Latent Class and Functional Data Analyses for the Investigation of Stiffness in Low Back Pain

by

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Abstract

Low back pain (LBP) is known to be a prevalent, debilitating and costly condition, not to mention the difficulty clinicians have treating it. But progress has been made, as it has recently been shown that instrumented L3 indentation generates force-displacement (F-D) data that is associated with patient-reported measures of disability. This is the first quantitative measure positively linked with a specific patient outcome. As such, F-D curves may be key in successfully sorting patients to appropriate treatments for LBP. Unfortunately, only single value representations of the complex biomechanical response described by these plots (e.g. terminal stiffness, regional stiffness) have been analyzed to date. A more thorough understanding of F-D data may improve success rates for treatment of LBP in a similar way that a thorough understanding of other biomechanical responses, such as an ECG, have allowed clinicians to identify patients at risk of disease or disability. As such, two specific functional statistical analysis techniques, functional data analysis (FDA) and latent class analysis (LCA) will be applied in an attempt to analyze and classify F-D curves in their entirety. Specifically, the three hypotheses that follow were tested in three separate experiments, each comprising a chapter in this thesis:

1. Functional data analysis (FDA) and a latent class analysis (LCA) will be able to cluster simulated functional data equally well. Since this is a novel application of LCA, a comparative application to a known technique is important.
2. FDA and LCA will perform at least as well as traditional statistics to cluster experimental F-D curves with a large effect size. Knowledge of FDA and LCA performance with respect to traditional statistics will guide interpretation of results when analyzing true clinical patient data.
3. FDA and LCA will perform at least as well as traditional statistics to identify clinical patient F-D curves after successful application of a LBP intervention. The findings developed and analyzed here would inform further work to enhance interpretations of stiffness with respect to patient outcomes.

The results of the first experiment served to identify that LCA emphasizes end values and overall curve proximity ahead of distinctive features of curve shape, while FDA emphasizes rates of change. In the second experiment, the FDA method performed as expected and grouped F-D curves by salient features of shape, though this did not associate with any specific patient identifiers. The dimensionality of the data did not maintain sufficient degrees of freedom for effective investigation by LCA. The third and final investigation did not perform as well as

anticipated, since a small effect size diminished the overall performance of fPCA. Again, dimensionality of the F-D data limited LCA analysis to only two clusters, neither of which were meaningful.

While outcomes of the second and third experiments were not as definitive as anticipated, valuable information with respect to F-D curve analysis was gleaned. Specifically, regional and terminal stiffness do not discard relevant biomechanical data in the case of post-hoc identification of responders and non-responders to a specific treatment.

As identifying the salient features of F-D curves could streamline and expedite the process of assigning appropriate treatment to LBP patients, thereby saving clinical cost, time and reducing frustration for patients, a thorough understanding of the stiffness phenomenon holds promise, since it has already been definitively linked to patient-reported recovery. Based on this work, some specific recommendations for data collection and analysis have emerged. Explicitly, a lack of correlation to measured demographics data may signal a need to collect different data, and it is therefore recommended that a comprehensive list of LBP risk factors be assembled and reviewed to ensure data collection is thorough. In terms of analysis, FDA requires a secondary step. This work employs a k-means clustering algorithm, but hierarchical clustering methods have been applied to biomechanics with success, and it may also be of interest to apply the LCA method in the secondary analysis. In addition, a time-based bivariate analysis, F-D phase-plane plots, or a piecewise curve analysis approach may emphasize information that is otherwise not apparent. Future work would ideally link quantitative stiffness measures to other clinical assessments including MRI, experimental biomechanics of functional spinal units, and theoretical biomechanical modelling to develop a full understanding of the stiffness phenomenon and the component motions comprising a bulk measurement of force and displacement.

Dedication

I would like to dedicate this thesis to my family. To my husband for supporting me throughout this journey, and especially to my two baby girls. You two littles have taught me more than words can convey.

"I love you right up to the moon – and back."
~Sam McBratney

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In addition to the mentorship and guidance provided by my primary advisor, I would be remiss to omit an extension of gratitude to Dr. Narasimha Prasad. Without his wise guidance in the statistical techniques applied in this thesis, I'm not sure I would have even known where to start. It is because of Dr. Prasad that I even know the words 'functional data analysis'. His guidance at the start of my journey to use the CRAN R Statistical Computing Environment is very much appreciated.

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Alphabetical List of Abbreviations

χ^2 ..... Pearson's chi-squared
κ ..... Cohen's kappa
λ ..... Smoothing Parameter
μ_D ..... Mean Difference
ADC ..... Apparent Diffusion Coefficient
b-spline ..... Basis Spline
BIC ..... Bayesian Information Criterion
CI ..... Confidence Interval
DD ..... Disc Degeneration
DoF ..... Degrees of Freedom
ECG ..... Electrocardiogram
F-D ..... Force-Displacement
FANOVA ..... Analysis of Variance of Mean Functions
FDA ..... Functional Data Analysis
FJ ..... Facet Joint
FJD ..... Facet Joint Degeneration
fPC ..... Functional Principle Component
fPCA ..... Functional Principle Components Analysis
GCV ..... Generalized Cross Validation Variable
GS ..... Global Stiffness
H_0 ..... Null Hypothesis
H_1 ..... Alternate Hypothesis
HANOVA ..... High-Dimensional Analysis of Variance
HS ..... Hypertonic Saline
IVD ..... Intervertebral Disc
L^2 ..... Likelihood Ratio chi-squared
L3 ..... 3rd Lumbar Vertebra
L4 ..... 4th Lumbar Vertebra
L5 ..... 5th Lumbar Vertebra
LBP ..... Low Back Pain
LC ..... Latent Class
LCA ..... Latent Class Analysis
LCRA ..... Latent Class Regression Analysis
LM ..... Lumbar Multifidus
MCID ..... Minimal Clinically Important Difference
ML ..... Maximum Likelihood
mm ..... millimeters
mODI ..... Modified Oswestry Disability Index
N ..... Newtons
NS ..... Isotonic Saline
PI ..... Probability Interval
R ..... CRAN R Statistical Computing Environment
r ..... Pearson's r Correlation Coefficient
SDA ..... Stepwise Differential Analysis
SMT ..... Spinal Manipulation Therapy
t ..... t-Statistic
TS ..... Terminal Stiffness
VARIMAX ..... Maximization of Variance

1. Introduction

Spinal stiffness is one quantitative measure that may be key in successfully separating patients who respond to a specific conservative low back pain treatment from those who likely will not. The importance of assigning the right patient to the right treatment at the right time cannot be understated in the case of something as prevalent, debilitating and costly as low back pain. This work was an attempt to analyze and classify measured force-displacement (stiffness) curves in their entirety, rather than using single-point representations of a full biomechanical measurement as has been done in the past. A background section commences this thesis to provide an overview of the state of low back pain science and treatment, including a section detailing the problem with patient diagnosis. Next, the objectives of the work contained herein are discussed, including motivation, hypotheses and rationale for the investigations that were undertaken. Three separate sections containing the specific methods, results and interpretations for each objective follow. A summary section outlining the implications for future work rounds out the discussion and concludes the document.

2. Background

Low back pain is an interesting and enigmatic challenge and the stakes are high, for the individual experiencing what can sometimes be debilitating pain, for the healthcare system upon whose shoulders it rests to properly diagnose, treat and resolve the problem, and for society who collectively foot the bill. The knowledgebase is therefore rich and extensive, and covers wide-ranging topics from qualitative studies of lived experiences to quantitative studies of intrinsic biomechanical phenomena. The discussion below is but a sample of the breadth and depth of the information available, and has been necessarily tailored to the investigation of spinal stiffness upon which this work focuses.

2.1 A Brief Overview of Low Back Pain

Most adults will experience low back pain (LBP) in their lifetime[2]. Recent estimates of costs related to LBP run from $7B to $10B annually; nearly a quarter of federal healthcare expenditures in Canada[3-5]. It ranks among the top three reasons for adults aged 18-65 to visit their doctor and while most common among the middle-aged, it is prevalent in all age categories[6, 7]. Unfortunately, less than 20% of cases are attributable to a diagnosable underlying pathology, and risk factors for its onset are unclear[2, 8]. Prior studies have shown that no single approach is successful in treating LBP, and of the minor proportion of cases that respond to treatment the effect size is small[2, 9]. This presents a problem for prescribing successful treatment, and the progression to chronic pain experienced in up to 15% of cases makes this difficult-to-treat disorder even more challenging to overcome[2, 9]. In addition, chronic pain sufferers are known to have a spectrum of adverse effects such as poor quality of life, increased rates of depression, anxiety, insomnia, and double the risk of suicide compared to the average[9, 10].

2.2 Low Back Pain and Stiffness

When a LBP patient says they feel 'stiff', what does that mean exactly? It is a common descriptor used by people experiencing musculoskeletal pain, but a patient-reported feeling of low back 'stiffness' does not necessarily translate to physical, quantitatively-measured stiffness in their lumbar region[11]. Practitioners also describe LBP patients in terms of their stiffness, or assess the impact of a clinical intervention based on changes in stiffness using manual posterior-anterior palpation assessments[12]. But actual, clinically significant changes in lumbar stiffness, as quantitatively measured by instrumented device, cannot be ascertained by hand[12, 13]. Given the lack of meaningful tools, describing 'stiffness' as a tool to assess improvement can therefore be considered controversial. As a scientific and clinical community it is our responsibility to ensure patient care is optimal and therefore a full understanding of patient lived experience is necessary. To do so, functional surveys such as the Roland-Morris questionnaire or the Oswestry Disability index should be augmented by meaningful quantitative measures that are well-associated with patient outcomes.

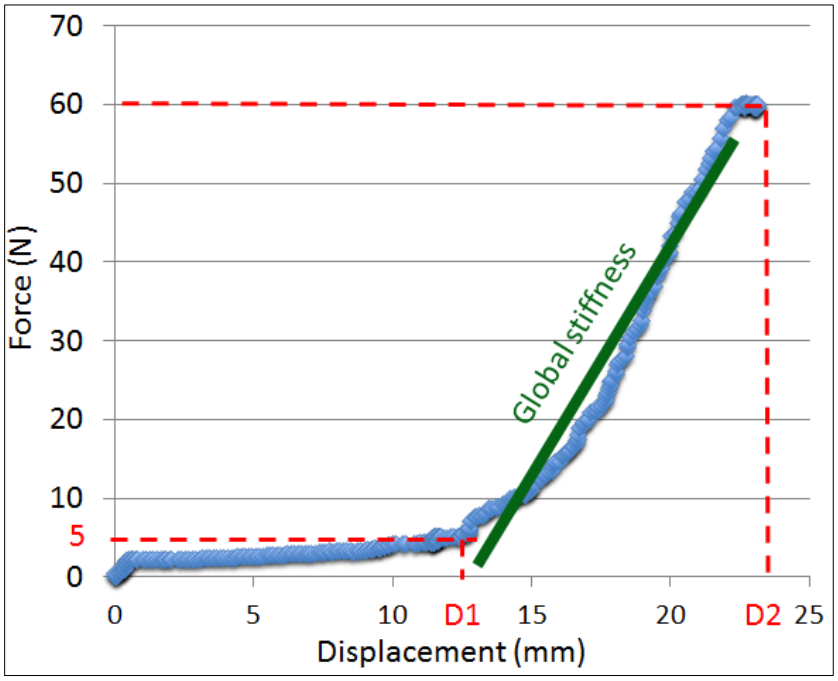
2.3 Previous Stiffness Research

Since the use of stiffness as a descriptor persists in clinical practice and in the literature, the need for a quantitative measure was established and investigated. The basis of this proposed investigation stems from the results of a recent study by Wong et al., having confirmed that LBP patients who reported at least the minimum clinically important difference (MCID) of 30% improvement in their modified Oswestry Disability Index (mODI) scores after treatment by spinal manipulation treatment (SMT) displayed quantitative physical changes that were not present in those who showed no improvement[14]. This same study also established that a reduction of at least two points on an 11-point numerical pain rating scale (0 to 10) was also associated with those same improvements[14]. The changes observed included an increased lumbar multifidus (LM) thickness ratio, an increased lumbar-disc apparent diffusion coefficient (ADC), and decreased stiffness in the lumbar region as measured by indentation at the spinous process of the third lumbar vertebra (L3)[14]. Those who did not report the MCID change in their mODI scores show none of these changes; their pre-treatment levels remained static following provision of SMT[14]. All measurements taken for this study have previously been shown to be reliable and repeatable[15].

Further description of the above three measures is in order to promote clarity in the discussion to follow. First, the primary phenomenon of interest from the previous work by Wong et al. is stiffness, and any references to stiffness throughout this work refers to quantitative force-displacement (F-D) measurements taken via a mechanical indentation device. This device applies 60 Newtons (N) of orthogonal pressure at the spinous process of the L3 vertebra of a patient in the prone position, and generates a F-D curve from which global stiffness (slope of the F-D curve) and terminal stiffness (force divided by displacement at the terminal load of 60N) can be calculated[15]. Figure 2.1 illustrates a typical F-D curve. The overlaid red line represents global stiffness (GS) and the dashed lines indicate terminal stiffness (TS). Second, an increase in contracted LM thickness ratio is indicative of improved muscle function and has been associated with pain reduction post-SMT[16]. Finally, ADC is a measure of the rate at which water diffuses into the nucleus puplosus of an intervertebral disc (IVD)[17]. An

improvement in water diffusion rates at the IVD has been hypothesized to contribute to pain reduction by creating more favourable intradiscal pressure gradients and enhancing nutrient and metabolite exchange[17].

Figure 2.1: Stiffness Measured via Mechanical Indentation



A typical Force-Displacement (F-D) stiffness curve is depicted above. The curve is generated by orthogonal force application to the spinous process of the third lumbar vertebra (L3) of a patient lying in the prone position. Force application in both of the clinical studies discussed in this document ranged from 0N to 60N. Global stiffness was calculated as the slope of the linear regression line shown in green (i.e. average slope of the F-D curve between 5N and 60N). Terminal stiffness was calculated as the change in force divided by the change in displacement (i.e. target load (60N) minus preload (5N), divided by maximal displacement (D2) minus displacement at the end of the preload (D1))[18]. Image credit: Wong et al.[18].

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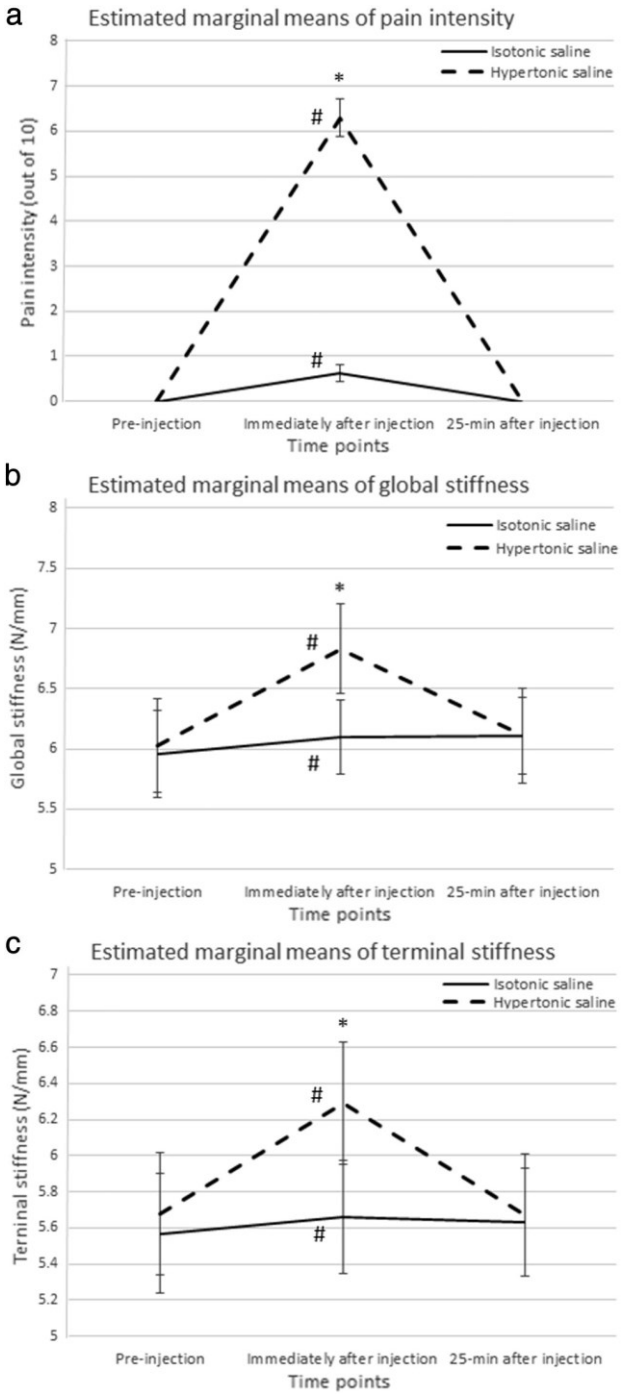
2.3.1 Pain Induction Study

There is evidence to suggest that the core stabilizing muscles of the spine may be implicated in LBP sufferers. Differences have been identified in baseline activity levels, maintenance of postural control, adaptability in balance activities, and muscle recruitment, activation and sustained contraction strategies[19-24]. In order to quantify the effects of acute LBP on muscle activity and stiffness, preliminary work was performed to induce temporary back pain in healthy control subjects[18]. In this experimental cross-over study, saline fluid was injected into the L3-L4 and L4-L5 interspinous ligaments[18]. The injections were either an isotonic saline (NS) control injection or an irritating hypertonic saline (HS) injection[18]. Spinal stiffness and muscle activity was measured before injection (non-painful state), after injection (non-painful state for NS injection, painful state for HS injection), and after a wash-out period (non-painful state)[18]. The experimentation was intended to verify muscle activity with respect to stiffness measurements. Results showed an increase in muscle activity and an increase in stiffness in the painful state as compared to the non-painful state[18]. Figure 2.2 illustrates the results. This data set was unique in that a quantifiable difference in spinal stiffness with a large effect size (Cohen's d = 1.2) was apparent in subjects who were experiencing temporary, induced LBP.

Figure 2.2: Pain Induction Study Graphical Results



Graphical results of the Pain Induction study conducted by Wong et al. are depicted above. Graph 'a' indicates the changes in pain intensity before, immediately after, and post-25 minute wash-out period for two types of injection. Isotonic saline (NS) was used for control, and hypertonic saline (HS) was used to induce temporary back pain. Graphs 'b' and 'c' similarly illustrate changes in global and terminal stiffness under the same injection conditions. * indicates a significant difference between the peak values between injection types, and # indicates a significant difference between the peak value for injection state versus baseline measurement of the same. Image credit: Wong et al.[18].

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2.3.2 Responders Study

In a study designed to determine if stiffness is related to LBP recovery, the between-subject baseline stiffness measurements did not reach significance between healthy controls and LBP patients, but did for some post-treatment outcomes. The lack of significance at baseline could have been due to the fact that there was no difference in stiffness between these sub-groups, or that the indentation tool being used was not sensitive enough to register the difference. A refinement of quantitative stiffness measurement has been designed and is currently undergoing a multi-centre trial in Canada, Denmark and Australia. The measures of interest that did reach significance are outlined in Table 2.1, below. It is apparent that stiffness, muscle activity and disc diffusion are related factors all showing improvement for responders, whereas moderate to severe facet joint degeneration was found to be a potential predictor for non-response[14, 25]. Stiffness changes by treatment are illustrated in Figure 2.3.

Table 2.1: Responders Study: Significant Findings [25]

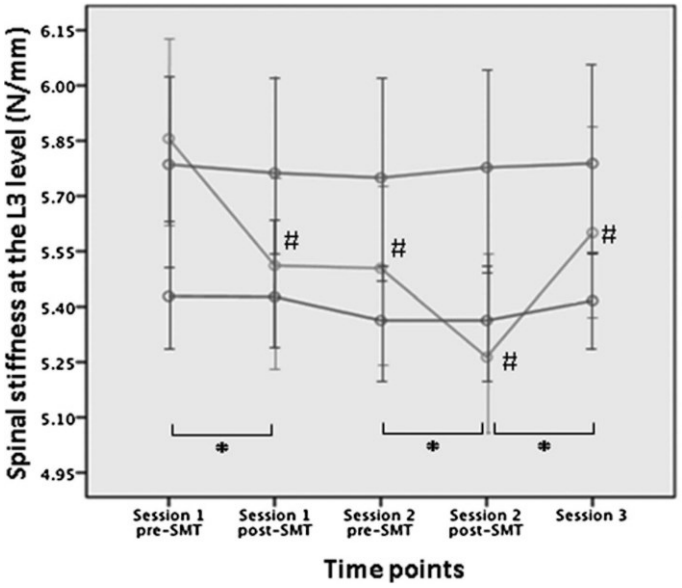
Group	Baseline Stiffness	FJD	Stiffness	LM Thickness	Disc ADC
Healthy	NS	NS	NS	NS	NS
Responder	NS	NS	$p<0.05$	$p<0.05$	$p<0.05$
Non-Responder	NS	$p=0.05$	NS	NS	NS

Significant improvements for SMT responders were global stiffness, lumbar multifidus thickness and intervertebral apparent diffusion coefficient. Facet joint degeneration was a finding of interest in non-responders; however significance was not quite reached. Findings are taken from Wong et al.[14]

Some amount of disc degeneration (DD) and facet joint degeneration (FJD) is common, tends to worsen with age, and is not generally associated with the presence of LBP[26, 27]. Severe disc degeneration is associated with a greater likelihood of LBP, especially chronic LBP, but is not a necessary precursor to the presence of LBP, nor is it associated with the severity of pain[26]. Severe FJD had only a weak correlation or no correlation with the presence of chronic LBP[26, 27]. The presence of DD has been associated with an increase in FJ contact pressures in the cervical spine[28]. Disc degeneration was also associated with a reduction in segment mobility at all stages of degeneration in the cervical spine, and had a greater impact on facet contact pressures which rose with degenerating discs, than on intradiscal pressure which fell[29].

These findings are not surprising, as they have been demonstrated time and again. The main point of the findings of the Wong et al. study, however, is that while no 'sorting' of LBP patients may have been possible ahead of treatment, some sorting could be done after treatment. All responders showed some improvement to their disc ADC, regardless of degeneration status, and non-responders were slightly more likely to display characteristics of moderate to severe FJD[14]. This study provided a breakthrough in the field of patient subgrouping. For the first time, a quantifiable biomechanical trait was positively correlated with patient-reported recovery in non-experimentally induced LBP. Like the Pain Induction study, a difference in spinal stiffness was apparent in subjects who reported a MCID change in pre- and post-SMT self-reported mODI scores, though the effect size was smaller (Cohen's d = 0.5). The findings and patient demographics collected in this data set therefore provided another unique opportunity for in-depth curve analysis.

Figure 2.3: Responder Study Graphical Results



Results of the Responders study conducted by Wong et al. are depicted in the graph above. The uppermost line illustrated the measured stiffness of a typical non-responder, with markers for each measurement and each treatment session. The lowermost line depicts the same for asymptomatic controls. The line that varies between the levels depicted for non-responders and asymptomatic controls is that of the responder subgroup. # indicates a statistically significant decrease in Responders' stiffness from the baseline measurement (Session 1, pre-SMT), and * indicates a statistically significant change in stiffness from the previous Responders' measurement. As can be seen, stiffness measurements overlapped for responders and non-responders prior to treatment by spinal manipulation therapy (SMT), but as SMT sessions progressed, stiffness was significantly impacted towards the level of asymptomatic controls. Image credit: Wong et al. [14].

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2.3.3 Potential Confounders

Spinal stiffness and F-D curves as a bulk measure were discussed in the preceding sections. It should be noted however, that there are potential confounding factors when applying force to a vertebra and measuring the resultant tissue displacement. To begin, the soft tissues surrounding a spine do not uniformly respond to loading. For example, a vertebra will display a viscoelastic response when tested in isolation; however, this property becomes insignificant with respect to the other, more pliable surrounding tissues in the spine when loaded together[30-33]. Spinal ligaments, intervertebral discs (IVD) and surrounding muscles cannot be so easily ignored. Spinal ligaments exhibit a viscoelastic and then nearly elastic response as they stretch, and display a stress-relaxation response under sustained load[34-37]. Ligaments also absorb energy under repetitive loading[36, 37]. The load response of an IVD is more complex and depends partly on the viscoelastic effect of the collagenous framework of the disc itself, and partly on poroelastic fluid migration across the IVD boundaries[38-40]. Specifically, IVD stiffness increases with increased strain rates and load cycling in all movement patterns, and disc hydration is an important component of mechanical response in compression and flexion[40-42]. It has also been shown that disc pressure, and thereby disc hydration, is impacted by ligamentous pre-strain[43]. Finally, spinal musculature is comprised of multiple layers in varying directions, significant variability in patient recruitment strategies, and significant variability in force generation based on its status (stretch, quiet, active, post-activation)[44].

A bulk measurement can therefore not possibly isolate the biomechanical response of any single tissue. To record a F-D curve for an individual and attempt to associate the resulting stiffness to any specific pathology is therefore a complex problem and subject to many layers of interpretation. Broadly speaking, the two studies above were able to identify that a change in bulk stiffness may be attributable to elevated muscle activity or to mechanical degeneration, and is associated with a significant reduction when an SMT intervention has been deemed successful.

2.3.4 Classifying Patients

The volume of research in the area of LBP prevention, treatment and recovery has not resulted in any concrete, fully successful approaches to treatment. There is an abundant supply of information that is sometimes applicable, in some cases. There are an abundance of subgrouping protocols in the literature, each attempting to make sense of the vastness of treatment alternatives clinicians face when attempting to help LBP patients recover[45]. One such protocol is a treatment-based approach that attempts to subgroup patients into three broad categories, based on the severity of their pain and functional limitations: symptom modulation, movement control, or functional optimization[46]. The clinical studies detailed above could be described as pre- and post-treatment assessments of a symptom modulation approach. But, as is the norm, the treatments were only successful for some patients. Applying a treatment and then seeing if it worked is too late in a clinical setting; patients need to identify treatments that will work ahead of trying them to reduce frustration, improve healthcare efficiency, and decrease downtime due to disability. The ability to identify appropriate treatments in advance of attempting them potentially improves outcomes as well, as there is evidence to suggest early and

effective treatment of pain prevents chronicity and the plethora of problems that accompany chronic pain and disability in the biopsychosocial sphere[47]. Finally, the significant financial cost associated with LBP could be reduced if the current trial-and-error approach were to be streamlined.

2.4 Problem Statement

A clear and objective delineation between SMT responders and non-responders has been identified in F-D measurement, providing both a potential diagnostic tool as well as a treatment approach for those who have been deemed to respond. This is a meaningful statement, since the analysis was completed using only single-value representations of global stiffness (GS) or terminal stiffness (TS) to convey a complex biomechanical response to an applied load. At present, it is unclear if the change in stiffness observed in responders is a muscular or mechanical effect. It is also unclear if the therapeutic effects of SMT are the result of improved muscular functioning, improved disc diffusion, or just a general loosening of stiffness in the low back. Finally, it is unclear if the lack of response in non-responders is due to an intrinsic patient characteristic, an acquired pain characteristic, a treatment approach, treatment duration, or a problem with precision or accuracy of measurement[14, 46, 48]. A more thorough understanding of a patient F-D curve in its entirety, and how it relates to patient physical characteristics, pain profiles and treatment responses may elucidate some of the questions outlined above, in a similar way that a thorough understanding of a 'normal' electrocardiogram (ECG) has allowed cardiologists to identify pathologies and patients at risk of heart problems. By continuing to evaluate only single-point snapshots of a biomechanical response, a powerful predictive or diagnostic tool for *a priori* identification of patient response is possibly being disregarded. This work provides a foundation for the exploratory investigation of latent subgroups of LBP patients, with the aim of discovering correlations between salient features of individual F-D curves and patient demographics, pain characteristics, response to treatment or any combination thereof.

2.5 Research Focus: Statistical Analysis of Spinal Stiffness Curves

The above discussion covered an overview of the current state of the knowledge base with respect to LBP, and a series of break-through studies that have resulted in quantifiable physical measures associated with clinically relevant improvements in a sub-group of LBP patients who respond to SMT. These studies have provided a basis for further investigation of stiffness as it relates to back pain. The results obtained were significant, but potentially under-represented by a single-point analysis approach to a complex biomechanical phenomenon. To address this possible shortcoming in the previous work, a complete curve analysis investigation will be undertaken with the goal of potentially identifying salient features contained within a patient's F-D curve that may have been disregarded by analysing only GS or TS.

2.5.1 Functional Data Analysis

Functional data analysis (FDA) is a relatively new technique and has been steadily increasing in usage since the turn of the 21st century[49-51]. Its underlying purpose is dimensionality reduction and the most popular application of FDA makes use of functional principle component analysis as the main tool for assessment[50, 51].

In order to apply FDA principles, the data to be analyzed must be fit to a twice-differentiable mathematical function and be relatively smooth[49, 50].

2.5.1.1 Functional Data Analysis: Data Smoothing

Noisy data can be fit and filtered in a variety of ways, leading to the entire field of study that is signal processing; a thorough review of the topic is beyond the scope of this work. For the purposes of analyzing F-D curves, curves were fit by the basis-spline (b-spline) technique. b-splines make use of polynomial segments, but have the added advantage of being differentiable to higher orders and were chosen for their relative simplicity, flexibility and speed of computation to construct smoothed linear combinations of functions[51, 52]. The smoothing parameter, lambda (λ), is estimated using a generalized cross validation (GCV) variable minimization procedure; however, the minimum GCV value should not be blindly applied as it may not result in the best-fit smooth[53]. Two plots, GCV vs. log-lambda and the associated degrees of freedom vs. log-lambda, are used to find a starting point for testing the smoothing parameter[53]. Smoothing was then applied in a monotonically increasing fashion for the purposes of this work, as the force-displacement relationship is strictly increasing. Roughness was penalized using the GCV-minimized lambda value and the 4th derivative of the b-spline smoothing function, and then lambda was iteratively adjusted until the optimal smoothing configuration was found.

2.5.1.2 Functional Data Analysis: Functional Principle Components Analysis

Functional principle components analysis (fPCA) is the most widely applied dimensionality-reduction tool used for analysis in FDA[50, 51]. fPCA transforms the smoothed data to a set of orthogonal principle components that are ordered such that the first few represent the greatest variation in the original data[51]. One drawback of fPCA is the predictability of the pattern of resulting scores, and therefore a rotation such as a maximization of variance (VARIMAX) is typically applied in practice[49, 53]. To help determine the optimal number of harmonics, principle component scores can be plotted and examined for orthogonality[49, 53]. It should be noted that the fPCA approach is not robust to outliers and visual examination of the plotted scores may be required[50].

2.5.1.3 Functional Data Analysis: Clustering

Once principle component scores are obtained, they can then be examined in an exploratory fashion to determine if any clusters of interest may emerge[49, 53]. Standard analysis techniques, such as percentage variance explained, clustering methods, and a multitude of others can then be directly extended to functional applications[50, 51]. Clustering is a popular partitioning method, most often used in an exploratory fashion to maximize of within-cluster similarities and between-cluster differences to identify instances of similarity between subjects[51]. Clustering and classification can occur by means of classical k-means methods, hierarchical clustering, Bayesian approaches and functional discriminant analysis, to name only a few[50]. Hierarchical clustering algorithms are most often applied, and perhaps the most informative[51]. The data under study in this work was drawn from small samples with few independent covariates and therefore a k-means clustering algorithm was chosen instead.

2.5.1.4 Functional Data Analysis: Explanatory and Outcome Variables

It should be noted that there are many other techniques available to analyze functional (or longitudinal) data and to help relate an outcome variable to an explanatory variable[51]. A sampling of such methods includes functional regression, analysis of variance of mean functions (FANOVA), functional data distributions, covariance functions, and a high-dimensional analysis of variance (HANOVA)[50, 51, 54]. These techniques are not within the scope of this work, but may provide fruitful avenues for future research.

2.5.1.5 Functional Data Analysis: Forecasting

The field of FDA is developing rapidly and in addition to the many linear methods listed above, options for non-linear analysis, stochastic methods, and machine learning approaches are increasing in research activity and are therefore becoming more accessible[50]. As such, FDA methods developed for trend forecasting, risk factor analysis, and treatment efficacy have been increasing in research as potential tools for prediction[51].

2.5.2 Latent Class Analysis

The basic premise behind a latent class analysis (LCA) is that coincident observable variables, when analysed together, can reveal a latent trait that cannot be observed directly[55]. LC clustering algorithms are analogous to k-means clustering algorithms; LC clustering takes advantage of probability-based distances rather than the Euclidean distances used when calculating k-means clusters[56]. The ultimate goal of LCA is therefore to identify a set of latent classes for which the observed indicators are locally independent[55]. This type of analysis was originally invented for categorical variable observations common in the social sciences; however the model has proved to be much more flexible than its intended application[55, 57]. There are a multitude of model specification options and each must be considered carefully. Latent class analysis works best when variables are defined and categorized to most closely match their collection format, and model misspecification can result in additional classes to account for violations of underlying assumptions[58]. The work to follow attempts to exploit this flexibility and represents a novel approach to LCA; what would typically be called a 'signal' is being re-defined as longitudinal data. A brief discussion of the elements and interpretation of LCA calculations follows.

2.5.2.1 Latent Class Analysis: Class Probabilities

There are two types of probabilities in a LCA: latent class probabilities and conditional probabilities. Latent class probabilities indicate the number of classes and the relative size of each class[55]. Latent classes must be locally independent (i.e. classes are mutually exclusive) and probabilities must sum to 1.0 (i.e. classes are exhaustive)[55]. Finding only a single class is equivalent to finding complete independence across variables[55]. In other words, a latent class analysis will maximize the similarity of responses within a class while maximizing the difference in responses between classes. Conditional probabilities, on the other hand, indicate the probability that any given member of a latent class will have a response to an observed variable that matches the predicted response for that class[55]. Conditional probabilities are calculated for each observed variable, at each response level for that variable, and must sum to 1.0[55].

2.5.2.2 Latent Class Analysis: Maximum Likelihood Estimates

It is only possible to accept a latent class model if the actual observed conditions deviate from the latent class predictions within the limits of chance[55]. The maximum likelihood (ML) estimates are analogous to the usual Pearson's chi-squared (χ^2) statistic and provide one measure of the limit within which the latent class model can be tested for fit[55, 56]. A model that does not fit is an indication that the assumption of local independence between classes has been violated, and the number of classes should be increased or local independence criteria relaxed (as appropriate) until a well-fit model is found[58]. The likelihood ratio chi-squared (L^2) can be partitioned by class to test latent class and conditional probabilities and is accepted at an alpha level of $p<0.05$ as per usual statistical convention[55]. It should be noted, however, that no single method can be relied upon exclusively, but rather must be considered in the context of their respective mathematical assumptions[56]. For example, sparse data violates the chi-squared distribution assumption for L2, ML function maximization can result in boundary or local solutions, and model parameters can have multiple ML estimates, resulting in an unidentified model[58]. As such, Bayesian statistics provide a useful alternative[58].

