BRACE YOURSELF: REDUCING MEDIAL KNEE LOADING FOR TREATMENT OF OSTEOARTHRITIS

by

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Abstract

Compared with healthy controls, subjects with medial knee osteoarthritis walk using similar kinematics but greater activation of knee-spanning muscles, especially on the lateral side of the knee (furthest from centerline of the body). Although muscle forces generally compress the knee joint, it had been speculated that this specific activation pattern actually reduces compressive loads across the medial (closest to centerline) side of the knee where osteoarthritis is most common. It is not feasible to measure intra-articular contact forces in biological human knee joints. Therefore, a musculoskeletal simulation was developed to estimate the effect of elevated activation on knee contact forces.

A generic musculoskeletal model was adapted to account for subject-specific frontal-plane alignment of the knee joint, and modified to isolate the medial and lateral components of the compressive knee contact load. The model’s predictions were validated using in vivo data obtained from a subject with an instrumented knee prosthesis. Subsequently, the model was used to demonstrate that elevated muscle activation, as found in osteoarthritis subjects, does not protect against harmful medial loads, but actually contribute to an increase in peak load shortly after heel-strike. Since osteoarthritis subjects did not appear to adopt a protective gait pattern, the second half of the dissertation was devoted to the evaluation of a clinical device that is known to reduce medial loads during gait: the knee unloader brace.

To accomplish medial unloading, braces apply a frontal plane abduction moment to the knee which, if large enough, would pry open the medial contact surfaces. A novel method was developed to non-invasively compute the abduction moment applied by the
brace to each subject’s leg using a mechanical stiffness calibration. The computed brace moment was incorporated into the musculoskeletal model in order to quantify relative contributions of muscle forces, inverse dynamic joint loads, and the applied brace load in reducing medial contact forces for treatment of medial knee osteoarthritis. The model revealed that kinematic, muscular, and inverse dynamic changes were dominated by the large applied brace moment. The medial unloading effect of knee braces could be enhanced by reducing external and muscle forces through gait modification.
Co-Authorship

While the primary responsibility for the work in this dissertation rests with the author, Scott Brandon, others have contributed to the work through scientific discussion, experimental collection, and proof-reading of manuscripts. I would like to gratefully acknowledge my collaborators as co-authors for the following manuscripts and conference proceedings:

Chapter 2


Chapter 3

- Brandon SCE, Saliba CM, Deluzio KJ. (in review) Sensitivity of Medial and Lateral Knee Contact Force Predictions to Frontal Plane Alignment and Contact Location. *Journal of Biomechanics.*

Chapter 4


Chapter 5


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Finally, I would like to gratefully acknowledge the invaluable roles of NSERC, NSERC-CREATE, Queen’s University, the Human Mobility Research Centre, and DonJoy Global Inc. in providing the funding and resources required for this study.
Statement of Originality

I hereby certify that all of the work described within this thesis is the original work of the author. Any published (or unpublished) ideas and/or techniques from the work of others are fully acknowledged in accordance with the standard referencing practices.

Scott Charles Elmer Brandon

November, 2014
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<th>Full Form</th>
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<td>Osteoarthritis</td>
<td>OA</td>
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<td>Electromyogram(s)</td>
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<td>Bodyweight</td>
<td>BW</td>
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<td>Total Knee Arthroplasty</td>
<td>TKA</td>
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<td>Standard Deviation</td>
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<td>Mean Principal Component Difference</td>
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CHAPTER 1
INTRODUCTION

1.1 Research Problem – Knee Osteoarthritis

Knee osteoarthritis (OA) is a disease that causes pain and impairs mobility in 40% of the global population over 70 years of age (WHO Scientific Group, 2003). In a healthy knee joint, articulating cartilage provides a near-frictionless, shock-absorbing layer between the tibia and femur (Figure 1.1A). However, in an end-stage osteoarthritic knee, articulating cartilage degrades to the extent that underlying bone is exposed (Figure 1.1B).

![Figure 1.1: Images of human femoral condyles showing healthy articular cartilage (A) and damage due to osteoarthritis (B). Medial refers to the side of the knee closest to the centerline of the body, while lateral is towards the outside of the leg. Images adapted from Lotz and Loser (2012) and Koshino et al. (2003).](image)

In osteoarthritis, joint damage is not restricted to articular cartilage; medical imaging studies reveal hardening and abnormal growth of the bones around the joint as well as
damage of meniscal tissue, which may even precede deterioration of articular cartilage 
(Bennett and Buckland-Wright, 2002). However, cartilage is particularly susceptible to 
damage because it is avascular, which reduces the supply of oxygen and nutrients and 
inhibits biological repair mechanisms. Furthermore, because cartilage is aneural, subjects 
often experience little to no pain until substantial cartilage damage has occurred. Once 
their knees become symptomatic, patients report pain during weight-bearing, stiffness 
after prolonged inactivity, crepitus or crunching during passive motion, and an overall 
decrease in functional ability (Bijlsma et al., 2011).

1.1.1 Mechanical Causation
The current body of evidence clearly implicates mechanical loading of cartilage in the 
initiation and progression of osteoarthritis (Felson, 2013). Animal studies have shown 
that when excessive knee loading is induced, osteoarthritis progression is accelerated 
(Appleton et al., 2007; Ogata et al., 1977). Conversely, when cartilage is unloaded, 
progression of OA may be slowed or even reversed (Deie et al., 2007; Lafeber et al., 
2006). However, it is difficult to quantify a threshold for harmful loading. One study 
exercised dogs for 75 minutes a day for 527 weeks while carrying jackets weighing 130% 
of their body weight, and found no change in cartilage health with respect to a control 
group (Newton et al., 1997). Another study increased loading in rabbit knees by 50% 
and 80% times bodyweight, and discovered progressive degeneration over 24 weeks that 
increased in severity in proportion with the applied load (Roehmllidt et al., 2012). To 
further complicate the issue, it is possible that joint load reduction is also harmful. In a 
study where lateral loading was decreased in rat knees, degenerative changes were 
observed in the articular cartilage (Roehmllidt et al., 2013). Perhaps the most compelling 
evidence for the role of mechanical loading in human subject osteoarthritis is given by the
relationship between occupational overuse and the joints affected by osteoarthritis. Cotton workers are more likely to get osteoarthritis in finger joints, jackhammer operators have a high incidence in elbow and wrist joints, and farmers have a high rate of incidence in hips and knees (Felson, 2013). There is little doubt that chronic excessive joint loading increases the risk of osteoarthritis. However, it is difficult to quantify thresholds for safe loading.

1.1.2 Effect on Gait Mechanics
For many people, walking is one of the primary activities of daily living during which the knee joints experience cyclic loading. Subjects with knee osteoarthritis walk more slowly than healthy control subjects (Andriacchi et al., 1977), and exhibit a reduced range of motion at hip, knee, and ankle joints (Al-Zahrani and Bakheit, 2002; Andriacchi et al., 1982; Astephen et al., 2008a) as well as decreased hip extension moments, hip adduction moments, hip internal rotation moments, knee flexion moments, and ankle dorsiflexion moments (Astephen et al., 2008a; Mundermann et al., 2005). Reductions in the magnitudes of gait speed and external joint loads should lead to a reduction in knee joint loading (Zhao et al., 2007). Unfortunately, subjects with osteoarthritis also exhibit two other gait characteristics which are related to elevated knee joint loading: increased knee adduction moments (Baliunas et al., 2002; Miyazaki et al., 2002; Weidenhielm et al., 1994) and increased antagonistic co-contraction of knee muscles (Heiden et al., 2009; Hubley-Kozey et al., 2006).
The knee adduction moment is largely developed by the ground reaction force acting at some distance about the knee joint centre (Figure 1.2A). For equilibrium, the adduction moment must be balanced primarily by the medial knee contact force (Figure 1.2B), therefore the magnitude of the adduction moment is positively correlated with medial contact loading (Trepczynski et al., 2014; Zhao et al., 2007). The finding of elevated adduction moments in osteoarthritis subjects (Baliunas et al., 2002; Hunt et al., 2006) appears to explain why osteoarthritis is most common in the medial compartment (McAlindon et al., 1992).

However, medial and lateral contact loads must equilibrate not only the adduction moment, but also the compressive action of muscle forces, which are recruited to stabilize the joints and to generate motion (Figure 1.2C). The fact that subjects with osteoarthritis show elevated levels of muscle activity during gait is believed to increase harmful joint
loading (Mills et al., 2013; Zeni et al., 2010), although it is possible that selective recruitment of lateral muscles could actually counterbalance the adduction moment and thereby reduce medial knee contact loads (Hubley-Kozey et al., 2006; Lloyd and Buchanan, 2001).

1.1.3 Biomechanical Treatment
Considering the mechanical etiology of knee osteoarthritis, there are therefore two main avenues which may be exploited to reduce medial joint loading in order to postpone disease progression: reduction of the adduction moment, or reduction of muscular activation. The external adduction moment applied to the knee might be reduced by adopting novel gait patterns (Fregly et al., 2009; Shull et al., 2013), employing assistive, gait-altering devices (Chew et al., 2007; Hansen et al., 2008; Keating et al., 1993), surgically altering limb alignment to reduce the lever arm of the ground reaction force about the knee joint centre (Prodromos et al., 1985), applying an opposite abduction moment using an external brace (Pollo et al., 2002) or internal device (Clifford et al., 2011), or simply by reducing body mass (Messier et al., 2014). Muscle activation might be reduced by adopting altered gait kinematics (Miller et al., 2013a; Walter et al., 2010) or by providing proprioceptive feedback or stabilization using knee braces (Ramsey et al., 2007). One of the greatest challenges common to all of these treatments is that it is not possible to measure the internal knee joint contact load, except in rare subjects with instrumented prostheses (D’Lima et al., 2006; Kutzner et al., 2010). Therefore, there are no clinical guidelines for safe joint loading thresholds during activities of daily living, nor targets for load reduction to prevent osteoarthritis progression.
Figure 1.3: Graphical representation of musculoskeletal model used in this thesis. The model has two legs and a torso segment, with 96 musculotendon actuators (red) and 25 degrees of freedom (Arnold et al., 2010; Delp and Loan, 1995; Delp et al., 2007). The model is scaled to match each subject’s stature and posture; the model shown above has been scaled to match the asymmetrical bowlegged alignment and standing posture of a medial knee osteoarthritis subject.
1.1.4 Musculoskeletal Modeling to Understand Osteoarthritis and Evaluate Treatments

Because measurement of \textit{in vivo} joint loading is infeasible, musculoskeletal models must be used to estimate changes in knee joint loads in response to osteoarthritis and clinical interventions (Figure 1.3). A musculoskeletal model is a mathematical representation of the human body. Typically, the skeletal structure is represented as a series of rigid segments connected by joints with rotational and translational degrees of freedom based on experimental observation (Seireg and Arvikar, 1975). Each coordinate is actuated by a set of musculotendon actuators with force-generating capacity and geometric lines of action defined from cadaveric and imaging studies (Crowninshield et al., 1978; Delp and Loan, 1995; Ward et al., 2009). The motion of the model is therefore governed by a system of differential equations relating the actuating forces to the masses of the segments and accelerations the coordinates, taking the form:

\[
[M(q, u, t)]\ddot{u} = f(q, u, t)
\]

\textbf{Equation 1.1}

Where:

\( M = \) mass matrix, whose elements can be functions of the generalized coordinates, \( q \), generalized speeds, \( u \) (time derivative of generalized coordinates), and time, \( t \)

\( \dot{u} = \) time derivative of generalized speeds (i.e. generalized accelerations)

\( f = \) forcing vector, as a function of generalized coordinates, \( q \), generalized speeds, \( u \), and time, \( t \)

Perhaps the greatest challenge in representing the human body as a mechanical system is that each joint has an overdetermined set of musculotendon actuators. While it is relatively simple to compute the net generalized load actuating each joint using rigid
body dynamics (Equation 1.1), it is much more difficult to distribute the actuating force amongst an indeterminate system of agonist muscles (Crowninshield and Brand, 1981). For example, the knee joint is often modeled as a single degree of freedom that is actuated by a system of thirteen muscle forces, not including the passive contributions of soft tissues (Pandy and Sasaki, 1998). Empirical models (Ackermann and van den Bogert, 2010; Crowninshield and Brand, 1981; Rasmussen et al., 2001), and assumptions about synergistic muscle activation (Caldwell and Chapman, 1991; Jamison and Caldwell, 1993; Sartori et al., 2012) can provide a mathematical basis for optimal load distribution between muscles. However, there are a near-infinite number of possible solutions to the distribution problem if, as in osteoarthritis subjects (Hubley-Kozey et al., 2006), antagonist muscles are simultaneously acting in opposite directions across a given joint. When antagonist co-contraction is present, the model can be informed with electromyogram (EMG) measurements of muscle activation (Brandon et al., 2014; Kumar et al., 2013; Lloyd and Besier, 2003) which, although not linearly related to muscle force (Buchanan et al., 2004), are readily available from superficial muscles.
Figure 1.4: Force balance to compute medial and lateral axial contact loads. $F_{\text{musc}}$ represents a muscle force acting at some distance from the lateral joint contact location. $F_{\text{external}}$ represents the ground reaction force, while $F_{\text{medial}}$ and $F_{\text{lateral}}$ are axial components of the compressive joint contact load, resolved along the inferior-superior axis of the tibia.

Once muscle forces are computed, it is possible to estimate the magnitude of the tibiofemoral contact load. Estimates of the total compressive load have ranged from 2 to 7 times bodyweight during level walking (Morrison, 1970; Schipplein and Andriacchi, 1991; Seireg and Arvikar, 1975). Using a quasistatic frontal plane moment balance it is possible to isolate the axial components of the medial and lateral contact loads (Figure 1.4), which are by far the greatest components of force during level gait (Kutzner et al., 2010; Shelburne et al., 2005). The moment balance equations for each instant in time are given as follows:
\[ F_{med} = \frac{M_{musc,LC} + M_{ID,LC} + \frac{3}{2}(d_c)F_{MCL} - M_{brace}}{d_c} \]  

Equation 1.2

Where:

\[ M_{musc,LC} = \sum_{i=1}^{n}(r_{i,LC})F_i \]

=sum of adduction moments generated by the \( n \) scalar muscle forces, \( F_i \), acting with moment arms \( r_{i,LC} \) about the lateral contact location in the frontal plane of the tibial reference frame

\[ M_{ID,LC} = \text{inverse dynamics moment in the frontal plane of the tibial reference frame about the lateral contact location} \]

\[ d_c = \text{contact width between the medial and lateral contact locations} \]

\[ F_{MCL} = \text{ligament force, recruited to set the numerator to zero if the remaining terms sum to less than zero, which would otherwise signify a physiologically impossible tensile contact force. The distance between contact locations, } d_c, \text{ is approximately 50% of the total joint width (Schipplein and Andriacchi, 1991). Therefore, the medial ligament force is assumed to act at a distance of } \frac{3}{2}(d_c) \text{ from the lateral contact location (i.e. at the margin of the joint).} \]

\[ M_{brace} = \text{external brace abduction moment applied in the tibial reference frame.} \]

This value is zero for unbraced trials.
\[ F_{lat} = \frac{-(M_{musc,MC} + M_{ID,MC} + \frac{3}{2}(d_c)F_{LCL}) + M_{brace}}{d_c} \]

Equation 1.3

Where:

\[ M_{musc,MC} = \sum_{i=1}^{n}(r_{i,MC})F_i \]

= sum of adduction moments generated by the \( n \) scalar muscle forces, \( F_i \), acting with moment arms, \( r_{i,MC} \), about the medial contact location in the frontal plane of the tibial reference frame.

\[ M_{ID,MC} = \text{inverse dynamics moment in the frontal plane of the tibial reference frame about the medial contact location} \]

\[ d_c = \text{contact width between the medial and lateral contact locations} \]

\[ F_{LCL} = \text{ligament force, recruited to set the numerator to zero if the remaining terms sum to less than zero, which would otherwise signify a physiologically impossible tensile contact force. The distance between contact locations, } d_c, \text{ is approximately 50% of the total joint width (Schipplein and Andriacchi, 1991). Therefore, the lateral ligament force is assumed to act at a distance of } \frac{3}{2}(d_c) \text{ from the medial contact location (i.e. at the margin of the joint).} \]

\[ M_{brace} = \text{external brace abduction moment applied in the tibial reference frame.} \]

This value is zero for unbraced trials.
1.1.5 Rationale
Mechanical joint loading has been implicated in osteoarthritis progression. Based on surrogate measures of medial compartment loading (knee adduction moment and antagonist muscle co-contraction, it is believed that, during gait, subjects with osteoarthritis place greater mechanical loads on their knee joints than healthy control subjects. However, because loads cannot be measured in vivo, the magnitude of this increase in medial contact loading is not well understood. Without this information, we cannot quantify how great a reduction must be achieved to restore healthy joint loading, nor can we evaluate the clinical performance of existing and novel biomechanical devices.

1.2 Contributions
The purpose of this thesis was to develop and implement musculoskeletal modeling tools to yield greater insight into the role of knee joint loading in the pathogenesis of knee osteoarthritis, and to improve our capacity to evaluate clinical treatments. This purpose was achieved through two primary objectives, each comprised of two specific aims.

1.2.1 Objective 1: Knee Contact Force Estimation in an Osteoarthritis Population
Many studies have estimated knee joint contact forces during walking, with peak load predictions ranging from 2 to 7 times bodyweight (BW) (Anderson and Pandy, 2001a; Costigan et al., 2002; Hansen et al., 2008; Messier et al., 2014; Mikosz et al., 1988; Morrison, 1970; Seireg and Arvikar, 1975). However, there have been relatively few musculoskeletal model predictions of medial and lateral knee contact loads in osteoarthritis subjects (Kumar et al., 2013; Winby et al., 2013). The recent availability of in vivo joint load measurements (Kutzner et al., 2010; Zhao and Banks, 2007) has facilitated validation and refinement of musculoskeletal model predictions. Therefore, the first objective of this thesis was to predict medial and lateral knee contact forces in an
osteoarthritis population in order to deepen our understanding of the causes of disease progression.

1.2.1.1 Specific Aim 1: Validation of Knee Contact Load Predictions
The first aim of this thesis was to implement a musculoskeletal model and validate its prediction of muscle and knee joint contact forces against in vivo data. This aim was achieved by adapting a musculoskeletal model (Arnold et al., 2010) to account for structural changes in frontal plane knee joint alignment as found in osteoarthritis subjects (Cooke et al., 1997), developing a method to resolve medial and lateral compartment forces (Winby et al., 2009), and implementing an appropriate optimization algorithm (Happee and Van der Helm, 1995).

1.2.1.2 Specific Aim 2: Characterization of Abnormal Muscle Activation in Osteoarthritis Subjects as Positive or Negative Effect
The second aim of the thesis was to test whether selective activation of lateral knee muscles, as detected from electromyogram (EMG) measurements in osteoarthritis subjects (Hubley-Kozey et al., 2006), would increase or decrease loading on the damaged medial condyle. This aim was achieved by predicting medial and lateral knee joint loads during gait, and perturbing the activation of relevant lateral muscles to simulate the effect found in osteoarthritis subjects.

1.2.2 Objective 2: Evaluation of Biomechanical Effectiveness of Knee Braces
Of the many biomechanical treatments available for patients with medial knee osteoarthritis (§1.1.3), knee braces have been shown to provide significant improvements in pain and functional ability (Steadman et al., 2014) with a much lower cost than end-stage total knee arthroplasty (Bitton, 2009). However, experimental evidence suggests that no single brace design will effectively offload the knee for every patient (Dennis et
al., 2006; Kutzner et al., 2011), and 30 to 50 percent of patients discontinue brace use within 1 month due to perceived marginal effectiveness (Brouwer et al., 2006). In order to develop more effective knee braces, it is necessary to quantify the magnitude of medial load reduction achieved by each brace, and to understand the mechanism causing this reduction. Therefore, the second objective of this thesis was to develop a method to incorporate the applied brace load into the musculoskeletal model, and to predict associated changes in medial and lateral knee contact loads.

1.2.2.1 Specific Aim 3: Non-invasive Measurement of Brace Abduction Moment
Consequently, the third aim of this thesis was to develop a method to measure the load applied by the knee brace to each subject’s leg during gait. As stated above, the goal was to estimate changes in medial loading that were solely due to the use of the brace; it was therefore necessary to ensure that this method would not alter the mechanics of the brace, impede locomotion, or modify the load transfer pathway from the brace to the leg.

A previous study reported a promising technique to compute brace loads based on measured deflection and known stiffness (Schmalz et al., 2010). In this thesis, the method was extended to be based on angular, rather than linear, displacement, in order to facilitate accurate load predictions independent of changes in knee flexion angles.

