Multivariate Techniques in Biomechanical Analysis

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Abstract

This work outlines the theoretical advantages of multivariate methods in biomechanical data, validates the proposed methods and outlines new clinical findings relating to knee osteoarthritis that were made possible by this approach.

New techniques were based on existing multivariate approaches, Partial Least Squares (PLS) and Non-negative Matrix Factorization (NMF) and validated using existing data sets. The new techniques developed, PCA-PLS-LDA (Principal Component Analysis – Partial Least Squares – Linear Discriminant Analysis), PCA-PLS-MLR (Principal Component Analysis – Partial Least Squares –Multiple Linear Regression) and Waveform Similarity (based on NMF) were developed to address the challenging characteristics of biomechanical data, variability and correlation. As a result, these new structure-seeking technique revealed new clinical findings.

The first new clinical finding relates to the relationship between pain, radiographic severity and mechanics. Simultaneous analysis of pain and radiographic severity outcomes, a first in biomechanics, revealed that the knee adduction moment's relationship to radiographic features is mediated by pain in subjects with moderate osteoarthritis.

The second clinical finding was quantifying the importance of neuromuscular patterns in brace effectiveness for patients with knee osteoarthritis. I found that brace effectiveness was more related to the patient's unbraced neuromuscular patterns than it was to mechanics, and that these neuromuscular patterns were more complicated than simply increased overall muscle activity, as previously thought.

Co-authorship Statement

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

Chapter 2:

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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 Any published (or unpublished) ideas and/or techniques from the work of others are fully acknowledged in accordance with the standard referencing practices.

Elizabeth Ann Hassan

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Table of Contents

List of Figures

List of Tables

Abbreviations and Definitions

BF - Biceps Femoris

CCI – Co-contraction Index

EMG – Elecromyography

KAM – Knee Adduction Moment (frontal plane moment, tending to rotate away from the midline)

KL – Kellegren-Lawrence Score

LDA – Linear Discriminant Analysis

LG - Lateral Gastrocnemius

MG - Medial Gastrocnemius

MLR – Multiple Linear Regression

NMF – Non-Negative Matrix Factorization

OA - Osteoarthritis

PCA – Principal Component Analysis

PLS – Partial Least Squares

r – Pearson's r (correlation coefficient)

R2 – R squared, explained variance

RVAS – Radiographic Visual Analog Score

ST – Semitendinosus

TA – Tibialis Anterior

VAF – Variance Accounted For

VL - Vastus Lateralis

VM - Vastus Meidalis

WOMAC – Western Ontario and McMaster University Arthritis Index

Chapter 1: Introduction

1.1 Problem Framing

"Not everything that can be counted counts,

and not everything that counts can be counted."

-William Bruce Cameron (1963)

In biomechanics research laboratories we now have the instrumentation to measure nearly any quantity that we choose with outstanding accuracy. The quality of these measurement technologies is improving every day and we now have the computing power to collect and process more data than ever before. However, one of the primary challenges is establishing which elements of these data are clinically meaningful and which are noise. To put this challenge in the language of the above quotation, we can count many things but we aren't always clear on whether they matter, or if we are neglecting to count something that is important.

Addressing this ambiguity about the best methods for quantifying and reporting clinical findings in biomechanics is the central topic of this thesis. I propose that multivariate methods address these analytic challenges more optimally than conventional univariate methods and have the potential to reveal new clinical findings. The data sets presented in this thesis are related to knee osteoarthritis; however, I hope that the insights and procedures could be widely applied to other biomechanics studies.

1.2 Knee Osteoarthritis

According to Gross and Hillstrom (2009), "Mobility limitations account for 80% of all chronic disabilities among seniors and knee OA is the single most prevalent cause." The substantial economic and human impact of knee osteoarthritis is well-documented (Boyer et al., 2012; Gross and Hillstrom, 2009; Pollo et al., 2002; Sharma et al., 1998; Toriyama et al., 2011), particularly for older adults. The clinical criteria for knee osteoarthritis is a combination of knee pain and radiographic indications (Henriksen et al., 2011). The radiographic indications include joint space narrowing, chondrocalcinosis, sclerosis, and osteophytes, commonly quantified by Kellgren-Lawrence (KL) score (Kellgren and Lawrence, 1957).

1.2.1 Mechanical and Neuromuscular Signatures of Knee OA

The gait mechanics and neuromuscular features most related to knee osteoarthritis are explored in Chapters 2, 3 and 5. Since knee osteoarthritis most commonly affects the medial compartment of the tibiofemoral joint (Pollo et al., 2002), the knee adduction moment has been a frequent target of both biomechanics studies and interventions designed to slow osteoarthritis progression (Henriksen et al., 2011; Kumar et al., 2013; Sharma et al., 1998; Shelburne et al., 2008). In general, patients with knee osteoarthritis have a higher knee adduction moment than healthy subjects, and this feature is related to indications of radiographic severity and progression (Astephen et al., 2008a; Henriksen et al., 2011; Sharma et al., 1998).

Other biomechanical factors that have been related to knee osteoarthritis have included:

- Knee adduction angle (Zifchock et al., 2011)
- Knee flexion angle (Astephen et al., 2008a)
- Knee flexion moment (Astephen et al., 2008a; Boyer et al., 2012; Chang et al., 2014; Deluzio and Astephen, 2007)
- Knee internal-external rotation moment (Deluzio and Astephen, 2008; Kaufman et al., 2001; McKean et al., 2007; Messier et al., 2014)
- Hip extension moments (Astephen et al., 2008a)
- Hip adduction moment (Astephen et al., 2008a; Mündermann et al., 2005)
- Hip Flexion Angle (Astephen et al 2008, Hunt et al, 2010)

The most prominent neuromuscular signature of knee osteoarthritis is increased co-contraction of the muscles surrounding the knee (Astephen et al., 2008a; Heiden et al., 2009; Hortobágyi et al., 2005; Hubley-Kozey et al., 2006; Lewek et al., 2005; Schmitt and Rudolph, 2008). The exact muscles involved in this increased muscle activity vary between these studies, but it was hypothesized to be a stabilization strategy to compensate for the reduced physical constraints of the damaged cartilage. Alternate hypotheses are that co-contraction unloads the medial condyle (Heiden et al., 2009; Hubley-Kozey et al., 2006) to compensate for the higher knee adduction moment in this group. Regardless of the cause of the co-contraction, the effect is potentially increased joint contact forces, which may accelerate disease progression (Brandon, 2015; Schmitt and Rudolph, 2008).

These findings indicate that the effects of knee osteoarthritis affect multiple joints in the lower limb, not just the knee and multiple planes of motion, not just the frontal plane (abduction-adduction). The presence of biomechanical and neuromuscular effects throughout the kinematic chain supports the concept of multivariate analysis methods, particularly because these quantities are often interrelated.

1.3 Reporting Findings in Biomechanics: Current State of the Art

Currently, the reporting of findings in biomechanics studies is still dominated by univariate analyses, that is, reporting of individual quantities and comparing them with t-tests or an ANOVA (for example, (Hurwitz et al., 2002; Pagani et al., 2012; Ramsey et al., 2007; Richards et al., 2005; Self et al., 2000). Typically, these outcomes are reported as peaks, ranges or means of kinematic, kinetic, or co-contraction measure. The advantage of this type of reporting is that the metrics may be related to a physical quantity and compared across similar studies. The disadvantage of this approach is the difficulty in addressing the multiple modalities of biomechanical changes and the inherent correlation between multiple variables.

If a multivariate measure is employed, a frequent choice is multiple linear regression, either with or without variable selection. This approach was employed by Brouwer et al., (2006); Fantini Pagani et al., (2013); Henriksen et al., (2011); Manal et al., (2000); Miyazaki et al., (2002); Zeni and Higginson, (2011). The suitability of this method to biomechanical data is limited by the inherent collinearity of biomechanical data, which may make stepwise variable selection unstable since Lachenbruch (1975) noted that discriminant function performance degrades with collinearity of inputs

Reporting findings with waveform methods such as Principal Component Analysis (PCA) (Deluzio and Astephen, 2007; Deluzio et al., 1997) or Statistical Parametric Mapping (SPM) (Vanrenterghem et al., 2012) has the advantage of accounting for data from the entire waveform, rather than simply means or peaks. This enables simultaneous analysis of factors such as range of motion, timing, loading rate and curve shape. PCA has been extensively applied to knee osteoarthritis (Astephen et al., 2008b; Gaudreault et al., 2011; Jones et al., 2008; Linley et al., 2010), gender differences in cutting performance (Landry et al., 2009), performance after knee arthroplasty (Astephen Wilson et al., 2010; Hatfield et al., 2011), and EMG signals (Davis and Vaughan, 1993; Hubley-Kozey et al., 2009). It has also been applied, but with a different methodology, for perception of biological motion (Troje, 2002).

Similar to univariate techniques, waveform methods have also been combined with multivariate approaches such as linear discriminant analysis (LDA), multiple linear regression (MLR), or classification trees. For example, Jones et al (2008) pre-processed with PCA and then applied the Dempster–Shafer theory of evidence to discriminate between normal and osteoarthritic subjects. Astephen et al (2008b) applied a Linear Discriminant Function (LDF) to combine principal component scores for EMG activity, hip and knee moments. This study was able to distinguish between normal, moderate, and severe OA, with correct classification rates of at least 80%. The variables in the LDF were different modalities and weighting for each discriminant function, and the authors were able to assign a functional interpretation to these changes between models. For example, severe OA subjects contained more range of motion elements because their posture was visibly different from the other groups, but moderate and normal gait were more similar with respect to kinematics.

The advantages of combining waveform metrics and multivariate approaches are that the multifactorial nature of the data set is preserved, the relative "importance" of factors can be assessed and can still be traced back to the physical quantities of interest, and discrete variables can be introduced.

1.4 Rationale

Although the gait mechanics of osteoarthritic patients have been thoroughly investigated (Andriacchi and Mündermann, 2006; Deluzio and Astephen, 2007; Felson, 2013; Mündermann et al., 2005), as have the functioning of conservative interventions such as insoles or bracing (Brandon, 2015; Pagani et al., 2012; Pollo et al., 2002; Ramsey et al., 2007; Shelburne et al., 2008), there is still some ambiguity in the precise mechanisms by which the treatments work, and who would benefit most from these interventions.

One possible explanation for the ambiguity regarding the functionality of interventions targeting knee osteoarthritis is that existing metrics for biomechanical data do not capture enough information about timing, simultaneity, or loading rate, or don't facilitate combining multiple factors into a single metric. The effects of knee osteoarthritis are a combination of kinematic, kinetic, and neuromuscular factors throughout the lower body; therefore, it is logical to pursue assessment metrics that are similarly multimodal.

I propose that an ideal analysis procedure is one that reflects the characteristics of the input data and preserves links to the physical quantities of interest.

1.4.1 Characteristics of an Ideal Analysis Procedure for Biomechanics Data

In the case of biomechanics data sets, the information is often collected while the patient or subject completes a dynamic task such as walking. Walking involves multiple joints and hence multiple degrees of freedom. When we observe the gait of different individuals, it's clear that there is subject-subject variability even in healthy gait. These variances are what allow us to easily recognize the gait of a friend or family member even when they are too far away to see their face (Troje, 2012). However, not all of this variability is necessarily related to the pathology or intervention of interest since some of it is the inherent variability of normal walking. It's not enough to say that two groups are different, we must elaborate to say that they are different in way that is related to the response variable, especially when conducting studies with relatively small numbers of participants.

During walking, the ankle, knee, and hip moments are related to each other because they are all calculated using the ground reaction force, which is the largest contributor to the joint moments. Similarly, in analyzing the contralateral and ipsilateral limbs of the same subject, they will contain much of the same information, since the data is from the same individual. This inherent correlation is a challenge for many regression techniques because they typically assume linear independence between the variables (no correlation).

1.4.2 Proposed Approach

I propose that multivariate techniques such as Partial Least Squares (PLS) and Non-negative Matrix Factorization (NMF) can form the foundation of ideal analysis techniques because they address two of the characteristics of biomechanical data that are challenging for univariate analyses: variability and collinearity.

Subject-subject variability is explicitly addressed by PLS (Partial Least Squares) because PLS extracts latent variables that explain the maximum amount of *covariance* between the input data (X) and the explanatory or grouping variables (Y). If the between group variance is larger than the within group variance, PCA and PLS are equivalent, but if the within group variance is large, PLS is superior for group discrimination (Barker and Rayens, 2003); the theoretical grounding for this combination is given by Barker and Rayens (2003) and Liu and Rayens (2007). NMF (Non-negative Matrix Factorization) of neuromuscular data addresses subject-subject variability by forming the basis of an analysis technique that is independent of normalization value, which is a large source of variability.

Collinearity is also addressed by PLS because the extraction of latent vectors is sequence independent, since it is based on singular value decomposition. There is no assumption of linear independence for the input data in PLS or NMF, unlike other regression techniques. This makes these techniques suitable for biomechanics data, which may contain collinear data.

1.5 Contributions

This work outlines the theoretical advantages of multivariate methods in biomechanical data, validates the proposed methods and outlines new clinical findings relating to knee osteoarthritis that were made possible by this approach. Chapters 2 and 4 are related to the methodology and theoretical suitability of multivariate techniques for biomechanical data. Chapters 3 and 5 apply these techniques to reveal the new clinical findings.

1.5.1 Specific Aim of Chapter 2

Chapter 2 sought to validate the use of a new technique, PCA-PLS-LDA as a structure seeking technique in biomechanics data. The proposed technique was validated against an exemplar paper using PCA-LDA, testing the ability of the proposed technique to separate control and osteoarthritic subjects based on knee mechanics. The PCA-PLS-LDA was found to be equivalent, and isolated waveform features of known clinical importance to osteoarthritis.

1.5.2 Specific Aim of Chapter 3

Although pain is the primary driver for patients seeking osteoarthritis treatment, linking pain to structural features (as shown on a radiograph) or functional characteristics (as found through biomechanical analysis) has proven to be challenging. The aim of Chapter 3 was to exploit a feature of PLS, simultaneous analysis of multiple response variables, to comment on the apparent discordance between pain, structural changes and functional changes due to knee osteoarthritis. I found a new pain mediated relationship between knee adduction moment and radiographic severity and achieved a higher explained variance than past analyses of pain or radiographic severity.

1.5.3 Specific Aim of Chapter 4

In Chapter 4, I examined the characteristics of neuromuscular data, and interrogated the suitability of NMF (Non-Negative Matrix Factorization), a relatively new multivariate technique that is common in neurological studies but novel to biomechanics work. I developed a novel method for analyzing muscle synergies, waveform similarity, and verified that it possesses theoretical and practical advantages over conventional co-contraction measures, notably independence from normalization value.

1.5.4 Specific Aim of Chapter 5

Using the technique that was validated in Chapter 4, Chapter 5 applied the new waveform similarity measure, and PLS, to reveal new clinical findings relating to the neuromuscular indicators of knee brace effectiveness for osteoarthritis. I hypothesized that brace effectiveness (as defined by reduction in the knee adduction moment while wearing the brace) would be related to the unbraced neuromuscular patterns. I found that this hypothesis was true, and that these neuromuscular patterns were more complicated than simply increased overall muscle activity, as previously thought.

Chapter 2: Partial Least Squares for Analysis of Biomechanics Data

2.1 Introduction

The goal of many biomechanical studies is to link a condition or intervention to the observed joint mechanics. In some cases, there may be a single variable of interest, but often multiple joints or data modalities may be clinically relevant. For example, adding a lateral wedge to footwear affects both the knee and hip biomechanics (Resende et al., 2014), and Anterior Cruciate Ligament deficiency and reconstruction results in both kinematic and neuromuscular asymmetries (Andriacchi and Dyrby, 2005; Bulgheroni et al., 1997; Oberländer et al., 2013).

Biomechanical data sets often contain correlated variables and may have large variances between subjects. These potentially interrelated differences pose a challenge for univariate statistical analysis, since multiple comparisons require significance corrections (such as Bonferroni or Holm-Sidak). Although it is possible to combine univariate data sets using linear discriminant analysis, it is most valid in situations with a small number of variables compared to the number of observations, and input variables that are independent of each other (Lachenbruch, 1975). Biomechanical data often violates both of these criteria: in clinical studies the number of participants in each group can be small, and the number of variables, as well as the covariance between them, can be large.

As an alternative, we propose a multivariate analysis technique that combines Principal Component Analysis, Partial Least Squares and Linear Discriminant Analysis. This proposed technique will allow for multiple simultaneous comparisons while solving the collinearity problem common in biomechanical analysis.

2.2 Background: Partial Least Squares

Partial Least Squares (PLS) was identified as a way of incorporating a large number of potentially correlated data streams into a single analysis for process control, with the goal of identifying process faults affecting the quality of output (Wold and Sjostrom, 2001). This type of process control problem parallels the challenges of analyzing biomechanical data. Both may have correlations between some of the input variables, both have a large number of input variables, and both may have a combination of temporal and magnitude effects. PLS has not yet been applied in biomechanics; the only known applications to biomechanical data are short examples in (Bourriez et al., 2005; Kaptein et al., 2014).

Related multivariate methods such as Principal Component Analysis (PCA) have been extensively used in biomechanics on its own (Astephen Wilson et al., 2010; Astephen et al., 2008b; Deluzio and Astephen, 2007; Deluzio et al., 1997; Gaudreault et al., 2011; Hatfield et al., 2011; Jones et al., 2008; Kirkwood et al., 2011; Landry et al., 2009; Linley et al., 2010) or in combination with linear discriminant analysis and other classification tools (Astephen et al., 2008b; Bittencourt et al., 2012; Jones et al., 2008). The appeal of PCA as an analysis tool or pre-processing step is its ability to capture changes in the shape of the waveform, rather than scalar metrics such as means or peaks.

Partial Least Squares (PLS) is a generalized form of Principal Component Analysis (PCA). Like PCA, PLS is a method of extracting components explaining variance in the data set. The key difference between PLS and PCA is that PCA extracts components that explain the maximum amount of *variance* in the data (X) but PLS extracts latent variables that explain the maximum amount of *covariance* between the input data (X) and the response or grouping variables (Y). If the between group variance is larger than the within group variance, the techniques are equivalent, but if the within group variance is large, PLS is superior for group discrimination (Barker and Rayens, 2003); the theoretical grounding for this combination is given by Barker and Rayens (2003) and Liu and Rayens (2007).

One of the strengths of PLS in combination with Linear Discriminant Analysis (LDA) is that PLS generates latent vectors that are linearly independent of one another. Therefore, PLS latent vectors are an ideal input to linear discriminant analysis since Lachenbruch (1975) noted that discriminant function performance degrades with collinearity of inputs. A single PCA also yields linearly independent components, however, combining multiple PCAs with LDA (as in the case of Deluzio and Astephen, 2007) does not guarantee independence, for example the PC1 scores of knee flexion angle and PC1 scores of the hip flexion angle may be correlated, even though they are orthogonal to their respective PC2. Principal components are extracted in order of maximal variance, and if the variables are related to one another mechanically the largest variance may have commonalities.

2.3 Purpose

The purpose of this chapter is to evaluate the performance of the proposed technique, Partial Least Squares and Linear Discriminant Analysis (PCA-PLS-LDA), for biomechanics data and validate it relative to previously published results on the same data set using PCA-LDA (Deluzio and Astephen, 2007). We hypothesize that PCA-PLS-LDA will have at least equivalent performance to PCA-LDA.

2.4 Methods

The previously published data set consists of knee kinematic and kinetic data from 63 asymptomatic control subjects and 50 subjects with severe osteoarthritis (Deluzio and Astephen, 2007). The subjects walked overground at a self-selected speed, monitored by an optoelectronic gait analysis system and force plate. The data set contains 3D knee angles and moments for the affected leg, computed with inverse dynamics, expressed in the tibial coordinate system.