2.5.2.3 Latent Class Analysis: Bayesian Information Criterion

Goodness-of-fit analyses for LC clustering can also be determined by minimization of the Bayesian information criterion (BIC)[56, 58]. As such, a brief discussion of Bayesian statistics is in order. To begin, there are two basic views of statistics: empirical or subjective[59]. The empirical view considers the frequency of a given outcome based on the repetition of an experiment, with the probability that the experimental outcome approaches reality increasing as the number of repetitions increases[59]. This construct leads to significance-level testing of a null hypothesis and confidence interval estimation[59]. By contrast, the subjective view adopted in Bayesian statistics is instead a personal estimation of the probability of a given event, based on the available evidence[59]. This construct allows for differences of opinions of researchers or differences in the availability of information, and leads to Bayesian probability intervals[59]. Confidence intervals (CI) and probability intervals (PI) are generally numerically close; however, their interpretation is greatly different at a conceptual level[59]. A CI indicates the percentage of randomly selected population samples that would contain the unknown probability of an event occurring; however, there is no way of knowing whether or not a particular sample falls within this percentage or if an erroneous rejection of the null hypothesis has occurred[59]. By contrast, a PI is calculated after estimation of a prior probability distribution and subsequent adjustment of that distribution after testing a population sample[59]. It is then possible to state that the actual population distribution matches the experimentally adjusted distribution within a specific level of certainty[59].

Prior and posterior distributions are the foundation of Bayesian statistics. As described above, a prior distribution is a measure of uncertainty based on available information and personal opinions and therefore may differ from one researcher to another. As such, researcher bias becomes evident by observation of the shape of that distribution, and is therefore open to peer scrutiny[59]. The posterior distribution is calculated after experimentation and is used to adjust prior probabilities to better reflect reality[59]. The adjusted probability can then be fed forward to estimate priors for future experimentation[59]. In most cases, the beta distribution is

used to describe the shape of Bayesian probabilities. There are two ways to choose the shape of the beta distribution: by trial-and-error until the shape approximates expected outcomes, or by specifying a mean value and standard deviation, then fitting the beta distribution to match[59]. In cases where no *a priori* information is available, a rectangular (noninformative) distribution is often assumed[59]. In other words, the shape of the distribution is a horizontal line, indicating that the probability a variable takes on a specific value is the same across the entire distribution[59]. Bayesian analysis with a noninformative prior often leads to results that numerically correspond to those obtained by classical analytical statistics, but as discussed above, interpretations are conceptually very different[59]. Multivariate analysis is another case where researchers often resort to rectangular distributions, in order to avoid the complex nature of determining a beta distribution for parameter interactions[59]. In all cases, the prior and posterior probabilities must sum to 1.0[59].

2.5.2.4 Latent Class Analysis: Degrees of Freedom

The number of estimable parameters limited by the degrees of freedom (DoF) available in the system, which must be positive for a latent class model to be valid[55]. If any of the conditional probabilities in a given class is found to be zero, the associated DoF can be reclaimed[55].

$$DoF = {}^{N}\Pi_{i=1}(K_i) - ({}^{N}\Sigma_{i=1}(K_i) - (N-1))T$$

Where[55]:

K_i=number of levels for each observed variable
T=number of classes
N=number of observed variables

2.5.2.5 Latent Class Analysis: Model Restrictions

A latent class model can be unrestricted, meaning that all parameters are identified and that there are no *a priori* constraints on either the conditional or latent class probabilities[55]. Unrestricted models can be prone to an identification problem, meaning that in some cases it is possible that more than one solution exists[55]. In the unidentified case, imposing restrictions to latent class or conditional probabilities, or both, can coerce the model to be identifiable[55]. Care must be taken to ensure that the restrictions applied still result in LC and conditional probabilities that sum to 1.0, and that no specific level of a measured variable has a conditional probability of 0.0 for all classes[55]. The system DoF must be decreased by the number of non-redundant restrictions applied[55].

There are a number of restrictions that can be applied. Equal LC probabilities indicate classes are of equal size, while equal conditional probabilities indicate observations of a specific level of a specific variable are equally likely between classes[55, 56]. When a LC restriction is defined to be a specific value, that value dictates the proportion of subjects to be assigned to a specific class[55]. Specific conditional probabilities dictate the probability that a given observation falls within a pre-defined class[55]. For ordinal, continuous or count data, a monotonically increasing restriction can be applied to the response indicators[56].

2.5.2.6 Latent Class Analysis: Estimation Procedures

LCA can be conducted in an exploratory or confirmatory fashion. In the case of exploratory analysis, no hypothesis is made with respect to latent class or conditional probabilities[55]. Instead, the goal of analysis is an attempt to identify classes based on observed variables[55]. An exploratory analysis is typically conducted with no restrictions and with no theory of classification outcomes[55]. Exploratory analyses are also employed to test the sufficiency of an existing theory[55]. Confirmatory analysis, on the other hand, is used to test *a priori* hypotheses of latent classifications. Confirmatory analyses impose restrictions on the LC model, and hypothesis testing of the latent class and conditional probability outcomes is conducted with respect to the imposed restrictions[55].

2.5.2.7 Latent Class Analysis: Sample Size Limitations

Though LCA does not require the assumption of multivariate normality, sample size is still a significant consideration[55]. Likelihood-ratio chi-squared significance tests for latent class and conditional probabilities are dependent on the system DoF[55]. As detailed in Section 2.5.2.4, DoF are dependent upon the number of and levels within the observed variables, and on the size of the sample population being observed. For the novel application being explored in this work, a delicate balance must therefore be struck between retention of data integrity and the limited number of subjects available for observation.

As discussed above, the BIC is a main component of model estimation. Stable estimation in terms of Bayesian statistics is also dependent on sample size[59]. Since the posterior distribution is a beta distribution with the parameters (a+x) and (n+a+b), where a and b come from the prior distribution and x and n come from the data, if a, b, x and n are all about the same then the prior distribution has a large effect on the data outcomes[59]. On the other hand, a large sample results in x and n dominating the shape of the posterior distribution, and a and b have little effect on the outcome[59]. When estimation is not stable, such as when there is a small sample (small n) or a large variance in the prior distribution and resulting beta function (large a and b), then priors can have a greater impact on the posterior distribution and the subjectivity of Bayesian statistics becomes apparent[59].

2.5.2.8 Latent Class Analysis: Covariates

Covariates can be included in LCA in an active or inactive manner. Active covariates affect the analysis output, while inactive covariates do not[58]. Inactive covariates can be used to generate a sort of 'class profile', or measures of the association between the covariates and the latent variable[58]. Class membership can then be predicted for new cases where indicator measurements may not be available[58]. In other words, an inactive covariate profile would be analogous *a priori* identification of LBP responders based on demographics data alone, without having to take a F-D stiffness measurement. One can imagine the impact such a tool could have to patient outcomes.

2.5.2.9 Latent Class Analysis: Regression Models

One form of latent class regression analysis (LCRA) can be conducted by analyzing a single predictor measurement with respect to a single nominal latent variable[58]. In the case of this work, the F-D curve would be treated as an ordered nominal variable, with displacement acting as the predictor measurement. LBP phenotypes would be the nominal latent variable under investigation[58]. The main difference between a standard LC cluster analysis and a LCRA is that a single dependent variable is considered[58]. In the case of F-D data redefined as a longitudinal response, this would be analogous to conducting a repeated-measures experiment, with displacement values being recorded over specific intervals of force. Covariates and restrictions can be applied in the same way as discussed above[58].

3. Objectives

There were three main objectives for this work. The first was to identify the behaviour of a novel application of latent class analysis as compared to a specialized statistical technique developed specifically for functional data. Since the main outcome was to determine comparative behaviour of two statistical techniques, Cohen's kappa statistic was used to guide interpretation of results[60, 61]. The next two objectives involved the application of each of the LCA and FDA statistical approaches to the previously discussed clinical LBP patient data obtained from the Pain Induction and the Responders studies. From these previous studies, it was evident that global and terminal stiffness were linked to patient outcomes; however, it was unknown whether a full F-D curve trace would be related in the same way. Put another way, it was unknown whether the dominant features of a full F-D curve trace was indeed the calculated stiffness, or whether the transition (non-linear) section of the curve trace had greater discriminatory power once it was included in the analysis.

If the transition section did indeed dominate the analysis, it was also then unknown whether patient outcomes would continue to be correlated, or if some other patient characteristic contributed most to a full F-D curve trace. Objective two was therefore to identify if LCA and FDA result in the same clustering outcomes as the original Pain Induction study. A before-and-after analysis approach was chosen for this data set because of the large effect size generated in the original experimental study, as discussed in Section 2.3.1. The final objective was then to apply the learnings generated from the overall behaviour of LCA and FDA from the first objective and their discriminatory capability from the second objective, to clinical F-D curve traces taken from Responders study patients who were truly experiencing LBP. This last set of analyses were applied in an exploratory fashion, in an attempt to identify patient features that may correlate to clinical F-D curve traces. Since this last objective was to identify whether subgroupings relevant to combinations of patient demographics or response to treatment were possible, alternate outcomes to the specific hypotheses made may have become evident.

3.1 Functional Data Analysis vs. Latent Class Analysis – Feasibility with Simulated Data

This feasibility study was designed to address Objective 1 and is discussed in Chapter 4.

3.1.1 Hypothesis

Functional data analysis and latent class analysis will perform equally well to cluster simulated functional data curves into each of three different curve types.

H_0: $\kappa \leq 0.6$ 'Moderate' or worse agreement between analysis techniques

H_1: $\kappa > 0.6$ 'Good' or better agreement between analysis techniques

3.1.2 Rationale

Since this is the first attempt at applying LCA to functional data with the goal of classifying curves by their overall shape, it is important to compare the application to a technique with a known outcome.

3.2 Functional Analysis Techniques vs. Traditional Statistics using Pain Induction Study Data

The Pain Induction Study data is analyzed in Chapter 5 and addresses Objective 2.

3.2.1 Hypotheses

Functional data analysis and latent class analysis will perform at least as well as the previous analysis by traditional statistics from the Pain Induction study in identifying hypertonic (HS, pain-inducing) vs. isotonic (NS, control) saline injection force-displacement curves.

For an isotonic saline injection:

H_0: $\mu_D=0$ No difference in the mean difference of measured stiffness before and after NS injection

H_1: $\mu_D\neq0$ A difference is apparent in the mean difference of measured stiffness before and after NS injection

The null hypothesis was not rejected for the NS injection case in the original Pain Induction study.

For a hypertonic saline injection:

H_0: $\mu_D=0$ No difference in the mean difference in measured stiffness before and after HS injection

H_1: $\mu_D\neq0$ A difference is apparent in the mean difference in measured stiffness before and after HS injection

The null hypothesis was rejected for the HS injection case in the original Pain Induction study.

In all cases, Cohen's kappa statistic was considered for in each of the above cases to guide interpretation of clustering outcomes for each of the FDA and LCA techniques.

3.2.2 Rationale

Identifying the performance of FDA and LCA in comparison to each other and to known outcomes from previously analyzed experimental data will inform interpretation of results when applying the techniques to clinical patient data from the Responders study.

3.3 Functional Analysis Techniques vs. Traditional Statistics using Responder Study Data

The Responders Study data is analyzed in Chapter 6 and addresses Objective 3.

3.3.1 Hypothesis

Functional data analysis and latent class analysis will perform at least as well as traditional statistics in identifying responder vs. non-responder force-displacement curves from the Responders study.

For the before-treatment case for both the Responders and Non-Responders subgroups:

H_0: $\mu_D=0$ No difference in the mean difference in measured stiffness between Responders and Non-Responders before treatment by SMT

H_1: $\mu_D\neq0$ A difference is apparent in the mean difference in measured stiffness between Responders and Non-Responders before treatment by SMT

The null hypothesis was not rejected for this between-subgroup case in the original Responders study.

For the after-treatment case for both the Responders and Non-Responders subgroups:

H_0: $\mu_D=0$ No difference in the mean difference in measured stiffness between Responders and Non-Responders after treatment by SMT

H_1: $\mu_D\neq0$ A difference is apparent in the mean difference in measured stiffness between Responders and Non-Responders after treatment by SMT

The null hypothesis was not rejected for this between-subgroup case in the original Responders study.

For the before-and-after treatment case for only the Responders subgroup:

H_0: $\mu_D=0$ No difference in the mean difference in measured stiffness before and after treatment by SMT

H_1: $\mu_D\neq0$ A difference is apparent in the mean difference in measured stiffness before and after treatment by SMT

The null hypothesis was rejected for this within-subgroup case in the original Responders study.

The kappa statistic was considered for in each of the above cases to guide interpretation of clustering outcomes for each of the FDA and LCA techniques.

3.3.2 Rationale

As highlighted above, the personal and financial costs of LBP are significant and the obvious goal is to treat LBP as quickly and effectively as possible. By identifying characteristics of patient F-D curves that could elucidate physical traits or quality of LBP that result in *a priori* treatment response, this work would lay the foundation to further develop a powerful tool to diagnose and treat LBP.

4. Application of Latent Class Analysis to Functional Data – A Feasibility Study

This section details the methods, results and conclusions drawn from testing FDA and LCA software packages using simulated functional data. The main outcome is to determine LCA software performance since this is a novel application of latent class analysis. Easily distinguished data will be used to formulate and validate package settings as compared to specialized statistical techniques developed specifically for functional data.

4.1 Background

Applying LCA in the novel way intended for this thesis could be called unorthodox. The typical application of the technique involves an analysis of responses to categorical variables over time. As discussed in section 2.5.2, the power of the technique lies in identifying latent subsets of patients by otherwise unmeasurable trends. In the application under study here, the data analyzed was a F-D curve that spanned only a couple seconds of actual time. The goal was to know if the F-D curves could be used to categorize patients into subgroups of responders and non-responders, as well as to investigate if there were any other possible subgroupings based on the shape of a subject's F-D curve and his or her demographics. The testing undertaken in this section informs model specification and sensitivity testing procedures with known data that can then be carried forward when analyzing clinical data with less obvious trends.

The goal of this study was to determine LCRA performance in comparison to FDA, which had a 100% classification success rate by design. As discussed in section 2.5.1, FDA is achieved by performing a functional principle components analysis (fPCA) to determine where the salient features of each functional data curve lay. Differentiating the curves allows for fPCA analysis of the rates of change of the curves in addition to analyzing the original data collection output. The data for analysis in the Evaluation phase was intentionally generated to be of three distinct curve types: linear, logarithmic, or exponential. These curves are described below and illustrated in the figures that follow.

4.2 Data Generation

In order to properly assess the outcomes of the FDA and LCRA analyses, a benchmark of their respective behaviours was required. As described in the previous section, the FDA technique is relatively new and does not have a fully developed knowledge base, and the LCRA technique is being applied in an unorthodox method, therefore, data with very specific identifiable characteristics was required. Two sets of simulated data were generated, each consisting of three distinct curve types: linear, logarithmic and exponential. Three variations of each curve type were used, resulting in a sample size of n=9 for each data set.

4.2.1 Data Set 1: Minimal Curve Overlap

Linear curves were generated by the following three equations to create unitless control curves:

$y_1 = 0.48*x$ $y_2 = 0.50*x$ $y_3 = 0.52*x$

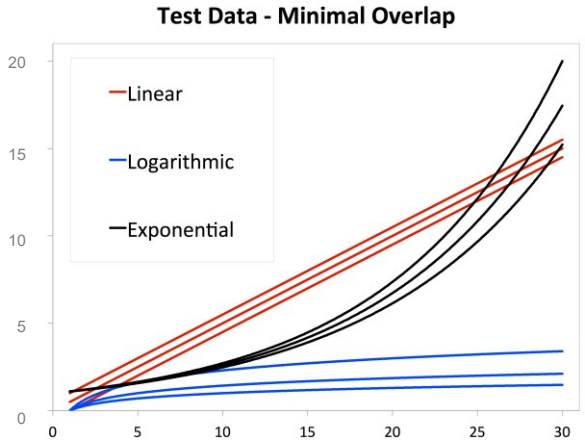
Logarithmic curves were generated by the following three equations:

$y_1 = \log_{10}(x)$ $y_2 = \log_5(x)$ $y_3 = \log_e(x)$

Exponential curves were generated by the following three equations:

$y_1 = 1.095^x$ $y_2 = 1.100^x$ $y_3 = 1.105^x$

Figure 4.1: Data Set 1: Minimal Curve Overlap



The chart above illustrates three generated curves used for testing latent class analysis performance against functional data analysis performance. Curves are easily deciphered by visual inspection.

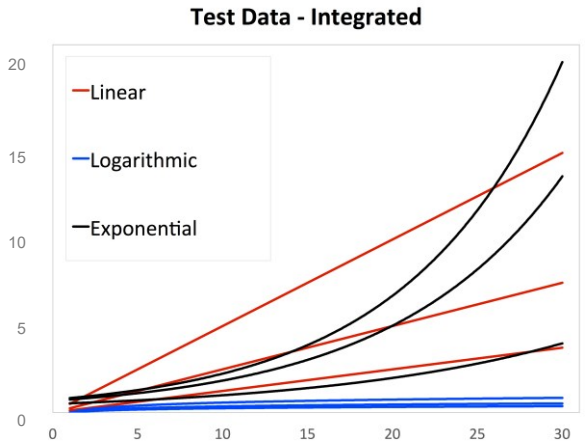
4.2.2 Data Set 2: Interspersed

Linear curves were generated by the following three equations to create unitless control curves:

$y_1 = 0.5*x$ $y_2 = x$ $y_3 = 2*x$

Logarithmic and exponential curves remained unchanged from those described in the previous section.

Figure 4.2: Data Set 2: Interspersed



The chart above illustrates three generated curves used for testing latent class analysis performance against functional data analysis performance. Curves are not easily deciphered by visual inspection.

4.3 Methods: Functional Data Analysis

Even though the data used in this stage of analysis was generated from known, smooth functions, the b-spline smoothing techniques were employed for consistency with the clinical data sections that follow. The functional data analysis was conducted in the R computing environment (The R Project for Statistical Computing v.3.3.3 "Another Canoe", 2017, Vienna, Austria) using the 'kmeans' function within the standard 'stats' package and the 'pca.fd' and 'varmx.pca.fd' functions within 'fda' add-on package[52, 62].

4.3.1 FDA Statistical Analysis

A functional principle components analysis was conducted from the smoothed functional data curves as described above. VARIMAX-rotated principle component were used to cluster the curves, their derivatives and their second derivatives. Rotated principal component scores were then plotted and clustered by k-means criteria. The resulting clusters were compared to the known curve types and misclassification rates were calculated.

4.4 Methods: Latent Class Regression Analysis

Latent class regression analysis was performed using the Latent GOLD computer package (Latent GOLD v.5.1, Statistical Innovations, Massachusetts, USA)[63]. The generated data described in Section 4.2 was re-sampled such that the salient features of the curves are preserved while keeping the dimensionality to a minimum with respect to the number of subjects available. Since consistency of input is important when comparing two analysis approaches, the data was first smoothed in a FDA-compatible manner, and then resampled for input to LCA as described in Section 4.2.2, below.

4.4.1 LCRA Model Specification Considerations

For this application, the dependent variable in a Latent GOLD LCA can be defined as being either ordinal or continuous. An analogy to help understand the application of LCA in this case is that the force variable is being treated as 'time' and the displacement variable is being treated as the dependent 'response' variable. If the force variable is treated as a continuous variable, then an assumption that the errors across each measurement along the continuous scale is normally distributed[64]. In reality this may not be the case, as the errors near the beginning of the load application may be greater than those at the end since there is more 'give' in the tissues before they reach their collective viscoelastic limit (i.e. the linear portion of the F-D curve). Alternatively, the force variable could be treated as a numeric ordinal variable, coercing the model to be a monotonic regression[64]. In either case, a 'small' sample size relative to the dimensionality of the data limits the number of latent classes that can be found[58].

4.4.2 Sensitivity testing

In order to perform a latent class analysis, it is necessary that the dimensionality of the data is not so great as to result in negative degrees of freedom when exploring classifications. Three sensitivity tests were performed for input data handling: grouping by every 2 millimetres (mm) displacement and 2 Newtons (N) force, by every 2mm

displacement and 5N force, and by every 1mm displacement and 1N force. This was done to explore the balance between retaining as much information as practicable versus the resulting degrees of freedom available for finding latent classes. The best outcome in terms of maximizing data retention while keeping dimensionality to a limit that allows for sufficient degrees of freedom will be carried forward to the next sensitivity tests.

Once the optimal grouping arrangement for dimensionality reduction was determined, two more sensitivity tests were performed. One test determined class-independence of the force predictor; if a predictor is class-independent, then the effects of the predictor would be equal for all classes[58]. In other words, class assignment would depend solely upon displacement and covariates, since the effects of force would be the same across classes. The other sensitivity test determined the impact of covariates and/or known class assignments. This was done by selecting inactive covariate, active covariate, or known class assignment options in the Latent GOLD model set-up and then comparing the results.

4.4.3 LCRA Clustering

Latent class assignments were performed in an exploratory fashion, using the BIC to evaluate the appropriateness of the resultant classifications. Classifications were compared to known pain status and misclassification rates were calculated.

4.5 Methods: Comparison of Functional Statistics Results

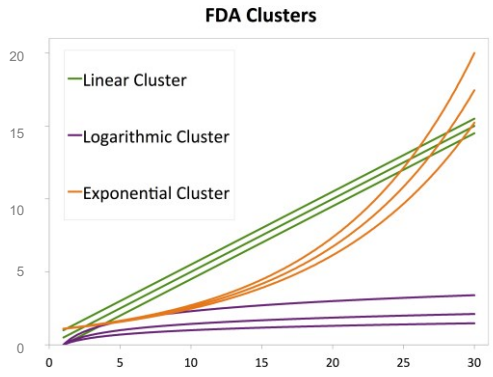
Cohen's kappa is often calculated to determine the level of agreement between a classification system (or between 'raters')[61]. Kappa was calculated for clustering results from the FDA and LCRA techniques for the three-class case only, since FDA does not correspond to a greater number of LCRA classifications.

4.6 Results: Functional Data Analysis

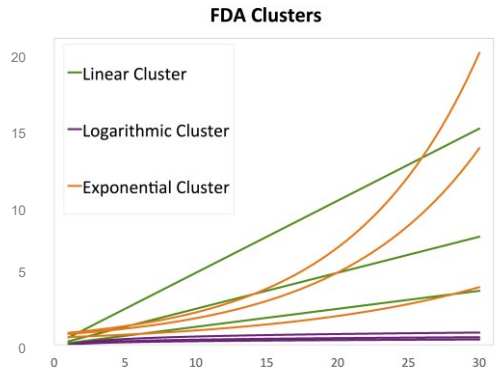
Results from the FDA analysis are plotted in the figures below. No misclassifications occurred with this technique.

Figure 4.3: Software Evaluation Results - FDA

4.3a: Minimal Curve Overlap



4.3b: Interspersed



The figures above show the functional data analysis clustering results of both the minimal overlap case and the interspersed case of the simulated functional data. Clusters match curve type in all cases.

4.7 Results: Latent Class Regression Analysis

4.7.1 LCRA Model Specification Results

When the force predictor was specified as a continuous variable, the classification resulted in an ever-decreasing BIC, which is an indication that the model is misspecified. As a numeric ordinal dependent variable, no more than three classes are defined, due to insufficient DoF.

4.7.2 Sensitivity Testing Results

Grouping sensitivity tests: There was no significance difference in the number of classes available between grouping by every 2N or by every 5N. As a result, the more conservative case of grouping by every 2N was carried forward to retain as much data as possible. The 1N grouping case resulted in problems with model definition for any more than one class and was therefore not carried forward to the next step in sensitivity testing. Table 4.1 illustrates dimensionality-reduction groupings and resultant degrees of freedom.

Table 4.1: Data Dimensionality Reduction by Grouping

		LL	**BIC(LL)**	**Npar**	**df**	**R^2**
Base Case 1: 1 Class Solution, Force @ 2N intervals	1-Class	-5634.5215	11303.7003	10	22	0.6317
Base Case 2: 1 Class Solution, Force @ 5N intervals	1-Class	-5328.6286	10688.4489	9	23	0.6283
Base Case 3: 1 Class Solution, Force @ 1N intervals	1-Class	-7399.6686	14861.7205	18	14	0.6377
Test Case 1: 2 Class Solution, Force @ 1N intervals Solution Not Defined	2-Class	-5821.2763	11770.7849	37	-5	0.8782
Test Case 2: 4 Class Solution, Force @ 2N intervals Solution Not Defined	4-Class	-2559.1188	5267.2642	43	-11	0.9552
Test Case 3: 4 Class Solution, Force @ 5N intervals Solution Not Defined	4-Class	-2543.9571	5223.0778	39	-7	0.9478

Results of a sampling frequency sensitivity test are tabulated above. The purpose of this dimesionality-reduction sensitivity test is to determine an optimal sampling frequency to maintain enough degrees of freedom to find latent classes for evaluation while still preserving the integrity of the data. Classificatios were tested at 1 through 4 classes.
As demonstrated above:

1. The degress of freedom become negative, (resulting in an undefined model) at 2 classes for sampling at every 1 N, and at 4 classes for both 2N and 5N sampling frequencies.
2. A sampling rate of every 2N or every 5N maintains enough degrees of freedom for 1, 2 or 3 classes to be found.
3. Neither a 2N or 5N sampling frequency allow enough degrees of freedom for 4 classes to be found.
4. LL = Log-likelihood ratio
5. BIC(LL) = Bayesian Information Criterion, based on LL
6. Npar = Number of parameters
7. df = Degrees of Freedom
8. R^2 = Proportion of variance explained

Force class-independence test: Force was not class independent. Table 4.2 illustrates force class dependence by BIC.

Table 4.2: Force Predictor Class-Independence Test

		LL	BIC(LL)	Npar	df	R^2
Base Case 1: 1-Class Solution	1-Class	-5634.5214	11303.7002	10	22	0.6317
Base Case 2: 2-Class Solution	2-Class	-4142.2398	8357.26	21	11	0.8663
Test Case 1: 2-Class Force Independence Test	2-Class	-4200.1929	8469.7006	20	12	0.8691
Base Case 3: 3-Class Solution	3-Class	-3168.6177	6448.1389	32	0	0.9002
Test Case 2: 3-Class Force Independence Test	3-Class	-3425.4864	6954.945	30	2	0.9197

The class-independence sensitivity test tabulated above indicates that force is not class-independent, as the model parameters differ between the class-dependent and class-independent states.

1. LL = Log-likelihood ratio
2. BIC(LL) = Bayesian Information Criterion, based on LL
3. Npar = Number of parameters
4. df = Degrees of Freedom
5. R^2 = Proportion of variance explained

To test for covariate and known class sensitivity, the results of the above two tests were applied with data grouping by every 2mm and 2N, and the force predictor defined as class-dependent. There was no change to misclassification rates in any of the three categories tested. Note that 'Known Class' for the 3-Class case was not meaningful as only 2 classes are 'known'.

Table 4.3: Covariate and Known Class Sensitivity Test

		BIC(LL)	Npar	df	p-value	R^2
Base Case 1: 1-Class Solution	1-Class	10688.4489	9	23	7.3e-2283	0.6283
Base Case 2: 2-Class Solution	2-Class	7854.3902	19	13	1.1e-1674	0.8597
Base Case 3: 3-Class Solution	3-Class	6903.8538	29	3	3.1e-1476	0.9126
Test Case 1: 3-Class Inactive Covariates Matches Base Case 2	3-Class	6903.8538	29	3	3.1e-1476	0.9126
Test Case 2: 3-Class Active Covariates 13 Misclassifications	3-Class	6205.8116	31	1	5.8e-1327	0.8943
Test Case 3: 2-Class Known Classifications 13 Misclassifications	2-Class	8680.0333	19	13	8.6e-1853	0.8224
Test Case 4: 3-Class Known Classifications Matches Base Case 2	3-Class	8715.0473	29	3	1.7e-1868	0.8225

Known-class sensitivity testing was compared to the 1, 2 and 3-class base cases in the table above. Applying known classes had no impact to misclassification rates. Covariate sensitivity was also tested by applying both active and inactive covariates, and then comparing them to the base case results. Covariates also did not impact misclassification rates.

1. LL = Log-likelihood ratio
2. BIC(LL) = Bayesian Information Criterion, based on LL
3. Npar = Number of parameters
4. df = Degrees of Freedom
5. R^2 = Proportion of variance explained

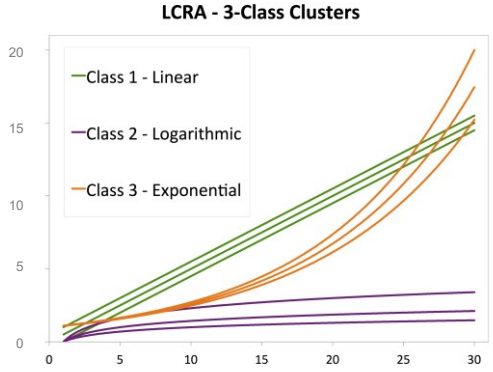
4.7.3 LCRA Clustering Results

To perform the final LCRA classification, the results from each of the above sensitivity tests were applied. Optimal data grouping was determined to be every 2mm and 2N, with the force predictor defined as class-dependent, and neither covariates nor the known-class options applied.

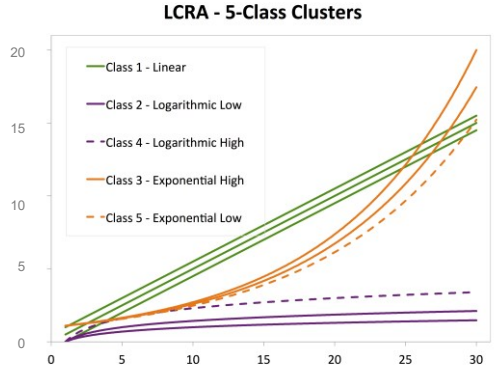
LCRA of the minimal overlap data set are plotted in Figure 4.4, sub-figures 'a' and 'b'. This technique was able to successfully group the curves by type in the 3-class case; however, the preferred solution was the 5-class case. LCRA of the interspersed data set are plotted in Figure 4.4, sub-figures 'c' and 'd'. The 3-class case included misclassifications in two of the three clusters. Only one cluster included a misclassified curve in the 6-class case.

Figure 4.4: Software Evaluation Results - LCRA

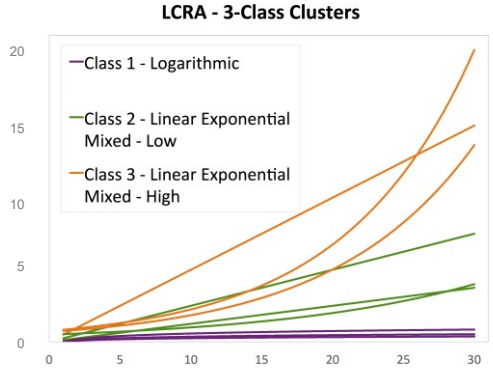
4.4a: Minimal Curve Overlap 3-Class



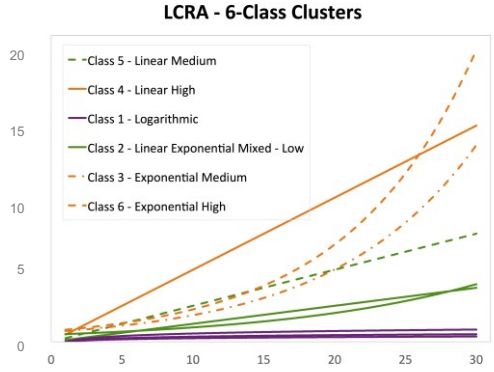
4.4b: Minimal Curve Overlap 3-Class



4.4c: Interspersed 3-Class



4.4d: Interspersed 6-Class



Clustering results of a latent class analysis of both the minimal overlap case and the interspersed case of the simulated functional data are illustrated in the sub-figures above. Solid colour-coded lines indicate classifications of the 3-Class solution. When solid lines become dashed, this is an indication that one of the three original classes has been subdivided into a secondary class. These subdivisions resulted in a lower BIC and a better model fit to the data.

4.8 Results: Comparison of Functional Analysis Techniques

Cohen's kappa was calculated for the linear and exponential curve types only, since the logarithmic classifications were in full agreement in all cases. Agreement was excellent in the case of minimal curve overlap ($\kappa = 1.0$) and only slight in the case of interspersed curve types ($\kappa = 0.3$).

4.9 Discussion and Conclusion

The FDA technique analyzes curve characteristics by means of fPCA, to determine how similar or different they are to each other in terms of their shape. It is this feature of the FDA technique that was exploited to ensure no misclassifications were obtained for the simulated data sets and is hypothesized to result in meaningful F-D curve groupings based on their nonlinear rate of change. The LCRA technique on the other hand, tended to put more emphasis on overall curve proximity ahead of rates of change, as can be seen by the clustering outcomes and the only slight level of agreement between the two techniques. The number of classes found can be interpreted as discrete response types or as levels of a continuum[55]. This feature of LCRA became evident in the preference for 5- and 6-class cases, indicating that a further subdivision of the colour-coded classification schemes into curves with dashed lines would be a better descriptor of sub-types within the three main classes. The preference for an increase in the number of classes can be rationalized when considering curve proximity and interspersion of termination points. Since the analyses conducted in the Pain Induction and Responders studies did not elucidate how slope and terminal stiffness relate within any given F-D curve, other than both being significant predictors of SMT response, this feasibility study supported the use of both LCA and FDA to investigate overall curve shape and its relationship to patient recovery and demographic data in subsequent chapters.

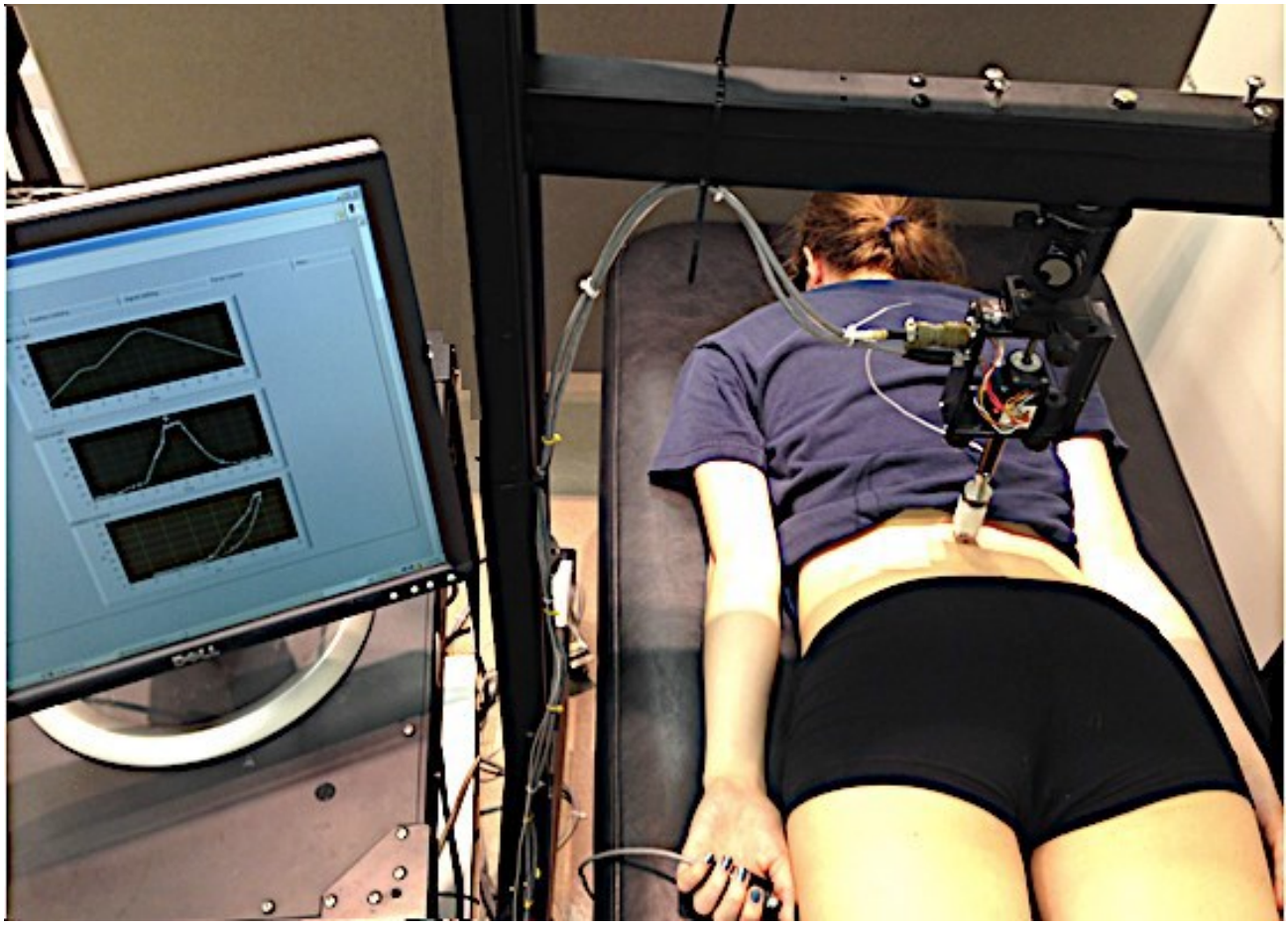
5. Comparison of Functional Data Analysis, Latent Class Analysis and Traditional Statistics of Spinal Segment Mobility in an Experimental Pain Induction Study

This section details a secondary examination of F-D data from the Pain Induction study, using FDA and LCA. The goals were to determine LCA and FDA software performance with experimental clinical data that had a large effect size and to compare these results to traditional statistical analyses, specifically a repeated-measures t-statistic and a repeated-measures, point-biserial Pearson's r correlation. Results were also be compared with the single data-point analysis performed in the original Pain Induction study.