1.2.2.2 Specific Aim 4: Quantification of Knee Unloading by Osteoarthritis Knee Braces
Finally, the fourth aim of this thesis was to quantify the mechanism, and magnitude, of medial load reduction due to osteoarthritis knee braces. This aim was achieved by developing and completing an experimental study of healthy and osteoarthritis subjects, and modeling their knee joint loading using the validated model developed through the first objective, and the brace load model developed in the third specific aim.
1.3 Thesis Structure

The chapters of this thesis were written as independent manuscripts. Because each chapter contains a critical review of important references, no separate literature review is provided. However, a comprehensive reference list is provided at the end of the thesis.

The first part of this thesis investigates the effect of altered muscular activation, as found in osteoarthritis subjects, on medial knee joint loads:

Chapter 2 describes the development and validation of the musculoskeletal model for estimation of medial and lateral knee joint loads. The model was validated against \textit{in vivo} measurements from a subject with an instrumented tibial prosthesis, and applied to analyze the effect of abnormal muscle activation in a population of eight subjects with medial knee osteoarthritis.

Chapter 3 describes the sensitivity of the musculoskeletal model to two important parameters: frontal plane alignment and frontal plane spacing between tibial contact locations. The model was perturbed throughout a range of realistic angles and contact widths to verify the importance of subject-specific scaling of each parameter for generating accurate contact estimates.

The second part of the thesis investigates the effectiveness of knee unloader braces for reducing medial knee joint loads as a clinical treatment for knee osteoarthritis:

Chapter 4 describes the development of a non-invasive method to measure the abduction moment applied by a knee brace to a subject’s leg. Using a custom mechanical testing apparatus, the frontal plane stiffness of each brace was quantified, and the brace moment was modeled as a linear function of deflection.
Chapter 5 evaluates the effectiveness of two different knee unloader braces for reducing medial knee contact loads during gait. Nine subjects with moderate knee osteoarthritis, and ten healthy control subjects, walked overground in the laboratory while wearing each brace. Brace effectiveness was quantified by combining the musculoskeletal model developed in Chapter 2 and Chapter 3 with the external brace load computed using the method from Chapter 4.

Finally, Chapter 6 provides a general discussion, and Chapter 7 provides recommendations and directions for future work.
CHAPTER 2

SELECTIVE LATERAL MUSCLE ACTIVATION IN MODERATE MEDIAL KNEE OSTEOARTHRITIS SUBJECTS DOES NOT UNLOAD MEDIAL KNEE CONDYLE

2.1 Contributions

Chapter 2 was published in the Journal of Biomechanics in 2014 (Brandon et al., 2014). I was the first author on the study, responsible for the study design, computational modeling, analysis, and preparation of the manuscript. The results presented in Chapter 2 contributed substantially to the completion of Specific Aim 1(§1.2.1.1), which was to develop and validate a musculoskeletal model to predict in vivo medial and lateral knee joint loads. Additionally, these results fulfilled the requirements of Specific Aim 2 (§1.2.1.2), which was to determine whether abnormal “OA-type” muscle activation patterns found in subjects with medial knee osteoarthritis are harmful or protective with regard to knee joint loading.

The model developed for this study was accurate within 0.3 BW when predicting changes in knee loads between gait conditions. Using this model, I found that the first peak medial knee contact force was significantly increased by the use of “OA-type” muscle activation patterns, although the overall (greater of the first or second) peak was unchanged. Thus, “OA-type” muscle activation is not an effective response for reducing medial knee contact loads, and may actually contribute to osteoarthritis progression. While “OA-type” selective activation of lateral muscles does not appear to reduce the medial knee contact load, it could allow subjects to increase knee joint stiffness without any further increase to the peak medial contact load.
2.2 Introduction

It is theoretically possible to perform two gait cycles with identical kinematics and ground reaction forces but using very different muscle activation patterns. While there is evidence that humans normally adopt an optimal muscle activation strategy to minimize metabolic cost (Anderson and Pandy, 2001b; Holt et al., 1991; Umberger and Martin, 2007), it has also been found that subjects with knee osteoarthritis walk with abnormal patterns of muscle activation despite exhibiting similar kinematics (Heiden et al., 2009; Hubley-Kozey et al., 2006; Zeni et al., 2010).

Why do subjects with osteoarthritis deviate from “optimal” muscle activation patterns? Given that the presence, severity, and risk of progression of knee osteoarthritis are strongly linked with excessive joint loading (Baliunas et al., 2002; Bennell et al., 2011; Miyazaki et al., 2002; Mundermann et al., 2005), and that muscle forces contribute greatly to knee contact forces (Shelburne et al., 2006), some researchers have speculated that abnormal muscle forces could be a primary cause of knee osteoarthritis (Bennell et al., 2008; Felson, 2009). Indeed, one of the hallmarks of knee osteoarthritis is elevated antagonistic co-contraction of quadriceps and hamstrings muscles during gait (Zeni et al., 2010), which is believed to result in greater joint loading.

However, subjects with moderate knee osteoarthritis exhibit significantly greater co-activation primarily in the lateral vasti and hamstrings muscles (Heiden et al., 2009; Hortobágyi et al., 2005; Mills et al., 2013) in conjunction with reduced activation in the medial gastrocnemius (Hubley-Kozey et al., 2006). It was speculated that, rather than causing knee osteoarthritis, these local changes in muscle activation could actually be a protective response aimed at decreasing the contact force on the damaged medial knee condyle. This distinction is extremely important because the two interpretations of
antagonism suggest diametrically opposed interventions for treatment of knee osteoarthritis.

Previous studies have used musculoskeletal models of varying complexity to compare knee joint loading in healthy and osteoarthritis subjects (Messier et al., 2005; Kumar et al., 2011; Richards and Higginson, 2010; Henriksen et al., 2006). An electromyogram (EMG)-driven model demonstrated that antagonistic co-contraction of quadriceps and hamstrings during gait will increase the medial contact force during gait (Kumar et al., 2011). None of these previous studies has addressed the hypothesis that selective antagonism of lateral muscle groups, independent of other changes in gait, could actually unload the medial condyle where osteoarthritis damage tends to be present.

The purpose of this study was to determine whether the selective lateral activation patterns characteristic of subjects with medial knee osteoarthritis could unload the medial condyle during gait while constraining the kinematics and ground reaction forces to remain unchanged. It is not feasible to experimentally alter neuromuscular patterns without changing kinematics and ground reaction forces; therefore, we used a constrained musculoskeletal modeling approach to address this research question. We hypothesized that despite elevated antagonist co-contraction, selective lateral activation of hamstrings and quadriceps muscles and inhibition of medial gastrocnemius would decrease the medial joint load.

2.3 Methods

2.3.1 Data

Lower limb marker trajectories and ground reaction forces (GRF) were collected from the affected limb of eight subjects with moderate medial knee osteoarthritis walking
overground at self-selected speeds (Table 2.1, Astephen et al., 2008). Kinematic data were sampled at 100Hz using an Optotrak 3D motion analysis system (Northern Digital Inc., Waterloo, ON). Ground reaction forces were sampled synchronously at 1000Hz using an AMTI force platform (Advanced Mechanical Technology Inc., Watertown, MA). Subjects had no history of knee pain or surgical intervention, KL grades between 1 and 3, and were not candidates for knee replacement surgery. Our objective was to assess “early-stage” individuals who had clinically diagnosed knee osteoarthritis, but whose gaits were not yet severely altered by factors such as pain, immobility, and joint instability. Standard frontal-plane short knee radiographs were obtained to compute varus alignment (Cooke et al., 2007; Moreland et al., 1987).

Table 2.1: Osteoarthritis subject characteristics. These eight subjects were selected as a subset of the population described in Astephen et al. (2008a). Where applicable, data are: Mean (standard deviation).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Kellgren-Lawrence</th>
<th>Height [m]</th>
<th>Weight [kg]</th>
<th>BMI [kg/m²]</th>
<th>Age [Years]</th>
<th>Speed [m/s]</th>
<th>Static varus alignment [deg]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3</td>
<td>1.73 (0.12)</td>
<td>93.3 (7.3)</td>
<td>32 (5)</td>
<td>60 (7)</td>
<td>1.3 (0.2)</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>

Electromyograms (EMG) were obtained from seven muscles spanning the affected knee: medial and lateral gastrocnemii, medial and lateral vasti, rectus femoris, biceps femoris, and semimembranosus (Hubley-Kozey et al., 2006). Raw EMG signals were full-wave rectified and low pass filtered at 6 Hz using a Butterworth filter, and then amplitude-normalized to the maximal value obtained for each muscle during maximal voluntary isometric contractions (MVIC) on a Cybex (Lumex, NY) dynamometer. The study was approved by the institutional ethics review board.
2.3.2 Musculoskeletal model

A 3D unilateral lower-limb musculoskeletal model (Arnold et al., 2010), including 7 segments, 11 degrees of freedom, and 44 individual heads of 35 muscles, was uniformly scaled to each subject based on the distance between the lateral knee epicondyle and lateral malleolus markers. This generic lower-limb model computes tibiofemoral joint translations as well as adduction and internal rotation angles as a function of the flexion degree of freedom. However, the variation in knee adduction angle throughout the gait cycle (~2 degrees) is less than the frontal plane angles observed in our subjects (Table 2.1). Consequently, we uncoupled the adduction degree of freedom from flexion and locked the adduction angle at each subject’s standing radiographic angle. Using OpenSim 3.0 (Delp et al., 2007), inverse kinematics, inverse dynamics, and muscle moment arms about the ankle, knee, and hip joints during gait were computed for each subject from the experimental GRF and motion capture data (Table 2.2).

Additionally, we included intermediate joints at medial and lateral knee contact locations which were locked during inverse kinematics, but unlocked during inverse dynamics computations to provide joint loads and muscle moment arms about each contact location. Within the generic model, these contact points were located 25% of the proximal tibial width (Schipplein and Andriacchi, 1991), or roughly 2.5cm (Iwaki et al., 2000; Yao et al., 2008) medial and lateral to the knee joint centre and, assuming spherical femoral condyles (Pandy et al., 1998), 25% of the same distance distal to the knee joint centre. Contact locations were fixed in the tibial frame to approximate translation with respect to the femur during knee flexion (Winby et al., 2009). For each subject, the distance from each contact location to the knee joint centre was uniformly scaled with the model as described above.
Table 2.2: Peak joint kinematics, joint moments, and ground reaction forces for the eight subjects during level gait at self-selected normal walking speed. These parameters were held constant for both “Baseline” and “OA-type” simulations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Location</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kinematics [degrees]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic Tilt</td>
<td>Late-stance</td>
<td>4.7 (6.6)</td>
</tr>
<tr>
<td>Hip Flexion</td>
<td>Heel-strike</td>
<td>24.4 (6.6)</td>
</tr>
<tr>
<td></td>
<td>Toe-off</td>
<td>-16.3 (7.4)</td>
</tr>
<tr>
<td>Knee Flexion</td>
<td>Early-stance</td>
<td>19.6 (8.5)</td>
</tr>
<tr>
<td></td>
<td>Swing</td>
<td>63.2 (4.8)</td>
</tr>
<tr>
<td>Ankle Dorsiflexion</td>
<td>Late-stance</td>
<td>8.3 (4.7)</td>
</tr>
<tr>
<td><strong>External Joint Moments [Nm/kg]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip Flexion</td>
<td>Early-stance</td>
<td>-0.8 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Late-stance</td>
<td>0.6 (0.2)</td>
</tr>
<tr>
<td>Hip Adduction</td>
<td>Early-stance</td>
<td>0.5 (0.1)</td>
</tr>
<tr>
<td></td>
<td>Late-stance</td>
<td>0.6 (0.1)</td>
</tr>
<tr>
<td>Knee Flexion</td>
<td>Early-stance</td>
<td>0.6 (0.4)</td>
</tr>
<tr>
<td></td>
<td>Late-stance</td>
<td>-0.4 (0.2)</td>
</tr>
<tr>
<td>Knee Adduction</td>
<td>Early-stance</td>
<td>0.4 (0.1)</td>
</tr>
<tr>
<td></td>
<td>Late-stance</td>
<td>0.4 (0.1)</td>
</tr>
<tr>
<td>Ankle Dorsiflexion</td>
<td>Late-stance</td>
<td>1.2 (0.2)</td>
</tr>
<tr>
<td><strong>Ground Reaction Force [N/body weight]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>Early-stance</td>
<td>-0.19</td>
</tr>
<tr>
<td></td>
<td>Late-stance</td>
<td>0.18 (0.05)</td>
</tr>
<tr>
<td>Vertical</td>
<td>Early-stance</td>
<td>1.09 (0.14)</td>
</tr>
<tr>
<td></td>
<td>Late-stance</td>
<td>1.05 (0.05)</td>
</tr>
<tr>
<td>Lateral</td>
<td>Heel-strike</td>
<td>0.06 (0.04)</td>
</tr>
<tr>
<td></td>
<td>Early-stance</td>
<td>-0.06</td>
</tr>
<tr>
<td></td>
<td>Late-stance</td>
<td>-0.05</td>
</tr>
</tbody>
</table>
2.3.3 Muscle Forces

“Baseline” muscle forces during a representative stride for each subject were estimated in Matlab (The Mathworks, Natick, MA) using static optimization to minimize a muscle area-weighted sum of squares of muscle stress at each instant in the gait cycle (Happee and Van der Helm, 1995; Brandon et al., 2011). Muscle forces were constrained to be positive, and to balance the inverse dynamics hip flexion, hip adduction, knee flexion, and ankle flexion moments. These “Baseline” muscle forces, computed using a generic cost function for “normal” gait (Crowninshield and Brand, 1981) are not expected to be representative of OA subjects who exhibit abnormal muscle activity (Hubley-Kozey et al., 2006). Instead, these muscle forces are an estimate of the baseline forces required to replicate the kinematics of these OA subjects.

2.3.4 OA-type perturbation

It was hypothesized that OA subjects exhibit additional changes in muscle activation that are not consistent with their kinematics. Therefore, joint kinematics and kinetics were held constant while muscle activations were perturbed from the “Baseline” condition to the “OA-type” condition. For each subject, vastus lateralis (VL), biceps femoris (LH), medial gastrocnemius (MG) activations were conservatively perturbed by adding the “mean principal component difference” (MPCD) between OA and control EMG (Hubley-Kozey et al., 2006) to the model-predicted “Baseline” muscle activations to define their “OA-type” activations (Figure 2.1). The MPCD perturbation was calculated for each muscle from the results of Hubley-Kozey et al. (2006) as the difference between mean principal component scores for OA and control groups, multiplied by the significant principal component pattern (Ramsay and Silverman, 1997).
Figure 2.1: Mean activation +/- standard deviation (shaded) across eight subjects for “Baseline” (dashed, blue) and “OA-type” (solid, red) conditions: A) Vastus lateralis (VL), B) Biceps femoris (LH), C) Medial gastrocnemius (MG). “Baseline” activation patterns were computed using the static optimization model. “OA-type” activation patterns were computed by adding the mean principal component difference between OA and healthy control subjects (MPCD, computed from results of Hubley-Kozey et al. (2006)) to the “Baseline” activations. These three muscles were perturbed to simulate “OA-type” EMG patterns because they have been shown to be activated differently by OA and healthy control subjects (Hubley-Kozey et al., 2006). The muscle activation patterns for this static optimization model correlate well with experimental EMG (§2.6).

Because these three muscle activation patterns were purposefully perturbed from the “Baseline” equilibrium solution, the sum of the muscle moments at the hip, knee, and ankle for this set of muscle activations would no longer balance the inverse dynamic moments applied to the model. Therefore, activations for the remaining 41 muscles were re-optimized in Matlab (The Mathworks, Natick, MA) to balance the inverse dynamic joint moments, using the same area-weighted stress-squared objective function, subject to the additional constraints that each muscle’s activation was greater than or equal to its “Baseline” activation, and that the three perturbed muscles (MG, VL, and LH) must maintain their prescribed patterns of activation.
2.3.5 Contact Model

For both “Baseline” and perturbed “OA-type” conditions, axial medial and lateral tibial contact forces were computed using a frontal-plane moment balance at tibial-fixed medial and lateral contact locations (Winby et al., 2009). If the moment balance at the medial condyle yielded a physiologically impossible tensile lateral contact force, the lateral condyle force was constrained to zero (i.e. unloaded) and a lateral collateral ligament force was added to the model at the lateral edge of the tibial plateau to maintain equilibrium (Winby et al., 2009). This contact model computes only the components of the medial and lateral tibiofemoral contact forces that are aligned with the long axis of the tibia. However, it has been shown that the shear components of tibiofemoral contact are comparatively small in magnitude (Kutzner et al., 2010; Shelburne et al., 2004). This musculoskeletal model can be used to predict medial and lateral axial contact loads within 0.3BW of in vivo measured loads and, more importantly, to estimate within 0.1BW the change in medial contact loads due to a gait perturbation (§2.6).

2.3.6 Statistics

Peak muscle forces, first and second peak medial, lateral, and total (combined) knee contact forces from “Baseline” and “OA-type” conditions were compared using a one-factor repeated measures ANOVA across the eight osteoarthritis subjects. An asymptomatic control group was not considered because the perturbation design of this study allowed each osteoarthritis subject to serve as their own control.
2.4 Results

2.4.1 OA-type Muscle Forces

Across the eight subjects, the mean change in muscle force due to the “OA-type” activation perturbation was largest for the vastus lateralis and medial gastrocnemius muscles, which were two of the directly perturbed muscles (Figure 2.2). The remaining 41 non-prescribed muscles responded to the “OA-type” perturbation indirectly in order to maintain equilibrium at each of the lower-limb joints. Listed in order of decreasing root mean square (RMS) change, the remaining muscles most affected by the perturbation were the lateral gastrocnemius, biceps femoris (SH), iliacus, semimembranosus, and sartorius (Figure 2.2). All other muscle forces were virtually unaffected by the “OA-type” perturbation.
2.4.2 Contact Forces

With a significance level of $P = 0.05$, the repeated-measures study design provided the statistical power to detect a 0.1 times bodyweight (BW) change in medial, lateral, or total knee contact force. The effect of the “OA-type” activation perturbation on tibiofemoral contact loads differed between the medial and lateral condyles. For the medial condyle, the “OA-type” perturbation caused a significant increase in contact force early in stance (2.1 to 2.4BW, $P < 0.01$); this shifted the peak medial contact force of 2.4BW from late-stance in the “Baseline” condition to early-stance in the “OA-type” condition, but did not change the overall peak magnitude (Figure 2.3A, Table 2.3). However, loading on the lateral condyle increased for both peaks (Figure 2.3B, Table 2.3). The greatest change in
the total knee contact force occurred in early stance, where the peak increased from 2.5 to 3.2BW due to the “OA-type” perturbation ($P < 0.01$).

Figure 2.3: Mean +/- standard deviation (shaded) medial (A), lateral (B), and total (C, sum) axial knee contact force during normal gait in eight subjects with moderate knee osteoarthritis. Forces predicted for “Baseline” condition (blue, dashed) were lower than those predicted after applying an “OA-type” activation perturbation (red, solid) to vastus lateralis, biceps femoris (LH), and medial gastrocnemius.

The model predicted lateral condylar unloading for four of the eight subjects for the “Baseline” condition, and three of eight subjects after the “OA-type” perturbation. Therefore, the lateral “ligament” force was recruited to maintain equilibrium for some or all of the period from 10% to 40% of the gait cycle. For the baseline condition, the mean peak “ligament” force across all eight subjects was 65N, while for the “OA-type” condition the mean peak force was just 27N. The maximum ligament force for any subject was 374N for the “Baseline” condition, and 173N for the “OA-type” condition.
Table 2.3: Changes in discrete measurements of knee contact forces due to “OA-type” activation perturbation

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>OA-Type</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lateral Condyle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak 1 [BW]</td>
<td>0.9 (0.3)</td>
<td>1.3 (0.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak 2 [BW]</td>
<td>0.8 (0.2)</td>
<td>1.0 (0.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Medial Condyle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak 1 [BW]</td>
<td>2.1 (0.5)</td>
<td>2.4 (0.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak 2 [BW]</td>
<td>2.4 (0.6)</td>
<td>2.3 (0.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Total Contact Load</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**2.4.3 Sensitivity to Baseline Muscle Forces**

These results motivated a follow-up question: would the effect of the “OA-type” perturbation on knee contact loads change if the “Baseline” muscle forces were different? To address this question, we computed for each subject a new set of muscle forces, “Baseline_stress5”, which minimized the sum of stress in each muscle raised to the fifth power. We then applied the same “OA-type” perturbation to the “Baseline_stress5” forces to estimate “OA-type_stress5” muscle and knee contact forces (Figure 2.4), and compared these results to our original “Baseline” and “OA-type” contact forces using a two-factor repeated measures ANOVA. There was no evidence of an interaction effect for any of the peak contact forces \((P>0.05)\); the “OA-type” perturbation caused a significant \((P<0.01)\)
increase in medial, lateral, and total contact loads regardless of the choice of baseline muscle forces (Figure 2.4).

