulations to be created and ensure the lowest marker errors on the created models. A scale factor is computed using measurements between markers to appropriately scale the sizes of each body segment. Additionally, the masses of each segment are adjusted accordingly so the total mass of the model body equals the experimentally measured mass properties of the subject. To ensure the masses of the subject-specific model segments are the same proportion as they are in the generic model, the segments masses are adjusted to preserve the mass distribution by scaling the masses using a constant factor. Next, the generic virtual markers on the Gait2392 model are repositioned on the model based on the location of the subjects' experimental markers to identify the appropriate joint centers and define the correct segment lengths [77]. This novel scaling algorithm uses the scale tool in OpenSim by iteratively working to find the closest match to the experimentally measured marker data set with a RMS marker error less than 2cm. The subjects' marker locations, determined from the experimental static pose, are compared to the virtual marker locations in the models' static pose to ensure a strong match (i.e. minimal error) between the model and experimental marker sets. The error is the calculated average of the distance between the two marker sets so that the resulting model most closely matches the subjects' experimentally measured mass properties and segment dimensions.

Because the experimental data for this research was collected at three separate gait retraining sessions on different dates, the experimental marker locations were slightly different for each trial and thus resulted in a slightly different marker set for each model. In order to compare each model and each separate gait trial accurately, this novel scaling algorithm accounts for these small differences by creating models for each gait condition (baseline normal gait, *post*-training toe-in gait, *follow-up* toe-in gait) based on an average scale factor. The scale factor is computed from measurements to scale the model's geometry accurately. The average scale factor is determined by combining the different scale factors from the three separate sessions to create a new scale factor. Using this new scale factor, a general model that represents each trial is created. Additionally, this novel scaling algorithm also determined which markers were simply misplaced in the experimental data collection process and needed to be moved to the correct bony landmark location to create an accurate model. This was done by comparing the locations of the markers, segment dimensions and proportions in the experimental static pose and the virtual markers in the model. The resulting, final scaled models were scaled with very small marker errors and took a fraction of the time to create in comparison to scaling by hand in OpenSim. Unlike when using the scaling tool by hand in the OpenSim GUI, this algorithm takes the guess-work and human error out of the process and makes the resulting models more accurate and comparable.

### *3.1.3 Inverse Kinematics*

Inverse kinematics (IK) generated values of model's generalized coordinates that best matched (RMS marker error < 2 cm) experimentally measured kinematics. IK calculates the ideal location to place the joint coordinates (angles and position) in the model to match the subjects' experimental joint coordinates at regular time points throughout the measured movement. Each subject's measured kinematics and ground reaction force data were processed to solve an optimal IK problem, minimizing errors between markers on the patient and markers on the model. The IK problem (Equation 1) minimizes the weighted square error at each frame in the experimental kinematics, where $\vec{x}_i^{subject}$ and $\vec{x}_i^{model}$ are the three-dimensional positions of the *i*th marker or joint center for the subject and model, $\theta_i^{subject}$ and $\theta_i^{model}$ are the values of the *j*th joint angle for the subject and model, and $w_i$ and $w_j$ are user defined factors that allow markers and joint angles to be weighted differently [77]. Specifically, IK utilizes this weighted least squares algorithm (Equation 1) to reduce errors between the experimental ($\vec{x}_i^{subject}$) and model ($\vec{x}_i^{model}$) markers and the generalized coordinates ($\theta_i^{subject}$ and $\theta_i^{model}$).

$$\text{Squared Error} = \sum_{i=1}^{markers} w_i(\vec{x}_i^{subject} - \vec{x}_i^{model})^2 + \sum_{j=1}^{joint\ angles} w_j(\vec{\theta}_j^{subject} - \vec{\theta}_j^{model})^2 \quad (1)$$

The weighting coefficients ($w_i$ and $w_j$) are adjusted to track the markers and coordinates in which the researcher has the greatest confidence, such that the resulting models' joint angles and positions most accurately track the experimental movement.

### *3.1.4 Inverse Dynamics*

Inverse dynamics (ID) determined generalized forces for each given movement. This process tracks the observed kinematics with experimental ground reaction forces; in particular, ID calculates kinetic information (forces and moments) from experimentally measured kinematic information (joint positions, angles, velocities, accelerations from the motion). ID uses the known motion of the model, from experimental data collection, to solve the traditional equations of motion (Equation 2) for the unknown generalized forces [81]. The ID process is necessary to match the estimated accelerations of the model to that of the experimentally measured motion of the subject.

$$\underbrace{\mathbf{M}(\mathbf{q})\ddot{\mathbf{q}} + \mathbf{C}(\mathbf{q},\dot{\mathbf{q}}) + \mathbf{G}(\mathbf{q})}_{\text{knowns}} = \underbrace{\tau}_{\text{unknowns}} \qquad (2)$$

where $N$ is the number of degrees of freedom;

$\boldsymbol{q}, \dot{\boldsymbol{q}}, \ddot{\boldsymbol{q}} \in \boldsymbol{R}^N$ are the vectors of generalized positions, velocities, and accelerations, respectively;

$\boldsymbol{M}(\boldsymbol{q}) \in \boldsymbol{R}^{N \times N}$ is the system mass matrix;

$\boldsymbol{C}(\boldsymbol{q}, \dot{\boldsymbol{q}}) \in \boldsymbol{R}^N$ is the vector of Coriolis and centrifugal forces;

$\boldsymbol{G}(\boldsymbol{q}) \in \boldsymbol{R}^N$ is the vector of gravitational forces;

and $\boldsymbol{\tau} \in \boldsymbol{R}^N$ is the vector of generalized forces.

### *3.1.5 Static Optimization*

SO [10] was implemented as an extension of ID to determine individual muscle activations and forces that produce the net joint moments at each instant in time consistent with the experimentally measured kinematics of the subject without violating muscle force limits. The resulting set of muscle forces produces net joint moments (Figure 6) at a discrete time, does not violate muscle force limits, and optimizes a performance criterion. The performance criterion is used to capture the goal of the neural control system, allowing the model to move the muscles consistent with the experimentally measured data by solving for a set of muscle excitations that produce a dynamic simulation that tracks the experimental data.

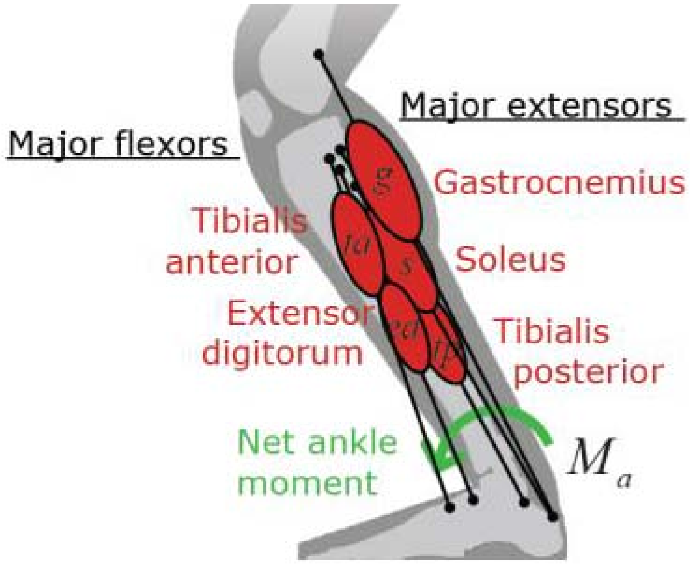


**Figure 6:** Example showing how to determine a net joint moment from muscle forces for the ankle joint during static optimization (SO) [82].

SO uses the known motion of the model to solve the equations of motion for the unknown generalized forces (i.e. joint torques) subject to constrained force-length velocity properties or minimizing the objective function (Equation 3). This is achieved by distributing the joint torques to muscle forces based on minimizing the sum of activations squared (Equation 3), subject to muscles forces generating equivalent generalized forces, with *A* being the moment-arm matrix, and τ is the net torque.

$$\text{minimize: } J(a) = \sum a_i^2 \quad (3)$$
$$\text{subject to: } [A]\left\{F^M(a)\right\} = \tau$$

SO was used because it is a well-established, computationally efficient method based on ID for estimating *in-vivo* muscle forces during movement. This approach has been widely used for over four decades to estimate muscle forces during gait because it produces strikingly similar results to dynamic optimization for muscle force estimation in gait with far less computing time [34]. It is important to note that SO is not a static problem but rather a “pseudo-dynamics” problem that determines results at each time step rather than over whole time like dynamic optimization. Finally, it was necessary to compare the simulated muscle excitations, joint moments, and ground reaction forces to the experimental data in order to verify that the solution was a reasonable representation of each subject's gait.

## 3.2 Muscle force modification strategies are not consistent for gait retraining to reduce the knee adduction moment in individuals with knee osteoarthritis

*This work was published in the Journal of Biomechanics in 2015:* Shull, P.B., Huang, Y., Schlotman, T.E., Reinbolt, J.A., "*Muscle force modification strategies are not consistent for gait retraining to reduce the knee adduction moment in individuals with knee osteoarthritis.*" Journal of Biomechanics, 2015. **48**(12): p. 3163-9.

### *3.2.1 Introduction*

Knee OA is a significant worldwide health concern characterized by joint pain and dysfunction and can lead to joint stiffness, muscle atrophy, and limb deformity [83]. In the United States, symptomatic knee OA affects 11% of women and 7% of men over age 60 [84]with similar incidence rates reported in China for men and even higher for Chinese women [85, 86]. Medications are often used to treat symptoms though disease progression generally leads to total knee replacement [87]. Knee loading is believed to contribute to the degeneration of articular cartilage associated with OA progression [88, 89]. Thus conservative interventions often seek to reduce knee loading for early stage knee OA.

The KAM is an important clinical measurement given the mechanical etiology of knee OA. In vivo instrumented knee replacement testing has revealed a strong correlation between medial compartment loading and the KAM [17, 90] and is thus often used as a surrogate measure of medial compartment loading. The first peak of the KAM has been linked with pain and the presence, severity, and progression of medial compartment knee OA [91-94] and the KAM impulse, area under the KAM-time curve, has been shown to be predictive of cartilage loss over 12 months [20].

Gait retraining is an effective method for reducing the KAM. Initial, proof-of-concept studies in healthy subjects showed that increased trunk sway, internal foot rotation (toe-in gait), reduced tibia angle, and medial thrust were all effective strategies for reducing the first peak KAM [25, 95-98], and gait retraining for individuals with knee OA has confirmed these initial trends for changes in foot progression angle and trunk sway [28, 99]. Gait changes have also been shown to improve symptoms. Shull et al. (2013b) demonstrated that toe-in gait reduced the first peak KAM, reduced pain, and increased function for individuals with symptomatic knee OA after 6 weeks of gait retraining [27]. Hunt and Takacs (2014) performed 10 weeks of gait retraining and showed that a toe-out gait modification reduced the second peak KAM, the KAM impulse, and knee pain [100].

Gait retraining paradigms have thus far focused primarily on the relationship between altered gait kinematics and KAM while neglecting the potentially crucial role that muscle forces might play in intervention. For example, internal muscle forces may lead to higher knee joint compartment loading that is not captured by the KAM [26]. In addition, uniform kinematic gait modifications shown to reduce knee loads for a population on average can actually be ineffective for individuals within that population [100, 101], which has led some to propose subject-specific modifications [15, 23, 97]. Muscle force modification strategies may thus be crucial to the efficacy of gait retraining.

Although there are many potential muscle force combinations that produce stable gait, humans are generally thought to select uniform muscle patterns while walking such as strategies based on fatigue cost functions or energy minimization [102-104]. Thus, we performed this study to test the hypothesis that a kinematic gait change known to reduce the KAM (i.e. toe-in gait) would be accompanied by a uniform muscle force modification strategy for individuals with symptomatic medial compartment knee OA. We further sought to determine the relative degree of force change across individual muscles for the gait modification. Identifying the combinations of muscle force modifications adopted by individuals with symptomatic knee OA provides an objective tool to study and potentially improve gait retraining.

### *3.2.2 Methods*

#### *Subjects*

Subjects were selected and trained by my collaborator, Dr. Peter B. Shull of Shanghai Jiao Tong University in Shanghai, China, during his time at Stanford University in Palo Alto, CA. Ten subjects with symptomatic, medial-compartment knee OA participated in this study (Appendix, Table 1). To be included, subjects were required to have radiographic evidence of medial compartment knee OA defined as Kellgren & Lawrence (K/L) Grade > 1. The K/L scale is comprised of four levels of increasing severity [105], Grade 1: doubtful narrowing of joint space and possible osteophytic lipping, Grade 2: definite osteophytes and possible narrowing of joint space, Grade 3: moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends, and Grade 4: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends. Subjects were also required to have self-reported medial compartment knee pain at least one day per week during the six weeks prior to participation, to be between 18 and 80 years, and to be able to walk unaided for at least 25 consecutive minutes. Exclusion criteria included: body mass index greater than 35; inability to adopt a new gait due to previous injury or surgery on back or lower extremities; use of a shoe insert or hinged knee brace; or corticosteroid injection within the previous six weeks. Gait retraining was focused on the limb with greatest self-reported knee pain (4 right legs, 6 left legs). All subjects gave informed, written consent for the collection and analysis of their gait data prior to participating, and the study was preapproved by the institutional review board.

***Experimental Data Collection***

The experimental data were collected and provided to me by my collaborator Dr. Peter B. Shull of Shanghai Jiao Tong University in Shanghai, China. Subjects performed weekly gait retraining sessions over six weeks to adopt a toe-in gait pattern (Appendix, Figure 7) and each session was experimentally recorded in a motion analysis laboratory. At the beginning of each testing session, a static standing calibration trial was performed with markers placed at the following locations: calcaneus, head of second metatarsal, head of the fifth metatarsal, lateral and medial malleoli, lateral and medial femoral epicondyles, lateral mid-shaft shank (2 markers), greater trochanter, lateral mid-shaft femur (2 markers), left and right anterior superior iliac spines, left and right posterior superior iliac spines, left and right acromion, and seventh cervical vertebrae. Medial malleolus and medial epicondyle markers were removed for subsequent walking trials. Marker trajectories were recorded with an eight-camera motion capture system (Vicon, Oxford Metrics Group, Oxford, UK) at 60 Hz, and treadmill forces and moments from a split belt instrumented treadmill (Bertec Corporation; Columbus, OH, USA) were recorded at 960 Hz.

Each gait retraining session used real-time streaming motion capture data and real-time feedback to achieve internal foot rotation for toe-in gait. During the first session, the subject walked for a two-minute warm up period establishing a preferred treadmill walking speed (average $1.22 \pm 0.21$ m/s), which was used for all subsequent trials, and then walked another two minutes during the normal gait trial. Afterward, gait retraining was performed for the remainder of the first session and all subsequent sessions to train a toe-in gait modification with a target 5° of internal foot rotation. A vibration motor (Engineering Acoustics, Inc, FL, USA) was hypoallergenically adhered to the lateral-proximal aspect of the fibula and provided real-time haptic (touch) feedback [97] on each step during stance to inform the subject of the desired foot progression angle. A single vibration pulse indicated a required decrease in foot progression angle (toe-in more) and two vibration pulses indicated a required increase in foot progression angle (toe-out more).

Data were analyzed from the *normal trial*, the initial walking trial performed at the beginning of the first session, and from the *toe-in trial*, the post-training walking trial performed following the six weeks of gait retraining. Subjects reported knee pain on a visual-analog pain scale before walking at the beginning of the normal trial session and the toe-in trial session. The visual-analog pain scale ranged from 0 'no hurt' to 10 'hurts worst' [106]. Toe-in gait, on average, decreased the foot progression angle by 7° ($p < 0.01$) and reduced the first peak KAM by 20% ($p < 0.01$) (Appendix, Figure 8, Appendix, Table 1). Knee pain was reduced by 2 points on the visual-analog pain scale ($p < 0.01$) (Appendix, Table 1).

***Muscle Force Estimation***

A three-dimensional, lower-limb musculoskeletal model with 12 degrees of freedom and 43 muscle–tendon actuators was created by modifying the Gait 2392 model in OpenSim [77]. The contralateral lower extremity, head, upper extremities, and torso were removed and represented as external, or residual, forces and torques acting on the pelvis. The position and orientation of the pelvis relative to ground was defined with 6 degrees of freedom. The remaining lower extremity joints were modeled as follows: the hip as a ball-and-socket joint, the knee as a planar joint with tibiofemoral and patellofemoral translational constraints as a function of knee flexion [78], and the ankle and subtalar joints as revolute joints [79]. All inertial parameters for the body segments of the model are derived from Anderson and Pandy (1999) [48]. Each muscle–tendon actuator was modeled as a Hill-type muscle in series with a tendon based on musculotendon parameters from Thelen et al. (2003) [80].

Twenty muscle-actuated dynamic simulations (ten consecutive steps from the end of the normal gait trial and ten consecutive steps from the end of the toe-in gait trial) for each subject during stance phase of gait were created using a three-step process. First, the musculoskeletal model was scaled to represent the experimentally measured size of the subject. Second, IK analysis was utilized to obtain values of generalized coordinates for the model that closely matched (RMS marker error < 2cm) the experimentally measured kinematics of each subject. Third, SO [10] was implemented as an extension of ID that solves the "distribution problem" (i.e. more muscles than joints) to determine individual muscle activations and forces producing the net joint moments at each instant in time that generate the experimentally measured kinematics of the subject.

***Data Analysis***

To analyze the muscle force modifications for toe-in gait, gait analysis data were filtered, anatomic conventions defined, simulated muscle forces estimated, and differences between normal and toe-in gait computed. Marker data were low-pass filtered at 6 Hz and force plate data at 50 Hz using a zero-lag fourth-order, Butterworth filter. Foot progression angle was defined in the laboratory horizontal plane as the angle between the line connecting the calcaneus and second metatarsal head and the line of forward progression, which was aligned with the long axis of the treadmill. Toe-out was considered positive. Muscle forces were estimated from the muscle-actuated dynamic simulations described in the section above. Mean muscle force was the muscle force estimate averaged over ten steps of stance. Repeated measures, one-way analysis of variance was used to detect a difference among muscle force estimates for normal and toe-in gait; Tukey's method was used for post-hoc pairwise comparison ($\alpha = 0.01$).

### *3.2.3 Results*

While significant muscle force modifications were evidenced within individuals, there were no consistent muscle force modifications across all subjects (Appendix, Table 2). Individuals altered muscle forces to achieve the toe-in gait modification by increasing force in some muscles and decreasing force in others (Appendix, Table 2). Muscle force profiles during stance for a typical subject demonstrate these muscle force tradeoffs showing increases in soleus and gluteus medius force and simultaneous decreases in vastus lateralis and rectus femoris force (Appendix, Figure 9).

### *3.2.4 Discussion*

This study examined muscle force modifications due to a toe-in gait kinematic modification as compared with normal gait and tested the hypothesis that consistent muscle pattern changes would emerge. Contrary to expectations, muscle force modifications were not consistent across subjects. Muscle force modifications were significant within individuals as evidenced by tradeoffs in the amount of force required among muscles.

Pain might help explain the lack of a uniform muscle force modification strategy for subjects in the present study. While previous research has suggested humans adopt consistent muscle force strategies and by assumption would also modify muscle forces uniformly, these models have been based on pain-free walking in healthy individuals [102-104]. However, all individuals in the present study experienced knee pain symptomatic of knee OA, and thus these assumptions may no longer hold. Henriksen et al. showed that adding experimental knee pain to healthy subjects caused changes in gait patterns in a way that reduced the KAM [107]. Similarly, when knee pain was reduced, individuals with symptomatic knee OA changed their gait patterns in a way that increased the KAM [108]. Thus there seems to be a cause-and-effect relationship between knee pain and gait changes, and it may be that this relationship extends to muscle force modifications as well as kinematic changes. Subjects in the present study had varying levels of knee pain and changes in knee pain pre- and post-training (Appendix, Table 1), which could at least partially account for the inconsistent muscle modification strategies. While pain measures are notoriously difficult to quantify due to subjectivity, future work focused on discovering a link between pain and muscle force strategies could shed light on this issue.

This study provides further evidence for the need to perform subject-specific gait retraining. While training a population to make uniform kinematic changes may work on average, generalized treatments may be ineffective for individuals. Hunt and Takacs (2014) showed that on average 10 weeks of toe-out gait retraining reduced the 2$^{nd}$ peak KAM for 15 individuals with symptomatic knee OA [100]. However, for five of the subjects, toe-out gait either did not change or increased the 2$^{nd}$ peak KAM. Similarly, Erhart et al. (2008) showed that variable stiffness shoes on average initiated gait changes to reduce the 1$^{st}$ peak KAM in a population of 79 individuals with symptomatic knee OA [101]. However, for 18% of these individuals, the 1$^{st}$ peak KAM either did not change or increased. Thus, is has been suggested that gait retraining should be subject-specific to ensure benefits for each individual [15]. Subject-specific training should account for subject-to-subject differences in muscle force strategies as they can affect internal forces potentially increasing knee loads, and it is important to identify which muscles necessitate higher forces to inform muscle fatigue and injury prevention. In particular, elevated muscle force is associated with increased muscle fatigue and soreness [109] and increased risk of muscle injury [110].

The findings in this study contribute to the growing body of literature on gait modification for treatment of early-stage knee OA. Barrios et al. (2010) showed that training subjects to adopt a gait with increased hip adduction and hip internal rotation significantly reduced the KAM [25]. Subjects were instructed to maintain a constant foot progression angle, causing distal kinematics to change, i.e., increased knee flexion and foot eversion. A similar phenomenon occurs for medial thrust gait, which encourages medializing the knee while maintaining a constant foot progression angle [23]. However, this modification may be less than optimal as increased knee flexion may increase the overall knee contact force counteracting the benefits of a reduced KAM in the medial compartment [26]. The toe-in gait modification performed in the present study does not constrain the foot progression angle or hip angles, and thus may be a more natural gait modification [28]. Toe-out gait allows similar freedom of movement for all lower limb kinematics, and several studies have shown that toe-out gait reduces the 2$^{nd}$ peak KAM while toe-in gait reduces the 1$^{st}$ peak [27, 28, 98, 111, 112]. Given the recent interest in wearable, portable systems for gait analysis and intervention [113], future real-time feedback gait retraining studies for knee OA may want to incorporate portable electromyographic sensing of muscle forces as complementary input to the feedback control loop. In addition to unassisted gait modifications, several devices have been shown to cause kinematic changes to reduce the KAM, including: center-of-pressure modifying shoes [114], lateral wedge insoles [115], variable stiffness shoes [101], and valgus knee braces [116].