5.1 Data Acquisition

The F-D curves for analysis were previously obtained by means of orthogonal application of force to the L3 spinous process of each subject in the prone position. The mechanical indentation device used to apply the force is pictured in Figure 5.1. The device was instrumented with a compressive-tension load cell transducer to measure applied force and a rotary encoder to measure displacement. Control of the device and data recording were managed via a customized LabVIEW 8.6 user interface (National Instruments, Austin, USA)[15].

Figure 5.1: Mechanical Indentation Device



An instrumented mechanical indentation device. A linear motor fitted with a compressive-tension load cell transducer applies a 0N-60N force orthogonal to the spinous process of the third lumbar vertebra of a participant lying in the prone position. Participants are instructed to hold their breath while the load is being applied. A rotary encoder records the resultant displacement. The device is controlled by a customized LabVIEW 8.6 user interface (National Instruments, Austin TX, USA). Image credit: Wong et al.[15].

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5.2 Subjects

5.2.1 Sample Size, Recruitment, and Randomization

The Pain Induction study consisted of 9 healthy control subjects in a cross-over design, recruited from the University of Alberta campus[18]. Ethical considerations as laid out by the University of Alberta Research Ethics Office and Freedom of Information and Protection of Privacy regulations were followed. Subjects were given either an isotonic saline (NS) injection with no pain induced or a hypertonic saline (HS) injection to induce temporary LBP, then crossed over to opposite groups at least 5 days later[18].

5.2.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria for the Pain Induction study were:

Table 5.1: Pain Induction Study Inclusion and Exclusion Criteria [18]

Inclusion Criteria	**Exclusion Criteria**
Adult participants aged 18 to 60 years	Medical "red flag" conditions
No history of LBP or pelvic pain in the last 12 months	Any major orthopedic, neurological or cardiorespiratory diseases
	Prior back or abdominal surgery
	Possible or confirmed pregnancy

5.2.3 Ethical Considerations

Ethical considerations as laid out by the University of Alberta Research Ethics Office were approved under application number Pro00027069. Freedom of Information and Protection of Privacy regulations were followed . Information was accessed with only anonymous subject numbers as identification and a separate ethics approval was therefore not required.

5.3 Data Processing

Data recording was started prior to contacting the tip of the mechanical indentation device with the subject. Once contact was made, the transducer was held in place for five seconds at five Newtons (N) of force to provide a common starting point for post-processing. The tip was again held in place at 60N of force for five seconds at the end of the indentation procedure prior to being reversed. F-D curves were recorded three times before each injection, three times after each injection and three times after 25 minutes had elapsed[18]. This was done in an attempt to mitigate the initial viscoelastic response of the tissues being tested, as discussed in section 2.3.3. In this work, only the last test immediately before injection and the first test immediately after were analyzed by FDA and LCRA, in an attempt to mitigate any confounding factors due to viscoelasticity.

5.3.1 Curve Registration

The data was manually registered to a starting position of 0mm displacement at 4N of force and an end point at 60N of force by means of a series of logical operations. The minimum force data cut-off was set after 4N of force was reached AND the force readings no longer dipped below 3N. This was done to eliminate the portion of data recordings taken prior to transducer contact with patient. The maximum force data cut-off was set after 58N of

force was reached AND the force readings did not exceed 60N. When force readings increased rapidly, the first reading over 60N was used as the cut-off value. This was done to eliminate the portion of data taken while transducer was being held in place or reversed. These criteria worked well for all but four traces. One required a minimum force cut-off after 5N of force was reached and three required a maximum force cut-off after 58N of force reached AND force did not exceed 59N, as 60N was never reached. Manual curve registration was preferred because cut-off criteria were not obvious enough in all of the F-D traces to be able to uniformly apply a landmark registration process. Figure A.1 shows raw data pre-processed within the 4N-60N range as well as the registered F-D curves, plotted to confirm successful registration.

5.3.2 Data Smoothing

Curve smoothing was performed using in the R computing environment (R v.3.3.3, The R Project for Statistical Computing, 2016), using the 'create.bspline.basis', 'fdpar' and 'smooth.monotone' functions within the 'fda' add-on package[52, 62]. Smoothing was achieved by b-spline basis functions in a monotonically increasing fashion, with knots defined for each Newton (N) of force. The smoothing coefficient, lambda (λ), was evaluated at the minimization point of GCV as described in Section 2.5.1 and tested for smoothing sensitivity to ensure the resulting representative curve most closely approximated the original data without over- or under-smoothing. The smoothed curves were then re-sampled at 0N to 60N of force. Figure A.2 illustrates the range of lambda values tested, and Figure A.3 shows the original registered raw data with respect to the calculated functional curves smoothed at λ=4.

5.3.3 Data Transformation

One further data processing step was conducted for FDA. The displacement data was transformed from absolute displacement to percentage of total displacement and re-centred at zero as follows:

$$Displacement_{Norm(i)} = (Displacement_{(i)} - Displacement_{(Min.)}) / (Displacement_{(Max.)} - Displacement_{(Min.)}) * 100\%$$

Where:

$Displacement_{Norm(i)}$=normalized value for each displacement sample point
$Displacement_{(i)}$=value at each displacement sample point
$Displacement_{(Min.)}$=minimum value of sampled displacement
$Displacement_{(Max.)}$=maximum value of sampled displacement

Transformation of force data was not required, as it was uniformly re-sampled after the smoothing process. Data transformation exaggerates the differences in curvature of the F-D curves. Figure A.4 shows a comparison between smoothed and transformed curves.

5.4 Methods: Comparison to Traditional Statistics

In the original Pain Induction study, a Generalized Estimating Equation (GEE) was used to determine the interactions between time and saline concentrations, and to account for the effects of demographics covariates[18]. For this work, a simple repeated-measures point-biserial Pearson correlation and repeated-measures t-statistic were calculated and compared to the GEE results, to ensure that the discriminatory features of the original single-point analyses were not eliminated as a result of the smoothing procedure. The two statistics are directly related, and one can be calculated from the other; however, the point-biserial Pearson's r-correlation accounts for sample size sensitivity whereas the t-statistic does not[65]. Calculations were completed using Microsoft Excel and the standard formulas for each statistic[65].

5.5 Methods: Functional Data Analysis

Functional data analysis was conducted in the R computing environment using the 'kmeans' function within the standard 'stats' package and the 'pca.fd' and 'varmx.pca.fd' functions within 'fda' add-on package[52, 62].

5.5.1 Functional Principle Components

A functional principle components analysis was conducted from the smoothed and the transformed functional data curves. VARIMAX-rotated principle component harmonics were tested for sensitivity to determine the appropriate number of principle component scores to carry forward for clustering for F-D curves, their derivative velocity-displacement curves, their second derivative acceleration-displacement curves, and the transformed F-D curves. Scatter plots of the principle component scores were evaluated for orthogonality and harmonics were set at the maximum number meaningful for each curve type.

5.5.2 FDA Statistical Analysis

Principal component scores derived from the above analyses were plotted and clustered by k-means criteria. The resulting clusters were compared to known pain status and misclassification rates were calculated.

5.6 Methods: Latent Class Regression Analysis

Latent class regression analysis was performed using the Latent GOLD computer package (Latent GOLD v.5.1, Statistical Innovations)[63]. Smoothed curves as described in Section 5.3.2 were re-sampled at 2N, 4N, 6N, 8N, 10N, 15N, 20N, 40N, 45N, 50N, 55N, 60N. The intervals were uneven to keep dimensionality to a minimum as discussed in Section 4, while still maintaining the integrity of the rapidly changing areas of the curves. Figure A.5 illustrates a comparison between the smoothed functional data and re-sampled data for input to LCRA.

5.6.1 LCRA Statistical Analysis

Latent class assignments were performed in an exploratory fashion, using the BIC to evaluate the appropriateness of the resultant classifications. Section 2.5.2.3 contains an explanation of the BIC and its application to latent classes. Based on the results obtained from the sensitivity testing performed in Section 4, the default settings of the Latent GOLD software were used with the Force predictor maintained as a class-dependent

variable and defined a numeric ordinal variable. Covariates were applied in the active state as a secondary analysis. Resultant classifications were compared to known pain status and misclassification rates were calculated.

5.7 Methods: Comparison of Functional Analysis Techniques

The level of agreement between the FDA and LCA functional techniques were evaluated by a Cohen's kappa statistic[61]. A kappa value less than zero indicated a disagreement between the two analyses[60]. Positive intervals were divided into poor (0.01 – 0.20), fair (0.21 – 0.40), moderate (0.41 – 0.60), good (0.61 – 0.80) or very good (0.81 – 1.00)[61].

5.8 Results: Comparison to Traditional Statistics

The results of a post-smooth analysis of GS and TS by traditional statistics are tabulated below and compared to the significant results of the original Pain Induction study. Smoothed curves were deemed to have retained the critical information for a single-point analysis.

Table 5.2: Comparison of Global and Terminal Stiffness Significance Tests After Data Smoothing[18]

	Significance (GEE)	**Significance (t-statistic)**	**Correlation (Pearson's r)**	**Effect Size (Cohen's d)**
Terminal Stiffness @ 60N Isotonic Saline (NS) Pre-Post Values	NS	NS	NS	N/A
Terminal Stiffness @ 60N Hypertonic Saline (HS) Pre-Post	Significant ($p < 0.05$)	Significant ($p < 0.01$)	Significant ($p < 0.01$)	Large ($d = 1.2$)
Terminal Stiffness @ 60N Post-Injection (Peak) Values	Significant ($p < 0.05$)	Significant ($p < 0.05$)	Significant ($p < 0.01$)	Medium ($d = 0.8$)
Slope @ 20-40N Isotonic Saline (NS) Pre-Post Values	NS	NS	NS	N/A
Slope @ 20-40N Hypertonic Saline (HS) Pre-Post	Significant ($p < 0.05$)	Significant ($p < 0.02$)	Significant ($p < 0.01$)	Large ($d = 1.4$)
Slope @ 20-40N Post-Injection (Peak) Values	Significant ($p < 0.05$)	Significant ($p < 0.05$)	Significant ($p < 0.01$)	Large ($d = 1.0$)

Generalized Estimating Equation (GEE) results are tabulated as described in the original Pain Induction study[18].
Global (GS) and Terminal (TS) Stiffness calculations are performed as described in the original Pain Induction study; other statistics are calculated using standard equations and smoothed data[18, 65]. Results are significant (with corresponding p-value or Cohen's d), not significant (NS) or not applicable (N/A).

5.9 Results: Functional Data Analysis

5.9.1 Functional Principle Components and Statistical Analysis

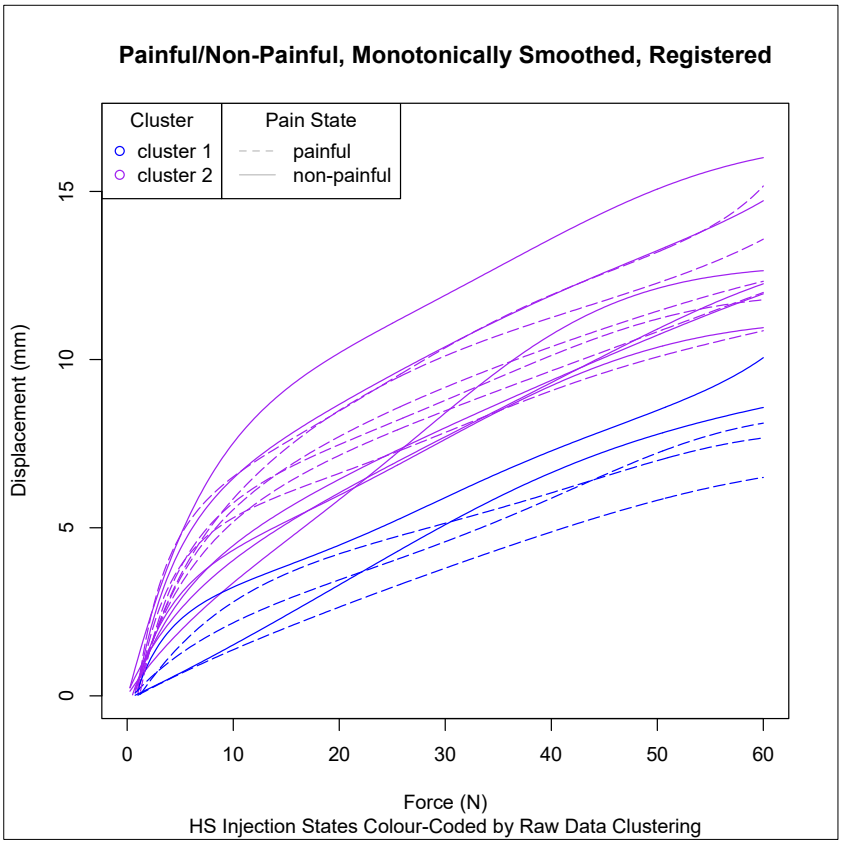
The number of meaningful harmonics for functional principle components analysis was dependent on the data curve type. As can be seen in Figure A.6, smoothed raw data optimized at four harmonics and transformed data optimized at three harmonics. First and second derivatives display interesting correlations for harmonics one, two and five, with the second derivatives amplifying the correlations displayed in the first derivative plots. Figure A.7 contains a closer look at the fifth harmonic for the second-derivative data. Figure A.6 also displays the results of a 2-cluster k-means clustering procedure. Percentage variability for each harmonic in each data curve format is

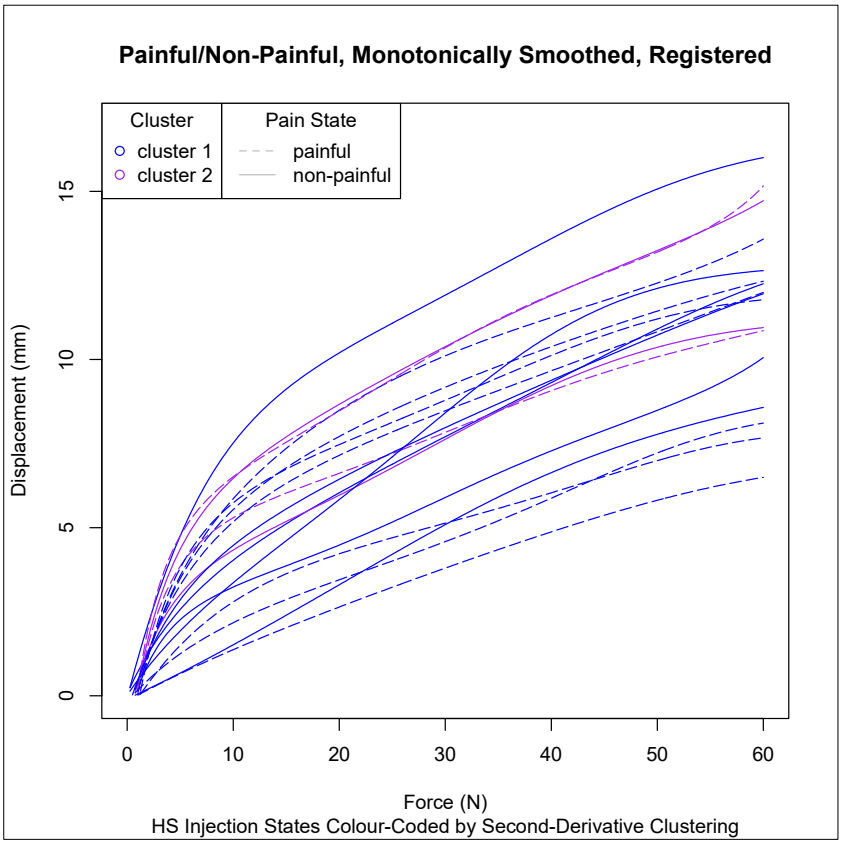
summarized in Table A.1, and Figures A.8 - A.11 illustrate the variations of the mean curve for each VARIMAX-rotated principle component.

Clustering by the k-means method resulted in high misclassification rates. Misclassifications ranged from approximately 30% to approximately 45% for any of the 2-cluster curve analyses. For the 4-cluster, combined-trait analysis case, misclassifications ranged from greater than 55% to approximately 70%. Tables A.2 – A.5 contain clustering and misclassification results for all cases. Smoothed raw data curves clustered by raw data and second derivative fPCA analysis only are shown in Figure 5.2.

Figure 5.2: fPCA and k-Means Clustering Results – Pain Induction Study

Raw data and second-derivative clustering of F-D curves showing high misclassifications rates. Misclassifications for curve analyses not shown were even greater.



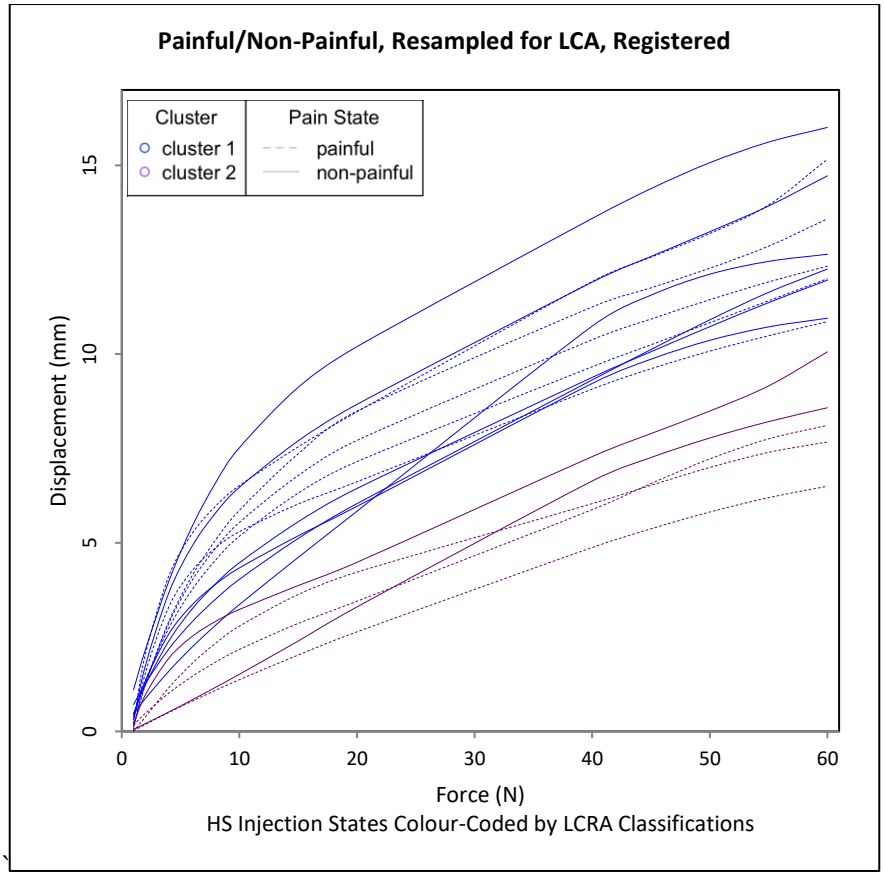


5.10 Results: Latent Class Analysis

The dimensionality of F-D data versus the number of subjects in the cohort prevented an analysis by injection type, due to insufficient degrees of freedom. A grouped analysis of all plots for all subjects did not result in meaningful clusters, as can be seen by the misclassification rates tabulated below. Specifically, clustering by LCRA resulted in misclassifications 37% of the time. Results are illustrated in Figure 5.3.

Figure 5.3: LCRA Clustering Results – Pain Induction Study

Latent class regression analysis clustering of F-D curves showing high misclassifications rates.



5.11 Results: Comparison of Functional Analysis Techniques

The level of agreement between FDA and LCA classifications was very good ($\kappa = 0.93$) for the raw data cases, but resulted in a calculated disagreement between the techniques ($\kappa < 0$) for all other cases.

5.12 Discussion

5.12.1 Functional Data Analysis Outcomes

As expected, a functional data analysis by k-means clustering of fPCA scores resulted in F-D plots grouped by rate-of-change features. On observation of the top plot in Figure 5.2 illustrating raw data clustering results, it can easily be seen that the curves are simply grouped by relative position of the linear portion of the F-D curves, with curves occupying the top half of the total group in one cluster and curves occupying the bottom half of the total group in another. It is also obvious from the plots that clustering in this way had no correlation to pain status. On the other hand, clustering results determined by second-derivative fPCA as depicted in the bottom plot in Figure 5.2 illustrate a more nuanced mechanism of curve segmentation. Further inspection of this plot reveals that a rapid rate-of-change in the "transition zone" region of the curve (between approximately 5N-10N) was the discriminating feature that resulted in the two clusters. This unfortunately did not associate with known patient traits from the clinical study.

A brief discussion will now be dedicated to principle component harmonics as depicted in Figures A.8 to A.11, and Table A.1. Harmonics were only considered to be meaningful if some associative relationship was obvious between fPC scores as illustrated in a scatter plot as depicted in Figure A.6. When data is scattered in a rectangular pattern, the optimal number of harmonics has been reached and an increase in harmonics will not improve discriminatory power[53]. The number of harmonics was unique to curve type, indicating that the differentiation of F-D curves and their resulting conversion to force-velocity and force-acceleration curves not only shifted the discriminatory importance to a different region of the curve, but also that this new region of importance was important in different ways. In other words, where the pre- or post-linear regions dominated the raw-data analysis with four different types of variant to the mean curve, the importance shifted to two different variants to the mean in the transition zone region when analyzing velocity and acceleration of the indenter tip instead of displacement.

First and second derivatives display interesting correlations for harmonics one, two and five, with the second derivatives amplifying the correlations displayed in the first derivative plots. On further investigation of harmonic five, depicted in Figure A.7, it can be seen that participant 6 seems to differ from the cluster of other F-D measurements. The difference is specifically found in the immediately post-painful injection state. A plot of the F-D curves for all participants in the same state does not immediately identify any serious difference between participant 6 and the rest; however, a plot of the second derivatives illustrates an exaggeration of the greater rate of change in the transition zone region for this participant, as well as an exaggeration of the tail near the terminal force measurements. The tail is most likely the factor contributing to the very different principle component scores in harmonic five, since there are other participants with similarly exaggerated transition zone region

accelerations that have not been grouped nearby. The tail itself is an artefact of smoothing since no such upturn exists in the raw data shown in Figure A.3, and can therefore be ignored. There is nothing in the patient demographics data that would identify participant 6 as being unique from the rest.

On observation of the original principle components that were fed into the k-means secondary analysis of the raw data (Figure A.8), it can be seen that the greatest weighting for discrimination between curves were fPC3, corresponding to the pre-linear region of the F-D curve (between approximately 10N–30N), and fPC4, corresponding to the post-linear region of the curve (between approximately 40N–50N). These two principle components account for nearly 80% of the variability in the curves, while the transition zone region accounts for only approximately 6% of the total variability. This is why the relatively linear regions of the F-D curves dominated the clustering status in the case of raw-data analysis and clustering. Once the curves have been differentiated, however, the greatest variability shifts to the transition zone region, as can be seen in Figures A.10 and A.11. This in turn resulted in the clustering status seen in the second-derivative case. The transformed data optimized at three harmonics with the emphasis shifted from pre- and post-linear curve sections in the raw data case to the transition zone and pre-linear curve sections in the transformed case, as shown in Figure A.9.

Importantly, it should be noted that while the k-means clustering procedure produces clusters by means of variability as explained by fPCA, there are other ways to analyze functional principle components. One such secondary analysis technique, stepwise-differential analysis (SDA), has recently been applied to the biomechanics of rowing with success[66-71]. SDA does not necessarily result in groupings by greatest variability explained, but rather by discriminating power on curve shape as applied to subject type. This is a powerful secondary analysis technique, and it is strongly recommended that it be pursued.

5.12.2 Latent Class Analysis Outcomes

The dimensionality of F-D data required to maintain curve integrity prevented an LCRA analysis by injection type due to insufficient degrees of freedom. A grouped analysis of all plots for all subjects did not result in meaningful clusters.

5.12.3 Comparison of Functional Analysis Techniques

The limitations of the LCA outcomes inhibit meaningful interpretations of level of agreement between functional statistics techniques.

5.13 Conclusion

The overall goal was to determine if a full curve analysis by LCRA and FDA software performed at least as well as traditional statistical analyses. While the results here did not achieve this goal, an important outcome was realized; subsections of force-displacement data (e.g. TS and GS) retain important clinical information about patient status.

6. Comparison of Functional Data Analysis, Latent Class Analysis and Traditional Statistics of Spinal Segment Mobility in a Clinical Responders LBP Study

This section details the methods, results and conclusions drawn after the Responders study F-D curves were analyzed with FDA and LCRA. The first main outcome was to determine if clinical patient data with a smaller effect size but larger sample size than was seen in the Pain Induction study would result in significant clustering by FDA or LCRA and to compare those outcomes to the single data-point analysis performed in the original study. Second, analysis by LCRA was explored in greater detail to determine if any sub-classes of patients would emerge, taking into account a larger cohort and several covariates.

6.1 Data Acquisition

The Responders study F-D curves for analysis were previously obtained in a similar way to the Pain Induction Study curves, and using the same device as described in Section 5.1.

6.2 Subjects

6.2.1 Sample Size, Recruitment, and Randomization

For the Responders study, both patients experiencing LBP and asymptomatic control subjects were recruited via advertising at local clinics and at local universities[14]. The study design was non-randomized; patients were assigned to SMT treatment and non-treatment groups equally, but were pre-screened as being predicted responders or non-responders based on a previously-established clinical prediction rule[14]. This was done to determine if the quantitative stiffness, LM thickness ratio, and disc ADC measures would correspond to commonly-utilized clinical prediction rules[14]. The sample size for each patient cohort was determined to be 57 asymptomatic controls and 32 patients with LBP[14].

6.2.2 Inclusion and Exclusion Criteria

The table below outlines inclusion and exclusion criteria for the Responders study:

Table 6.1: Responders Study Inclusion and Exclusion Criteria [14]

Inclusion Criteria	**Exclusion Criteria**
Adult participants aged 18 to 60 years	Medical "red flag" conditions
LBP participants were included if:	Signs of nerve root compression
LBP with or without leg symptoms	Scoliosis
Intensity of at least 2 on the 11-point numeric pain rating scale	Osteoporosis
mODI score of at least 20%.	Joint hypermobility syndrome
Asymptomatic control participants were included if:	Previous lumbosacral surgery
No current LBP	SMT/stabilization exercise treatment in the last 4 weeks
No history of LBP that required sick leave in the last 12 months	

6.2.3 Ethical Considerations

Ethical considerations were approved under the same approvals as for the Pain Induction study, as detailed in Section 5.2.3.

6.3 Data Processing

Data recording was completed as detailed in Section 5.3.

6.3.1 Curve Registration

As with the Pain Induction study data, F-D curves were manually registered to a starting position of 0mm displacement at 4N and an end point at 60N. A series of logical operations were executed as follows: Minimum force data cut-off was set after 5N of force was reached AND the force readings no longer dipped below 4N AND force did not exceed 7N AND no more than two nodes of oscillation were recorded. The variability in F-D recordings prior to transducer contact with patient was wide and this was done to eliminate the portion of data recordings taken before application of test loads. The maximum force data cut-off was set after 58N of force was reached AND the force readings did not exceed 60N. When force readings increased rapidly, the first reading over 60N was used as the cut-off value. As with the Pain Induction study data, this was done to eliminate the readings taken while the transducer was being held in place or reversed. Manual curve registration was again preferred because variability in cut-off criteria prevented an automated landmark registration process. Figure B.1 shows raw data pre-processed within the 4N-60N range as well as the registered F-D curves, plotted to confirm successful registration.

6.3.2 Data Smoothing

Curve smoothing was performed as detailed in Section 5.3.2. Figure B.2 illustrates the range of lambda values tested, and Figure B.3 shows the original registered raw data with respect to the calculated functional curves smoothed at λ=3.5.

6.3.3 Data Transformation

The same data transformation procedure detailed in Section 5.3.3 was followed to normalize the Responders study F-D curves. Figure B.4 shows a comparison between smoothed and transformed curves.

6.4 Methods: Comparison to traditional statistics

Repeated-measures analyses of covariance were completed in the original Responders study, to account for time, LBP status and response status as determined by self-reported mODI[14]. Similar to the procedure described in Section 5.4, a repeated-measures point-biserial Pearson correlation and repeated-measures t-statistic are calculated and compared to the Responders study results, to ensure that the discriminatory features of the original single-point analyses are not eliminated as a result of the smoothing procedure.

6.5 Methods: Functional Data Analysis

Functional data analysis was conducted by exactly similar procedures as detailed in Section 5.5 for the Pain Induction study.

6.6 Methods: Latent Class Regression Analysis

Latent class regression analysis was also performed in accordance with the procedure followed for the Pain Induction study, similar to that described in Section 5.6. A comparison between the smoothed functional data and re-sampled data for input to LCRA is illustrated in Figure B.5.

6.6.1 LCRA Statistical analysis

Settings for the latent class analysis were as described in Section 5.6.1.

6.7 Methods: Comparison of Functional Analysis Techniques

Cohen's kappa is calculated to evaluate the performance of the FDA and LCA functional data analyses with respect to each other[61].

6.8 Results: Comparison to Traditional Statistics

The significant results obtained from the original Responders study are compared to a post-smooth analysis of GS and TS by traditional statistics in the table below. As with the Pain Induction study analyses, smoothed curves were deemed to have retained the critical information for a single-point analysis.

Table 6.2: Comparison of Stiffness Significance Tests After Data Smoothing[14]

	Significance (ANCOVA)	**Significance (t-statistic)**	**Correlation (Pearson's r)**	**Effect Size (Cohen's d)**
Terminal Stiffness @ 60N All Participants Pre-Post Values	NT	NS	NS	N/A
Terminal Stiffness @ 60N Responders (R) Pre-Post Values	Significant ($p < 0.01$)	Significant ($p < 0.01$)	Significant ($p < 0.01$)	Small ($d = 0.4$)
Terminal Stiffness @ 60N Non-Responders (NR) Pre-Post Values	NS	NS	NS	N/A

Analysis of covariance (ANCOVA) results are tabulated as described in the original Responders study[14].
Stiffness calculations are performed as described in the original Responders study; other statistics are calculated using standard equations and smoothed data[18, 65]. Results are significant (with corresponding p-value or Cohen's d), not significant (NS), not tested (NT) or not applicable (N/A).

6.9 Results: Functional Data Analysis

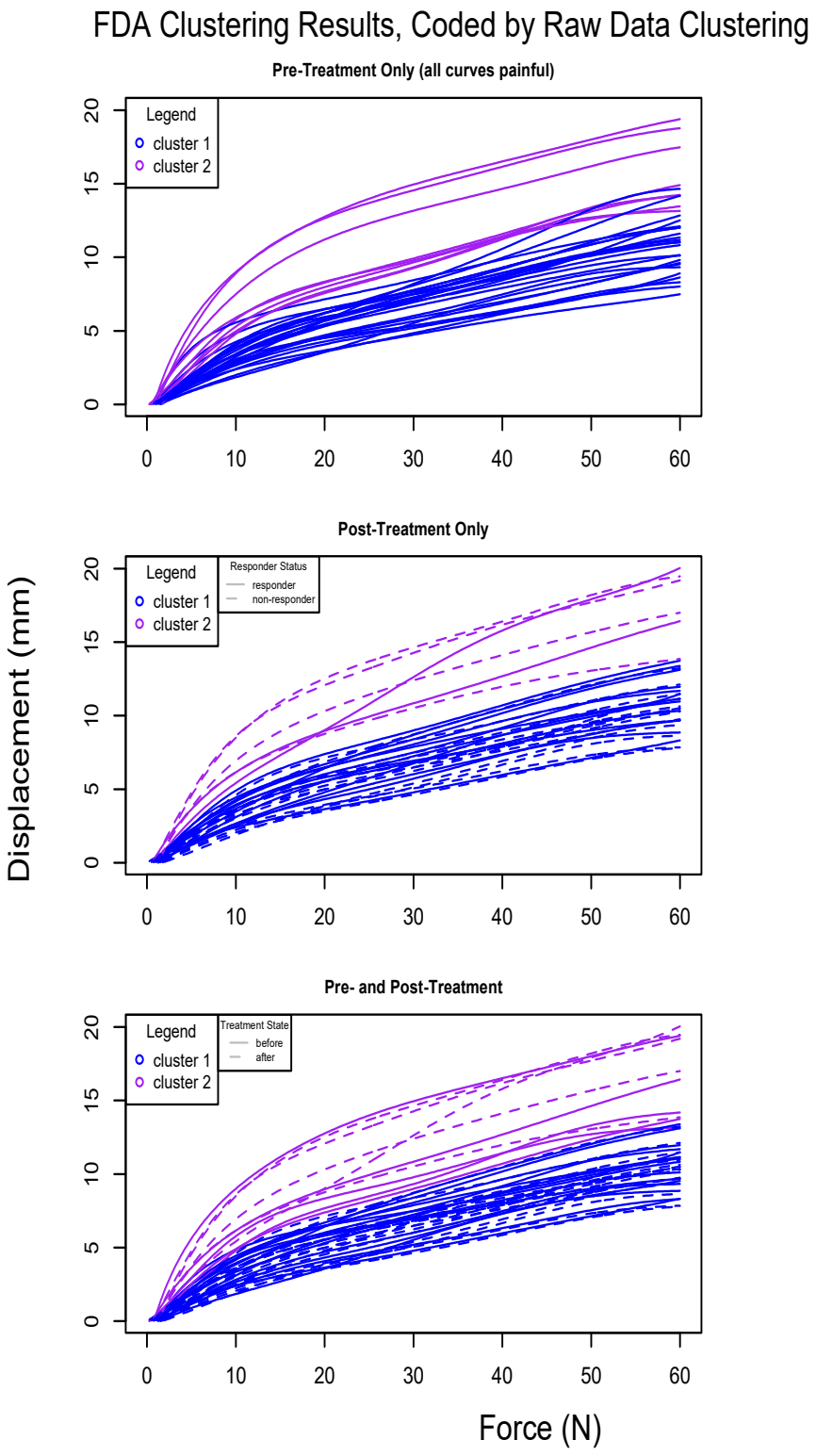
6.9.1 Functional Principle Components and Statistical Analysis

The number of meaningful harmonics for functional principle components analysis was dependent on the data curve type. As can be seen in Figure B.6 smoothed raw data optimized at six harmonics. First derivatives did not display strong correlations at any harmonic and second derivatives only displayed interesting correlations for harmonics one and two. The transformed data optimized at five harmonics. Figure B.6 also displays the results of a 2-cluster k-means clustering procedure. Percentage variability for each harmonic in each data curve format is

summarized in the Table B.1 and Figures B.7 - B.9 illustrates the variations of the mean curve for each VARIMAX-rotated principle component.