Figure 2.4: Mean contact forces predicted for follow-up simulation conditions
“Baseline_stress5” (dashed, blue) and “OA-type_stress5” (solid, red) are superimposed over original “Baseline” and “OA-type” results from Figure 2.3. Medial (A), lateral (B), and total (C,sum) axial knee contact force predictions were greater when using the stress5 objective criterion than using the original weighted stress2 criterion. The “OA-type” perturbation significantly increased first peak medial load, and both first and second peaks for lateral and total loads under the follow-up “_stress5” condition.
2.5 Discussion

Contrary to our hypothesis, the “OA-type” perturbation did not decrease the medial knee contact force. However, the perturbation increased the medial contact force only slightly during early stance (Figure 2.3A, 15-30% gait cycle, Table 2.3), and the overall peak (the greater of the first or second peak) medial contact force was unchanged. The lateral knee contact force, in comparison, was greater throughout the gait cycle, and the increase on the lateral condyle due to the “OA-type” perturbation was greater than on the medial (Figure 2.3B, Table 2.3). Thus, these analyses do not support our hypothesis that OA subjects selectively activate lateral muscles, beyond any changes required by their gait kinematics, in an attempt to unload the medial knee condyle. Alternatively, it appears that selective lateral activation could be an effective strategy for subjects with medial osteoarthritis to increase overall joint stiffness (Schmitt and Rudolph, 2008) without large increases in contact force on the damaged medial compartment.

This study tested the hypothesis that a pattern of selective lateral knee muscle activation, as seen in OA subjects, could reduce medial knee contact forces independent of changes in kinematics and kinetics. We are not aware of any studies where gait kinematics were constrained and differences in muscle coordination were recorded; such a study would be difficult, if not impossible, to experimentally perform. However, differences in neuromuscular control of knee muscles, without corresponding changes in joint kinetics, have been observed during isokinetic activities, particularly in subjects with patellar pain (Christou, 2004; Owings and Grabiner, 2002). Given that joint pain is also a primary symptom of knee osteoarthritis (Maly et al., 2006), it is reasonable to hypothesize that an osteoarthritis population might, similarly, alter their muscle coordination without corresponding changes in gait kinematics and kinetics.
In this study, we predicted “Baseline” muscle forces to match experimental gait data from subjects with moderate knee osteoarthritis. There are small, but significant, differences in gait kinematics and kinetics between healthy control and moderate OA subjects (Astephen et al., 2008a; Kaufman et al., 2001), which may have predisposed our “Baseline” forces towards “OA-type” co-contraction (Richards and Higginson, 2010). However, preferential activation of lateral muscles, as seen in OA subjects, is energetically non-optimal (Crowninshield and Brand, 1981), and would not be predicted by our static optimization function. Additionally, our “Baseline” contact force estimates fall within the 2-3.5BW range typically reported from in vivo measurements (Kutzner et al., 2010; Fregly et al., 2012), and are considerably lower than other recent modeling predictions greater than 4BW (Winby et al., 2009; Richards and Higginson, 2010). Finally, we were primarily interested in the effect of the “OA-type” perturbation; our follow-up simulation (Figure 2.4) demonstrated that the “OA-type” perturbation increased first peak medial and both peak lateral contact forces, regardless of the choice for “Baseline” muscle forces.

We validated our model (§2.6) by comparing model predictions of muscle activations and joint contact forces with EMG measurements and synchronized in vivo knee force measurements for a single subject with an instrumented joint implant (Fregly et al., 2012). Our model’s peak medial load prediction error of 0.3BW was similar to another recent validated modeling study (Lin et al., 2010), although this error is also similar in magnitude to the effect sizes measured in vivo for subjects walking with and without assistive knee braces (Kutzner et al., 2011). However, when we examined the model’s ability to predict, blinded, changes in joint loading due to gait perturbations, we found that the model consistently predicted the correct direction of perturbation, and was
accurate within 0.03BW\(^1\) for all loads except first peak lateral (error 0.3BW) and total (error 0.2BW) loads (§2.6, Table 2.4). Thus, we designed a study where the outcome measure was not an absolute prediction of medial contact force, but rather a perturbation in contact force between model conditions.

Table 2.4: Mean (SD) Blind predictions of contact force for a single subject with an instrumented tibial implant from the Second Grand Challenge to Predict Knee Loading, across four normal walking trials and five “trunk sway” trials.

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<tbody>
<tr>
<td></td>
<td>in vivo Predicted</td>
<td>in vivo Predicted</td>
<td>in vivo Predicted</td>
</tr>
<tr>
<td>Medial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak 1</td>
<td>0.9 (0.1)</td>
<td>1.4 (0.2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Peak 2</td>
<td>1.3 (0.2)</td>
<td>1.2 (0.2)</td>
<td>-0.1</td>
</tr>
<tr>
<td>Lateral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak 1</td>
<td>1.3 (0.1)</td>
<td>1.7 (0.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Peak 2</td>
<td>0.9 (0.0)</td>
<td>0.8 (0.2)</td>
<td>-0.1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak 1</td>
<td>2.2 (0.3)</td>
<td>3.1 (0.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Peak 2</td>
<td>2.2 (0.2)</td>
<td>1.9 (0.2)</td>
<td>-0.2</td>
</tr>
</tbody>
</table>

To better understand changes in knee loading, we investigated the direct contribution of knee-spanning muscles to medial and lateral joint loads. In accordance with previous studies, (Sritharan et al., 2012; Winby et al., 2009) hamstrings dominated early-stance loading, followed by quadriceps at the first peak and gastrocnemius at the second peak contact forces. In this study, the early-stance increase in medial contact load between “Baseline” and “OA-type” conditions was primarily due to increased vastus lateralis,

\(^1\) Due to rounding, this difference is not visible in Table 2.4. Instead, the rounded “Delta” values are equal for in vivo and predicted first and second medial compartment, second peak lateral compartment, and second peak total joint loads. See the last two columns on the right side of the table.
sartorius, and semimembranosus forces (Table 2.3, Figure 2.2). Similarly, vastus lateralis and biceps femoris (short and long heads) were primarily responsible for the early-stance increase in lateral contact force. Elevated vastus lateralis activation from the “OA-type” perturbation caused a net increase in the early-stance internal knee extension moment which was countered by biceps femoris (SH), semimembranosus, and sartorius muscles in proportion with their cost in the optimization function. If the biceps femoris (LH) perturbation had been sufficient to balance the increased vastus lateralis knee extension moment, or if biceps femoris (SH) activation had also been perturbed, it is possible that semimembranosus and sartorius need not have been recruited and there might have been no change, or even a decrease, in first peak medial contact force. However, such a large increase solely in biceps femoris (LH) force would not correspond with EMG observations (Hubley-Kozey et al., 2006; Mills et al., 2013) or optimal muscle endurance (Crowninshield and Brand, 1981). During late-stance, there was an increase in lateral gastrocnemius force which caused the increase in lateral knee contact loads, while the slight decrease in medial gastrocnemius force was not enough to generate a substantial change in medial contact force (Table 2.3, Figure 2.2).

When the “OA-type” perturbation was applied, with the exception of a prescribed decrease for medial gastrocnemius, all other muscle activations were constrained to be greater than or equal to their “Baseline” values. Osteoarthritis subjects exhibit elevated, not decreased, muscle activation in quadriceps and hamstrings (Astephen et al., 2008b; Hortobágyi et al., 2005; Hubley-Kozey et al., 2006; Mills et al., 2013); therefore, this lower-bound on “OA-type” muscle activations was required to create a realistic “OA-type” perturbation and to ensure that the greatest change in muscle forces were attributed to the directly perturbed muscles: vastus lateralis, medial gastrocnemius, and biceps femoris.
It is important to consider that these results are based on a single, general, model of the musculoskeletal geometry that was uniformly scaled to the stature of each subject (Arnold et al., 2010). With respect to each individual, the model certainly includes errors in musculoskeletal geometry and relative muscle strength which could have biased the solution (Cleather and Bull, 2012; Fregly et al., 2012b; Wagner et al., 2013). There is a need to develop a greater understanding of the effect of modeling parameters and constraints, and to validate these models with in vivo measurements.

Muscles that do not span the knee can affect knee joint loading because they can accelerate other limb segments, thereby altering the ground reaction force and the knee contact loads through dynamic coupling (Chen, 2006; Hamner et al., 2010; Neptune and McGowan, 2011; Sritharan et al., 2012). Sritharan et al. (2012) showed that during gait, the contribution of non-knee-spanning muscles is primarily via changes in the ground reaction force. Because our model perturbation constrained body kinematics and external loads to be constant, we found a change in only one non-knee-spanning muscle: iliacus (Figure 2.2). However, iliacus has not been shown to be a primary contributor to medial or lateral knee loads during gait (Sritharan et al., 2012), and since the ground reaction force was constant, this non-knee-spanning muscle is unlikely to have altered knee loading. Future studies could investigate the combined effect of altered kinematics, ground reaction forces, and “OA-type” muscle activation on medial condylar loading in osteoarthritis subjects.

It is often assumed that static optimization models cannot account for antagonist muscle co-contraction, which is elevated in knee osteoarthritis subjects. In fact, Ait-Haddou et al. (2000) showed that models, such as the one in this study, that include biarticular muscles and are constrained to balance inverse dynamics loads across multiple joints will predict
some antagonist co-contraction. Richards and Higginson (2010) predicted co-contraction changes with increasing osteoarthritis severity using OpenSim’s computed muscle control algorithm, which includes static optimization to distribute muscle forces (Thelen and Anderson, 2006). Our model, likewise, predicted antagonist co-contraction at the knee which was elevated due to the “OA-type” perturbation (Figure 2.2).

The literature is divided between studies that have (Hurwitz et al., 1998; Kumar et al., 2012; Shelburne et al., 2006) and have not (Sritharan et al., 2012; Winby et al., 2009) predicted lateral condylar unloading and ligament recruitment. Our model predicted lateral unloading at some point in the first 40% of the gait cycle for four of the eight subjects in the “Baseline” condition, and three subjects in the “OA-type” condition. Selective “OA-type” lateral activation shifted condylar loading to the lateral compartment (Figure 2.3) and reduced the maximum “ligament” force from 374N to just 173N, perhaps reflecting the important role of lateral muscle co-contraction in stabilizing the knee adduction moment during gait (Winby et al., 2009). Across all subjects and trials, the maximum predicted “ligament” force of 374N was considerably lower than a reported mean lateral collateral ligament failure strength of 750N (Maynard et al., 1996), although higher than we would expect during normal gait.

The mediolateral contact force distribution at the knee is sensitive to the contact locations. During the stance phase of gait when the knee is flexed less than 30 degrees, the medial and lateral contact points translate roughly 3mm in the anterior-posterior and mediolateral directions (Hamai et al., 2009; Iwaki et al., 2000; Kozanek et al., 2009). While such translations are not inconsequental, we performed a sensitivity analysis +/- 5mm for each contact location and found less than 5% changes in estimated joint loads. Similarly, Winby et al. 2009 and Srithanan et al. 2012 perturbed contact locations up to
10mm, and found less than 10% changes in joint loads. In this study, the contact locations were constant between “Baseline” and “OA-type” perturbations, therefore the changes in contact loads that were detected between conditions are likely true effects, even if our contact location assumption introduced a systematic offset.

The strength of the present study is its isolation of a specific factor (muscle activation) and its effects on knee joint loading. Our hypothesis that OA subjects alter muscle activation without corresponding changes in kinematics and kinetics could not be tested experimentally; however, we used a musculoskeletal model to predict that selective activation of lateral knee muscles, as found in subjects with medial knee OA, would not independently reduce medial knee contact loads. The early-stance increase in medial contact load due to the “OA-type” perturbation could implicate this selective activation strategy as a cause of knee osteoarthritis. However, the largest increase in the contact load was found at the lateral condyle. Therefore, it is possible that selective lateral muscle activation is a compensation aimed at increasing joint stability with minimal change in medial load, rather than simply decreasing medial joint load. This study provides further evidence that the role of muscles cannot be ignored in the pathogenesis of knee osteoarthritis, and that musculoskeletal simulation may be essential for developing suitable clinical interventions.
2.6 Model Validation

In order to evaluate the sensitivity of medial and lateral knee contact forces to muscle activation patterns, it was essential to first demonstrate that our model could predict realistic joint contact and muscle forces. We used the model to predict (blinded) the knee contact force from public gait data for a single subject with an instrumented tibial implant, then compared these forces with synchronized *in vivo* measurements from the same subject (Fregly et al., 2012). These results were previously presented as part of the 2011 Second Grand Challenge to Predict *In Vivo* Knee Joint Loads (Brandon et al., 2011).

Figure 2.5: Blinded knee contact force predictions (green) versus in vivo measured loads (black) over four trials of normal walking (A-C) and five trials of “Trunk sway” walking (D-F) for a single validation subject (mean +/- shaded SD). The model was accurate within 0.03BW in predicting the change in first and second peak medial, and second peak lateral contact loads between normal and “trunk sway” conditions.
2.6.1 Knee Contact Force – Normal Gait

For the grand challenge data during normal gait the model under-predicted the magnitude of the peak medial knee contact force by an average of 0.3BW during early stance and 0.2BW during late stance (Figure 2.5A, Table 2.4). For the lateral contact force, the model under-predicted the magnitude of the peak lateral contact force by 0.4BW early in stance, but over-predicted second peak by 0.1BW (Figure 2.5B, Table 2.4). Combined, these measurements under-predicted the early-stance peak total contact force by 0.7BW, while matching the late-stance peak within 0.2BW (Figure 2.5C, Table 2.4). These predictions were the most accurate entry in the 2011 Grand Challenge.

2.6.2 Muscle Activation Patterns

The periods of muscle activation patterns predicted by the static optimization model were similar to the experimental EMG (Figure 2.6). The cross-correlations of muscle activation patterns with their respective EMG ranged between 0.48 and 0.93 (Table 2.5), which is comparable to results from a similar optimization model (van den Bogert et al., 2008). For all but three muscles the predicted muscle activation lagged behind the measured EMG (Table 2.5); this lag is expected as there is a physiological lag of 10-100ms (Corcos et al., 1992), or about 1-10% of the gait cycle, between excitation (EMG) and muscle force generation.
Figure 2.6: EMG (grey shaded, Mean +/- 1SD) versus blinded muscle activation predictions from static optimization model (solid green lines) over the same four trials of normal walking.

Adductor magnus exhibited the worst cross-correlation with the EMG (0.48, Table 2.5) as it lacked activity from 30-100% of the gait cycle. Further analysis revealed that the missing activation was provided by the agonist adductor brevis. While this difference in muscle activation distribution indicates a limitation of our modeling assumptions, muscles that do not span the knee contribute to the knee contact force via dynamic coupling (Sasaki and Neptune, 2010). Therefore, assuming that these agonist adductor muscles have similar effects on intersegment kinematics, our model would have captured the combined contribution of these adductor muscles to the medial contact force via dynamic coupling.
Table 2.5: Mean cross-correlations and signal lag (% Gait Cycle) between surface electromyograms (EMG) and predicted (blinded) muscle activation patterns. A positive lag is expected, due to the electromechanical delay between the muscle excitation signal (EMG) and muscle force generation, but lag may also be influenced by conduction velocity from the innervation zone to the surface electrode.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Cross-correlation</th>
<th>Lag (% Gait)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vastus Lateralis</td>
<td>0.76</td>
<td>2</td>
</tr>
<tr>
<td>Vastus Medialis</td>
<td>0.80</td>
<td>3</td>
</tr>
<tr>
<td>Rectus Femoris</td>
<td>0.66</td>
<td>-2</td>
</tr>
<tr>
<td>Biceps Femoris (LH)</td>
<td>0.67</td>
<td>-3</td>
</tr>
<tr>
<td>Semimembranosus</td>
<td>0.66</td>
<td>-3</td>
</tr>
<tr>
<td>Medial Gastrocnemius</td>
<td>0.93</td>
<td>7</td>
</tr>
<tr>
<td>Lateral Gastrocnemius</td>
<td>0.88</td>
<td>2</td>
</tr>
<tr>
<td>Soleus</td>
<td>0.93</td>
<td>1</td>
</tr>
<tr>
<td>Tibialis Anterior</td>
<td>0.72</td>
<td>0</td>
</tr>
<tr>
<td>Peroneus Longus</td>
<td>0.81</td>
<td>6</td>
</tr>
<tr>
<td>Adductor Magnus</td>
<td>0.48</td>
<td>1</td>
</tr>
<tr>
<td>Tensor Fascia Lata</td>
<td>0.89</td>
<td>8</td>
</tr>
<tr>
<td>Gluteus Maximus</td>
<td>0.80</td>
<td>1</td>
</tr>
<tr>
<td>Gluteus Medius</td>
<td>0.88</td>
<td>4</td>
</tr>
</tbody>
</table>
2.6.3 Change in Knee Contact Forces due to a Gait Perturbation

The purpose of this study was to compare different muscle force distributions using an identical model. In order to have clinical relevance, it was necessary to show that the model is sensitive to changes in knee contact forces due to a gait perturbation. Therefore, we predicted, blinded, the knee contact forces for Grand Challenge gait trials where the subject adopted an abnormal “Trunk Sway” gait pattern in an attempt to reduce medial joint loading (Fregly et al., 2007). As with our normal gait predictions, the model slightly under-predicted the medial, lateral, and total joint contact forces by approximately 0.1 to 0.5BW. However, when we compared the change in contact force predicted by the model to the change measured in vivo, we found that the model was in close agreement (i.e. within 0.03BW) for all except first peak lateral contact loads (0.3BW error) and the corresponding first peak total contact load (0.2BW error) (Table 2.4, column 3). In each case, the model predicted the correct direction of perturbation (i.e. increase or decrease in contact load). Additionally, even though the change in lateral contact loading differed between the model and in vivo measurement, the absolute magnitude of the lateral load was within 0.1BW of the in vivo value. Therefore, even though our model cannot precisely predict the magnitude of in vivo loads, by using the same model for both initial and perturbed conditions we are able to investigate the change in loading due to parameters that could not be experimentally tested.
CHAPTER 3

SENSITIVITY OF MEDIAL AND LATERAL KNEE CONTACT FORCE PREDICTIONS TO FRONTAL PLANE ALIGNMENT AND CONTACT LOCATION

3.1.1 Contributions

Chapter 3 was submitted to the Journal of Biomechanics in October, 2014 (manuscript ID: BM-S-14-01510). As first author on the study, and I was responsible for the study design, collection of experimental data, analysis, and preparation of the manuscript. Chris Saliba, the second author, performed the computational simulations to perturb knee contact width and frontal plane alignment for each subject. M.J. Brown, A.C. Clansey, and A. M. Morton were instrumental in collection of experimental data. The results presented in Chapter 3 in combination with results from Chapter 2, fulfilled the requirements of Specific Aim 1 (§1.2.1.1), which was to develop and validate a musculoskeletal model to predict *in vivo* medial and lateral knee joint loads.

This study used a computer model to test a realistic range of frontal plane knee alignment and contact widths that could be found in a population with osteoarthritis. Results show that failure to account for subject-specific knee alignment and contact widths in musculoskeletal models of osteoarthritis subjects could easily introduce errors of 0.2BW, or roughly 10% of the medial contact load. While it is well known that knee alignment and contact widths will influence mediolateral distribution of contact force, many modeling studies have not considered these parameters. Thus, this paper provides an important reference to guide model development and temper interpretation of modeling results.
3.2 Introduction

Medial and lateral tibiofemoral contact loads are difficult to estimate due to a complicated system of deformable surfaces and redundant actuators (D’Lima et al., 2012). Nevertheless, many studies attempt to compute knee contact forces because they are linked to cartilage degradation (Ogata et al., 1977) and the pathogenesis of knee osteoarthritis (Englund, 2010). As studies continue to design (Fregly et al., 2007; Shull et al., 2011) and evaluate (Kutzner et al., 2011) interventions that reduce harmful loading, it is important to improve accuracy in predicting knee contact loads. Two model parameters with great potential to affect mediolateral distribution, but which have not been thoroughly evaluated in literature, are frontal plane knee alignment and intercondylar contact width.

The knee adduction angle is linearly proportional to the adduction moment applied to the knee during gait (Heller et al., 2003; Hsu et al., 1990). Similarly, the knee adduction moment is correlated, although perhaps non-linearly, with the medial contact load (Trepczynski et al., 2014; Walter et al., 2010). Previous studies investigating the direct relationship between knee adduction angle and medial contact load have reported linear (Hsu et al., 1990) and non-linear increases in medial load of up to 3 times bodyweight (BW) due to an 8° increase in adduction angle (Heller et al., 2003). However, in vivo measurements show differences of roughly 1BW between subjects with alignments of -4.5° and 6.5° (Trepczynski et al., 2014), with a significant correlation between adduction angle and medial loading only during early stance (Kutzner et al., 2013). Although some studies have implemented subject-specific alignment in modeling knee contact loads (Gerus et al., 2013; Messier et al., 2014), its contribution to medial load prediction accuracy has not been quantified. Medial loads are highly sensitive to frontal plane
alignment, but this sensitivity varies between models and has not yet shown strong agreement with \textit{in vivo} measurements.