Though there are different approaches to estimate muscle forces from experimental data, we chose SO because it is a well-established, computationally efficient method based on ID for estimating in-vivo muscle forces during movement [10]. This approach has been widely used for more than four decades to estimate muscle forces during gait. Another common modeling approach is dynamic optimization, based on forward dynamics, which has been shown to produce nearly equivalent solutions to SO during gait for predicted muscle forces and joint contact forces [34]. However, dynamic optimization tends to be computationally expensive, typically requiring 1000 times more computation time than SO. Erdemir et al. (2007) provide an extensive review of various modeling approaches including ID-based SO, optimal control strategies, and alternative methodologies for model-based estimation of muscle forces [117]. Although different approaches may result in different muscle force estimates, the relationship of muscle force modifications observed between normal and toe-in gait would not be likely to change because SO was performed consistently across all subjects and the muscle force estimates are constrained by the experimental data and net joint torques generating the movement.

In conclusion, this study showed that muscle force modifications were not consistent for toe-in gait retraining to reduce the KAM in individuals with knee OA. It may be that self-selected muscle pattern changes are not uniform for gait modification particularly for individuals with knee pain. Thus, there is a need for subject-specific gait retraining which accounts for variations in muscle force modification strategies. Future studies focused on altering knee loads should not assume consistent muscle force modifications for a given kinematic gait change across subjects and should consider muscle forces in addition to kinematics in gait retraining paradigms.

## 3.3 Toe-in gait reduces the varus-valgus contact moment in individuals with knee osteoarthritis

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### *3.3.1 Introduction*

Knee OA is a painful chronic condition causing physical disability for elderly adults worldwide. Over 8.6 million U.S. adults report arthritis as their leading cause of physical disability, leading to loss of mobility and overall quality of life [118]. OA is the most prevalent form of arthritis affecting 14% of U.S. adults aged 25 years and older [119] and accounts for over 55% of all arthritis-related hospital admissions [120]. Knee OA, the most common type of OA, is characterized by decreased neuromuscular control, weakened knee musculature, and knee joint instability, with symptoms developing slowly over time [16] and carries high socioeconomic costs [15]. Currently, treatment options are limited to pain management until the disease progresses to a point where pain is no longer manageable and a joint replacement surgery is necessary.

To better treat patients with knee OA, it is necessary to understand the internal knee joint contact loads (i.e., forces and moments). Computational models and experimental gait analysis are often used to determine musculoskeletal loads *in silico* because non-invasive *in vivo* measurements (Appendix, Figure 10c) are not possible for patients currently suffering from knee OA [18]. Knee joint contact loads are considered major contributors to articular cartilage degeneration associated with OA progression [20] and patients with knee OA exhibit increased joint loads during gait [21], which potentially may be mitigated with gait modification. Patients with knee OA suffer medial compartment degeneration nearly 10 times more often than lateral compartment, likely due to greater medial knee forces during gait and daily activities [89]. Changes in knee kinematics and kinetics associated with knee OA lead to abnormal coordination to maintain stability, causing a significant increase in the external KAM [16]. Presence, severity, and progression of medial knee OA has been correlated with KAM, which is commonly used to assess medial knee loading [15] due to high correlation with measured medial knee contact force [17]. ID has traditionally been used to estimate the net joint loads, such as KAM, during movement (Appendix, Figure 10a), but this approach does not account for muscle forces when estimating joint contact loads. Additionally, KAM reductions may be achieved without corresponding reductions in medial contact forces [26]. Determining internal joint contact loads (Appendix, Figure 10b), including muscle forces, will lead to a better understanding of joint mechanics and overall musculoskeletal function [18]. One knee joint contact load deserving further exploration is the varus-valgus contact moment (VVCM). The VVCM, determined with OpenSim's JRA [10], is an internal knee joint contact moment directly related to unbalanced loading between the medial and lateral compartments (Appendix, Figure 10b), as patients with medial knee OA have increased varus alignment and greater medial loading during gait and daily activities [22]. The VVCM results from a higher order method than ID which includes muscle forces when determining joint contact loads and provides an improved estimate of medial knee contact forces in patients with natural knees, as there is no other way to obtain this measurement. Importantly, internal knee joint contact loads, such as the VVCM, may change when gait is modified to alleviate symptoms of knee OA.

Gait modification is a conservative intervention strategy for treating knee OA symptoms. Different modification strategies reduce the first, and generally larger, peak KAM, including slowed walking speed, decreased stride length, increased medial-lateral trunk sway, and lateral heel wedges [15, 23, 24], and these modifications subsequently reduce pain associated with knee OA and slow disease progression [15, 22]. There are far fewer studies on the effects of toe-in gait; despite the fact, it reduces the peak KAM for patients with knee OA [15, 28]. Toe-in gait modification, internally rotating the feet to reduce foot progression angle, reduces the first peak KAM without impacting the knee flexion moment in patients with medial knee OA, though the effects on joint contact loads remain unknown [27, 28]. Though several studies investigated various gait modifications, few focus on toe-in gait and far fewer on joint contact loads accounting for muscle forces, which have been found to be different following gait modification [19]. A better understanding of the effects of toe-in gait modification on joint contact loads is necessary to use this modification as a treatment strategy for patients with knee OA.

This study determined the effects of toe-in gait modification on the knee joint contact loads in individuals with medial knee OA. We hypothesized that toe-in gait will change the VVCM in subjects with medial knee OA. We tested this hypothesis by comparing the knee joint contact loads during *normal gait* and different sessions (*post-training* and *follow-up*) of *toe-in gait*. Identifying changes in knee joint contact loads with toe-in gait contributes to our understanding of this modification and provides insights needed to improve gait modification programs minimizing detrimental knee joint contact loads associated with the progression of OA.

### *3.3.2 Methods*

Three hundred subject-specific, muscle-actuated dynamic simulations were created to reproduce the gait dynamics during *normal* and *toe-in gait* trials of 10 subjects with radiographic evidence of medial compartment knee OA. The simulations were used to conduct subsequent analyses of knee joint contact loads and changes in these loads between gait conditions.

#### *Experimental Data Collection*

The experimental gait analysis data were collected from 10 subjects (Appendix, Table 1) with symptomatic, medial-compartment knee OA [27]. Inclusion criteria required that each subject (i) had radiographic evidence of medial compartment knee OA as defined by a Kellgren & Lawrence (K/L) Grade>1 [105], (ii) had self-reported medial compartment knee pain at least one day per week during the 6 weeks prior to participation, (iii) was between 18 and 80 years of age, and (iv) was able to walk unaided for at least 25 consecutive minutes. Exclusion criteria prevented each subject from (i) having a corticosteroid injection within the previous six weeks, (ii) using shoe inserts or a hinged knee brace, (iii) being unable to adopt a new gait due to previous injury or surgery on the back or lower extremities, (iv) or having a body mass index

(BMI) greater than 35. The subjects were trained to adopt the *toe-in gait* modification over the course of six weeks [27]. To determine the knee joint load changes due to gait modification, experimental gait analysis data were analyzed for *normal gait* (session prior to *toe-in gait* training), *post-training toe-in gait* (session following the 6-week training regimen), and *follow-up toe-in gait* (session 1 month after the 6-week training regimen ended). The *toe-in gait* modification, a 7° decrease in the foot progression angle, reduced the first peak KAM by 20%, and reduced symptomatic knee pain by 2 points on a visual-analog scale from 0 to 10, on average [28]. All subjects gave informed, written consent for collection and analysis of their gait data prior to participating, and the study was preapproved by the institutional review board.

***Musculoskeletal Models and Simulations***

A generic, three-dimensional, lower-limb musculoskeletal model consisting of 12 degrees of freedom and 43 muscle-tendon actuators was created by modifying the Gait2392 model in OpenSim to match experimental data of the ipsilateral limb and pelvis [77]. The contralateral lower extremity, head, upper extremities, and torso were removed and replaced by external, or residual, forces and torques acting on the pelvis. The pelvis position and orientation was defined relative to the ground with 6 degrees of freedom, the hip as a ball-and-socket joint, the knee as a planar joint with tibiofemoral and patellofemoral translational constraints as a function of knee flexion [78], and the ankle and subtalar joints as revolute joints [79]. All body segment inertial parameters were derived from Anderson and Pandy (1999) [48]. The muscle-tendon actuators were modeled as Hill-type muscles in series with a tendon based on musculotendon parameters from Thelen et al. (2003) [80].

Subject-specific musculoskeletal models were then created for each of the 10 subjects. In total, 30 muscle-actuated dynamic simulations (10 consecutive *normal gait* steps from the end of the trial before *toe-in gait* training, 10 consecutive *post-training toe-in gait* steps from the end of the trial after the 6-week training regimen, and 10 consecutive *follow-up toe-in gait* steps from the end of the retention trial 1 month following the end of training) were created for each subject during the stance phase of gait using a three-step process. First, the generic musculoskeletal model was scaled to represent the experimentally measured size of each subject. Second, IK generated values of model's generalized coordinates that best matched (RMS marker error < 2 cm) experimentally measured kinematics. Third, SO [10] determined individual muscle activations and resulting muscle forces that produced the net joint moments consistent with the experimentally measured kinematics and GRFs.

***Knee Joint Contact Load Analysis***

To determine changes in knee joint contact loads (i.e., forces and moments) between gait conditions, the contact loads were estimated using JRA in OpenSim (Appendix, Figure 10b) [10]. This analysis calculates joint contact forces and moments transferred between consecutive bodies resulting from all motions and forces acting on the model, including muscle-tendon actuators, using multibody dynamics. Analogous to traditional ID, the equations of motion of the multibody system are represented in terms of generalized coordinates and forces; however, muscle forces or internal joint contact loads are not required to solve these equations for the generalized forces, or net joint loads. Therefore, JRA carries out an important, additional step incorporating muscle forces along with joint kinematics and GRFs to determine the resultant joint contact loads [121]. This analysis results in 6 different outputs, including contact forces in the x-, y-, and z-directions, or anterior shear, superior compression, and lateral shear, respectively, and contact moments about the x-, y-, and z-axes, or varus-valgus, internal-external rotation, and flexion-extension. The goal is to extract insights from the subject-specific models and gait simulations to better understand the experimentally measured motion [10]. Joint contact forces were normalized by each subject's body weight (%BW) and moments by body weight times height (%BW*HT). The knee joint contact loads were compared between gait conditions where the first peak KAM occurs during stance, which is thought to have the largest effect on joint loads as the first peak is generally the larger of the two peaks in KAM [22] during stance and is widely used to evaluate efficacy of gait modification strategies.

We evaluated our hypothesis comparing the knee joint contact loads between gait conditions by conducting a paired sample, two-tailed *t*-test at the 0.01 significance level. A paired *t*-test was used to make comparisons for the same subject before and after gait modification, and a two-tailed test was used due to not having an *a priori* expectation about directionality of change (i.e., each joint contact load may increase or decrease). The null hypothesis was that the difference in each joint contact load between *normal* and *toe-in gait* was zero. A low p-value of 0.01 was used because there is strong evidence against the null hypothesis, meaning we expect changes in the joint loads between normal and toe-in gait due to the kinematic and kinetic changes seen with toe-in gait, thus the null hypothesis will most likely be rejected. The test was performed against the two-tailed alternative hypothesis that each joint contact load either increased or decreased, on average, in the simulations of *toe-in gait* compared to *normal gait*.

***Validation of the Varus-Valgus Contact Moment***

We validated our modeling, simulation, and analysis approaches using experimental data collected from an instrumented knee implant (eKnee) available from the 4th Knee Grand Challenge [122] because our subjects have natural knees with medial OA and, thus, direct *in* vivo joint load measurements are not possible. The collected data did not include toe-in gait modification; consequently, we chose to compare normal and medial thrust gait. Both medial thrust and toe-in gait have been shown to reduce the first peak KAM for patients with knee OA [24, 27]; therefore, medial thrust gait is an appropriate modification for validating the VVCM. Four subject-specific, muscle-actuated dynamic simulations (2 consecutive normal gait steps and 2 consecutive medial thrust gait steps) were created for the 4th Knee Grand Challenge subject during the stance phase of gait using the same modeling, simulation, and joint contact load analysis process described above. The VVCM was compared to experimentally measured eKnee medial forces during normal and medial thrust gait. Values of the VVCM and eKnee medial force were respectively averaged between 20% and 35% stance, where the first peak KAM is known to occur, and compared between gait conditions. To further validate our approach, the relationship between the VVCM and experimentally measured eKnee medial force was evaluated with a correlation analysis to determine whether and how strongly the variation in VVCM was related to eKnee forces before and after gait modification.

### *3.3.3 Results*

Following *toe-in gait* modification, patients with medial knee OA reduced their VVCM, while all other knee contact loads remained unchanged. The knee joint contact load results were evaluated at 27% of stance, where the first peak KAM occurs, on average, for subjects in this study (Appendix, Figure 11a). At the *post-training* session, the VVCM significantly decreased ($p<0.01$) approximately 15%, on average, when subjects walked with *toe-in gait* (3.0±0.7 %BW*HT) compared to *normal gait* (3.5±0.8 %BW*HT) (Appendix, Figure 11b, Appendix, Table 3). While the VVCM significantly decreased, there were no significant differences in the compressive and shear knee joint contact forces ($p>0.16$) nor flexion-extension and internal-external rotation contact moments ($p>0.09$) during *toe-in gait* compared to *normal gait*

(Appendix, Table 3). Furthermore, these results were further improved 1 month following the end of gait retraining. At the *follow-up* session, the VVCM significantly decreased ($p<0.01$) approximately 17%, on average, when subjects walked with *toe-in gait* (2.9±0.7 %BW*HT) compared to *normal gait* (3.5±0.8 %BW*HT) (Appendix, Figure 11c, Table 3). Again, there were no significant differences in the compressive and shear knee joint contact forces ($p>0.13$) nor flexion-extension and internal-external rotation contact moments ($p>0.06$) during *toe-in gait* compared to *normal gait* (Appendix, Table 3).

Our modeling, simulation, and analysis approaches generated results consistent with eKnee data collected during the 4$^{th}$ Knee Grand Challenge [122]. The knee joint contact load results were evaluated between 20% and 35% stance, where the first peak KAM is known to occur. The experimentally measured eKnee medial forces (Appendix, Figure 12a) decreased approximately 8.9%, on average, when the subject walked with medial thrust gait (137 %BW) compared to normal gait (150 %BW). The VVCM, from JRA, shows similar changes during stance (Appendix, Figure 12b). The VVCM decreased approximately 8.0%, on average, when the subject walked with medial thrust gait (1.5 %BW*HT) compared to normal gait (1.7 %BW*HT). Furthermore, the VVCM showed high correlation to and varies as a function of the eKnee medial force during both normal gait ($R^2$=0.93, Appendix, Figure 13a) and medial thrust gait ($R^2$=0.94, Appendix, Figure 13b). This comparison confirms that a reduction in the VVCM while all other loads remained relatively the same, as seen in our study, represents a reduction in the knee contact force in the diseased, osteoarthritic medial compartment of the joint.

### *3.3.4 Discussion*

How gait modifications affect internal joint loads on natural knees with medial OA is an open question and answers are necessary to effectively use gait modifications as a conservative intervention strategy. Through *in silico* approaches validated with *in vivo* measurements, we confirmed our hypothesis and determined *toe-in gait* significantly reduces the VVCM, the contact moment directly related to unbalanced loading between the medial and lateral knee joint, compared to *normal gait* in subjects with medial knee OA. All subjects uniformly reduced the VVCM, while adopting different muscle force modifications [19], and further improved at the 1-month follow-up session. The VVCM decrease is consistent with first peak KAM decrease observed during toe-in gait [27, 28]; furthermore, our results provide new insights about subject-specific contact load changes in natural knees. The VVCM changes during toe-in gait were accompanied by no significant changes in the flexion-extension and internal-external rotation contact moments or the compressive and shear contact forces, thus the VVCM decrease represents a reduction in the contact force on the diseased medial knee compartment. This change was validated by comparing with the experimentally measured medial contact force from the 4$^{th}$ Knee Grand Challenge [122].

Some possible explanations for the uniform reduction in VVCM across all subjects while there were inconsistent changes in muscle forces [19] include pain management or tolerance and varying degrees of knee OA severity. Pain relief, the primary goal of treating knee OA, is likely to influence VVCM changes, as modified joint loads during gait can be a consequence of pain management [123]. As such, how long a patient has symptomatic knee OA and manages pain by altering kinematics could lead to different muscle and joint load changes. Subjects may alter joint mechanics differently to continue knee function with less pain, as gait and neuromuscular pattern differences exist between patients with varying degrees of knee OA [124]. Understanding the relationship between pain and subsequent alterations in gait, including modifications of joint contact loads and kinematics, is critical to advancing treatments for knee OA because increased knee joint loads are considered major contributors to the development and progression of this disease [93, 123, 125].

There were a few limitations in our study and the results should be interpreted in context with our research challenges. First, SO, rather than dynamic optimization, was used to determined muscle forces in the simulations. We chose SO because of its low computational expense and availability in OpenSim to create the large amount of 300 simulations (10 subjects with 30 each). Additionally, static and dynamic optimization are essentially equivalent for estimating *in vivo* quantities such as muscle forces and joint contact loads during gait [34]. Therefore, SO results should not significantly affect conclusions drawn from this study.

Second, the knee joint contact loads were not localized to the medial and lateral compartments of the joint. The load values reported in the current study represent the whole knee joint contact loads, rather the medial compartment where subjects exhibit radiographic evidence of knee OA. The VVCM directly relates to the unbalanced contact forces on the medial and lateral knee compartments causing the bone-on-bone contact characteristic of OA, thus finding a reduction in this contact moment shows an improvement for patients with medial knee OA. We do not see this variable selection as a major limitation because our modeling, simulation, and analysis approaches were validated through favorable comparisons to instrumented knee implant data [126]. Although the absolute magnitude of knee joint contact loads may change if we made different modeling assumptions, our conclusions regarding the relative reduction in VVCM during *toe-in gait* compared to *normal gait* would be unlikely to change significantly because the same assumptions would be used across gait conditions.

Finally, the VVCM changes remain an *in silico* estimate for subjects with knee OA in this study. Though actual bone and joint contact loads (Appendix, Figure 6c) can be determined with higher order analyses or direct *in vivo* measurement from an instrumented knee implant, these loads are not available for subjects having natural knees with OA before undergoing total knee replacements; therefore, the contact loads are, with good reason, estimated using the knee joint contact load analysis described earlier.

Our results add to an increasing body of knowledge needing further research to determine optimized subject-specific gait modifications for early treatment of knee OA. Determining knee joint contact loads is important in understanding the efficacy of gait modification strategies, as these loads have a large impact on the net KAM in normal gait [18], and thus should be included in studying different strategies. While we found a uniform VVCM decrease across subjects, individual subjects had varying amounts of changes with some improving more than others, which agrees with others showing KAM decreases do not guarantee joint contact load decreases [23, 26] and different patterns of knee contact forces exist across subjects with severe knee OA [127]. However, these studies did not investigate toe-in gait and had much smaller sample sizes compared to our study; therefore, it is unknown the extent to which their results can be generalized to different modification strategies within larger populations. Furthermore, many studies have investigated the effectiveness of gait modification to reduce the knee loads for patients with knee OA showing a wide range of results, though toe-in gait has been studied far less than other modification strategies and has not been included in instrumented knee studies. Previous studies found the use of bilateral hiking poles significantly reduces medial and lateral knee compartment forces, and found many modifications reduce external knee moments, including toe-out, slow speed, decreased stride length, medial-lateral trunk sway, lateral heel wedges, walking with a cane, and medial thrust gait [24, 128]. Future studies should include toe-in gait modification as it has been shown to reduce the net KAM [15, 28] while the peak knee flexion moment remains unchanged [27].

Further research is necessary to determine optimal, whole-body kinematics to minimize joint loads through gait modification. Currently, there are few studies investigating the design of subject-specific gait modification patterns, though some have shown promise. One group designed novel gait modifications with potential clinical benefits using optimizations of subject-specific, full-body gait models [23]. Additionally, this group found subject-specific cost functions combined with subject-specific gait models can predict clinically significant gait features for designing rehabilitation and surgical treatments optimized to individual patient needs [129]. Optimal subject-specific gait training in the future may combine a number of previously reported modification strategies to reduce the net external KAM and joint contact loading to improve knee function and slow progression of knee OA.

This study found toe-in gait modification reduces the VVCM in individuals with knee OA. The uniform improvement in the VVCM despite non-uniform self-selected muscle patterns [19] to achieve toe-in gait modification shows the efficacy of toe-in gait to improve overall knee function for individuals with knee OA, especially with these positive results being retained in all subjects after 1 month. Because certain subjects are able to reduce this contact load more than others, it may be beneficial to further analyze individual muscle activities and significant features of modified gait to improve toe-in gait modification for all patients with knee OA. Our results show the potential of toe-in gait modification for early treatment of knee OA and this work can be implemented into future studies of optimal subject-specific gait modification strategies that would be able to account for variation in joint contact loads on an individual basis.

# CHAPTER FOUR: SPECIFIC AIM 2-
# SELECTED SIGNIFICANT FEATURES OF GAIT WITH THE GREATEST POTENTIAL TO DECREASE JOINT LOADS FOR PATIENTS WITH KNEE OA

In aim 2, data mining and machine learning techniques were applied to select a set of significant features of gait that differentiate between subjects with high and low knee joint contact loads during toe-in gait. The goal of specific aim 2 was to discover the significant features of gait that have the potential to decrease harmful knee joint loads. This study was accomplished by further analyzing simulation data to identify significant features through a machine learning technique based on a pseudo-quadratic discriminant analysis with a 10-fold k-fold cross validation of the gait data. This investigation will clarify the potential of gait modification to decrease joint loads.

## 4.1 Significant Features of Toe-in Gait with Potential to Lower Knee Joint Contact Loads of Individuals with Knee Osteoarthritis: Implications for Improving Gait Modifications

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### *4.1.1 Introduction*

Knee OA is a chronic condition causing physical disability in 14% of U.S. adults aged 25 and older [119]. This disease is characterized by decreased neuromuscular control, weakened knee musculature, and knee joint instability. Currently, treatment options are limited to pain management until pain is no longer manageable and a joint replacement surgery is necessary. A better understanding of whole-body kinematics, or features of gait, used during toe-in gait modification to reduce joint loading is necessary to use this modification as a treatment strategy for patients with knee OA and design optimal patient-specific modifications in the future.