The PCA-PLS-LDA analysis procedure is as shown in **Figure 2.1**:

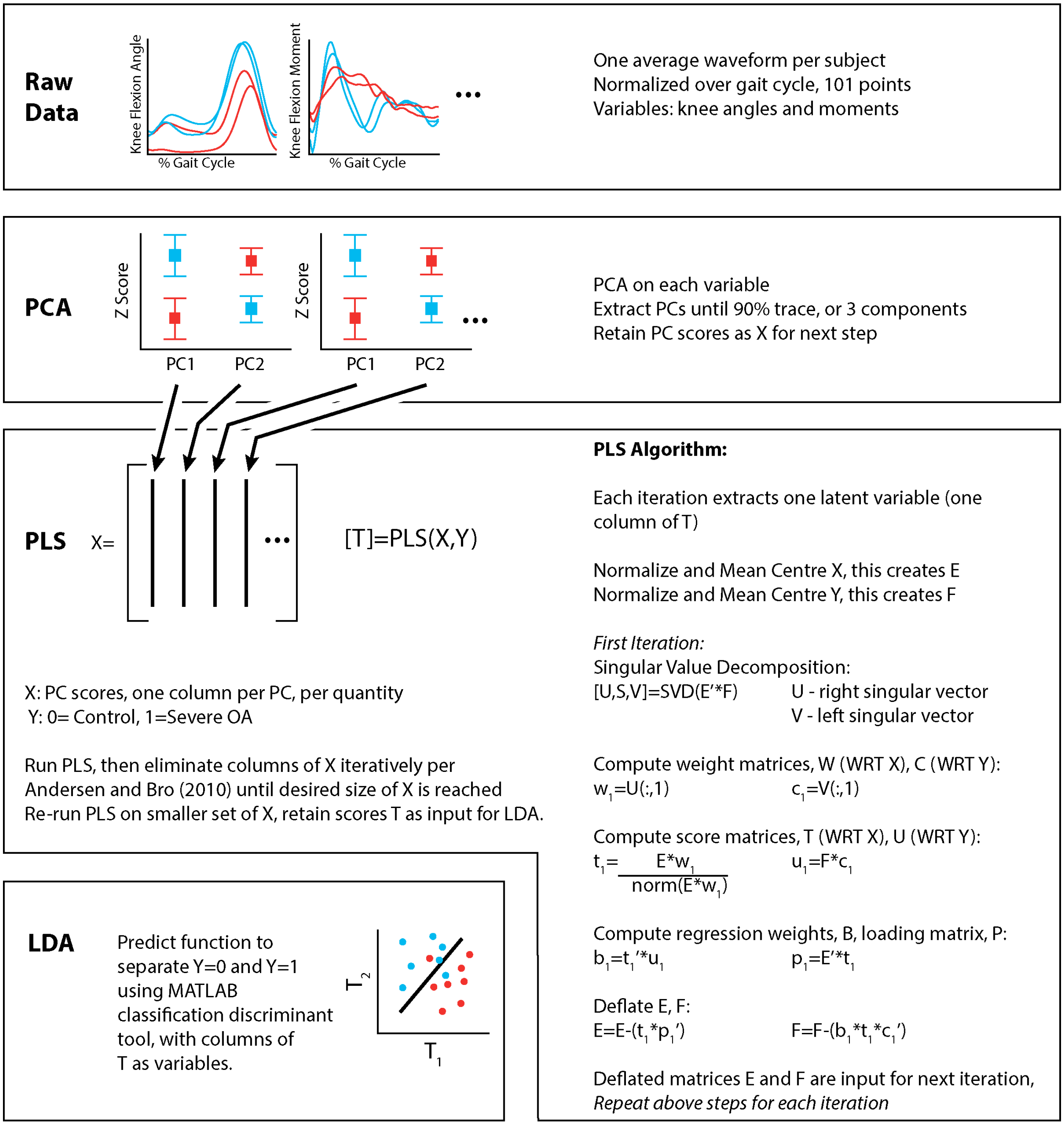

Figure 2.1: Analysis method summary and PLS algorithm

2.4.1 PCA

The PCA analysis was conducted using custom MATLAB code; the PCA algorithm is described by Deluzio and Astephen (2007). Briefly, PCA finds a set of loading vectors (U) that transforms the data (X) to a reduced, orthogonal set of principal component scores (Z), $Z=U^TX$. The loading vectors (U) are the eigenvectors of the covariance matrix of X.

The inputs (X) to the PCA analyses were average waveforms normalized to the gait cycle (101 points), one observation per subject. A 90% trace criterion (Jackson, 2004) was used to determine the correct number of components to extract, up to a maximum of three. Pre-processing with PCA is computationally equivalent to PLS on a single large matrix containing all of the data according to Chin (2013) and Westerhuis et al. (1998); this was confirmed by our calculations on this data set. The advantage of pre-processing with PCA is a more straightforward interpretation of the regression weights (B), as they correspond to a waveform feature rather than to individual frames of data.

2.4.2 PLS

The PLS algorithm is iterative and the extracted orthogonal components are in order of maximum variability. This algorithm is well described elsewhere (Abdi, 2010), the key differences between PLS and PCA is that PCA decomposes the covariance of X using eigenvectors, PLS decomposes the covariance of X and Y using the singular value decomposition (SVD). Other formulations of the PLS algorithm (Wold and Sjostrom, 2001) were tested and found to be equivalent, which is consistent with Helland's findings (1988).

The PLS process is summarized in Figure 2.1 for convenience. Briefly, the first step is to mean centre and normalize the both data (X) and response variables (Y), creating E and F. The left and right singular vectors of the matrix E'*F are the first columns in the weight matrices, W and C. These are used to calculate the scores and regression weights, followed by deflation of E and F, forming the input for the next iteration (to extract the next component). This is repeated until the desired number of components is reached (in this case, two).

As in most multivariate techniques, the selection of the number of inputs to include, and the number of latent variables to extract using PLS, can be somewhat subjective. Including all of the input variables in a data set may lead to over fitting and making interpretation more difficult, as can extracting too many latent variables. The number of columns in X was reduced to a more parsimonious set using the iterative variable importance to projection (VIP) criteria described in Andersen and Bro (2010) (VIP calculation shown in Equation 1); in this procedure the least important variable is discarded, the PLS is re-run, and this process is repeated until the desired number of variables is reached. The desired number of variables or latent vectors was defined as the smallest set without discriminant performance degrading, as measured by the misclassification rate.

Equation 2.1: VIP (Variable Importance to Projection) where j is the variable of interest, J is the total number of variables in X, f is the component of interest, F is the total number of components extracted, w are the weightings from PLS, SSY_f is the sum of squares of explained variance for the f^{th} component, SSY_{total} is the sum of squares of explained variance for all components

$$VIP_j = \sqrt{\frac{\sum_{f=1}^{F} w_{jf}^2 \cdot SSY_f \cdot J}{SSY_{total} \cdot F}}$$

Model validity was checked using a randomization test, according to the procedure described in Szymanska et al (2012); this test checks whether the model is better than coincidence. The Y values were randomized, and the misclassification rate is calculated repeatedly (in this case, 1000 times). If the non-randomized misclassification rate is not significantly different from the randomized values, as measured with a t-test, the model is invalid.

Linear discriminant analysis on the PLS latent vector scores was conducted with built in MATLAB functions. The performance, as measured by misclassification rate, of the PCA-PLS-LDA processing technique was compared to PCA-LDA (the technique in the exemplar study, Deluzio and Astephen, 2007), plus the misclassification rate using the peak and PC scores of the knee adduction moment. The rationale for comparing to the knee adduction moment is its common use as a surrogate measure for medial knee joint loading in studies of knee osteoarthritis (Baliunas et al., 2002; Hurwitz et al., 2002; Sharma et al., 1998).

2.5 Results

In this analysis, we evaluated the discriminant performance over a range of possible inclusion criteria and found that for this data set, the performance is fairly stable over the range of 3 to 13 input variables, ranging from 5 to 11% misclassification. We chose 5 variables as being a balance between a low misclassification rate and ease of interpretability (based on Figure 2.2), and it was comparable to the results presented in the original paper (Deluzio and Astephen, 2007). With 5 input variables, extracting a third latent variable did not improve the prediction, as shown in Figure 2.2; therefore, the analysis used two latent vectors for parsimony. All of the combinations of number of input variables and number of extracted latent variables shown in Figure 2.2 passed the randomization model validity test, with p values less than 0.01.

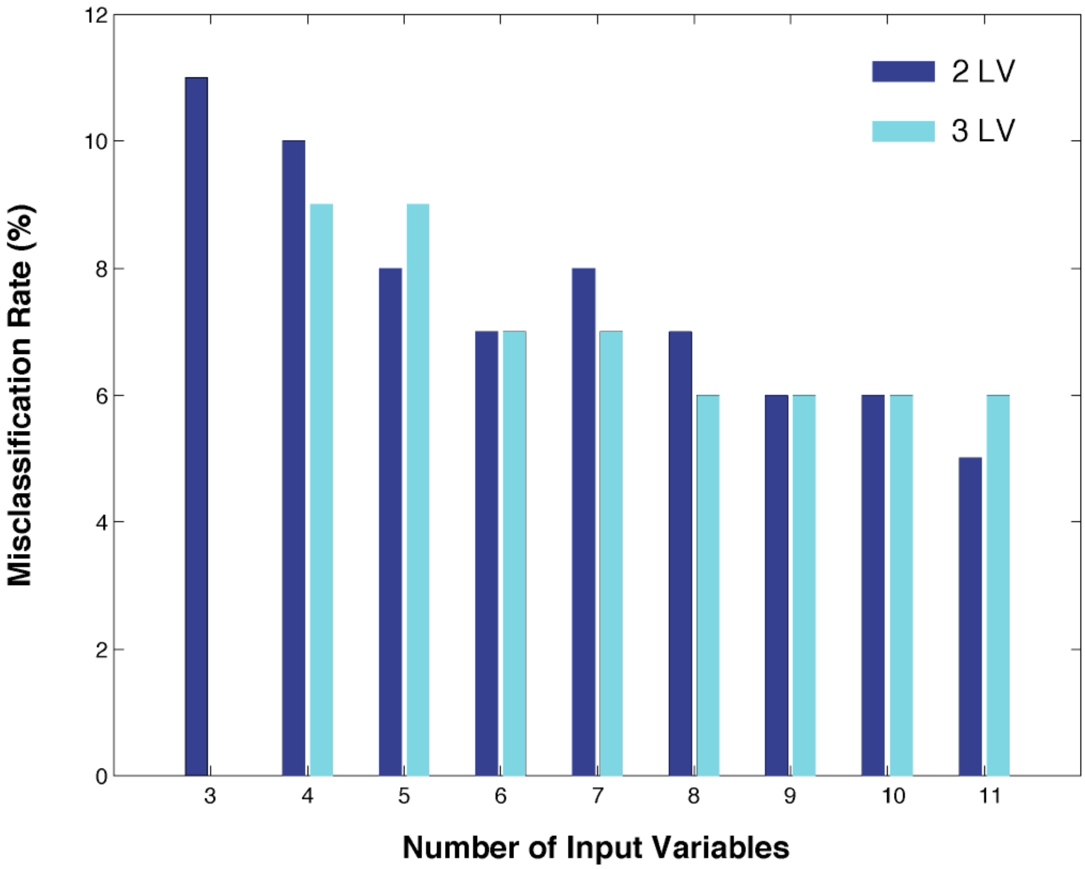

Figure 2.2: Influence of number of variables and extracted components on misclassification rate. The analysis was repeated for between 3 and 11 variables remaining in X (after the VIP variable selection procedure, this was the number of input variables) and both 2 and 3 latent vectors extracted by PLS. These latent vectors were the input to the LDA and the misclassification rate (Control vs OA) was computed using a leave one out procedure.

Using the scores (T_1, T_2) of these two latent vectors, it was possible to separate the groups with a linear discriminant function, as shown in Figure 2.3. The misclassification rate was 7%, using a leave one out procedure, which is close to Deluzio and Astephen's 8% rate (2007); both techniques were better than peak knee adduction moment (KAM) alone, or a single set of knee adduction moment principal component scores, as shown in Figure 2.4. The PCA-PLS-LDA variable selection procedure resulted in similar variables as PCA-LDA being identified as most important to the prediction, PC2 of the flexion moment and PC2 of the flexion angle, as shown in Figure 2.5. The differences between the techniques were the inclusion of the flexion moment PC1 as the third variable in the PCA-LDA set and the addition of the adduction moment PC2 and the Flexion Moment PC1 as the 4^{th} and 5^{th} variables in the PCA-PLS-LDA set. The flexion moment PC1 and the flexion angle PC1 are correlated (r=0.41), which may be why they were in one set but not in the other. However, these variables did not contribute much to the discriminant performance for either technique, since the first two variables on their own have 11.5% and 9.7% misclassification rates for PCA-PLS-LDA and PCA-LDA respectively, compared to 7% and 8% with the full set.

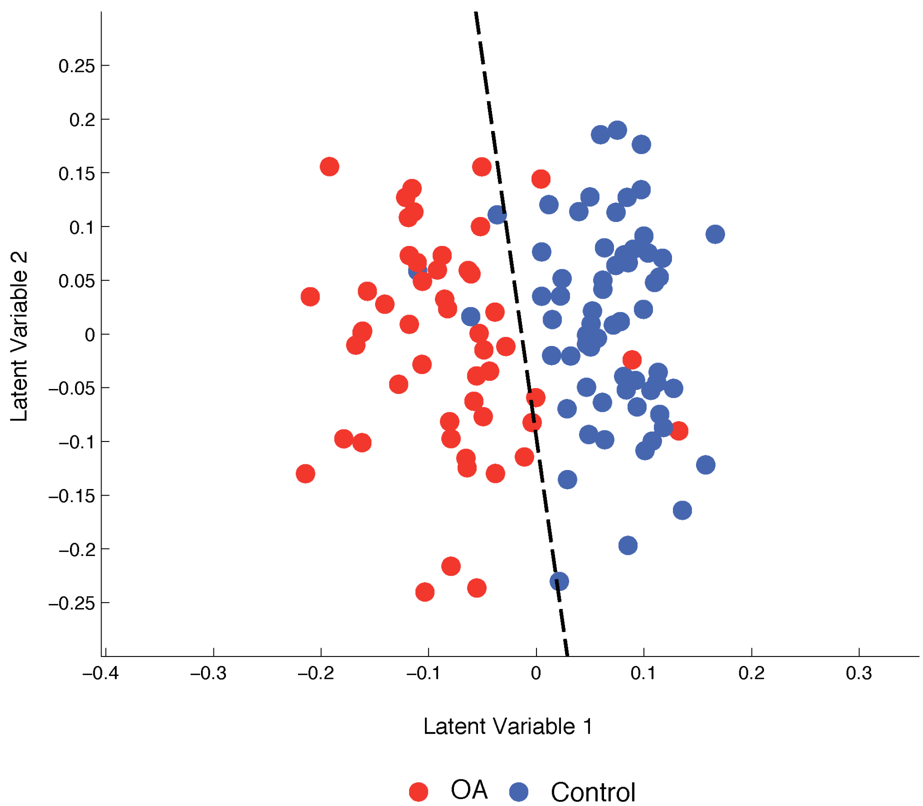

Figure 2.3: Each point corresponds to one observation's scores of theta observation on the two extracted latent variables (T_1, T_2). The linear discriminant function is shown as a black dashed line. The groups are well separated, with a 7% misclassification rate by leave one out.

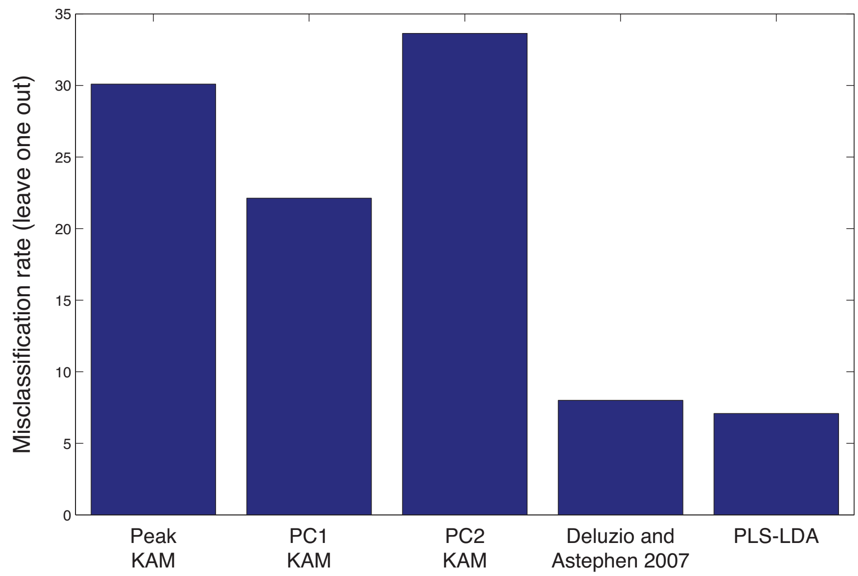

Figure 2.4: Misclassification rate based on leave one out procedure for peak, PC1, PC2 scores of the knee adduction moment, the rate quoted by Deluzio and Astephen for PCA-LDA and PCA-PLS-LDA with variable selection

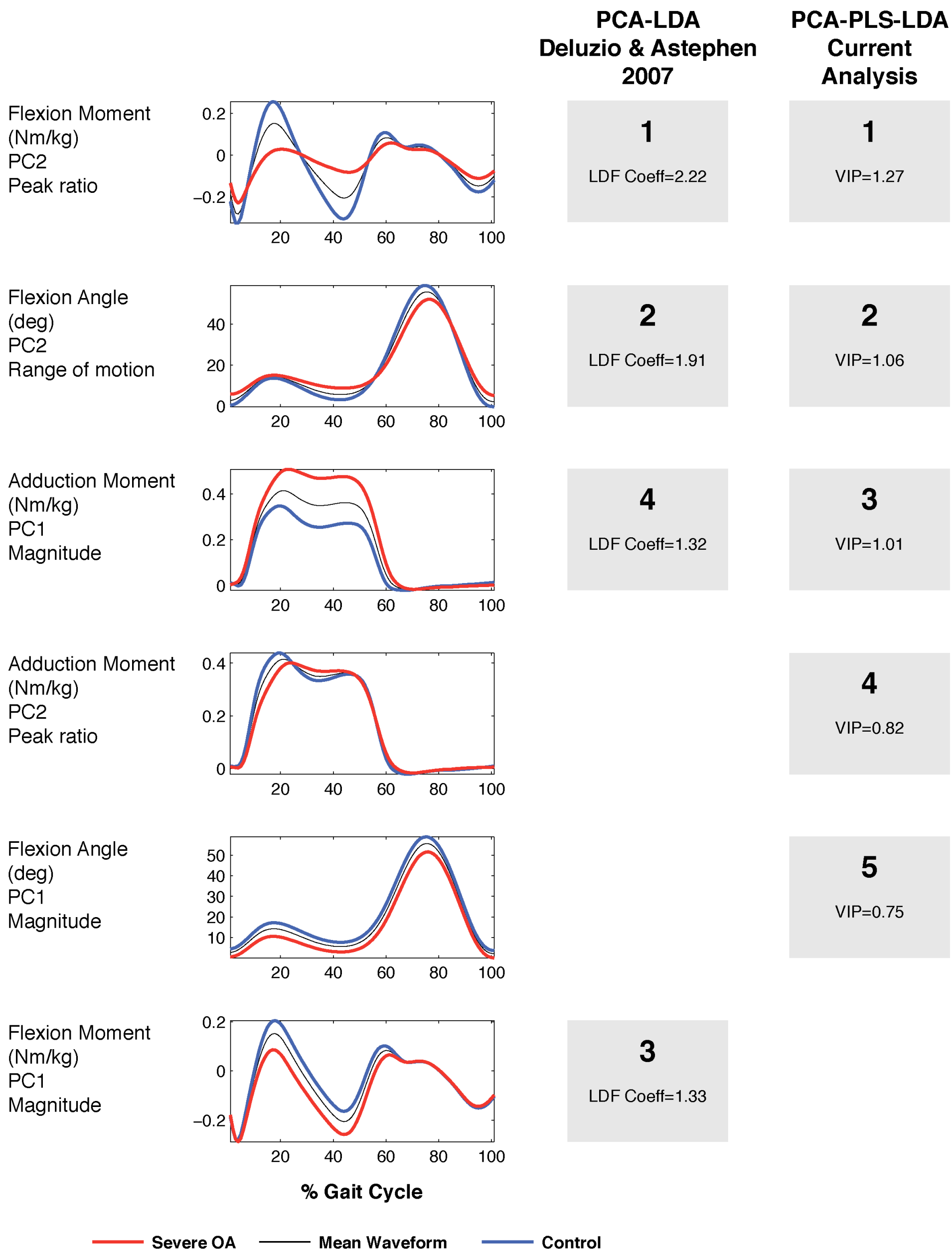

Figure 2.5: Input variables that were selected using the stepwise procedure (PCA-LDA in Deluzio and Astephen, 2007) and iterative PLS procedure (PCA-PLS-LDA) in current analysis). The ranks of the first two input variables are the same for both techniques but different for variables 3-5. VIP is the variable importance to prediction measure, calculated as part of the iterative PLS procedure, LDF coeff is the coefficient from the linear discriminant function as described in Deluzio and Astephen 2007. The waveform corresponding to the average score for each group, control and severe OA are shown on the plots.

2.6 Discussion

The exemplar paper (Deluzio and Astephen, 2007) was chosen to provide an easy separable discriminant problem to validate the new technique. Our results indicate that PCA-PLS-LDA can at least equal PCA-LDA, and that both techniques exceed the performance of analyzing single quantities or components. Both techniques extracted variables that are known to be relevant to knee osteoarthritis: the knee flexion moment, the knee flexion angle, and the knee adduction moment (Astephen Wilson et al., 2011; Baliunas et al., 2002; M Henriksen et al., 2011a; Mündermann et al., 2005; Zifchock et al., 2011). This indicates that the PCA-PLS-LDA procedure is isolating variables of known clinical importance.

An additional feature of the PLS procedure is sequence independent variable selection, which is a potential advantage over stepwise procedures, since Klecka (1980) noted that stepwise procedures do not necessarily guarantee an optimal set of variables. Hoskuldsson (2001) noted that stepwise procedures increase the risk of over-fitting because the inclusion criteria is for fit, rather than predictive ability, and Chong and Jun (2005) noted that stepwise methods have poor performance in cases of collinearity between variables.