To our knowledge, no previous study has quantified the sensitivity of knee load predictions to intercondylar contact width. The problem is challenging; contact points are non-stationary on the tibial surface (Liu et al., 2010), contact locations are difficult to measure (Haladik et al., 2013), and knee morphology varies depending on sex (Mensch and Amstutz, 1975) and ethnicity (Mahfouz et al., 2012). Haladik et al. (2013) estimated medial contact locations that were further than lateral contact locations from the centre of the tibial plateau. Conversely, Yao et al. (2008) estimated symmetrical locations. Minns et al. (1981) showed that lateral condylar unloading will occur if the medial contact location is close to the joint centre, but modeled this change by shifting the tibia with respect to the femur in the frontal plane while maintaining a constant contact width. While subject-specific prescription of contact locations is currently limited by measurement accuracy, it is important to quantify the error which could be introduced due to variation in contact width.

It is, therefore, well-established that medial and lateral knee loads are sensitive to knee alignment and contact locations. This sensitivity is however model-dependent, and cannot be assumed from previous studies. Furthermore, because alignment is linearly related to the adduction moment, and contact forces are proportional to the moment divided by contact width, it is likely that there is a significant interaction between these two parameters. The purpose of this study was to quantify the sensitivity of medial and lateral tibiofemoral contact loads to simultaneous changes in knee adduction angle and knee contact width using a generic musculoskeletal model.
3.3 Methods

3.3.1 Subjects
Eleven subjects were recruited to perform overground gait as part of a larger study comparing moderate medial knee osteoarthritis subjects with healthy control subjects. Subjects were between 20 and 65 years of age, recreationally active and able to walk a city block, not currently taking medications for any neurological, cardiovascular, or metabolic disorders, and had no lower-limb injuries or surgeries within the last year. Medial knee osteoarthritis was diagnosed by an orthopaedic surgeon based on radiographic and symptomatic evidence. However, as the purpose of this study was simply to investigate the sensitivity of knee contact force estimates to modeling parameters, four osteoarthritis and seven control subjects were pooled into a single heterogeneous subject group (Table 3.1). Subjects provided written informed consent, and the study was approved by the institutional ethics review board.

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<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
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<tr>
<td><strong>Table 3.1: Mean (SD) subject characteristics</strong></td>
<td></td>
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<tr>
<td>Osteoarthritis</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age [years]</td>
<td>50 (12)</td>
<td></td>
</tr>
<tr>
<td>Height [m]</td>
<td>1.74 (10)</td>
<td></td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>81 (17)</td>
<td></td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>27 (4)</td>
<td></td>
</tr>
<tr>
<td>HKA (deg)</td>
<td>4.8 (5.5)</td>
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</table>
3.3.2 Apparatus
Subjects wore their own walking or running shoes and laboratory-provided lycra shorts and sleeveless shirts. A set of sixty-four 12.7mm diameter retroreflective tracking markers was adhered to participants' feet, legs, pelvis, torso, head, and arms (Miller et al., 2013b). Seventeen additional retroreflective markers were placed on the participants for a static calibration trial in the anatomical position and subsequently removed. An eleven camera (Oqus 400, Qualisys, Gothenburg, Sweden) passive motion capture system recorded marker trajectories while participants walked overground across six tandem force platforms (4 x Custom BP model, 2 x BP400600NC, AMTI, Watertown, MA, USA). Motion and ground reaction forces were sampled synchronously in QTM (Qualisys, Gothenburg, Sweden) at 200Hz, and 1000Hz, respectively.

3.3.3 Procedures
To compute functional joint centres, a two-legged squat trial and a two-legged standing hip circumduction (hula) trial were performed while holding a handrail for stability.

Functional hip joint locations were computed using a least-squares spherical fit method similar to Piazza et al. (2001), with combined data from hula and squat trials uniformly sampled across the range of motion. Functional knee joint locations were computed from the squat trial as the intersection of the mean helical axis (Woltring et al., 1985) with the mid-joint plane, which was defined to be perpendicular to the helical axis and intersecting with the midpoint of medial and lateral landmarks. Helical axes were computed for each frame relative to a single reference frame where the leg was fully extended, retaining only estimates with angles greater than 15 degrees and less than 70 degrees to minimize numerical and soft tissue error, respectively. Following the calibration trials, participants were instructed to perform eight overground trials across
the 10m walkway at their normal self-selected pace. Each subject obtained a standing full-length lower-limb teleroentgenogram for measurement of frontal plane knee alignment.

3.3.4 Data Analysis
Marker trajectories and ground reaction forces were filtered using a second order dual-pass butterworth filter with 6Hz and 12Hz low-pass cut-off frequencies, respectively, automatically segmented right and left leg strides, and time-normalized to 100% of the gait cycle in Matlab (R2012b, The MathWorks, Natick, MA, USA). The leg of interest was randomly selected for control subjects, and chosen as the most-affected limb in osteoarthritis subjects. For each subject, a single representative stride was selected for the leg of interest as the stride with the smallest root mean square difference from the intra-subject mean vertical ground reaction force.

3.3.5 Musculoskeletal Model
As previously described (Brandon et al., 2014), a generic OpenSim musculoskeletal model (Delp et al., 2007) was modified to allow computation of medial and lateral knee contact forces while including subject-specific frontal plane alignment. For this study, two versions of the model were scaled identically for each subject based on anatomical reference markers. The first version included a frontal plane degree of freedom at the knee, which was locked at a prescribed angle for each simulation. This model was used to compute inverse kinematics, to reduce residuals, to solve for muscle activations, and to compute the total axial joint contact force (IK, RRA, CMC, and Joint Reaction Analysis in OpenSim 3.0, Lerner et al., 2013). A second version of the model was created with medial and lateral contact locations centred on the tibial plateau (Brandon et al., 2014). This model was used to compute muscle moment arms and inverse dynamic loads about
each of the contact locations in order to solve for axial medial and lateral tibiofemoral contact loads (Winby et al., 2009).

### 3.3.6 Sensitivity Analysis

For each subject, a simulation was performed at each combination of five frontal plane angles (-10, -5, 0, 5, 10 degrees varus) and three contact widths (4, 5, and 6 cm) (Figure 3.1). Contact widths were set prior to scaling the generic model and are reported at these nominal values; however, individual contact widths varied slightly due to scaling. Frontal plane angles ranging from -10 to 10 degrees were chosen to capture a realistic range for subjects with osteoarthritis (Cooke et al., 1997; Heller et al., 2003). Contact widths ranging from 4 to 6 cm were selected to capture two standard deviations about the mean during normal gait, as estimated using computed tomography (CT) model-based estimates (Haladik et al., 2013) and in vitro pressure measurements (Wang et al., 2014). Thus, fifteen estimates of medial and lateral knee contact forces during gait were obtained for each of the eleven subjects.
Figure 3.1: Contact width and adduction angle perturbation. Left: medial and lateral contact locations were fixed in the tibial plateau, and spaced symmetrically about the joint centre with the specified contact width. Right: adduction angles were perturbed from +10 (green) to -10 (red) degrees of varus alignment (White = 0 degrees, default).

3.3.8 Statistics
First peak (0-20% gait), second peak (40-60% gait) and the stance phase mean (0-60% gait) medial, lateral, and overall knee contact forces were computed for each subject and normalised to body weight (BW). The sensitivity of each parameter to knee adduction angle and contact width was evaluated using a two-factor repeated measures ANOVA (proc mixed, SAS 9.4, SAS Institute Inc., Cary, NC, USA) with significance $\alpha = 0.05$. Sensitivity was quantified for each parameter using a linear model:
Parameter = $A + B^{*}\theta_{\text{add}} + C^{*}r_{cw} + D^{*}\theta_{\text{add}}^{*}r_{cw}$ \hspace{1cm} \text{Equation 3.1}

Where:

$A, B, C, D$ = model constants

$\theta_{\text{add}}$ = adduction angle [deg]

$r_{cw}$ = contact width [cm]

$(B + D^{*}r_{cw})$ = sensitivity to adduction angle [BW/deg] at $r_{cw}$ = constant

$(C + D^{*}\theta_{\text{add}})$ = sensitivity to contact width [BW/cm] at $\theta_{\text{add}}$ = constant
3.4 Results

For the default condition (0° adduction angle, 5cm contact width), mean overall peak medial, lateral, and total contact loads were 2.8, 1.24, and 3.84 times body weight (BW), respectively (Table 3.2). Changes in knee adduction angle and contact width redistributed the contact force between medial and lateral condyles, but did not affect the total contact load (Table 3.2). Stance mean, first peak, and second peak medial contact forces increased by approximately 3% bodyweight per one degree (BW/deg) increase in adduction angle (P<0.01, Figure 3.2A,C, Table 3.2). Lateral contact forces showed opposite (-3% BW/deg), sensitivity to knee adduction angle (P<0.01, Figure 3.3A,C, Table 3.2). However, there was a significant interaction between contact width and knee adduction angle (P<0.01), and the sensitivity to contact width varied between medial and lateral condyles, and between peak and stance mean parameters (Table 3.2).

Table 3.2: Knee contact force sensitivity to adduction angle and contact width

<table>
<thead>
<tr>
<th></th>
<th>Default Force Mean (SD) (Angle = 0°, Width = 5cm) [BW]</th>
<th>Adduction Angle Sensitivity (Contact Width = 5cm) [BW/deg]</th>
<th>Contact Width Sensitivity (Adduction Angle = 0°) [BW/cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stance Mean</td>
<td>1.85 (0.16)</td>
<td>0.03</td>
<td>-0.12</td>
</tr>
<tr>
<td>Peak 1</td>
<td>2.54 (0.44)</td>
<td>0.03</td>
<td>-0.20</td>
</tr>
<tr>
<td>Peak 2</td>
<td>2.79 (0.56)</td>
<td>0.04</td>
<td>-0.18</td>
</tr>
<tr>
<td>Lateral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stance Mean</td>
<td>0.72 (0.12)</td>
<td>-0.03</td>
<td>0.11</td>
</tr>
<tr>
<td>Peak 1</td>
<td>1.15 (0.17)</td>
<td>-0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Peak 2</td>
<td>1.24 (0.40)</td>
<td>-0.03</td>
<td>0.08</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stance Mean</td>
<td>2.57 (0.25)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Peak 1</td>
<td>3.18 (0.48)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Peak 2</td>
<td>3.84 (0.92)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant (P > 0.05)
Medial contact loads were reduced by 12-20% bodyweight per one centimeter (BW/cm) increase in contact width, depending on the parameter of interest (P<0.01, Figure 3.2B, Table 3.2). Medial knee contact loads were more sensitive to changes in contact width at larger adduction angles (interaction, P<0.01), with sensitivity of 20% BW/cm at 10 degrees adduction, and 6% BW/cm at -10 degrees adduction (Figure 3.2C). Medial load sensitivity to changes in knee adduction angle was greater at small contact widths (4% BW/deg at 4cm, Figure 3.2C) than at large contact widths (2% BW/deg at 6cm, Figure 3.2C).

There was no significant change in first peak lateral contact loads due to increasing contact width (P = 0.09, Figure 3.3B, Table 3.2); however, second peak and stance mean parameters significantly increased by 8% and 11% BW/cm, respectively as contact width increased (P <0.01, Figure 3.3B,C, Table 3.2). Lateral contact loads were more sensitive
(interaction, $P<0.01$) to changes in contact width at larger adduction angles, with sensitivity of 16% BW/cm at 10 degrees adduction, and 6% BW/cm at -10 degrees adduction (Figure 3.3C). Sensitivity of lateral loads to changes in knee adduction angle was greater at small contact widths (-4% BW/deg at 4cm, Figure 3.3C) than at large contact widths (-2% BW/deg at 6cm, Figure 3.3C).

Figure 3.3: Changes in lateral load due to adduction angle and contact width perturbations. A) Sensitivity to adduction angles of -10 (thick dashed, red), -5 (thin dashed, red), 0 (dot-dashed, black), 5 (thin solid, green), and 10 (thick solid, green) degrees. B) Sensitivity to contact widths of 4cm (dashed), 5cm (solid) and 6cm (dotted). C) Interaction between adduction angle and contact widths (Line styles as in B: 4cm–dashed, 5cm – solid, 6cm – dotted). (For interpretation of references to colour in this figure legend, the reader is referred to the web version of this article).

To fully understand the mechanism of load distribution due to adduction angle changes, we isolated inverse dynamics and muscular contributions to medial and lateral loading (Figure 3.4). As adduction angle increased, the external adduction moment about the lateral condyle also increased, which caused a linear increase in medial loads (Figure 3.4A). During early stance, this increase in medial load was slightly attenuated by a decrease in the muscular contribution; with increasing adduction angles, the lateral condyle rotated closer to the quadriceps line of action thereby reducing their moment.
arms and contribution to medial loading (Figure 3.4B). Conversely, lateral loads decreased as adduction angles increased. When the adduction angle was negative, a negative (abduction) external moment about the medial condyle caused an increase in lateral loading (Figure 3.4C). However, when the adduction angle was positive there was a positive (adduction) external moment about the medial condyle, which would have caused lateral lift-off were it not for the muscular contribution (Figure 3.4D). As the adduction angle increased, the early-stance muscular contribution to lateral loading increased due to larger moment arms of the quadriceps about the medial condyle (Figure 3.4D).
Figure 3.4: Contributions of inverse dynamics (external moments) and muscle forces to changes in knee contact loads due to adduction angle perturbation at constant nominal contact width of 5cm. A) Inverse dynamics contribution to medial loads. B) Muscle contribution to medial load C) Inverse dynamics contribution to lateral loads D) Muscle contribution to lateral loads. Angles are -10 (thick dashed, red), -5 (thin dashed, red), 0 (dot-dashed, black), 5 (thin solid, green), and 10 (thick solid, green) degrees. The change in external adduction moment due to altered frontal plane alignment dominated the smaller change in muscle forces due to altered lever arms. (For interpretation of references to colour in this figure legend, the reader is referred to the web version of this article).
3.5 Discussion

The purpose of this study was to quantify the sensitivity of medial and lateral knee contact force predictions to changes in frontal plane alignment and intercondylar contact width. Using a detailed musculoskeletal model (Delp et al., 2007), we showed that increasing the knee adduction angle in the model increased the medial, and decreased the lateral contact load by roughly 3%BW/deg. Increasing the contact width caused a 10-20%BW/cm decrease in medial and increase in lateral loads, depending on the peak or magnitude measure. Furthermore, there was a significant interaction between adduction angle and contact width. As contact width decreased, the model was more sensitive to changes in adduction angle. As adduction angle increased, changes in contact width caused greater changes medial and lateral in contact loads.

Sensitivity values of 3%BW/deg, or 10-20%BW/cm are significant considering typical ranges of adduction angles and contact widths. Subjects with medial knee osteoarthritis typically exhibit mean (SD) adduction angles of 7 (5) degrees, while healthy adults have angles of 1 (3) degrees (Cooke et al., 1997). Using the current model, failure to account for altered alignment in OA subjects would cause underestimation of their pathologically elevated medial contact loads by roughly 18% BW. Contact widths are more difficult to measure in vivo, but recent studies suggest that intercondylar spacing varies by 1cm or more between subjects; this would result in a 10-20%BW change in estimated medial and lateral knee contact loads (Haladik et al., 2013; Wang et al., 2014). In vivo measurements of knee loads have revealed medial force reductions due to gait interventions ranging from 15%BW (Zhao et al., 2007) to 40%BW (Kutzner et al., 2011). In order for musculoskeletal models to effectively predict and evaluate gait interventions
with effects of this magnitude, it is important to model subject-specific knee alignment and contact width.

Medial, lateral, and total peak knee contact loads of 2.8BW, 1.24BW, and 3.84BW, respectively, from this study are in close agreement with magnitudes reported using similar models (Richards and Higginson, 2010; Winby et al., 2009), although slightly higher than typically reported in vivo (Kutzner et al., 2010; Zhao et al., 2007). Kutzner et al. (2013) reported a significant correlation between adduction angle and in vivo medial loads, but did not provide the sensitivity; combining alignment data from (Kutzner et al., 2013) with peak medial loads for the same subjects across a range of activities (Trepczynski et al., 2014), we compute a linear sensitivity of 3.2%BW/deg, which is very similar to the 3%BW/deg estimated in the current study. Hsu et al. (Hsu et al., 1990) used a bed of springs model to determine that the medial proportion of the total tibiofemoral force increased by approximately 4.5% per degree of adduction angle. Assuming conservative total knee load of 2.5BW (Kutzner et al., 2010), this would result in a large medial load sensitivity of approximately 11%BW/deg. Heller et al. (2003) performed a similar study to analyze sensitivity of contact loads to frontal plane alignment, and found that the knee adduction moment increased linearly with increasing knee adduction angle. However, their model required muscle forces to balance the frontal plane moment at the knee; as adduction angles and moments were increased, estimated peak contact forces rose non-linearly to an unrealistic 7.4BW. In the current study, the frontal plane moment was balanced primarily by redistribution of medial and lateral contact forces (Trepczynski et al., 2014), and secondarily by recruitment of passive forces to represent collateral ligaments (Brandon et al., 2014). Thus, medial
contact load increased linearly with knee adduction angle at a conservative rate of 3%BW/deg, which is in close agreement with \textit{in vivo} results.

Results from this study suggest that contact width is an important parameter in load distribution, with sensitivity ranging from 10-20%BW/cm. To our knowledge, no previous study has examined the sensitivity of mediolateral load distribution to contact width. With present technology it is difficult to accurately measure contact locations \textit{in vivo} (Haladik et al., 2013; Wang et al., 2014); the fact that validation is challenging increases the need to understand a model’s sensitivity to contact width assumptions. Furthermore, it is unclear whether medial and lateral contact locations should be constrained to symmetrical frontal plane distribution about the joint centre, even in joints with unicompartmental osteoarthritis. Future work with high resolution imaging (Farrokhi et al., 2014), finite element models (Adouni and Shirazi-Adl, 2014), or \textit{in vitro} pressure measurements (Wang et al., 2014) may reduce uncertainty in modeling tibiofemoral contact locations. In the absence of such data, contact width could be a useful parameter for tuning subject-specific model predictions to match \textit{in vivo} measurements.

One limitation in this study was that the model was perturbed from negative ten (valgus) to positive ten (varus) degrees of knee adduction; however, none of the eleven subjects included in this study exhibited negative radiographic frontal plane knee alignment (Table 3.1). While medial loads predicted in the negative alignment simulations would not reflect \textit{in vivo} loading for these subjects, the purpose of the study was simply to demonstrate a linear relationship between mediolateral distribution and adduction angles. A second limitation is that the knee contact model in this study recruits medial and lateral collateral ligaments only when the applied frontal plane moment cannot be
balanced by shifting 100% of the knee contact load onto either the medial or lateral condyle (Brandon et al., 2014; Winby et al., 2009). Recently, Marouane et al. (2013) used a finite element model to demonstrate that while passive lateral collateral ligament (LCL) loads are relatively small in the presence of external knee adduction moments, medial collateral ligament (MCL) loads can be significant if the applied moment is in the negative (i.e. abduction) direction. Thus, our model could under-recruit the MCL for the extreme negative adduction angle conditions (e.g. -10 deg), which would cause overestimation of load transfer to the lateral condyle. Nevertheless, the mediolateral distribution exhibited a linear response throughout the range of angle perturbations, so it is unlikely that this limitation influenced results in this study. A third limitation in this study is that muscle forces did not change for either adduction angle or contact width perturbations. Some studies have suggested that subjects might alter muscle activation to resist applied external adduction moments, specifically through enhanced recruitment of lateral hamstrings (Adouni and Shirazi-Adl, 2014; Astephen et al., 2008b). Once again, this would have caused our model to overestimate sensitivity of mediolateral distribution to frontal plane alignment perturbations. However, it is unclear whether the model would overestimate the increase in medial force since enhanced lateral hamstrings recruitment is often balanced in the sagittal plane by enhanced quadriceps recruitment; this co-contraction can nullify any potential reduction in medial load that would have occurred due to activation of lateral hamstrings alone (Brandon et al., 2014).
Figure 3.5: Example (vastus lateralis) of error in muscle contributions to medial and lateral loading after 60% of the gait cycle, or during the swing phase of gait. The error is caused by discontinuities in moment arms, and is greatest for varus angles of 5 (thin solid, green), and 10 (thick solid, green) degrees, and smallest for -10 (thick dashed, red), -5 (thin dashed, red), 0 (dot-dashed, black) degree alignment. This artifact occurs because the Gait2392 model (Delp et al., 2007) defines conditional wrapping points which are only active at certain flexion angles (i.e. during swing). However, when the knee adduction angle is altered these conditional path points no longer fall along the muscle line of action, and therefore introduce sudden changes in moment arms. This model would be inappropriate for high-flexion activities without modification of conditional wrapping points.