Gait modification has been proposed as an early intervention strategy to treat knee OA by mitigating knee joint contact loads. These loads are considered major contributors to articular cartilage degeneration associated with OA progression [20] as patients with knee OA exhibit increased joint loads during gait [21]. KAM is a common measure used to assess medial knee loading [15] due to high correlation with measured medial knee contact force [17], presence, severity, and progression of medial knee OA; however, this approach does not account for muscle forces when estimating joint loads. Internal joint contact loads, such as VVCM, account for muscle forces which change following gait modification [19]. VVCM, determined with OpenSim JRA, is an internal knee joint contact moment directly related to unbalanced loading between medial and lateral knee compartments and accounts for muscle forces [10]. Importantly, VVCM is reduced with toe-in gait (Appendix, Table 4). Because the modifications of features of gait that allow subjects to reduce joint loading are not well understood, it is important to determine these features to improve efficacy of gait modification. Understanding which features have the greatest potential to reduce harmful joint loads, such as VVCM, allows researchers to develop and test improved gait modification strategies to progress this method as a treatment for patients with knee OA. Instead of training subjects to walk based on one modification feature, such as a decreased foot progression angle in toe-in gait, subjects can likely be trained with more features to increase the effectiveness of gait retraining and maximize benefits to patients by further alleviating knee OA symptoms with reduced joint loading.

To determine which features of gait are most significant, the high dimensionality of human gait data must be reduced because predictive power decreases as dimensionality increases [130]. Machine learning is well-recognized method in computer science for discovering models, patterns, such as feature selection, in data. The goal of feature selection is to use a set of candidate features and select a subset with the best performance under a certain classification system to manage large amounts of irrelevant features. While there are many algorithms for feature selection, one of the most widely used is sequential forward search [131]. Sequential forward search uses a wrapper method to evaluate a specific subset of features inducing a model from a training group with the model used for prediction and classification of a testing group. Because wrapper approaches carry the risk of over fitting [132, 133], cross-validation was implemented. Cross-validation separates the data, using some for training and the rest for testing, and uses measures of fit to estimate the model's predictive performance, so not all of the data is used to build the model [134].

This study utilized machine learning to develop and test a model for selecting significant features of toe-in gait with the greatest potential to reduce VVCM. Additionally, because subjects reduce VVCM by varying amounts, we tested another model for selecting a different or additional set of significant features of toe-in gait for the top performing subjects, or those with the greatest reduction in VVCM. We tested the models using a forward sequential feature selection (fSFS) algorithm with pseudo-quadratic discriminant analysis (pQDA) and 10-fold cross validation to determine the significant features of toe-in gait. Identifying changes in whole-body kinematics and kinetics, or features of movement, during toe-in gait contributes to our understanding of this modification and provides insights needed to improve gait retraining programs aiming to minimize detrimental knee joint contact loads associated with the progression of knee OA.

#### *4.1.2 Methods*

Three hundred subject-specific, muscle-actuated dynamic simulations were created to reproduce the gait dynamics during *normal* and *toe-in gait* trials of 10 subjects with radiographic evidence of medial compartment knee OA. The results of these simulations (e.g., kinematics and kinetics) were used to conduct a subsequent machine learning forward feature selection to determine the significant features of toe-in gait with the greatest potential to reduce VVCM.

***Experimental Data Collection***

Experimental gait analysis data were collected from 10 subjects (Appendix, Table 4) with symptomatic, medial-compartment knee OA trained over the course of six weeks to adopt a 7° decrease in foot progression angle to achieve a *toe-in gait* modification [27] (see Shull, et. al 2013b for more experimental data collection details). Experimental gait analysis data were analyzed for *normal gait* (session prior to *toe-in gait* training), *post-training toe-in gait* (session following the 6-week training regimen), and *follow-up toe-in gait* (session 1 month after the 6-week training regimen ended) to determine the knee joint load changes due to gait modification. *Toe-in gait* modification, reduced the first peak KAM by 20%, and reduced symptomatic knee pain by 2 points on a visual-analog scale from 0 to 10, on average [28]. All subjects gave informed, written consent for collection and analysis of their gait data prior to participating, and the study was preapproved by the institutional review board.

*Musculoskeletal Models and Simulations*

A generic, three-dimensional, lower-limb musculoskeletal model consisting of 12 degrees of freedom and 43 muscle-tendon actuators was created by modifying the Gait2392 model in OpenSim to match experimental data of the ipsilateral limb and pelvis [77]. The contralateral lower extremity, head, upper extremities, and torso were removed and replaced by external, or residual, forces and torques acting on the pelvis. The pelvis position and orientation were defined relative to the ground with 6 degrees of freedom, the hip as a ball-and-socket joint, the knee as a planar joint with tibiofemoral and patellofemoral translational constraints as a function of knee flexion [78], and the ankle and subtalar joints as revolute joints [79]. All body segment inertial parameters were derived from Anderson and Pandy (1999) [48]. The muscle-tendon actuators were modeled as Hill-type muscles in series with a tendon based on musculotendon parameters [80].

A subject-specific musculoskeletal model and 30 muscle-actuated dynamic simulations (10 consecutive *normal gait* steps from the end of the trial before *toe-in gait* training, 10 consecutive *post-training toe-in gait* steps from the end of the trial after the 6-week training regimen, and 10 consecutive *follow-up toe-in gait* steps from the end of the retention trial 1 month following the end of training) was created for each subject during the stance phase of gait using a multi-step process. First, the generic musculoskeletal model was scaled to represent the experimentally measured size of each subject. Second, IK generated values of model's generalized coordinates that best matched (RMS marker error < 2 cm) experimentally measured kinematics. Third, SO [77] determined individual muscle activations and resulting muscle forces that produced the net joint moments consistent with the experimentally measured kinematics and GRFs. Finally, JRA in OpenSim [10] estimated contact loads to determine changes in knee joint contact loads (i.e., forces and moments) between gait conditions. This analysis calculates joint contact forces and moments transferred between consecutive bodies resulting from all motions and forces acting on the model. The equations of motion of the multibody system, represented in terms of generalized coordinates and forces, are solved analogous to ID, but includes an additional step incorporating muscle forces with joint kinematics and GRFs to determine resultant joint contact loads [121].

***Subject Performance Grouping***

To determine the features of gait with potential to reduce VVCM, we first grouped subjects based on the change in VVCM from normal (*baseline*) to toe-in gait (*post-training* and *follow-up* sessions) (Appendix, Figure 14b). The subjects were grouped separately for changes at *post-training* and *follow-up* because some exhibited further decrease in VVCM at follow-up as compared to post-training. This grouping allowed us to determine the top performing subjects, or those with the most improvement. These subjects moved to a better grouping at follow-up, such that group 1 was the worst group and group 6 was the best. The six groups were defined by the amount of change in VVCM from normal to toe-in gait, using the average decrease in VVCM (14%) as the basis for forming each group. Each group was formed by adding or subtracting half of the average decrease (7%) to space each group evenly around the average decrease, with the addition of a slight increase group to account for more variability in the subjects tested (Appendix, Table 5). Six groups were determined so small changes between subjects would be accounted for in the differences between groupings. These groupings allow the specific changes in each significant feature to be considered between varying amounts of improvement using toe-in gait to better understand how to improve this modification for optimal benefits to the patients in the future. Group 1 included subjects with an increase in VVCM. At the post-training session, group 1 contained 2 subjects and 3 subjects at follow-up. Group 2 included subjects having a 0-6.99% (well below average) decrease in VVCM, with 2 subjects at the post-training session, and 1 subject at follow-up. Group 3 included subjects having a 7-13.99% (below average) decrease in VVCM with 3 subjects at the post-training session and 1 subject at follow-up. Group 4 included subjects having a 14-20.99% (average) decrease in VVCM, with no subjects at the post-training session and 2 subjects at follow-up. Group 5 included subjects having a 21-27.99% (above average) decrease in VVCM, with 2 subjects at the post-training session and 1 subject at follow-up. Group 6 included subjects having a 28% or greater (well above average) decrease in VVCM, with 1 subject at the post-training session and 2 subjects at follow-up.

The choice of 6 groups could impact the results of this study; therefore we compared feature selection results of different numbers of groups to understand the effects of varying the number of groups on the selection of significant features of gait. This comparison serves to validate the use of 6 groups in this study, by comparing the selected features and the order in which they are selected to those in the different groupings. We compared the selected feature results of our 6 groups to results for 5, 4, 3, and 2 groups, respectively. These additional groupings were created in a similar manner to creating the 6 groups, such that each grouping was centered on the average decrease (14%) in VVCM by adding or subtracting half the average decrease to form the additional groups (7%) (Appendix, Table 5).

***Dimensionality Reduction via Forward Sequential Feature Selection***

Machine learning was used to address the high dimensionality of data from our simulations of gait and select a subset of the most significant features. A supervised process trained a model to predict desired results using a fSFS algorithm in a wrapper fashion on all simulation results for all subjects with 10-fold cross validation [135] and pQDA. The pQDA was used to allow covariance matrices to vary among classes by inverting the covariance matrix using the pseudo inverse.

The fSFS algorithm used 96 different features from our simulations (Appendix, Figure 14a), including GRF, motion from IK, joint moments from ID, muscle force estimates from SO, and joint contact loads from JRA during normal gait (*baseline*) and toe-in gait (*post-training* and *follow-up* sessions) (Appendix, Figure 14a). Because we are interested in the features of gait with the potential to reduce VVCM, feature selection was based on the reduction in VVCM following toe-in gait compared to normal gait using the subject performance groups described earlier (Appendix, Figure 14b). To obtain a set of significant features of toe-in gait, the fSFS algorithm used two main components, the objective function and sequential search. The objective function, known as the criterion, was minimized over all possible feature subsets; in our case, the criterion was the misclassification error (MCE) found during cross validation. We used a forward search (Appendix, Figure 14c) to sequentially add features from the simulation data while evaluating the MCE.

The prediction performance of feature subsets identified during this supervised learning process was evaluated by dividing the simulation input data into training and test data sets based on 10-fold cross validation [135]. The 10-fold cross-validation separated the input data into 10 equal-sized data sets or folds and progressively used 9 sets for training and the remaining set for testing and calculation of the MCE. Next, fSFS selects a subset of features by sequentially adding features until the criterion stopping condition, minimizing MCE, is satisfied. From the training data, features are selected and fit with a pQDA model and the performance of each candidate feature subset is evaluated and compared. The test data is then used to evaluate the performance of the final selected feature. fSFS continues until local minimum MCE is found, and then the entire fSFS process repeats 10 times, until all observations are used for both training and validation or testing. Importantly, each observation is only used once as a validation or test set. Finally, a final average of each repetition determines the subset of features selected as target outputs (Appendix, Figure 14d).

#### *4.1.3 Results*

Sixteen significant features were identified from 96 different features of toe-in gait with the potential to reduce VVCM. The percentage of correct predictions made by the pQDA was 98.8%, on average, across the 10 cross-validation folds ($R^2$ = 0.97). The selected significant features of toe-in gait included ground reactions (vertical reaction force), motion (pelvis list, rotation, tilt, height, and mediolateral position, hip flexion, adduction, and rotation), joint moments (KAM), muscle force estimates (biceps femoris short head, gluteus maximus anterior, and gluteus maximus middle), and joint contact loads (hip compression and anterior shear force, and metatarsophalangeal flexion-extension contact moment) (Appendix, Table 6, *post-training*; Appendix, Table 7, *follow-up*). The top 3 features selected, hip rotation, KAM, and pelvis list.

There were 4 (of the 10) subjects classified as top performers because they exhibited further decrease in VVCM between post-training and follow-up. These subjects had a slightly different set of significant features to achieve improvements. Eleven significant features were identified from 96 total features of toe-in gait for this group. The percentage of correct predictions made by the pQDA model was 100%, on average, across the 10 cross-validation folds ($R^2$ = 0.98). For top performers, selected significant features of toe-in gait included ground reactions (mediolateral reaction force, free torque), motion (pelvis list, rotation, tilt, and height, hip adduction and rotation), joint moments (hip adduction moment) and joint contact loads (hip superior compression force, knee flexion-extension contact moment) (Appendix, Table 8). The top 3 features for top performing subjects were pelvis list and tilt, and hip rotation.

In comparing the effects of varying the number of groupings on the selection of features to validate the use of 6 groups in this study, we found that varying the number of groups selected similar features in a similar order despite different amounts of groups (Appendix, Table 9). The use of 5 groups selected 57% of the same features as using 6 groups. The use of 4 groups had 34%, 3 groups had 41%, and 2 groups had 53% of the same selected features as using 6 groups

(Appendix, Table 10). Hip rotation appeared as the top selected feature in 6, 5, and 4 groups, and was in the top 6 selected features for 3 and 2 groups. Hip rotation, pelvis tilt, and pelvis height were in the top 6 selected features for all of the groupings as well. Additionally, every grouping showed hip rotation, pelvis tilt, pelvis height, hip adduction, and biceps femoris short head force to be significant features to decrease VVCM during toe-in gait (Appendix, Table 9). Importantly, predictive power decreased with the number of groupings, such that having 6, 5, and 4 groups had 99% correct predictions across the 10 cross-validation folds, while using only 3 groups had 98% correct predictions and 2 groups had only 91% correct predictions (Appendix, Table 10). Finally, 14 out of 16 selected features when using 6 groups, as in this study, were also selected in at least two of the other groupings, showing the selected features in this study are truly significant for decreasing VVCM, regardless of number of groups used during feature selection (Appendix, Table 9).

#### *4.1.4 Discussion*

How subjects achieve gait modifications by altering whole-body kinematics and kinetics is an open question and answers are necessary to effectively use gait modifications as a conservative intervention strategy for treating knee OA. Using machine learning, we determined significant features of *toe-in gait* that reduce VVCM, the contact moment directly related to unbalanced loading between the medial and lateral knee joint, in subjects with medial knee OA. Generally, the identified significant features were focused on the hip and ankle, not the knee itself. Additionally, we determined a set of significant features of gait for top performing subjects, or those with the most VVCM decrease. While top performers shared many of the same features from the entire group, importantly, different significant features were identified in these subjects. Each of the identified significant features of toe-in gait are associated with a decrease in knee joint contact loads, which supports the use of clinical motion analysis and musculoskeletal simulation to better understand gait modification as an early intervention treatment strategy for patients with knee OA. We validated our methods for feature selection by investigating the effects of varying the number of groups during feature selection and comparing the results to those using 6 groups as in this study. The selected features of gait should be targeted in future gait modification studies to maximize benefits for patients. For example, while measuring foot progression angle to achieve toe-in gait in real time during gait retraining, these other features may also be measured to improve the efficacy of gait retraining. Targeting these significant features helps realize the potential of gait modification to treat knee OA by alleviating symptoms and lowering knee joint loads associated with disease progression.

Of the 16 selected features in this study, the top 3 features were very telling. The top 3 features, hip rotation, KAM, and pelvis list, were those the change in VVCM was most sensitive to when selecting features to minimize the MCE. Because subjects walked with toe-in gait and reduced VVCM and KAM (Appendix, Table 4), we anticipated hip rotation, resulting from decreasing the foot progression angle in toe-in gait, and KAM, a common measure of medial knee loading that decreases with toe-in gait, to be two of the top features. These features resulting as top features support the use of toe-in gait to improve symptoms for patients with medial knee OA and the use of KAM to assess efficacy of gait modification strategies. Also, pelvis list and hip rotation as top features shows major changes are being made at the hip joint and pelvis to improve symptoms at the knee. However, it is unknown whether these changes may negatively affect the hip and pelvis or lower back with prolonged use of toe-in gait. Additionally, for top performing subjects, the top 3 features were similar to those of the entire group, including pelvis list and tilt, and hip rotation, and were focused around the hip and pelvis. Future studies should consider the hip and pelvis in addition to the knee to fully assess the efficacy of gait modification strategies for treating patients with knee OA. Investigating optimal outputs for these features to minimize harmful knee joint loading in the future will help determine the most efficient method for gait retraining.

Comparing the results of varying the number of subject groupings during feature selection validated the use of 6 groups in this study. We compared the feature selection results of our 6 groups to the results using 5, 4, 3, and 2 groups all centered around the average decrease in VVCM as well. We found that 88% of the selected features in this study appear as significant regardless of the number of groupings. 14 out of the 16 selected features with 6 groups appear as significant features in two or more groupings, with the last two selected, metatarsophalangeal flexion-extension moment and gluteus maximus anterior force, being those that were not similar to any of the other groupings. This suggests that these last two features may not have a large impact on decreasing VVCM. Additionally, hip rotation was the top selected feature for 6, 5, and 4 groups, and was in the top 6 selected features for 3 and 2 groups, highlighting this feature to most significant for decreasing VVCM during toe-in gait. Finally, hip rotation, pelvis tilt, pelvis height, biceps femoris short head force, and hip adduction were significant features in all groupings, indicating these may be the most important features to be targeted in future gait retraining studies to decrease harmful joint loading in patients with medial knee OA. Importantly, using different numbers of groups yielded different sets of significant features. However, each of the groupings had many of the same selected features, for example 5 groups had 57% of the same features as using 6 groups, while 4, 3, and 2 groups had 34%, 41%, and 53% respectively. Additionally, as the number of groups decreases, the predictive power also decreases, such that using 6 groups had 99% correct predictions, while using 2 groups only had 91% correct. These results indicate that using fewer groupings may not be able to correctly classify the significant features as accurately and using more groups. Using more groupings helps highlight the smaller, unique differences between each subject during toe-in gait, utilizing more information about gait on a subject-specific basis to select features more efficiently, while using fewer groups yields more generalized results that may be significant on average but not on an individual basis. Therefore, the use of 6 groups is a valid choice in this study to select significant features of gait to decrease VVCM for individuals with medial knee OA.

Some possible explanations for the selected feature sets differing between the entire group and the top performers could be that top performers identified how to enhance the toe-in gait retraining in such a way that works best for their specific body anthropometry and reduced pain or discomfort. Also, subjects adopted unique muscle force modifications to achieve toe-in gait modification [19], thus the key to reducing joint loads very likely lies in subject-specific modification patterns. Additionally, a major side effect of knee OA is pain, thus it is probable there is a cause-and-effect relationship between knee pain and gait changes, and it may be that this relationship is present in selecting features of gait between different subject groups [107, 108, 123]. Also, subjects in this study presented varying amounts of knee pain and changes in knee pain both pre- and post-training (Appendix, Table 4), which could contribute to varied sets of significant features.

There were a few limitations in our current study. First, changes in muscle forces and VVCM in this study remain an *in silico* estimate for subjects with knee OA. Higher order analyses can determine actual joint contact loads and muscle forces through a direct *in vivo* measurement from an instrumented knee implant and EMG. However, EMG was not available for this subject group and *in vivo* measurements are not available for subjects with natural knees with OA before undergoing a total joint replacement. Therefore, simulated muscle forces and joint loads are estimated, with good reason, using the modeling and simulation methods described earlier.

Second, while we found significant features of gait with potential to reduce harmful joint loads during toe-in gait, it is important to note that different sets of features may be found for other gait modification strategies. Many studies investigated different modification strategies which reduce the first peak KAM similar to toe-in gait [27, 28], including slowed walking speed, decreased stride length, increased medial-lateral trunk sway, and lateral heel wedges [15, 23, 24], and these modifications subsequently reduce pain associated with knee OA and slow disease progression [15, 22]. However, the significant features of toe-in gait in this study were selected to achieve the same ultimate goal of reducing loading in the medial knee joint compartment. Thus, it is likely that using these different gait modification strategies will produce similar results. Additionally, modification studies found training subjects to adopt a gait pattern with increased hip adduction and internal rotation as well as using a medial thrust gait, or medializing the knee while maintaining a constant foot progression angle, can significantly reduce KAM [23, 25], but also increase knee flexion which may increase overall knee contact force and counteract the potential benefits of a reduced KAM [26]. Toe-in gait, however, does not constrain hip angles or foot progression angle and may be a more natural modification strategy [113].

The results of this study highlight the need for further research to develop subject-specific optimized gait modifications for better treatment of knee OA. Determining significant features of gait is important for understanding specific changes occurring during gait modification and the effectiveness of this treatment strategy for reducing joint loads and should be included in studying optimal gait modification paradigms. Many studies focus on using gait modification for treating early-stage knee OA, but few have investigated which features of the modification have the most potential to positively impact joint contact loads and provide the most benefits for individuals with knee OA. In the future, it will be useful to incorporate these features of gait in evaluating gait modification strategies and designing optimal subject-specific gait modifications that account for variation in joint contact loads on an individual basis. Our results show the potential of toe-in gait to be used for early treatment of knee OA and this work can be implemented into future studies to improve this modification for optimal joint contact load results.

# CHAPTER FIVE: SPECIFIC AIM 3- TESTABLE GAIT MODIFICATIONS TO MINIMIZE KNEE JOINT LOADS DESIGNED USING SURROGATE-BASED OPTIMIZATION

In aim 3, surrogate models based on polynomial response surfaces were created to characterize the gait-load relationships of the modified gait and efficiently find optimal modifications for specific patients. The goal of specific aim 3 was to understand how the significant features influence gait modification and how they can be used to create testable gait modifications to decrease joint loads on an individual basis. This study was accomplished by fitting the joint loads as a multidimensional quadratic function of the most significant features of gait modifications. Then, optimizations varied the gait modification patterns to determine the optimal gait modification strategies that minimize harmful knee joint loads. This investigation clarified the potential of surrogate-based optimization to design testable gait modification strategies to minimize knee joint loads. This analysis provides new guidelines for determining if, and under what conditions, gait modifications are likely to decrease joint loads and benefit specific patients.

## 5.1 Using surrogate-based optimization to design testable gait modification strategies with potential to minimize varus-valgus contact moment

### *5.1.1 Introduction*

Knee OA is a prevalent, chronic condition characterized by decreased neuromuscular control, weakened knee musculature, and knee joint instability, with symptoms developing slowly over time [16]. Despite the need for early, effective treatment, few clinical options are available and are limited to pain management, though gait modification has shown promise as an early intervention strategy by mitigating harmful knee joint contact loads. These loads are considered major contributors to articular cartilage degeneration associated with OA progression [20], thus reducing these loads is especially vital for treating patients with knee OA.

One of the most common measurements of joint loading, the external KAM, has been correlated with presence, severity, and progression of medial knee OA [15]. While KAM exhibits two peaks during the gait cycle, only the first peak in early stance has been shown to be higher in patients with knee OA as compared to healthy individuals [91, 136, 137], thus lowering the first peak KAM is a key design factor in creating gait modification strategies. Because *in vivo* measurements of medial loading cannot be measured noninvasively, KAM is often used as an external measurement to assess gait modification strategies due to a high correlation with measured medial knee contact force [17]; however, this approach does not account for muscle forces when estimating joint contact loads and does not guarantee a decrease in medial contact force during gait [26]. Determining internal joint contact loads, such as VVCM, that account for muscle forces gives a better understanding of joint mechanics and overall musculoskeletal function as this analysis includes muscle forces which change following gait modification [18, 19]. VVCM, determined with OpenSim's JRA [10], is an internal knee joint contact moment directly related to unbalanced loading between the medial and lateral compartments resulting from a higher order method than ID which includes muscle forces when determining joint contact loads. Importantly, because VVCM directly impacts medial knee OA, reducing this joint contact load should be of highest priority in design gait modification strategies for treating knee OA.