In this data set, the correlation between the selected input variables ranged from -0.15 to 0.65. Although the stepwise procedure used in Deluzio and Astephen (2007) chose similar variables to the PCA-PLS-LDA set, forward and backward selection procedures on the same set yielded different results, which indicated possible collinearity. To confirm the presence of collinearity, the condition number of the data set cross dispersion matrix (X'X) was calculated, 1.53×10^6. A very large value such as this indicates an ill-conditioned matrix and the potential for non-unique solutions, which may affect the performance of variable selection techniques (Draper and Smith, 1998). In contrast, the condition number of the latent variable scores matrix (T) was 1, indicating a well-conditioned matrix. If the goal of our analysis was purely discrimination, a non-unique solution might be acceptable. However, since we are attempting to uncover an underlying structure in the data and relate that to a physical phenomenon (a waveform feature), a unique solution would be preferable.

2.7 Conclusions

The presented case study shows that PLS is at least as good as PCA on its own as a pre-processing step for LDA, but it possesses some theoretical statistical and practical interpretation advantages. In particular, the ability of the technique to cope with collinear data, a common occurrence in biomechanics analyses, is an advantage over stepwise variable selection, and ensures optimal discriminant performance. Although PLS has been previously described as a "shotgun" technique (Kaptein et al., 2014), the use of PCA preprocessing, objective variable selection criteria, and model validity checks, as described in this chapter, maintain the links to the original data and ensure that the relationships between variables are not due to chance, but instead represent a way of revealing differences between groups that span multiple biomechanical variables.

Chapter 3: Multivariate Analysis of Knee Osteoarthritis Radiographic Severity and Pain

3.1 Introduction

Knee osteoarthritis is a condition that requires both radiographic and symptomatic evidence to arrive at a diagnosis. Pain is typically the symptom that causes a patient to seek treatment, and then radiographs of the knee are examined for degenerative changes at the joint, such as joint space narrowing and osteophytes.

However, despite both being required for a diagnosis, pain and radiographic indicators of knee osteoarthritis are not well correlated. Intuitively, it would make sense for radiographic signs of osteoarthritis severity to be closely related to both pain and joint mechanics during gait. However, quantifying this relationship has proven to be analytically challenging, particularly in patients with mild or moderate osteoarthritis because in this population, pain and radiographic severity are not well correlated (Barker et al., 2004; Bedson and Croft, 2008; Henriksen et al., 2011; Hubley-Kozey et al., 2009). Using separate analyses Astephen Wilson *et al.* (2011) found biomechanical factors relating to both pain and radiographic severity. They found that pain related to stride characteristics, but not to mechanics, and the knee adduction moment related to radiographic severity. Zifchock *et al.* (2011) found that knee adduction moment did not correlate with pain, a finding echoed by Maly *et al*. (2008). In contrast, Henriksen *et al.* (2011) linked increased pain to decreased peak knee adduction moment and Heiden *et al*. (2009) found the opposite, with larger knee adduction moments being related to reduced pain.

3.2 Proposed Analysis Strategy: PLS

Partial Least Squares (PLS) is a generalized form of Principal Component Analysis (PCA). Like PCA, PLS is a method of extracting components explaining variance in the data set. The key difference between PLS and PCA is that PCA extracts components that explain the maximum amount of *variance* in the data (X) but PLS extracts latent variables that explain the maximum amount of *covariance* between the input data (X) and the explanatory or grouping variables (Y). If the between group variance is larger than the within group variance, the techniques are equivalent, but if the within group variance is large, PLS is superior for group discrimination (Barker and Rayens, 2003); the theoretical grounding for this combination is given by Barker and Rayens (2003) and Liu and Rayens (2007).

PLS was developed in the chemometrics literature as a way of incorporating a large number of potentially correlated data streams into a single analysis for process control. The goal was to identify process faults affecting the quality of output (Wold and Sjostrom, 2001), for example, correlating a poor quality plastic to a particular temperature or pressure value. It is possible for “quality” to have multiple response variables (for example, weight and colour). PLS decomposes the covariance between the data, X (e.g. temperature and pressure), and response, Y (e.g. weight and colour), and therefore it allows for factors relating to both aspects of “quality” to be identified.

This feature of multiple, continuous response variables is useful in the current analysis because it allows for pain and radiographic severity to be assessed simultaneously, and explicitly account for the correlation structure in the data. To the author’s knowledge, the ability to extract variables explaining two response variables is unique among multivariate statistical techniques.

3.3 Rationale

The previous literature on the topic of the pain-radiographic severity-mechanics relationship in subjects with moderate osteoarthritis is inconclusive. Part of the ambiguity may be related to the inherent subjectivity of pain measurement; however, some of it may be due to the inability of univariate analyses to address the collinearity and multiple response variables present in this data set. This chapter seeks to address this analysis challenge using PLS and multiple linear regression (MLR), exploiting PLS's ability to incorporate multiple, continuous grouping variables.

3.4 Methods

3.4.1 Data Set

The data set included hip, knee, and ankle kinematic (angle) and kinetic (moment) data from the affected limbs of 37 subjects with mild to moderate medial compartment knee osteoarthritis; the details of the data collection were summarized in Astephen Wilson *et al* (2011). Briefly, subjects walked at their self-selected speed in a motion capture lab, while observed with an optoelectronic system, force plate and electromyography (although only the motion and force data was used in this analysis). The 3D angles and moments were computed using inverse dynamics and the moments were normalized to body mass.

The response (Y) variables were radiographic VAS (Visual Analog Scale, average of grade from two surgeons, mean 4.4, range 1.1 to 8.3) and the pain subscale from the WOMAC Score (mean 7.2, range 0 to 18). The Kellgren-Lawrence (KL) Score for these patients ranged from 1 to 4.

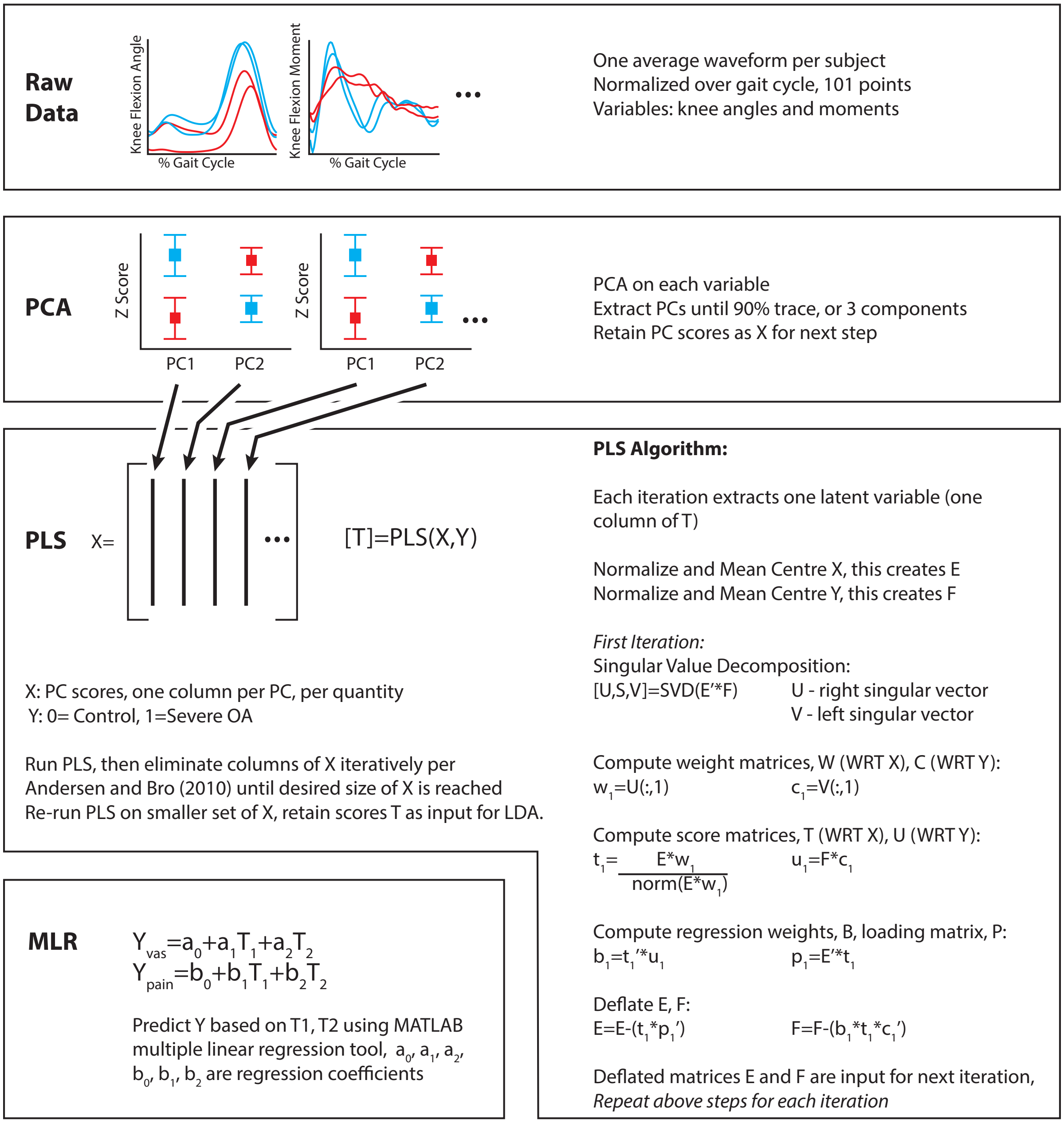

Figure 3.1: Analysis method summary and PLS algorithm

3.4.2 Pre-Processing

The PCA analysis was conducted using custom MATLAB code; the PCA algorithm is described by Deluzio and Astephen (2007). Briefly, PCA finds a set of loading vectors (U) that transforms the data

(X) to a reduced, orthogonal set of principal component scores (Z), $Z=U^TX$. The loading vectors (U) are the eigenvectors of the covariance matrix of X.

The inputs (X) to the PCA analyses were average waveforms normalized to the gait cycle (101 points), including one observation per patient. A 90% trace criterion (Jackson, 2004) was used to determine the correct number of components to extract, up to a maximum of three. Pre-processing with PCA is computationally equivalent to PLS on a single large matrix containing all of the data according to Chin (2013) and Westerhuis et al. (1998); this was confirmed by our calculations on this data set. The advantage of pre-processing with PCA is a more straightforward interpretation of the regression weights (B), as they correspond to a waveform feature rather than to individual frames of data.

3.4.3 PLS

The PLS algorithm is iterative and the extracted orthogonal components are in order of maximum variability. This algorithm is well described elsewhere (Abdi, 2010), the key differences between PLS and PCA is that PCA decomposes the covariance of X using eigenvectors, PLS decomposes the covariance of X and Y using the singular value decomposition (SVD). Other formulations of the PLS algorithm (Wold and Sjostrom, 2001) were tested and found to be equivalent, which is consistent with Helland's findings (1988).

The PLS process is summarized in Figure 2.1 for convenience. Briefly, the first step is to mean centre and normalize both the data (X) and response variables (Y), creating E and F. The left and right singular vectors of the matrix E'*F are the first columns in the weight matrices, W and C. These are used to calculate the scores and regression weights, followed by deflation of E and F, forming the input for the next iteration (to extract the next component). This is repeated until the desired number of components is reached (in this case, two).

As in most multivariate techniques, the selection of the number of inputs to include, and the number of latent variables to extract using PLS, can be subjective. Including all of the input variables in a data set may lead to over fitting and making interpretation more difficult, as can extracting too many latent variables. The number of columns in X was reduced to a more parsimonious set using the iterative variable importance to projection (VIP) criteria described in Andersen and Bro (2010) (VIP calculation shown in Equation 3.1); in this procedure the least important variable is discarded, the PLS is re-run, and this process is repeated until the desired number of variables is reached. The desired number of variables or latent vectors was defined as the smallest set without explained variance degrading, as measured by the explained variance of the MLR, conducted with built-in MATLAB functions. The sensitivity of the model to outliers was tested with a leave one out test, with 1000 repetitions. The importance of the variables to each response variable was assessed using the regression weights (B_{PLS}), calculated with Equation 3.2.

Equation 3.1: VIP (Variable Importance to Projection) where j is the variable of interest, J is the total number of variables in X, f is the component of interest, F is the total number of components extracted, w are the weightings from PLS, SSY_f is the sum of squares of explained variance for the f^{th} component, SSY_{total} is the sum of squares of explained variance for all components

$$VIP_j = \sqrt{\frac{\sum_{f=1}^{F} w_{jf}^2 \cdot SSY_f \cdot J}{SSY_{total} \cdot F}}$$

Equation 3.2: Calculation of B_{PLS} regression weights equal to the Moore-Penrose pseudo-inverse of P^T (transpose of the loading matrix), multiplied by B (weight matrix with respect to X) and C^T (transpose of the weight matrix with respect to Y)

$$B_{PLS} = (P^{T+})BC^T$$

3.5 Results

The variable selection process identified kinematic and kinetic variables that predict pain and RVAS (radiographic severity visual analog score) as shown in Figure 3.2. The PLS process calculates regression weights, which are an indication of how important a variable is to the prediction of each response variable (Y_{vas} and Y_{pain}).

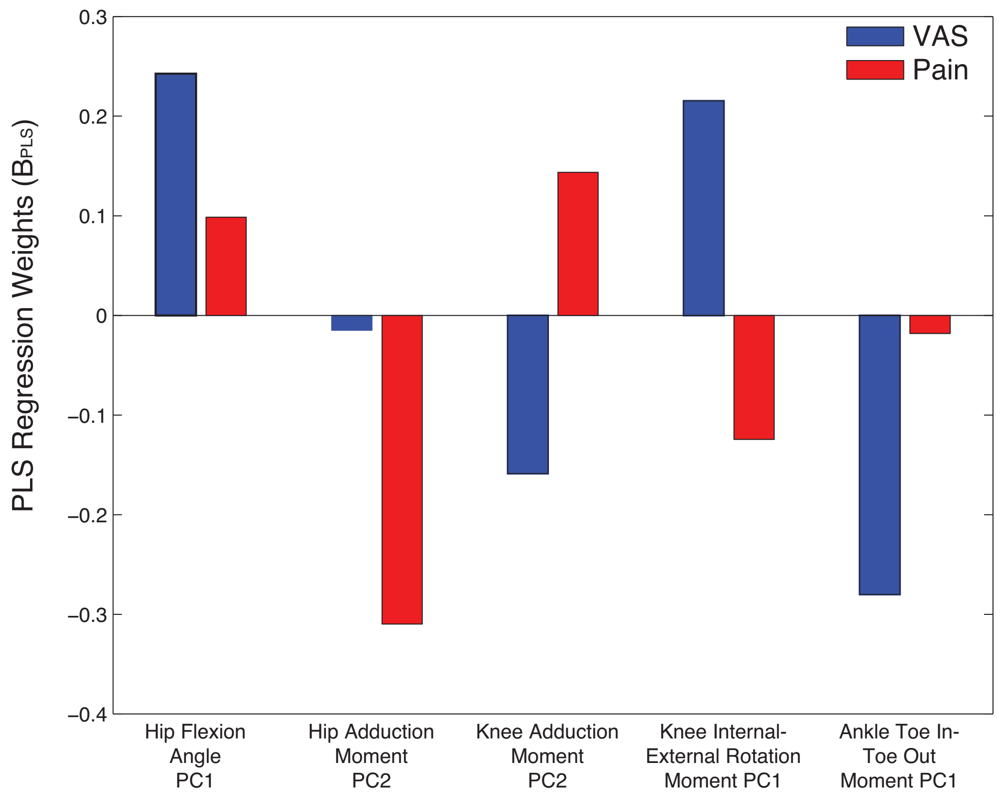

Figure 3.2: Regression weights for retained variables to explain radiographic severity (RVAS) and pain. A larger value indicates that a variable is more important, and a sign difference indicates that the variables "move" in an opposite direction, for example, the correlations between the knee adduction moment PC2 score and radiographic severity is in the opposite direction as the correlation with pain, but the relative importance is similar.

The variables identified as being important to the prediction spanned the hip, knee and ankle. In general, severity and pain were not associated with each other (r=0.07), and the relationships between mechanics and pain and radiographic severity were different. There ware some variables that were only related to one for the response variable, for example, the ankle toe in-toe out moment was only related to RVAS and the hip adduction moment was only related to pain. In contrast, the knee adduction moment was related to both pain and RVAS, but in an opposite sense, as shown in in Figure 3.2, since the signs of the regression weights were different. Multiple linear regressions revealed that mechanics better explained radiographic severity than pain, with R^2 values of 0.3 for RVAS, 0.2 for pain. The waveform features and how they are affected by pain and RVAS are illustrated in Figures 3.4-3.8.

To visualize the relationships between the isolated variables and the response variables (pain and radiographic severity), the data was clustered using a k-means algorithm in MATLAB with 5 repetitions. The observations were clustered as shown in Figure 3.3, and based on this clustering the average PC score for each waveform feature was calculated for each pain-severity group. Those average group scores were used to adjust the average waveform to show the effect of both pain and RVAS. The cluster containing two observations with extreme pain scores were not included in Figures 3.4-3.8.

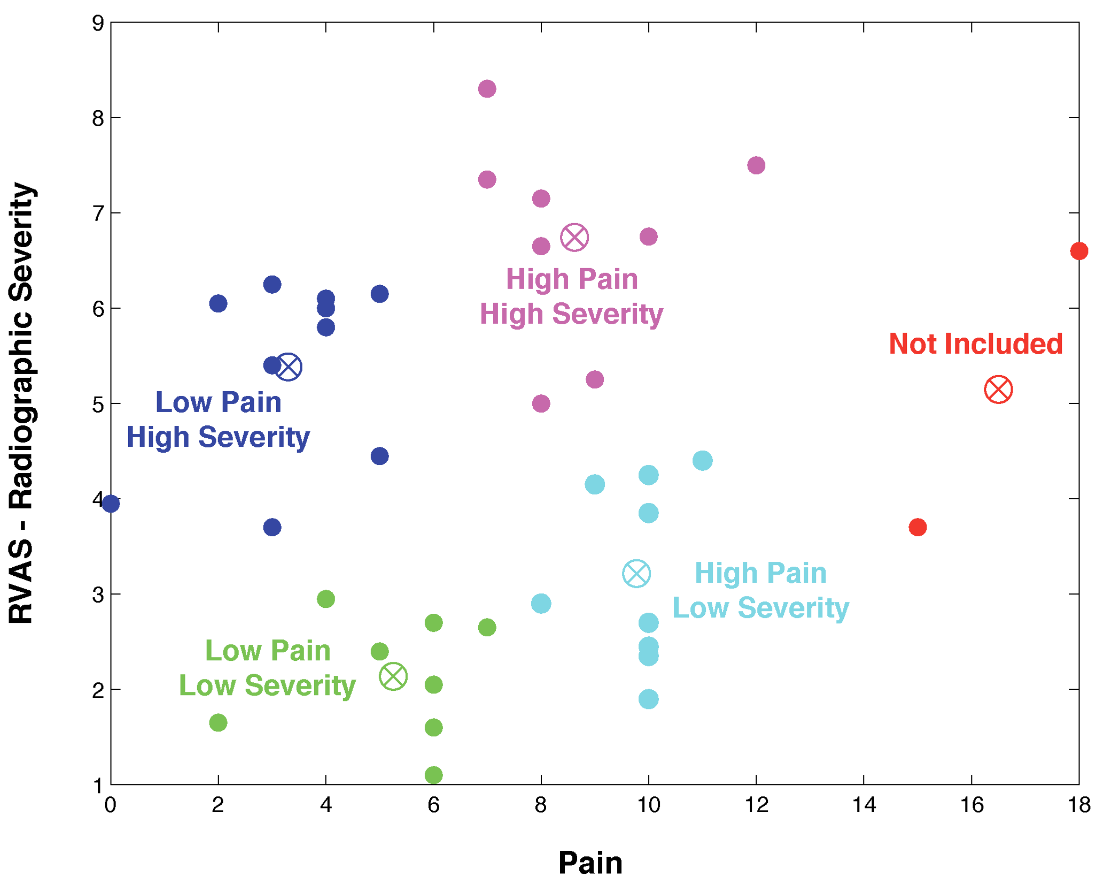

Figure 3.3: K-means clustering of subjects based on WOMAC pain score and RVAS score. Each observation is shown as a solid dot, the mean scores in each group are shown as a cross.