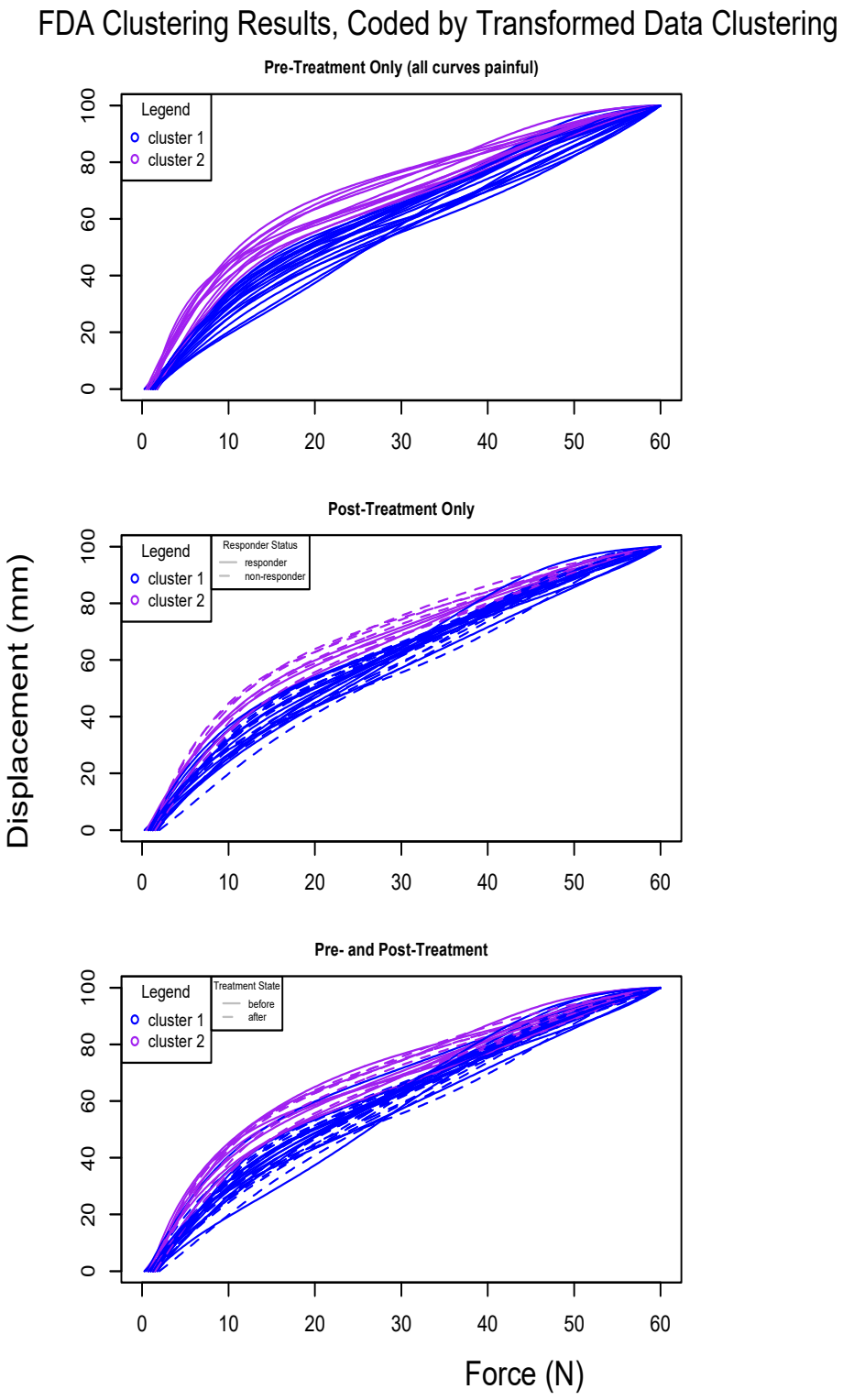
Misclassification rates are summarized in Tables B.2 – B.14. Clustering by the k-means method resulted in high misclassification rates in all cases. Specifically, clustering by raw data curves resulted in a 44% misclassification rate, clustering by second derivatives resulted in misclassifications 47% of the time, and transformed data resulted in a 50% misclassification rate. Smoothed raw data curves clustered by raw data, transformed data, first and second derivative fPCA analysis are shown in Figures 6.1 – 6.4.

Figure 6.1: fPCA and k-Means Clustering Results – Responders Study



Raw data and raw-data clustering of F-D curves showing high misclassification rates.

Figure 6.2: fPCA and k-Means Clustering Results – Responders Study



Transformed data and transformed-data clustering of F-D curves showing high misclassification rates.

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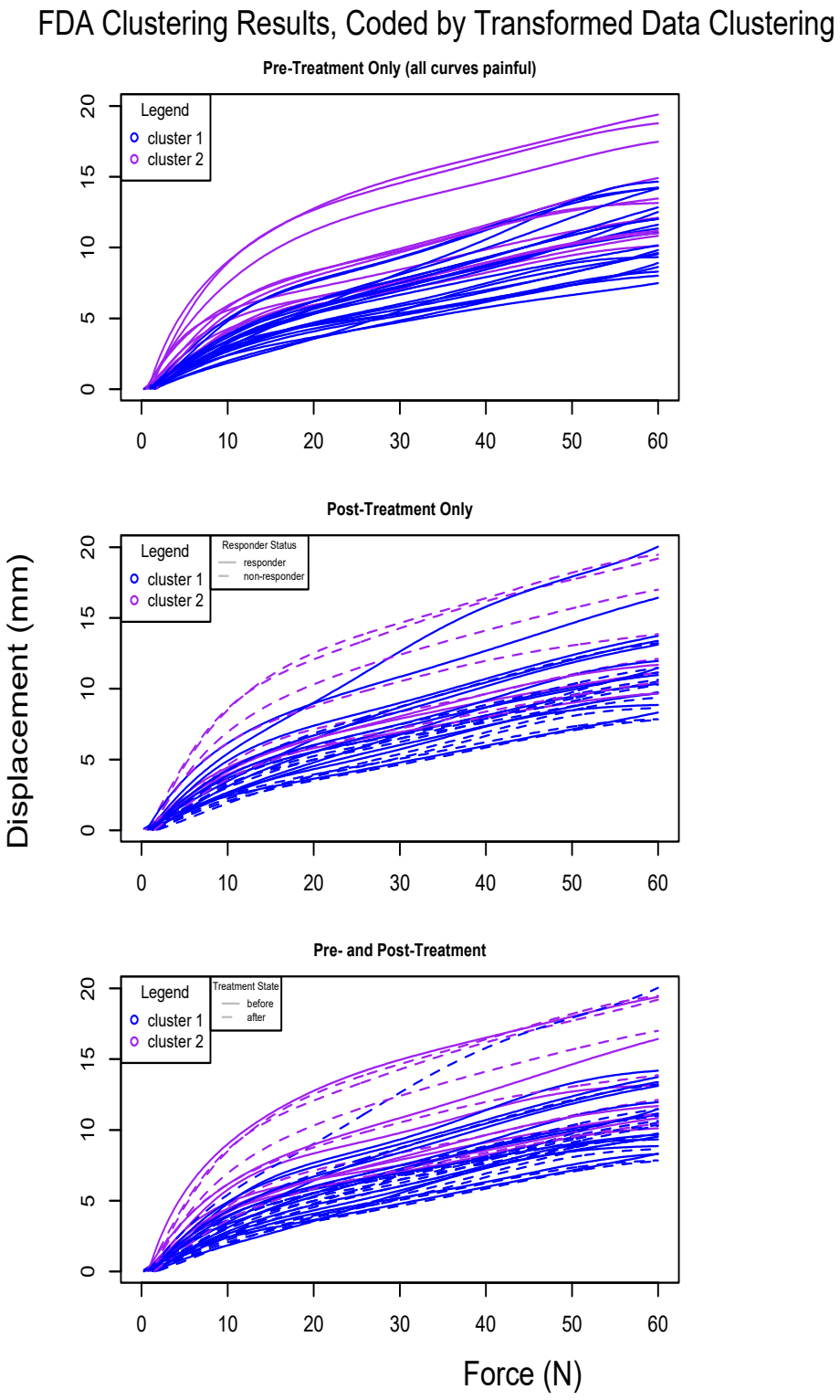
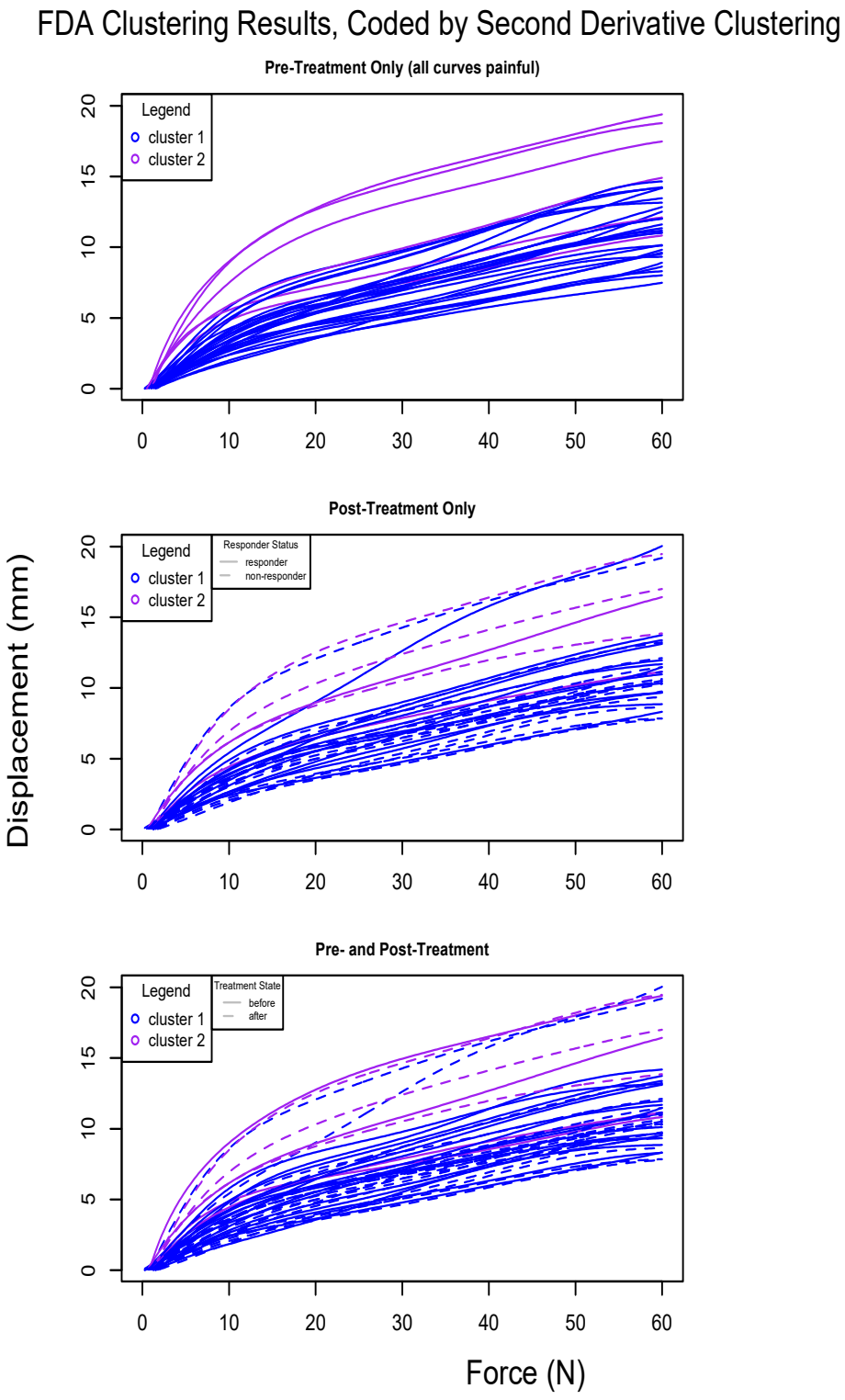
Figure 6.3: fPCA and k-Means Clustering Results – Responders Study



Raw data and transformed-data clustering of F-D curves showing high misclassification rates.

Back

Figure 6.4: fPCA and k-Means Clustering Results – Responders Study



Raw data and 2nd-derivative clustering of F-D curves showing high misclassification rates.

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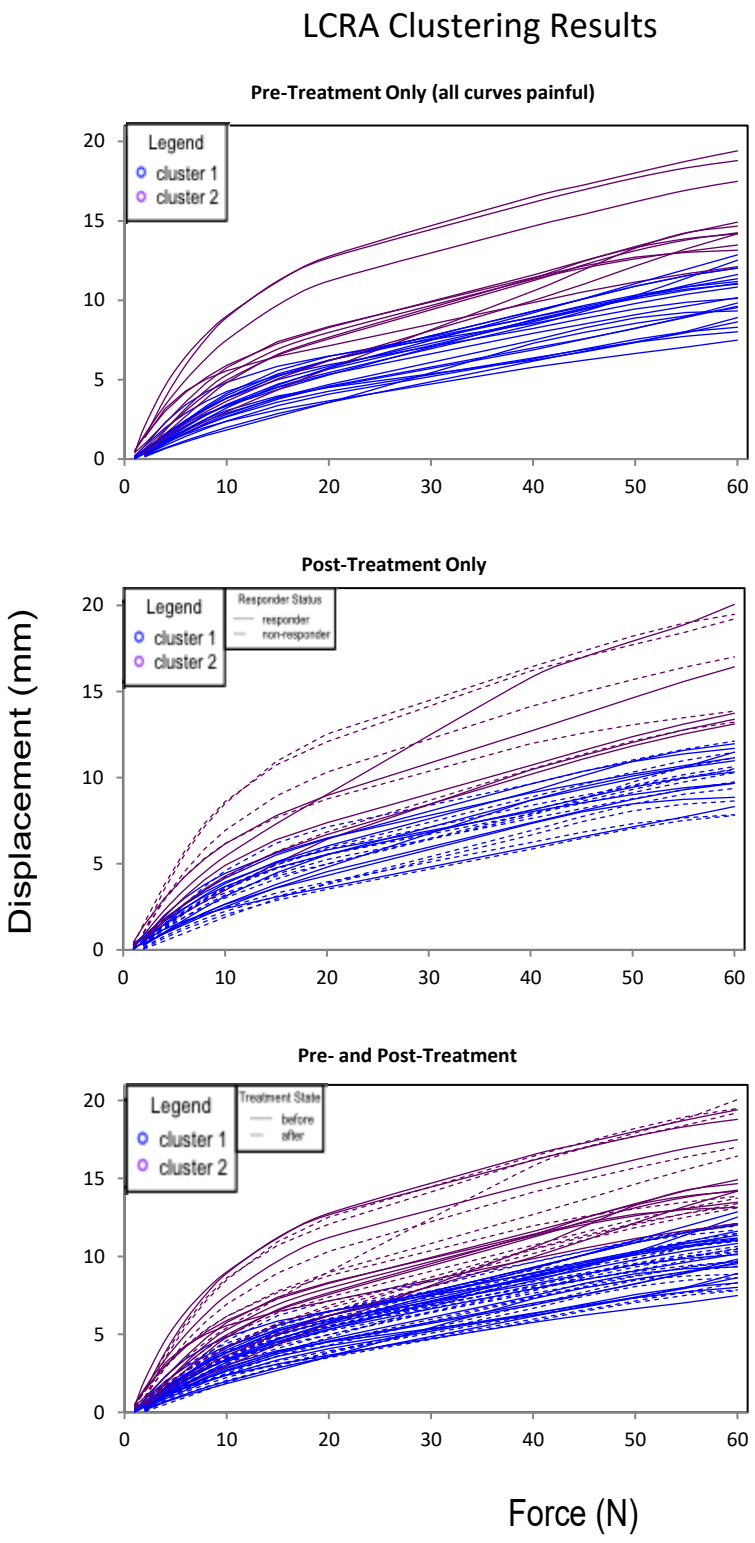
6.10 Results: Latent Class Analysis

The dimensionality of F-D data versus the number of subjects in the cohort allowed for only two clusters, due to a restriction in degrees of freedom. Clustering by LCRA resulted in misclassifications nearly 50% of the time, as tabulated below. The addition of covariates to the LCRA did not impact clustering outcomes. Smoothed raw data curves clustered by latent class regression analysis are shown in Figure 6.5.

Figure 6.5: LCRA Clustering Results – Responders Study



Latent class clustering of F-D curves showing high misclassification rates.

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6.11 Results: Comparison of Functional Analysis Techniques

Level of classification agreement between functional techniques for responders results was good ($\kappa = 0.78$) for the raw data cases, but only moderate ($\kappa = 0.45$) for the derivative and transformed cases. The non-responders group resulted in a calculated disagreement between the techniques ($\kappa < 0$) for all cases.

6.12 Discussion

6.12.1 Functional Data Analysis Outcomes

In this secondary analysis of Responders study data, the FDA method did not perform as well as anticipated, and force-displacement groupings were not as obvious as those from the Pain Induction study. It is hypothesized that this shortcoming is due the comparatively smaller effect size in the Responders study dataset. This analysis unfortunately did not therefore associate with known patient traits from the clinical Responders study. It is also obvious from the plots that the fPCA clustering results achieved had no correlation to pain or responder status. As before, observation of the plots in Figure B.7 indicate that the curves are simply grouped by relative position of the linear portions of the F-D curves, with curves occupying the top half of the total group in one cluster and curves occupying the bottom half of the total group in another. This was true regardless of treatment condition or pain status. The groupings became more nuanced when analyzed in the transformed state, or when derivatives of the original raw data curves were analyzed; however, these new groupings still did not associate with known patient traits from the clinical study. Specifically, the transformed data analysis was most successful at emphasizing differences in the "transition zone" region of the curves (between approximately 5N – 10N) and overall slope, as can be seen in comparing Figure B.8. Clustering by derivatives was less effective, as changes in curvature within the first 2N of force application (approximately 66% of the total variability) and amplitude variations in the transition zone region (approximately 30% of the total variability) overtook the fPCA, as can be seen in Table 6.2 and Figure B.9. This was the case for both first and second derivative fPCs.

On observation of the original principle components that were fed into the k-means secondary analysis (Figures B.7 – B.9), it can be seen that the greatest weighting for discrimination between curves in the raw data state were fPC2, corresponding to the "pre-linear" region of the F-D curve (between approximately 10N–30N), fPC3, corresponding to the "linear" region of the F-D curve (between approximately 20N–40N), and fPC5, corresponding to the "post-linear" region of the curve (between approximately 40N–50N). These three principle components account for nearly 85% of the variability in the curves, while the transition zone region accounts for only approximately 6% of the total variability. This is consistent with the Pain Induction fPCA results, and is the reason that the relatively linear regions of the F-D curves dominated the clustering status in the case of raw-data analysis and clustering. fPC1 in the transformed data case becomes the greatest attribute of variability at nearly 35%, which corresponds to variations in slope in the pre-linear and linear regions of the curves. The next most important component is fPC3, corresponding to variations in amplitude in the transition zone region. Once the curves have been differentiated, the greatest variability shifts to the transition zone region. These results indicate what can be seen intuitively when observing the curves: that the transition zone regions are unique; and what

has already been shown in the single-point analyses already conducted in the original studies: that the slope of the linear region of the curves matters.

It should importantly be noted that while the k-means clustering procedure produces clusters by means of variability as explained by fPCA, there are other ways to analyze functional principle components. One such secondary analysis technique, stepwise-differential analysis (SDA), has recently been applied to the biomechanics of rowing with success[66-71]. SDA does not necessarily result in groupings by greatest variability explained, but rather by discriminating power on curve shape as applied to subject type. This is a powerful secondary analysis technique, and it is strongly recommended that it be pursued.

6.12.2 Latent Class Analysis Outcomes

The dimensionality of F-D data required to maintain curve integrity limited the LCRA analysis to only two clusters, neither of which were meaningful. The overall goal was to determine if known sub-groups can be identified from spinal stiffness curves using advanced analytical techniques. While our results here did not achieve this goal, an important outcome was realized; subsections of force-displacement data (e.g. terminal stiffness or linear slope) retain important clinical information about patient status.

6.12.3 Comparison of Results

The level of agreement between functional statistics techniques was again limited by the LCA outcomes, as was the case in the previous analysis of Pain Induction study data. In this case, there is however a trend that indicates some level of agreement between functional statistics for responders F-D curves as compared to non-responders F-D curves. Some agreement is present, even if it is at a low level, when responders are analyzed, whereas non-responders F-D curves result in across-the-board disagreement between techniques.

6.13 Conclusion

The overall goal was to determine if a full curve analysis by LCRA and FDA software, with data from a larger sample size but smaller effect size, performed at least as well as traditional statistical analyses. While the results here did not achieve this goal, an important outcome was realized; subsections of force-displacement data (e.g. terminal stiffness or linear slope) retain important clinical information about patient status.

7. Thesis Discussion

It has been established that stiffness measurement can be effective to delineate patients who have responded or not to a specific LBP intervention, but the original analysis was completed using only single-value representations of regional or terminal stiffness to convey a complex biomechanical response to an applied load. A fuller understanding of which features of individual F-D curves relate to patient demographics, pain characteristics, response to treatment, or any combination thereof may facilitate *a priori* identification of LBP patient response. Therefore, this work lays an important foundation for the exploratory investigation of latent subgroups of LBP patients.

Previous comparable work in the study of functional curve analysis is limited, though informative. FDA is a relatively new analysis technique, and while it has been applied in a variety of ways to date, none have the breadth and depth of knowledge behind them to be easily transferred to biomechanical studies. Almost all applications begin with an fPCA, and then proceed to a secondary statistical analysis from there. The fPCA can be conducted in a univariate fashion as was done here, or in a bivariate or multivariate approach. In this work, a k-means clustering procedure was followed; however, other secondary fPC analysis techniques, such as SDA has also been applied with success in other studies of biomechanics and would be a worthwhile investigation in the future. LCRA as applied here has been a completely novel application. While other latent class regression analyses have been conducted, the application of the technique to analyse a biomechanical response curve has not yet been attempted, which is a strength of this thesis.

The overarching goal of this work was intended to identify practicable functional statistical techniques for the analysis of patient F-D curves, with accompanying hypotheses that the techniques chosen would successfully group patients by pain (Pain Induction) or recovery (Responders) status. The first experiment was conducted using simulated data that was designed to be easily discernible by FDA. The study and was intended to provide a foundation to specify and interpret an LCRA model of patient F-D curves, since the application is unique and interpretation could have been cumbersome without some preliminary testing. The results identified that the LCRA technique emphasizes end values and overall curve proximity ahead of distinctive features of curve shape. At this time, it is still unknown which specific features of a F-D relate to patient status, other than that terminal and regional stiffness are associated with a favourable response to SMT. Therefore, both FDA and LCRA were carried forward to investigate overall curve shape and its relationship to pain status with experimental data where a large effect size was observed.

Next, the Pain Induction study F-D curves were examined with the aim of evaluating FDA and LCRA performance with experimental data that had a large effect size (Cohen's $d \geq 0.8$). As expected, the FDA method grouped F-D curves by salient features of shape. The dimensionality of the data required to maintain curve integrity far exceeded the number of subjects required to maintain sufficient degrees of freedom to perform LCRA by injection type, and a grouped analysis for all subjects did not result in meaningful clusters. While the results obtained did not achieve the objective of matched or better performance compared to traditional statistics, an important

outcome was realized. Subsections of force-displacement data (e.g. terminal stiffness or linear slope) retain important clinical information about patient status. Though the results of curve analysis were not clustered as effectively as anticipated, analysis with a clinical cohort was still pursued to understand if groupings would improve with true clinical LBP patients, and more thorough demographic information.

In the Responders study, more F-D curves were available for analysis thanks to a greater number of participants, but they were not as obvious to distinguish as those from the Pain Induction study since the effect size was only moderate (Cohen's $d \geq 0.5$). Unfortunately, the final curve analysis investigation therefore did not perform as well as anticipated. Similar to the previous LCRA outcome, dimensionality of the re-sampled F-D data described in Section 6.6 limited the LCRA analysis to only two clusters, neither of which were meaningful. It should be noted that the sample size for this work was still relatively small compared to the dimensionality of the data, and it is hypothesized that the curve analysis shortcomings are at least in part due to this shortcoming.

Of crucial note, the patient demographic information collected in the original clinical studies may have omitted an important discriminatory factor. It is possible that something other than pain status, sex or BMI could have resulted in a significant association between F-D curve shape and patient LBP status. Overall, this work has laid a foundation for investigation that should be further pursued, as a predictive or diagnostic tool for a-priori identification of LBP patient response is still desperately needed and the clinical work that led to this line of enquiry holds promise for a breakthrough.

7.1 Strengths and Limitations

The analyses contained within this thesis are the first to apply functional statistics to a quantitative measure of LBP patient stiffness. While the outcomes did not align with data that had been collected, the doorway was opened for future work in this area. Two techniques were tested and some comprehensive recommendations for future work are outlined in the following section.

Both FDA and LCRA are sensitive to sample size. In both clinical studies, the number of participants did not greatly offset the dimensionality of the functional data curves being analyzed. The large effect size apparent in the Pain Induction study somewhat balanced the shortcoming in number of participants; however, it was not enough to identify patient or pain characteristics that may have been driving the clustering results. As such, a pooled analysis of F-D traces collected for subjects in any study in which the same mechanical indentation device was used is recommended. Subjects could be grouped by any combination of pain status or commonly collected demographics data across methodologies.

7.2 Future Work

Stiffness has been linked to an improvement LBP outcomes in some cases, but an *a priori* determination of which patients are most likely respond to treatment has yet to be been identified. This work was an attempt to further analyze this phenomenon to determine if data contained in patient F-D curves had been inadvertently discarded when reducing the information to two single-point representations for the purposes of statistical analysis of

patient response. Unfortunately, the curves clustering outcomes achieved did not align with known patient characteristics. Aside from pooled analyses or acquisition of more F-D curves from more subjects, other specific recommendations for analysis have become clear. First and foremost, patient demographics should be more thorough. Sex, height and weight may not be the discriminating co-factors to potential recovery as a result of SMT. It is recommended that the knowledgebase be assessed and a comprehensive list of LBP risk factors be assembled for use in questionnaire format for demographics data collection in future studies. Also, a more thorough description LBP including quality and location should be added to questions recording pain history and duration.

In addition to recommendations around patient data collection, some specific data analysis recommendations may be fruitful avenues of research. K-means clustering of fPCA scores is only one form of statistical analysis available with the FDA technique. Other hierarchical clustering methods such as the SDA example given in Chapter 6 have been applied with success in the field of biomechanical analysis. In addition, a time-based bivariate analysis of force and displacement could be employed. Perhaps de-coupling force and displacement may emphasize information that is otherwise not apparent enough to be detected when performing the fPCA. F-D phase-plane plots, used to directly assess the relationship between the raw data and its derivatives, may also provide further insight. Finally, it may be of interest to use the LCA method to analyse fPCA scores. It was apparent by the results obtained in both the Pain Induction and Responders study curves that raw data analyses resulted in an emphasis on the primarily linear sections of an F-D curve, while differentiating the curves shifted the emphasis to the transition zone regions. Investigating both sections together may provide a discriminating factor that is not apparent when investigating each scenario individually. Finally, an individual, piecewise investigation of each region of a F-D curve could perhaps result in a more sensitive fPCA outcome, since only the discriminating features of each section of the curve would be analyzed, without dilution by dissimilar regions. For example, the curvature in the transition zone region would be the only discriminating factor for principle components, since slope of the linear region or termination point at the end of the curves would be eliminated from the analysis.

Lastly, there has been much discussion regarding the analysis of F-D curves; however, the biomechanics comprising a F-D measurement are complex and not yet fully understood. Important future work to examine the component motions comprising a bulk measurement of force and displacement is required to be able to fully understand stiffness in the low back. Two approaches to this problem are necessary: direct observation and mathematical simulation. As such, MRI studies to measure when and how tissues are moving under load would be beneficial, as would biomechanical finite element modelling to help determine what is contributing most to stiffness. The Pain Induction and Responders studies discussed in the early sections of this document have pointed to muscle activity and intervertebral discs as starting points for such investigations. The quantitative measurement of stiffness and its correlation to pain and recovery are new and there are currently far more questions than answers!

7.3 Significance

Identifying the salient features of a patient F-D curves could streamline and expedite the process of LBP patient data collection, saving time for clinicians, frustration for patients, and possibly expediting recovery of one of the most common, costly and debilitating illnesses experienced in North America at this time. F-D curve analysis holds promise, since certain biomechanical markers, namely slope and terminal stiffness, have been definitively linked to patient-reported recovery. Future work would delve even further into F-D curve characteristics in combination with additional clinical assessments including MRI, basic science with ex-vivo functional spinal units, and biomechanical modelling in an attempt to answer some of the more difficult questions outlined herein.

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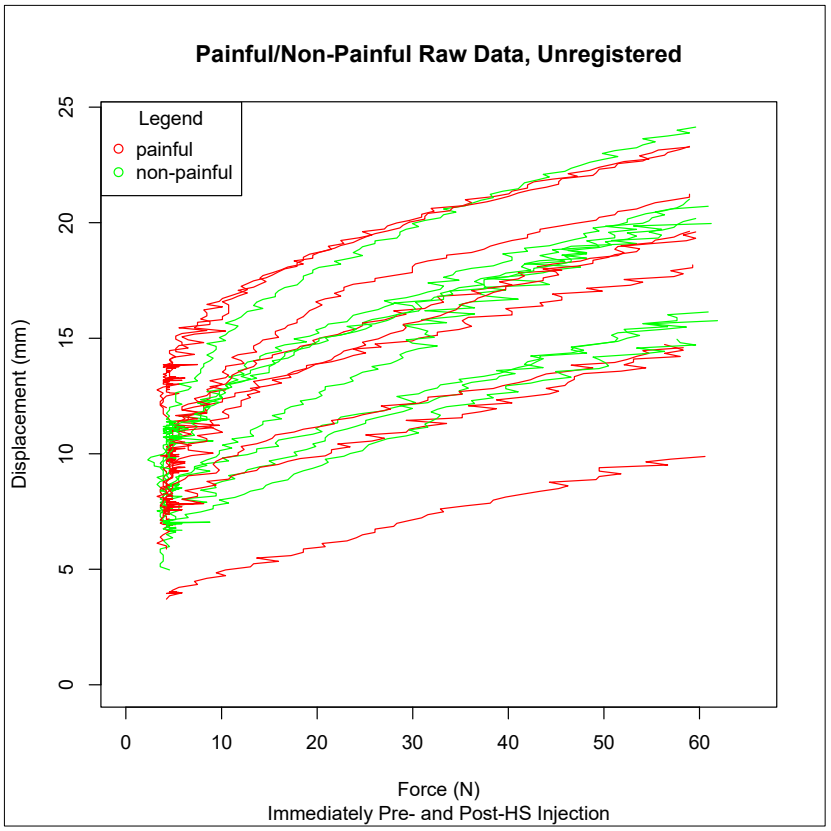
Appendix 1: Pain Induction Study Data Processing Figures and Tables

Figure A.1: Curve Registration – Pain Induction Study

Two graphs showing raw (top) and registered (bottom) force-displacement data from the Pain Induction study.



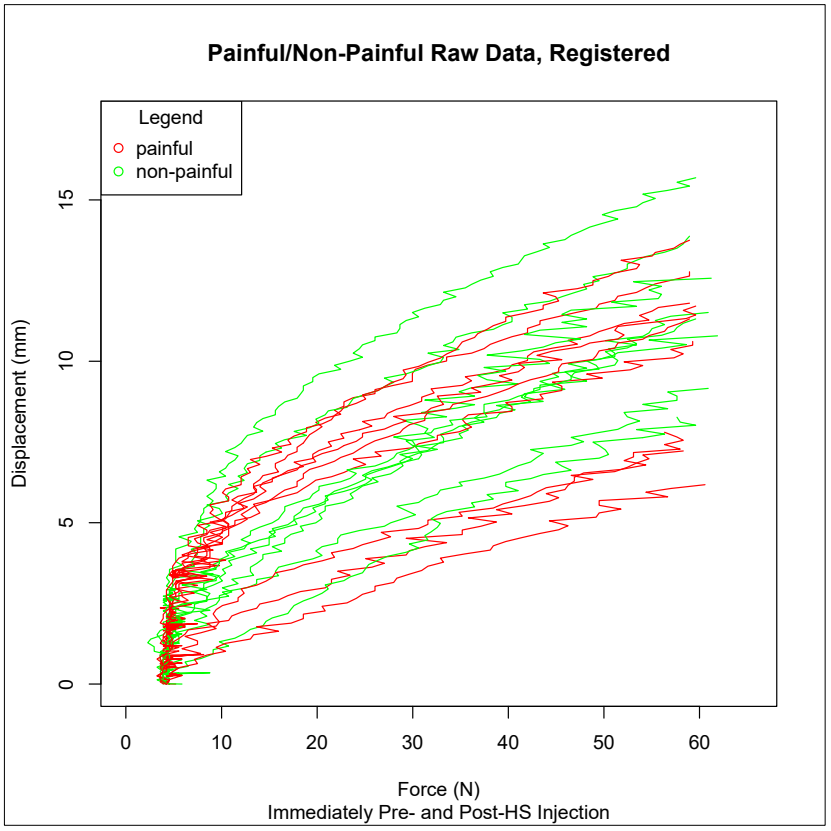


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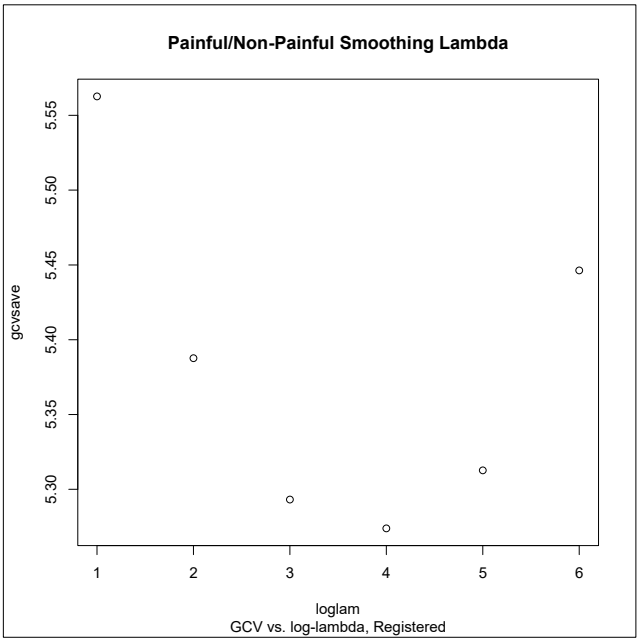
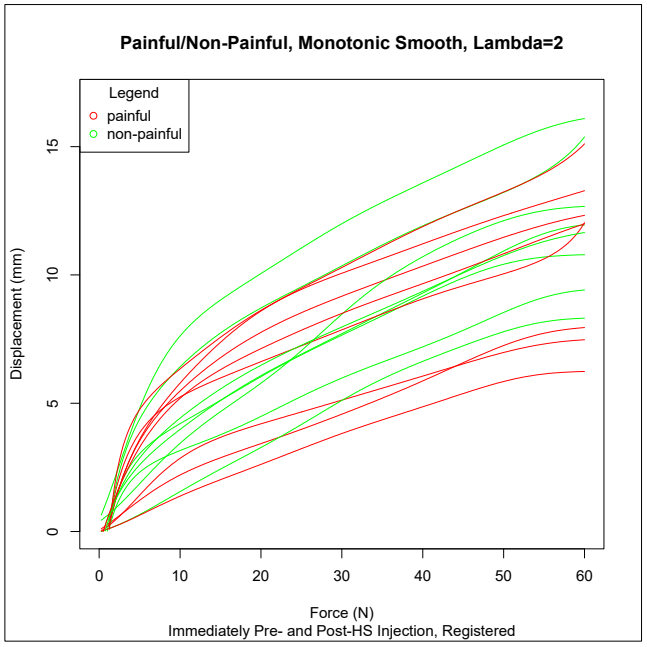
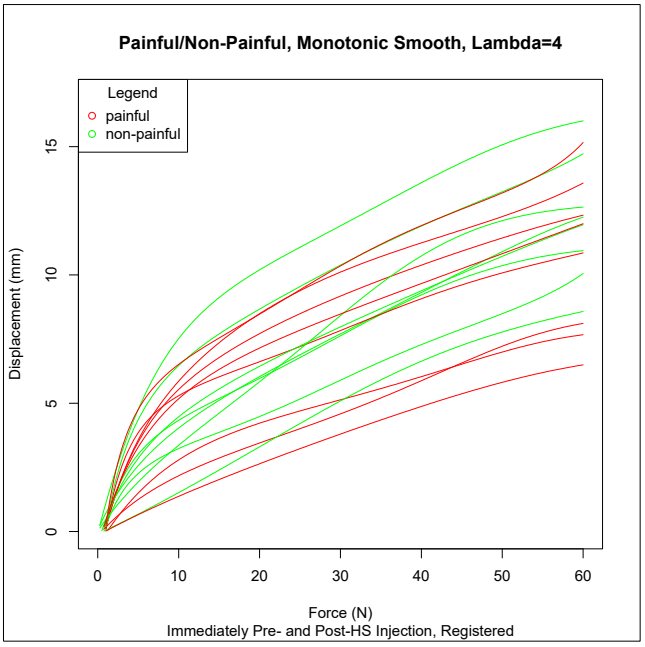
Figure A.2: Lambda Sensitivity Testing – Pain Induction Study







The smoothing value, lambda, chosen near the GCV-minimization point and tested for sensitivity to avoid over- or under-smoothing. Under smoothing at $\lambda=2$ is evident by the misalignment near zero and the exaggerated tails near 60N on some F-D traces. Over-smoothing at $\lambda=6$ resulted in a computationally singular system and could therefore not be calculated.