Though numerous studies have investigated various gait modifications, few focus on optimizing these gait patterns in order to minimize joint loads. Optimizing gait modification strategies allows for more efficient treatment of knee OA, reducing symptoms and delaying disease progression by mitigating harmful joint loads. Optimization methods can be used to determine a feasible combination of model parameters, such as significant features of gait, and produce natural gait patterns that minimize joint loading. Full-body models and simulations with optimization computational methods have previously been used to identify relationships between whole-body kinematics and peak knee moments during walking using OpenSim (simtk.org, Stanford, Ca)  musculoskeletal modeling software [23]. Optimization of human movement is highly complex and involves high dimensionality with 10 or more design variables, making these large-scale problems with high computational expense of iterative evaluation of the cost function and constraints [138]. Gradient-based optimization methods were the first to be parallelized for human movement [139-141] and have been widely used in large-scale problems investigating human movement [23, 139, 140, 142-146]. Creating testable, optimized gait modification patterns allows researchers and experimentalists to use this information to test new patients in the future with more immediate benefits to those patients.

High computational expense can be a limiting factor in optimization problems; however, response surface optimization provides a methodology to address this limitation [147]. Response surface optimization is a rapid evaluation approach that has successfully been used in many other studies to eradicate computational bottlenecks. These surfaces are multidimensional surfaces fit to outputs of interest, such as VVCM, predicted by a model or measured experimentally. The coefficients of the mathematical form of the response surface are determined to provide the best fit between the output of interest as a function of desired design variables, such as significant features of gait, and the surface approximation acts as a surrogate for engineering analyses when optimizations are performed [147]. Importantly, with highly dimensional gait data, response surfaces provide a rapid evaluation method for optimizing with many design variables, allowing optimal gait modification patterns to minimize joint loading to be developed with lower computational expense.

This study determined testable gait modification strategies to minimize joint contact loads, specifically minimizing VVCM. We used surrogate response surfaces based on significant features of gait and a gradient-based optimization to determine an optimal gait modification strategy to minimize VVCM for patients with medial knee OA. Identifying unique gait patterns to minimize knee joint loads associated with the progression of OA contributes to our understanding of gait modification and provides insights needed to improve gait modification programs to provide optimal benefits to patients.

### *5.1.2 Methods*

Three hundred subject-specific, muscle-actuated dynamic simulations were created to reproduce the gait dynamics during *normal* and *toe-in gait* trials of 10 subjects with radiographic evidence of medial compartment knee OA. The results of analyzing these simulations were used to construct surrogate response surfaces reflecting the subjects' gait analysis data that were used to create testable, optimized gait modification strategies.

#### *Experimental Data Collection*

The experimental gait analysis data were collected from 10 subjects (Appendix, Table 4) with symptomatic, medial-compartment knee OA [27]. To be selected, subjects were evaluated with both inclusion and exclusion criteria (see Shull 2013b for more experimental data collection details). To develop a surrogate-based response surface reflecting the gait analysis data, experimental gait analysis data were analyzed for *normal gait* (session prior to *toe-in gait* training), *post-training toe-in gait* (session following the 6-week training regimen), and *follow-up toe-in gait* (session 1 month after the 6-week training regimen ended). The *toe-in gait* modification, a 7° decrease in the foot progression angle, reduced the first peak KAM by 20%, and reduced symptomatic knee pain by 2 points on a visual-analog scale from 0 to 10, on average [28]. All subjects gave informed, written consent for collection and analysis of their gait data prior to participating, and the study was preapproved by the institutional review board.

***Musculoskeletal Models and Simulations***

A generic, three-dimensional, lower-limb musculoskeletal model consisting of 12 degrees of freedom and 43 muscle-tendon actuators was created by modifying the Gait2392 model in OpenSim to match experimental data of the ipsilateral limb and pelvis [77]. The contralateral lower extremity, head, upper extremities, and torso were removed and replaced by external, or residual, forces and torques acting on the pelvis. The pelvis position and orientation was defined relative to the ground with 6 degrees of freedom, the hip as a ball-and-socket joint, the knee as a planar joint with tibiofemoral and patellofemoral translational constraints as a function of knee flexion [78], and the ankle and subtalar joints as revolute joints [79]. All body segment inertial parameters were derived from Anderson and Pandy (1999) [48]. The muscle-tendon actuators were modeled as Hill-type muscles in series with a tendon based on musculotendon parameters [80].

Thirty subject-specific muscle-actuated dynamic simulations (10 consecutive *normal gait* steps from the end of the trial before *toe-in gait* training, 10 consecutive *post-training toe-in gait* steps from the end of the trial after the 6-week training regimen, and 10 consecutive *follow-up toe-in gait* steps from the end of the retention trial 1 month following the end of training) were created for each subject during the stance phase of gait. First, the generic musculoskeletal model was scaled to represent the experimentally measured size of each subject. Second, IK generated values of model's generalized coordinates that best matched (RMS marker error $< 2$ cm) experimentally measured kinematics. Third, SO [77] determined individual muscle activations and resulting muscle forces that produced the net joint moments consistent with the experimentally measured kinematics and GRFs. Finally, JRA in OpenSim [10] estimated contact loads to determine changes in knee joint contact loads (i.e., forces and moments) between gait conditions. This analysis calculates joint contact forces and moments transferred between consecutive bodies resulting from all motions and forces acting on the model, including muscle-tendon actuators, using multibody dynamics. Because muscle forces or internal joint contact loads are not required to solve the equations of motion of the multibody system, JRA carries out an important, additional step incorporating muscle forces along with joint kinematics and GRFs to determine the resultant joint contact loads [121].

The outputs from these OpenSim analyses were used as inputs for feature selection to determine the most significant features of gait with the greatest potential to reduce VVCM. Subjects were grouped subjects based on the amount of change in their VVCM from normal gait (*baseline*) to toe-in gait during two different sessions (*post-training* and *follow-up*) in order to determine which features of toe-in gait have the greatest potential to decrease VVCM. The subjects were grouped separately for changes at *post-training* and *follow-up* because some subjects saw a further decrease in VVCM at follow-up as compared to post-training.

***Selecting Significant Features of Gait***

A supervised process trained a model to predict desired results using a forward sequential feature selection (fSFS) algorithm in a wrapper fashion on all simulation results for all subjects with 10-fold cross validation [135] and pseudo-quadratic analysis (pQDA). The pQDA was used to allow covariance matrices to vary among classes by inverting the covariance matrix using the pseudo inverse.

The fSFS algorithm compared 96 total features from our OpenSim simulations. Because we are interested in the features of gait with the greatest potential to reduce joint loads, feature selection was based on the reduction in VVCM following toe-in gait compared to normal gait using the subject groupings. The objective function, the misclassification error (MCE) found during the cross validation, of the fSFS was minimized over all possible feature subsets. We used a forward search to sequentially add features from the simulation data while evaluating the MCE.

The prediction performance of feature subsets identified during this supervised learning process was evaluated by dividing the simulation input data into training and test data sets based on 10-fold cross validation [135]. The 10-fold cross-validation separated the input data into 10 equal-sized data sets or folds and progressively used 9 sets for training and the remaining set for testing and calculation of the MCE. fSFS continued until local minimum MCE was found, and then repeated the process until all observations were used for both training and validation or testing. Importantly, each observation is only used once as a validation or test set. In the end, a final average of each repetition determines the subset of features selected as target outputs.

***Surrogate Response Surfaces***

To determine the optimal gait modification strategy to minimize joint contact loads, we created surrogate models of joint loads as a function of significant features for each percent of stance. These surrogate models were based on a multivariable polynomial regression fit, characterizing the gait-load relationships of modified gait. First, VVCM was fit as a multidimensional quadratic function of the selected significant features of gait for each percent of stance (0-100%). The coefficients of the approximating function for the response surface were determined using data from the musculoskeletal simulations of the experimentally measured gait analysis. The approximate functions of significant features were fit to match joint load data using regression. We constructed a quadratic polynomial response surface, of the form

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1^2 + \beta_4 x_2^2 + \beta_5 x_1 x_2 + \cdots + \beta_i x_n + \beta_i x_n^2 + \beta_i x_{n-1} x_n \quad (1)$$

where $y$ is the optimal VVCM, $\beta_i$ ($i$=0,...,153) are the coefficients identified to fit simulation data, and $x_n$ (n =1,...,16) are the design variables or significant features of gait determined from the musculoskeletal simulations of toe-in gait.

Each subject was represented on the surrogate response surface as cluster of points representing each the 10 measured steps from each gait analysis trial at each point during stance (10 consecutive *normal gait* steps from the end of the trial before *toe-in gait* training, 10 consecutive *post-training toe-in gait* steps from the end of the trial after the 6-week training regimen, and 10 consecutive *follow-up toe-in gait* steps from the end of the retention trial 1 month following the end of training). As the subjects move through stance from 0-100%, the surface changes, as does the global minimum, to represent the different kinematic changes made during gait. The accuracy of the surrogate response surfaces was measured using the errors between the polynomial surfaces and the gait analysis data used to construct them. The quadratic degree of the polynomial surface was selected due to a good fit and high coefficient of determination ($R^2$) between the simulation gait data and response surface.

***Gradient-based Optimization to Minimize Knee Joint Loads***

To create a testable, optimal gait modification strategy to minimize harmful joint contact loads, a cost function was created from the surrogate response surface of the gait-load relationships. This function represented VVCM with respect to the design variables or the selected significant features of gait. To obtain the global minimum, 1,000 nonlinear optimizations were performed for each percent of stance (0-100%) using a gradient-based optimizer function, *fmincon*, in the Matlab Optimization Toolbox (Matlab version 2014a, The MathWorks Inc., Natick, Ma) [148]. The optimizer iteratively searched the quadratic response surface cost function to determine the minimum VVCM at each percent of stance by varying the different significant features of gait. Finally, the cost function results from each of the 1,000 optimizations were compared to find the global minimum of the group for each percent of stance from 0% (heel-strike) to 100% (toe-off).

To ensure the optimal values of the significant features of gait were physically attainable and represented a human gait pattern, lower and upper bounds were set for each of the features of gait from the simulated gait data. Initially, for 0% stance, the bounds were set to be between the mean value plus or minus one standard deviation of each feature from the subjects' simulation data. This allowed the optimizer to determine a starting point within the natural bounds of the gait data. For 1-100% stance, the bounds were set based on the slopes of the gait data significant features. Because there is a tradeoff between a minimized output and the smoothness of the design variable curves through stance, we systematically increased the amount each lower and upper bound was allowed to vary by plus or minus 10% of the natural slope of the gait data. This was done until the minimized VVCM was equal to or less than the mean VVCM of the subjects' gait data to ensure the results reflected optimized features that minimized VVCM for the subjects tested. The features of gait were allowed to vary by plus or minus 40% of the natural slope of the gait data, ensuring the resulting optimized gait minimized VVCM and was natural and comfortable to be incorporated into daily living for patients with knee OA. Allowing each feature to vary based on the natural slope was done to ensure the resulting optimal values were physically attainable between each time step. For example, it would not be possible to switch from the maximum value to minimum value in one time step, thus these bounds ensure a physically reasonable change to prevent that issue.

### *5.1.3 Results*

Surrogate-based optimization determined a physically attainable optimal gait modification strategy to minimize VVCM for patients with medial knee OA based on 16 significant features of gait including ground reactions (vertical reaction force), motion (pelvis list, rotation, tilt, height, and mediolateral position, hip flexion, adduction, and rotation), joint moments (KAM), muscle force estimates (biceps femoris short head, gluteus maximus anterior, and gluteus maximus middle), and joint contact loads (hip compression and anterior shear force, and metatarsophalangeal flexion-extension contact moment). Of these 16 features, the top 3, or those features the fSFS algorithm was most sensitive to in reducing VVCM, were hip rotation, KAM, and pelvis list. While a surface with all 16 design variables cannot be visualized, we constructed multiple surfaces with the top 3 features of gait, hip rotation, KAM, and pelvis list, to visualize the fit between a surface approximation and gait data (Appendix, Figure 15).

The quadratic surrogate response surface had a high correlation fit to the data from the significant features of gait ($R^2$=0.99), allowing for an extremely accurate representation of the simulated gait data during the optimization. The VVCM was minimized in comparison to the mean and standard deviation of the subject gait data (Appendix, Figure 16). The results of each feature of gait from the optimizations were plotted to show the optimal output of each selected feature over full stance in comparison to the mean and standard deviation of the subjects' data resulting from our simulations (Appendix, Figure 17). The optimized results indicated many kinematic changes to minimize VVCM including an increase in internal hip rotation to decrease the foot progression angle, pelvis rotation to rotate the ipsilateral limb forward, and pelvis height to stand taller. The results also show a decrease is necessary in pelvis list and pelvis tilt, or moving toward the contralateral limb, pelvis mediolateral position, or moving the pelvis more towards the midline, hip flexion, or lengthening the leg to stand taller, and hip adduction, or a wider stance width.

### *5.1.4 Discussion*

Because knee loading is a major contributor to the progression of knee OA, reducing this loading is a key factor in designing efficient treatment plans. Gait modification has been proposed as one such treatment method to mitigate harmful joint loads, however; the most efficient methods to minimize internal joint loading are not well understood. Through the use of surrogate-based optimization, we developed testable optimized gait modification strategies to minimize harmful internal joint loads in patients with knee OA.

This study optimized outputs of 16 significant features of gait with potential to reduce VVCM in order to minimize this joint contact load for patients with medial knee OA. As expected, the optimized gait pattern utilized a combination of previously studied gait modification strategies, making whole body kinematic and kinetic changes to minimize VVCM. Each of the identified significant features of toe-in gait are associated with a decrease in knee joint contact loads and the optimized outputs highlight the key changes to be made during gait modification to ensure the most effectiveness in treating knee OA, which supports the use of clinical motion analysis and musculoskeletal simulation to better understand gait modification as an early intervention treatment strategy for patients with knee OA. These results highlight the major kinematic changes being made at the hip and pelvis in order to minimize contact loading at the knee. Future gait modification studies should consider and monitor these kinematic changes during gait retraining for individuals with medial knee OA, training subjects to adopt this optimized gait pattern to realize the most benefits of gait modification.

There were a few limitations in our current study that should be taken into consideration when evaluating our results. First, the muscle forces were estimated using SO rather than a dynamic optimization due to its low computational expense and ready availability in OpenSim to create a large amount of simulations (300 total for 10 subjects with 30 simulations each). However, SO produces results that are nearly equivalent to dynamic optimization for estimating *in vivo* quantities such as joint contact loads and muscle forces during gait [34]. Also, VVCM is an *in silico* estimate for subjects with knee OA resulting from JRA in OpenSim. Higher order analyses can directly determine actual joint contact loads and muscle forces through a direct *in vivo* measurement from an instrumented knee implant and EMG, though, EMG was not available for this subject group and *in vivo* measurements are not available for subjects with natural knees with OA before undergoing a total joint replacement. Therefore, the simulated muscle forces and joint loads are estimated, with good reason, using the modeling and simulation methods described earlier and should not impact the conclusions drawn in this study.

Second, the results of this study reflect optimized features of gait that minimize VVCM based on experimentally measured toe-in gait data. Because the data were collected with subjects walking with a decreased foot progression angle, these results should be considered in relation to this specific gait modification strategy. However, our results complement a previous study which predicted an optimized gait with a “medial-thrust” method, with decreased pelvis rotation, and slightly decreased pelvis tilt for one subject with knee OA [23]. With the addition of numerous subjects with knee OA, this study adds to a body of knowledge suggesting that kinematic changes at the pelvis may be the most effective way to decrease knee loading in individuals with knee OA. Also, our optimized result for hip rotation, having more internal rotation in early stance and an external rotation in late stance support previously findings that while toe-in gait reduces the first peak KAM [27, 28], toe-out reduces the second peak [91, 111, 149, 150]. Additionally, many previous studies have investigated different modification strategies reduce the first peak KAM similar to toe-in gait [27, 28], including slowed walking speed, decreased stride length, increased medial-lateral trunk sway, and lateral heel wedges [15, 23, 24], and these modifications subsequently reduce pain associated with knee OA and slow disease progression [15, 22]. However, the significant features of toe-in gait used in this study were selected to achieve the same ultimate goal of reducing loading in the medial knee joint compartment and, thus, would likely be the same or similar to significant features of other gait modification strategies to reduce joint loads. One important reason to further study toe-in gait, though, is that many modification studies find that training subjects to adopt a gait pattern with increased hip adduction and internal rotation as well as using a medial thrust gait, or medializing the knee while maintaining a constant foot progression angle, can significantly reduce KAM [23, 25], this can also increase knee flexion which may increase overall knee contact force and counteract the potential benefits of a reduced KAM [26]. Toe-in gait, however, does not constrain the hip angles or foot progression angle and may be a more natural modification strategy [113] to use for creating optimal gait modification patterns to minimize harmful joint loads for patients with knee OA.

Additionally, an assumption in our computational methodology was that the selected cost function coefficients and optimized results were representative of the gait data of this specific subject group. The bounds for each feature of gait varied during the optimization were set to be within the natural slope of the gait data for only the subjects tested in this study. With a different subject group, or with additional subjects, the slopes and bounds would be different and result in different optimized outputs. Additionally, there are different filtering or optimization penalty methods that would changes the bounds and result in different values for the features of gait.

However, we used the subjects' own gait data to create the bounds in this study to ensure the optimized results to reflect a more natural gait designed specifically for these subjects. With these results, experimentalists can now tailor gait modification studies to subjects with knee OA and design more efficient gait modification strategies. With more studies in the future, more data can be added to the surrogate response surface, and the optimization can be updated and refined. These results highlight the potential of simulation-based medicine to make an impact in patient lives, improving outcomes and reducing costs of healthcare with tailor-made treatment options.

The results of this study highlight the key features to be considered in designing subject-specific gait modifications to improve effectiveness of this method as an early intervention treatment for knee OA. Additionally, these results highlight the need for further research to develop personalized gait modifications to best treat patients with knee OA. Many studies focus on using gait modification for treating early-stage knee OA, but few have investigated optimized gait patterns using features of the modification with the most potential to positively impact the joint contact loads and provide the most benefits for subjects with knee OA. Using modeling and simulation to develop optimized gait modification to be used as a treatment for knee OA can greatly improve patient care and reduce healthcare costs as well [10]. Finally, our results show the potential of gait modification for early treatment of knee OA and this work can be implemented into future studies to test and improve this modification for optimal results and benefits to patients with knee OA.

# CHAPTER SIX: FINAL CONCLUSIONS AND RECOMMENDATIONS

Knee OA is a significant global problem with no effective treatments available. Slowing the progression of disability for these patients will have a large impact across the globe. Completing this research has allowed for principles that govern relationships between muscles contributions and purposeful movement like gait modification to be uncovered. This work also lays a foundation for future studies to further improve knee OA treatment. Combining experiments and simulation-based approaches leads to a better understanding of movement modification and treatment plans for patients with knee OA in the future. Patient-specific models and simulations created in this dissertation will help to realize the potential of simulation-based medicine in identifying new treatments and lay a framework for future gait modification studies. The described ***research activities*** fully enabled scientific tools and simulations to investigate gait modifications that minimize patient-specific joint loads to study gait rehabilitation for patients with knee OA. The ***specific benefits*** of this research include the utility of simulation-based medicine to discover new rehabilitation strategies and facilitate patient-specific treatments reducing pain and physical disability to maintain independence and a good quality of life.

## 6.1 Significance of Research

Effective early intervention, non-invasive treatment strategies have potential to drastically improve the quality of life for patients with knee OA and prolong the need for invasive interventions such as a high tibial osteotomy or total joint replacement. However, improving early treatment interventions, such as gait modification, is challenging because the cause-and-effect relationships between muscle forces and joint loading with respect to gait modification and knee OA are not well understood. Dynamic simulations, as used in this research, provide the framework needed to determine, study, and understand the role of muscle forces and joint loads before and after gait modification to clarify this relationship. Utilizing simulations helps highlight the potential of gait modification as an early intervention treatment strategy by identifying how gait modification affects muscle forces and joint loads to determine optimal gait patterns to minimize harmful joint loading.

Linking the detailed knowledge of the neuromusculoskeletal system to fully understand both normal and disordered movement is a major challenge in biomechanics research. The models, computational tools, and optimal gait patterns developed in this research have a wide variety of applications to addressing the many questions in biomechanics problems. While many studies have investigated gait modification strategies in connection with the KAM, few have investigated the impact of gait modification on internal knee joint contact loads and how to minimize these loads for optimal effectiveness in treating knee OA symptoms. With the new understanding of how to minimize joint loading and the development of a novel, automated scaling algorithm, this research can greatly impact future studies investigating all different types of biomechanical problems. We anticipate the insights gained from this research will provide new guidelines to creating, testing, and study new gait modifications for treating knee OA or other musculoskeletal disorders.

This work developed methodologies for interpreting how gait modification impacts the whole-body kinematics and kinetics for patients with knee OA, developed a novel scaling algorithm, and provided new testable guidelines for future gait modification studies. The simulations developed used freely available musculoskeletal modeling and simulation software with many user extensible capabilities that allows these results to be shared with other biomechanical researchers across the globe. To date, there has been 163,000 downloads of the many models, simulations, and software from the project's website with over 27,000 active users [151]. This research adds to this community and further highlights the need for additional studies of the whole-body biomechanics of gait modification in patients with knee OA.

## 6.2 Research Innovation

Currently, there is a gap between the experimental approaches used by physicians, physical therapists, and rehabilitation scientists and the computer simulation approaches used by engineers, mathematicians, and computer scientists. Movement science has long been driven by observations alone, but many key variables to understanding human movement can not be observed [10]. However, musculoskeletal modeling and simulation allows for these variables to be estimated. The reaserch detailed in this dissertation combines these different approaches and forms a working relationship that allows each field to benefit from the strengths of others.