3.5.1 Knee Adduction Moment

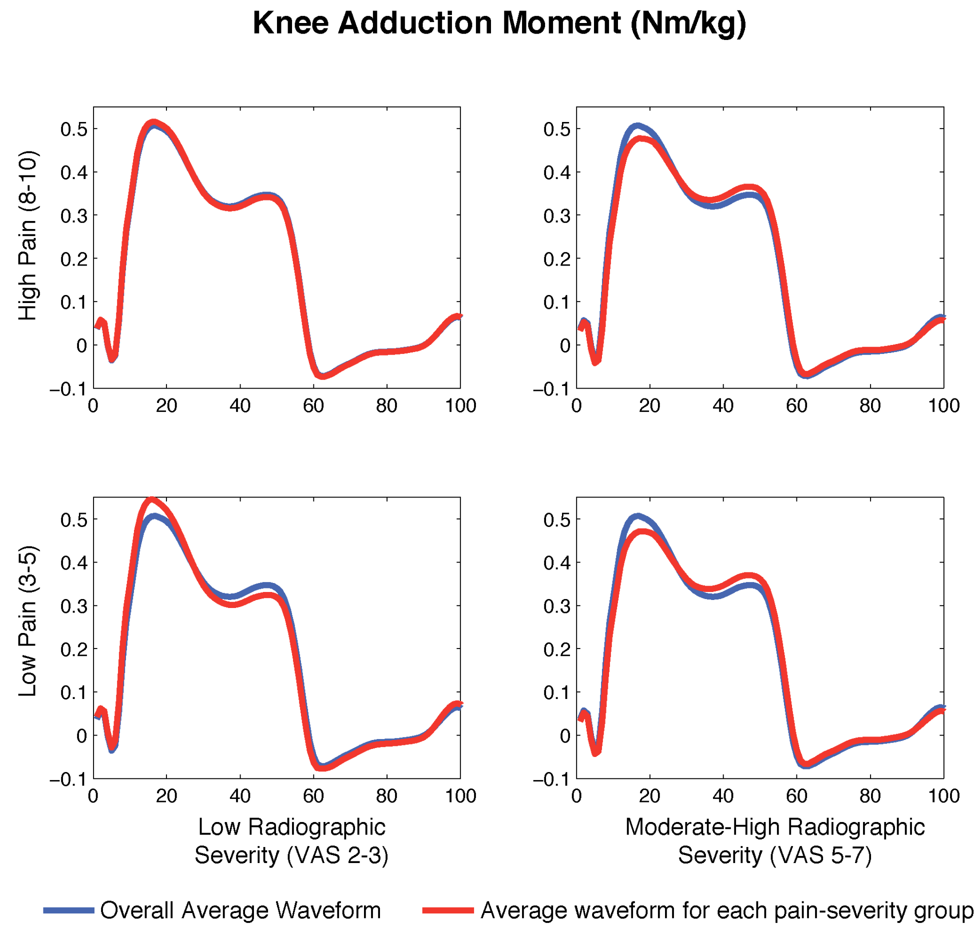

Figure 3.4: Effect of pain and radiographic severity on the knee adduction moment

Figure 3.4 illustrates the effect of pain and RVAS on the knee adduction moment waveform. The knee adduction moment PC2 relates to both pain and RVAS, but in an opposite sense (as shown in Figure 3.2). The waveform feature PC2 corresponded to the size of the 1st peak. At high radiographic severity, there is a minimal effect of increasing pain, the average waveforms for both high RVAS groups were similar, with a lower than average peak. In contrast, the effect of pain in the low RVAS groups was more significant, with low pain and low RVAS being associated with a higher than average 1st peak.

3.5.2 Hip Flexion Angle

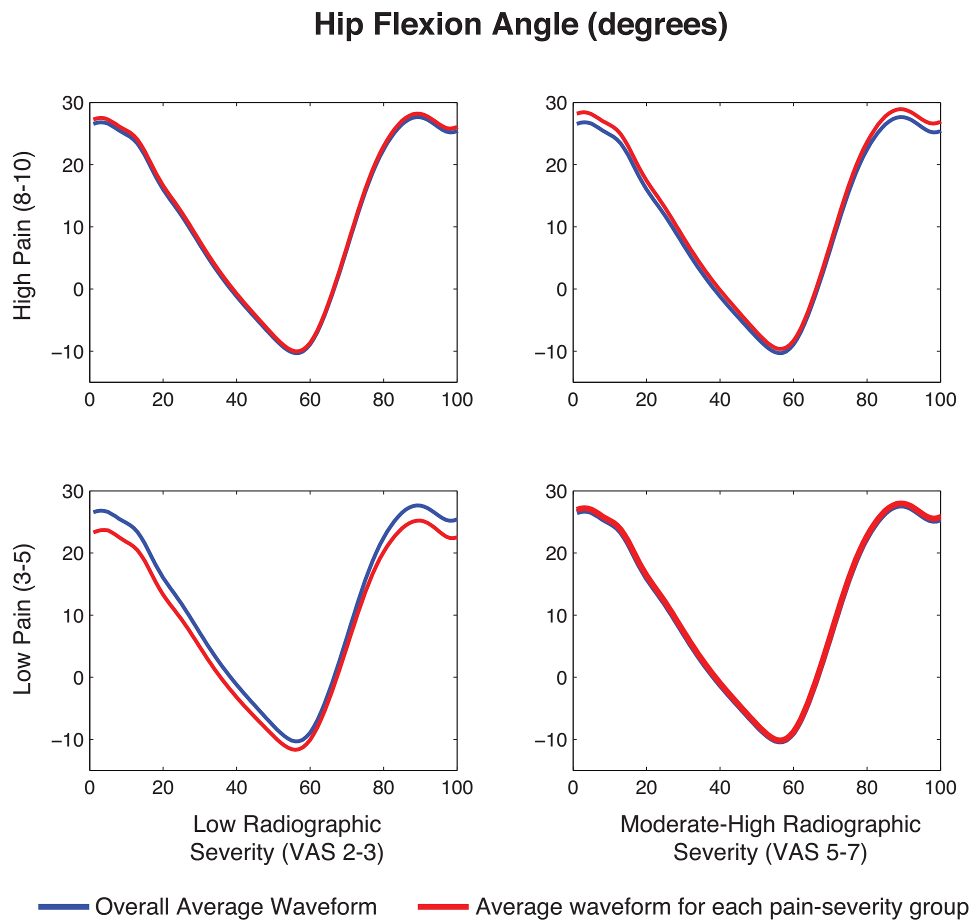

Figure 3.5: Effect of pain and radiographic severity on hip flexion angle, average waveform, and waveform corresponding to the average PC score for each pain-severity group

Figure 3.5 illustrates the effect of pain and RVAS on the hip flexion angle waveform. The hip flexion angle PC1 relates to both pain and RVAS, and in the same direction (as shown in Figure 3.2). This waveform feature corresponds to range of motion. The low pain-low radiographic severity group has a larger range of motion than the other groups, and appears to land in a straighter (less flexed) posture than the other groups.

3.5.3 Hip Adduction Moment

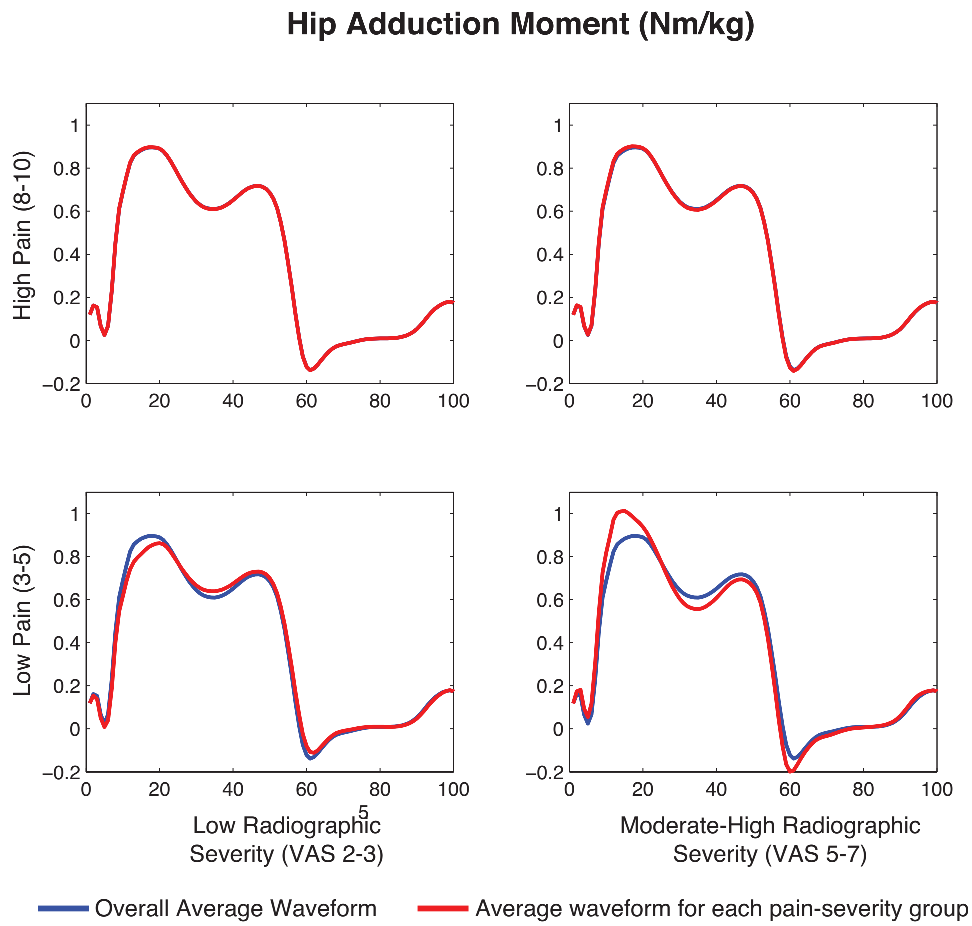

Figure 3.6: Effect of pain and radiographic severity on hip adduction moment waveform

Figure 3.6 illustrates the effect of pain on the hip adduction moment waveform. The hip adduction moment PC2 relates primarily to pain (as shown in Figure 3.2). This waveform feature corresponds to a larger 1st peak, and bigger ratio between the peaks. At high pain levels, there is no effect of radiographic severity: both groups are close to the average waveform. However, the high radiographic severity-low pain group had a larger 1st peak hip adduction moment, and bigger ratio between the peaks than the low pain-low severity group, which had a slightly lower than average 1st peak.

3.5.4 Knee Internal External Rotation Moment

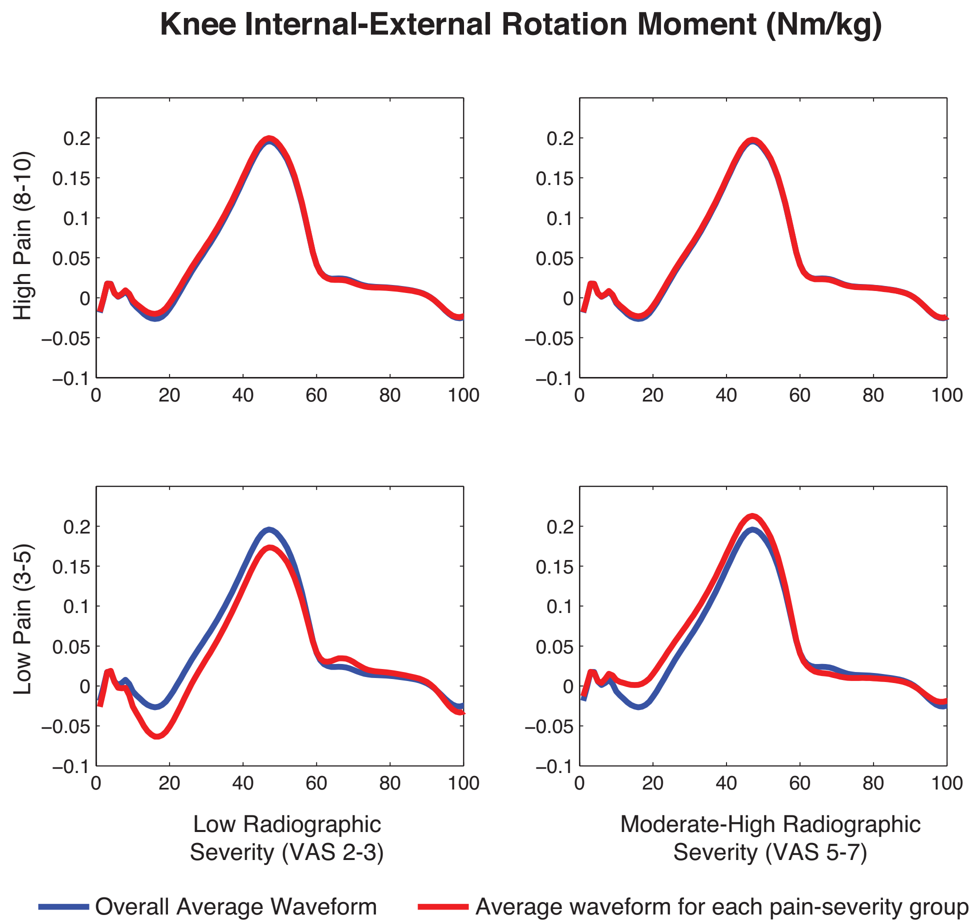

Figure 3.7: Effect of pain and radiographic severity on knee internal external rotation moment

Figure 3.7 illustrates the effect of pain and RVAS on the knee internal-external rotation moment waveform. The knee internal-external rotation PC1 relates to both pain and RVAS (as shown in Figure 3.2). This waveform feature corresponds to a larger peak in late stance. At high pain levels, there is no effect of radiographic severity: both groups are close to the average waveform. However, the high radiographic severity-low pain group had a larger peak than the low pain-low severity group, which had a slightly lower than average peak.

3.5.5 Ankle Toe In-Toe out Moment

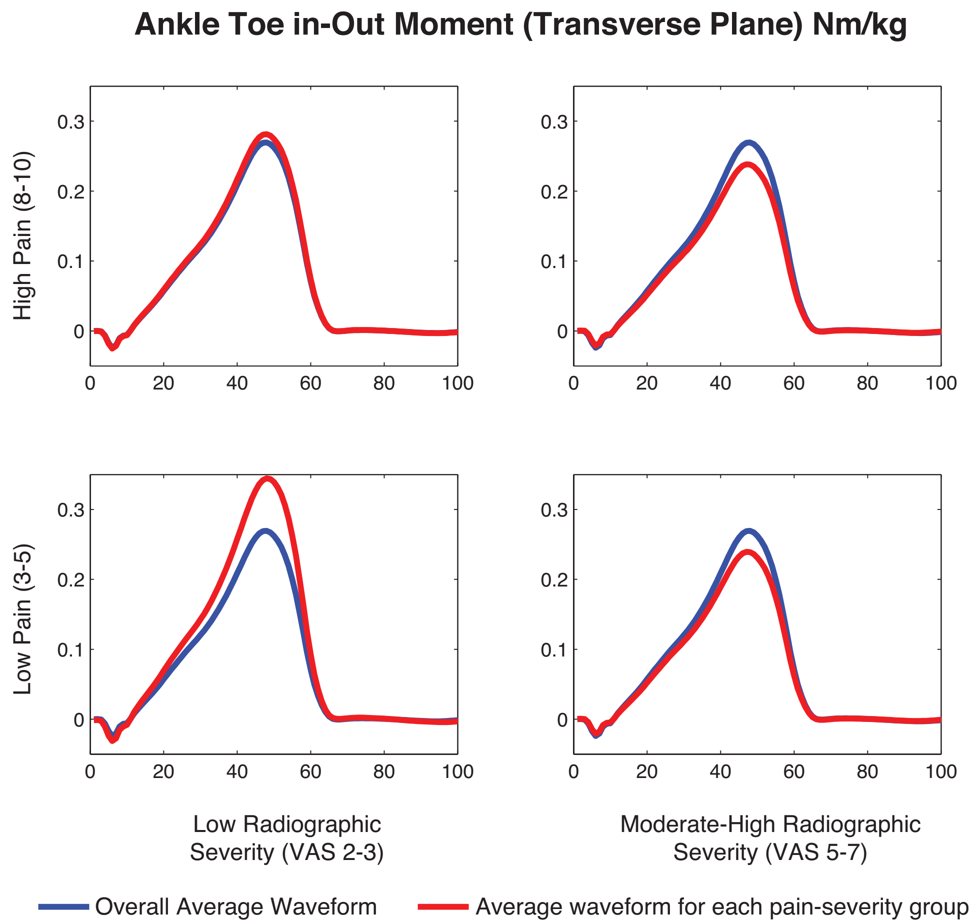

Figure 3.8: Effect of pain and radiographic severity on ankle toe in-toe out moment

Figure 3.8 illustrates the effect of pain and RVAS on the ankle toe in-toe out (transverse plane) moment waveform. The ankle toe in-toe out moment PC1 relates primarily to RVAS (as shown in Figure 3.2). This waveform feature corresponds to a larger peak. At high RVAS, there is no effect of pain: both groups are slightly below average. However, the low radiographic severity-low pain group had a larger peak than the high pain-low severity group, which was close to average.

3.6 Discussion

This study quantified the most important biomechanical features that explain both pain and radiographic severity in this population. The quantities identified by the analysis are consistent with previous univariate analyses regarding kinematic and kinetic quantities corresponding to knee osteoarthritis radiographic severity, as summarized in Table 3.1 below. It is an encouraging sign that the PLS identified variables that were meaningful and clinically relevant. The identification of the ankle transverse plane moment is a “new” finding; however, approximately 80% of the variance in the ankle transverse plane moment can be explained by the lateral ankle force (or lateral ground reaction force) in this data set. The lateral ground reaction force has previously been identified as a characteristic of knee OA patients by Mündermann *et al.* (2005). Given the close relationship between the transverse plane moment and lateral ground reaction force, although the ankle toe in-out rotation moment has not been explicitly identified by past literature, it is supported by the Mündermann work.

Table 3.1: Summary table comparing the findings of this study with past studies of OA mechanics and radiographic severity

Hip Flexion Angle	Astephen et al 2008, Hunt et al (2010)
Hip Adduction Moment	Astephen et al 2008, Mundermann et al (2005), Metcalfe et al (2013), Butler et al (2011), Hunt et al (2010), Linley et al (2010)
Knee Adduction Moment	Astephen Wilson et al (2011), Zifchock et al (2011), Henriksen et al (2011), Mundermann et al (2005), Metcalfe et al (2013), Bailunas et al (2002)
Knee Int-Ext Moment	Astephen et al 2008, Kaufman et al (2001), McKean et al (2007), Messier et al (2005)
Ankle Toe In Toe out Moment	Mündermann *et al* (2005)* (Lateral Ground Reaction Force)

Fewer previous studies have quantified the relationship with pain and biomechanical features. The previous work by Astephen Wilson *et al.* (2011) on the same data set was not able to link pain to joint mechanics. However, the current analysis was able to do this using the same data, a new finding.

The importance of knee adduction moment to knee osteoarthritis in general is consistent with the previous literature relating radiographic severity to this feature. However, the pain-radiographic severity interrelationship is a novel result. Henriksen *et al.* (2011) noted the relationship between this variable and pain, but they analyzed the peak knee adduction moment, and the PC2 extracted by this analysis appears to contain additional information related to the curve shape, as shown in Figure 3.6**.** Zifchock *et al.* (2011) found slightly different measures of importance: the peak knee adduction angle and the knee flexion range of motion were related to pain.

A key strength of this work was the simultaneous analysis of the pain-radiographic severity-mechanics relationship. Individual multiple linear regressions would have selected a different variable set for each response variable (pain and radiographic severity). Although the two variables are poorly correlated, they depend on the same mechanical variables, which have correlation coefficients with each other of up to 0.7. This level of correlation may make stepwise variable selection less accurate, but is acceptable in PLS analysis. An interesting finding is the different pain-severity-mechanics relationship in the hip and knee adduction moment waveforms. These two measures are well correlated and are in the same plane, so intuitively one would think that they would respond similarly to pain and severity. However, Figures 3.4 and 3.6 show that while the hip is sensitive to pain, the knee adduction moment relates to both response variables but in an opposite sense. Although the knee adduction moment is well linked to radiographic severity by past studies, our work suggests that the knee adduction moment-severity relationship is mediated by pain in this population; this is a new finding that may explain why in past work the correlation between knee adduction moment and radiographic severity was moderate rather than strong.

Although the overall variance explained in the current analysis was modest (0.2 for pain and 0.3 for radiographic severity) this was higher than that achieved by both Henriksen and Astephen-Wilson. This suggests that the additional kinematic and kinetic variables from multiple joints, and the use of principal component scores to summarize waveform features in a simultaneous analysis extracts additional insights from data sets such as this one.

3.7 Conclusions

This chapter introduced a novel method for quantifying and visualizing multiple response variables for biomechanical analyses. This is a technical innovation that has not been achieved in previous biomechanics literature to our knowledge. The new clinical findings suggest that mechanics can be linked to both radiographic severity and pain in moderate OA patients, but that multivariate methods may be required to quantify the pain-radiographic severity-mechanics relationship.

Chapter 4 : Non-Negative Matrix Factorization for Neuromuscular Analysis

4.1 Introduction

The aim of many knee osteoarthritis treatments is the reduction of the joint contact force, in an attempt to alleviate pain and slow disease progression. Although the precise relationship between the contact load and disease progression is not yet fully understood (Andriacchi and Mündermann, 2006), we do know that joint contact loads at the knee are the net effect of the ground reaction force and forces generated by muscle activation (Bennell et al., 2013) and that high knee adduction moments are related to disease progression (Miyazaki et al., 2002). Therefore, a more thorough understanding of the contribution of muscle activation to the knee joint loads is desirable.