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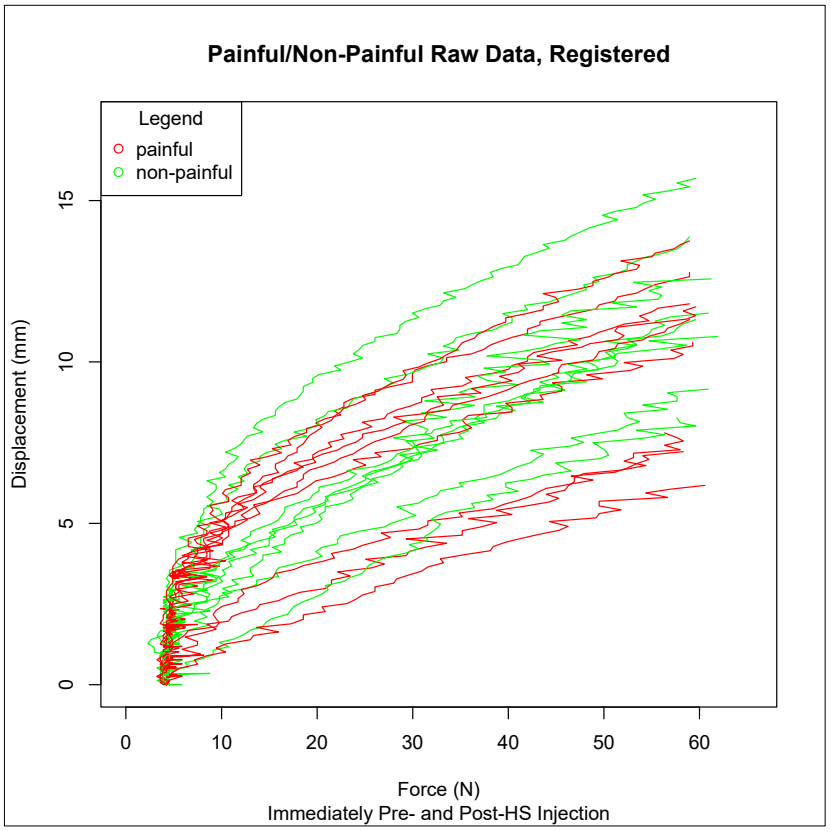
Figure A.3: Raw vs. Smoothed F-D Curves – Pain Induction Study

Graphs showing registered (top) and smoothed (bottom) force-displacement data from the Pain Induction study.



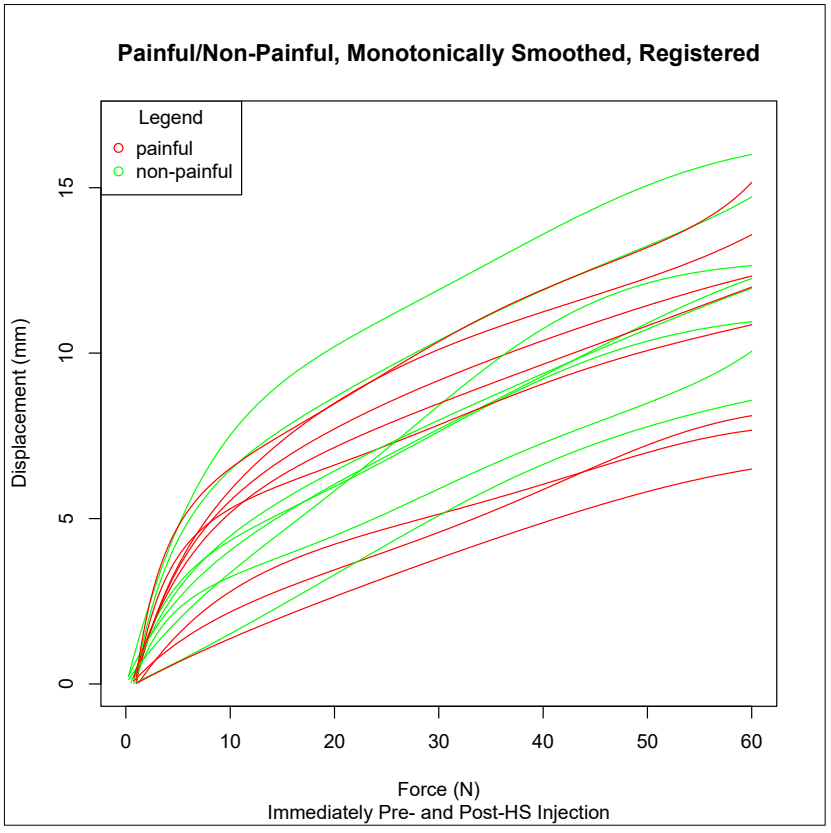


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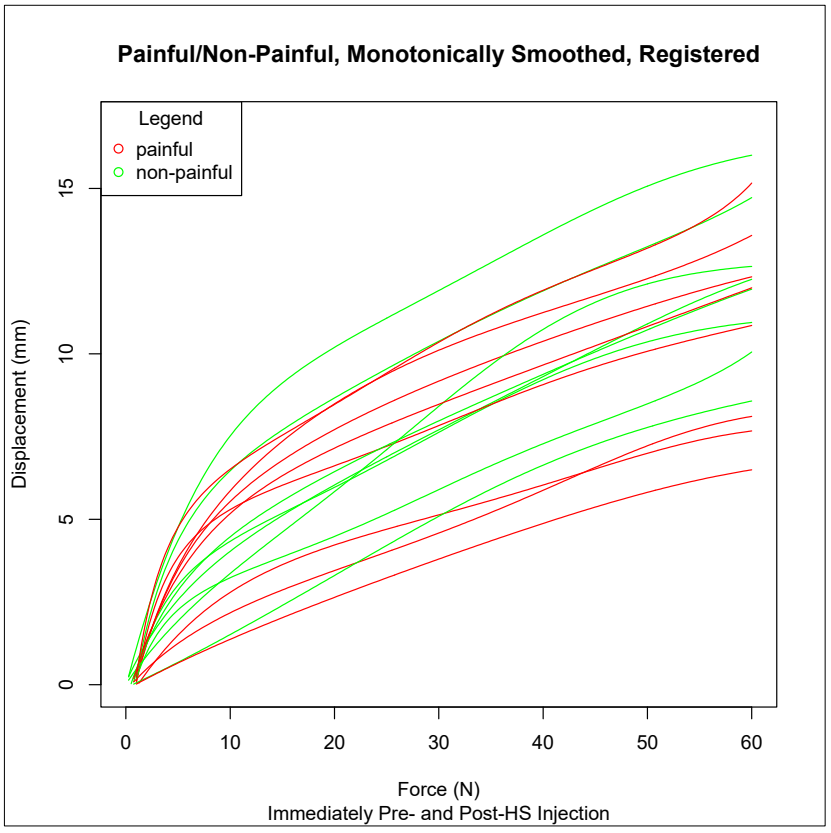
Figure A.4: Transformed Data for Functional Data Analysis – Pain Induction Study

Graphs showing smoothed (top) and transformed (bottom) force-displacement data from the Pain Induction study.



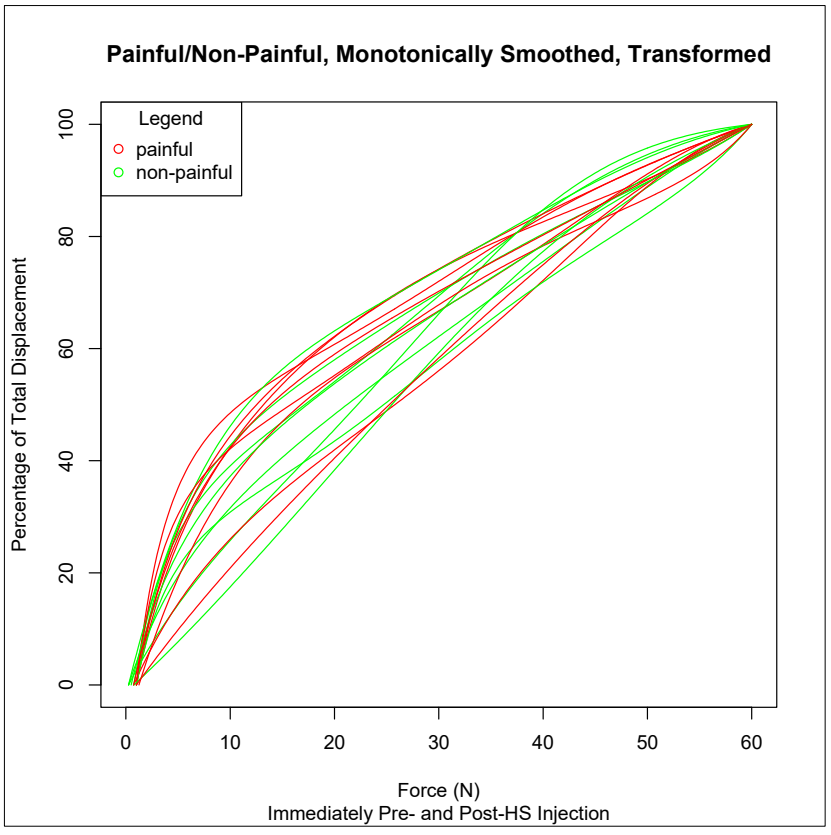


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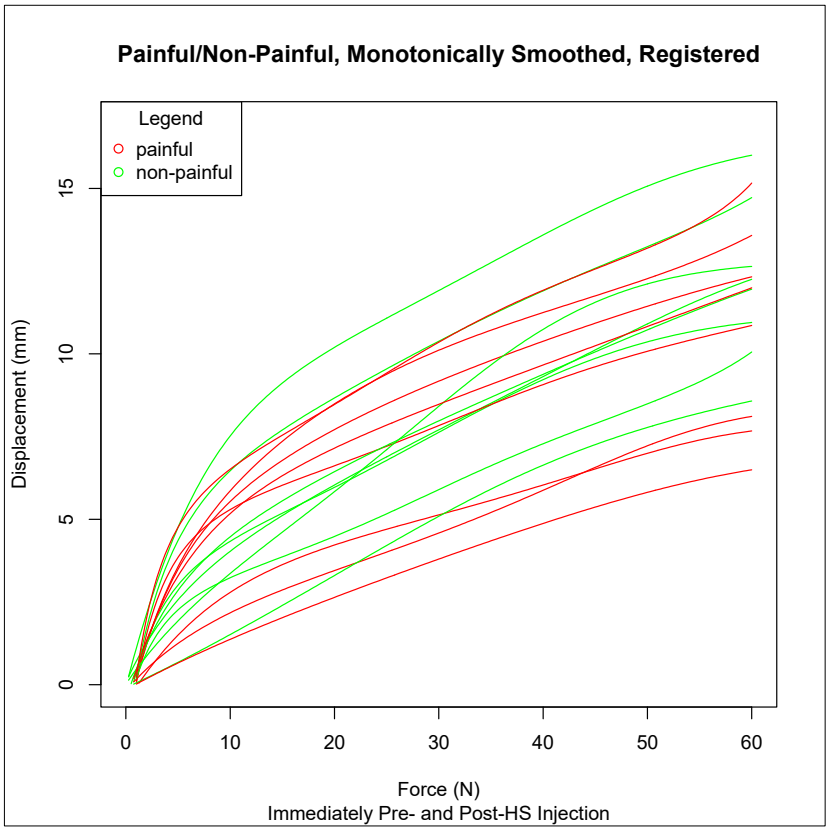
Figure A.5: Re-Sampled Data for Latent Class Analysis – Pain Induction Study

Graphs showing the smoothed force-displacement data from the Pain Induction study as output from R (top), and the re-sampled data for input to LCA (bottom).



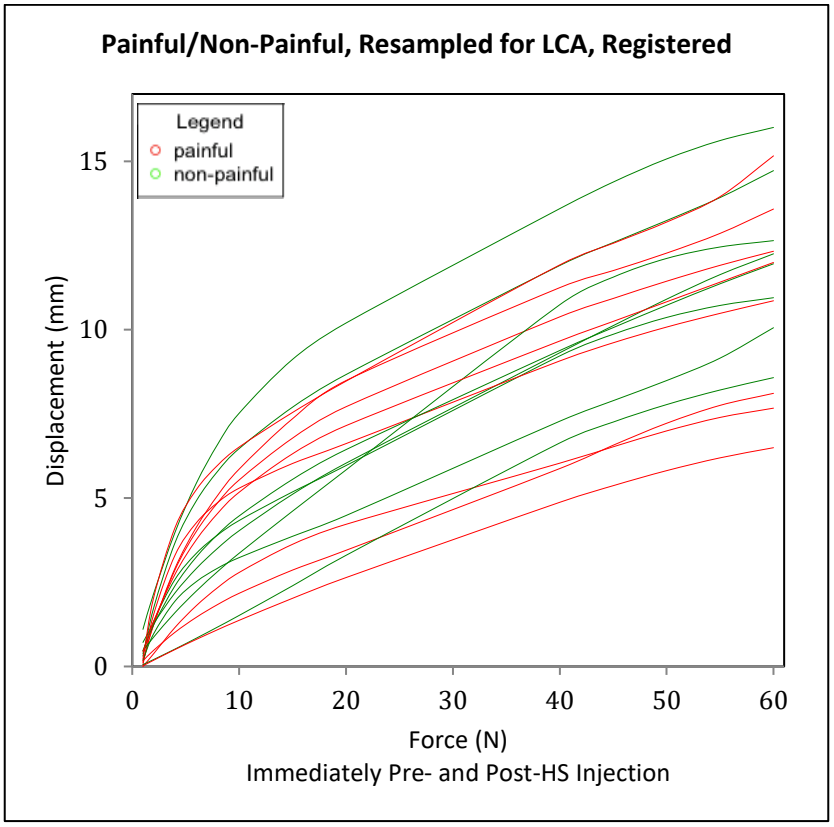


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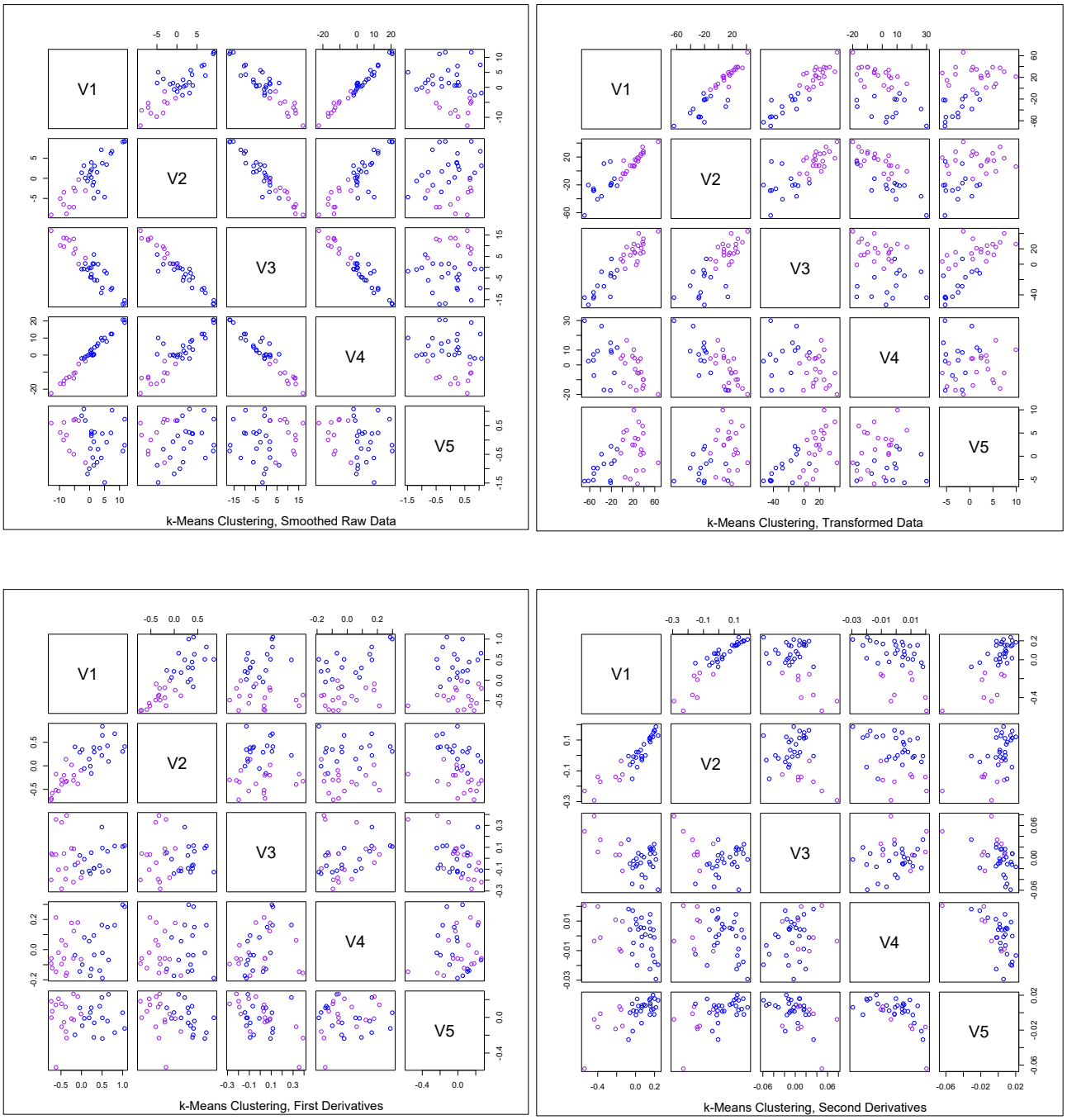
Figure A.6: fPC Scatter Plots – Pain Induction Study



Functional principle component scatter plots comparing orthogonality between functional principle components. The top left series of plots for the smoothed raw data from the Pain Induction study reveals that only the first four functional principle components are meaningful. Similarly, the plots for first and second derivatives (bottom row) indicate two meaningful functional principle components, while the plot for transformed data (top right) indicates three. Of note, harmonic 5 in the second derivative case (bottom right) displays a data arrangement that warrants further investigation.

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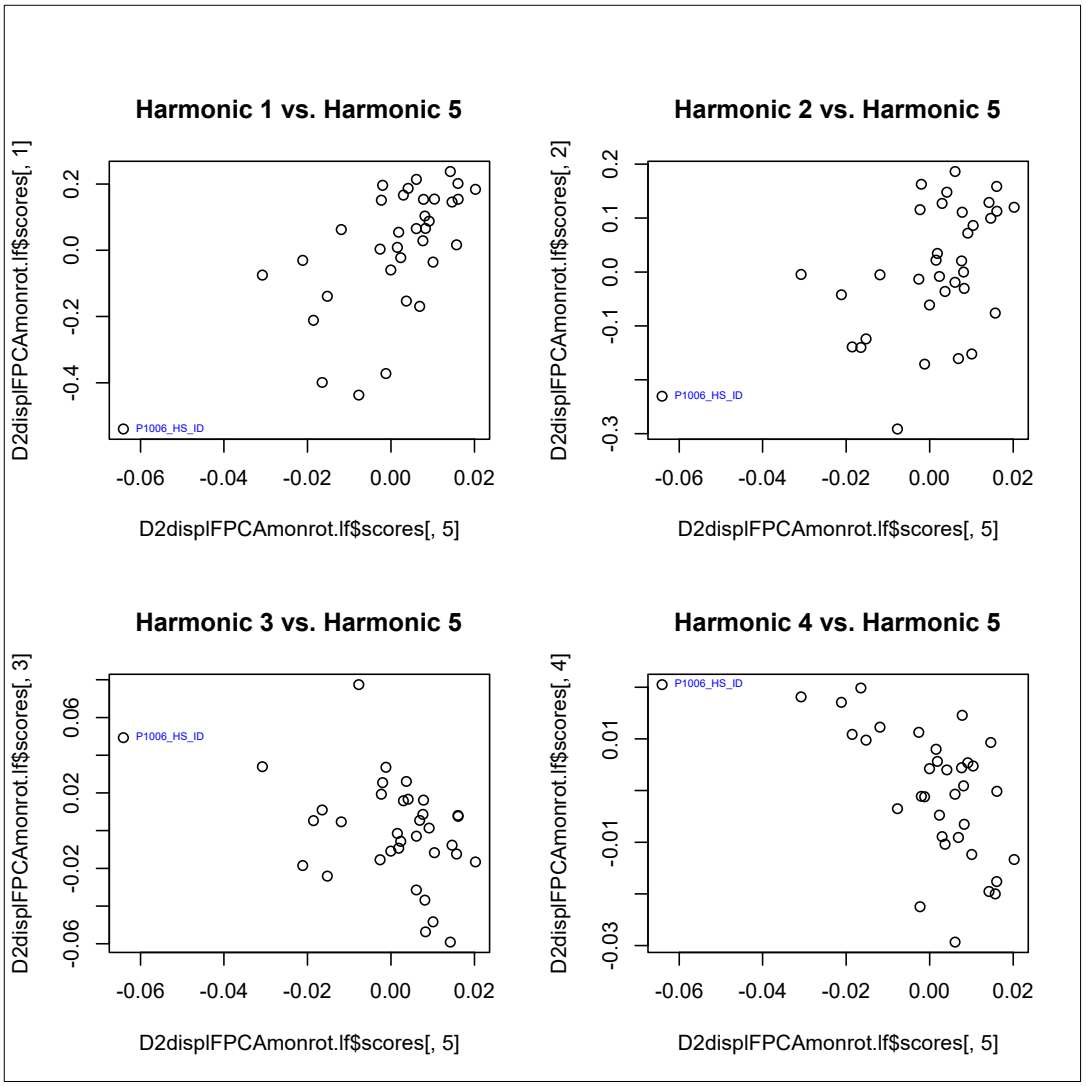
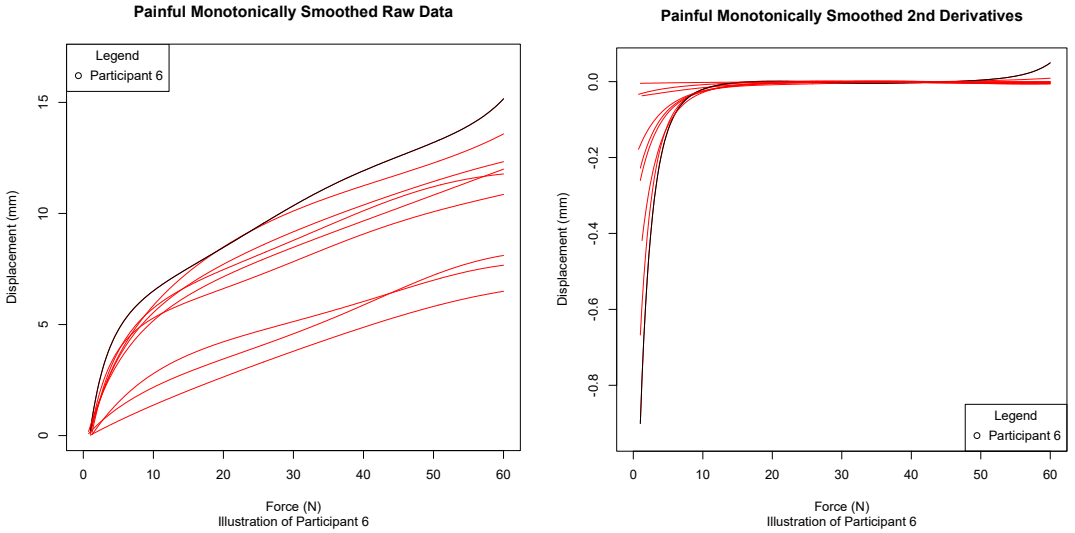
Figure A.7: Fifth Harmonic Investigation – Pain Induction Study





An investigation of a potential outlier in the fifth harmonic in the second derivative set of force-displacement curves for the Pain Induction study data. Back

Table A.1: Percentage Variation Explained by Each Functional Principle Component

Smoothed Data	Principle Component Function	Rotated Harmonic Percentage Variance
Raw Data	1	18.4
	2	5.5
	3	27.7
	4	48.3
	Total	*99.9*
1st Derivative	1	63.5
	2	24.8
	Total	*88.3*
2nd Derivative	1	78.7
	2	20.1
	Total	*98.8*
Transformed	1	58.8
	2	16.6
	3	23.5
	Total	*98.8*

The table above contains the percentage of variance explained by each functional principle component for each data state explored (raw, transformed, first and second derivatives).

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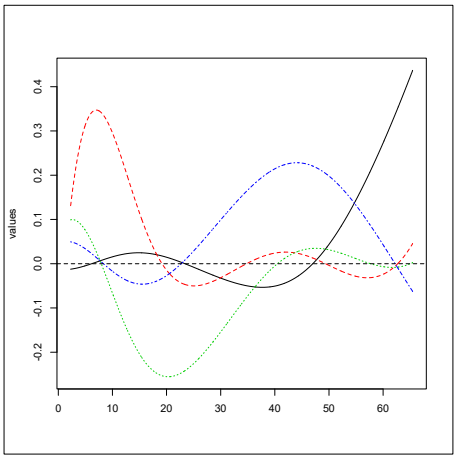
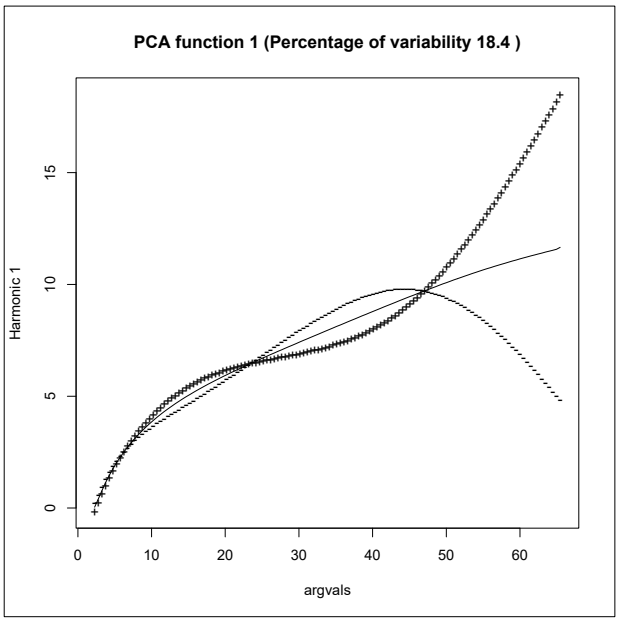
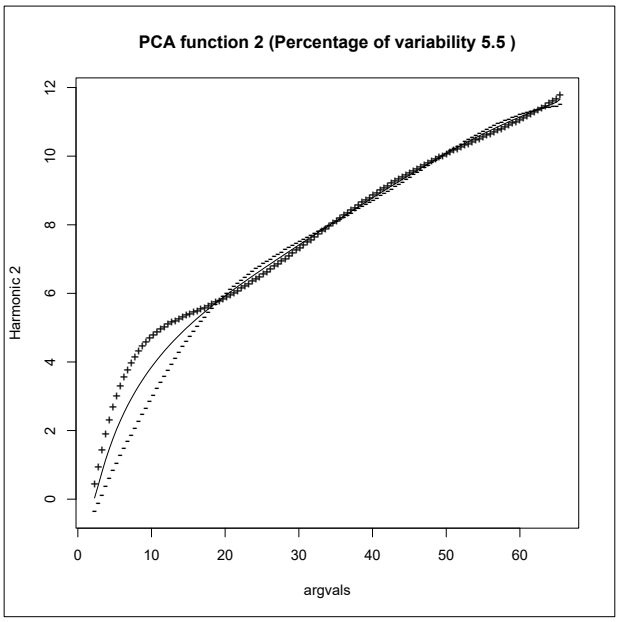
Figure A.8: Functional Principle Component Curves – Smoothed Raw Data – Pain Induction Study

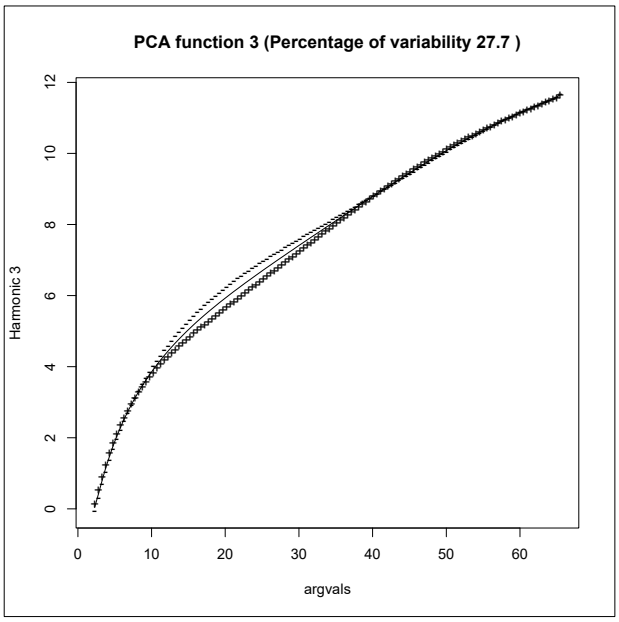
This series of graphs is for the smoothed raw data. Figures A.9 – A.11 show the same information for the transformed data, first and second derivatives, respectively.

The graph to the right illustrates each of the fPCA curves, with the mean curve subtracted. Each of the four graphs below show the mean curve and the shape of the variability explained by each principle component function.









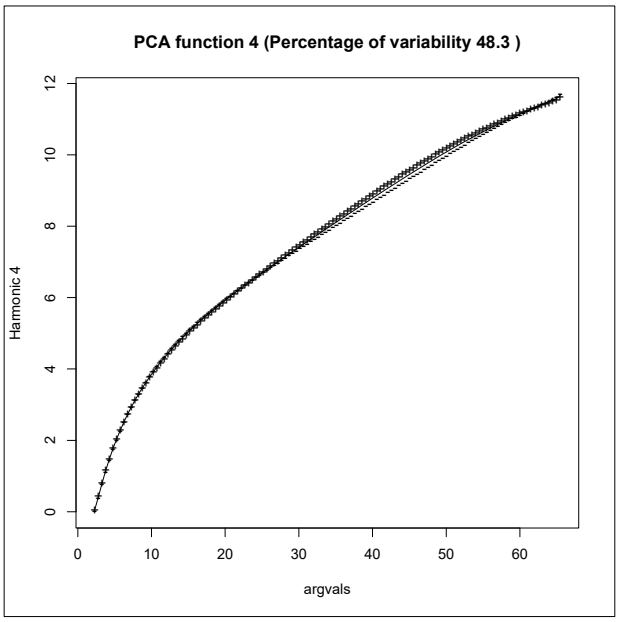


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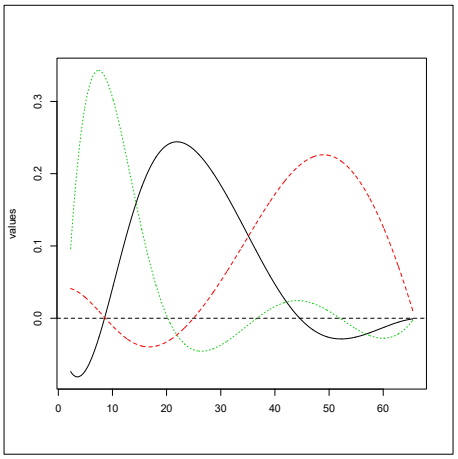
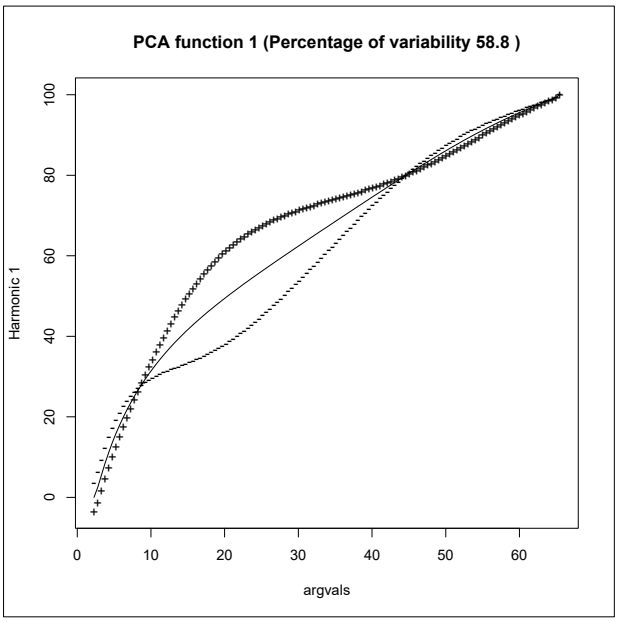
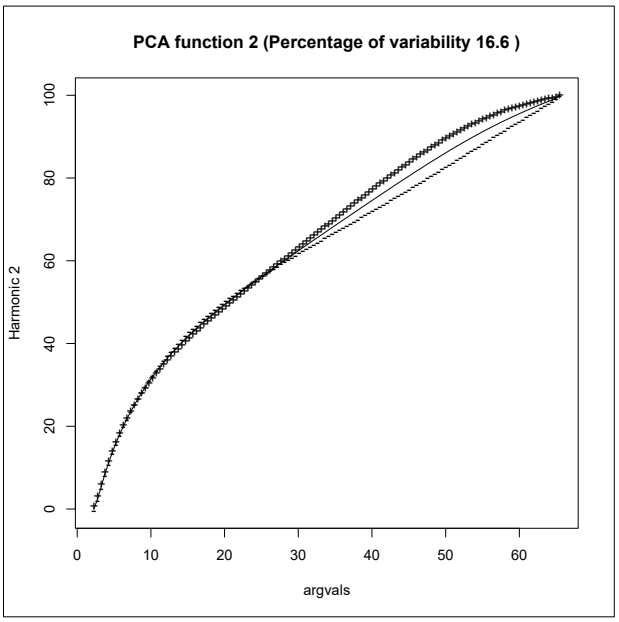
Figure A.9: Functional Principle Component Curves – Transformed Data – Pain Induction Study

This series of graphs is for the transformed smoothed raw data. Figures A.8, A.10 and A.11 show the same information for raw data, first and second derivatives, respectively.