Experimental approaches have contributed a great detail of knowledge to our understanding of biomechanics and human movement, but these advances are inherently limited in nature. Many important variables, such as muscle forces and joint loads, are difficult to measure, and in the case of patients currently suffering from a musculoskeletal disorder, impossible to measure without invasive measures. Without these variables, the detailed cause-and-effect relationships between muscle forces and joint biomechanics to purposeful movement has limited the progress of this type of research. Because muscles can accelerate joints they do not cross and body segments they are not attached to, it is extremely difficult to measure the full effect of muscles during movement. Additionally, without an instrumented implant, directly measuring joint loading is not possible. In order to determine these muscle forces and joint loads during gait in patients with knee OA, a novel approach was required. This approach was driven by the use of a unique set of tools found in musculoskeletal modeling to achieve this task.

The use of these models and simulations has considerable potential to improve patient care and reduce the high healthcare costs of treating movement disorders. Muscle-actuated dynamic modeling and simulation provides the necessary scientific framework needed to complement experimental approaches to estimate and understand those key variables, identify the cause-and-effect relationships and predict outcomes [9, 10]. In the research detailed in this dissertation, the use of muscle-actuated, dynamic models and simulations helped to bridge the gap between experimental and computer approaches to further our understanding of human movement.

This work advanced basic knowledge and understanding of human movement by combining experimental data and observation with computer models and simulations. A major benefit to this work is the use of OpenSim, freely available open source software. The direct benefits to patients suffering from musculoskeletal diseases and disorders can be accelerated with these results being readily available and shared throughout the biomechanics research community with the use of this software.

## 6.3 Fundamental Contributions

The main objective of this research was to uncover the muscle forces and joint loads associated with gait modification and the specific features of gait with the greatest potential to reduce joint loads to design optimal gait modification patterns that minmize joint loading. The goal of this research was to maximize the potential of a gait modification by investigating subject-specific gait modifications to minimize joint loads and improve overall joint function for treating patients with knee OA. The research presented in this dissertation was able to fully accomplish this goal and complete these objectives.

SO and JRA techniques have both been widely used to previously study movement biomechanics and understand muscle forces and joint loading during gait. However, their use in this work was the first of its kind to apply these tools to understand the effectiveness of gait modification and design optimal gait patterns. Developing subject-specific gait modification for many subjects with knee OA allowed this research to be tailored to directly benefit this large global demographic and get to the root of the resarch questions being asked. Because the patients in this study had medial compartment knee OA, the most common form of knee OA, this study focused on understanding how gait modification can improve symptoms in this area of the knee joint. However, there is no model that fully represents the knee with the medial and lateral compartments. While some such knee models are being developed [152], currently the best option is an estimation using the direction of the internal knee joint contact loads using JRA as done in this study. The use of estimated loading is a legitimate limitation to this study and highlights the need for the develpoment of more complex and advanced models in the musculoskeletal software to more accurately represent human anatomy and physiology. As more studies are done highlighitng the differences between medial and lateral knee joint loadings, more advanced models will be developed and incorporated into modeling and simulation software for wide use and applications. Furthermore, the implementation of these tools to understand gait modification for treating knee OA is an important step in knee OA research. The results show that ignoring muscle force modifications, by only investigating the KAM, is a serious limitation in studies of this type. We found the more approriate representation of knee loading is determined with JRA that incorporates the muscle forces when determing joint loads, because muscle forces are different after gait modification [19]. Specifically for patients with medial knee OA, the VVCM proved to be an accurate indicator of joint loading at the site of the disease, as this load directly relates to the unblanced forces experienced in the medial and lateral compartments. Thus, reducing this load should be a key factor in designing gait modifications for treating medial knee OA.

Machine learning techniques used in this research draw from many different fields to detect the significant features of gait with the greatest potential to reduce harmful joint loading. The techniques used in this study uncovered patterns within the biomechanical data. Forward sequential feature selection (fSFS) with pseudo-quadratic discriminant analysis (pQDA) and 10 fold cross validation analyses were used to identify the features of gait, including GRFs, IK angles, ID moments, SO muscle forces, and JRA contact loads, with the greatest potential to reduce harmful joint loads. Sixteen out of 96 features were found to have a significant impact in reducing joint loading in patients with medial knee OA. Interestingly, these selected features were focused more around the hip and ankle joint rather than the knee itself where the patients have OA. The significance of finding these features is that this information can be used to improve gait modifcation effectiveness for treating knee OA. In this study, these features were used to fit a surrogate response surface to use for a gradient-based optimization to develop optimal gait modification strategies for minimizing harmful joint loading. By varying the selected significant features of gait to determine the optimial gait pattern with minimal joint loading throughout stance, the benefits of gait modification can be maximized.

The key contributions of this work include the creation and use of subject-specific musculoskeletal models and simulations to assess the individual muscle forces and joint loadings during gait modification in patients with knee OA. Musculoskeletal models and computational tools are crucial to biomechanical research because they allow researchers to fully evaluate the relationship between joint movement biomechanics and muscle function. This work developed unique methodologies for examining the potential of gait modification to serve as an early intervention, non-invasive treatment for knee OA by developing testable, optimal gait patterns to minimize joint loading. With these optimal gait modification patterns, experimentalists can study patients with these modifcations to see how these patterns impact their disease. It has been suggested that gait modification can delay the progression of the knee OA, so developing the most effective methods is necessary to realize the potential of gait modification.

## 6.4 Summary

All three studies presented in this dissertation found the importance of understanding joint loading during gait modification in patients with knee OA. Millions of people currently suffer from knee OA across the globe, with numbers expected to continue to rise in coming years. Gait modification, as studied in this work, has shown promise to serve as an early, non-invasive treatment for alleviating symptoms of knee OA and delaying progression of the disease. Gait modification paradigms typically focus on modifying kinematics, though the underlying muscle force modification responsible for the kinematic changes and the corresponding joint loads have largely remained unknown. This work sought to maximize the potential of gait modification to treat knee OA by investigating toe-in gait modification and developing an optimal gait pattern based on findings.

The muscle force analysis found that subjects adopt unique muscle for activation patterns while walking with the same desired gait modification, toe-in gait. Even though subjects adopted unique muscle forces to achieve toe-in gait modification, the subject group was able to uniformly reduce the VVCM. From these results, it was evident that subjects are able to subconsciously adapt their gait in such a way to minimize pain from OA and improve overall joint functionality. This result highlighted the need to determine the specific whole-body kinematics, or features of gait, subjects were altering during gait in order to reduce the VVCM and see the most benefits from toe-in gait modification. This study found that only 16 out of 96 total features were significant in reducing joint loading. With these selected features, optimal gait modification strategies were developed with the goal of minimizing harmful joint loads. These findings were preliminary in that they set a testable framework for future studies to investigate the optimal gait patterns developed with these significant features of gait that minimize harmful joint loading for patients with knee OA. In the end, this work was successful in investigating the complex relationship between joint biomechanics and muscle function in respect to gait modification treatment for knee OA.

## 6.5 Glossary

The following terms are used throughout this dissertation.

**Acceleration** — The rate of change of velocity. Measure of the change in a body's velocity.

**Adduction** — Movement where the limb moves toward the midline of the body

**Anterior** — Refers to the front of the body.

**Biceps femoris short head** — One of the lateral hamstring muscles. It functions to flex the knee and laterally rotate the leg when the knee is flexed.

**Center of mass** — The point about which a body's mass is equally distributed.

**Cross-validation** Model validation technique for assessing the results of a statistical analysis. This technique combines measures of fit to determine a more accurate estimate of a model's prediction performance.

**Degree of freedom** A single coordinate of relative motion between two bodies. Such a coordinate responds without constraint or imposed motion to externally applied forces or torques. For translational motion, a DOF is a linear coordinate along a single direction. For rotational motion, a DOF is an angular coordinate about a single, fixed axis.

**Distal** The more distant of two or more objects with respect to the origin or point of reference.

**Dorsiflexion** The motion that occurs when the toes move up toward the tibia.

**Extension** Movement that moves two limbs farther apart, increasing the angle between them, which occurs in the sagittal plane.

**External Rotation** Motion that rotates away from the midline of the body.

**Femur** The bone that is located between the hip and knee joints.

**Flexion** Movement that moves two limbs closer together, reducing the angle between them, which occurs in the sagittal plane.

**Force** An action or effect applied to the body that tends to produce acceleration.

**Force plate** A transducer that is set in the floor to measure about some specified point, the force and torque applied by the foot to the ground. These devices provide measures of the three components of the resultant ground reaction force vector and the three components of the resultant torque vector.

**Forward dynamics** Utilizes know known forces and torques to calculate motion.

**Free torque** Torque acting on the foot as a result from a rotation of the foot when in contact with the ground.

**Frontal plane** This is one of three planes used to divide and describe the body. This plane separates the anterior and posterior sections of the body. Knee adduction-abduction occurs in this plane.

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|---|---|
| **Gait modification** | Altering gait to achieve reduced loading for patients with a musculoskeletal disease. These can be learned, where a patient is taught to walk differently, or assisted, with the use of an assistive object like a cane. |
| **Generalized coordinates** | A set of coordinates (or parameters) that uniquely describes the geometric position and orientation of a body or system of bodies. Any set of coordinates that are used to describe the motion of a physical system. |
| **Gluteus Maximus** | Muscle that acts on the posterior thigh. It functions to extend and laterally rotate the thigh at the hip. |
| **Gradient-based optimization** | An optimization algorithm that searches cost functions for a minimum value. |
| **Graphical user interface** | A visual way of interacting with a computer. This can be done using windows, icons, and menus. |
| **Ground reaction force** | The force exerted by the ground that is equal and opposite to a force applied to the ground by an impacting object (e.g. foot). |
| **Hip adduction-abduction** | Motion of the shank within the frontal plane as seen by an observer positioned along the anterior-posterior axis. |
| **Hip flexion-extension** | Motion of the shank within the sagittal plane as seen by an observer positioned along the medial-lateral axis. |
| **Hip internal-external rotation** | Motion of the medial-lateral axis of the shank within the transverse plane as viewed by an observer positioned along the longitudinal axis. |
| **Inferior** | Refers to the lower or bottom half of a structure or body. |
| **Injury** | Describes damage to the tissue caused by physical trauma. |
| **Internal rotation** | Motion that rotates toward the midline of the body. |
| **Inverse kinematics** | A process that derives joint angles from experimental marker data. |
| **Joint contact load** | Load (i.e. forces and moments) carried by the joint structure itself. |
| **Joint stability** | The ability of a joint to resist dislocation and maintain an appropriate functional position throughout its range of motion. |
| **Kinematics** | Describes movement without regard to the forces involved. |

| | |
|---|---|
| **Kinetics** | Describes movement with regard to the forces involved. |
| **Knee adduction-abduction** | Motion of the long axis of the shank within the frontal plane as seen by an observer positioned along the anterior-posterior axis of the thigh. |
| **Knee adduction moment** | Motion of the long axis of the shank within the frontal plane as seen by an observer positioned along the anterior-posterior axis of the thigh. |
| **Knee flexion-extension** | Motion of the long axis of the shank within the sagittal plane as seen by an observer positioned along the medial-lateral axis of the thigh. |
| **Knee internal-external rotation** | Motion of the medial-lateral axis of the shank with respect to the medial-lateral axis of the thigh within the transverse plane as viewed by an observer positioned along the longitudinal axis of the shank. |
| **Knee Lateral Compartment** | Portion of the knee joint located away from the midline or center of the body |
| **Knee Medial Compartment** | Portion of the knee joint located along the midline or center of the body |
| **Lateral** | Located away from the midline or center of the body. |
| **Lateral gastrocnemius** | One of the muscles that makes up the calf muscle complex. It lies on the lateral side of the posterior portion of the tibia. It functions to plantarflex the foot and flex the knee. |
| **Machine Learning** | A type of artificial intelligence that allows a computer to learn without explicitly being programmed. Focuses on the development of a model that can change with new data. |
| **Medial** | Refers to the midline or center of the body. |
| **Medial thrust gait** | Gait modification that involves medializing the knee during the stance phase of gait. |
| **Mediolateral** | Refers to the direction from side to side or from the medial to lateral side of the body. |
| **Moment** | The effect of a force that tends to rotate or bend a body or segment. |
| **Newton** | Unit of force (N). |

| | |
|---|---|
| **Osteoarthritis** | A type of arthritis that occurs when the articular cartilage at the end of bones wears away. |
| **Plantarflexion** | The motion that occurs when the toes away from the tibia. |
| **Pelvis List** | Motion of the pelvis downward (obliquity) to increase the effective length of the shank at toe-off and heel-strike. |
| **Pelvis Rotation** | Motion of the pelvis such that anterior rotation occurs at heel-strike and posterior rotation occurs at toe-off to increase the effective length of the leg. |
| **Pelvis Tilt** | Motion of the pelvis in respect to the thigh. Motion can move anterior-posterior or mediolateral. |
| **Posterior** | Refers to the back plane of the body. |
| **Proximal** | The closer of two or more objects with respect to the origin or point of reference. |
| **Sagittal plane** | One of three planes used to divide and describe the body. This plane divides the right and left halves of the body. Knee flexion-extension occurs in this plane. |
| **Static Optimization** | An algorithm that uses optimization to estimate individual muscle forces during dynamic movements. |
| **Superior** | Refers to the upper or top half of a structure or body. |
| **Tibia** | One of two bones located between the knee and ankle joint. |
| **Transverse plane** | One of three planes used to divide and describe the body. This plane dives the superior and inferior halves of the body. Knee internal-external rotation occurs in this plane. |
| **Toe-in gait** | Gait modification that involves decreasing the foot progression angle, or turning toes slightly inward. |
| **Torque** | The effect of a force that tends to cause a rotation or twisting about an axis. |
| **Valgus** | Medial deviation of a joint (e.g., knock-kneed). |
| **Varus** | Lateral deviation of a joint (e.g., bowlegged). |
| **Velocity** | The rate of change of position of an object. |

## 6.5 List of Acronyms

The following terms are used in acronym form throughout this dissertation.

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|---|---|
| **BW** | Bodyweight |
| **BW*HT** | Bodyweight times Height |
| **EMG** | Electromyography |
| **fSFS** | Forward Sequential Feature Selection |
| **GRF** | Ground Reaction Force |
| **GUI** | Graphical User Interface |
| **ID** | Inverse Dynamics |
| **IK** | Inverse Kinematics |
| **JRA** | Joint Reaction Analysis |
| **KAM** | Knee Adduction Moment |
| **OA** | Osteoarthritis |
| **pQDA** | Pseudo-Quadratic Discriminant Analysis |
| **SO** | Static Optimization |
| **VVCM** | Varus-Valgus Contact Moment |

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# APPENDIX

**Table 1:** Subject demographics.

| | Mean (SD) |
|---|---|
| **Gender** | F: 4, M: 6 |
| **Age (year)** | 60 (13) |
| **Height (cm)** | 171 (9) |
| **Mass (kg)** | 79 (20) |
| **BMI (kg/m2)** | 26.6 (4.7) |
| **Kellgren & Lawrence grade** | II: 2, III: 6, IV: 1 |
| **Foot Progression Angle (deg)** | |
| ***Normal Gait*** | 2.1 (4.0) |
| ***Toe-in Gait*** | -5.1 (5.1)* |
| **Knee Adduction Moment (%BW*HT)** | |
| ***Normal Gait*** | 3.11 (1.40) |
| ***Toe-in Gait*** | 2.61 (1.47)* |
| **Visual Analog Pain Score** | |
| ***Normal Gait*** | 3.2 (2.30) |
| ***Toe-in Gait*** | 1.35 (0.88)* |

** Represents a significant difference compared to normal gait at the $p<0.01$ significance level.*

**Figure 7:** A representative subject walking with (left) normal gait and (right) toe-in gait. The subject internally rotated the foot by 6° which reduced the first peak knee adduction moment by 20%.

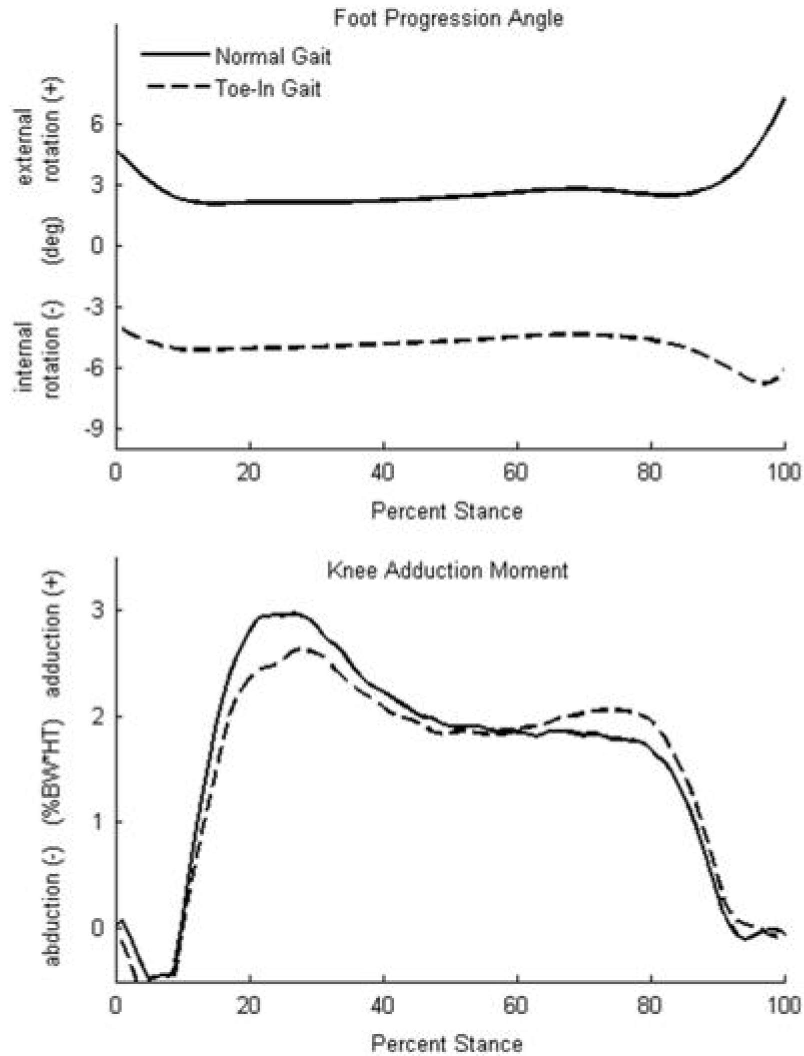


**Figure 8:** Averaged (top) foot progression angle and (bottom) knee adduction moment for all subjects for normal and toe-in gait.

**Table 2:** Percent change in mean muscle force between baseline and toe-in gait for all subjects. Though muscle forces changed within subjects, there were no muscle force modifications across all subjects.