One way of exploring the role of musculature in knee osteoarthritis gait is through surface electromyography (EMG). However, these signals are analytically challenging, with large subject-subject variability and noisy signals. This chapter proposes and validates a multivariate approach that is a better match the characteristics of EMG signals than conventional analyses, and hence has the potential to improve the analytic value of the signals, both for knee osteoarthritis researchers and others in biomechanics. First, the current state of the art will be reviewed, the new technique will be introduced and finally validated with two experiments.

4.2 Background: EMG processing and normalization

Raw EMG signals appear as shown in Figure 4.1a: this is a noisy signal that alternates from negative to positive. The magnitude of this raw signal cannot be used for comparison between individuals or between muscles because it is influenced by factors such as electrode placement, skin preparation, subcutaneous fat, and muscle size (Benoit et al., 2003; French et al., 2015; Oliveira et al., 2014). To facilitate comparison between individuals and conditions, the signal is processed and normalized so that instead of being expressed in volts, it is expressed as a percentage of some nominal value such as the maximum recorded value.

The EMG processing procedure is described in Figure 4.1 and is based on that of Hubley-Kozey *et al.* (2006), although the process is common across many authors with only minor variations. First, the signal is rectified so that it no longer alternates, and then the bias in the signal is removed. The bias value is calculated from a resting trial. Then the signal is band pass filtered at 20 Hz and 450 Hz, and enveloped with a zero-lag dual pass Butterworth filter at 6 Hz. This yields a smooth waveform, that is then time-normalized over the gait cycle (initial contact to initial contact, containing both stance and swing phase). This signal is still in volts, so to compare between individuals or conditions it is divided by a normalization value that represents a "maximum." As a result, the signal magnitude is expressed in terms of a percent of this maximum value. The choice of this value is an important one and the options for normalization have been thoroughly reviewed by Burden (2010). Normalization to maximum voluntary contraction is a popular choice because the maximum is thought to be more reliable day-to-day and subject-to-subject, although the exact relationship between the isometric properties of the muscle and dynamic remain unknown (Benoit et al., 2003). Maximal voluntary contractions are often achieved through the use of an isokinetic dynamometer, which is potentially time consuming and uncomfortable for subjects, particularly if a large number of muscles are being evaluated. Rutherford *et al.* (2011a) noted that different subjects achieved maximal EMG values during different exercises targeting the same muscle group and proposes that investigators use more than one isometric exercise per muscle group, further lengthening the protocol duration. Alternatively, normalization to a peak from the dynamic task may be suitable if the goal is within-individual and within-muscle comparisons. However, Burden cautions that task-based normalizations reduce the "true biological variation" and hence reduce the sensitivity; therefore they are not recommended for comparing signals between muscles, trials, or individuals. Maximal contraction normalization techniques are thought to have superior test-retest reliability, and are a better choice for comparisons between individuals, since the denominator is more consistent (the absolute maximum) (Burden, 2010).

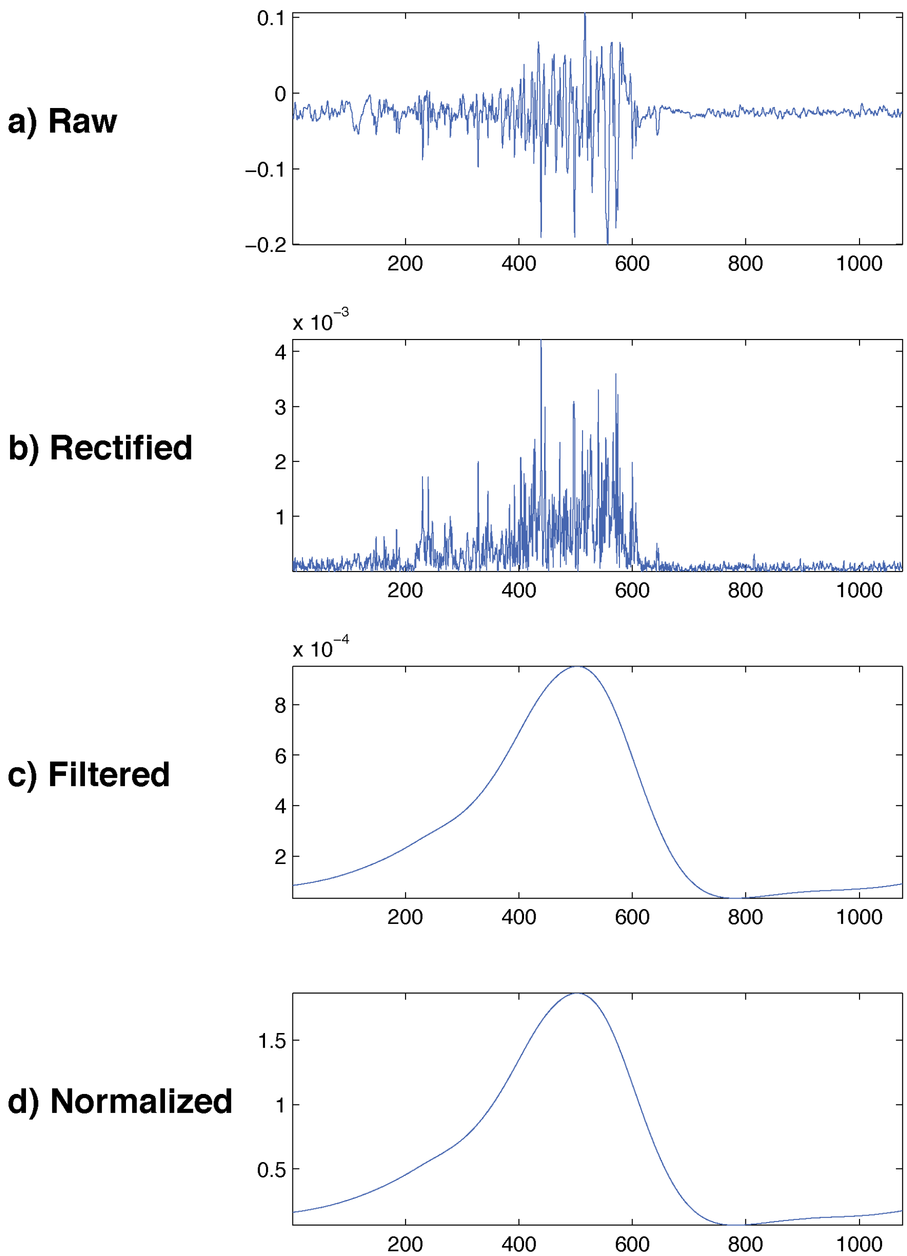

Figure 4.1: Lateral Gastrocnemius signal subject 1, MVIC normalized

4.3 Existing Neuromuscular Analysis Approaches

4.3.1 Co-contraction index by Rudolph

The co-contraction index (CCI), developed by Rudolph *et al*. (2000) is widely cited in the knee osteoarthritis literature (Childs et al., 2004; Heiden et al., 2009; Hortobágyi et al., 2005; Lewek et al., 2005, 2004; Ramsey et al., 2007; Zeni et al., 2010) and in other studies of knee biomechanics. For example, Besier *et al*. (2001) used CCI to quantify the difference between anticipated and unanticipated run and cut maneuvers. The use of the CCI and related techniques in knee osteoarthritis literature is summarized in Table 4.1.

The co-contraction index is the ratio of the two signals of interest, multiplied by the sum of their magnitudes. This value is summed over a specified range, often from some duration pre-contact to the first peak knee adduction moment (Rudolph et al., 2000), and divided by the number of data points (n), as shown in the Equation 4.1 below.

Equation 4.1: Co-contraction Index (CCI) per Rudolph et al 2000

$$CCI = \frac{\sum_{i=1}^{n} \left(\frac{low \;\; signal_i}{high \;\; signal_i} \right) * (low \;\; signal_i + high \;\; signal_i)}{n}$$

The high and low signals are assessed at each i*th* frame. A large value for CCI indicates that the magnitudes of the two EMG signals magnitudes are large and roughly equal. Variations on the CCI exist in which more than two muscles are considered, for example, Heiden *et al*. (2009) grouped the hamstrings and quadriceps muscles together and then the medial and lateral muscles together, termed "directed co-contraction ratios", as did Fantini Pagani *et al*. (2013).

The co-contraction index is appealing because it reduces the two waveforms into one number, which can then be compared with a t-test or ANOVA to determine if the differences between the two groups or conditions of interest are statistically significant. However, as we will describe numerically in Sections 4.7 and 4.8, the disadvantage of the CCI is that by summing these quantities, it does not capture changes in the timing of muscle activation, the curve shape. As noted by Hubley-Kozey *et al*. (2009), to interpret a CCI, one must also examine the knee adduction moment waveform (or the waveform that is used as the epoch criteria), making the analysis less straightforward. The CCI is sensitive to the overall magnitude of the signal and hence the normalization value (Knarr et al., 2012), which is a potential source of variability. In particular, this sensitivity to magnitude is important because different muscle groups have different properties (Davis and Vaughan, 1993), for example the gastrocnemius muscles are close to the surface and don't have as much adipose tissue as the quadriceps muscles. This means that the magnitude of the quadriceps EMG signal could be quite low, in spite of being fully activated. An additional disadvantage of co-contraction approaches is the theoretical possibility of scores up to 200% (or 2), which doesn't reflect the underlying physiology, since muscles can't be 200% synchronized.

Table 4.1: Summary of CCI related analysis techniques used for EMG data in knee OA literature.

Author	*Technique*	*Research Question*
Al-Khlaifat *et al*., 2015	CCI per Rudolph *et al* 2000	Effect of exercise program
Childs *et al*., 2004	CCI per Rudolph *et al* 2000	Control vs OA, walking
Collins *et al*., 2014	CCI	Interlimb Symmetry, stiffness in knee OA, walking
Heiden *et al*., 2009	"Directed co-contraction ratios" for hamstrings, knee flexors extensors, medial-lateral	Control vs OA, walking
Hortobágyi *et al.*, 2005	"coactivity ratio"	Control vs OA, walking, stairs
Lewek *et al*., 2004	CCI	Role of frontal plane laxity, OA vs controls, walking
Lewek *et al*., 2005	CCI per Rudolph *et al* 2000	Response to standing on translating platform, OA vs controls
Liikavainio *et al*., 2010	CCI computed during 5 epochs	Control vs OA, walking, stairs
Metcalfe *et al*., 2013	CCI	Effect on contralateral limb, OA vs control, walking
Patsika *et al*., 2014	"Coactivity Ratios", similar but not identical procedure to Rudolph, summed during agonist and antagonist function	Muscle strength in women with OA, compared to controls
Ramsey *et al*., 2007	CCI per Rudolph *et al* 2000	Bracing effectiveness in OA
Schmitt and Rudolph, 2008	CCI per Rudolph *et al* 2000	stable vs unstable OA, walking with perturbation
Zeni *et al*., 2010	CCI per Rudolph *et al* 2000	Relationship between co-contraction and OA severity, plus controls

4.3.2 Multivariate Approaches

An alternative to co-contraction analyses is a PCA-based approach aimed at incorporating information about the waveform shape. The construction of the input matrix varies between authors, as does the epoch of interest, as summarized in Table 4.2. However, PCA and the related techniques (such as Principal Patterns or Karhunen-Loève expansion) share a common feature: the isolation of a small number of principal components (or patterns or factors) that explain maximal variance in the data. The advantage of these techniques is that the components and scores can be mapped to physical or temporal quantities, such as magnitude or peak timing. However, the disadvantage of the technique is the first component extracted explains maximal variance, which is almost always magnitude in EMG data sets. Magnitude is a characteristic of EMG signals that is variable between subjects and muscle groups. Therefore, interpretation of the first principal component score (or whichever component is attributed to magnitude) is sensitive to subject-subject variability and may not yield significant differences between study groups. Generally, PCA-based techniques have analyzed each muscle individually(Astephen et al., 2008b; Rutherford et al., 2011b), and while this approach can identify differences in activation patterns, they were not aimed at assessing muscle synergy.

There are non-PCA multivariate approaches applied to EMG data from biomechanics studies are included in Table 4.2. This list is not comprehensive, but the key point is that many of these techniques are mathematically similar, for example Factor Analysis and NMF both extract factors/synergies and scores, and the decompositions involved in Karhunen-Loève expansion and PCA are different only in name.

Table 4.2:Multivariate approaches to EMG analysis

Authors	*Technique*	*Application*
Shiavi and Griffin, 1981	Karhunen-Loève expansion	No application given
Davis and Vaughan, 1993	Factor analysis and multidimensional scaling, co-activity assessed by common area under curve	Used by (Tedroff et al., 2008) to compare lower extremity muscle function in children with and without cerebral palsy
Sadeghi *et al*., 2002	PCA	Function of flexors-extensors in able bodied gait
Ivanenko *et al*., 2004	Factor analysis	Quantifying number of synergies in normal gait
Hof *et al*., 2005	Deviation from "normal profile" measured with normalized mean square difference	Used by (Boerboom et al., 2001) to detect atypical hamstring activity post ACL reconstruction
Lauer *et al*., 2005	Continuous Wavelet Transform and PCA	Cerebral Palsy compared to control, children
Hubley-Kozey *et al*., 2006	PCA on each muscle group (quadriceps, hamstring, gastrocnemius)	Neuromuscular alterations in OA, walking, compare to controls
Houck *et al*., 2007	Fourier Analysis and Cluster Analysis	Control compared to ACL deficient during cutting task
Astephen *et al*., 2008	PCA+LDA (PCA on each muscle separately, stepwise LDA on scores)	Control vs moderate vs severe OA, walking
Hubley-Kozey *et al*., 2009	PCA on all muscles together, (co-contraction defined as principal pattern 1 score, compared results to CCI)	Control vs moderate vs severe OA, walking
Rutherford *et al*., 2011	PCA on each muscle group (quadriceps, hamstring, gastrocnemius)	Control vs moderate vs severe OA, walking, influence of walking speed
Fallah-Yakhdani *et al*., 2012	Generalized Estimating Equations on co-contraction time, dynamics stability, kinematic variability	Pre and post total knee replacement
Frey-Law and Avin, 2013	Generalized Estimating Equations, Factor analysis and Cluster Analysis	Compared generalized versus joint-specific influences on muscle co-activation
Chvatal and Ting, 2013	NMF	Quantify muscle synergies use in recovery from perturbations while walking
Rutherford *et al*., 2013	PCA on each muscle group (quadriceps, hamstring, gastrocnemius)	Mild vs moderate vs severe OA during walking
Robinson *et al*., 2015	Statistical Parametric Mapping (vector field analysis)	Young vs Adult differences in EMG profiles
Martino *et al*., 2015	NMF	Neuromuscular adjustments to unstable conditions

4.4 The rationale for using NMF for biomechanical studies

The idea of quantifying muscle synergies through Non-negative Matrix Factorization (NMF) originated in neuroscience research. Tresch *et al.* (1999) used this approach to quantify the effect of stimulation location on muscle activity in frogs. They identified a small number of muscle synergies that could represent the muscle activations of nine muscles of the frog's leg, and quantified how similar these muscle activation patterns were using the normalized dot product of the scores. Subsequent work on human subjects suggested that muscle activity in gait (Ivanenko et al., 2004; Oliveira et al., 2014) and postural tasks (Ting and Macpherson, 2005) could similarly be represented by a small number of synergies and that these synergies reflect the organization of the neural system. In the current biomechanics literature, NMF has been used for optimizing muscle activations in musculoskeletal modeling (Neptune et al., 2009), and when used as an optimization strategy, it may improve prediction of knee contact forces (Walter et al., 2014).

One of the desirable properties of NMF is the non-negative constraint: both the scores and synergy vectors must be positive. Other decomposition techniques, such as PCA, allow scores and vectors to contain negative values. However, EMG data must always be positive, therefore the additive nature of the NMF decomposition allows for easier interpretation of the scores and synergies (Ting and Chvatal, 2010).

A computational challenge that has limited the implementation of NMF is the non-uniqueness of the solutions generated by default algorithms (such as the MATLAB *nnmf* function). This is a key difference between NMF and PCA; the vectors in PCA are constrained to be orthogonal and of maximal variance. However, in NMF, the synergies can be non-orthogonal and are optimized for reconstructing the data and minimizing the least squares differences, rather than explained variance, as shown in Figure 4.2. The reason for the non-uniqueness can be visualized by imagining the synergies as describing a cone that contains all the data. A larger cone that contains the first cone would also provide a solution that is equivalent, or a cone of a slightly different shape could also describe the data equally well (Donoho and Stodden, 2004). Various attempts have been made to improve the stability of these algorithms, including alternating algorithms (Berry et al., 2007), multiplicative update algorithms (Lee and Seung, 2001), and sparseness constraints (Hoyer, 2004).

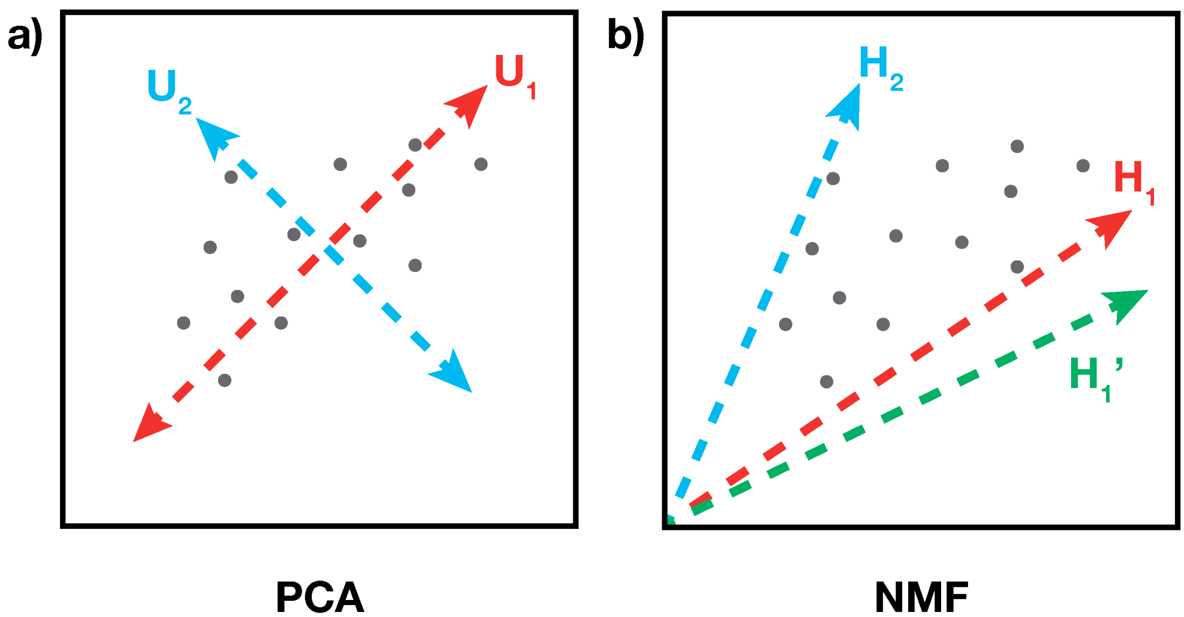

Figure 4.2: a) Schematic of PCA vectors (U_1 and U_2) compared to b) NMF synergies (H_1 and H_2) on the same data set. Note that H_1' is a different vector from H_1, but may explain the variance in the data set equally well.

4.5 NMF Procedure

The general NMF procedure is as follows (Lee and Seung, 1999):

1. Arrange the input data X into a matrix.
2. Specify the number of components to be extracted.
3. Start with random positive matrices for initial guesses of W (scores) and H (synergies).
4. Calculate X_{recon}=WH.

5. Iterate, recalculate W, H so that least squares difference between X and X_{recon} is minimized.
6. When iteration doesn't improve the estimate of X, stop iterating.

The success in estimating W and H and the correct number of synergies to extract can be quantified by Variance Accounted For (VAF) (Barroso et al., 2014), as shown in **Equation 4.2.** However, Ting and Chvatal (2010) cautioned that strictly applying the VAF criteria can result in over-fitting. In contrast, Tresch *et al*. (1999) suggested estimating the appropriate number of synergies by performing PCA on the data set, and evaluating the number of components that achieve 90% variance explained and extracting that number of synergies.

Equation 4.2: Variance Accounted For (VAF) per Barroso et al 2014

$$VAF = 1 - \frac{\sum (X_{reconstructed} - X_{actual})^2}{\sum (X_{reconstructed})^2} = 1 - \frac{SSE}{SST}$$

4.6 Data Set

This data set will be used for both experiments in this chapter; it was collected as part of a larger study of bracing for knee osteoarthritis, as described in Brandon (2015). This chapter presents EMG data from the overground, no brace condition from both the 17 osteoarthritic and 21 control subjects. This study was approved by the institutional ethics review board. Participants completed a WOMAC questionnaire and provided written informed consent.

The participants were instrumented with a full body data set of 81 retro-reflective markers, which were observed with 11 Qualisys Oqus Cameras (Oqus 400, Qualisys, Gothenburg, Sweden) at 200 Hz. The participants walked across six tandem force platforms (4x custom BP model, 2xBP400600NC, AMTI, Watertown MA, USA). EMG data was collected at 1000 Hz with a Trigno Wireless EMG system (Delsys Inc, Boston MA, USA).