The graph to the right illustrates each of the fPCA curves, with the mean curve subtracted. Each of the four graphs below show the mean curve and the shape of the variability explained by each principle component function.







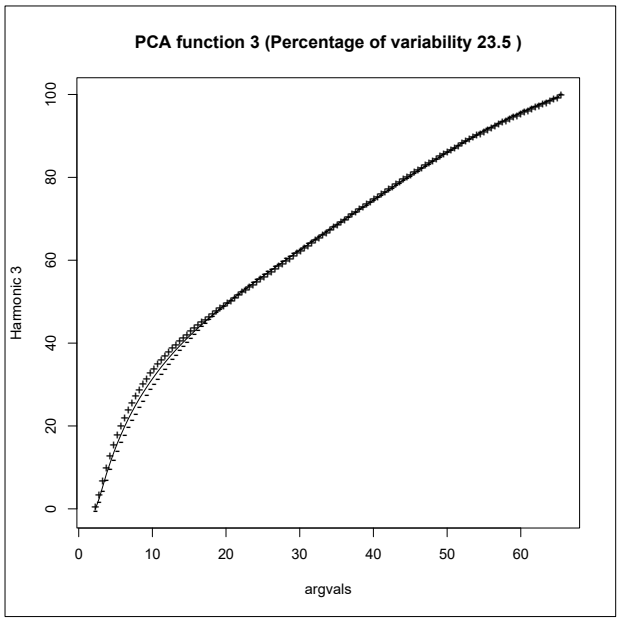


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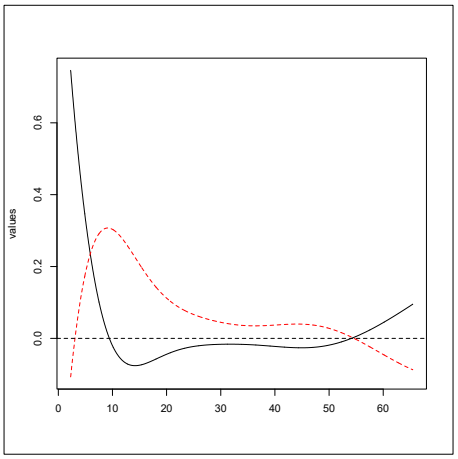
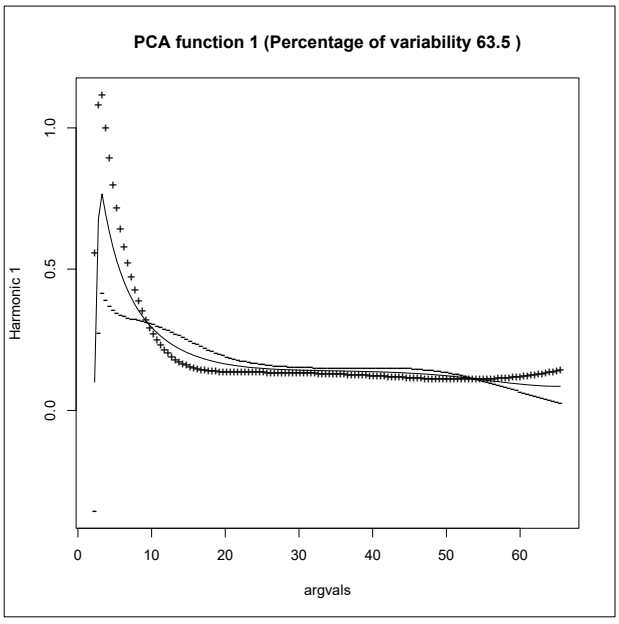
Figure A.10: Functional Principle Component Curves – First Derivatives – Pain Induction Study

This series of graphs is for first derivatives of the smoothed raw data. Figures A.8, A.9 and A.11 show the same information for raw data, transformed data and second derivatives, respectively.

The graph to the right illustrates each of the fPCA curves, with the mean curve subtracted. Each of the four graphs below show the mean curve and the shape of the variability explained by each principle component function.





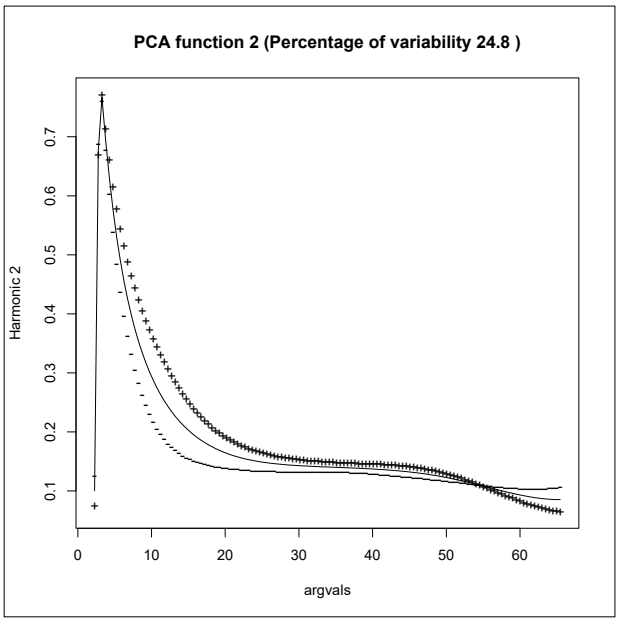


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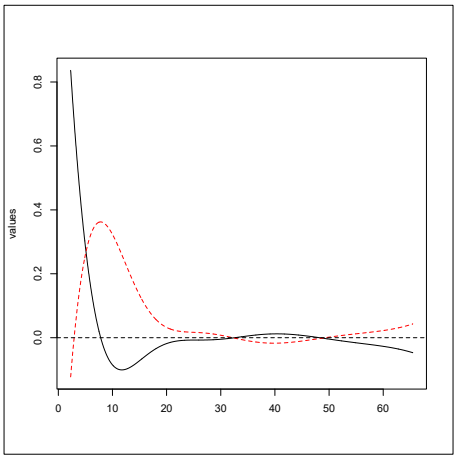
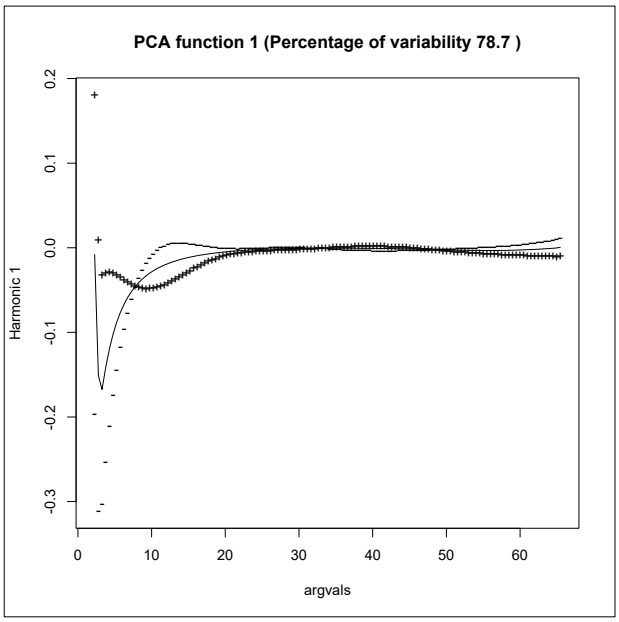
Figure A.11: Functional Principle Component Curves – Second Derivatives – Pain Induction Study

This series of graphs is for second derivatives of the smoothed raw data. Figures A.8 – A.10 show the same information for raw data, transformed data and first derivatives, respectively.

The graph to the right illustrates each of the fPCA curves, with the mean curve subtracted. Each of the two graphs below show the mean curve and the shape of the variability explained by each principle component function.





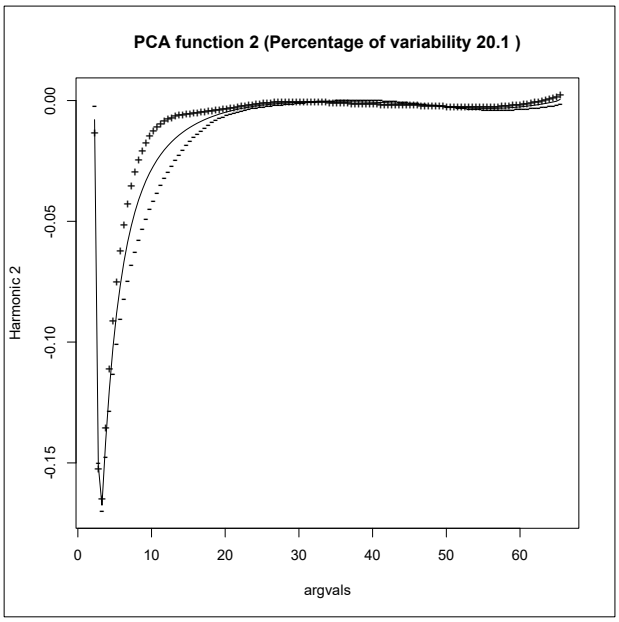


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Table A.2: Misclassifications of Pre- and Post-Injection Pain Status as a result of 2-Cluster k-Means Clustering

		Raw Data		1st Derivatives		2nd Derivatives		Transformed Data	
Subject	**True Classification**	**Cluster Pain State (Cluster)**	**Misclass.**	**Cluster Pain State (Cluster)**	**Misclass.**	**Cluster Pain State (Cluster)**	**Misclass.**	**Cluster Pain State (Cluster)**	**Misclass.**
PNP-1-HS-0	NP	NP (2)		NP (1)		NP (1)		NP (2)	
PNP-1-HS-1	P	NP (2)	Y	P (2)		NP (1)	Y	P (1)	
PNP-1-NS-0	NP	NP (2)		P (2)	Y	NP (1)		P (1)	Y
PNP-1-NS-1	NP	NP (2)		P (2)	Y	P (2)	Y	NP (2)	
PNP-2-HS-0	NP	NP (2)		P (2)	Y	P (2)	Y	P (1)	Y
PNP-2-HS-1	P	NP (2)	Y	P (2)		P (2)		P (1)	
PNP-2-NS-0	NP	NP (2)		P (2)	Y	NP (1)		P (1)	Y
PNP-2-NS-1	NP	NP (2)		NP (1)		NP (1)		P (1)	Y
PNP-3-HS-0	NP	NP (2)		P (2)	Y	P (2)	Y	P (1)	Y
PNP-3-HS-1	P	NP (2)	Y	P (2)		NP (1)	Y	P (1)	
PNP-3-NS-0	NP	NP (2)		P (2)	Y	NP (1)		P (1)	Y
PNP-3-NS-1	NP	NP (2)		P (2)	Y	NP (1)		P (1)	Y
PNP-4-HS-0	NP	NP (2)		NP (1)		NP (1)		NP (2)	
PNP-4-HS-1	P	P (1)		NP (1)	Y	NP (1)	Y	NP (2)	Y
PNP-4-NS-0	NP	NP (2)		NP (1)		NP (1)		NP (2)	
PNP-4-NS-1	NP	NP (2)		NP (1)		NP (1)		NP (2)	
PNP-5-HS-0	NP	P (1)	Y	NP (1)		NP (1)		NP (2)	
PNP-5-HS-1	P	P (1)		NP (1)	Y	NP (1)	Y	P (1)	
PNP-5-NS-0	NP	P (1)	Y	NP (1)		NP (1)		P (1)	Y
PNP-5-NS-1	NP	P (1)	Y	NP (1)		NP (1)		NP (2)	
PNP-6-HS-0	NP	NP (2)		P (2)	Y	NP (1)		P (1)	Y
PNP-6-HS-1	P	NP (2)	Y	P (2)		P (2)		P (1)	
PNP-6-NS-0	NP	NP (2)		P (2)	Y	P (2)	Y	P (1)	Y
PNP-6-NS-1	NP	NP (2)		P (2)	Y	P (2)	Y	P (1)	Y
PNP-7-HS-0	NP	P (1)	Y	NP (1)		NP (1)		NP (2)	
PNP-7-HS-1	P	P (1)		NP (1)	Y	NP (1)	Y	NP (2)	Y
PNP-7-NS-0	NP	P (1)	Y	NP (1)		NP (1)		NP (2)	
PNP-7-NS-1	NP	P (1)	Y	NP (1)		NP (1)		NP (2)	
PNP-8-HS-1	P	NP (2)	Y	P (2)		P (2)		P (1)	
PNP-8-NS-0	NP	NP (2)		P (2)	Y	NP (1)		P (1)	Y
PNP-8-NS-1	NP	NP (2)		NP (1)		NP (1)		P (1)	Y
PNP-9-HS-0	NP	NP (2)		P (2)	Y	NP (1)		P (1)	Y
PNP-9-HS-1	P	NP (2)	Y	P (2)		NP (1)	Y	P (1)	
PNP-9-NS-0	NP	NP (2)		NP (1)		NP (1)		NP (2)	
PNP-9-NS-1	NP	NP (2)		NP (1)		NP (1)		NP (2)	
Total:	*35*	*Total:*	*12*	*Total:*	*15*	*Total:*	*11*	*Total:*	*16*
		Misclass.:	*34%*	*Misclass.:*	*43%*	*Misclass.:*	*31%*	*Misclass.:*	*46%*

Trait Classification Code Legend	
Pain Induction Study Participant	PNP
Treatment Code: Hypertonic Saline	HS
Treatment Code: Isotonic Saline	NS
Painful State (HS)	P
Non-Painful State (NS)	NP

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Table A.3: Misclassifications of Pain Induction Study Subjects by Sex as a result of 2-Cluster k-Means Clustering

Subject	True Classification	Raw Data		1st Derivatives		2nd Derivatives		Transformed Data	
		Cluster Gender (Cluster)	Misclass.	Cluster Gender (Cluster)	Misclass.	Cluster Gender (Cluster)	Misclass.	Cluster Gender (Cluster)	Misclass.
PNP-1-HS-0	M	F (2)	Y	M (1)		F (1)	Y	M (2)	
PNP-1-HS-1	M	F (2)	Y	F (2)	Y	F (1)	Y	F (1)	Y
PNP-1-NS-0	M	F (2)	Y	F (2)	Y	F (1)	Y	F (1)	Y
PNP-1-NS-1	M	F (2)	Y	F (2)	Y	M (2)		M (2)	
PNP-2-HS-0	F	F (2)		F (2)		M (2)	Y	F (1)	
PNP-2-HS-1	F	F (2)		F (2)		M (2)	Y	F (1)	
PNP-2-NS-0	F	F (2)		F (2)		F (1)		F (1)	
PNP-2-NS-1	F	F (2)		M (1)	Y	F (1)		F (1)	
PNP-3-HS-0	F	F (2)		F (2)		M (2)	Y	F (1)	
PNP-3-HS-1	F	F (2)		F (2)		F (1)		F (1)	
PNP-3-NS-0	F	F (2)		F (2)		F (1)		F (1)	
PNP-3-NS-1	F	F (2)		F (2)		F (1)		F (1)	
PNP-4-HS-0	F	F (2)		M (1)	Y	F (1)		M (2)	Y
PNP-4-HS-1	F	M (1)	Y	M (1)	Y	F (1)		M (2)	Y
PNP-4-NS-0	F	F (2)		M (1)	Y	F (1)		M (2)	Y
PNP-4-NS-1	F	F (2)		M (1)	Y	F (1)		M (2)	Y
PNP-5-HS-0	M	M (1)		M (1)		F (1)	Y	M (2)	
PNP-5-HS-1	M	M (1)		M (1)		F (1)	Y	F (1)	Y
PNP-5-NS-0	M	M (1)		M (1)		F (1)	Y	F (1)	Y
PNP-5-NS-1	M	M (1)		M (1)		F (1)	Y	M (2)	
PNP-6-HS-0	F	F (2)		F (2)		F (1)		F (1)	
PNP-6-HS-1	F	F (2)		F (2)		M (2)	Y	F (1)	
PNP-6-NS-0	F	F (2)		F (2)		M (2)	Y	F (1)	
PNP-6-NS-1	F	F (2)		F (2)		M (2)	Y	F (1)	
PNP-7-HS-0	F	M (1)	Y	M (1)	Y	F (1)		M (2)	Y
PNP-7-HS-1	F	M (1)	Y	M (1)	Y	F (1)		M (2)	Y
PNP-7-NS-0	F	M (1)	Y	M (1)	Y	F (1)		M (2)	Y
PNP-7-NS-1	F	M (1)	Y	M (1)	Y	F (1)		M (2)	Y
PNP-8-HS-1	M	F (2)	Y	F (2)	Y	M (2)		F (1)	Y
PNP-8-NS-0	M	F (2)	Y	F (2)	Y	F (1)	Y	F (1)	Y
PNP-8-NS-1	M	F (2)	Y	M (1)		F (1)	Y	F (1)	Y
PNP-9-HS-0	F	F (2)		F (2)		F (1)		F (1)	
PNP-9-HS-1	F	F (2)		F (2)		F (1)		F (1)	
PNP-9-NS-0	F	F (2)		M (1)	Y	F (1)		M (2)	Y
PNP-9-NS-1	F	F (2)		M (1)	Y	F (1)		M (2)	Y
Total:	*35*	*Total:*	*12*	*Total:*	*16*	*Total:*	*15*	*Total:*	*17*
		Misclass.:	*34%*	*Misclass.:*	*46%*	*Misclass.:*	*43%*	*Misclass.:*	*49%*

Trait Classification Code Legend	
Pain Induction Study Participant	PNP
Treatment Code: Hypertonic Saline	HS
Treatment Code: Isotonic Saline	NS
Male	M
Female	F

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Table A.4: Misclassifications of Pain Induction Study Subjects by BMI as a result of 2-Cluster k-Means Clustering

Subject	True Classification	Raw Data		1st Derivatives		2nd Derivatives		Transformed Data	
		Cluster BMI Code (Cluster)	Misclass.	Cluster BMI Code (Cluster)	Misclass.	Cluster BMI Code (Cluster)	Misclass.	Cluster BMI Code (Cluster)	Misclass.
PNP-1-HS-0	Ov	N (2)	Y	N (1)	Y	N (1)	Y	Ov (2)	
PNP-1-HS-1	Ov	N (2)	Y	Ov (2)		N (1)	Y	N (1)	Y
PNP-1-NS-0	Ov	N (2)	Y	Ov (2)		N (1)	Y	N (1)	Y
PNP-1-NS-1	Ov	N (2)	Y	Ov (2)		Ov (2)		Ov (2)	
PNP-2-HS-0	N	N (2)		Ov (2)	Y	Ov (2)	Y	N (1)	
PNP-2-HS-1	N	N (2)		Ov (2)	Y	Ov (2)	Y	N (1)	
PNP-2-NS-0	N	N (2)		Ov (2)	Y	N (1)		N (1)	
PNP-2-NS-1	N	N (2)		N (1)		N (1)		N (1)	
PNP-3-HS-0	N	N (2)		Ov (2)	Y	Ov (2)	Y	N (1)	
PNP-3-HS-1	N	N (2)		Ov (2)	Y	N (1)		N (1)	
PNP-3-NS-0	N	N (2)		Ov (2)	Y	N (1)		N (1)	
PNP-3-NS-1	N	N (2)		Ov (2)	Y	N (1)		N (1)	
PNP-4-HS-0	N	N (2)		N (1)		N (1)		Ov (2)	Y
PNP-4-HS-1	N	Ov (1)	Y	N (1)		N (1)		Ov (2)	Y
PNP-4-NS-0	N	N (2)		N (1)		N (1)		Ov (2)	Y
PNP-4-NS-1	N	N (2)		N (1)		N (1)		Ov (2)	Y
PNP-5-HS-0	N	Ov (1)	Y	N (1)		N (1)		Ov (2)	Y
PNP-5-HS-1	N	Ov (1)	Y	N (1)		N (1)		N (1)	
PNP-5-NS-0	N	Ov (1)	Y	N (1)		N (1)		N (1)	
PNP-5-NS-1	N	Ov (1)	Y	N (1)		N (1)		Ov (2)	Y
PNP-6-HS-0	N	N (2)		Ov (2)	Y	N (1)		N (1)	
PNP-6-HS-1	N	N (2)		Ov (2)	Y	Ov (2)	Y	N (1)	
PNP-6-NS-0	N	N (2)		Ov (2)	Y	Ov (2)	Y	N (1)	
PNP-6-NS-1	N	N (2)		Ov (2)	Y	Ov (2)	Y	N (1)	
PNP-7-HS-0	N	Ov (1)	Y	N (1)		N (1)		Ov (2)	Y
PNP-7-HS-1	N	Ov (1)	Y	N (1)		N (1)		Ov (2)	Y
PNP-7-NS-0	N	Ov (1)	Y	N (1)		N (1)		Ov (2)	Y
PNP-7-NS-1	N	Ov (1)	Y	N (1)		N (1)		Ov (2)	Y
PNP-8-HS-1	N	N (2)		Ov (2)	Y	Ov (2)	Y	N (1)	
PNP-8-NS-0	N	N (2)		Ov (2)	Y	N (1)		N (1)	
PNP-8-NS-1	N	N (2)		N (1)		N (1)		N (1)	
PNP-9-HS-0	N	N (2)		Ov (2)	Y	N (1)		N (1)	
PNP-9-HS-1	N	N (2)		Ov (2)	Y	N (1)		N (1)	
PNP-9-NS-0	N	N (2)		N (1)		N (1)		Ov (2)	Y
PNP-9-NS-1	N	N (2)		N (1)		N (1)		Ov (2)	Y
Total:	*35*	*Total:*	*13*	*Total:*	*16*	*Total:*	*10*	*Total:*	*14*
		Misclass.:	*37%*	*Misclass.:*	*46%*	*Misclass.:*	*29%*	*Misclass.:*	*40%*

Trait Classification Code Legend	
Pain Induction Study Participant	PNP
Treatment Code: Hypertonic Saline	HS
Treatment Code: Isotonic Saline	NS
Body Mass Index: Normal	N
Body Mass Index: Overweight	Ov
Body Mass Index: Obese	Ob

Dichotomization of Body Mass Index measurements categorized in accordance with the Canadian guidelines for body weight classification in adults[1].

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Table A.5: Misclassifications of Pre- and Post-Injection Pain Status and Sex as a result of 4-Cluster k-Means Clustering

		Raw Data		1st Derivatives		2nd Derivatives		Transformed Data	
Subject	**Classification Code**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**
PNP-1-HS-0	2	4	Y	1	Y	3	Y	1	Y
PNP-1-HS-1	1	1		3	Y	3	Y	4	Y
PNP-1-NS-0	2	4	Y	4	Y	3	Y	4	Y
PNP-1-NS-1	2	1	Y	3	Y	2		1	Y
PNP-2-HS-0	4	4		4		1	Y	4	
PNP-2-HS-1	3	4	Y	3		2	Y	4	Y
PNP-2-NS-0	4	4		4		3	Y	4	
PNP-2-NS-1	4	4		4		3	Y	4	
PNP-3-HS-0	4	1	Y	3	Y	1	Y	4	
PNP-3-HS-1	3	1	Y	3		1	Y	4	Y
PNP-3-NS-0	4	1	Y	4		3	Y	4	
PNP-3-NS-1	4	4		4		3	Y	4	
PNP-4-HS-0	4	4		1	Y	4		2	Y
PNP-4-HS-1	3	3		2	Y	4	Y	3	
PNP-4-NS-0	4	1	Y	1	Y	4		2	Y
PNP-4-NS-1	4	4		1	Y	4		3	Y
PNP-5-HS-0	1	3	Y	1		1		3	Y
PNP-5-HS-1	2	3	Y	1	Y	4	Y	1	Y
PNP-5-NS-0	1	3	Y	1		3	Y	1	
PNP-5-NS-1	1	3	Y	1		4	Y	1	
PNP-6-HS-0	3	2	Y	3		3		4	Y
PNP-6-HS-1	4	1	Y	3	Y	2	Y	1	Y
PNP-6-NS-0	3	2	Y	3		1	Y	4	Y
PNP-6-NS-1	3	2	Y	3		2	Y	4	Y
PNP-7-HS-0	3	3		2	Y	4	Y	3	
PNP-7-HS-1	4	3	Y	2	Y	4		3	Y
PNP-7-NS-0	3	3		2	Y	4	Y	3	
PNP-7-NS-1	3	3		2	Y	4	Y	3	
PNP-8-HS-1	1	1		3	Y	1		4	Y
PNP-8-NS-0	2	1	Y	3	Y	1	Y	4	Y
PNP-8-NS-1	2	4	Y	4	Y	4	Y	4	Y
PNP-9-HS-0	4	4		4		3	Y	1	Y
PNP-9-HS-1	3	4	Y	4	Y	3		4	Y
PNP-9-NS-0	4	4		4		3	Y	1	Y
PNP-9-NS-1	4	4		1	Y	4		2	Y
Total Participants:	*35*	*Total:*	*20*	*Total:*	*20*	*Total:*	*25*	*Total:*	*23*
		Misclass.:	*57%*	*Misclass.:*	*57%*	*Misclass.:*	*71%*	*Misclass.:*	*66%*

Trait Classification Code Legend	
Pain Induction Study Participant	PNP
Treatment Code: Hypertonic Saline	HS
Treatment Code: Isotonic Saline	NS
Pain + Male	1
No Pain + Male	2
Pain + Female	3
No Pain+Female	4

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Table A.6: Misclassifications of Pre- and Post-Injection Pain Status as a result of LCRA Clustering

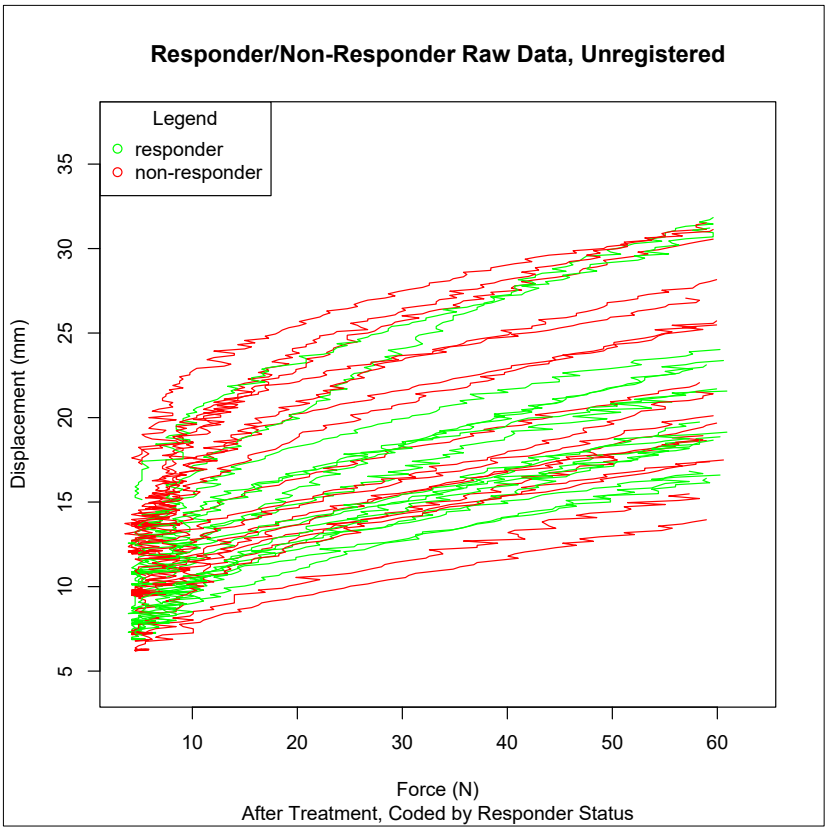
Subject	True Classification	2-Class LCRA	Misclass.
PNP-1-HS-0	NP	NP (1)	
PNP-1-HS-1	P	NP (1)	Y
PNP-1-NS-0	NP	NP (1)	
PNP-1-NS-1	NP	NP (1)	
PNP-2-HS-0	NP	NP (1)	
PNP-2-HS-1	P	NP (1)	Y
PNP-2-NS-0	NP	NP (1)	
PNP-2-NS-1	NP	P (2)	Y
PNP-3-HS-0	NP	NP (1)	
PNP-3-HS-1	P	NP (1)	Y
PNP-3-NS-0	NP	NP (1)	
PNP-3-NS-1	NP	NP (1)	
PNP-4-HS-0	NP	NP (1)	
PNP-4-HS-1	P	P (2)	
PNP-4-NS-0	NP	NP (1)	
PNP-4-NS-1	NP	NP (1)	
PNP-5-HS-0	NP	P (2)	Y
PNP-5-HS-1	P	P (2)	
PNP-5-NS-0	NP	P (2)	Y
PNP-5-NS-1	NP	P (2)	Y
PNP-6-HS-0	NP	NP (1)	
PNP-6-HS-1	P	NP (1)	Y
PNP-6-NS-0	NP	NP (1)	
PNP-6-NS-1	NP	NP (1)	
PNP-7-HS-0	NP	P (2)	Y
PNP-7-HS-1	P	P (2)	
PNP-7-NS-0	NP	P (2)	Y
PNP-7-NS-1	NP	P (2)	Y
PNP-8-HS-1	P	NP (1)	Y
PNP-8-NS-0	NP	NP (1)	
PNP-8-NS-1	NP	NP (1)	
PNP-9-HS-0	NP	NP (1)	
PNP-9-HS-1	P	NP (1)	Y
PNP-9-NS-0	NP	NP (1)	
PNP-9-NS-1	NP	NP (1)	
		Total:	*13*

Trait Classification Code Legend	
Pain Induction Study Participant	PNP
Treatment Code: Hypertonic Saline	HS
Treatment Code: Isotonic Saline	NS
Painful State (HS)	P
Non-Painful State (NS)	NP

Appendix 2: Responders Study Data Processing Figures and Tables

Figure B.1: Curve Registration – Responders Study

Two graphs showing raw (top) and registered (bottom) force-displacement data from the Responders study. F-D curves are coded by responder status.



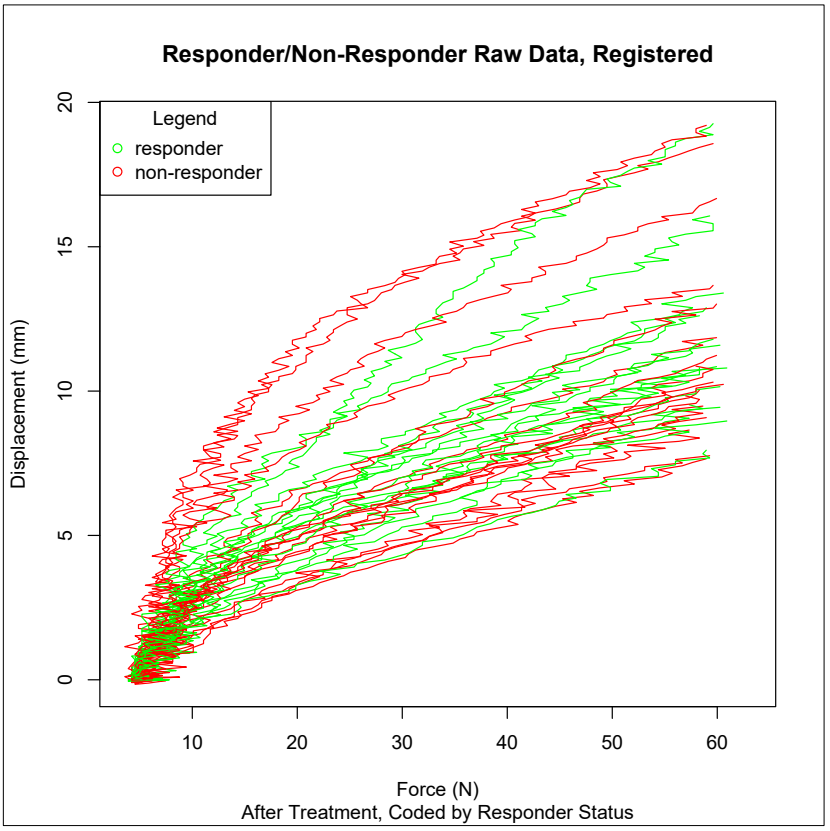


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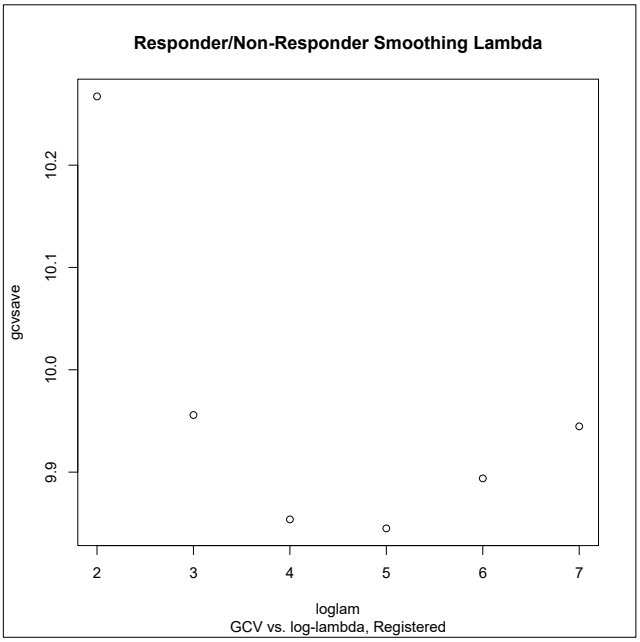
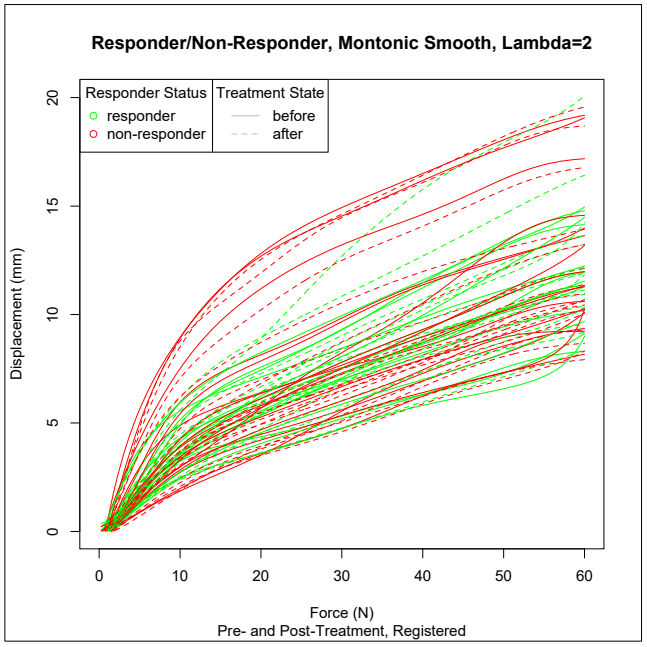
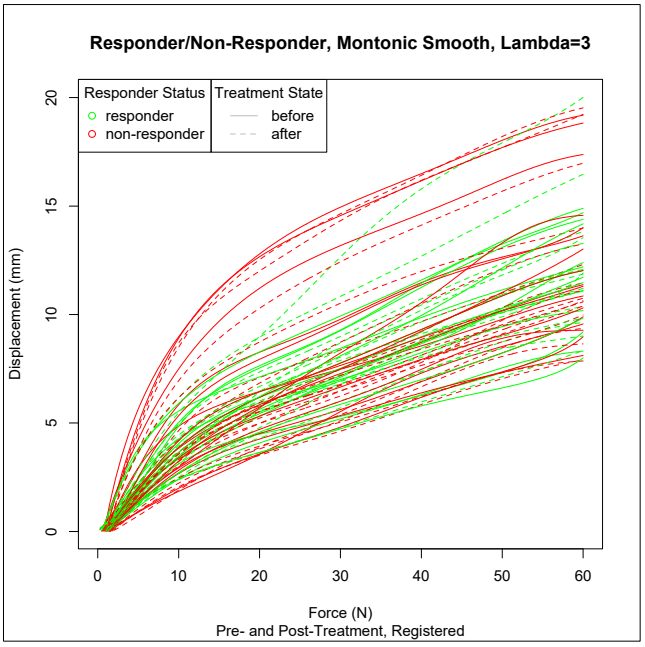
Figure B.2: Lambda Sensitivity Testing – Responders Study







The smoothing value, lambda, was chosen near the GCV-minimization point and tested for sensitivity to avoid over- or under-smoothing. Under smoothing at λ=2 is evident by the exaggerated tails near 60N on some F-D traces. Testing for over-smoothing was not possible, as the maximum lambda value possible to avoid a computationally singular system was λ=3.5.