Perhaps the most important limitation of this study relates to the broader implementation of subject-specific alignment through the use of this open source model (Delp et al., 2007). In this model, muscle lines of action are defined by origin, insertion, and intermediate wrapping points defined on appropriate bodies. However, when the tibia is rotated in the frontal plane any wrapping points defined with respect to the tibia must also rotate, and thus no longer fall along the muscle path from origin to insertion. While the change in moment arms is small, it has not been validated. Furthermore, because some wrapping points are recruited only during specific ranges of knee flexion angles it is important to screen for discontinuities in moment arms and contact force predictions. In this study, the peak knee loads occurred during stance, where flexion angles are relatively stable and discontinuities were not an issue (Figure 3.5).
Medial and lateral knee contact loads are difficult to predict (Fregly et al., 2012a), but they are also powerful outcome measures for treatment of musculoskeletal diseases such as knee osteoarthritis (Kutzner et al., 2011; Zhao et al., 2007). This study demonstrated that medial and lateral knee loads can vary up to 20%BW due to realistic variation in both knee adduction angle and intercondylar contact width parameters. Furthermore, this is the first study to show that there is a significant interaction between alignment and contact width; contact width is more important at large adduction angles, and knee loads are more sensitive to alignment with narrow contact widths. There are significant technological challenges in the implementation and validation of subject-specific parameters. However, it may be particularly important to consider these factors when comparing knee loads between populations that differ in knee alignment or condylar morphology.
CHAPTER 4

A CALIBRATED STIFFNESS METHOD TO COMPUTE UNLOADER BRACE KNEE ABDUCTION MOMENTS USING ADDUCTION DEFLECTION ANGLES

4.1 Contributions

Chapter 4 was submitted to the Journal of Biomechanics in November, 2014 (manuscript ID: BM-S-14-0155). I was the first author on the study, and I was responsible for the study design, construction of the apparatus, experimental collection, analysis, and preparation of the manuscript. Marcus Brown provided invaluable assistance during apparatus construction, initial pilot testing, and data collection, performed the initial analysis on pilot data to verify that the method produced realistic results. The study presented in Chapter 4 fulfilled the requirements of Specific Aim 3 (§1.2.2.1), which was to develop a non-invasive method to measure the abduction moment applied by a knee brace to a subject’s leg.

This study describes a novel method for computation of the external brace abduction moment based on abduction deflection angles and calibrated stiffness. A linear regression model was developed to estimate mean (SD) stiffness of 0.75(0.04) and 0.44 (0.02) Nm/deg for OA Assist and OA Adjuster 3 braces, respectively, with no clinically significant change at different flexion angles or between brace sizes. Therefore, the novel method described in this chapter could be applied to high flexion activities, with an estimated error in stiffness of less than 0.1Nm/deg, or roughly 1Nm at maximum deflection, due to improper, and clinically unlikely, tightening of the brace straps.
4.2 Introduction

Braces for medial knee osteoarthritis apply an external abduction moment to the knee joint in order to reduce loading on the damaged medial tibiofemoral compartment (Ramsey et al., 2007). One of the most common designs available on the market consists of a lightweight deformable beam that is attached to the lateral side of the affected leg using straps on the thigh and shank (Fantini Pagani et al., 2013; Gaasbeek et al., 2007; Jones et al., 2013; Richards et al., 2005). The brace is tightened by the user to apply a medially-directed load to the lateral side of the knee joint. This lateral load, in conjunction with medial thigh and shank reaction loads, results in a net “three-point bending” load that produces an external abduction moment at the knee joint.

There is evidence that the brace abduction moment can effectively reduce medial knee contact loads. Fluoroscopic measurements have demonstrated that knee unloader braces can increase medial joint separation, although not all braces are equally effective (Dennis et al., 2006). Likewise, in vivo measurements show 0 to 40 percent reductions in medial knee loads due to bracing, depending on the subject and brace design (Kutzner et al., 2011). Other studies have estimated the reduction in medial loading using musculoskeletal modeling (Pollo et al., 2002), or by computing a reduction in the net external adduction moment at the knee (Draganich et al., 2006; Pagani et al., 2010). In order to understand differences between brace designs, it is essential to measure dynamically the abduction moment applied by the brace to the knee joint during gait.

Previous studies have measured the brace abduction moment by interposing load sensors between the brace and the leg (Self et al., 2000), instrumenting the brace directly with strain gauges (Pollo et al., 2002), affixing load cells in parallel with the lateral brace beam (Fantini Pagani et al., 2010), or using a linear stiffness model to relate measured
deflection to moment (Kutzner et al., 2011; Schmalz et al., 2010). The first three methods of instrumentation offer accuracy at the expense of invasiveness, both for the subject and for the mechanical integrity of the brace. The latter method, measuring deflection to estimate the moment, is appealing because it can be applied easily to various braces and subjects with minimal disturbance. However, these previous deflection models have calibrated the moment-deflection relationship only with the brace in a fully-extended position, and were applied only to full-leg braces. Furthermore, Schmalz et al. (2010) define brace deflection using just three markers; brace deflection will be accurate when the leg is fully extended, but will increase in error as the knee is flexed since the adduction deflection cannot be resolved from flexion.

If brace motion were tracked, instead, using two clusters of three or more markers, it would be possible to decompose the brace rotation into flexion, adduction, and internal rotation components (Wu et al., 2002). With this formulation, it would be possible to compute brace deflection at any knee flexion angle. Therefore, the purpose of this study was to develop a calibrated stiffness model for three point bending osteoarthritis knee braces that is not influenced by flexion angle, and to demonstrate this model’s sensitivity to brace size and design.
4.3 Methods

4.3.1 Apparatus

Four OA Adjuster 3 (sizes S,M,L,XL) and four OA Assist off-the-shelf knee braces (sizes S,M,L,XL) were obtained for this study (Figure 4.1, DJO Global, Vista, California). Both brace models apply the three-point bending principle using a deformable lateral beam in contact with the lateral knee epicondyle. However, OA Assist brace has only a single lateral beam and uses a screw-type tightening mechanism at the epicondyle, while the OA Adjuster 3 brace has both lateral and medial beams and uses proximal and distal hinge-based tightening mechanisms. Motion capture data were collected at 200Hz using an 11-camera passive system (Oqus 400, Qualisys, Gothenburg, Sweden). Two force platforms (custom BP model, AMTI, Watertown, MA, USA) were used to measure six degree-of-freedom reaction forces synchronously at 1000Hz in Qualisys Track Manager (Qualisys, Gothenburg, Sweden). Clusters of four 12.7 mm reflective markers were adhered to the lateral beam of the thigh and shank brace segments. Markers were aligned with the inferior and superior edges of the two straps closest to the joint centre. One additional marker defined the location of the brace joint centre (Figure 4.1).
Figure 4.1: A) OAasssist (DJO Global, Vista, CA, USA) and B) OA Adjuster 3 (DJO Global, Vista, CA, USA) knee braces selected for this study. For each brace, proximal and distal clusters of four retroreflective tracking markers were attached along the lateral beam of the brace, and were used to compute brace angles. A single marker was fixed at the joint line. For the fully-extended static pose, the resultant of vectors $v_1$ and $v_2$ defined the inferior-superior anatomical direction.

A custom apparatus was constructed for these stiffness experiments (Figure 4.2). Two sections of 2” acrylonitrile butadiene styrene (ABS) pipe were wrapped in layers of ½” ethylene vinyl acetate (EVA) foam to roughly approximate the stiffness and diameter of soft tissue on a human thigh and shank. These pipes were rigidly bolted to two ¾” plywood frames, which in turn were bolted to the two 6 degree-of-freedom force platforms (AMTI, Massachusetts). The plywood frames included slotted tracks to allow attachment in any position from 0 to 60 degrees of brace flexion.
Figure 4.2: Custom mechanical testing apparatus. A) Top view showing OA Adjuster 3 strapped to two ABS pipes. The brace is in roughly 30 degrees of flexion. Plywood frames are bolted to two force platforms for measuring the ground reaction force. B) Side view showing a researcher applying the quasistatic point load to the epicondylar pad of the brace. This load caused a frontal plane “three point bending” moment and corresponding adduction deflection angle, which was measured using the clusters of retroreflective markers. C) A free body diagram depicting three-dimensional reaction forces and moments at each force platform (F1, M1, F2, M2), vectors from the force platform technical origins to the joint centre (r1, r2), and two independent estimates of the internal brace abduction moment, projected onto the shank anatomical adduction axis (Mb1, Mb2). The mean of moments M1 and M2 was taken as the brace abduction moment.
4.3.2 Procedure

For each trial, the brace was strapped to the apparatus by a researcher experienced in brace application in human subjects (MJB). A functional trial was recorded while flexing the brace through its full range of motion, and a fully-extended static unloaded trial was recorded to define anatomical reference frames.

Without adjusting the straps connecting the brace to the plywood frames, the brace was moved to the desired flexion angle and the plywood frames were rigidly bolted to the force platforms. If, after bolting, the force platforms measured shear forces exceeding 5N, the plywood frames were loosened and re-positioned slightly to eliminate pre-loading. The researcher then applied 2-3 vertical loading cycles to the brace joint centre to verify visually that the brace was not slipping on the apparatus.

Finally, brace stiffness trials were recorded while a quasi-static lateral load was manually applied to the brace joint centre. This loading direction simulates the force applied by the brace to the femoral epicondyle in human subjects. The load was increased linearly from 0 to ~175N over 3-4 seconds, then decreased linearly over the same period. A peak load of approximately 175N was selected from pilot work to yield a peak brace moment of 10Nm in accordance with previously reported moments for other braces (Gaasbeek et al., 2007; Pollo et al., 2002).

To test the effect of brace size, all eight braces (four sizes of two brace types) were tested at 0 degrees flexion angle. Four trials, consisting of both loading and unloading cycles, were performed for each brace to identify any differences in stiffness between sizes, and to verify the linear relationship between brace abduction moment and brace adduction deflection angles.
To test the effect of flexion angle, four deflection trials were performed at nine nominal flexion angles of 0, 5, 10, 15, 20, 25, 30, 40, and 50 degrees using the extra-large (XL) size of each brace type. The nominal flexion angles were measured during testing using a goniometer, but reported using the joint angles computed from motion capture data.

4.3.3 Data Processing

Motion and force data were filtered using a 6Hz low-pass second order dual pass butterworth filter in Matlab (The MathWorks, Natick, MA, USA). The functional helical flexion axis of the brace (Marin et al., 2003; Woltring et al., 1985) defined the primary anatomical axis, $\vec{X}$. An inferior-superior axis of the brace, $\vec{V}_{is}$, was computed as the mean of two vectors, $\vec{v}_1$ and $\vec{v}_2$, between the four tracking markers closest to the joint in the fully-extended static pose (Figure 4.1). The adduction axis, $\vec{Y}$, was defined to be mutually perpendicular to $\vec{V}_{is}$ and $\vec{X}$. Finally, the long axis of the brace, $\vec{Z}$, was mutually perpendicular to $\vec{Y}$ and $\vec{X}$. Euler angles were computed between the thigh and shank brace anatomical frames defined above using the joint coordinate system XYZ rotation sequence (Grood and Suntay, 1983). Brace deflection angles were computed as the difference between the instantaneous and initial (unloaded) angles for each trial.

The net internal joint moment, assuming static equilibrium, was independently computed from each force platform as the three-dimensional force platform reaction moment plus the cross-product of the reaction force with the instantaneous vector from the force platform technical origin to the brace joint centre (Figure 4.2). The net moment from each platform was set to zero when the brace was unloaded at the start of each trial. Additionally, for any subsequent frames where the two estimates of the brace moment differed by more than 1Nm, indicating that the experimenter did not apply a purely vertical point load at the joint centre, data were discarded. The brace abduction moment
was computed as the mean of these two estimates, expressed about the adduction axis 
($\bar{Y}$), of the shank anatomical frame.

4.3.4 Regression Modeling

4.3.4.1 Effect of Brace Size

The brace abduction moment was modeled in Matlab (regstats, v2012b, The Mathworks, 
Natick, MA, USA) for each of the 8 braces, as well as pooled across all four sizes for each 
brace, as a linear function of brace adduction deflection according to the equation:

$$M_{brace} = A \times \theta_A$$  \hspace{1cm} \text{Equation 4.1}

where:

$$M_{brace} = \text{Brace abduction moment}$$

$$A = \text{Brace stiffness in abduction direction [Nm/deg]}$$

$$\theta_A = \text{Brace adduction deflection angle [deg]}$$

Brace stiffness, $A$, was compared between the four sizes (S-XL) for each brace type (OA 
Adjuster 3 and OA Assist) using one-factor ANOVA and Tukey-Kramer post-hoc tests ($\alpha = 
0.05$) in Matlab (v2012b, The Mathworks, Natick, MA, USA).

Linear regression model fit was assessed using coefficient of determination ($R^2$), which 
was computed based on the sum of squares due to error (SSE) and the sum of squares 
total (SST):

$$R^2 = 1 - \frac{\text{SSE}}{\text{SST}}$$  \hspace{1cm} \text{Equation 4.2}

This form of $R^2$ is technically invalid without a constant in the regression model, and can 
lead to inflated, or even negative values for $R^2$ (Eisenhauer, 2003). However, the error is
minimal if the constant would be close to zero if it was included in the model, and alternative solutions for $R^2$ are less desirable because they aren’t directly comparable to this conventional form (Eisenhauer, 2003). A constant was not included in this regression model because it is physically impossible to achieve a spring force with zero deflection. Model linearity was assessed by computing 95% confidence intervals on model residual moments at each adduction deflection angle ($θ_a$).

4.3.4.2 Effect of Flexion Angle

Brace stiffness, A, was computed (Equation 4.1) at each of the nine discrete flexion angles for one size (XL) of each brace. The possible interaction of flexion angle with brace stiffness was investigated using a one-factor ANOVA and Tukey-Kramer post-hoc tests ($α = 0.05$) in Matlab (v2012b, The Mathworks, Natick, MA, USA).

4.3.5 Model Sensitivity to Strap Tension

For the stiffness tests described above, the brace was strapped to the apparatus by an experienced researcher (MJB) using strap tension subjectively similar to that employed when applying the brace to a human leg. However, during pilot testing, the magnitude of brace deflection for a given applied load appeared to be highly sensitive to the tightness of the two straps closest to the knee joint. Therefore, we performed four additional trials using one size (XL) of each brace model with straps in both maximally tightened and completely loose conditions at zero flexion angle to examine the possible range of error due to strap tension.
4.3.6 Model Predictions During Gait

Finally, to compare our calibrated stiffness regression model predictions with published data, we computed brace moments using a set of brace angles collected in 19 subjects (9M, 10F, 49±11 years, 173±10 cm, 81±19 kg) who walked overground at self-selected speed while wearing the OA Adjuster 3, then the OA Assist braces. These subjects were instructed to tighten the brace to a maximal level they would tolerate for a use period of 4 hours corresponding with a functional activity such as work, shopping, or exercise (Giori, 2004; Jones et al., 2013). Subjects gave informed consent, and the study was approved by the institutional review board.

4.4 Results

4.4.1 Effect of Brace Size

Both brace models exhibited a linear relationship between abduction moment and adduction angle throughout the range of applied moments (0-10Nm, Figure 4.3A,B). The linear regression model (Equation 4.1) explained 96 and 95 percent of the variance in adduction moments for OA Assist and OA Adjuster 3 designs, respectively. In order to achieve a maximum abduction moment of 10Nm, the OA Assist brace was deflected roughly 13 degrees in the frontal plane, while the OA Adjuster 3 was deflected 22 degrees.
Figure 4.3: Linear regression models (A, B) and residual error bounded by 95% confidence intervals (C, D) of brace moment as a function of adduction deflection angle. In each plot, raw data (black, dashed) are shown from all braces sizes (S, M, L, XL). A) OA Assist exhibited deflections up to 10 degrees, with a linear stiffness of 0.75 Nm/deg (red, solid). B) OA Adjuster 3 exhibited deflections up to 20 degrees, with a linear stiffness of 0.44 Nm/deg (red, solid). C) The linear stiffness model predicted OA Assist moments within 95% confidence intervals (red, solid) of 0.9 Nm. D) OA Adjuster 3 showed hysteresis; the model under-predicted moments during loading, and over-predicted moments during unloading, with 95% confidence intervals (red, solid) of 1.4 Nm.
The overall stiffness in the frontal plane, pooled across all four sizes, was estimated to be 0.75Nm/deg for the OA Assist brace and 0.44Nm/deg for the OA Adjuster 3 brace (Table 4.1). Each brace size showed small variation in stiffness across the deflection trials, with intra-brace standard deviations of less than 0.06Nm/deg (Table 4.1). The ANOVA and post hoc comparisons revealed statistical differences between the brace sizes for both OA Assist and OA Adjuster 3 models (Table 4.1, P<0.05). However, the mean stiffness for each size fell within 0.05Nm/deg of the pooled mean stiffness for both brace models (Table 4.1, Figure 4.3A,B), which represents roughly 1Nm error for a maximal 20 degree deflection.

Table 4.1: Mean (SD) brace stiffness [Nm/deg]. Dashed lines indicate significant Tukey-Kramer post-hoc comparisons (P < 0.05)

<table>
<thead>
<tr>
<th>Size</th>
<th>Brace</th>
<th>Pooled</th>
<th>S</th>
<th>M</th>
<th>L</th>
<th>XL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OA Assist</td>
<td>0.75</td>
<td>0.70</td>
<td>0.78</td>
<td>0.77</td>
<td>0.75</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.04)</td>
<td>(0.06)</td>
<td>(0.02)</td>
<td>(0.02)</td>
<td>(0.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OA Adjuster 3</td>
<td>0.44</td>
<td>0.41</td>
<td>0.44</td>
<td>0.46</td>
<td>0.42</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.02)</td>
<td>(0.01)</td>
<td>(0.01)</td>
<td>(0.02)</td>
<td>(0.01)</td>
<td></td>
</tr>
</tbody>
</table>

Residual error between the linear regression model and measured data was relatively constant throughout the range of measured adduction angles (Figure 4.4C,D). The OA Assist brace exhibited a tightly packed error distribution with 95% confidence limits of ± 0.9Nm. The OA Adjuster 3 brace showed hysteresis where the error was positive (underestimated brace moment) during the loading phase, and negative (overestimated
moment) during unloading. However, the 95% confidence interval throughout the measured range was only slightly larger at ±1.4Nm.

4.4.2 Effect of Flexion Angle

Stiffness was independent of flexion angle for the OA Assist brace (P = 0.08, Figure 4.4A), and significantly different only between 0 and 32 degree conditions (P = 0.02, Figure 4.4B) for the OA Adjuster 3 (P = 0.02), with no evidence of a linear trend. For each brace, four of nine flexion trials exhibited stiffness within one standard deviation of the pooled mean across all brace sizes, with the remaining five trials clustered closely around this range (Figure 4.4).

![Figure 4.4: Stiffness versus flexion for the extra-large (XL) size of A) OAasssist and B) OA Adjuster 3. Mean ± standard deviation of brace stiffness is shown at nine discrete flexion angles (black, solid), bounded by ± 1 standard deviation (red, solid) from the mean stiffness (Figure 4.3) measured at a static angle of 0 degrees across all four sizes for each brace. Inter- and intra-trial variance was large compared with any change in stiffness with flexion angle.](image-url)
4.4.3 Sensitivity to Strap Tension

The OA Adjuster 3 brace (Figure 4.5B) was more sensitive to strap tension than the OA Assist brace (Figure 4.5A); stiffness ranged from 0.3 to 0.6Nm/deg, and 0.67 to 0.80 Nm/deg for the OAdjuster III and OA Assist braces, respectively, between maximally loose and maximally tight conditions. For each brace type, the mean stiffness derived using subjectively realistic strap tension fell roughly in the middle of this range (Figure 4.5).

Figure 4.5: Effect of Strap Tension. Brace stiffness computed for OA Assist (A) and OA Adjuster 3 (B) braces with straps in maximally tight (dot-dash, black; upper lines) and completely loose (dotted, black; lower lines) conditions, compared with mean stiffness for each brace (red, solid) which was computed using subjectively realistic strap tension (Figure 4.3. The OA Adjuster 3 (B) was more sensitive to strap tension than OA Assist (A); however, the maximum possible error in stiffness, or difference in slope, (B – OA Adjuster 3) was less than 0.15 Nm/deg.

4.4.4 Model Predictions During Gait

In a sample of 19 subjects, mean abduction deflection angles throughout gait were 9 and 8 degrees for the OA Assist and OAadjuster braces, respectively. These angles were relatively constant throughout stance, with a slight decrease at toe-off and small increase during swing (Figure 4.6). Based on these angles, we predicted mean external brace
abduction moments throughout gait of 7.3Nm and 3.6Nm for the OA Assist and OA Adjuster 3 braces, respectively (Figure 4.6).