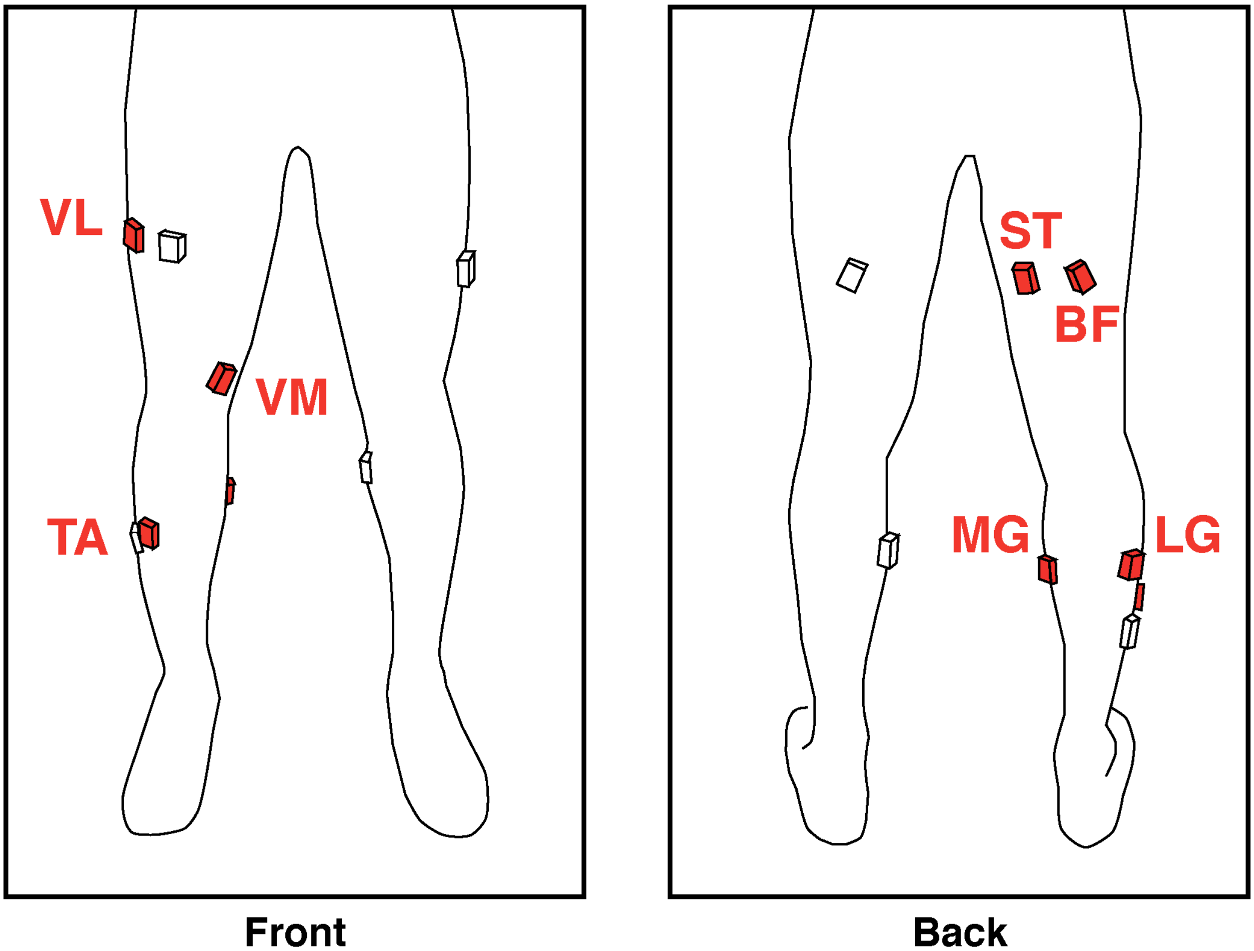

Figure 4.3:Electrode placement, with electrodes used in analysis highlighted in red.

EMG electrodes were located on both the affected and unaffected leg and hip, according to the SENIAM guidelines (Seniam, 2012) on the rectus femoris, vastus medialis, vastus lateralis, biceps femoris, semitendinosus, medial gastrocnemius, lateral gastrocnemius, tibialis anterior, soleus, glueteus maximums, gluteus medius, and tensor fascia lata. In this chapter, we only analyzed the data from the affected limb and the rectus femoris, vastus medialis, vastus lateralis, biceps femoris, semitendinosus, medial gastrocnemius, lateral gastrocnemius, tibialis anterior muscles, as shown in Figure 4.3. The positions of the vastus lateralis and medialis electrodes were adjusted distally from the SENIAM guidelines to avoid interference with the brace (even though it was not worn for the trials analyzed in this chapter).

4.6.1 Data Processing

EMG Data was rectified, filtered and normalized following the procedure in Section 4.2. Gait cycles were identified based on the foot contact with the force plates. One gait cycle for each condition was used, normalized to the peak value in all the trials for that subject for each muscle. Normalization to a dynamic maximum was used because of data loss in some subjects due electrode detachment prior to the MVIC trials.

The EMG waveforms were decomposed into scores using non-negative matrix factorization (NMF) as summarized in Figure 4.4. A large matrix of all of the EMG waveforms, with all subjects and all muscles was decomposed using NMF. The algorithm was the NNLS function from the NMF Toolbox for MATLAB developed by Li and Ngom (2013). This formulation (like all NMF algorithms) does not provide a truly unique solution, however; this algorithm was tested on this data set and arrived at stable solutions with insignificant differences between each run.

Waveform similarity (WS) for each pair was computed as the normalized dot product of the scores (W) from the NMF process (Tresch et al., 1999). For comparison, the co-contraction index (CCI) was computed based on Equation 4.1 over the same interval as the NMF factorization.

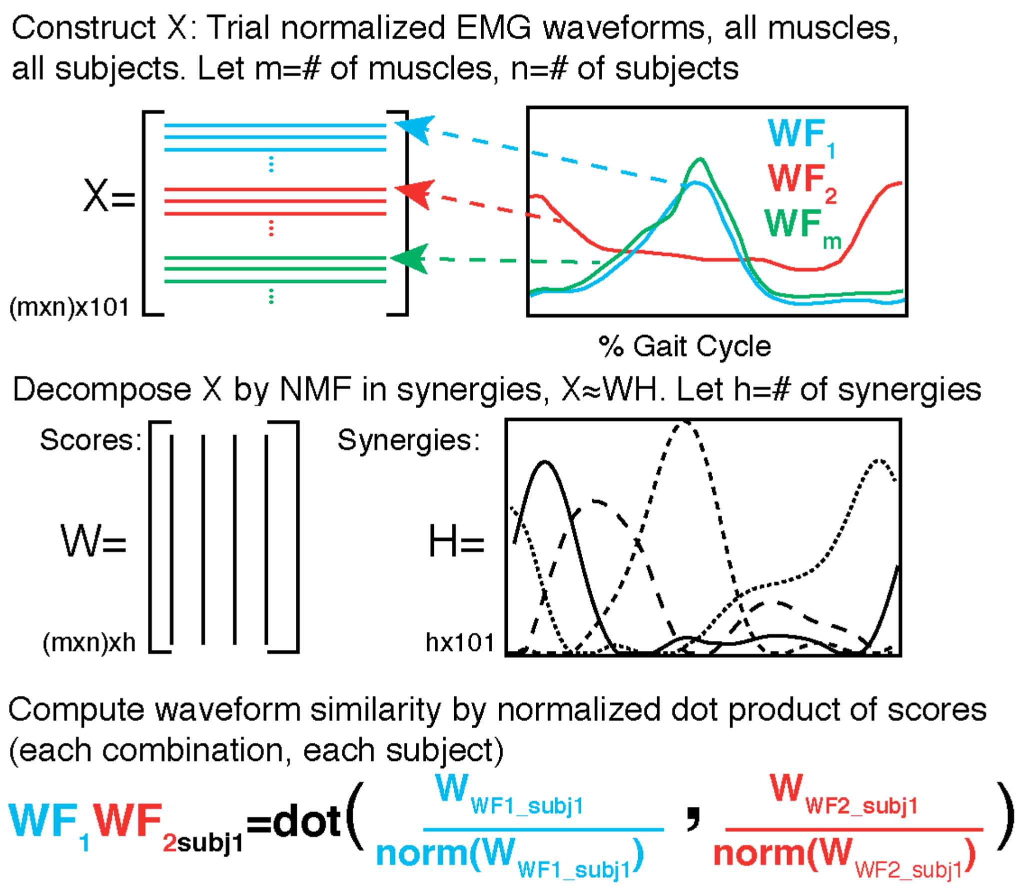

Figure 4.4: NMF process

4.7 Experiment 1: CCI vs. WS on Perturbed Data

4.7.1 Hypothesis

Examining Equation 4.1, the sum of the two signals at the end of the equation should make the co-contraction index sensitive to the overall magnitude of the signal, which is dictated by the normalization value. Therefore, the first experiment was designed to test the hypothesis that CCI computations are more sensitive to normalization value than waveform similarity by NMF (WS). It is hypothesized that the normalized dot product in WS computations will result in a value that is independent of normalization value, but the sum element in the CCI formula will result in the CCI value varying.

4.7.2 Methods

The base case was a single trial normalized waveform from each subject's Vastus Lateralis. We simulated the effect of varying normalization values using a scale factor ranging from 0.8 to 1.2 (plus-minus 20%), as shown in Figure 4.5. The CCI and waveform similarity by NMF was computed for each of the perturbed waveforms relative to the original (base case) waveform. This process was performed for each subject in the data set, but only one subject is shown in the results for clarity.

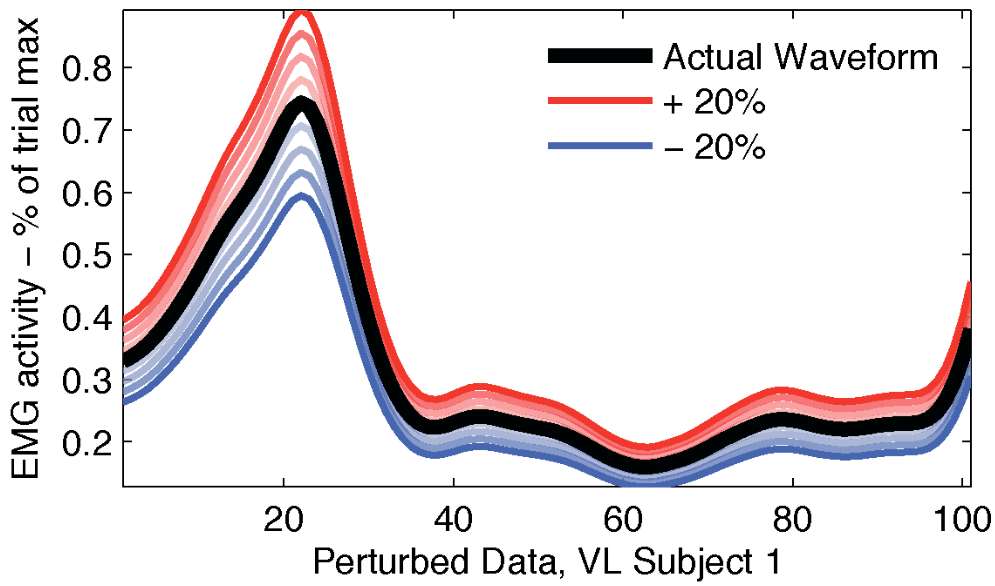

Figure 4.5: The "base" case is actual data, trial normalized (thick black line). The thin coloured lines are that waveform, perturbed by multiplying by a number from 0.8-1.2 simulating variation in the normalization value.

4.7.3 Results

As shown in Figure 4.5 waveform similarity by the NMF procedure is invariant and equal to one over the range of perturbation values. In contrast, the CCI ranged from 0.6 to 0.82 over the interval of perturbation values in the example subject. These values were typical for all subjects.

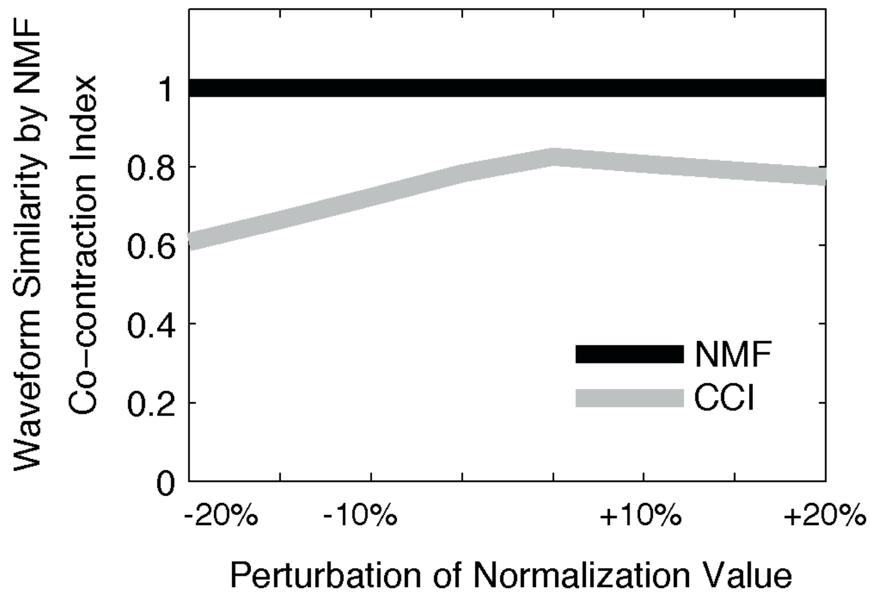

Figure 4.6: The NMF waveform similarity (WS) and CCI were computed between the base case and each perturbed waveform

The use of the dot product in the NMF co-contraction procedure ensured that the waveform similarity values were independent of normalization value, but the CCI was sensitive to normalization. Therefore, comparing the CCI values between muscles with different characteristics, subjects with different maximal activations during MVIC or different peak identification techniques may result in larger than desired variability, which has the potential to mask significant experimental results.

4.8 Experiment 2: Comparison of Muscle Pairs

4.8.1 Hypothesis

In the example in Section 4.7, the influence of normalization value on a single subject, single muscle was examined. However, in experimental data, there will be additional variability between muscles. This experiment was designed to test WS and CCI performance on muscle pairs.

4.8.2 Methods

The computations in this experiment follow an identical procedure to the example Section 4.7, except with respect to the matrix construction, which contained 36 subjects, all 7 muscles (vastus lateralis, vastus medialis, biceps femoris, semitendinosus, tibialis anterior, medial and lateral gastrocnemius). This process was repeated for all subjects, but only one is shown for clarity.

WS and CCI scores were computed for one subject for two muscle pairs, medial-lateral gastrocnemius and semitendinosus and vastus lateralis. These pairs were chosen to represent a set that was likely well synchronized (gastrocnemius) and a set that is likely asynchronous (hamstrings and quadriceps).

4.8.3 Results

The muscles of the gastrocnemius (medial and lateral) have a common insertion at the Achilles tendon and common function, plantar flexion of the ankle. Hence, they are expected to have similar patterns and magnitude. In contrast, the semitendinosus is a knee flexor and the vastus lateralis is a knee extensor, which serve opposite functions. Therefore, we would expect that the co-contraction of the medial-lateral gastrocnemius pair to be higher than that of the vastus lateralis-semitendinosus pair. However, when the CCI was computed for one subject, the value was 0.43. This is higher than the average CCI for the gastrocnemius pair, 0.19, even though visually the gastrocnemius pair is more similar (Figure 4.6). The NMF waveform similarity procedure gave a score of 0.95 for the gastrocnemius pair, and a lower score of 0.69 for the vastus lateralis-semitendinosus pair, as expected based on Figure 4.6. The reason for the discrepancy between the techniques was the difference in overall magnitude of the signals; in the case of the gastrocnemius there are large areas of low signal, meaning the sum portion (high+low) of the CCI calculation was low for much of the waveform. In contrast, the vastus lateralis-semitendinosus pair had an overall longer and higher duration of activity, and so even though the peak timing was different, the overall CCI was higher.

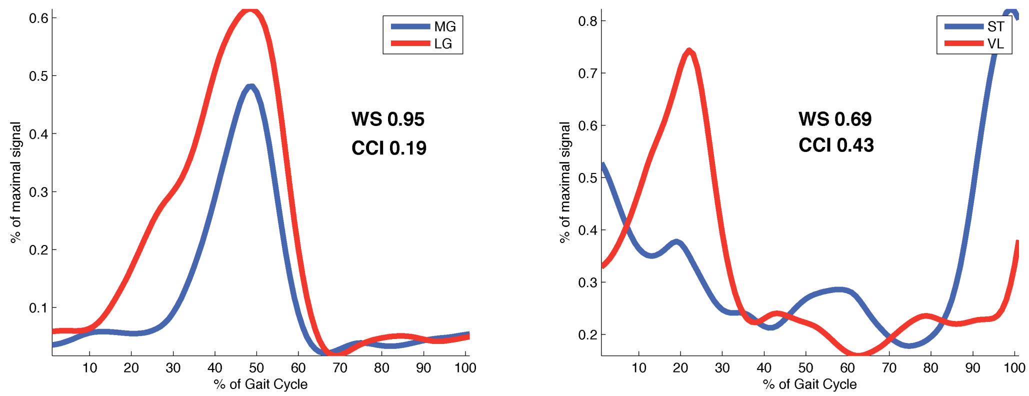

Figure 4.7: The CCI for the pair on the right (ST-VL) is higher than the one on the left (MG-LG), even though the signals on the left are more similar. In contrast, the difference is reflected in the NMF waveform similarity score.

4.9 Discussion

As shown by the two experiments in sections 4.7-4.8, WS provides an alternative to co-contraction indices, with several computational advantages, most notably the ability to summarize timing and shape data and independence from uncertainty regarding the normalization value. These properties make NMF waveform similarity measure more physiologically relevant and potentially less sensitive to subject-subject variability in magnitude. Other multivariate approaches, such as PCA are not independent of magnitude; in many cases the first PC extracted is the magnitude or an offset term. This is a key difference between PCA or factor analysis approaches and NMF; one that is important since it is acknowledged that raw EMG magnitude is not well-associated with force generation (Hug et al., 2015). Previous work has suggested that the time domain (curve shape) is more informative than the magnitude domain (Hortobágyi et al., 2005; Houck et al., 2007), and NMF analysis addresses the time domain more explicitly than CCI.

An important point to note is that CCI and WS serve different functions. A large CCI index indicates if two signals are both similar and both large. The magnitude independence of WS means that it quantifies how similar two signals are; that is, two signals that are both low could have the same WS score as two signals that are high. Therefore, a low WS score should be interpreted as "these signals are not synchronized," and a high NMF-WS score should be interpreted as "these signals are synchronized." Determining whether or not this score is related to increased or decreased joint contact force would require examination of the weightings and waveforms.

A drawback of NMF methods is that past work using this method can be difficult to interpret, as understanding a waveform as a sum of synergies and scores can be difficult for investigators unfamiliar with multivariate methods. However, the use of a dot product summarizes the waveforms as a scalar that is easy to understand. The positivity constraint ensures that indeterminacy with respect to the dot product is not possible (e.g. the dot product of two vectors at +90 and -90 degrees would both be 0, but -90 isn't possible with a positive constraint), and the use of a normalized dot product makes intuitive sense: opposite waveforms have a dot product of 0, identical waveforms have a value of 1, the closer the value to 1, the more similar the waveforms. The use of a dot product ignores the information given by the scores for each synergy, which could provide insight regarding *how* the waveforms are different (for example, is it in early stance or late stance that the waveforms are most similar?). Investigators interested in this level of detail would be able to interrogate the meaning of the synergies and scores the same way that is common in PCA analysis of biomechanics data,; Tresch *et al*. (1999) did this when they performed NMF on each animal individually and then compared the synergies' shapes for each animal in addition to analyzing the dot products.

The computational details regarding the extraction of the synergies is an important element to note when examining results generated by this technique. For example, Steele *et al*. (2013) noted that the number of different muscles included in the input matrix affects the synergies extracted, and although this paper was directed at modeling applications, it is an observation that is relevant to any researcher using this technique. The muscle synergies reflect the input data, change the input data, and the extracted synergies with necessarily change as well. Another limitation of this technique as noted by Tresch and Jarc (2009) and Burkholder and Van Antwerp (2013) was that the synergies typically reflect task constraints, for example the synergies extracted during cycling would be different from those during walking. However, in the case of most biomechanical analyses, data is only compared within tasks, and generalizing beyond the activity studied is rare, unlike the neuroscience applications that the Tresch and Jarc article was directed towards.

4.10 Conclusions

NMF formed the basis of an improved neuromuscular synergy measure with that is more intuitive and physiologically relevant than a conventional CCI measure. Of particular interest is the elimination of dependence on normalization value, which is a potential source of uncertainty. If researchers are confronted with large subject-subject differences in normalization values, or an incomplete set of MVIC normalization values, NMF provides an appealing alternative.