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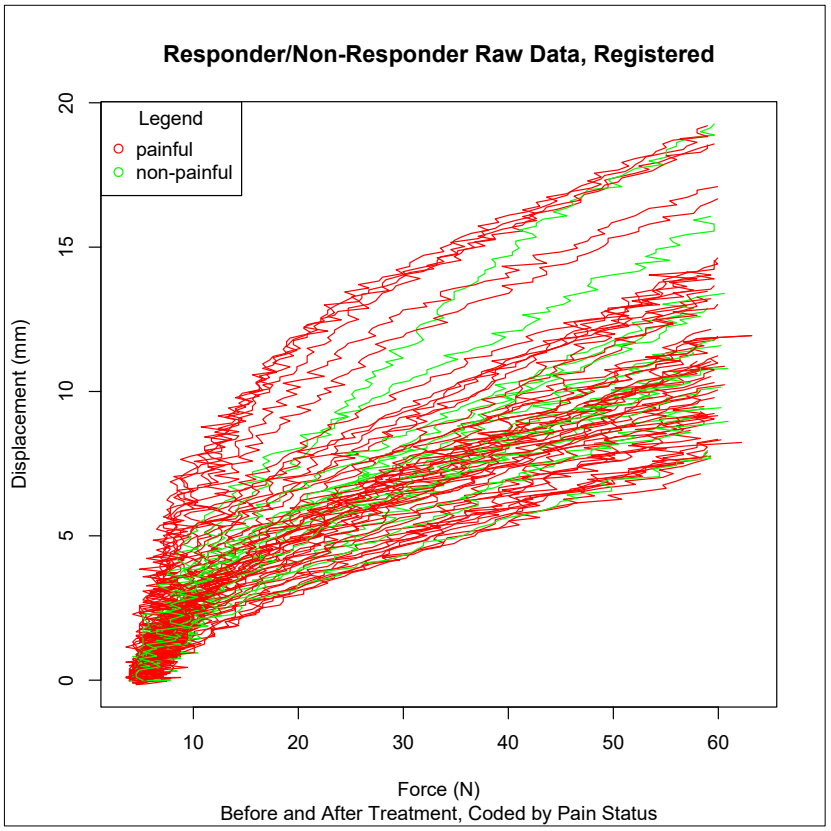
Figure B.3: Raw vs. Smoothed F-D Curves – Responders Study

Graphs showing registered force-displacement curves from the Responders study, coded by post-SMT recovery status (top) and smoothed force-displacement curves coded by responder status and treatment state (bottom).



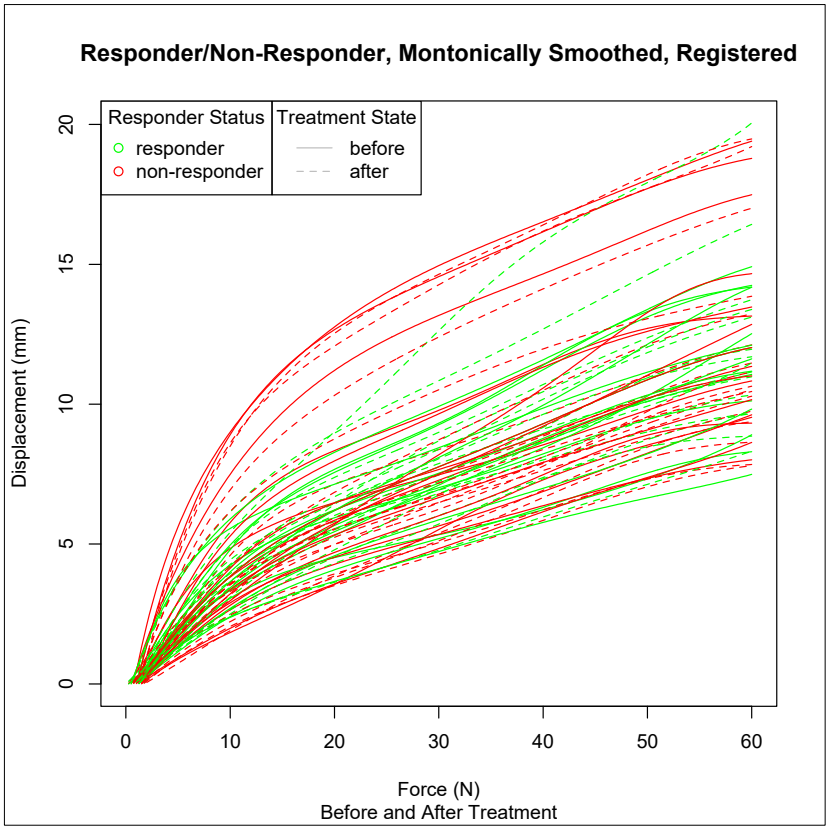


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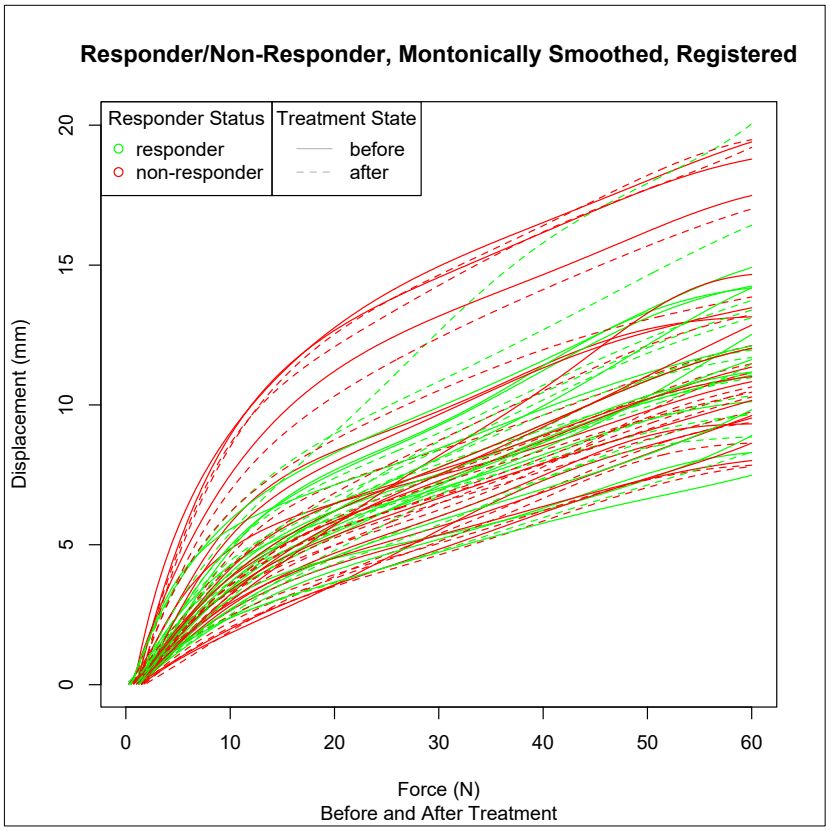
Figure B.4: Transformed Data for Functional Data Analysis – Responders Study

Graphs showing smoothed force-displacement curves from the Responders study, coded by responder status and treatment state (top) and the transformed version of the same curves (bottom).



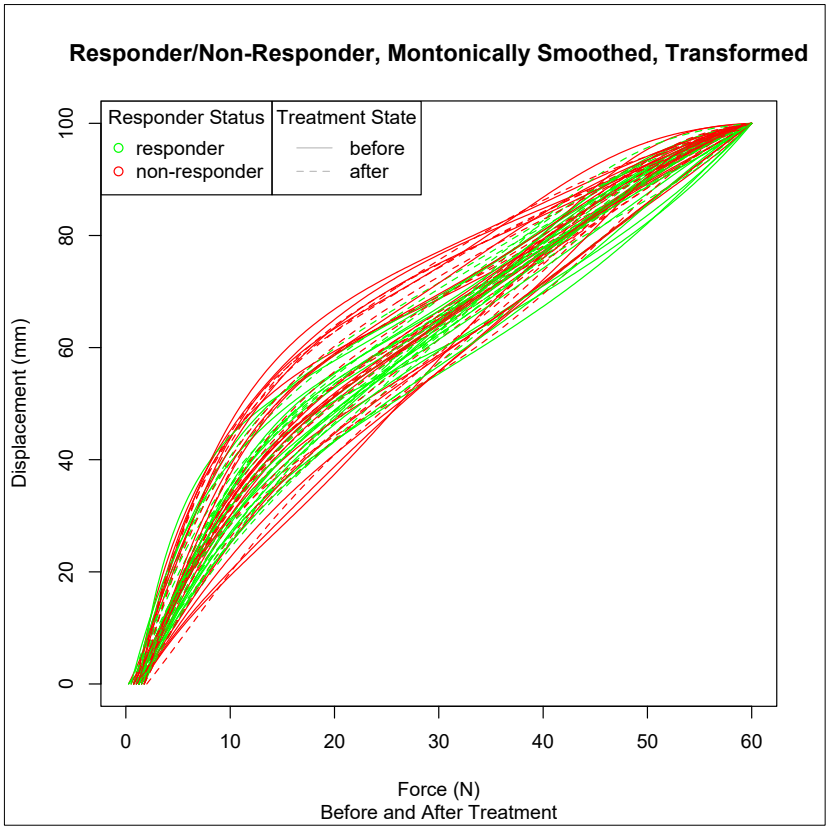


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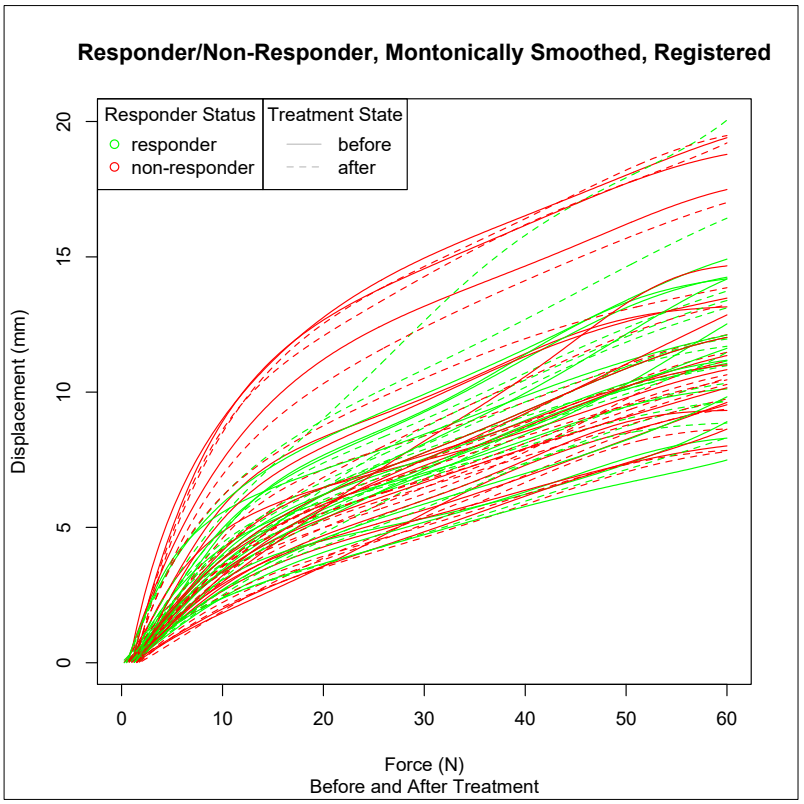
Figure B.5: Re-Sampled Data for Latent Class Analysis – Responders Study



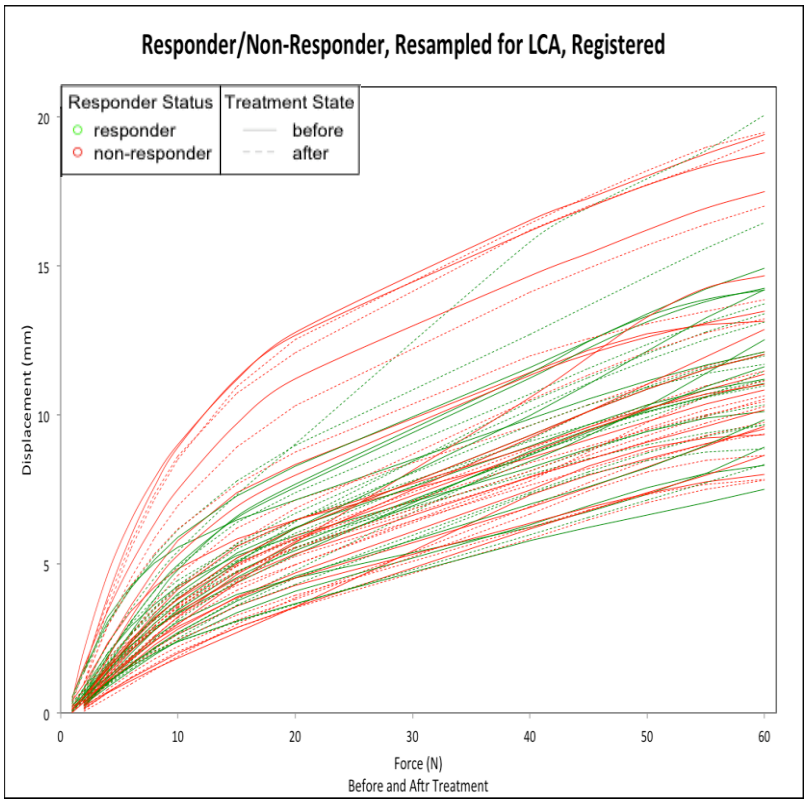


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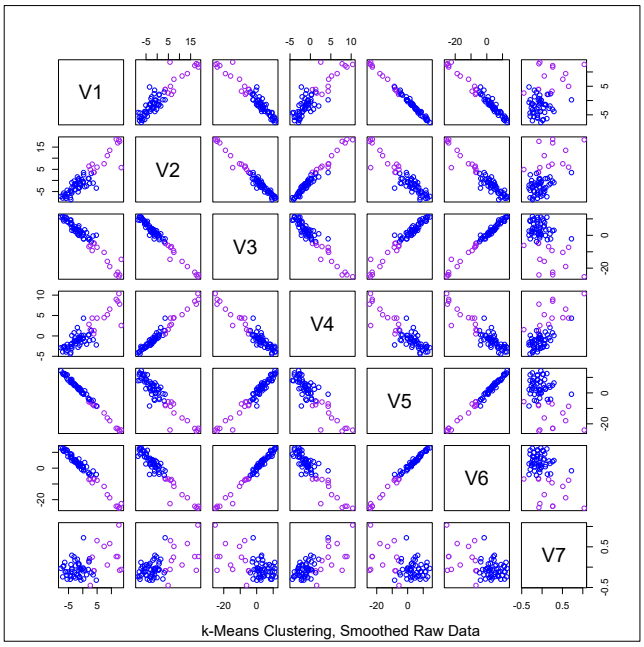
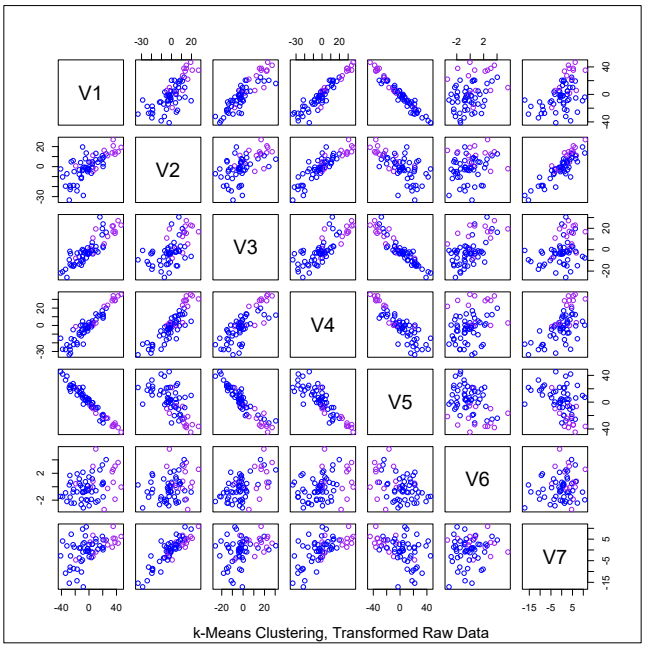
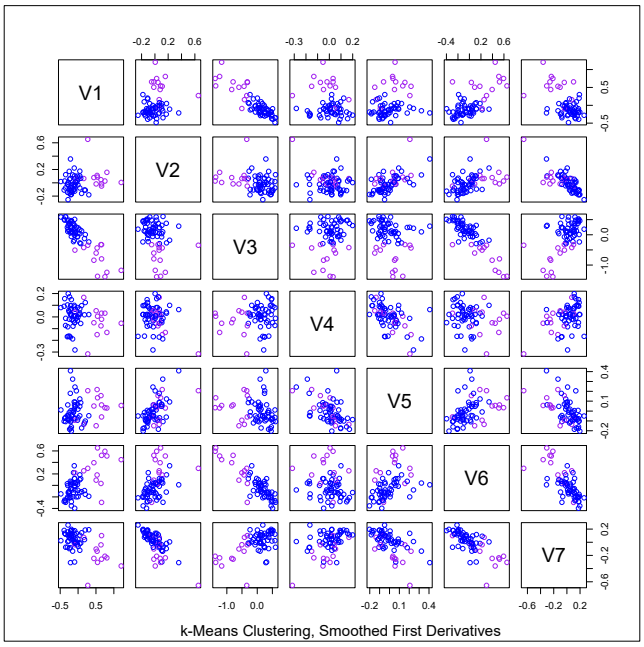
Figure B.6: fPC Scatter Plots – Responders Study







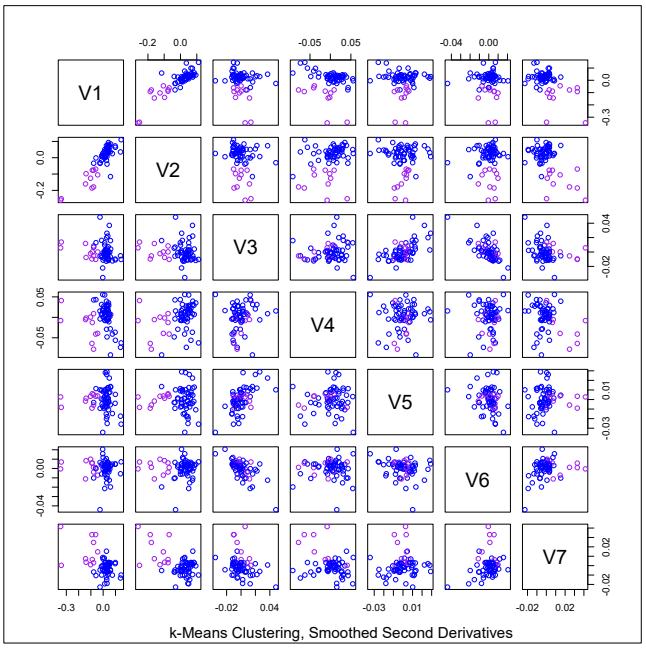


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Table B.1: Percentage Variation Explained by Each Harmonic

Monotonic Smoothing Equation	Principle Component Function	Rotated Harmonic Percentage Variance
Raw Data	1	10
	2	22.6
	3	29.2
	4	6.1
	5	31.6
	6	0.4
	Total	*99.9*
2nd Derivative	1	66.5
	2	29.4
	Total	*95.9*
Transformed	1	36
	2	5.2
	3	33.8
	4	19.3
	5	5.7
	Total	*100*

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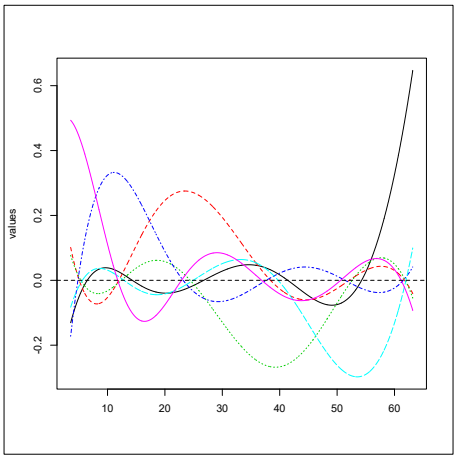
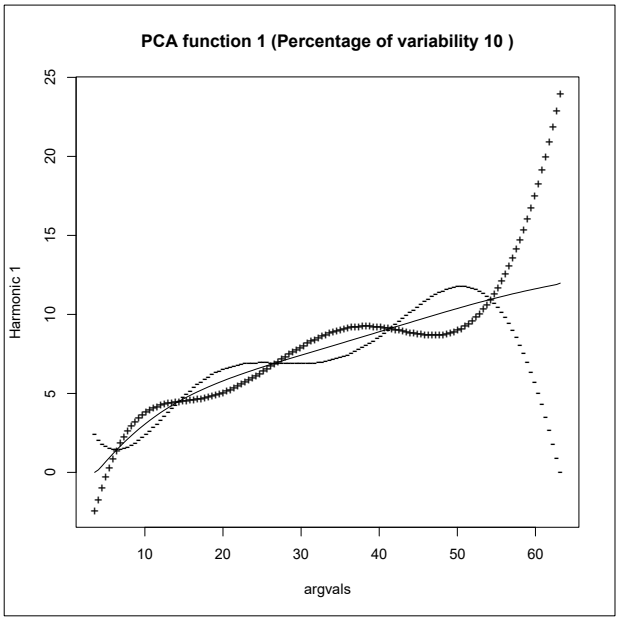
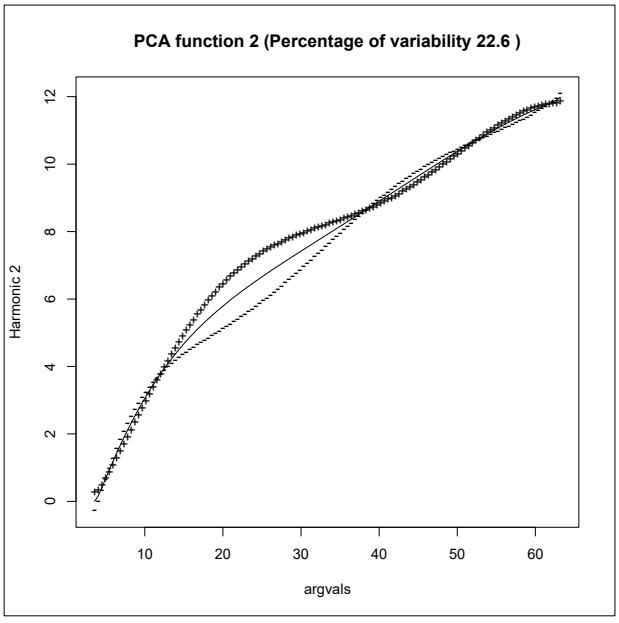
Figure B.7: Functional Principle Component Curves – Smoothed Raw Data – Responders Study

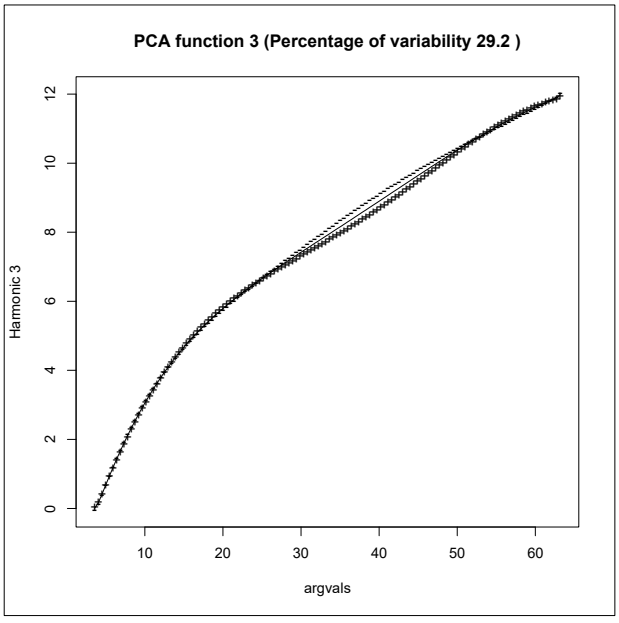
This series of graphs is for the smoothed raw data. Figures B.8 and B.9 show the same information for the transformed data and second derivatives, respectively.

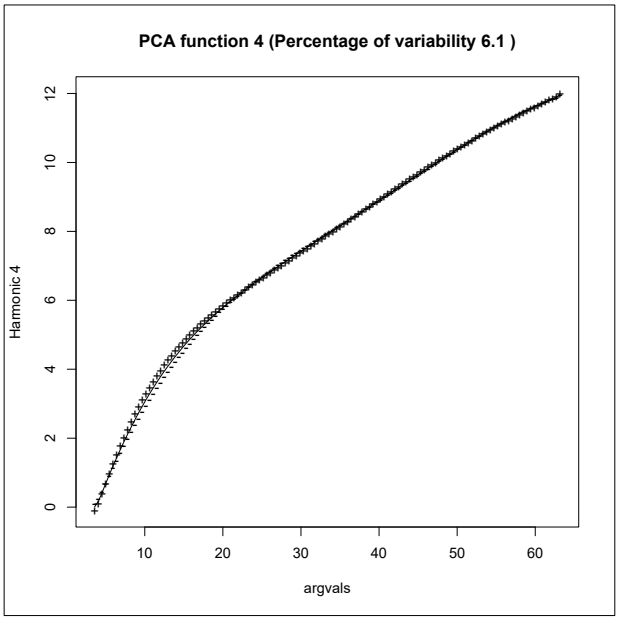
The graph to the right illustrates each of the fPCA curves, with the mean curve subtracted. Each of the six graphs below show the mean curve and the shape of the variability explained by each principle component function.

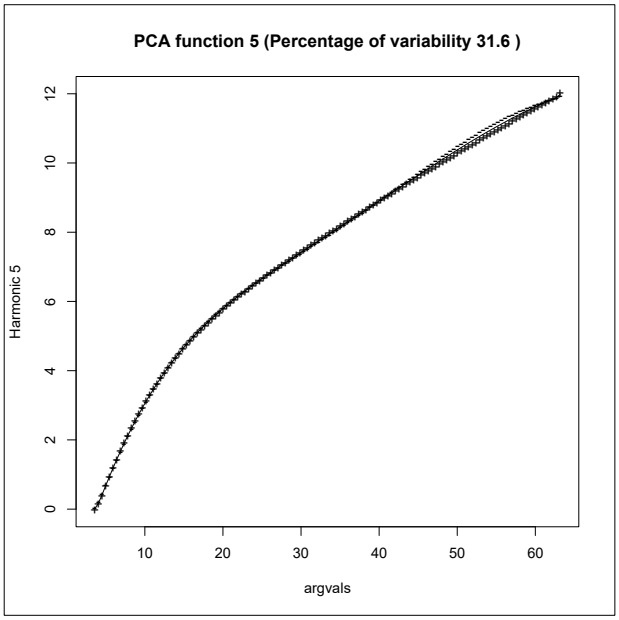











PCA function 5 (Percentage of variability 31.6)
Harmonic 5
argvals
0
2
4
6
8
10
12
10
20
30
40
50
60

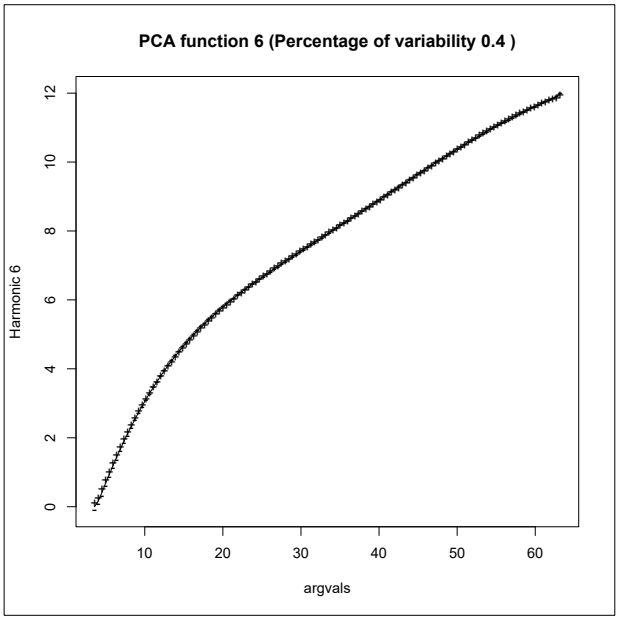

PCA function 6 (Percentage of variability 0.4)
Harmonic 6
argvals
0
2
4
6
8
10
12
10
20
30
40
50
60

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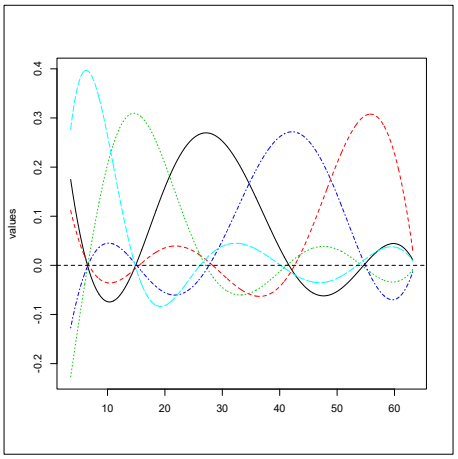
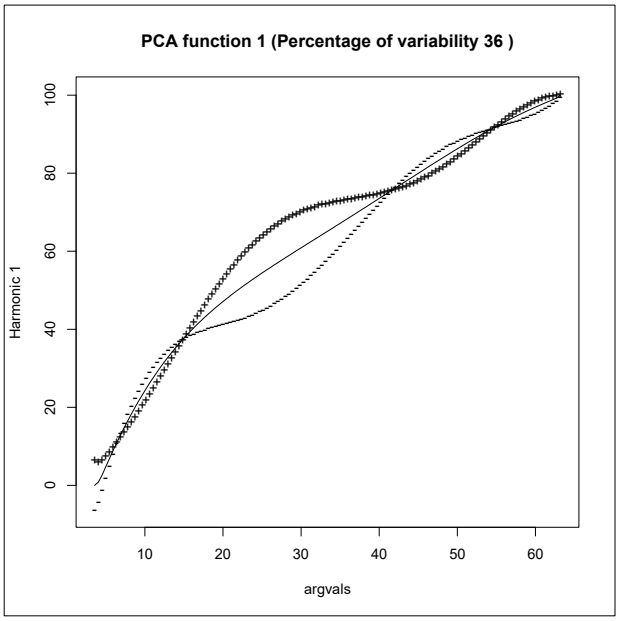
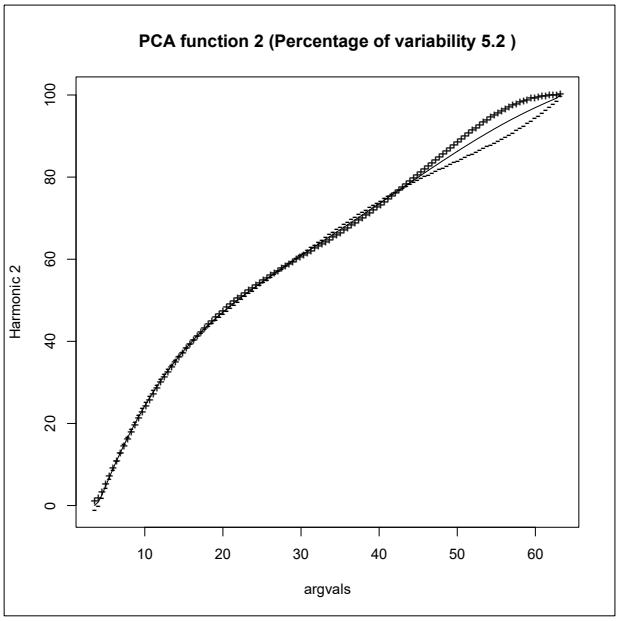
Figure B.8: Functional Principle Component Curves – Transformed Data – Responders Study

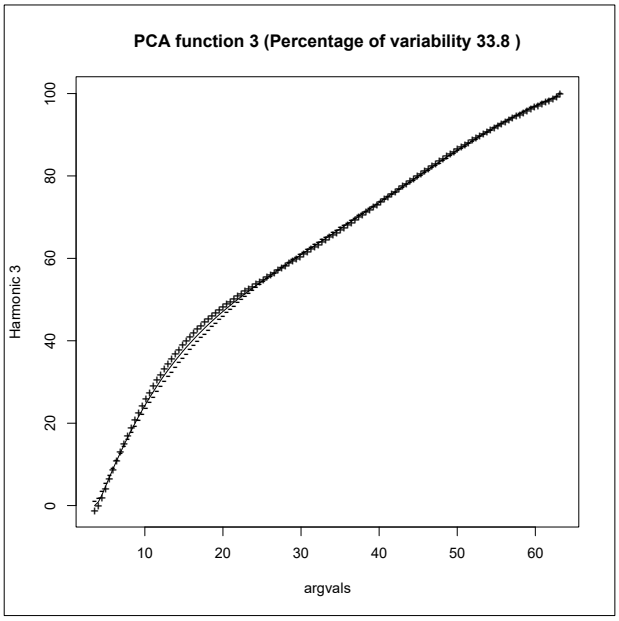
This series of graphs is for the transformed smoothed raw data. Figures B.7 and B.9 show the same information for raw data and second derivatives, respectively.