Figure 4.6: Mean ± SD brace angles (top) and corresponding moments (bottom) from 19 subjects wearing the OA Assist (left, A,C) and OA Adjuster 3 (right, B,D) braces. Braces were adjusted to provide a different abduction moment for each subject based on users’ subjective comfort, and the OA Adjuster 3 (B, D) was always worn first, followed by the OA Assist (A, C). Therefore differences in moments and angles between braces may not reflect true differences in brace performance during clinical use. Instead, these data demonstrate that our novel calibrated stiffness method predicts relatively constant brace deflection angles and moments throughout the entire gait cycle, and that these predictions are unaffected by knee flexion. Furthermore, the predicted moments are similar to previous estimates and measurements in literature.
4.5 Discussion

The objective of this study was to develop a non-invasive method to measure the external abduction moment applied by an “unloader” knee brace to the knee joint. Using a custom mechanical testing apparatus, it was shown that this brace moment can be modeled as a linear function of frontal plane brace deflection angles, and that the linear relationship is independent of the brace flexion angle. This calibrated stiffness method applied to both single- and dual-hinge brace designs, although the dual-hinge design exhibited greater hysteresis and a slightly larger error of 1.4 Nm.

Kutzner et al. (2011) reported respective linear spring constants of 9.8 N/mm and 4.0 N/mm for MOS Genu (long version, Bauerfiend AG, Germany) and GenuArthro (Otto Bock HealthCare, GmbH, Germany) braces when supported over their full lengths spanning roughly from the greater trochanter to the distal shank. Assuming a brace length of 0.75m, this would yield equivalent adduction stiffness values of 1.2 Nm/deg and 0.5 Nm/deg for MOS and GenuArthro braces, respectively, which are similar to the 0.75 Nm/deg and 0.44 Nm/deg values obtained for the shorter brace models in this study.

Brace abduction moments reported in literature have ranged from 3Nm (Self et al., 2000) to roughly 11Nm (Fantini Pagani et al., 2012; Pollo et al., 2002), depending on subject comfort and brace design. In a sample of 19 subjects who self-selected brace tightness, we estimated brace moments ranging from 0.6 to 14.5Nm and 0 to 8.4Nm for OA Assist and OA Adjuster 3 braces, respectively. Comparing these magnitudes with a typical inverse dynamics knee adduction moment of roughly 50Nm, these studies show that unloader knee braces provide a clinically significant (10-20%) reduction in external joint loading (Fantini Pagani et al., 2012), depending on the subject and brace design.
The linear calibrated stiffness model developed in this study was accurate within 95% confidence intervals of ±0.9 Nm and ±1.4 Nm for OA Assist and OA Adjuster 3 models, respectively (Figure 4.3) during mechanical testing. A perfectly linear relationship would be expected if the braces were constructed using only Hookean materials; however, for human comfort, both brace models necessarily include viscoelastic padding in series with the linear elastic aluminum lateral beam. Viscoelastic padding, as well as compliance in the hinge joints, may have contributed to the hysteresis in this study. Given that a 10 Nm brace intervention would be considered large (Fantini Pagani et al., 2012; Pollo et al., 2002), the 1 Nm (10%) error in the predicted brace moment is not insignificant; it may be important to perform a sensitivity analysis for any effects computed using this model.

The mechanical testing procedure developed in this study was sensitive to the tension of the brace straps closest to the knee joint (Figure 4.5). The upper limit was obtained when straps were tightened to a level that would not be tolerable in human subjects, effectively clamping the lateral beam to a shorter length. The lower stiffness limit, obtained with these straps completely loose, could not occur in vivo unless the subject had zero tissue stiffness or failed to attach the brace properly. However, the researcher in this study (MJB) was experienced in applying these braces to human subjects, and applied a realistic level of strap tension during mechanical testing. Given that a previous study using a different type of unloader brace found limited sensitivity to strap tension (Pollo et al., 2002), it is unlikely that the in vivo stiffness would range as far as these upper and lower extremes (Figure 4.5).

The lack of in vivo validation is a significant limitation of this study. Due to soft tissue compliance, thigh and shank reaction forces might occur at different locations when worn on a human leg versus a mechanical apparatus. Given the observed sensitivity to strap
tension (Figure 4.5), it’s likely that the EVA foam (similar to that used for cushioning insoles) in the mechanical apparatus is stiffer than human soft tissue, especially compared with the tissue of knee osteoarthritis subjects who exhibit elevated body mass (Sharma et al., 2006). However, even under extreme conditions we have computed upper and lower bounds on this error to be less than ±0.15 Nm/deg (Figure 4.5); these limits could be used to perform a sensitivity analysis when applying the calibrated stiffness model. Future studies could evaluate the linear model’s \textit{in vivo} performance using a gold standard such as a strain-gauge instrumented brace.

Despite limitations in accuracy, the calibrated stiffness model developed in this study has significant advantages over existing alternatives. Firstly, with the exception of affixing near-massless reflective markers, the brace is unmodified. Therefore, the method could be applied easily to various brace sizes, or even subjects’ custom braces. Other methods of measurement, such as interposing a load-sensing element between the brace and the leg (Self et al., 2000) or affixing strain gauges (Fantini Pagani et al., 2012), are invasive and may alter the brace performance. Secondly, because stiffness is defined in terms of angular, rather than linear (Kutzner et al., 2011; Schmalz et al., 2010), deflection the model can be applied to higher flexion activities such as the stair climbing, incline walking, or the swing phase of gait. While higher flexion angles increase the possibility of error due to kinematic cross-talk in adduction angles, this can be minimized through careful calibration of the flexion axis (Schache et al., 2006). Lastly, the stiffness computed in this study can be applied easily by other researchers using the same braces without requiring further mechanical testing or instrumentation.

This study verified that OA Assist and OA Adjuster 3 knee unloader braces operate according to the three-point bending principle; tightening the brace results in frontal
plane bending of the lateral brace beam, which is linearly proportional to the external abduction moment applied to the knee. Predicted brace stiffness and moment values are similar to previously reported values, and accurate within 1.5 Nm of applied moments using a mechanical apparatus. Future work should validate this model *in vivo* using a gold standard such as strain gauge instrumentation.
CHAPTER 5

CONTRIBUTIONS OF MUSCLES AND EXTERNAL FORCES TO MEDIAL LOAD REDUCTION DUE TO OSTEOARTHRITIS BRACE

5.1 Contributions

Chapter 5 is in preparation for submission to the Journal of Biomechanics. I was the first author on the study, and I was responsible for the study design, experimental collection, analysis, and preparation of the manuscript. Dr. Adam Clansey, Amy Morton, and Marcus Brown provided invaluable assistance during data collection. Dr. Aaron Campbell assisted with subject recruitment and provided clinical insight, while Dr. Jim Richards enabled the brace donation from DJO Global, provided pilot data, and critically reviewed the study design and results. The study presented in Chapter 5 fulfilled the requirements of Specific Aim 4 (§1.2.2.2), which was to quantify the reduction in medial knee joint loading due to two different knee unloader braces.

This study describes a novel application of a musculoskeletal model, including the contribution of the brace abduction moment (Chapter 4), to quantify the relative contributions of external joint loads, muscle activation, and the applied brace abduction moment to reducing medial loads during gait. Across all subjects, medial loads were reduced by 0.1 to 0.3 times bodyweight (BW), while lateral loads increased by 0.1 to 0.2 BW. Changes in gait kinematics due to bracing were subtle, and had little effect on medial and lateral joint loads. However, when subjects were fitted with either knee brace, the model predicted increased activation of gastrocnemii muscles, which inhibited the ability of the brace to reduce medial loading. The musculoskeletal model in this study
predicted a realistic range of medial load reductions, which were primarily due to the
direct application of an abduction moment to each subject’s knee.

5.2 Introduction
Knee osteoarthritis is a mechanical disease wherein the near-frictionless layer of shock
absorbing cartilage in the knee joint is progressively degraded by physical forces (Felson,
2013). In the United States alone, more than 9 million people suffer pain and reduced
mobility as a result of knee osteoarthritis, with an inflation-adjusted economic burden
exceeding $100 billion (Bitton, 2009). Osteoarthritis progression may be inhibited by
reducing exposure to large compressive loads (Waller et al., 2011), particularly on the
medial side where damage is most common (Wise et al., 2012). Consequently,
interventions such as knee bracing have been developed to postpone disease progression.

Despite their great potential for conservative management of medial knee osteoarthritis,
knee braces are not uniformly effective. In one study, 25% of participants discontinued
brace use within 3 months, citing a lack of perceived benefit and some discomfort
(Brouwer et al., 2006). Further evidence for the lack of brace effectiveness was given by
fluoroscopic (Dennis et al., 2006) and \textit{in vivo} joint load (Kutzner et al., 2011) studies,
which showed that some subjects may not experience medial contact force reductions due
to bracing.

There are three primary mechanisms through which a knee brace might unload the
medial condyle: direct application of an external abduction moment, reduced joint
loading through altered gait kinematics, or modified muscle activation. Previous studies
have measured brace abduction moments up to 12Nm in magnitude (Gaasbeek et al.,
2007; Kutzner et al., 2011; Self et al., 2000), which theoretically decreases medial
compartment loading by 12% (Shelburne et al., 2008). Additionally, bracing can alter
gait kinematics (Gaasbeek et al., 2007; Jones et al., 2013; Orishimo et al., 2012) kinetics
(Ramsey et al., 2007; Toriyama et al., 2011), and antagonistic co-contraction of
quadriiceps, hamstrings, and gastrocnemii (Fantini Pagani et al., 2013; Ramsey et al.,
2007). To our knowledge, only one previous study has used a musculoskeletal model to
estimate medial load reductions of 17% (Pollo et al., 2002). However, this study
implemented a simplified model that did not allow for co-contraction of quadriiceps or
hamstrings, did not include gastrocnemii or many other muscles, equilibrated only knee
flexion moments, and did not account for changes in muscle moment arms during knee
flexion or between subjects.

Therefore, the purpose of the current study was to quantify the relative contributions of
external joint loads, muscle activation, and the applied brace abduction moment to
reducing medial loads during gait, using a detailed musculoskeletal model. The
secondary aim was to investigate changes in these mechanisms between two different
knee braces, and between osteoarthritis and control subjects.
5.3 Methods

5.3.1 Participants

Participants were between 20 and 65 years of age, recreationally active and able to walk a city block (400 m), not currently taking medications for any neurological, cardiovascular, or metabolic disorders, and had no lower-limb injuries or surgeries within the last year (Table 5.1). Ten participants with moderate medial knee osteoarthritis, diagnosed by an orthopaedic surgeon, formed the osteoarthritis group; one participant failed to complete an x-ray, and was excluded. Osteoarthritis participants had been prescribed a knee brace, but had not used one prior to this study. Ten participants with no history of any lower-limb disease formed the control group. Participants were provided with lycra shorts and a sleeveless shirt, and wore their own walking or running shoes. Participants completed the WOMAC questionnaire to assess knee health (Bellamy, 2005; Roos et al., 1999), and provided written, informed consent. The study was approved by the institutional ethics review board (Appendix A).

Table 5.1: Participant Characteristics: Mean (SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Osteoarthritis</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>4</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Age [years]</td>
<td>55 (3)</td>
<td>45 (13)</td>
<td>0.04</td>
</tr>
<tr>
<td>Height [m]</td>
<td>1.70 (0.09)</td>
<td>1.73 (0.11)</td>
<td>0.52</td>
</tr>
<tr>
<td>Mass [kg]</td>
<td>89 (21)</td>
<td>74 (15)</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>31 (5)</td>
<td>25 (2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HKA [deg, -° varus]</td>
<td>-7.9 (7.3)</td>
<td>-1.3 (2.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Medial Joint Space [mm]*</td>
<td>2.6 (2.5)</td>
<td>5.5 (0.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WOMAC - Pain</td>
<td>72 (19)</td>
<td>100 (1.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WOMAC - Stiffness</td>
<td>53 (21)</td>
<td>98 (7.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WOMAC - Function</td>
<td>63 (16)</td>
<td>99 (1.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WOMAC - Total</td>
<td>64 (17)</td>
<td>99 (1.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gait Speed [m/s]</td>
<td>1.6 (0.1)</td>
<td>1.4 (0.1)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
5.3.2 Experimental Setup

Eighty-one retroreflective markers were adhered to participants’ upper and lower limbs (Miller et al., 2013b). For overground trials, markers were recorded at 200Hz by an eleven camera passive motion capture system (Oqus 400, Qualisys, Gothenburg, Sweden) while ground reaction forces were measured synchronously at 1000Hz using six tandem force platforms (4 x Custom BP model, 2 x BP400600NC, AMTI, Watertown, MA, USA). For treadmill trials, a seven camera (Oqus 400, Qualisys, Gothenburg, Sweden) system recorded marker trajectories while ground reaction forces were recorded using a dual-belt instrumented treadmill (Tandem Force Sensing Treadmill, AMTI, Watertown, MA, USA).

Synchronized surface electromyograms (EMG) (Trigno Wireless EMG System, Delsys Inc, Boston, MA, USA) were recorded at 1000Hz. Measurement sites were shaved, debrided, and cleaned with alcohol, then electrodes were adhered above twelve muscles on the braced leg: rectus femoris, vastus medialis, vastus lateralis, biceps femoris, semitendinosus, medial gastrocnemius, lateral gastrocnemius, tibialis anterior, soleus, gluteus maximus, gluteus medius, and tensor fascia lata. Three additional electrodes were placed on the contralateral leg to measure vastus lateralis, biceps femoris, and medial gastrocnemius muscles, which are affected by medial knee osteoarthritis (Hubley-Kozey et al., 2006). Electrodes were located according to Seniam guidelines (www.seniam.org), with the exception of vastus lateralis and vastus medialis. Due to geometric interference with the brace (Figure 5.1), electrodes for these muscles were placed distal to the brace strap, but as far as possible from the knee joint to avoid regions of muscle innervation (Barbero et al., 2012) and large skin motion artifact (De Luca et al., 2010).
Figure 5.1: OA Assist (A) and OA Adjuster 3 (B) knee braces (DJO Global, Vista, CA, USA) used in this study, shown for example on a varus-aligned subject with medial knee osteoarthritis. Reflective markers are visible along the lateral beam of each brace, and were used to compute brace adduction deflection angles as the brace was tightened to apply an unloading moment. Velcro wraps (Fabrifoam, Exton, PA, USA) wraps used to affix tracking clusters to the thigh and shank are visible proximal and distal to the brace. Trigno EMG electrodes (Delsys, Boston, MA, USA) are secured beneath athletic tape, proximal to the knee joint, to measure signals from vastus lateralis and vastus medialis.

5.3.3 Knee Braces

Two off-the-shelf osteoarthritis knee braces were used in this study: OA Assist and OA Adjuster 3 (DJO Global, Vista, CA, USA) (Figure 5.1). Both designs employ a deformable lateral beam to apply a three-point-bending load to the knee joint (Chew et al., 2007), but exhibit substantial design differences. The OA Assist brace has a single lateral beam and a screw-based load adjustment mechanism (Figure 5.1A), while the OA Adjuster 3 brace has both medial and lateral beams and a hinge-based load adjustment (Figure 5.1). Braces were fitted according to manufacturer guidelines.
Using a mechanical calibration similar to Schmalz et al. (2010), each brace was modeled as a spring with stiffness of 0.75 Nm/degree and 0.44 Nm/degree for the OA Assist and OA Adjuster 3 braces, respectively. Retroreflective markers affixed to the lateral brace beam (Figure 5.1) to track brace adduction deflection angles, which were multiplied by stiffness to yield brace abduction moments. Equal and opposite abduction moments were expressed in the tibial anatomical frame, and applied as external loads to the tibia and femur.

### 5.3.4 Procedure

Four calibration trials were performed: a static anatomical pose, overground walking to determine self-selected speed, two-legged squatting, and two-legged standing hip circumduction (hula). Following calibration, participants performed gait trials in three conditions in the following order: unbraced, fitted with the OA Adjuster 3 brace, and fitted with the OA Assist brace. The OA Assist brace was always tested last due to its potential interference with EMG sensors (Figure 5.1A). For each brace condition, subjects performed level and inclined (10% grade) treadmill trials, then eight overground trials at self-selected speed. Treadmill trials were thirty seconds in duration, and were performed at the target overground speed for level and 0.2 m/s slower for incline trials, to control for speed as an effect of the braces (Draganich et al., 2006). Participants were given 5 minutes of rest between brace conditions.

After the gait trials, participants performed nine maximum voluntary isometric contractions on a dynamometer (System 4, Biodex Medical Systems Inc, Shirly, NY, USA): knee extension and flexion at 90 degrees, contralateral knee extension and flexion at 90 degrees, ankle plantarflexion and dorsiflexion at 0 degrees (neutral position), contralateral ankle plantarflexion at 0 degrees, hip extension at 30 degrees, and hip
abduction at 20 degrees. For each test, participants were given verbal encouragement for two, three-second contractions with 30 seconds of rest (Hubley-Kozey et al., 2006). Finally, participants obtained a standing full-length teleroentgenogram for measurement of frontal plane knee alignment (Cooke et al., 2007), medial joint space (Buckland-Wright et al., 1995), limb length, and hip joint spacing. The x-ray distance was fixed at 2.84m to control for distortion.

5.3.5 Data Processing
Marker trajectories and ground reaction forces were filtered using a second order dual-pass butterworth filter with 6Hz and 12Hz low-pass cut-off frequencies, respectively (Lerner et al., 2013), and segmented into right and left leg strides in Matlab (R2012b, The MathWorks, Natick, MA, USA). Electromyogram data were band-pass filtered (20-450Hz, Trigno, Delsys Inc, Boston, MA, USA), full-wave rectified, enveloped with a 6Hz low-pass second order zero lag butterworth filter (Winby et al., 2013), and normalized to the maximum magnitude (MVC) obtained across all gait and isometric trials (Hubley-Kozey et al., 2006). Additionally, based on post-hoc analysis of roughly 800 trials, EMG signals were discarded for any trials where peak normalized activation was less than 10% MVC, or un-normalized signals exceeded thresholds of 0.6 V for isometric and 0.3 V for gait trials.

For each participant, a representative stride with vertical ground reaction force closest to the intra-subject mean was selected for each brace condition. We observed no change in walking speed due to bracing in overground gait (Table 5.1); therefore, we have restricted our analysis in this paper only to the overground condition. Thus, for each participant, three dynamic trials (unbraced, OA Assist, and OA Adjuster 3) and one static calibration trial were exported for musculoskeletal modeling.
5.3.6 Musculoskeletal Model

A generic musculoskeletal model with two legs, a torso, and 96 muscles (Arnold et al., 2010) was modified to include subject-specific frontal plane alignment and medial and lateral contact locations (Brandon et al., 2014). To compensate for errors in moment arms when the pelvis segment was scaled larger than the femur, we removed the wrapping surface for one fibre of the adductor magnus (mid) muscle, and uniformly reduced the size of all pelvis wrapping surfaces by 23%. In a similar model (Gait 2393, Delp et al., 2007), adductor magnus does not have any wrapping points, and uniform scaling should not greatly affect muscle force distribution. For comparison with EMG, muscle strengths were increased by a factor of 2.5.

The model was scaled to each participant based on radiographic leg length (legs), radiographic hip joint spacing (pelvis), and anatomical markers (torso). Inverse kinematics, inverse dynamics, residual reduction (RRA), and muscle analysis were performed using OpenSim 3.2 (Delp et al., 2007). Muscle forces were estimated using static optimization, and tibiofemoral contact loads were estimated in Matlab (R2012b, The MathWorks, Natick, MA, USA) (Brandon et al., 2014; Winby et al., 2009).

5.3.7 Statistical Analysis

Subject characteristics were compared using unpaired t-tests. Discrete measures from medial, lateral, and total contact loads, as well as gait speeds, joint kinematics, joint moments, cumulative EMG (cEMG), and cumulative model muscle activation (cAct), were compared between brace conditions and subject groups using a two-factor ANOVA with Brace as a repeated factor, and planned Sidak post-hoc contrasts between brace conditions. Significance (α) was set at 0.05.
5.4 Results

Osteoarthritis participants were older, walked slower, and had greater body mass index (BMI), greater varus alignment, reduced medial joint space, and lower WOMAC scores than control subjects (Table 5.1). Gait speed was unaffected by bracing ($P > 0.9$).

5.4.1 Joint Kinematics

Both braces caused a significant increase in late-stance hip extension angles ($P < 0.01$, Figure 5.2A,E), decrease in late-stance hip abduction angles ($P = 0.02$, Figure 5.2B,F), decrease in early-stance ($P = 0.02$) and mid-swing knee flexion angles ($P < 0.01$, Figure 5.2C,G), and decrease in late-stance ankle dorsiflexion ($P < 0.01$, Figure 5.2D,H).