| Muscles | Subjects | | | | | | | | | | Mean | STD | p-Value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | | | |
| Adductor brevis | −51.5 | −24.4 | 9.7 | 102.3 | 164.2 | 171.0 | 52.9 | −38.4 | 38.6 | −4.8 | 42.0 | 80.4 | 0.13 |
| Adductor longus | −52.6 | 37.8 | 250.2 | 82.6 | 212.8 | −38.3 | 159.9 | 2.3 | −24.8 | −5.8 | 62.4 | 109.4 | 0.10 |
| Adductor magnus 1 | 32.3 | −32.7 | 2.0 | 6.1 | −32.7 | 755.1 | 57.8 | −47.9 | 18.8 | −18.7 | 74.0 | 241.5 | 0.36 |
| Adductor magnus 2 | 68.8 | −21.1 | −3.0 | 10.5 | −29.6 | 199.1 | 30.7 | −18.1 | −0.4 | −8.1 | 22.9 | 68.2 | 0.32 |
| Adductor magnus 3 | 72.9 | 43.4 | 4.6 | 50.9 | 32.0 | −38.8 | 8.8 | −12.2 | 45.6 | 8.1 | 21.6 | 33.5 | 0.07 |
| Biceps femoris long head | 99.9 | 1.3 | −0.8 | 37.3 | −27.5 | −19.0 | −19.9 | 8.5 | 27.3 | 14.0 | 12.1 | 37.2 | 0.33 |
| Biceps femoris short head | 11.5 | −41.4 | 13.8 | −22.7 | 496.8 | −47.9 | −49.8 | 37.7 | −60.4 | 54.6 | 39.2 | 165.6 | 0.47 |
| Extensor digitorum longus | −22.9 | −2.2 | −8.9 | −35.3 | 25.5 | 226.2 | −43.8 | −31.7 | 7.0 | −18.0 | 9.6 | 78.9 | 0.71 |
| Extensor hallucis longus | −8.8 | 5.0 | −13.7 | −21.5 | 8.1 | 127.1 | −29.8 | −14.3 | −0.7 | −10.2 | 4.1 | 44.7 | 0.78 |
| Flexor digitorum longus | 0.1 | 4.0 | −6.8 | 3.7 | −14.9 | 1.6 | 0.4 | 0.9 | 12.0 | −13.2 | −1.2 | 8.2 | 0.65 |
| Flexor hallucis longus | 0.8 | 1.7 | −6.0 | 8.6 | −27.1 | −10.1 | 11.7 | 4.6 | 18.5 | −15.3 | −1.3 | 13.6 | 0.78 |
| Gastrocnemius lateral head | 13.8 | −8.3 | 3.8 | −4.5 | 105.2 | −34.3 | −15.0 | 25.1 | −27.0 | 36.2 | 9.5 | 40.2 | 0.47 |
| Gastrocnemius medial head | 14.4 | −9.1 | 3.7 | −4.2 | 110.0 | −35.8 | −15.6 | 26.0 | −28.0 | 40.6 | 10.2 | 42.2 | 0.46 |
| Gemellus | 146.8 | −67.6 | −64.2 | −56.7 | −94.7 | 2098.4 | −48.8 | 31.7 | 9.9 | −50.8 | 190.4 | 674.1 | 0.40 |
| Gluteus maximus 1 | 42.9 | −19.7 | −32.2 | −14.2 | −70.1 | 71.5 | −24.9 | 42.2 | 52.3 | 18.4 | 6.6 | 45.4 | 0.66 |
| Gluteus maximus 2 | 66.5 | −28.8 | −37.6 | −17.7 | −84.6 | 98.2 | −16.5 | 33.5 | 65.9 | 13.9 | 9.3 | 56.6 | 0.62 |
| Gluteus maximus 3 | 104.6 | 16.0 | 3.9 | 11.8 | −42.6 | 45.1 | 23.8 | 0.3 | 28.9 | −1.2 | 19.1 | 38.0 | 0.15 |
| Gluteus medius 1 | −33.4 | 81.4 | 28.9 | 10.1 | 115.9 | −48.5 | −19.1 | 16.4 | −3.1 | 27.6 | 17.6 | 50.3 | 0.30 |
| Gluteus medius 2 | −3.2 | 7.5 | −7.2 | −9.1 | −2.7 | −14.9 | −21.5 | 19.3 | 1.1 | 12.5 | −1.8 | 12.4 | 0.65 |
| Gluteus medius 3 | 16.1 | −14.6 | −30.0 | −26.4 | −53.7 | 83.5 | −29.8 | 22.4 | 13.3 | 2.6 | −1.6 | 38.7 | 0.90 |
| Gluteus minimus 1 | −33.0 | 94.9 | 28.6 | 3.6 | 258.9 | −59.0 | −6.6 | 3.8 | −12.2 | 27.7 | 30.7 | 90.0 | 0.31 |
| Gluteus minimus 2 | −17.0 | 29.7 | 13.4 | −4.3 | 68.2 | −39.7 | −10.3 | 8.4 | −3.3 | 19.0 | 6.4 | 29.3 | 0.51 |
| Gluteus minimus 3 | −6.0 | 6.4 | 1.7 | −12.6 | −8.2 | −4.1 | −18.9 | 17.5 | 2.2 | 10.3 | −1.2 | 11.0 | 0.74 |
| Gracilis | −6.6 | −23.4 | 86.0 | 24.2 | 101.7 | −8.0 | 3.9 | −2.5 | −45.3 | 59.9 | 19.0 | 48.3 | 0.25 |
| Iliacus | −23.2 | 25.2 | 24.7 | −2.9 | 342.9 | −36.6 | −20.2 | −3.8 | −44.0 | 0.0 | 26.2 | 113.6 | 0.48 |
| Pectineus | −33.1 | 13.9 | 147.7 | 47.3 | 189.1 | −23.3 | 74.2 | −16.1 | −23.2 | 6.0 | 38.3 | 77.0 | 0.15 |
| Peroneus brevis | 0.3 | 6.0 | −8.2 | −3.1 | −2.1 | 25.3 | −12.1 | −5.2 | 1.3 | −6.8 | −0.5 | 10.4 | 0.89 |
| Peroneus longus | −4.5 | 5.2 | 1.6 | 12.0 | −16.0 | −4.1 | 8.1 | −2.2 | 22.8 | −14.7 | 0.8 | 11.9 | 0.83 |
| Peroneus tertius | −4.8 | 4.1 | −13.0 | −16.9 | 6.3 | 96.2 | −26.1 | −8.4 | −1.4 | −9.0 | 2.7 | 34.2 | 0.81 |
| Piriformis | 23.1 | −28.0 | −35.6 | −49.5 | −78.2 | 447.5 | −37.4 | 31.7 | 3.9 | −13.1 | 26.4 | 151.7 | 0.59 |
| Psoas major | −20.1 | 22.6 | 21.2 | −6.1 | 325.6 | −28.8 | −26.6 | 0.9 | −45.8 | 0.1 | 24.3 | 108.1 | 0.50 |
| Quadratus femoris | 51.0 | −64.1 | −28.3 | −53.2 | −92.4 | 318.3 | 78.2 | −4.3 | 20.5 | −45.3 | 18.0 | 118.1 | 0.64 |
| Rectus femoris | −46.9 | −38.8 | −38.5 | −27.1 | −59.2 | 223.1 | 98.3 | −33.1 | 20.7 | −67.2 | 3.1 | 91.2 | 0.92 |
| Sartorius | 2.6 | −48.3 | −21.1 | −35.6 | 2.8 | 100.2 | −22.0 | 6.3 | −24.0 | −15.5 | −5.5 | 41.0 | 0.68 |
| Semimembranosus | 79.7 | 40.3 | 7.1 | 24.5 | 58.1 | −17.3 | −35.9 | 15.7 | −16.8 | 29.8 | 18.5 | 35.9 | 0.14 |
| Semitendinosus | 60.1 | 74.7 | 13.8 | 52.8 | 451.4 | −60.6 | −19.1 | −0.7 | −43.4 | 37.0 | 56.6 | 145.8 | 0.25 |
| Soleus | 8.9 | 2.5 | −5.1 | 12.7 | −46.3 | −17.5 | 31.4 | 5.6 | 38.2 | −5.8 | 2.4 | 24.0 | 0.75 |
| Tensor fasciae latae | −14.9 | −12.0 | −15.3 | −39.5 | 1.5 | 5.9 | −3.1 | −3.4 | −24.7 | −9.4 | −11.5 | 13.3 | 0.02 |
| Tibialis anterior | −24.5 | 0.3 | −7.4 | −39.3 | 23.0 | 282.3 | −45.5 | −37.2 | 13.7 | −19.3 | 14.6 | 96.8 | 0.64 |
| Tibialis posterior | −2.6 | 3.7 | 2.8 | 12.5 | −29.5 | −10.4 | 20.3 | 1.0 | 27.7 | −8.2 | 1.7 | 16.3 | 0.75 |
| Vastus intermedius | 0.7 | 3.0 | −29.3 | −6.6 | −77.6 | 90.8 | 103.9 | −18.6 | 32.6 | −28.4 | 7.1 | 55.4 | 0.70 |
| Vastus lateralis | 0.2 | 2.8 | −30.8 | −6.6 | −79.9 | 95.6 | 117.3 | −18.7 | 34.4 | −28.3 | 8.6 | 59.5 | 0.66 |
| Vastus medialis | 0.8 | 2.6 | −31.2 | −6.1 | −79.5 | 95.7 | 119.5 | −18.5 | 33.7 | −28.4 | 8.9 | 59.9 | 0.65 |

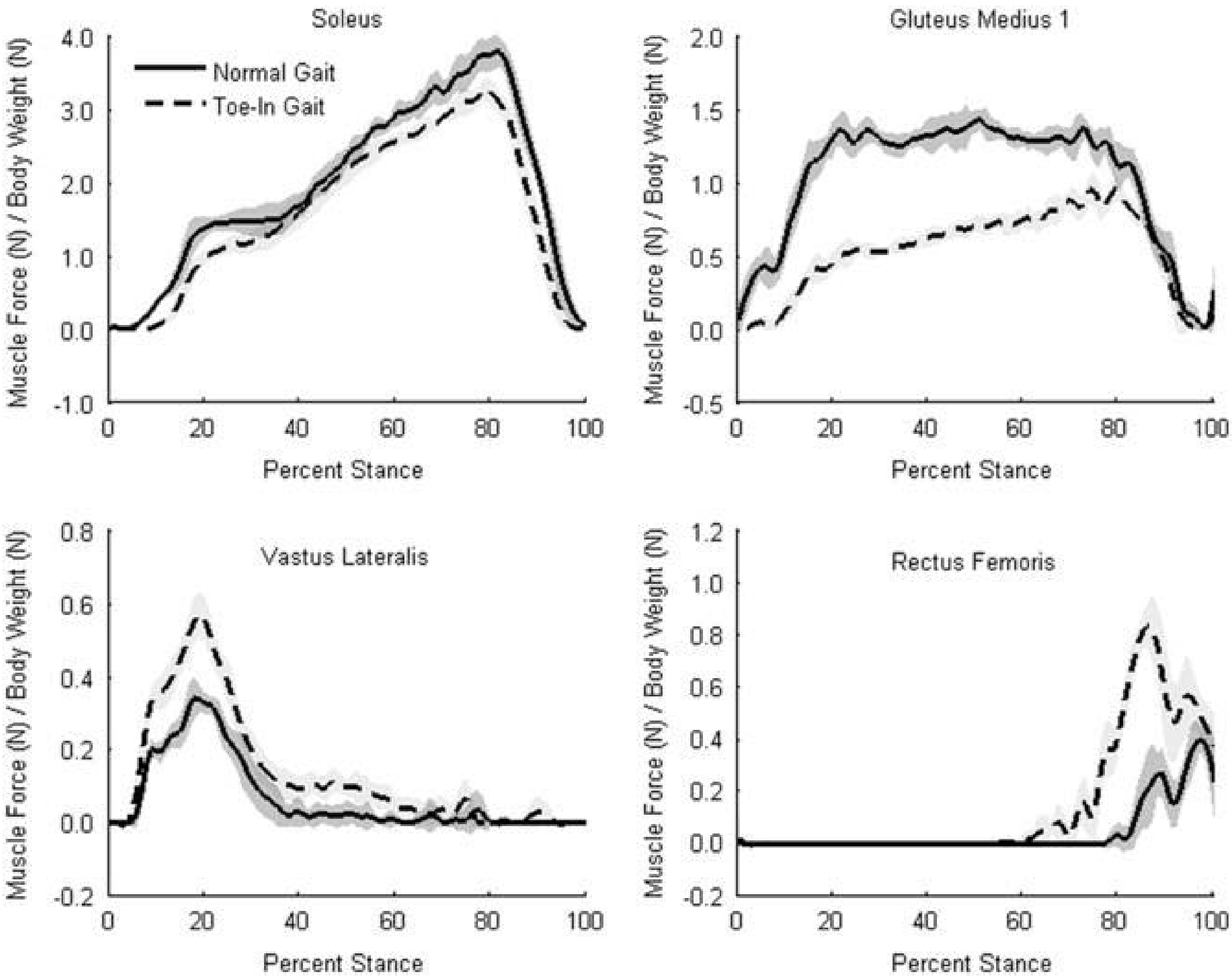


**Figure 9:** Example muscle force profiles from a representative showing muscle force tradeoffs to perform toe-in gait. Soleus and gluteus medius forces decreased, while vastus lateralis and rectus femoris forces increased. Muscle forces are averaged over ten steps of stance and shading represents one standard deviation. Significant muscle force modifications were evidenced in individuals like this representative subject, though no consistent muscle force modifications emerged for the gait modification across all subjects.

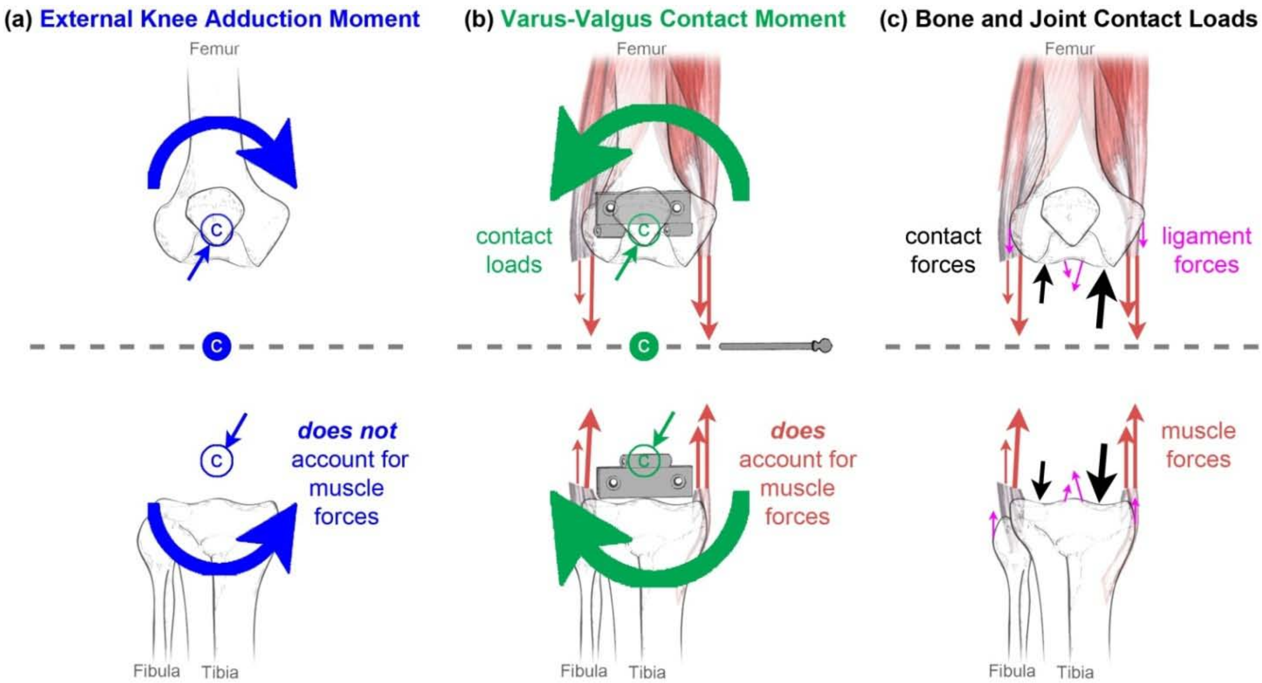


**Figure 10:** Illustrations showing the differing orders of approximations made through analyses of joint kinetics for an example planar knee joint. The net external knee adduction moment (KAM) (a, *blue curved arrows*) about the joint center results from a traditional inverse dynamics analysis determining the net generalized forces responsible for the movement. Very importantly for our case, the net KAM is determined without regard for the effects of internal muscle forces, which may be different following gait modification. The varus-valgus contact moment (VVCM) (b, *green curved arrows*) about the joint center results from a joint reaction analysis, taking into account the same forces and moments used for inverse dynamics but also includes the internal muscle force estimates (b and c, *red straight arrows*). This contact moment is directly related to the unbalanced bone-on-bone forces experienced by the medial and lateral knee joint compartments. As illustrated in this example of the knee modeled as a revolute joint, the VVCM is necessary to carry loads of the joint structure maintaining the joint motion of the two-piece hinge rotating about a common pin (*gray shaded*). The bone and joint contact loads (c, *black straight arrows*) may be obtained from higher-order analyses or measurements with an instrumented knee implant. Ultimately, the net external KAM (a) is a rough *first-order approximation* and the VVCM (b) is a *second-order approximation* with additional details related to the muscle forces affecting joint contact loads (c).

**Figure 11:** All subjects showed, on average, (a) a reduction in the first peak external knee adduction moment located at 27% stance during the *post-training* session at the end of 6 weeks of training from normal gait (*green, solid)*, (b) a 14.7% decrease ($p<0.01$) in the varus-valgus contact moment (VVCM), the load directly related to the unbalanced contact forces on the medial and lateral knee joint compartments during gait, at this same point in stance during the *post-training* session at the end of 6 weeks of training (*red, dashed)*, and (c) a 16.7% decrease ($p<0.01$) in the VVCM at this same point in stance during the *follow-up* session 1-month after the end of 6 weeks of training (*blue, dashed)*.

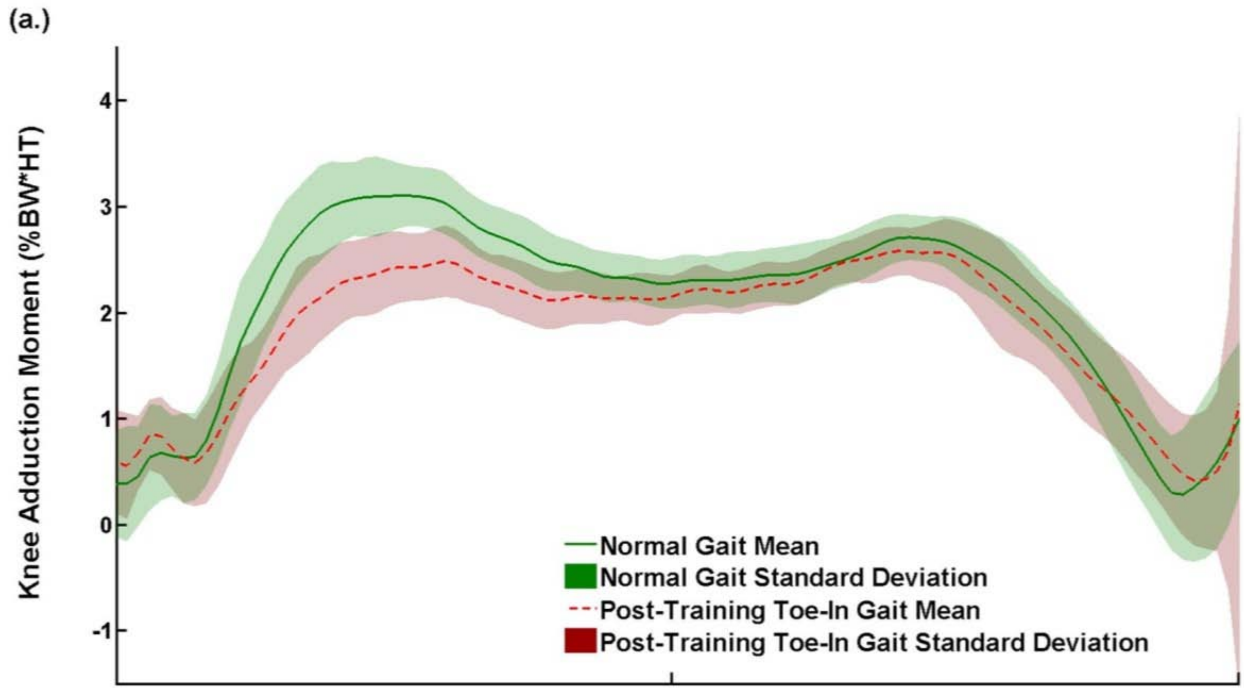


**Figure 11:** Continued.

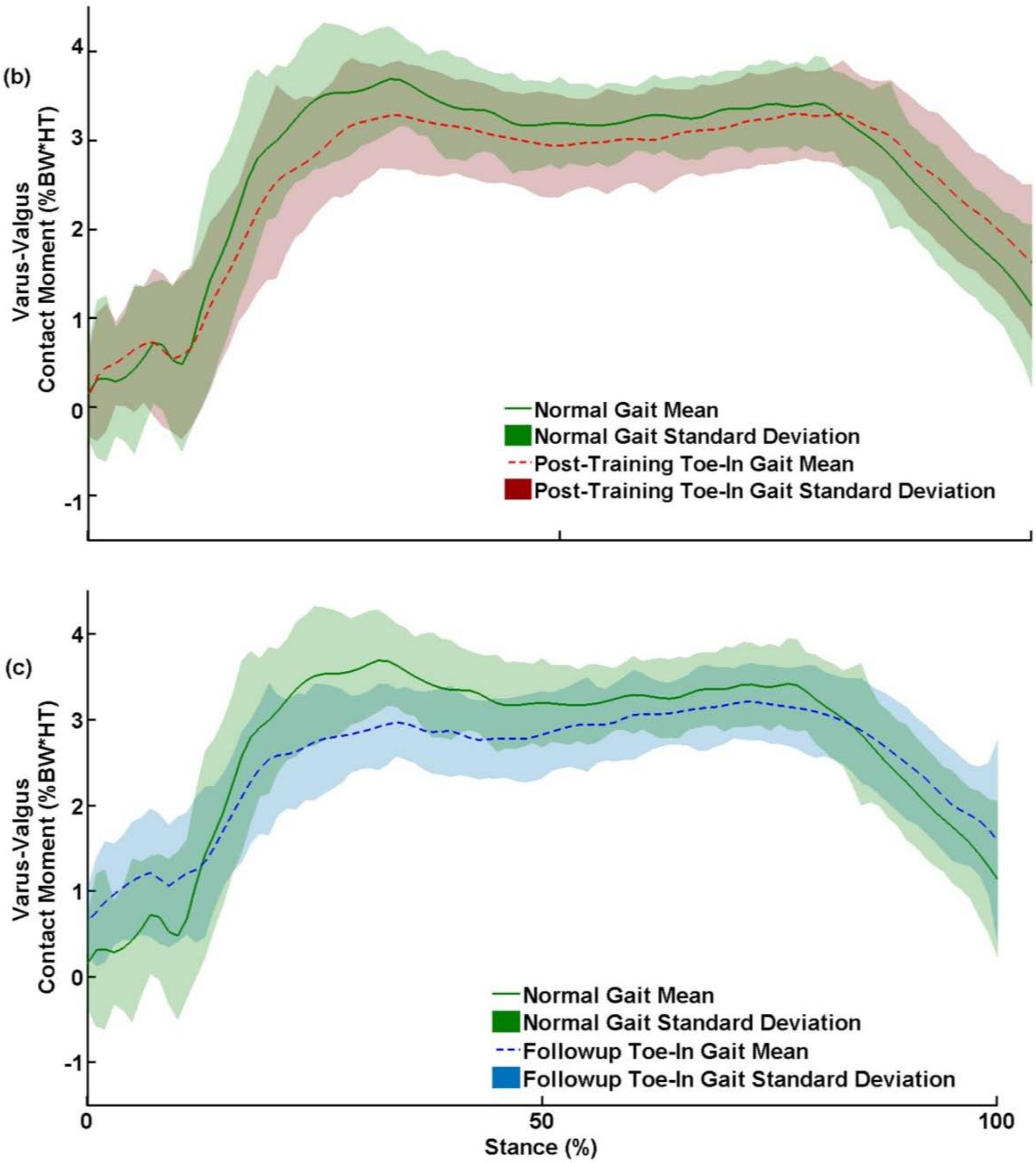


**Figure 11:** Continued.

**Table 3:** Summary of knee joint contact load means and standard deviations (SD) for normal and toe-in gait at the location in stance of the first peak net external knee adduction moment (KAM). The most relevant second-order approximation to the actual medial and lateral contact forces associated with knee osteoarthritis (OA) is the positive varus-valgus contact moment (VVCM), responsible for unbalanced compression of the medial compartment of the knee joint with respect to the lateral compartment. At the post-training session, the VVCM significantly decreased ($p<0.01$) during toe-in gait, while all other knee joint contact loads showed no significant change ($p>0.09$). These results were retained at the follow-up session. The VCCM significantly decreased ($p<0.01$) during toe-in gait, while all other knee joint contact loads showed no significant change ($p>0.06$).

| **Knee Joint Contact Loads** | | **Mean (SD) at First Peak KAM** | | |
|---|---|---|---|---|
| | | | *Toe-in Gait* | |
| *Moments (%BW*HT)* | | *Normal Gait* | *Post-training* | *Follow-up* |
| | **Varus-Valgus Contact** | **3.52 (0.78)** | **3.01 (0.65)*** | **2.94 (0.69)*** |
| | Internal-External Rotation | 0.309 (0.35) | 0.307 (0.28) | 0.425 (0.61) |
| | Flexion-Extension | 1.41 (0.25) | 1.54 (0.23) | 1.41 (0.25) |
| *Forces (%BW)* | | | | |
| | Anterior Shear | 119 (14.2) | 130 (13.5) | 127 (13.6) |
| | Superior Compression | 256 (17.7) | 260 (14.6) | 259 (13.9) |
| | Lateral Shear | 4.71 (2.79) | 4.33 (2.38) | 4.11 (2.37) |