Chapter 5 : Neuromuscular indications of brace effectiveness

5.1 Introduction

Knee osteoarthritis has been described as a disease that is driven by joint mechanics, Felson (2013) stated that "once OA has developed, pathomechanics overwhelms all other factors," with abnormal joint loading playing a critical part in the "vicious cycle" of disease progression. This opinion is shared by numerous other authors including Andriacchi and Mündermann (2006) and Miyazaki *et al.* (2002).

The prominent role of mechanics in OA progression has resulted in interventions designed to address abnormal mechanics. Many of these interventions, both conservative and surgical, target the knee adduction moment; in general, patients with radiographic indicators of knee osteoarthritis tend to have a higher first peak knee adduction moment than control subjects (Baliunas et al., 2002; Lewek et al., 2004). Although this feature does not explain all of the variance in medial contact load in this group (Walter et al., 2010), it can be considered a surrogate measure for medial joint load (Andriacchi and Mündermann, 2006).

This chapter seeks to evaluate the role of neuromuscular patterns in the functionality of knee osteoarthritis braces. Since muscle activity contributes to the net knee joint load, it is logical to examine the activity of the muscles through EMG analysis and establish their relationship to the brace response

5.2 Background: Neuromuscular Signatures of Knee OA

One of the neuromuscular signatures of knee osteoarthritis is increased co-contraction of the muscles surrounding the knee (Astephen et al., 2008a; Heiden et al., 2009; Hortobágyi et al., 2005; Hubley-Kozey et al., 2006; Lewek et al., 2005; Schmitt and Rudolph, 2008), as summarized in Table 5.1 on the following page.

Table 5.1: Summary of studies of neuromuscular characteristics of knee OA during gait

Hortobágyi et al., 2005	Higher hamstring activation if OA
Lewek et al., 2005	More medial co-contraction if OA
Heiden et al., 2009 Hubley-Kozey et al., 2006	More lateral co-contraction if OA
Schmitt and Rudolph, 2008 Astephen et al., 2008b Zeni et al., 2010	Generally higher coactivity if OA
Childs et al., 2004	Longer activation and higher coactivity if OA

Increased co-contraction is hypothesized to be a stabilization strategy; Ramsey et al (2007) stated that "joint laxity and mediolateral instability necessitate increased muscle activity and co-activation of antagonist muscles to stabilize the knee." This rationale has been echoed by others, (Hubley-Kozey et al., 2009; Lewek et al., 2005), although it should be noted that knee "stability" is difficult to quantify objectively, and is commonly quantified by the patient's subjective perception of giving way. Another hypothesis was that increased lateral co-contraction reduces the medial joint load mechanically, by counteracting the knee adduction moment (Heiden et al., 2009; Hubley-Kozey et al., 2006). Heiden *et al*. (2009) highlighted the difference between these two hypotheses, terming them generalized and directed co-contraction.

A potential deleterious effect of increased co-contraction, whether directed or generalized, is increased joint contact forces, a consequence noted by multiple authors (Brandon, 2015; Lloyd and Buchanan, 2001; Ramsey et al., 2007). Increasing contact force in a group that already has increased medial joint loads could exacerbate the existing pathomechanics and increase the rate of disease progression (Brandon, 2015; Schmitt and Rudolph, 2008).

5.3 Knee Unloader Braces

Knee unloader braces were developed to address the knee adduction moment directly. These braces use three-point loading to counteract the higher knee adduction moment in this group and hence reduce the medial joint load (Ramsey et al., 2007), as shown in Figure 5.1. However, patients' response to bracing is not consistent: some patients experience a large reduction in the knee adduction moment while others do not. Over time, patient compliance is poor (Brouwer et al., 2006), which was attributed by Dessery *et al*. (2014) to a lack of perceived benefit and aesthetic concerns; Moyer *et al*. (2015) noted similar patient concerns.

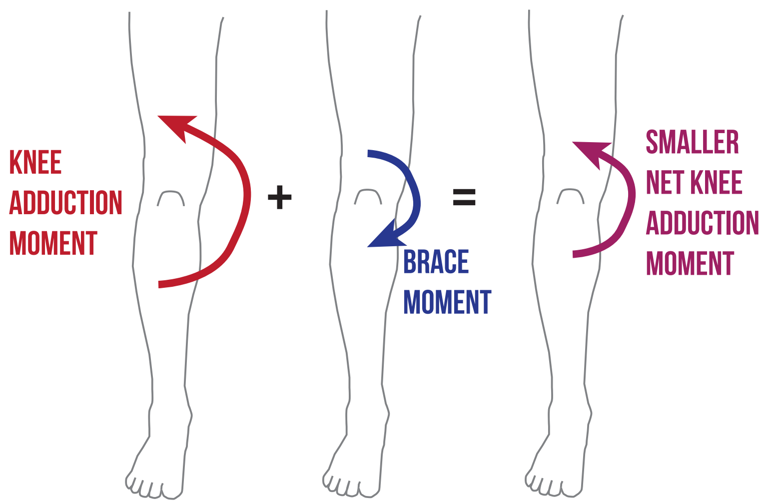

Figure 5.1: Schematic of brace function, the externally measured net knee adduction moment is countered by the moment applied by the brace in the opposite direction, resulting in a smaller net knee adduction moment.

A recent review of studies of brace effectiveness indicated that "Overall, there was a moderate-to-large, statistically significant difference favoring the valgus brace group for improvement in the KAM" (Moyer et al., 2015), with a mean reduction of about 10% of the external knee adduction moment. This amount of reduction is consistent with the KAM reductions presented in Brandon (2015) and Schmalz *et al*. (2010). Another review by Rannou *et al.* (2010) suggested that bracing's effects are "modest" and that unloader braces be combined with other conservative treatment options, an option echoed by the OARSI guidelines for the non-surgical management of knee osteoarthritis (McAlindon et al., 2014), who reported the evidence for effectiveness as being “fair” and use as a treatment “appropriate.” In contrast, other studies have indicated no effect of bracing, for example, Dessery *et al*. (2014) noted that none of the three braces they tested affected the first peak knee adduction moment, although these braces were not instrumented, as in the studies by Fantini Pagani (2012) and the work presented in this dissertation.

The mechanism for brace effectiveness is still ambiguous; one rationale is that they act mechanically by changing the alignment. Komistek *et al*. (1999) noted that unloader braces alleviated pain by separating the medial condyles during gait, as observed with fluoroscopy during walking. This study did not simultaneously evaluate the joint biomechanics, but noted that obese subjects were not able to achieve condylar separation and did not experience a reduction in pain. The alignment rationale is supported by studies that noted a variance in response dependent on static alignment; Gaasbeek *et al*. (2007) noted that pain reduction with bracing was higher for patients with more varus malalignment. In contrast, Fantini Pagani *et al*. (2012) noted that the knee adduction moment reduction was not related to the baseline (unbraced) varus alignment and the knee adduction moment was reduced even if the brace was not adjusted (no load applied to the knee). This finding prompted Moyer *et al*. (2015) to propose investigations beyond the frontal plane kinematics and kinetics.

An alternative rationale for brace effectiveness is that bracing reduces co-contraction, and hence the medial contact force. This was introduced by Ramsey *et al*. (2007), who stated that “when a brace is worn for the treatment of medial compartment osteoarthritis of the knee, pain relief may be the result of reduced muscle co-contraction, mediated by the brace mechanically stabilizing the knee.” Reduced co-contraction as a result of bracing has been reported by the Ramsey study, along with Fantini Pagani *et al*. (2013). The specific patterns of reduced co-contraction are different between the studies; Ramsey found that the vastus lateralis-lateral hamstring co-contraction changed, and Fantini Pagani *et al*. (2013) found that the medial lateral co-contraction was affected by bracing. The timing of the changes also was different between the studies, with Fantini Pagani reporting pre-contact and late stance changes and Ramsey reporting changes around the time of the peak knee adduction moment. Muscle activation has been related to a substantial portion of the joint contact load by modeling studies (Winby et al., 2009), so it is possible that co-contraction contributes to brace effectiveness and may explain some of the variance in brace response. It should be noted that all of these studies quantified the response to bracing based on the co-contraction index or co-contraction ratios.

5.4 Rationale

Based on the wide spectrum of past mechanical and neuromuscular findings related to knee osteoarthritis, we hypothesize that brace effectiveness will be related to neuromuscular patterns, specifically to those during unbraced gait. Given the potential subject-subject variability in EMG analyses, we propose that a multivariate approach using waveform similarity is warranted.

5.5 Methods

5.5.1 Data Collection

The data set used for this chapter was collected as part of a larger study of bracing for knee osteoarthritis, as described in Brandon (2015). This study was approved by the institutional ethics review board. Participants completed a WOMAC questionnaire and provided written informed consent.

This chapter presents EMG data from the 17 osteoarthritic subjects walking overground with and without an off-the-shelf osteoarthritis brace. The brace was an OA Assist Brace (DJO Global, Vista, CA, USA). This brace applied a 3-point load, with a lateral beam and screw based load adjustment mechanism.

The participants were instrumented with a full body data set of 81 retro-reflective markers, which were observed with 11 Qualisys Oqus Cameras (Oqus 400, Qualisys, Gothenburg, Sweden) at 200 Hz. The participants walked across six tandem force platforms (4x custom BP model, 2xBP400600NC, AMTI, Watertown MA, USA). EMG data was collected at 1000 Hz with a Trigno Wireless EMG system (Delsys Inc, Boston MA, USA). The applied brace moment was calculated using on markers on the brace and the brace deflection was multiplied by the calibrated brace stiffness, as described in Brandon (2015).

EMG electrodes were located on both the affected and unaffected leg and hip, according to the SENIAM guidelines (Seniam, 2012) on the rectus femoris, vastus medialis, vastus lateralis, biceps femoris, semitendinosus, medial gastrocnemius, lateral gastrocnemius, tibialis anterior, soleus, glueteus maximums, gluteus medius, and tensor fascia lata, as shown in Figure 5.2. In this chapter, we only analyzed the data from the affected limb in the unbraced condition, the vastus medialis, vastus lateralis, biceps femoris, semitendinosus, medial gastrocnemius, lateral gastrocnemius, tibialis anterior muscles. The positions of the vastus lateralis and medialis electrodes were adjusted distally from the SENIAM guidelines to avoid interference with the brace (even though it was not worn for the trials analyzed in this chapter).

The response variable, Y, was quantified as the percent difference in peak knee adduction moment (selected from 0 to 40% of the gait cycle) between unbraced and braced overground walking conditions.

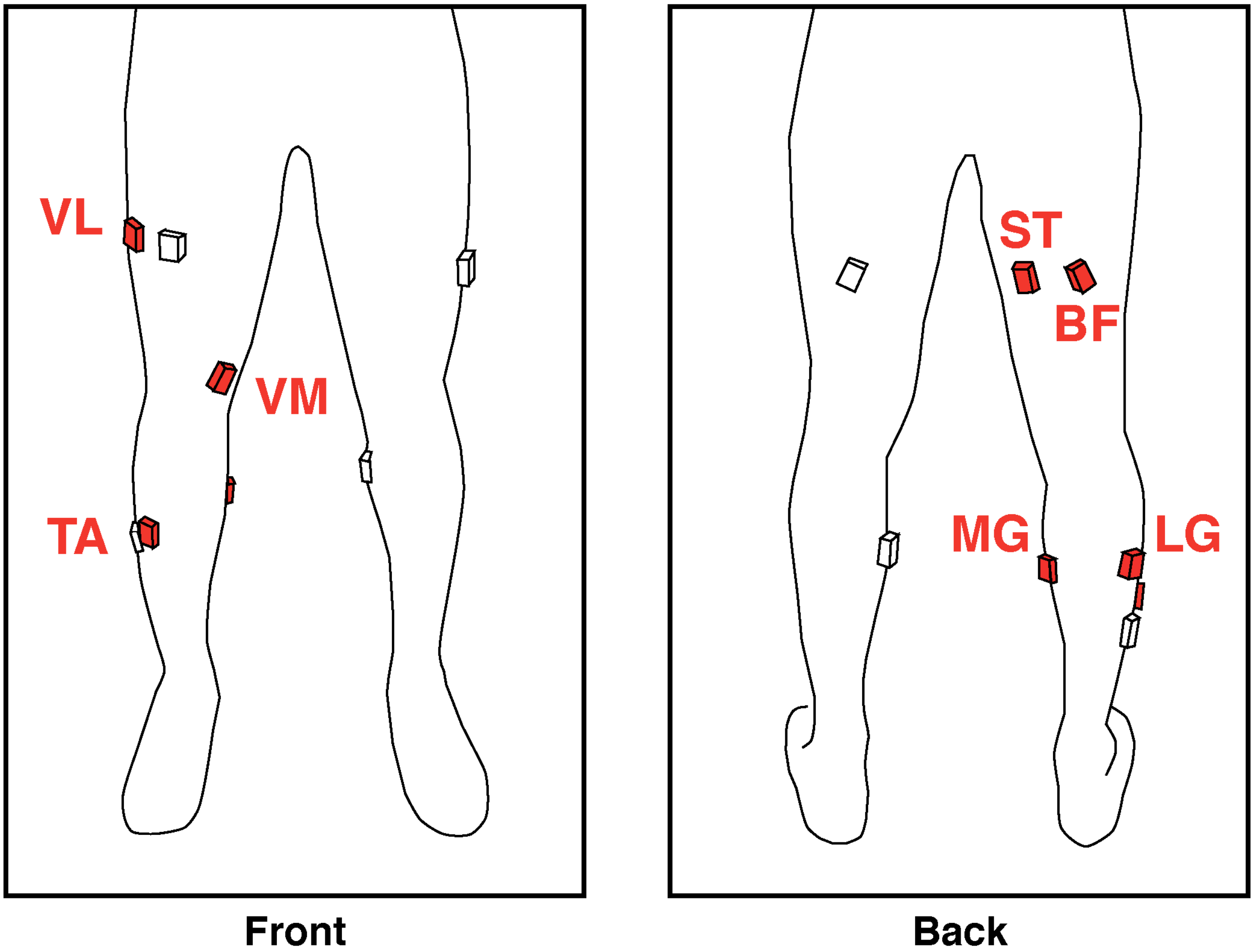

Figure 5.2: Location of EMG electrodes, the electrodes used in this analysis on the affected limb are highlighted in red. The VL electrode was adjusted distally for brace position.

5.5.2 EMG processing

EMG Data for one stride per subject was rectified, filtered and time normalized to gait cycle (Hubley-Kozey et al., 2006) in MATLAB (MathWorks, Natick, MA, USA). This process is described in detail in Chapter 4, Figure 4.1, briefly the procedure was as follows:

- Signal rectified
- Bias removed using value from resting trial
- Band pass filter at 20 and 450 Hz

- Linear envelope with zero-lag dual pass Butterworth filter at 6 Hz
- Normalized to dynamic maximum in all gait trials

5.5.3 NMF and PLS

A matrix (X) was constructed of the processed EMG waveforms (unbraced condition, ipsilateral limb) for 7 muscles for all subjects (both OA and control), as described in Figure 5.2. The muscles were the Vastus Meidalis (VM), Vastus Lateralis (VL), Semitendinosus (ST), Biceps Femoris (BF), Medial Gastrocnemius (MG), Lateral Gastrocnemius (LG) and Tibialis Anterior. The entire gait cycle was included so that the epochs identified by both the Fantini Pagani et al. (2013 and the Ramsey et al. (2007) studies would be included (pre-contact, peak knee adduction moment and late stance).

This matrix (X) was decomposed into four muscle synergies (H) and corresponding scores (W) using NMF, which is similar to principal component analysis (PCA) but with a positive constraint. The *nmfnnls* algorithm minimizes the least squares difference between the synergy model (WH) and input data (X) (Li and Ngom, 2013). This formulation (like all NMF algorithms) does not provide a truly unique solution, however, this algorithm was tested on this data set and arrived at stable solutions with clinically insignificant differences between each run.

Waveform similarity (WS) was computed as the normalized dot product of the NMF scores between muscles (Tresch et al., 1999). Each muscle pair for the osteoarthritic subjects (17 in total) was combined to form a matrix (Z), which was analyzed with Partial Least Squares (PLS). Seven muscles resulted in 21 muscle pairs; this set was reduced to a more manageable set of four using the iterative criteria described in Andersen and Bro (2010). The output of the PLS was a set of regression weightings that identified the four most important muscle pairs for predicting the percentage change in the KAM between the braced and unbraced conditions, which was the Y variable. The stability of the PLS model was tested over 10,000 repetitions with leaving one observation out to ensure that the model was not related to a single outlier observation(Abdi, 2010), a risk when working with small sample sizes . The model identified was the most frequently occurring.

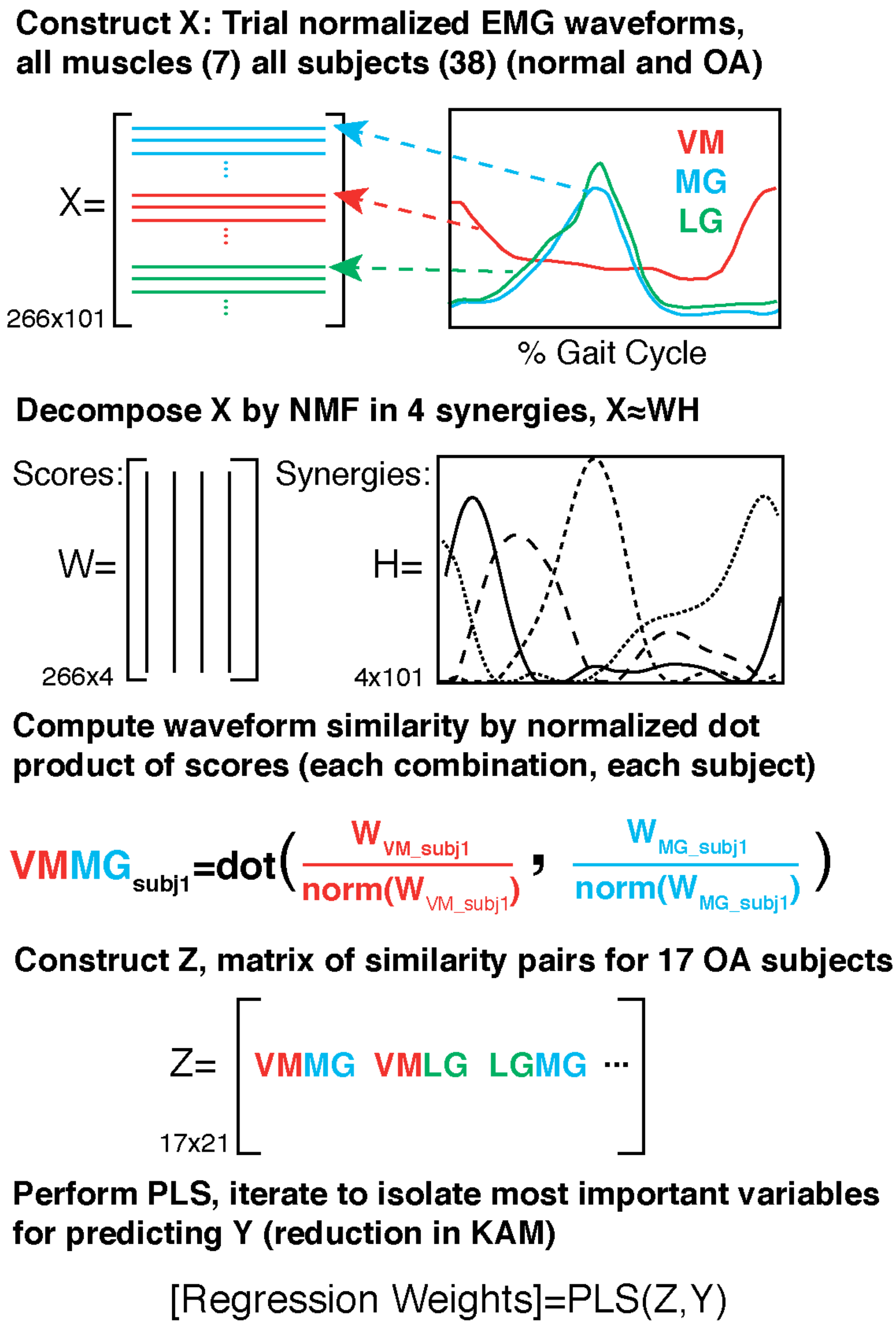

Figure 5.3: Analysis Workflow

5.6 Results

5.6.1 Predictors of brace effectiveness in OA subjects

Four predictors explained 74% of the variance in brace response for the OA subjects, with brace effectiveness defined as reduction in the knee adduction moment with brace use compared to the unbraced condition. The predictors of brace effectiveness were: BF-VL (Bicep Femoris-Vastus Lateralis), BF-VL (Bicep Femoris-Vastus Medialis), LG-MG (Lateral-Medial Gastrocnemius) and MG-VM (Medial Gastrocnemius-Vastus Medialis), as shown in Figure 5.4. The regression weights were 0.38, 0.35, -0.37 and -0.37. This indicates that all four pairs were of roughly equal importance, and that brace effectiveness was associated with highly synchronized BF-VL and BF-VM activity and less synchronized LG-MG and MG-VM activity. Typical waveforms for highly synchronized and less synchronized activity are shown in Figure 5.5. The NMF model used to calculate these synergies achieved a variance accounted for (VAF) of 81%, an acceptable value.