Osteoarthritis subjects exhibited significantly different kinematics from control subjects for every parameter ($P < 0.05$). During mid-swing, subjects with the OA Adjuster 3 decreased knee flexion by 2 degrees more than with the OA Assist brace (control: $P = 0.07$, osteoarthritis: $P < 0.01$, Figure 5.2C,G).
Figure 5.2: Mean hip flexion (A), hip adduction (B), knee flexion (C), and ankle dorsiflexion (D) angles for control (solid) and osteoarthritis (dashed) groups. OA Assist (green), and OA Adjuster 3 (blue) brace conditions were significantly different from the unbraced (red) condition for these angles (P<0.05), as measured by peak parameters (*, P < 0.05) and the integral throughout the gait cycle. Significant pairwise comparisons (†, P < 0.05) between brace conditions were detected in both osteoarthritis and control groups for hip flexion and knee flexion angles, but only in the osteoarthritis subjects for ankle dorsiflexion angles. For the knee flexion angle, only the second peak interaction plot is shown (G), although the brace condition main effect was also significant for at first peak (C). For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
5.4.2 Joint Moments

Both braces increased early-stance hip flexion moments (\( P = 0.01 \), Figure 5.3A), increased late-stance hip internal rotation moments (\( P < 0.01 \), Figure 5.3B), and increased late-stance external knee extension (propulsive) moments (\( P < 0.01 \), Figure 5.3C,H). External knee adduction moments were unaffected by bracing (\( P > 0.49 \) Figure 5.3D,I), but the net moment was significantly reduced due to the brace abduction moment (\( P < 0.01 \), Figure 5.3E,J). Osteoarthritis subjects selected a larger brace abduction moment than the control subjects for both braces, (\( P < 0.08 \), Table 5.2) and both groups accommodated a larger brace moment with the OA Assist brace than the OA Adjuster 3 brace (\( P < 0.01 \), Table 5.2).

Table 5.2: Unloading brace abduction moment applied to the knee. Mean (SD) reported across all subjects.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>OA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA Assist [Nm]</td>
<td>6 (2)</td>
<td>9 (4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>OA Adjuster 3 [Nm]</td>
<td>2 (1)</td>
<td>5 (2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P-value (braces)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>
Figure 5.3: Mean hip flexion (A), hip internal rotation (B), knee flexion (C), knee adduction (D, without including brace external moment) and net knee adduction (E, including brace external moment) moments for control (solid) and osteoarthritis (dashed) subjects. OA Assist (green), and OA Adjuster 3 (blue) brace conditions were significantly different from the unbraced (red) condition for these joint moments (P<0.05), as measured by peak parameters and the integral throughout the gait cycle. Interaction plots (F-J) show mean +/- SEM peak estimates for each brace condition (red, green, blue) and subject group (left = control, right = OA) at locations where a significant main effect due to bracing was detected (*, P < 0.05). Significant pairwise comparisons (†, P < 0.05, F-J) between brace conditions were found for osteoarthritis, but not control subjects in hip flexion, hip internal rotation, and knee flexion moments. For the net knee adduction moment, only the first peak interaction plot is shown (J), although the brace effect was also significant and of similar magnitude at the second peak (E). For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.
5.4.3 Knee Contact Forces

Bracing reduced medial contact loads by 0.1 to 0.3 times bodyweight (BW), or roughly 10% (P < 0.04, Table 5.3, Figure 5.4A), with no difference between braces (P > 0.62) or between subject groups (P > 0.53, Table 5.3). The medial load integral was reduced more for the OA Assist than the OA Adjuster 3 brace (P = 0.01, Figure 5.3D, Table 5.3), and more for osteoarthritis subjects than control subjects (P = 0.08).

Bracing increased late-stance peak lateral contact loads by 0.1 to 0.2 BW (P < 0.01), with no difference between braces (P > 0.92, Table 5.3, Figure 5.3B). The lateral load integral (Figure 5.3E) was significantly greater when fitted with either brace (P < 0.01).

First peak total contact loads decreased due to brace use (P = 0.05), but there was no change in the second peak (P > 0.56, Figure 5.3C) or integral throughout gait (P = 0.49, Figure 5.3F). Osteoarthritis subjects had significantly lower late-stance total loads than control subjects (P = 0.02).

Table 5.3: Change in contact loads due to bracing. Mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Medial</th>
<th></th>
<th>Lateral</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OA Assist</td>
<td>-0.2 (0.2)</td>
<td>-0.1 (0.2)</td>
<td>-12 (9)</td>
<td>0.2 (0.1)</td>
<td>16 (10)</td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td>-0.3 (0.2)</td>
<td>-0.1 (0.2)</td>
<td>-16 (6)</td>
<td>0.2 (0.2)</td>
<td>16 (7)</td>
<td></td>
</tr>
<tr>
<td>OA Adjuster</td>
<td>-0.1 (0.2)</td>
<td>-0.0 (0.1)</td>
<td>-7 (7)</td>
<td>0.2 (0.2)</td>
<td>7 (5)</td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td>-0.3 (0.3)</td>
<td>-0.0 (0.2)</td>
<td>-9 (6)</td>
<td>0.1 (0.2)</td>
<td>9 (7)</td>
<td></td>
</tr>
</tbody>
</table>

Bold: significant change in joint load due to bracing (Sidak post-hoc test, P < 0.05)
Figure 5.4: Mean medial (A), lateral (B), and total (C) knee contact forces for control (solid) and osteoarthritis (dashed) subjects during overground gait. OA Assist (green), and OA Adjuster 3 (blue) brace conditions were significantly different from the unbraced (red) condition for these joint moments (P<0.05), as measured by peak parameters and the integral throughout the gait cycle. Interaction plots show mean +/- SEM predictions of the cumulative medial (D), lateral (E), and total knee contact force (F), integrated throughout the gait cycle. Medial loads (A,D) decreased for both OA Assist (green) and OA Adjuster 3 (blue) conditions, as compared with the unbraced condition (red), while lateral loads increased due to bracing (B,E). Combined, there was no change in the integral of the total knee contact force due to brace use (F). For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.
5.4.4 Contributions to Joint Contact Loads

Throughout the gait cycle, the brace abduction moment contributed 0.1BW and 0.2BW toward reducing medial knee contact loads for OA Assist and OA Adjuster 3 braces, respectively (Figure 5.5C,E). The inverse dynamics contribution medial and lateral contact forces was unaffected by bracing (Figure 5.5C,D,E,F). During late stance, the contribution of gastrocnemii to medial loading was increased due to brace use, which inhibited the overall reduction in medial loading (Figure 5.5C,E).

Quadriceps muscles contributed less force to medial and lateral loading in braced conditions (Figure 5.5C,D,E,F). Hamstrings muscles made a negligible contribution to medial contact loads (Figure 5.5C,E), but were responsible for a late-stance increase in lateral loading due to bracing (Figure 5.5D,F).
Figure 5.5: Contributions to medial (A,C,E) and lateral (B,D,F) knee contact loads in osteoarthritis subjects. Each plot shows the contributions of quadriceps (dot-dashed, purple), hamstrings (dotted, cyan), gastrocnemii (solid, orange), and inverse dynamics forces (dashed, black) to the joint load (shaded, grey), with the brace contribution (thick solid, black) shown for OA Assist (C,D) and OA Adjuster 3 (E,F) conditions. The first two plots show contributions to the total (shaded, grey) medial (A) and lateral (B) contact forces during unbraced gait, while the bottom four plots show changes in joint load contributions when subjects were fitted with OA Assist (C,D) and OA Adjuster 3 (E,F) braces as compared with the unbraced condition (A,B). The external abduction moment applied by the brace (thick solid, black) acted to reduce medial contact loads by a relatively constant 0.2 times bodyweight (BW) throughout the gait cycle for the OA Assist brace, and 0.1 BW for the OA Adjuster 3 brace. However, in both brace conditions the unloading action of the brace was inhibited by increased contributions from gastrocnemii (solid, orange) during late-stance (C,E).
5.4.5 Muscle Activation

Muscle activations predicted by the musculoskeletal model were similar in timing and magnitude to EMG measurements (Figure 5.6). Only two significant changes in EMG were detected due to bracing: a decrease in semitendinosus excitation \((P = 0.05, \text{Figure 5.6E})\), and a decrease in lateral gastrocnemius excitation that was present only for osteoarthritis subjects using the OA Assist brace \((P = 0.02, \text{Figure 5.6G})\). In contrast, the model predicted no change in semitendinosus activation (Figure 5.6L) and an increase in lateral gastrocnemius activation that was evident only for osteoarthritis subjects using the OA Assist brace \((P < 0.01, \text{Figure 5.6N})\). Across both osteoarthritis and control groups, the model also predicted a decrease in vastus lateralis \((P = 0.01)\), vastus medialis \((P = 0.01)\), and rectus femoris \((P = 0.01)\) activation (Figure 5.6H,I,J), and, only in osteoarthritis subjects, an increase in biceps femoris short head \((P < 0.01)\) and medial gastrocnemius \((P < 0.01)\) activation (Figure 5.6K,M).
Figure 5.6: Mean enveloped EMG (A-G) and predicted muscle activation (H-N) for osteoarthritis (dashed) and control (solid) subjects for seven muscles spanning the knee joint. Vastus lateralis (A,H), vastus medialis (B,I), rectus femoris (C,J), biceps femoris short head (D,K), semitendinosus (E,L), medial gastrocnemius (F,M), and lateral gastrocnemius (G,N) all showed significant changes due to the use of OA Assist (green) and OA Adjuster 3 (blue) braces, as compared with the unbraced condition (red). For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.
5.5 Discussion
The use of a knee brace decreased medial knee contact loads by 0.1-0.3 BW (Table 5.3) in both osteoarthritis and control subjects during overground gait. This medial knee contact load reduction was primarily caused by the unloading abduction moment applied by the brace to the knee joint (Figure 5.5). Bracing did not reduce the total knee load, but rather shifted loading from the medial to the lateral condyle (Figure 5.4).

The mean peak medial and total contact loads predicted in this study of 2.9 BW and 5 BW (Figure 5.4) are similar in magnitude to previous total contact load estimates of 4.4 BW (Richards and Higginson, 2010), although greater than medial and total loads of 1.95BW and 2.6BW, respectively, recorded in vivo (Kutzner et al., 2010). However, self-selected walking speeds in the current study were faster than in the previous modeling study (1.6 vs 1.3m/s, Richards and Higginson, 2010), which would have contributed to larger joint loads (Zhao et al., 2007). The difference in gait speeds between healthy and osteoarthritis subjects (Table 5.1) could also explain why healthy subjects exhibited larger joint loads (Figure 5.4).

More importantly, we predicted mean reductions in medial loading of roughly 5 to 15% (Table 5.3), which is similar to the range of 8 to 17% reported using a different brace design and a simplified musculoskeletal model (Pollo et al., 2002). In vivo measurements in three subjects revealed mean reductions in medial knee loads of 7 to 23% during gait, with a range of 0 to 40%, for two different brace designs (Kutzner et al., 2011). In this study, we found a similar range in medial load reduction from 0 to 35% between subjects; thus, our model appears to provide realistic subject-specific predictions of medial load reduction due to knee bracing.
The largest contributor to this medial load reduction was the abduction moment applied by the brace to the knee joint (Figure 5.5C,E). Based on a known stiffness for each brace and measured deflection angles for each subject, we computed a relatively constant brace abduction moment during gait, which, independent of other factors, would have reduced medial compartment loading by approximately 0.2 BW for the OAssist brace, and 0.1BW for the OA Adjuster 3 brace (Figure 5.5, Table 5.3). However, the change in medial and lateral loads due to bracing was not constant throughout the gait cycle due to varying contributions of muscle forces (Figure 5.5C,D,E,F).

Previous studies have reported a decrease in antagonist co-contraction of hamstrings, gastrocnemii, and quadriceps muscles when subjects use an unloader knee brace (Fantini Pagani et al., 2013; Ramsey et al., 2007). In this study, as a result of reduced external knee flexion moments in the braced conditions (Figure 5.3C), there was a small but significant decrease in quadriceps activation (Figure 5.6), which contributed to the reduction of medial and lateral contact forces (Figure 5.5C,D,E,F). By comparison, measured EMG data showed no change in vastus lateralis (P = 0.49) and rectus femoris (P = 0.95), and a small decrease in vastus medialis that was not significant (P = 0.11, Figure 5.6).

The model predicted a significant increase in gastrocnemii and biceps femoris short head activation during late stance (Figure 5.6), which inhibited the reduction in second peak medial loads by roughly 50% and 100% for OA Assist and OA Adjuster 3 braces, respectively (Figure 5.5C,E). This late-stance increase in gastrocnemii force appears to contradict a decrease in lateral gastrocnemius EMG (Figure 5.6G) as well as previous reports of decreased activation (Fantini Pagani et al., 2013). It is possible that the model predictions could be improved by penalizing gastrocnemii activation (Steele et al., 2012);
however, Fantini-Pagani (2013) reported decreased gastrocnemius excitation only during loading and early-stance, and not at the late-stance peak. Furthermore, it is difficult to conclude whether the small decrease in EMG in this study (Figure 5.6G) was actually due to reduced muscle excitation, or was an artifact of reduced skin motion when the brace was clamped on the skin adjacent to the measurement site (De Luca et al., 2010).

While some studies have reported a reduction in the knee adduction moment due to knee bracing (Arazpour et al., 2012; Toriyama et al., 2011), others found no change (Hewett et al., 1998; Pollo et al., 2002; Schmalz et al., 2010). In this study, there was no change in the knee adduction moment (Figure 5.3D), and therefore a negligible contribution of the inverse dynamics load to changes in the medial and lateral knee contact forces due to bracing (Figure 4.5). Although medial loads can be reduced by adopting novel gait kinematics (Fregly et al., 2009), this mechanism was not employed by the two knee unloader braces tested in this study. However, it is possible that a longitudinal study would reveal additional neuromuscular and kinematic adaptations.

Across all subjects, the OA Assist applied a greater unloading moment to the knee than the OA Adjuster 3 brace (Figure 4.5, Table 5.2). Both braces were adjusted by an experienced researcher (MJB) to provide a maximal abduction moment that would be perceived as comfortable by the subject for a four hour period. However, the OA Adjuster 3 brace was always tested first (§5.3.2); therefore, it is likely that the increased abduction moments observed in OA Assist braces as compared to the OA Adjuster 3 braces (Table 5.2) represents an acclimatization effect due to the fixed trial sequence.

One of the primary limitations of this study is that the model's prediction of muscle forces is based on optimization; this type of model cannot easily capture proprioceptive changes
in antagonist muscle co-contraction (Lloyd and Besier, 2003). However, we did not
detect substantial changes in EMG (Figure 5.6), and the model did predict a decrease in
the quadriceps contribution to medial contact loads due to bracing (Figure 5.5).
Additionally, the predicted reduction in medial loading was similar to in vivo
measurements (Kutzner et al., 2011).

Knee unloader braces are effective in reducing medial knee loads through the application
of an external abduction moment, although the magnitude of the reduction appears to
vary greatly between subjects. While these braces in this study were both from the same
manufacturer (DJO Global, Vista, CA, USA), it is likely that the dominance of the applied
abduction moment in reducing medial loads (Figure 5.5) can be generalized to other
unloader braces which apply the same principle of three-point bending.

5.6 Acknowledgements
The sixteen knee braces used in this study were supplied by DJO Global Inc.
CHAPTER 6

DISCUSSION

6.1 Summary
The work in this dissertation was motivated by a growing need to develop clinically and economically effective treatments for knee osteoarthritis. Previous studies have implicated compressive knee contact loads in the incidence and progression of knee osteoarthritis (Felson, 2013; Miyazaki et al., 2002), and suggested that treatments designed to reduce knee loading might provide symptomatic relief (Beaudreuil et al., 2009; Waller et al., 2011). Other studies have, irreconcilably, suggested that abnormal muscle activation patterns found in osteoarthritis subjects were responsible for either causing (Bennell et al., 2008; Zeni et al., 2010) or protecting against (Heiden et al., 2009; Hubley-Kozey et al., 2006) the progression of knee osteoarthritis. In order to gain a greater understanding of the pathomechanics of knee osteoarthritis, it was necessary to develop a method to quantify medial knee contact loads during gait in osteoarthritis subjects, and to evaluate changes in these loads resulting from clinical treatments.

6.2 OA-type Activation
One of the greatest challenges in modeling knee loading in osteoarthritis subjects is to address the issue of co-contraction of antagonistic muscles. Antagonistic co-contraction is generally undesirable: it increases metabolic cost (Ackermann and Schiehlen, 2006; Umberger and Martin, 2007) and elevates joint contact forces (Kutzner et al., 2010; Zhao et al., 2007), which could damage joints (Englund, 2010; Ogata et al., 1977). Why, then, do osteoarthritis subjects show elevated antagonism?
There are three leading explanations in literature. The first theory (Hubley-Kozey et al., 2006), which was tested in this dissertation (Chapter 2), suggested that selective antagonist contraction on the lateral side of the knee joint could provide an abduction moment about the knee joint centre, which would reduce medial knee contact loading. In this thesis, a conservative perturbation was applied to increase biceps femoris and vastus lateralis activation, and to decrease medial hamstrings activation, based on the mean difference between osteoarthritis and healthy control subjects. Medial contact loading was not reduced by this perturbation, and therefore it was concluded that this “OA-type” activation strategy is not a protective response.

In examining the contributions of each muscle group to the medial load, it is clear why this was the case (Figure 6.1). Quadriceps muscles are the primary muscular contributors to first peak loading (Demers et al., 2014; Sritharan et al., 2012; Winby et al., 2009, Figure 1.1). All quadriceps muscles connect to the tibia via the patellar ligament; therefore, there is no mechanical advantage to be exercised by selectively activating the lateral vastus instead of the medial vastus muscle. The only way to reduce the quadriceps contribution to medial loading is to reduce, not increase, activation. Thus, the “OA-type” pattern did not decrease first peak contact loads. Gastrocnemii are the largest contributors to late-stance second peak medial contact loads (Demers et al., 2014; Sritharan et al., 2012; Winby et al., 2009, Figure 1.1). Because the two heads of the gastrocnemii insert on opposite sides of the knee joint, it is possible to equilibrate sagittal plane knee and ankle moments while redistributing load from the medial to lateral gastrocnemius. In this thesis, however, the prescribed decrease in medial gastrocnemius activation was insufficient to generate a substantial reduction in medial contact loads. Hamstrings muscles contribute to medial loading only during early stance and late in
swing; they are not primary contributors throughout the stance phase of gait when peak medial loading occurs (Demers et al., 2014; Sritharan et al., 2012; Winby et al., 2009). In Figure 6.1, hamstrings activation would have to nearly triple before the hamstrings contribution to medial loading matched the quadriceps contribution at the first peak. Since osteoarthritis subjects exhibit a similar pattern of hamstrings activation to control subjects (Chapter 2), changing the magnitude of activation will have little impact on peak loading. If the muscle forces were optimized simply to reduce medial knee contact force, it would have been possible to achieve medial unloading via selective lateral activation (Demers et al., 2014; Fregly et al., 2007; Miller et al., 2013a). However, when muscle forces were constrained to match physiological distribution and conservative differences between osteoarthritis and control subjects, there was no reduction in medial load.

![Figure 6.1: Contributions of quadriceps (purple, dot-dashed), hamstrings (cyan, dotted), gastrocnemii (orange, solid), and inverse dynamics (black, dashed) to medial knee contact load (grey, shaded) during gait. This figure is re-printed from Figure 5.5A.](image)

The second proposed explanation for elevated co-contraction in osteoarthritis subjects is that this activation strategy increases the stability of the knee joint. Indeed, increased co-
contraction is associated with self-reported instability (Schmitt and Rudolph, 2008) and increased translation (Farrokhi et al., 2014) of the knee joint in osteoarthritis subjects. Osteoarthritic knees may become unstable due to combined effects of muscle weakness, cartilage erosion, and stretching or softening of tissues around the joint (Sharma et al., 1999). Increasing the force in muscles around the knee increases the stiffness of the joint (Bergmark, 1989; Cort and Potvin, 2012), which reduces the likelihood that the knee will buckle under a perturbation. However, increasing stability in this manner will necessarily increase joint contact force, which places the joint at risk of osteoarthritis progression. Future work should evaluate whether knee joint stability could be increased in osteoarthritis subjects without the need for elevated muscle activation.

Finally, the third proposed theory is that increased muscular co-contraction is a response to pain in the joint (Boyer et al., 2012). While this could be somehow linked to a need for stability as described above, the relationship between antagonistic muscle activation and pain has not been investigated (Boyer et al., 2012). Future work could examine whether antagonism is affected by the use of a pharmaceutical intervention.