** Represents a significant difference compared to normal gait at the p<0.01 significance level.*

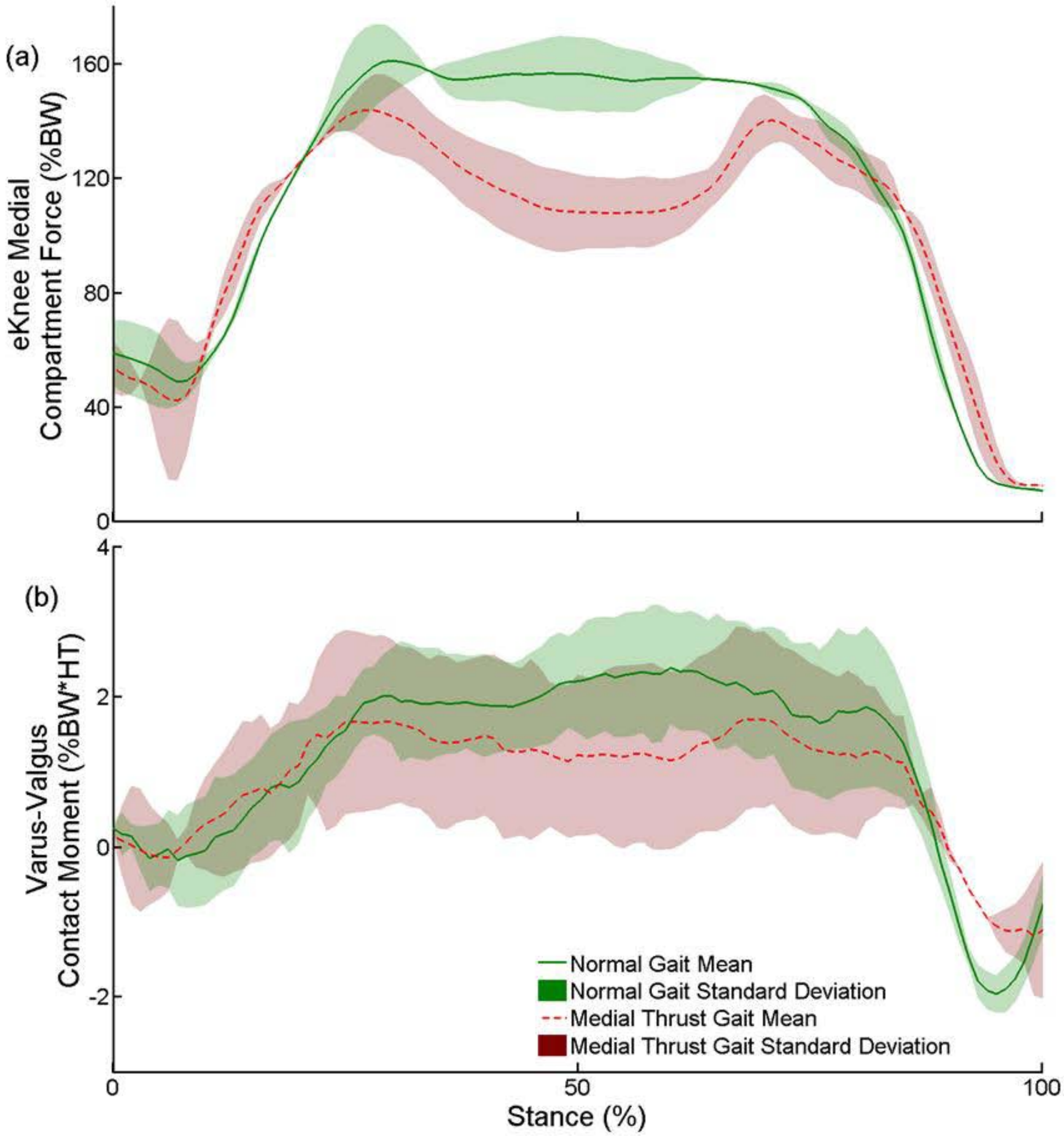


**Figure 12:** Validation of varus-valgus contact moment (VVCM) using normal and medial thrust gait data collected from an instrumented knee implant (eKnee) available from the 4th Knee Grand Challenge competition. The (a) eKnee medial force measured from an instrumented knee decreases following medial thrust gait modification. Similarly, the (b) VVCM computed from joint reaction analysis follows this same trend, showing a decrease following medial thrust gait modification.

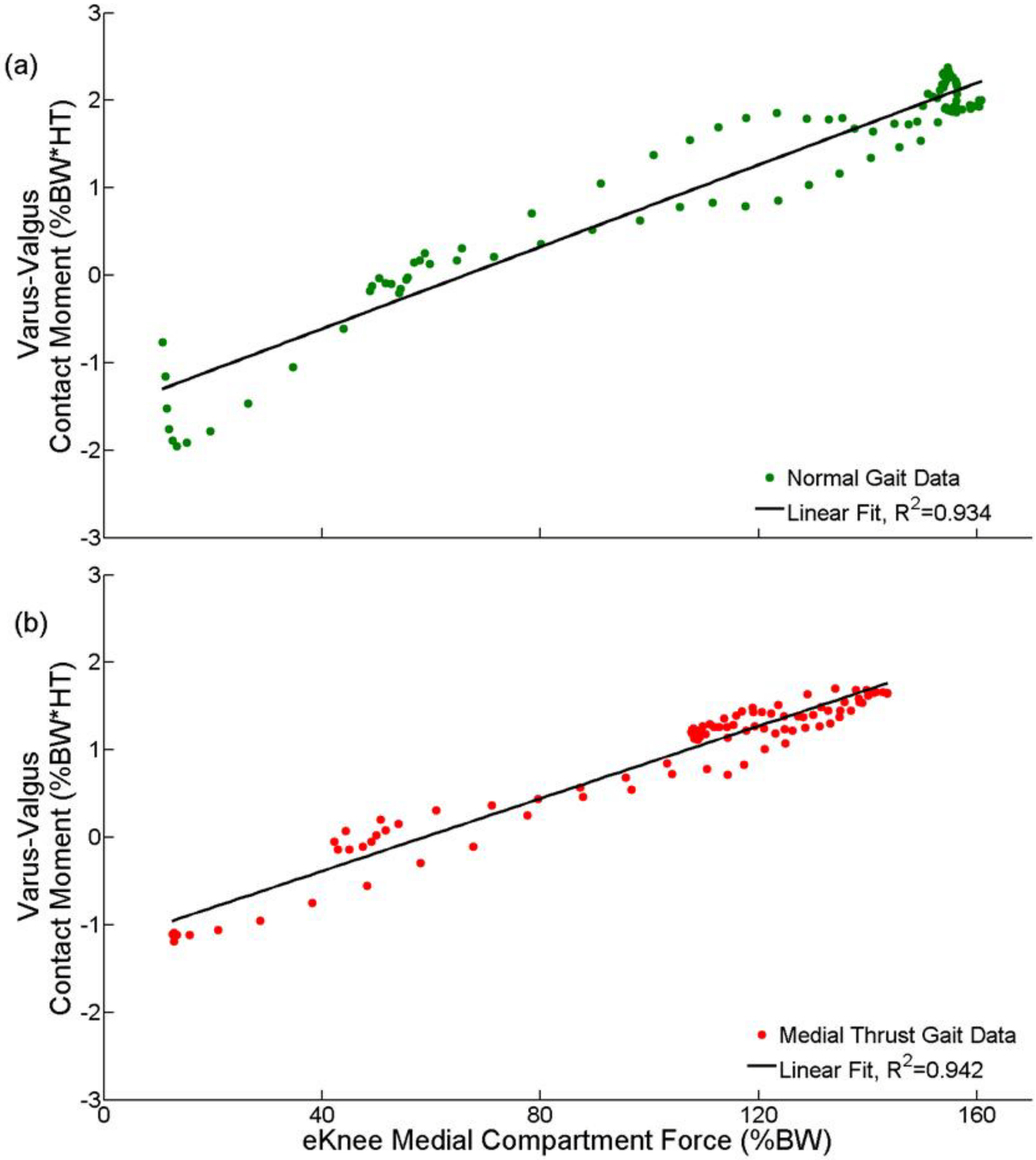


**Figure 13:** The correlation between the experimentally measured eKnee medial force and the model estimated varus-valgus contact moments (VVCM) for (a) normal gait and (b) medial thrust gait from 0-100% stance yields high coefficients of determination, R2= 0.934 and R2=0.942, respectively. This correlation shows the relationship between eKnee medial force and VVCM, such that the variation in VVCM is strongly related to the experimentally measured eKnee medial force before and after gait modification.

**Table 4:** Subject demographics for 10 subjects with medial compartment knee OA. Subjects were trained to walk with a 7° decrease in foot progression angle to achieve toe-in gait modification. With toe-in gait, subjects decreased knee adduction moment (KAM) by 20%, varus-valgus contact moment (VVCM) by 14.7% at post-training, VVCM by 16.7% at follow-up, and improved their visual analog pain score.

| | Mean (SD) |
|---|---|
| **Gender** | F: 4, M: 6 |
| **Age (year)** | 60 (13) |
| **Height (cm)** | 171 (9) |
| **Mass (kg)** | 79 (20) |
| **BMI (kg/m2)** | 26.6 (4.7) |
| **Kellgren & Lawrence grade** | II: 2, III: 6, IV: 1 |
| **Foot Progression Angle (deg)** | |
| ***Normal Gait*** | 2.1 (4.0) |
| ***Toe-in Gait*** | -5.1 (5.1)* |
| **Knee Adduction Moment (%BW*HT)** | |
| ***Normal Gait*** | 3.11 (1.40) |
| ***Toe-in Gait*** | 2.61 (1.47)* |
| **Varus-Valgus Contact Moment (%BW*HT)** | |
| ***Normal Gait*** | 3.52 (0.78) |
| ***Post-Training Toe-in Gait*** | 3.01 (0.65)* |
| ***Follow-up Toe-in Gait*** | 2.94 (0.69)* |
| **Visual Analog Pain Score** | |
| ***Normal Gait*** | 3.2 (2.30) |
| ***Toe-in Gait*** | 1.35 (0.88)* |

** Represents a significant difference compared to normal gait at the p<0.01 significance level.*

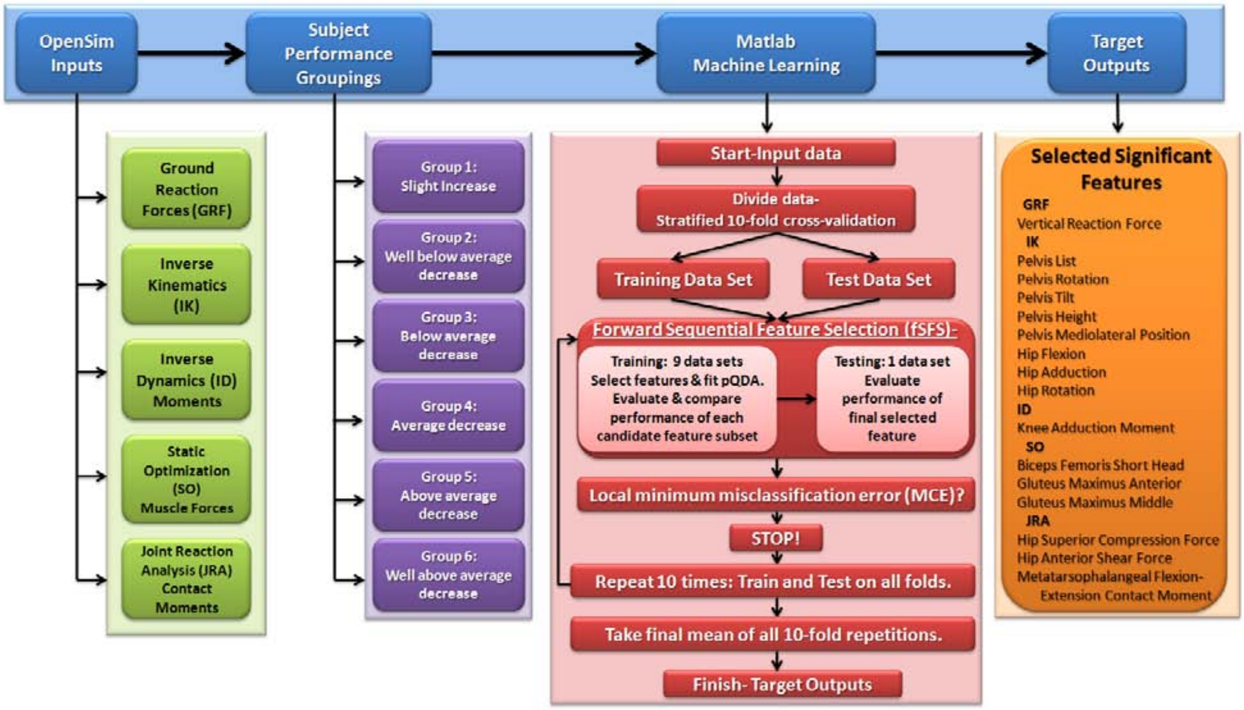


**Figure 14:** Schematic showing the forward sequential feature selection process from beginning to end. First, OpenSim modeling and simulation determines the initial inputs (a) or the various features of gait. These inputs include ground reaction forces (GRF), inverse kinematics (IK), inverse dynamics moments (ID), static optimization muscle forces (SO), and joint reaction analysis joint contact loads (JRA). Second, subjects are grouped based on performance (b) following toe-in gait analysis. These groupings are based on the amount of change in the varus-valgus contact moment (VVCM) following toe-in gait at both the *post-training* and *follow-up* sessions. Third, machine learning in Matlab (c) is used to carry out forward sequential feature selection to determine the significant features of gait with the potential to reduce joint loads during toe-in gait. To begin, the OpenSim input data is divided into testing and training groups using 10-fold cross validation. The data is separated into 10 folds, where 9 are used for training and 1 used for testing. Using the forward sequential feature selection (fSFS) algorithm, the training data is fit with a pseudo-quadratic discriminant analysis (pQDA) model to select features. Each possible subset of features is evaluated and compared before being validated with the testing data. The test data evaluates the final selected feature set. This will continue until a local minimum of the misclassification error (MCE) is found. The fSFS algorithm process repeats 10 times, going through each of the 10 cross validation folds until each observation is used for testing and training. Then a final average of the results of each fold repetition determines the final set of selected features. The final average contains the selected significant features of gait, or the target outputs (d).

**Table 5:** Summary of the grouping parameters used to create each group for comparing the effects of the number of groups on the feature selection process.

| **Number of Groups** | **Percent Decrease in VVCM** | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
| **6** | *Increase* | 0-6.99% | 7-13.99% | 14-20.99% | 21-27.99% | 28% + |
| **5** | < 7% | 7-13.99% | 14-20.99% | 21-27.99% | 28% + | |
| **4** | < 7% | 7-13.99% | 14-20.99% | 21% + | | |
| **3** | < 14% | 14-20.99% | 21% + | | | |
| **2** | < 14% | 14% + | | | | |

**Table 6:** Summary of average and standard deviation (SD) normalized values over stance of each selected significant feature of gait for all subject performance groupings at for toe-in gait at the *post-training* session. Forces were normalized by %BW and moments by %BW*HT. We used 10-fold cross-validation to estimate the ability of the regression model to make predictions for a new group with 98.8% of features correctly classified on average across the 10 cross-validation folds ($R^2$ = 0.97). The significant features included ground reactions (vertical reaction force), motion (pelvis list, rotation, tilt, height, and mediolateral position, hip flexion, adduction, and rotation), joint moments (knee adduction moment), muscle force estimates (biceps femoris short head, gluteus maximus anterior, and gluteus maximus middle), and joint contact loads (hip compression and anterior shear force, and metatarsophalangeal flexion-extension contact moment). Group 1 (n=2), the worst group, included subjects with a slight increase in varus-valgus contact moment (VVCM). Group 2 (n=3) included subjects with a 0-6.99%, or well below average, decrease in VVCM. Group 3 (n=2) included subjects with a 7-13.99%, below average, decrease in VVCM. It is important to note that there were no subjects in group 4, or those subjects with a 14-20.99% (average) decrease in VVCM, at post-training, thus there are no results for this group. Group 5 (n=2) included subjects with a 21-27.99% (above average) decrease in VVCM. Group 6 (n=1), the best group, included subjects with a 28% or greater (well above average) decrease in VVCM.

**Table 6:** Continued.

| Significant Feature | Baseline Average (SD) | Post-Training Average (SD) | | | | |
|---|---|---|---|---|---|---|
| | *All Subjects* | *Group 1* | *Group 2* | *Group 3* | *Group 5* | *Group 6* |
| ***GRF*** | | | | | | |
| Vertical Reaction Force | 76.7 (46.0) | 52.3 (60.4) | 67.4 (27.8) | 84.2 (34.1) | 104 (49.6) | 85.7 (32.5) |
| ***IK*** | | | | | | |
| Pelvis List | 1.58 (4.66) | 0.295 (2.27) | -2.89 (2.47) | -1.00 (3.97) | 3.76 (3.09) | 7.53 (1.97) |
| Pelvis Rotation | 0.336 (3.65) | 0.0708 (3.94) | -0.687 (6.01) | -1.39 (2.36) | -4.35 (4.35) | 0.629 (3.64) |
| Pelvis Tilt | -4.22 (8.09) | -3.58 (6.06) | -0.712 (4.16) | -6.01 (1.59) | 5.41 (4.27) | 4.84 (2.94) |
| Pelvis Height | 0.946 (0.0603) | 0.955 (0.0242) | 0.926 (0.0272) | 0.935 (0.0337) | 0.987 (0.0715) | 0.984 (0.0146) |
| Pelvis Mediolateral Position | -0.502 (0.0260) | -0.497 (0.0175) | -0.472 (0.0195) | -0.484 (0.0153) | -0.496 (0.0126) | -0.490 (0.00119) |
| Hip Flexion | 12.4 (18.1) | 8.98 (18.1) | 7.73 (17.3) | 15.0 (16.7) | 17.6 (14.9) | -3.58 (12.6) |
| Hip Adduction | 0.356 (6.12) | 1.97 (3.41) | 1.72 (5.42) | -8.82 (7.52) | 4.93 (4.92) | -6.64 (3.14) |
| Hip Rotation | -1.72 (7.63) | 10.7 (6.46) | -4.23 (13.3) | -8.47 (10.0) | -5.31 (3.88) | 13.7 (2.46) |
| ***ID*** | | | | | | |
| Knee Adduction Moment | 0.684 (2.02) | 1.07 (1.17) | -0.664 (1.62) | 0.837 (2.19) | 2.00 (1.21) | -0.227 (0.697) |
| ***SO*** | | | | | | |
| Biceps Femoris Short Head | 24.8 (25.3) | 17.3 (19.7) | 36.3 (29.8) | 25.5 (28.4) | 5.33 (5.74) | 8.76 (9.15) |
| Gluteus Maximus Anterior | 11.2 (9.31) | 10.9 (10.4) | 8.37 (7.22) | 10.9 (8.79) | 15.4 (9.70) | 6.91 (4.86) |
| Gluteus Maximus Middle | 19.1 (20.1) | 16.0 (20.6) | 15.8 (17.3) | 18.8 (20.1) | 24.7 (19.8) | 9.79 (10.3) |
| ***JRA*** | | | | | | |
| Hip Superior Compression Force | -72.8 (276) | -260 (87.2) | 86.6 (263) | -5.56 (253) | -301 (84.7) | 226 (55.2) |
| Hip Anterior Shear Force | -24.4 (82.3) | -68.3 (32.9) | 28.8 (72.1) | -0.103 (72.6) | -96.9 (38.8) | 52.9 (20.4) |
| Metatarsophalangeal Flexion-Extension Contact Moment | 0.0103 (0.0103) | 0.0096 (0.0069) | 0.0118 (0.0116) | 0.0114 (0.0096) | 0.0094 (0.0093) | 0.0108 (0.0055) |

**Table 7:** Summary of average and standard deviation (SD) normalized values over stance of each selected significant feature of gait for all subject performance groupings at for toe-in gait at the *follow-up* session with 98.8% of features correctly classified on average across the 10 cross-validation folds ($R^2$ = 0.97). Forces were normalized by %BW and moments by %BW*HT. The significant features included ground reactions (vertical reaction force), motion (pelvis list, rotation, tilt, height, and mediolateral position, hip flexion, adduction, and rotation), joint moments (knee adduction moment), muscle force estimates (biceps femoris short head, gluteus maximus anterior, and gluteus maximus middle), and joint contact loads (hip compression and anterior shear force, and metatarsophalangeal flexion-extension contact moment). The baseline (*normal gait*) gait data has only one group for all subjects as this is the starting point for all subjects. The subject groupings for the follow-up (*toe-in* gait) data contain different subjects than the groupings for the post-training (*toe-in gait*, Table 2) data as some subjects improved to a new, better grouping at follow-up as compared to post-training. To improve to a better grouping, subjects saw a greater change in varus-valgus contact moment (VVCM) and moved to a different subject grouping based on the amount of change in VVCM, such that group 1 was the worst with a slight increase in VVCM and group 6 was the best with the most decrease in VVCM. Group 1 (n=3), the worst group, included subjects with a slight increase in VVCM. Group 2 (n=1) included subjects with a 0-6.99%, or well below average, decrease in VVCM. Group 3 (n=1) included subjects with a 7-13.99%, below average, decrease in VVCM. Group 4 (n=2) included subjects with a 14-20.99% (average) decrease in VVCM. Group 5 (n=1) included subjects with a 21-27.99% (above average) decrease in VVCM. Group 6 (n=2), the best group, included subjects with a 28% or greater (well above average) decrease in VVCM.