Kinematic, kinetic, and radiographic alignment features were also tested for their ability to explain variance in response to the brace; however, none of them matched the performance of the neuromuscular pairs, with mechanical factors only able to explain 50% of the variance. In a combined mechanical and neuromuscular analysis, only one mechanical factor survived the selection process, the first PC of the ankle inversion-eversion moment, corresponding to the magnitude. This factor provided only 10% of the total 74% variance explained.

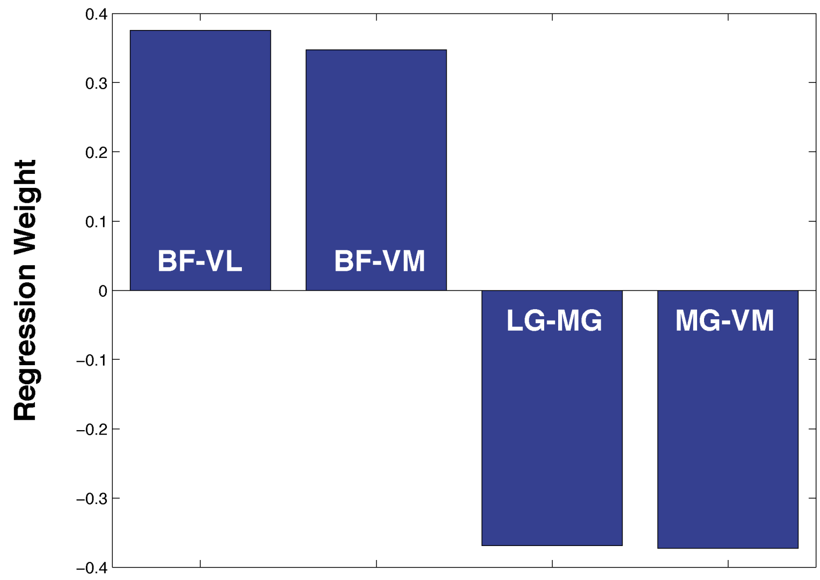

Figure 5.4: Regression weights of extracted variables explaining brace effectiveness

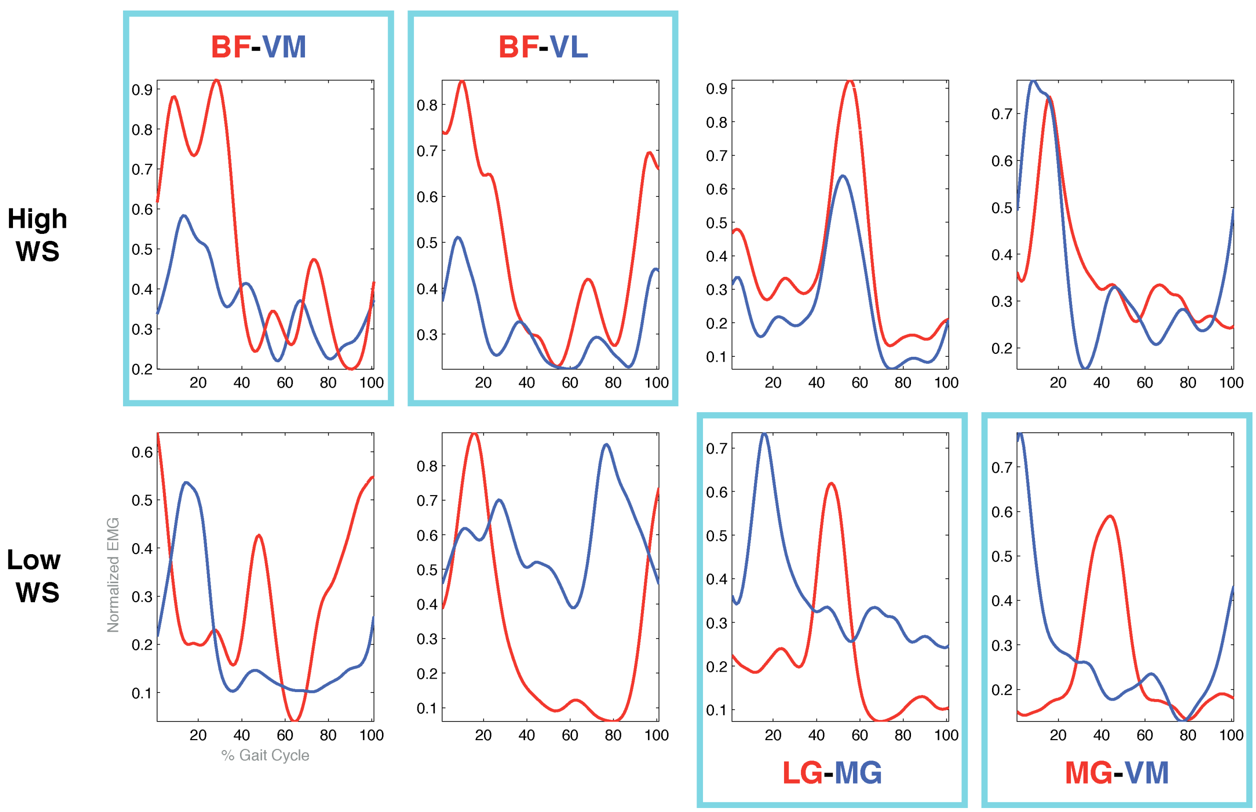

Figure 5.5: Typical EMG waveforms for both high and low WS scores. Conditions corresponding to brace effectiveness are highlighted in light blue

5.6.2 OA vs control

The PLS process was repeated on the normal subjects (n=21). The brace effectiveness (defined as reduction in the knee adduction moment with brace use compared to the unbraced condition) was less related to neuromuscular factors for the normal subjects, with only 33% of the variance explained compared to 73% for the osteoarthritis subjects, as shown in Figure 5.6. The variables that were identified by the iterative process were different from the osteoarthritic subjects, as were the weights, as shown in Figure 5.7.

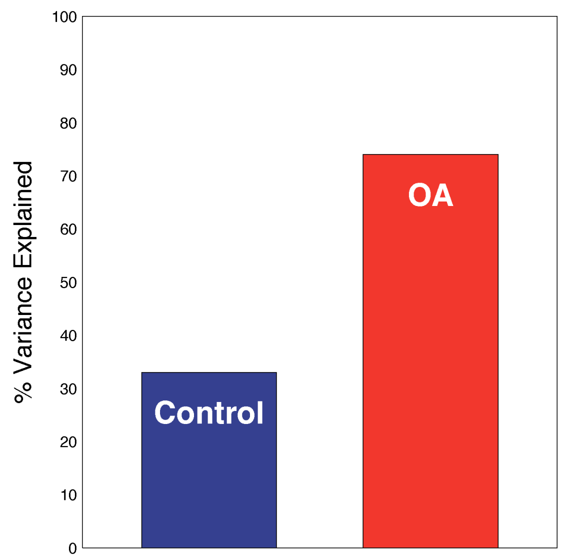

Figure 5.6: The brace response variance explained by the neuromuscular WS measures for the control subjects was 33%, compared with 74% for OA subjects.

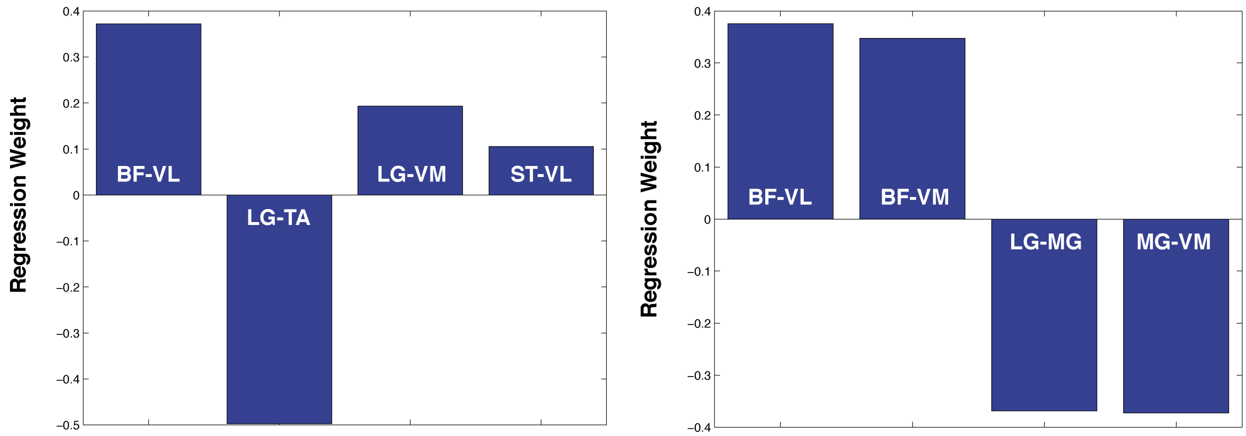

Figure 5.7: Comparison of neuromuscular factors relating to brace effectiveness for control (left) and OA subjects (right)

5.7 Discussion

A novel finding, distinct from past work is that it was not simply elevated co-contraction in general that dictated brace effectiveness, but also a specific pattern of increased and decreased synchronization. Increased co-contraction in osteoarthritic subjects has been previously reported in the literature (Hubley-Kozey et al., 2006), but this is the first known work to link coordination with the effectiveness of a knee brace in reducing the KAM.

A second novel finding of this work is the identification of a potentially different mechanism of brace effectiveness in OA and control subjects. Previous studies have included a control group either for comparison or on its own in bracing studies (Fantini Pagani et al., 2010). Our results indicate that this may not yield informative results relating to arthritic subjects, since the osteoarthritic subjects brace response seem to be dominated by neuromuscular factors, but in controls, neuromuscular factors are not predictive. This makes sense given the previous literature suggesting that osteoarthritic patients have more co-contraction in general amongst osteoarthritis patients.

The identification of these quantities was made possible by the combination of multivariate techniques, NMF, and PLS. Initially this analysis was attempted with a stepwise linear regression in place of the PLS step, but the collinearity dependence of the stepwise technique (Wold et al., 1984) resulted in poor stability from between runs. Similarly, the use of a conventional co-contraction index would have masked the results due to the variability in the EMG normalization magnitudes. Other work (Winby et al., 2009) has indicated that EMG magnitude is poorly correlated with joint force production, so a magnitude independent measure of neuromuscular activity may be appropriate when commenting on attempts to reduce the medial joint load.

Our rationale for defining brace effectiveness as the percentage change in the 1st peak KAM is supported by a similar studies that used the percentage change in the external knee adduction moment for a study of bracing (Dessery et al., 2014; Fantini Pagani et al., 2010). Other studies have indicated that the external knee adduction moment is not a perfect surrogate for the internal medial contact force (Walter et al., 2010). These authors suggest that a full musculoskeletal model is required to comment on reductions in medial contact force. However, the studies that point out the difference between medial contact force and external knee adduction moment are on a small number of patients with instrumented total knee replacements. In the case of the Kutzner *et al*. (2011) study, this patient had a total knee with neutral alignment and no pain, which is atypical of patients with moderate osteoarthritis, particularly those who respond to bracing as a result of varus malalignment, a factor noted by Ramsey *et al*. (2007).

In comparison to the neuromuscular findings from Fantini Pagani *et al*. (2013) and Ramsey *et al*. (2007), the role of hamstring and quadriceps activity is similar. Ramsey suggested that the brace mechanism is the result of altered co-contraction as a result of the brace. Our data set did not contain a sufficient number of subjects with good braced data to conclusively disprove this, but examining the pairs that Ramsey identified for the 8 subjects for whom we had complete data, this does not seem to be the case in our data set. As shown in Figure 5.8, there are no differences in the waveform similarity between the braced and unbraced condition for the pairs identified by Ramsey. Therefore, we can tentatively suggest that rather than bracing affecting the neuromuscular pattern and reducing pain, there is something inherent in the patients' unbraced neuromuscular pattern that enables the brace to function. This is a cautious suggestion, because the sample size is small, and the patients only wore the brace on one occasion. It is possible that more sustained brace use could confound these findings, or that the populations of the Ramsey study and the current data set are different.

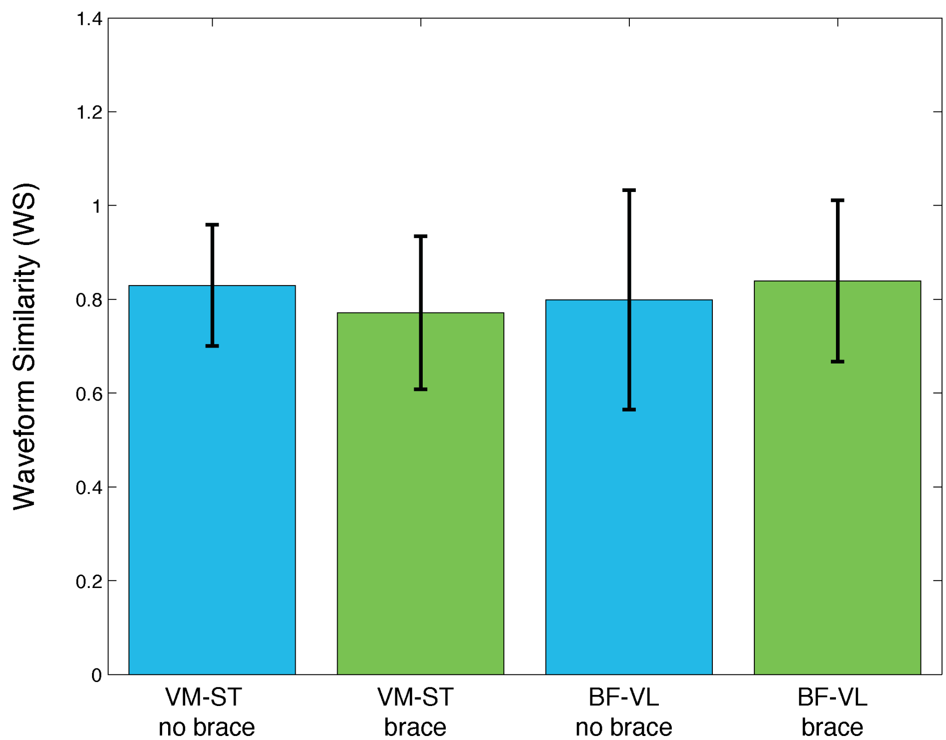

Figure 5.8: Comparison to Ramsey et al (2007) findings

5.8 Conclusions

Implementation of a NMF-based waveform similarity measure (WS) and PLS showed that brace effectiveness is related to neuromuscular patterns in knee OA patients, but that response is more nuanced than overall elevated co-contraction. This mechanism was different in control subjects and OA subjects, which suggests that brace function is different in these groups, and caution should be used if a brace is validated on control subjects.

The importance of selective synchronization of the quadriceps and hamstring muscles to brace response suggests that it may someday be possible to use biofeedback to train patients to use their brace more effectively, or screen potential bracing patients based on their neuromuscular patterns.

Chapter 6 : Conclusions and final thoughts

6.1 Key conclusions

The central, overarching topic of the thesis, as described in Chapter 1, was to develop ideal methods for analyzing biomechanical findings, with ideal being one that addresses the challenging aspects of the data, variability and collinearity, while simultaneously retaining physical interpretability. This was achieved by applying the multivariate techniques sequentially and at each stage matching the technique to the characteristics of the specific data type. Processing angles and moments with PCA is a literature-supported choice for data reduction, and further variable selection with PLS allows for optimized discriminant performance.

The value of PLS as a valid variable selection strategy was repeatedly proven in Chapters 2, 3 and 5. In particular, it is notable that it was successful as a structure seeking technique because it identified variables that were previously identified by past literature as being related to knee osteoarthritis. This is an indication that the PLS procedure is objectively identifying valid clinical targets, which addresses one of the major concerns with multivariate analyses in general.

A feature of PLS that enabled a novel clinical finding in Chapter 3 is the possibility of multiple, continuous response variables (Y). Simultaneous analysis of multiple response variables is a new technique in biomechanics.

In Chapter 4, the application of NMF enabled an entirely new technique for neuromuscular analysis in gait. The newly developed technique results in easily interpretable scores that can be combined into an intuitive measure of neuromuscular coordination. In Chapter 5, this was used to identify neuromuscular factors that could predict effectiveness of a conservative treatment for knee osteoarthritis. These factors were more predictive of brace response than mechanics, a new finding.

6.2 Clinical findings related to Knee Osteoarthritis

This thesis presents two major new findings relating to knee osteoarthritis of relevance to both primary care health care providers and brace designers. The first is the new relationship between the knee adduction moment and pain and radiographic severity. Although the knee adduction moment is well linked to radiographic severity by past studies, our work suggests that the knee adduction moment-severity relationship is mediated by pain in moderate OA subjects.

The second new finding is the importance of neuromuscular factors in brace response. The neuromuscular patterns identified are more nuanced than overall elevated co-contraction and this mechanism was different in control subjects and OA subjects, which suggests that brace function is different in these groups. The variance explained by neuromuscular patterns is high, 74%, more than mechanical factors.

6.3 Technical Recommendations

The generalized multivariate analysis procedure proposed by this thesis can be summarized as:

1. Pre-process data as appropriate (e.g. filter marker trajectories, filter and normalize EMG waveforms).
2. Arrange the data into input matrices, one row per condition and subject. Process each input matrix with either PCA (angles and moments) or NMF-WS (EMG).
3. Arrange the scores from the PCA and/or NMF-WS into a matrix X, one column for each PC score or NMF-WF score.
4. Arrange the response variable(s) in Y, one column for each response.

5. Run PLS with iterative variable selection on X and Y until the desired number of variables in X is achieved.
6. Interpret scores or weightings, possibly with MLR or LDA.

Alternate methods are possible at each step, for example, multiple different methods such as Factor Analysis would be similar to NMF, and Canonical Correlation Analysis could substitute for PLS, and multiple different formulations of variable selection are possible within PLS. This methodology isn't held as truly "ideal," but as one that both reflects the characteristics of the data and has also been tested thoroughly.

One of the major difficulties with these methods are the subjective analysis choices that must be made at each step of the process. Although many analysis methods require choices such as choosing a significance level or variable selection criteria, it is particularly important in techniques such as PLS or PCA to avoid over fitting. The following analysis strategies are proposed based on the author's experience:

- Cross-validation is important, particularly with small samples. The approach described by Szymańska *et al*. (2012) and used in Chapter 2 is particularly suited to discriminant problems. In the other analyses, leave one out procedures were used. These are simple to implement and provide some indication as to how much a single remarkable observation influences the data. If the cross-validation process reveals large differences run-run, the analysis is not stable and therefore not suited to these techniques.
- Overreliance on measures such as the R2, PRESS, RESS, and VAF statistics should be avoided. Although they are appealingly quantitative, in the case of discriminant applications they are meaningless (since they are better suited to continuous variables), and can lead to over fitting. Stability in the face of cross-validation is more important.

- If a variable survived the process but doesn't make physical sense, it should be manually interrogated. This is a sign of a possible outlier, or a problem with the pre-processing (e.g. the wrong principal component in the wrong column, a filtering problem, a calculation problem).
- Depending on the PCA algorithm, the sign of the PC scores may not be intuitive. To avoid confusion when interpreting the weightings, it is useful to reconstruct the waveforms and examine the principal component directions manually.
- The correct number of components or synergies to extract by PCA, PLS, and NMF is a topic of intense debate in the literature. My approach was to use a conventional 90% trace approach for PCA, up to a maximum of 3 components. If I had included 4 components the analysis likely would have been much the same, since the 4th variable in these data sets explain so little variance it likely would not have survived the variable selection process. In PLS, I chose two latent variables. In the case of Chapter 2, this allowed for the discriminant analysis to be visualized easily and was the smallest number of components that achieved a suitable discriminant function. In the case of NMF analyses, I used 4 synergies because this was a literature-supported choice that reconstructed variables suitably well. Using 3 or 5 synergies yielded similar results.

Although there is apparent subjectivity in the choices required in an analysis such as this one, which presents the peril of misapplication, another framing is that this approach allows for flexibility with respect to the particulars of a given analysis. Although it requires expertise and manual checks, this approach of combining multivariate techniques is a proven way to analyze multiple response variables in the case of variability and correlation.

6.4 Future work

Multivariate approaches such as this provide an almost unlimited potential to data mine old data sets in search of new findings, as we did in Chapter 2. I think that this is a valuable potential application of this work. Equally interesting would be the potential to aggregate data from multiple labs by using the lab identification as a variable, which would allow the variables that change between labs to be identified, as well as the ones that are invariant.

The experiment in Chapter 5 merely skims the surface of neuromuscular analysis relating to bracing or other conservative interventions for knee osteoarthritis. The preliminary work on the subset of braced data that is complete suggests that the neuromuscular patterns are fairly invariant between the braced and unbraced conditions. This finding is parallel to the work in the ACL literature relating to some patients being "copers" and "non copers," people who are either able to dynamically stabilize their knee or not. The idea of an osteoarthritis patient having a neuromuscular pattern that dynamically stabilizes the knee, and that pattern being inherent to the patient, is an exciting new concept in the osteoarthritis literature, and one that merits further work.

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