6.3 Modeling Approach: Optimization vs EMG-Driven

There are primarily two approaches which have been taken to solve the muscle force distribution problem: optimization or EMG-driven modeling. Both methods been used to provide reasonable estimations of joint loading in osteoarthritis subjects (Kumar et al., 2013; Richards and Higginson, 2010), although it is difficult to validate predictions in vivo.

In selecting a modeling approach, it is important to consider the accuracy of the input data. EMG-driven models supply experimental measurements of electrical muscle
excitation signals as input data. These measurements are subject to error from skin motion artifact, cross-talk from surrounding muscles, and changes in impedance between the muscle and the electrode (De Luca et al., 2010). Optimization models supply the generalized forces (net joint moments) as input data, which are subject to error as a result of uncertainty in joint locations and axes of rotation as well as error in measurement of external forces and segment mass parameters. Both EMG and joint moment input data are sensitive to errors in processing, particularly in the design of filters for frequency-domain analysis (Bisseling and Hof, 2006; Chiari et al., 2005; Clancy et al., 2002; De Luca et al., 2010). Notwithstanding the personal bias or capabilities of researchers, it is difficult to select one modeling approach based on the accuracy of its input data.

Likewise, neither method is clearly superior in the quality of its transfer function from input data to muscle forces. EMG-driven models must calibrate a non-linear relationship between measured excitation and force generation individually for each muscle and each subject (Buchanan et al., 2004; Lloyd and Besier, 2003; Sartori et al., 2012; Winby et al., 2008). Optimization models minimize an objective function related to muscle force and/or area. Although most optimization models have converged on minimization of the sum of squares of muscle stress as the objective function of choice, there is a lack of consensus regarding the weighting of this cost function across muscle groups (Ackermann and van den Bogert, 2010; Crowininshield and Brand, 1981; Happee and Van der Helm, 1995; Rasmussen et al., 2001; Steele et al., 2012).

The primary advantage of EMG-driven models is that they directly prescribe appropriate levels of activation for each muscle, therefore avoiding any issues in predicting antagonist co-contraction. However, because EMG data are generally available only for superficial
muscles (Gerus et al., 2013), simplifying assumptions must be made regarding the system of muscles at the knee joint. Small, deep muscles are either eliminated from the model or constrained such that their activation matches that of agonist muscles (Lloyd and Besier, 2003). It is difficult to know whether or not it is appropriate to apply the same assumptions of muscle synergy in both healthy control and osteoarthritis populations, especially considering the known differences in co-activation of antagonist muscles. Furthermore, when small muscles are excluded from the model, large muscles necessarily, albeit marginally, increase their force; this increases the sensitivity of the model to changes in the activation of large muscles that are included in the model.

This thesis used an optimization approach because it provides superior flexibility with regard to the number of individual muscle forces which can be prescribed. The muscle distribution problem was solved using an empirically-derived criterion to minimize the sum of the squares of muscle stress (Crowninshield and Brand, 1981; Happee and Van der Helm, 1995) while simultaneously balancing inverse dynamic loads applied to the hip, knee, and ankle joints. Although this approach has yielded reasonable approximations of knee loading as compared with in vivo measurements (Brandon et al., 2014), it is unclear how this criterion should be adjusted to account for abnormal muscle activation patterns in osteoarthritis subjects. In this thesis (Chapter 2), a novel approach was developed to prescribe an EMG-derived perturbation to the optimization model. Thus, the optimization model simultaneously distributed forces in a large set of muscles while satisfying physiological levels of antagonist co-contraction informed from EMG measurements. The approach is not perfect; the perturbation ignored the non-linear transformation from excitation (EMG) to muscle force, and the optimization model did not utilize a detailed Hill-type muscle model (Hill, 1938; Zajac, 1989). Despite these
limitations, the model produced realistic predictions of changes in knee loads due to “OA-type” muscle activation patterns (Chapter 2).

Future studies should continue to explore methods to exploit the strengths of both EMG-driven and optimization approaches; namely, to develop novel methods to incorporate EMG data into objective functions in order to obtain more accurate muscle force predictions while retaining musculotendon complexity. Additionally, optimal control methods from the field of robotics might enable computationally-efficient predictions of joint loading for tasks with greater demand than level walking (Erez et al., 2013).

6.4 Brace Effectiveness
The second objective of this thesis was to quantify the biomechanical effectiveness of unloader knee braces for subjects with medial knee osteoarthritis. Using a novel method to incorporate the brace load into the musculoskeletal model, it was found that the greatest contributor to reduced medial knee contact loads was the abduction moment applied by the brace to the subject’s knee. Changes in muscle forces and gait kinematics were relatively small (Chapter 5).

Because the brace abduction moment was the primary contributor to medial knee unloading, and osteoarthritis subjects adjusted the braces to apply a greater abduction moment than control subjects, the medial load reduction was proportionally greater in osteoarthritis than control subjects (Figure 5.5, Table 5.2). The most logical explanation for this discrepancy is that, as reported previously (Pagani et al., 2010; Ramsey and Russell, 2009; Steadman et al., 2014) bracing reduces medial knee pain in the osteoarthritis subjects, and therefore they were willing to tolerate a greater applied brace abduction moment and associated discomfort than were the control subjects. Differences
in joint kinematics and kinetics between osteoarthritis and control subjects in this thesis were consistent with previous studies (Baliunas et al., 2002; Mundermann et al., 2005), particularly elevated knee adduction moments and a decrease in early-stance knee flexion moments (Figure 5.3). Although we did not observe a significant difference in the response of osteoarthritis and control subjects to knee bracing, post hoc changes in hip and knee moments were significant only for the osteoarthritis group (Figure 5.3). It is possible that future analysis of the demanding level and inclined treadmill tasks from this experiment might reveal inter-group differences in the response to knee bracing. If present, these differences would necessitate the recruitment of osteoarthritis subjects for any future studies evaluating the clinical performance of knee braces.

The results of this study have important implications for unloader brace design and conservative treatment of knee osteoarthritis. Firstly, current unloader designs, emphasizing the application of a large abduction moment to the knee joint, are effective. Therefore, if braces can be designed, or comfortably adjusted, to apply greater abduction moments to the knee joint, an enhanced reduction in medial loading might be achieved with relatively minimal changes in gait kinematics or muscle activation. Secondly, considering that inverse dynamic loads and muscle forces are the two greatest contributors to medial loading (Figure 6.1), it may be desirable to design a brace that beneficially alters these parameters. Studies have shown little (Pollo et al., 2002; Toriyama et al., 2011) or no (Beaudreuil et al., 2009; Ebert et al., 2014) effect of knee bracing on the external knee adduction moment during gait. However, a brace could be designed to encourage kinematic modifications, such as medialization of the knee or toe-out gait (Fregly et al., 2009), which would reduce the large contribution of external loading to medial contact forces. Lastly, future designs should consider that gastrocnemii
are both the primary muscular contributors to medial joint loading during late-stance and leading contributors to increased joint loading due to brace use (Figure 4.5). If a brace could be designed to reduce gastrocnemii activation (Miller et al., 2013a), the medial load reduction that results from bracing might be enhanced.

In this thesis, the optimization model did not predict changes in gastrocnemii activation which matched the EMG measurements with and without bracing. Additionally, the model was not constrained to enforce antagonist co-contraction. Using a perturbation approach similar to Chapter 2, it would be relatively easy to constrain the activation of gastrocnemii and other muscles to more closely follow patterns found in EMG. It is also possible that a refined objective function could be implemented which would penalize gastrocnemii recruitment to a more appropriate level. While these muscle activation changes were relatively small, and made a minor contribution to medial knee contact reduction, future musculoskeletal modeling studies could provide enhanced analysis of the effect of knee braces on joint contact loads.
CHAPTER 7

RECOMMENDATIONS FOR FUTURE WORK

The work in this thesis represents a strong contribution to our understanding of the role of muscle forces in the progression of knee osteoarthritis, and to the unloading mechanism of knee braces. Recommendations for future work are listed below:

7.1 Model Improvements

1. Account for discrepancy between model-predicted and EMG-measured gastrocnemii activation (§5.4.5), either by prescribing activation as described in Chapter 2, or by penalizing gastrocnemii recruitment as previously reported (Steele et al., 2012)

2. Refine the knee model to include contributions from passive structures, to predict contact stress as opposed to simple forces, to allow changing contact locations that are consistent with dynamics and knee morphology, and to account for shear forces at the knee joint (Thelen et al., 2014)

3. Refine the objective function to predict co-contraction in proportion with some measure of joint stability (Cashaback et al., 2014)

7.2 Evaluation of braces

1. Include sagittal plane loads applied by the brace to the knee joint. Qualitatively, we observed some resistance to knee flexion when manipulating the brace by hand. This resistance, or damping, might be incorporated into the model to improve muscle force estimates.
2. Validate brace abduction moment measurements using direct measurement from strain gauges

3. Validate predictions of changes in knee loads resulting from braces using in vivo data from subjects with instrumented knee prostheses wearing braces

4. Develop a viscoelastic model of the brace and soft tissues, which can be included in the musculoskeletal model, and thereby used for predictive simulations where brace loading is not measured.

The ultimate goal of this work would be to develop a musculoskeletal model which could be used to predict, and evaluate, effectiveness of novel knee brace designs. If the primary cause for elevated co-contraction in osteoarthritis subjects is indeed stability, it might be possible to design more effective, minimalist braces to provide joint stability and thereby reduce knee contact forces and prevent osteoarthritis progression. Based on the results of this thesis, it is proposed that these novel braces should both apply an external abduction moment and, through position or force feedback, alter joint kinematics to reduce inverse dynamics loads and muscle forces.
REFERENCES


Chen, G., 2006. Induced acceleration contributions to locomotion dynamics are not physically well defined. Gait Posture 23, 37–44.


Appendix A

Ethics Approval for Clinical Study

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW
July 16, 2013

Dr. Kevin Deluzio
Department of Mechanical and Materials Engineering
Queen’s University

Dear Dr. Deluzio

Study Title: MECH-047-13 Effectiveness of Knee Unloader Bracing To Reduce Medial Knee Contact Force During Gait.
File # 6010273
Co-Investigators: Dr. A. Campbell, Mr. S. Brandon, Mrs. A. Morton, Mr. M. Brown

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol, peer review, WOMAC questionnaire, recruitment letter, revised information/consent form – controls and revised information/consent form – osteoarthritis participants for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

**Reporting of Amendments**: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file # 6010273 in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

**Reporting of Serious Adverse Events**: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file 6010273 in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

**Reporting of Complaints**: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

**Annual Renewal**: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

[Signature]
Chair, Research Ethics Board
July 16, 2013

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete
QUEEN’S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards and operates in compliance with the Tri-Council Policy Statement; Part C Division 5 of the Food and Drug Regulations, OHRP, and U.S. DHHS Code of Federal Regulations Title 45, Part 46 and carries out its functions in a manner consistent with Good Clinical Practices.

Federalwide Assurance Number: #FWA00004184, #IRB00001173

Current 2013 membership of the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board:

Dr. A.F. Clark, Emeritus Professor, Department of Biomedical and Molecular Sciences, Queen's University (Chair)

Dr. H. Abdollah, Professor, Department of Medicine, Queen's University

Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University

Dr. C. Cline, Assistant Professor, Department of Medicine, Director, Office of Bioethics, Queen's University, Clinical Ethicist, Kingston General Hospital

Dr. M. Evans, Community Member

Ms. J. Hudacin, Community Member

Dr. B. Kisilevsky, Professor, School of Nursing, Departments of Psychology and Obstetrics and Gynaecology, Queen's University

Dr. J. MacKenzie, Pediatric Geneticist, Department of Paediatrics, Queen's University

Mr. D. McNaughton, Community Member

Ms. P. Newman, Pharmacist, Clinical Care Specialist and Clinical Lead, Quality and Safety, Pharmacy Services, Kingston General Hospital

Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute

Dr. A. Singh, Professor, Department of Psychiatry, Queen's University

Ms. K. Weisbaum, LL.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)
QUEEN'S UNIVERSITY HEALTH SCIENCES AND AFFILIATED TEACHING HOSPITALS
RESEARCH ETHICS BOARD ANNUAL RENEWAL

Queen's University, in accordance with the "Tri-Council Policy Statement 2, 2010" prepared by the Interagency Advisory Panel on Research Ethics for the Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada requires that research projects involving human participants be reviewed annually to determine their acceptability on ethical grounds.

A Research Ethics Board composed of:

Dr. A.F. Clark, Emeritus Professor, Department of Biomedical and Molecular Sciences, Queen's University (Chair)
Dr. H. Abdollah, Professor, Department of Medicine, Queen's University
Dr. C. Cline, Assistant Professor, Department of Medicine, Director, Office of Bioethics, Queen's University, Clinical Ethicist, Kingston General Hospital
Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University
Dr. M. Evans, Community Member
Ms. J. Hudacin, Community Member
Mr. D. McNaughton, Community Member
Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute
Dr. M. Sawhney, Assistant Professor, School of Nursing, Queen's University
Dr. A. Singh, Professor, Department of Psychiatry, Queen's University
Dr. J. Walia, Assistant Professor and Clinical Geneticist, Department of Paediatrics, Queen's University and Kingston General Hospital
Ms. K. Weisbaum, LL.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)

has reviewed the request for renewal of Research Ethics Board approval for the project “Effectiveness of Knee Unloader Bracing To Reduce Medial Knee Contact Force During Gait.” as proposed by Dr. K. Deluzio of the Department of Mechanical and Materials Engineering, at Queen's University. The approval is renewed for one year, effective July 16, 2014. If there are any further amendments or changes to the protocol affecting the participants in this study, it is the responsibility of the principal investigator to notify the Research Ethics Board. Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other adverse events must be reported within 15 days after becoming aware of the information.

Date: July 03, 2014
Chair, Health Sciences Research Ethics Board
Renewal 1[x] Renewal 2 [ ] Extension [ ] Code# MECH-047-13 Romeo file# 6010273
Appendix B

Experimental Apparatus

Figure B.1: Illustration of motion capture marker set.
Table B.1: Marker names for experimental motion capture

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**Bold** = calibration only: remove after static calibration(17)
Figure B.2: Marker set applied to each brace to track adduction deflection angles. The OA Assist brace (left) contains a joint, distal to the flexion hinge, which allows a small range of axial rotation. Consequently, the rotation of this joint was tracked between the h1mid_cluster and the h1dist_cluster. Due to small cluster dimensions and motion capture accuracy, it was difficult to compute accurate internal-external rotation angle.
Figure B.3: Example subject wearing tracking clusters, secured with Velcro to Fabrifoam (Exton, PA, USA) wraps. Individual tracking markers are adhered using double-sided tape, and foot markers are additionally secured with elasticized athletic tape. This subject is wearing an OA Adjuster 3 brace (DJO Global, Vista, CA, USA). EMG sensors (Delsys Inc, Boston, MA, USA) are visible on anterior thigh. These sensors were over-taped with elastic athletic tape for most subjects in the study to avoid dislodgement.
Figure B.4: EMG Sensor placement and functional tests for palpation and signal verification.
Figure B.5: Setup for maximum isometric voluntary contraction tests on Biodex System 4 (Biodex Medical Systems Inc, Shirly, NY, USA)
Appendix C
OpenSim Model Structure

Figure C.1: Hip Joint Axes. The hip joint is represented by a 3 degree-of-freedom (DOF) “custom joint” (ball joint), with a body-fixed ZXY Euler rotation sequence. Hip flexion is the primary rotation, occurring about the pelvis-fixed mediolateral axis Zp. Hip adduction is the secondary rotation occurring about an intermediate floating axis mutually perpendicular to Zp and Yp. Finally, hip internal rotation occurs about the femur-fixed axis Yf, which is directed from the hip joint centre to the knee joint centre.
Figure C.2: Knee Joint Axes. In the standard Arnold model (Arnold et al., 2010), the knee is represented as a 1 DOF joint with flexion about the $Z_{f_w}$ axis and coupled rotations and translations for the remaining 5 DOF. In order to prescribe subject-specific frontal plane alignment, an additional adduction degree of freedom was introduced to the model. The knee joint is therefore represented by a modified 2 degree-of-freedom (DOF) “custom joint”, with a body-fixed ZXY Euler rotation sequence as illustrated above. Knee flexion is the primary rotation, occurring about the femur-fixed mediolateral axis $Z_{f_w}$. Knee adduction occurs about the floating axis (not shown), which is mutually perpendicular to $Z_{f_w}$ and $Y_{t_w}$. In this dissertation, the knee adduction DOF was fixed at each subject’s radiographic frontal plane angle, and locked in this position for all subsequent analyses. Coupled axial rotation and translation are prescribed as functions of flexion using equations derived by Walker et al. (1988), unlike other OpenSim models using the relationships of Yamaguchi and Zajac (1989). NOTE: The reference frames above include the subscript _w, which denotes that these axes are aligned according to the Walker (1988) coordinate systems, and are not coincident with the femur-fixed frame defined for hip joint rotation in the previous figure.
Figure C.3: Ankle Joint Axes. Ankle plantarflexion occurs about an oblique axis with unit vector: (-0.10, -0.17, 0.98), roughly depicted by the blue axis above. This unit vector is defined in the tibial anatomical frame, with its origin at the centre of the talus; shown above, $Y_t$ is aligned with long axis of tibia. The Arnold (2010) model also includes subtalar (inversion-eversion) and metatarsal-phalangeal joints. However, throughout this dissertation these degrees of freedom were locked in the neutral position as they are not well measured by surface (and shoe!)-based motion capture and significantly increase computational errors when performing residual reduction and computed muscle control in OpenSim.
Figure C.4: Front, Side, and Rear views of OpenSim model showing 96 muscle lines of action (94 plus 2 patellar ligaments).
Table C.1: Muscle names and cross-sectional areas in the Arnold (2010) model.

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<td>1444</td>
<td>3609</td>
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<tr>
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<td>Erector spinae</td>
<td>ercspn</td>
<td>41.0</td>
<td>2500</td>
<td>6250</td>
</tr>
<tr>
<td>46</td>
<td>Internal oblique</td>
<td>intobl</td>
<td>14.8</td>
<td>900</td>
<td>2250</td>
</tr>
<tr>
<td>47</td>
<td>External oblique</td>
<td>extobl</td>
<td>14.8</td>
<td>900</td>
<td>2250</td>
</tr>
<tr>
<td>48</td>
<td>Patellar Ligament</td>
<td>patlig</td>
<td><em>REMOVED FROM MODEL</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Specific tension of 61 N/cm² assumed for all muscles to relate Peak Force to PCSA.
** Scaling of muscle strength by 2.5 was performed to ensure peak normalized gastrocnemius activation was similar between model and EMG.
N.B. There was no upper bound on muscle forces in optimization; therefore this scale factor affected only the normalization, not distribution, of force.
***The Patellar ligament was replaced by extending each of the quadriceps through the patella to insert on the tibia. Thus, it is possible to compute the knee moment arms for each quadriceps muscle as the partial derivative of the muscle length with respect to each coordinate.
Figure C.5: Wrapping ellipsoid geometry for medial gastrocnemius muscle in Arnold (2010) model. Wrapping surfaces (cyan) are defined as ellipsoids, which are fixed in local body reference frames (e.g. top ellipsoid is fixed in femur frame to represent condylar surfaces). OpenSim solves for the shortest, smooth path across this surface in order to determine the muscle line of action, length, change in length with respect to each coordinate (partial derivative), and therefore moment arms (Arnold et al., 2010).
Figure C.6: Wrapping geometry for medial gastrocnemius Gait2392 model (Delp et al., 2007). Instead of wrapping surfaces, this model uses a series of discrete, frictionless wrapping points (i.e. pulleys) for each muscle. Some points are always active, and others are conditional; that is, the wrapping point is only active within a specified range of motion when physical interference would be observed between muscles and other tissues or bones. This method is effective, but if muscle paths are altered (e.g. origin and insertion re-aligned by adding an adduction angle), the conditional wrapping points will no longer be defined in the correct location and could introduce discontinuities.
Figure C.7: Errors in wrapping paths due to unequal scaling of limb segments (Iliacus example). Left: correct use of wrapping surface. All path points (origin, insertion, anterior path) lie outside the wrapping surface, and the muscle path curves smoothly around the surface once intersection is detected. Right: path point falls inside wrapping surface, therefore the muscle never intersects the surface and a straight muscle path is used.

Considering dynamic movements, if wrapping surfaces are inappropriately sized or shaped, a muscle could oscillate between interior and exterior positions with respect to the wrapping surface. This would yield discontinuous moment arms. The problem is unlikely to occur if equal scaling factors are used for adjacent segments. However, in this study the pelvis and leg lengths were scaled using radiographic measurements, and pelvis scaling factors were greater than femur scaling factors by up to 23%. Consequently, all pelvis wrapping surfaces were decreased in size by 23% to eliminate the possibility of discontinuous moment arms, as seen on the right.