**Table 7:** Continued.

| Significant Feature | Baseline Average (SD) | Follow-up Average (SD) | | | | | |
|---|---|---|---|---|---|---|---|
| | *All Subjects* | *Group 1* | *Group 2* | *Group 3* | *Group 4* | *Group 5* | Group 6 |
| ***GRF*** | | | | | | | |
| Vertical Reaction Force | 76.7 (46.0) | 60.8 (53.6) | 55.6 (23.8) | 93.3 (37.1) | 72.6 (28.2) | 77.3 (29.3) | 108 (47.6) |
| ***IK*** | | | | | | | |
| Pelvis List | 1.58 (4.66) | 4.00 (5.63) | 0.850 (1.92) | 0.690 (2.24) | -4.33 (1.57) | 3.26 (2.73) | 7.62 (2.41) |
| Pelvis Rotation | 0.336 (3.65) | 0.583 (3.02) | 5.74e-04 (2.73) | 0.281 (2.12) | -0.116 (7.16) | 0.308 (1.24) | -3.51 (6.97) |
| Pelvis Tilt | -4.22 (8.09) | -0.835 (8.56) | -0.0344 (1.16) | -6.00 (1.09) | -4.00 (4.58) | -5.50 (4.40) | -1.75 (4.40) |
| Pelvis Height | 0.946 (0.0603) | 0.944 (0.0248) | 0.935 (0.0162) | 0.902 (0.0162) | 0.913 (0.0360) | 0.961 (0.0168) | 1.02 (0.0497) |
| Pelvis Mediolateral Position | -0.502 (0.0260) | -0.508 (5.63) | -0.461 (0.0081) | -0.502 (0.0115) | -0.477 (0.0196) | -0.473 (0.0168) | -0.501 (0.0140) |
| Hip Flexion | 12.4 (18.1) | 6.36 (20.5) | 3.54 (14.4) | 16.8 (17.6) | 14.4 (16.4) | 15.6 (11.7) | 8.51 (15.3) |
| Hip Adduction | 0.356 (6.12) | 5.46 (5.97) | 1.83 (2.33) | -7.16 (3.65) | 1.18 (5.91) | -1.72 (3.52) | 1.23 (9.30) |
| Hip Rotation | -1.72 (7.63) | 6.53 (7.67) | 9.96 (1.98) | -3.72 (2.26) | -14.5 (10.7) | 3.20 (2.20) | 8.84 (4.87) |
| ***ID*** | | | | | | | |
| Knee Adduction Moment | 0.684 (2.02) | 2.01 (1.47) | -1.29 (1.32) | 2.90 (1.86) | -0.343 (1.34) | -0.109 (0.461) | 0.892 (1.57) |
| ***SO*** | | | | | | | |
| Biceps Femoris Short Head | 24.8 (25.3) | 13.6 (16.5) | 14.8 (13.2) | 8.49 (8.87) | 39.5 (27.7) | 22.4 (18.2) | 6.99 (8.90) |
| Gluteus Maximus Anterior | 11.2 (9.31) | 10.7 (11.2) | 7.65 (6.14) | 12.6 (9.71) | 8.71 (8.22) | 9.61 (8.90) | 11.6 (7.43) |
| Gluteus Maximus Middle | 19.1 (20.1) | 16.2 (22.0) | 10.6 (12.1) | 18.8 (18.2) | 19.2 (21.0) | 19.8 (24.6) | 18.1 (15.6) |
| ***JRA*** | | | | | | | |
| Hip Superior Compression Force | -72.8 (276) | -278 (98.4) | 267 (97.3) | -254 (93.1) | 10.1 (261) | 226 (68.8) | -35.9 (275) |
| Hip Anterior Shear Force | -24.4 (82.3) | -78.9 (41.2) | 69.3 (25.2) | -77.2 (38.9) | 7.96 (77.9) | 59.2 (17.5) | -21.2 (83.1) |
| Metatarsophalangeal Flexion-Extension Contact Moment | 0.0103 (0.0103) | 0.0088 (0.0085) | 0.0160 (0.0166) | 0.0115 (0.0081) | 0.0095 (0.0083) | 0.0117 (0.0083) | 0.009 (0.0082) |

**Table 8:** Summary of average and standard deviation (SD) normalized values over stance of each selected significant feature of gait for the top performing subjects at all gait sessions with 100% of features correctly classified on average across the 10 cross-validation folds ($R^2$=0.98). Forces were normalized by %BW and moments by %BW*HT. The selected features from ground reaction force (GRF) readings were the mediolateral reaction force and ground free torque. The selected features from inverse kinematics (IK) include pelvis list, tilt, height, and mediolateral position, and hip adduction and rotation. The selected features from inverse dynamics (ID) include the joint moment, hip adduction moment. Finally, the selected features from joint contact load analysis (JRA) were the superior compression contact force at the hip joints and the knee flexion-extension contact moment.

| Significant Feature | Top Performing Subjects | | |
|---|---|---|---|
| | *Baseline Average (SD)* | *Post-Training Average (SD)* | *Follow-up Average (SD)* |
| ***GRF*** | | | |
| Mediolateral Reaction Force | 5.49 (4.04) | 0.298 (5.97) | 0.644 (5.90) |
| Free Torque | 0.0386 (0.118) | 0.0536 (0.162) | 0.0281 (0.131) |
| ***IK*** | | | |
| Pelvis List | 0.0423 (4.63) | 0.187 (4.50) | 0.301 (5.25) |
| Pelvis Rotation | 1.51 (3.63) | -2.19 (6.40) | -2.39 (6.72) |
| Pelvis Tilt | -2.38 (9.11) | -4.17 (5.14) | -4.71 (4.14) |
| Pelvis Height | 0.964 (0.0727) | 0.967 (0.0600) | 0.965 (0.0699) |
| Hip Adduction | 1.21 (6.71) | 1.11 (6.06) | 2.50 (6.73) |
| Hip Rotation | -1.34 (7.02) | -6.09 (9.13) | -5.23 (12.1) |
| ***ID*** | | | |
| Hip Adduction Moment | -2.75 (1.78) | -2.55 (1.59) | -2.37 (1.48) |
| ***JRA*** | | | |
| Hip Superior Compression Force | -29.5 (293) | -20.9 (281) | -14.0 (269) |
| Knee Flexion-Extension Contact Moment | 0.747 (0.293) | 0.753 (0.311) | 0.752 (0.332) |

**Table 9:** Comparison of the effects of varying the number of groups during feature selection, highlighting which of the selected features with 6 groups from this study also appear in 5, 4, 3, and 2 groups, respectively. 14 out of the 16 selected features (88%) with 6 groups appear as significant features in two or more groupings, with the last two selected, metatarsophalangeal flexion-extension moment and gluteus maximus anterior force, being those that were not similar to any of the other groupings. This suggests that these last two features may not have a large impact on decreasing VVCM. Additionally, hip rotation was the top selected feature for 6, 5, and 4 groups, and was in the top 6 selected features for 3 and 2 groups, highlighting this feature to most significant for decreasing VVCM during toe-in gait. Finally, hip rotation, pelvis tilt, pelvis height, biceps femoris short head force, and hip adduction were significant features in all groupings, indicating these may be the most important features to be targeted in future gait retraining studies to decrease harmful joint loading in patients with medial knee OA. In the end, these results validate the use of 6 groups during feature selection in this study, as 88% of these selected features appeared in the other groupings as well.

| **Number of Groups** | **Selected Signficant Features of Gait in Order of Selection** | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hip Rotation* | Knee Adduction Moment | Pelvis List | Pelvis Tilt* | Pelvis Height* | Hip Superior Compression Force | Hip Flexion | Biceps Femoris Short Head* | Pelvis Rotation | Pelvis Mediolateral Position | Gluteus Maximus Middle | Hip Adduction* | Vertical Reaction Force | Hip Anterior Shear Force | Metatarsophalangeal Flexion-Extension Contact Moment | Gluteus Maximus Anterior |
| **6** | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| **5** | • | • | • | • | • | • | • | • | • | • | | • | • | | | |
| **4** | • | • | • | • | • | | • | • | | | • | • | • | • | | |
| **3** | • | | • | • | • | | | • | • | • | • | • | • | • | | |
| **2** | • | | | • | • | | | • | | • | • | • | | • | | |

** Indicates this feature was significant in all groupings.*

**Table 10:** Comparison of the predictive power and percentage of similar selected features between 6 groups as used in this study and varied numbers of groups during feature selection. Predictive power decreases and the number of groups decreases, such that using 6, 5, or 4 groups had 99% correct predictions across the 10 cross-validation folds, using 3 groups had 98% correct predictions, and using 2 groups had 91% correct predictions. These results indicate that using fewer groupings may not be able to correctly classify the significant features as accurately and using more groups. Using more groupings helps highlight the smaller, unique differences between each subject during toe-in gait, utilizing more information about gait on a subject-specific basis to select features more efficiently, while using fewer groups yields more generalized results that may be significant on average but not on an individual basis. Importantly, using different numbers of groups yielded different sets of significant features. However, each of the groupings had many of the same selected features, for example 5 groups had 57% of the same features as using 6 groups, while 4, 3, and 2 groups had 34%, 41%, and 53% respectively. These results validate the use of 6 groups in the same set of features appear to be significant, regardless of the number of groups used during feature selection.

| Number of Groups | Percent Correct Predictions | Number of Selected Features | Percentage of Same Features |
|---|---|---|---|
| **6** | 99% | 16 | |
| **5** | 99% | 21 | 57% |
| **4** | 99% | 32 | 34% |
| **3** | 98% | 27 | 41% |
| **2** | 91% | 15 | 53% |

**Figure 15**: Example surrogate response surfaces. While the approximate surface for the optimization in this study had 16 design variables, or features of gait, these surfaces are visual representations of how the simulated gait data fits with the surrogate response surface for two features at a time. The surfaces shown represent the response surface approximation for combinations of the top 3 selected significant features of gait including (a) hip rotation and knee adduction moment ($R^2$=0.83), (b) hip rotation and pelvis list ($R^2$=0.55), and (c) knee adduction moment and pelvis list ($R^2$=0.78). To visualize the fit of the simulated gait data to the response surface, the gait data were plotted over the surface (pink, open circles). Because the response surface moves and changes through stance, these visuals represent only 1% of stance, specifically showing 27% of stance of the average location of the first peak knee adduction moment (KAM) for the subjects in this study. Note the fit of two features at 27% stance is different than the fit of all 16 features over full stance (0-100%) used for the surrogate-based optimization in this study and serves as a visual example of how a surface can be fit to gait data.

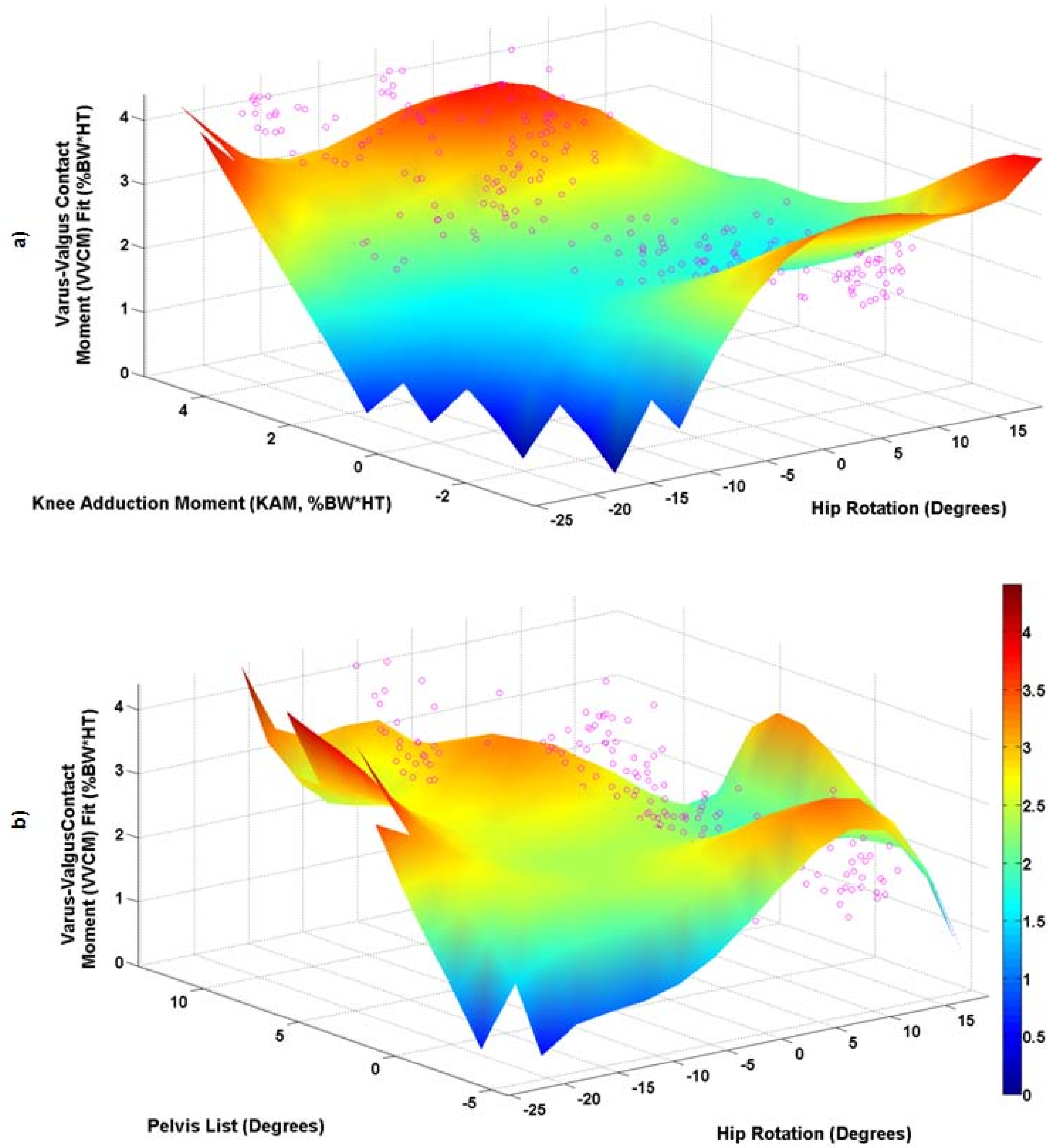


**Figure 15:** Continued.

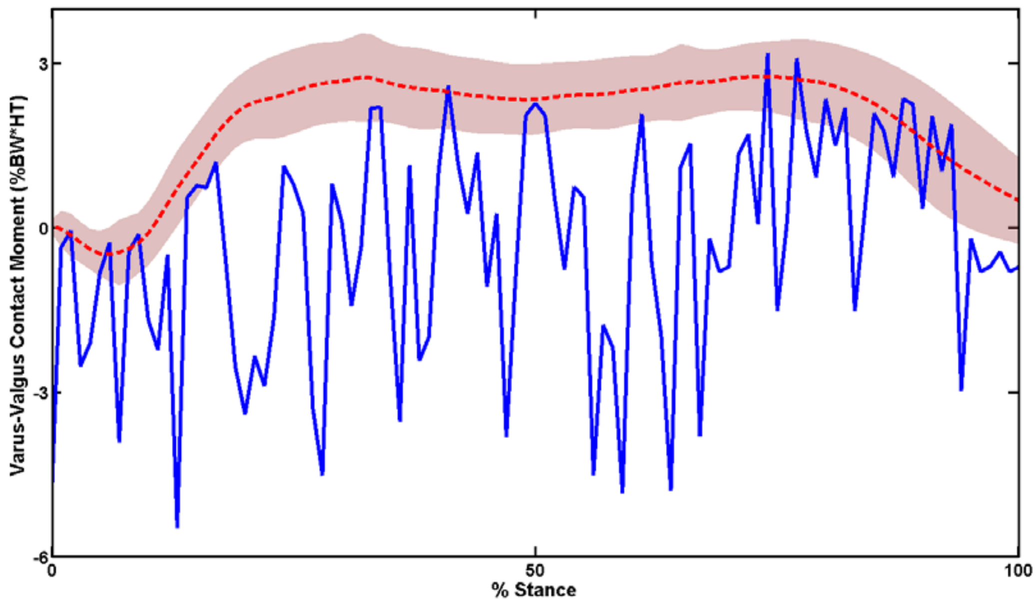


**Figure 16:** By varying significant features of gait, the optimizer was able to minimize the varus-valgus contact moment (VVCM) (*blue,* solid) in comparison to the mean and standard deviation of the subject data (*red, dashed*) for individuals with medial knee OA. The VVCM was minimized to be less than the mean of the subject data for most of the stance phase of gait. The few time steps where the VVCM was slightly larger than the mean were still within 1 standard deviation.

**Figure 17:** Target design variables (*blue, solid*) for the sixteen significant features of gait over stance as determined from a surrogate-based optimization compared to the mean and standard deviation of the subjects' simulation data (*red, dashed*). The sixteen features include ground reactions (vertical reaction force), motion (pelvis list, rotation, tilt, height, and mediolateral position, hip flexion, adduction, and rotation), joint moments (knee adduction moment), muscle force estimates (biceps femoris short head, gluteus maximus anterior, and gluteus maximus middle), and joint contact loads (hip compression and anterior shear force, and metatarsophalangeal flexion-extension contact moment). The top 3 selected features were hip rotation, knee adduction moment, and pelvis list. These results serve as recommendations to minimize VVCM by incorporating the kinematic changes in future gait retraining studies. For example, hip rotation should be increased, or further rotate the ipsilateral limb internally, and pelvis list should be decreased to increase obliquity on the contralateral limb for minimized VVCM with toe-in gait.

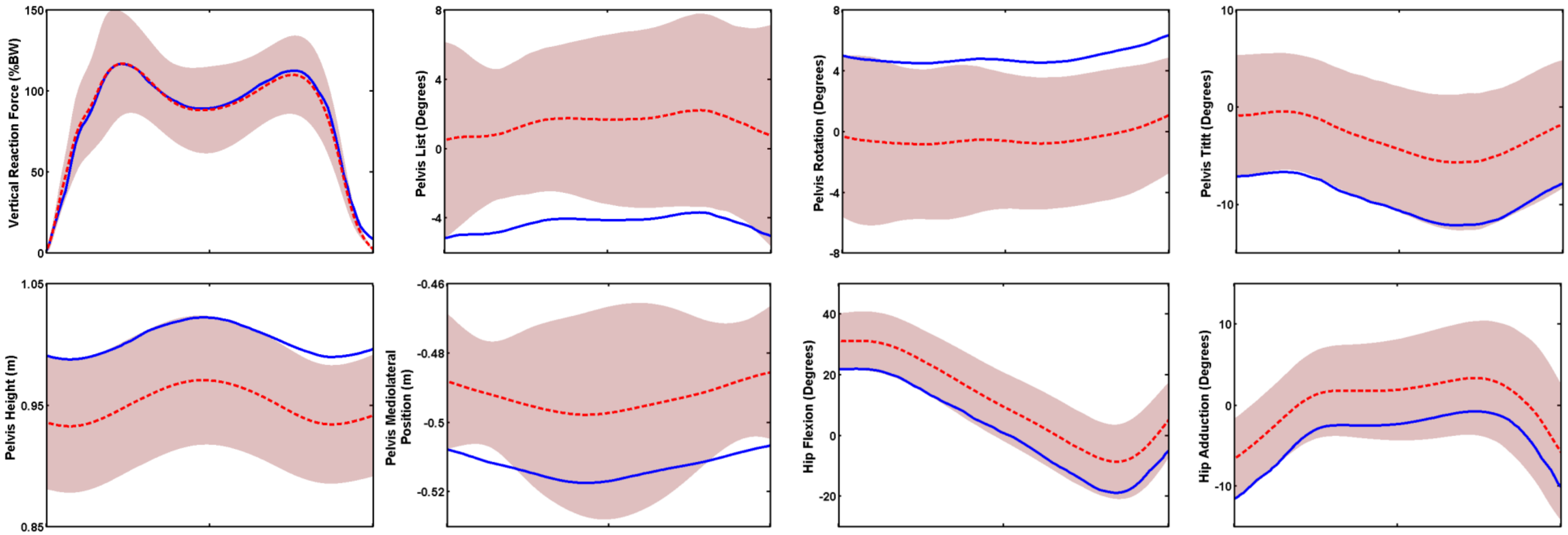


**Figure 16:** Continued.

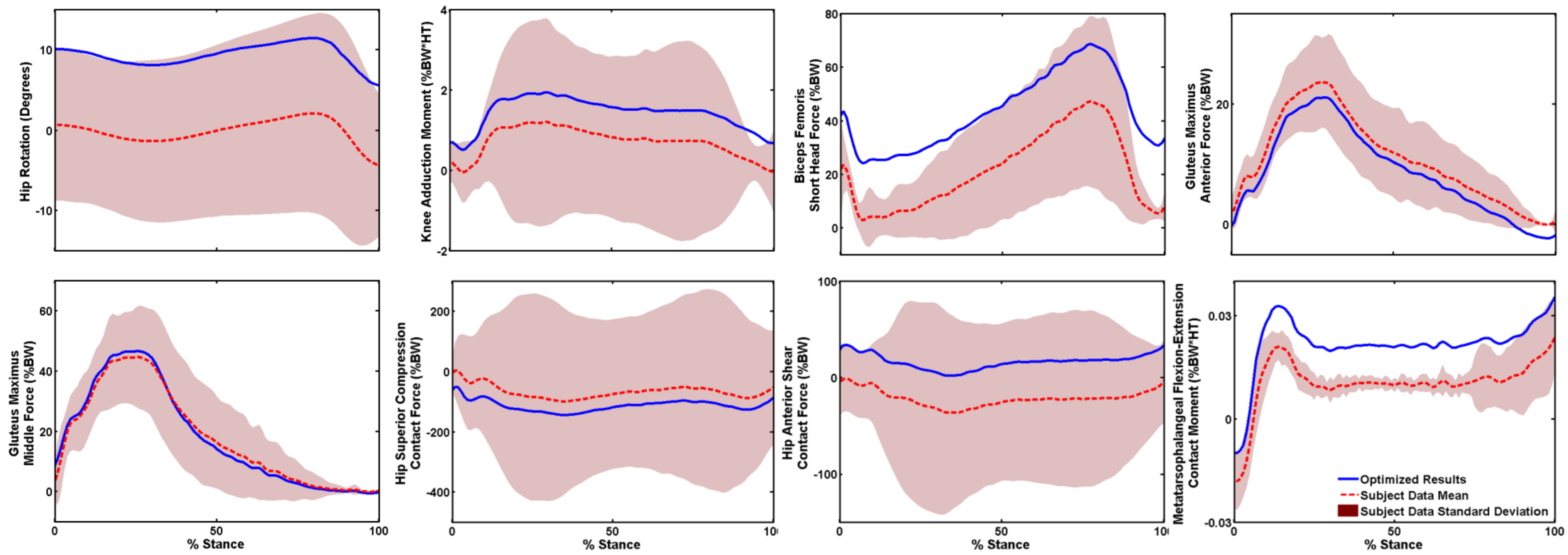


**Figure 17:** Continued.

# VITA

Taylor Elyse Schlotman was born in Ft. Thomas, Kentucky, on August 5th, 1991. She grew up in Florence, Kentucky. She graduated from Boone County High School in Florence, Kentucky in 2009. She received her Bachelor's Degree in Biomedical Engineering and a minor in Materials Science and Engineering from the University of Tennessee, Knoxville, in the Spring of 2013. During her time at UT, she worked in the Athletic Department with the swimming and diving team and completed an internship in computer science and mathematics at Oak Ridge National Laboratory. She began the M.S./Ph.D. program at the University of Tennessee, Knoxville in the fall of 2013, working in computational biomechanics in the Reinbolt Research Group, where she completed her Master's Degree in Biomedical Engineering in the Spring of 2016.