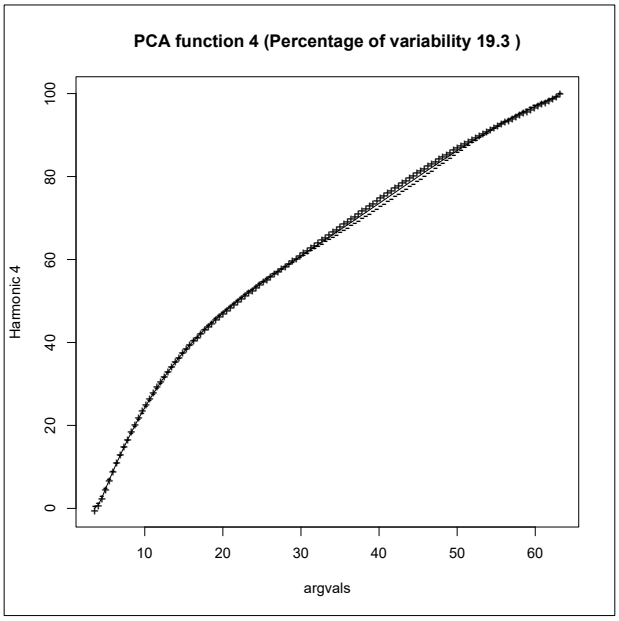
The graph to the right illustrates each of the fPCA curves, with the mean curve subtracted. Each of the five graphs below show the mean curve and the shape of the variability explained by each principle component function.











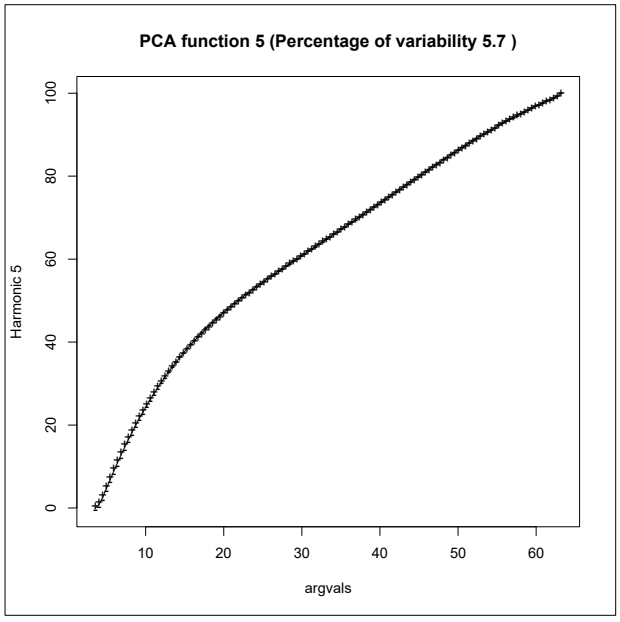

PCA function 5 (Percentage of variability 5.7)
Harmonic 5
0
20
40
60
80
100
10
20
30
40
50
60
argvals

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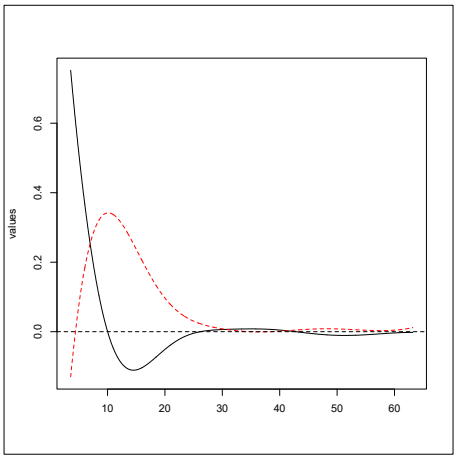
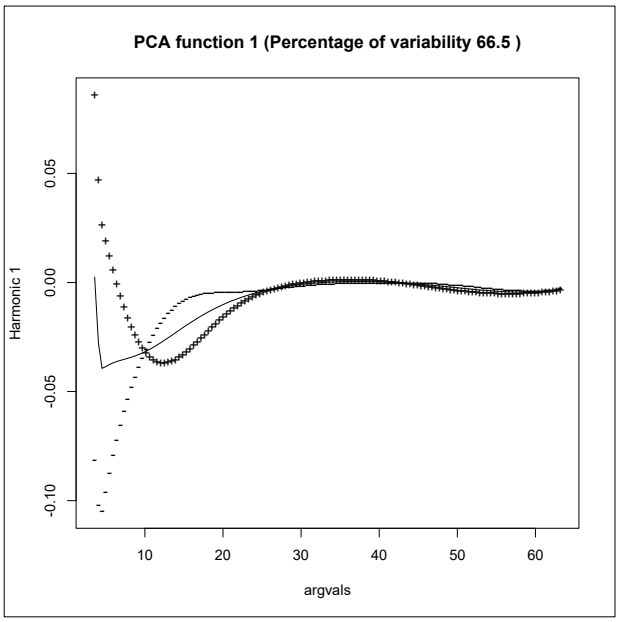
Figure B.9: Functional Principle Component Curves – Second Derivatives – Responders Study

This series of graphs is for second derivatives of the smoothed raw data. Figures B.7 and B.8 show the same information for raw data and transformed data, respectively.

The graph to the right illustrates each of the fPCA curves, with the mean curve subtracted. Each of the two graphs below show the mean curve and the shape of the variability explained by each principle component function.





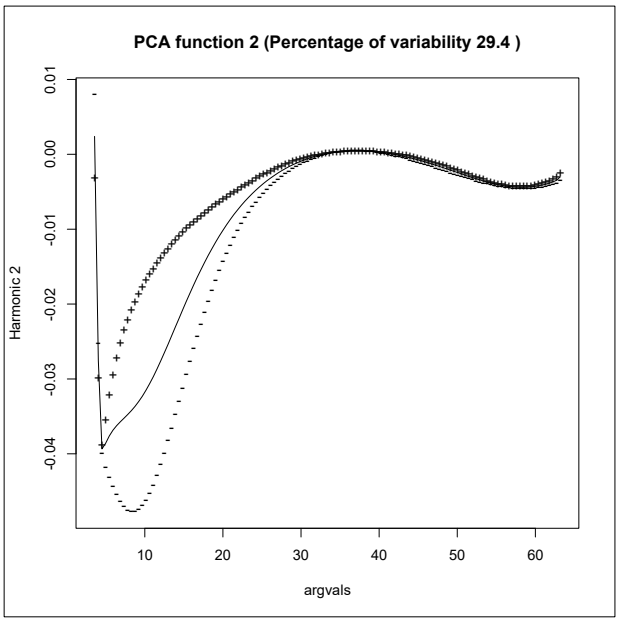


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Table B.2: Misclassifications of Pre-SMT Responder Status as a result of 2-Cluster k-Means Clustering

Pre-Treatment Curves		Raw Data		2nd Derivatives		Transformed Data	
Subject	**True Classification**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**
RNR-1	R	R (1)		R (1)		R (1)	
RNR-2	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-3	R	R (1)		R (1)		R (1)	
RNR-4	NR	NR (2)		NR (2)		NR (2)	
RNR-5	NR	R (1)	Y	NR (2)		NR (2)	
RNR-6	R	R (1)		R (1)		NR (2)	Y
RNR-7	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-8	NR	NR (2)		R (1)	Y	NR (2)	
RNR-9	R	NR (2)	Y	R (1)		R (1)	
RNR-10	R	R (1)		R (1)		R (1)	
RNR-11	R	R (1)		R (1)		R (1)	
RNR-12	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-13	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-14	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-15	R	R (1)		NR (2)	Y	NR (2)	Y
RNR-16	NR	NR (2)		NR (2)		NR (2)	
RNR-17	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-18	R	R (1)		R (1)		R (1)	
RNR-19	R	NR (2)	Y	R (1)		R (1)	
RNR-20	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-21	R	R (1)		R (1)		NR (2)	Y
RNR-22	NR	NR (2)		NR (2)		NR (2)	
RNR-23	R	NR (2)	Y	NR (2)	Y	NR (2)	Y
RNR-24	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-25	R	R (1)		R (1)		R (1)	
RNR-26	NR	R (1)	Y	R (1)	Y	NR (2)	
RNR-27	NR	NR (2)		R (1)	Y	NR (2)	
RNR-28	R	R (1)		R (1)		R (1)	
RNR-29	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-30	R	R (1)		R (1)		R (1)	
RNR-31	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-32	R	R (1)		R (1)		R (1)	
Total:	*32*	*Total:*	*15*	*Total:*	*15*	*Total:*	*14*
		Misclass.:	*47%*	*Misclass.:*	*47%*	*Misclass.:*	*44%*

Trait Classification Code Legend	
Responders Study Participant	RNR
Response Code: Responder	R
Response Code: Non-Responder	NR

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Table B.3: Misclassifications of Post-SMT Responder Status as a result of 2-Cluster k-Means Clustering

Post-Treatment Curves		Raw Data		2nd Derivatives		Transformed Data	
Subject	**True Classification**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**
RNR-1	R	R (1)		R (1)		R (1)	
RNR-2	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-3	R	R (1)		R (1)		R (1)	
RNR-4	NR	NR (2)		R (1)	Y	NR (2)	
RNR-5	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-6	R	R (1)		R (1)		R (1)	
RNR-7	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-8	NR	R (1)	Y	R (1)	Y	NR (2)	
RNR-9	R	NR (2)	Y	R (1)		R (1)	
RNR-10	R	R (1)		R (1)		R (1)	
RNR-11	R	R (1)		R (1)		NR (2)	Y
RNR-12	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-13	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-14	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-15	R	R (1)		NR (2)	Y	NR (2)	Y
RNR-16	NR	NR (2)		NR (2)		NR (2)	
RNR-17	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-18	R	R (1)		R (1)		R (1)	
RNR-19	R	R (1)		R (1)		R (1)	
RNR-20	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-21	R	R (1)		R (1)		NR (2)	Y
RNR-22	NR	NR (2)		NR (2)		NR (2)	
RNR-23	R	NR (2)	Y	NR (2)	Y	R (1)	
RNR-24	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-25	R	R (1)		R (1)		R (1)	
RNR-26	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-27	NR	NR (2)		NR (2)		NR (2)	
RNR-28	R	R (1)		R (1)		R (1)	
RNR-29	NR	R (1)	Y	R (1)	Y	NR (2)	
RNR-30	R	R (1)		R (1)		R (1)	
RNR-31	NR	R (1)	Y	R (1)	Y	R (1)	Y
RNR-32	R	R (1)		R (1)		R (1)	
Total:	*32*	*Total:*	*15*	*Total:*	*16*	*Total:*	*14*
		Misclass.:	*47%*	*Misclass.:*	*50%*	*Misclass.:*	*44%*

Trait Classification Code Legend	
Responders Study Participant	RNR
Response Code: Responder	R
Response Code: Non-Responder	NR

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Table B.4: Misclassifications of Pre- and Post-SMT Responders as a result of 2-Cluster k-Means Clustering

Pre- and Post- Treatment Curves, Responders Only		Raw Data		2nd Derivatives	
Subject	**True Classification**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**
RNR-1	Pre	Post (2)	Y	Pre (1)	
	Post	Post (2)		Post (2)	
RNR-3	Pre	Post (2)	Y	Post (2)	Y
	Post	Post (2)		Post (2)	
RNR-6	Pre	Post (2)	Y	Post (2)	Y
	Post	Post (2)		Post (2)	
RNR-9	Pre	Pre (1)		Post (2)	Y
	Post	Pre (1)	Y	Post (2)	
RNR-10	Pre	Post (2)	Y	Post (2)	Y
	Post	Pre (1)	Y	Post (2)	
RNR-11	Pre	Post (2)	Y	Post (2)	Y
	Post	Post (2)		Post (2)	
RNR-15	Pre	Pre (1)		Pre (1)	
	Post	Post (2)		Pre (1)	Y
RNR-18	Pre	Post (2)	Y	Post (2)	Y
	Post	Post (2)		Post (2)	
RNR-19	Pre	Pre (1)		Post (2)	Y
	Post	Pre (1)	Y	Post (2)	
RNR-21	Pre	Post (2)	Y	Post (2)	Y
	Post	Post (2)		Post (2)	
RNR-23	Pre	Pre (1)		Pre (1)	
	Post	Pre (1)	Y	Pre (1)	Y
RNR-25	Pre	Post (2)	Y	Post (2)	Y
	Post	Post (2)		Post (2)	
RNR-28	Pre	Post (2)	Y	Post (2)	Y
	Post	Post (2)		Post (2)	
RNR-30	Pre	Post (2)	Y	Post (2)	Y
	Post	Post (2)		Post (2)	
RNR-32	Pre	Pre (1)		Post (2)	Y
	Post	Pre (1)		Post (2)	
Total:	*30*	*Total:*	*14*	*Total:*	*14*
		Misclass.:	*47%*	*Misclass.:*	*47%*

Trait Classification Code Legend	
Responders Study Participant	RNR
Response Code: Responder	R
Response Code: Non-Responder	NR
Treatment Code: Pre-SMT	Pre
Treatment Code: Post-SMT	Post

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Table B.5: Misclassifications of Pre-SMT Sex as a result of 2-Cluster k-Means Clustering

Pre-Treatment Curves		Raw Data		2nd Derivatives		Transformed Data	
Subject	**True Classification**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**
RNR-1	F	F (1)		F (1)		F (1)	
RNR-2	F	F (1)		F (1)		F (1)	
RNR-3	F	F (1)		F (1)		F (1)	
RNR-4	F	M (2)	Y	M (2)	Y	M (2)	Y
RNR-5	F	F (1)		M (2)	Y	M (2)	Y
RNR-6	M	F (1)	Y	F (1)	Y	M (2)	
RNR-7	F	F (1)		F (1)		F (1)	
RNR-8	M	M (2)		F (1)	Y	M (2)	
RNR-9	F	M (2)	Y	F (1)		F (1)	
RNR-10	F	F (1)		F (1)		F (1)	
RNR-11	M	F (1)	Y	F (1)	Y	F (1)	Y
RNR-12	M	F (1)	Y	F (1)	Y	F (1)	Y
RNR-13	M	F (1)	Y	F (1)	Y	F (1)	Y
RNR-14	M	F (1)	Y	F (1)	Y	F (1)	Y
RNR-15	M	F (1)	Y	M (2)		M (2)	
RNR-16	F	M (2)	Y	M (2)	Y	M (2)	Y
RNR-17	F	F (1)		F (1)		F (1)	
RNR-18	F	F (1)		F (1)		F (1)	
RNR-19	M	M (2)		F (1)	Y	F (1)	Y
RNR-20	F	F (1)		F (1)		F (1)	
RNR-21	M	F (1)	Y	F (1)	Y	M (2)	
RNR-22	F	M (2)	Y	M (2)	Y	M (2)	Y
RNR-23	F	M (2)	Y	M (2)	Y	M (2)	Y
RNR-24	F	F (1)		F (1)		F (1)	
RNR-25	F	F (1)		F (1)		F (1)	
RNR-26	F	F (1)		F (1)		M (2)	Y
RNR-27	F	M (2)	Y	F (1)		M (2)	Y
RNR-28	F	F (1)		F (1)		F (1)	
RNR-29	M	F (1)	Y	F (1)	Y	F (1)	Y
RNR-30	M	F (1)	Y	F (1)	Y	F (1)	Y
RNR-31	F	F (1)		F (1)		F (1)	
RNR-32	F	F (1)		F (1)		F (1)	
Total:	*32*	*Total:*	*15*	*Total:*	*15*	*Total:*	*14*
		Misclass.:	*47%*	*Misclass.:*	*47%*	*Misclass.:*	*44%*

Trait Classification Code Legend	
Responders Study Participant	RNR
Response Code: Responder	R
Response Code: Non-Responder	NR
Male	M
Female	F

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Table B.6: Misclassifications of Post-SMT Sex as a result of 2-Cluster k-Means Clustering

Post-Treatment Curves		Raw Data		2nd Derivatives		Transformed Data	
Subject	**True Classification**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**
RNR-1	F	M (1)	Y	F (1)		F (1)	
RNR-2	F	M (1)	Y	F (1)		F (1)	
RNR-3	F	M (1)	Y	F (1)		F (1)	
RNR-4	F	F (2)		F (1)		M (2)	Y
RNR-5	F	M (1)	Y	F (1)		F (1)	
RNR-6	M	M (1)		F (1)	Y	F (1)	Y
RNR-7	F	M (1)	Y	F (1)		F (1)	
RNR-8	M	M (1)		F (1)	Y	M (2)	
RNR-9	F	F (2)		F (1)		F (1)	
RNR-10	F	M (1)	Y	F (1)		F (1)	
RNR-11	M	M (1)		F (1)	Y	M (2)	
RNR-12	M	M (1)		F (1)	Y	F (1)	Y
RNR-13	M	M (1)		F (1)	Y	F (1)	Y
RNR-14	M	M (1)		F (1)	Y	F (1)	Y
RNR-15	M	M (1)		M (2)		M (2)	
RNR-16	F	F (2)		M (2)	Y	M (2)	Y
RNR-17	F	M (1)	Y	F (1)		F (1)	
RNR-18	F	M (1)	Y	F (1)		F (1)	
RNR-19	M	M (1)		F (1)	Y	F (1)	Y
RNR-20	F	M (1)	Y	F (1)		F (1)	
RNR-21	M	M (1)		F (1)	Y	M (2)	
RNR-22	F	F (2)		M (2)	Y	M (2)	Y
RNR-23	F	F (2)		M (2)	Y	F (1)	
RNR-24	F	M (1)	Y	F (1)		F (1)	
RNR-25	F	M (1)	Y	F (1)		F (1)	
RNR-26	F	M (1)	Y	F (1)		F (1)	
RNR-27	F	F (2)		M (2)	Y	M (2)	Y
RNR-28	F	M (1)	Y	F (1)		F (1)	
RNR-29	M	M (1)		F (1)	Y	M (2)	
RNR-30	M	M (1)	Y	F (1)	Y	F (1)	
RNR-31	F	M (1)	Y	F (1)		F (1)	
RNR-32	F	M (1)	Y	F (1)		F (1)	
Total:	*32*	*Total:*	*16*	*Total:*	*14*	*Total:*	*9*
		Misclass.:	*50%*	*Misclass.:*	*44%*	*Misclass.:*	*28%*

Trait Classification Code Legend	
Responders Study Participant	RNR
Response Code: Responder	R
Response Code: Non-Responder	NR
Male	M
Female	F

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Table B.7: Misclassifications of Pre-SMT BMI as a result of 2-Cluster k-Means Clustering

Pre-Treatment Curves		Raw Data		2nd Derivatives		Transformed Data	
Subject	**True Classification**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**
RNR-1	N	1		1		1	
RNR-2	N	1		1		1	
RNR-3	N	1		1		1	
RNR-4	Ov	2		2		2	
RNR-5	N	1		2	Y	2	Y
RNR-6	Ob	1	Y	1	Y	2	
RNR-7	N	1		1		1	
RNR-8	Ov	2		1	Y	2	
RNR-9	Ov	2		1	Y	1	Y
RNR-10	N	1		1		1	
RNR-11	Ov	1	Y	1	Y	1	Y
RNR-12	N	1		1		1	
RNR-13	N	1		1		1	
RNR-14	N	1		1		1	
RNR-15	Ov	1	Y	2		2	
RNR-16	Ob	2		2		2	
RNR-17	Ob	1	Y	1	Y	1	Y
RNR-18	N	1		1		1	
RNR-19	Ov	2		1	Y	1	Y
RNR-20	U	1		1		1	
RNR-21	N	1		1		2	Y
RNR-22	Ob	2		2		2	
RNR-23	Ov	2		2		2	
RNR-24	N	1		1		1	
RNR-25	Ov	1	Y	1	Y	1	Y
RNR-26	Ov	1	Y	1	Y	2	
RNR-27	Ob	2		1	Y	2	
RNR-28	N	1		1		1	
RNR-29	N	1		1		1	
RNR-30	Ov	1	Y	1	Y	1	Y
RNR-31	N	1		1		1	
RNR-32	N	1		1		1	
Total:	*32*	*Total:*	*7*	*Total:*	*11*	*Total:*	*8*
		Misclass.:	*22%*	*Misclass.:*	*34%*	*Misclass.:*	*25%*

Trait Classification Code Legend			
Responders Study Participant	RNR		
Response Code: Responder	R		
Response Code: Non-Responder	NR		
Body Mass Index: Underweight	U	N or U	1
Body Mass Index: Normal	N		
Body Mass Index: Overweight	Ov	Ov or Ob	2
Body Mass Index: Obese	Ob		

Back

Table B.8: Misclassifications of Post-SMT BMI as a result of 2-Cluster k-Means Clustering

Post-Treatment Curves		Raw Data		2nd Derivatives		Transformed Data	
Subject	True Classification	Cluster	Misclass.	Cluster	Misclass.	Cluster	Misclass.
RNR-1	N	1		1		1	
RNR-2	N	1		1		1	
RNR-3	N	1		1		1	
RNR-4	Ov	2		1	Y	2	
RNR-5	N	1		1		1	
RNR-6	Ob	1	Y	1	Y	1	Y
RNR-7	N	1		1		1	
RNR-8	Ov	1	Y	1	Y	2	
RNR-9	Ov	2		1	Y	1	Y
RNR-10	N	1		1		1	
RNR-11	Ov	1	Y	1	Y	2	
RNR-12	N	1		1		1	
RNR-13	N	1		1		1	
RNR-14	N	1		1		1	
RNR-15	Ov	1	Y	2		2	
RNR-16	Ob	2		2		2	
RNR-17	Ob	1	Y	1	Y	1	Y
RNR-18	N	1		1		1	
RNR-19	Ov	1	Y	1	Y	1	Y
RNR-20	U	1		1		1	
RNR-21	N	1		1		2	Y
RNR-22	Ob	2		2		2	
RNR-23	Ov	2		2		1	Y
RNR-24	N	1		1		1	
RNR-25	Ov	1	Y	1	Y	1	Y
RNR-26	Ov	1	Y	1	Y	1	Y
RNR-27	Ob	2		2		2	
RNR-28	N	1		1		1	
RNR-29	N	1		1		2	Y
RNR-30	Ov	1	Y	1	Y	1	Y
RNR-31	N	1		1		1	
RNR-32	N	1		1		1	
Total:	*32*	*Total:*	*9*	*Total:*	*10*	*Total:*	*10*
		Misclass.:	*28%*	*Misclass.:*	*31%*	*Misclass.:*	*31%*

Trait Classification Code Legend			
Responders Study Participant	RNR		
Response Code: Responder	R		
Response Code: Non-Responder	NR		
Body Mass Index: Underweight	U	N or U	1
Body Mass Index: Normal	N		
Body Mass Index: Overweight	Ov	Ov or Ob	2
Body Mass Index: Obese	Ob		

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Table B.9: Misclassifications of Pre-SMT LBP History as a result of 2-Cluster k-Means Clustering

Pre-Treatment Curves		Raw Data		2nd Derivatives		Transformed Data	
Subject	**True Classification**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**
RNR-1	Y	Y (1)		Y (1)		Y (1)	
RNR-2	Y	Y (1)		Y (1)		Y (1)	
RNR-3	N	Y (1)	Y	Y (1)	Y	Y (1)	Y
RNR-4	Y	N (2)	Y	N (2)	Y	N (2)	Y
RNR-5	Y	Y (1)		N (2)	Y	N (2)	Y
RNR-6	Y	Y (1)		Y (1)		N (2)	Y
RNR-7	Y	Y (1)		Y (1)		Y (1)	
RNR-8	Y	N (2)	Y	Y (1)		N (2)	Y
RNR-9	Y	N (2)	Y	Y (1)		Y (1)	
RNR-10	Y	Y (1)		Y (1)		Y (1)	
RNR-11	Y	Y (1)		Y (1)		Y (1)	
RNR-12	N	Y (1)	Y	Y (1)	Y	Y (1)	Y
RNR-13	Y	Y (1)		Y (1)		Y (1)	
RNR-14	Y	Y (1)		Y (1)		Y (1)	
RNR-15	Y	Y (1)		N (2)	Y	N (2)	Y
RNR-16	Y	N (2)	Y	N (2)	Y	N (2)	Y
RNR-17	Y	Y (1)		Y (1)		Y (1)	
RNR-18	Y	Y (1)		Y (1)		Y (1)	
RNR-19	Y	N (2)	Y	Y (1)		Y (1)	
RNR-20	Y	Y (1)		Y (1)		Y (1)	
RNR-21	Y	Y (1)		Y (1)		N (2)	
RNR-22	Y	N (2)	Y	N (2)	Y	N (2)	Y
RNR-23	Y	N (2)	Y	N (2)	Y	N (2)	Y
RNR-24	N	Y (1)	Y	Y (1)	Y	Y (1)	Y
RNR-25	Y	Y (1)		Y (1)		Y (1)	
RNR-26	N	Y (1)	Y	Y (1)	Y	N (2)	
RNR-27	Y	N (2)	Y	Y (1)		N (2)	Y
RNR-28	Y	Y (1)		Y (1)		Y (1)	
RNR-29	Y	Y (1)		Y (1)		Y (1)	
RNR-30	Y	Y (1)		Y (1)		Y (1)	
RNR-31	Y	Y (1)		Y (1)		Y (1)	
RNR-32	Y	Y (1)		Y (1)		Y (1)	
Total:	*32*	*Total:*	*12*	*Total:*	*10*	*Total:*	*12*
		Misclass.:	*38%*	*Misclass.:*	*31%*	*Misclass.:*	*38%*

Trait Classification Code Legend	
Responders Study Participant	RNR
Response Code: Responder	R
Response Code: Non-Responder	NR
Previous History of LBP: Present	Y
Previous History of LBP: Absent	N

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Table B.10: Misclassifications of Post-SMT LBP History as a result of 2-Cluster k-Means Clustering

Post-Treatment Curves		Raw Data		2nd Derivatives		Transformed Data	
Subject	**True Classification**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**
RNR-1	Y	Y (1)		Y (1)		Y (1)	
RNR-2	Y	Y (1)		Y (1)		Y (1)	
RNR-3	N	Y (1)	Y	Y (1)	Y	Y (1)	Y
RNR-4	Y	N (2)	Y	Y (1)		N (2)	Y
RNR-5	Y	Y (1)		Y (1)		Y (1)	
RNR-6	Y	Y (1)		Y (1)		Y (1)	
RNR-7	Y	Y (1)		Y (1)		Y (1)	
RNR-8	Y	Y (1)		Y (1)		N (2)	Y
RNR-9	Y	N (2)	Y	Y (1)		Y (1)	
RNR-10	Y	Y (1)		Y (1)		Y (1)	
RNR-11	Y	Y (1)		Y (1)		N (2)	Y
RNR-12	N	Y (1)	Y	Y (1)	Y	Y (1)	Y
RNR-13	Y	Y (1)		Y (1)		Y (1)	
RNR-14	Y	Y (1)		Y (1)		Y (1)	
RNR-15	Y	Y (1)		N (2)	Y	N (2)	Y
RNR-16	Y	N (2)	Y	N (2)	Y	N (2)	Y
RNR-17	Y	Y (1)		Y (1)		Y (1)	
RNR-18	Y	Y (1)		Y (1)		Y (1)	
RNR-19	Y	Y (1)		Y (1)		Y (1)	
RNR-20	Y	Y (1)		Y (1)		Y (1)	
RNR-21	Y	Y (1)		Y (1)		N (2)	Y
RNR-22	Y	N (2)	Y	N (2)	Y	N (2)	Y
RNR-23	Y	N (2)	Y	N (2)	Y	Y (1)	
RNR-24	N	Y (1)	Y	Y (1)	Y	Y (1)	Y
RNR-25	Y	Y (1)		Y (1)		Y (1)	
RNR-26	N	Y (1)	Y	Y (1)	Y	Y (1)	Y
RNR-27	Y	N (2)	Y	N (2)	Y	N (2)	Y
RNR-28	Y	Y (1)		Y (1)		Y (1)	
RNR-29	Y	Y (1)		Y (1)		N (2)	Y
RNR-30	Y	Y (1)		Y (1)		Y (1)	
RNR-31	Y	Y (1)		Y (1)		Y (1)	
RNR-32	Y	Y (1)		Y (1)		Y (1)	
Total:	*32*	*Total:*	*10*	*Total:*	*9*	*Total:*	*13*
		Misclass.:	*31%*	*Misclass.:*	*28%*	*Misclass.:*	*41%*

Trait Classification Code Legend	
Responders Study Participant	RNR
Response Code: Responder	R
Response Code: Non-Responder	NR
Previous History of LBP: Present	Y
Previous History of LBP: Absent	N

Back

Table B.11: Misclassifications of Pre-SMT LBP Duration as a result of 2-Cluster k-Means Clustering

Pre-Treatment Curves		Raw Data		2nd Derivatives		Transformed Data	
Subject	**True Classification**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**
RNR-1	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-2	C	C (1)		C (1)		C (1)	
RNR-3	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-4	A	A (2)		A (2)		A (2)	
RNR-5	A	C (1)	Y	A (2)		A (2)	
RNR-6	A	C (1)	Y	C (1)	Y	A (2)	
RNR-7	C	C (1)		C (1)		C (1)	
RNR-8	A	A (2)		C (1)	Y	A (2)	
RNR-9	A	A (2)		C (1)	Y	C (1)	Y
RNR-10	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-11	C	C (1)		C (1)		C (1)	
RNR-12	C	C (1)		C (1)		C (1)	
RNR-13	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-14	C	C (1)		C (1)		C (1)	
RNR-15	A	C (1)	Y	A (2)		A (2)	
RNR-16	A	A (2)		A (2)		A (2)	
RNR-17	C	C (1)		C (1)		C (1)	
RNR-18	C	C (1)		C (1)		C (1)	
RNR-19	A	A (2)		C (1)	Y	C (1)	Y
RNR-20	C	C (1)		C (1)		C (1)	
RNR-21	C	C (1)		C (1)		A (2)	Y
RNR-22	C	A (2)	Y	A (2)	Y	A (2)	Y
RNR-23	A	A (2)		A (2)		A (2)	
RNR-24	C	C (1)		C (1)		C (1)	
RNR-25	C	C (1)		C (1)		C (1)	
RNR-26	A	C (1)	Y	C (1)	Y	A (2)	
RNR-27	A	A (2)		C (1)	Y	A (2)	
RNR-28	C	C (1)		C (1)		C (1)	
RNR-29	C	C (1)		C (1)		C (1)	
RNR-30	C	C (1)		C (1)		C (1)	
RNR-31	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-32	C	C (1)		C (1)		C (1)	
Total:	*32*	*Total:*	*10*	*Total:*	*12*	*Total:*	*9*
		Misclass.:	*31%*	*Misclass.:*	*38%*	*Misclass.:*	*28%*

Trait Classification Code Legend	
Responders Study Participant	RNR
Response Code: Responder	R
Response Code: Non-Responder	NR
Duration of LBP: Acute	A
Duration of LBP: Chronic	C

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Table B.12: Misclassifications of Post-SMT LBP Duration as a result of 2-Cluster k-Means Clustering

Post-Treatment Curves		Raw Data		2nd Derivatives		Transformed Data	
Subject	**True Classification**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**	**Cluster**	**Misclass.**
RNR-1	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-2	C	C (1)		C (1)		C (1)	
RNR-3	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-4	A	A (2)		C (1)	Y	A (2)	
RNR-5	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-6	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-7	C	C (1)		C (1)		C (1)	
RNR-8	A	C (1)	Y	C (1)	Y	A (2)	
RNR-9	A	A (2)		C (1)	Y	C (1)	Y
RNR-10	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-11	C	C (1)		C (1)		A (2)	Y
RNR-12	C	C (1)		C (1)		C (1)	
RNR-13	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-14	C	C (1)		C (1)		C (1)	
RNR-15	A	C (1)	Y	A (2)		A (2)	
RNR-16	A	A (2)		A (2)		A (2)	
RNR-17	C	C (1)		C (1)		C (1)	
RNR-18	C	C (1)		C (1)		C (1)	
RNR-19	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-20	C	C (1)		C (1)		C (1)	
RNR-21	C	C (1)		C (1)		A (2)	Y
RNR-22	C	A (2)	Y	A (2)	Y	A (2)	Y
RNR-23	A	A (2)		A (2)		C (1)	Y
RNR-24	C	C (1)		C (1)		C (1)	
RNR-25	C	C (1)		C (1)		C (1)	
RNR-26	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-27	A	A (2)		A (2)		A (2)	
RNR-28	C	C (1)		C (1)		C (1)	
RNR-29	C	C (1)		C (1)		A (2)	Y
RNR-30	C	C (1)		C (1)		C (1)	
RNR-31	A	C (1)	Y	C (1)	Y	C (1)	Y
RNR-32	C	C (1)		C (1)		C (1)	
Total:	*32*	*Total:*	*12*	*Total:*	*13*	*Total:*	*15*
		Misclass.:	*38%*	*Misclass.:*	*41%*	*Misclass.:*	*47%*

Trait Classification Code Legend	
Responders Study Participant	RNR
Response Code: Responder	R
Response Code: Non-Responder	NR
Duration of LBP: Acute	A
Duration of LBP: Chronic	C

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Table B.13: Misclassifications of Pre-SMT Responder Status as a result of LCRA Clustering

Pre-Treatment Curves		LCRA 2-Class		LCRA w/ Cov	
Subject	**True Classification**	**Class**	**Misclass.**	**Class**	**Misclass.**
RNR-1	R	R (1)		R (1)	
RNR-2	NR	R (1)	Y	R (1)	Y
RNR-3	R	R (1)		R (1)	
RNR-4	NR	NR (2)		NR (2)	
RNR-5	NR	R (1)	Y	R (1)	Y
RNR-6	R	R (1)		R (1)	
RNR-7	NR	R (1)	Y	R (1)	Y
RNR-8	NR	NR (2)		NR (2)	
RNR-9	R	NR (2)	Y	NR (2)	Y
RNR-10	R	R (1)		R (1)	
RNR-11	R	R (1)		R (1)	
RNR-12	NR	R (1)	Y	R (1)	Y
RNR-13	NR	R (1)	Y	R (1)	Y
RNR-14	NR	R (1)	Y	R (1)	Y
RNR-15	R	NR (2)	Y	NR (2)	Y
RNR-16	NR	NR (2)		NR (2)	
RNR-17	NR	R (1)	Y	R (1)	Y
RNR-18	R	R (1)		R (1)	
RNR-19	R	NR (2)	Y	NR (2)	Y
RNR-20	NR	R (1)	Y	R (1)	Y
RNR-21	R	R (1)		R (1)	
RNR-22	NR	NR (2)		NR (2)	
RNR-23	R	NR (2)	Y	NR (2)	Y
RNR-24	NR	NR (2)		NR (2)	
RNR-25	R	R (1)		R (1)	
RNR-26	NR	R (1)	Y	R (1)	Y
RNR-27	NR	NR (2)		NR (2)	
RNR-28	R	R (1)		R (1)	
RNR-29	NR	R (1)	Y	R (1)	Y
RNR-30	R	R (1)		R (1)	
RNR-31	NR	R (1)	Y	R (1)	Y
RNR-32	R	NR (2)	Y	NR (2)	Y
Total:	*32*	*Total:*	*16*	*Total:*	*16*
		Misclass.:	*50%*	*Misclass.:*	*50%*

Trait Classification Code Legend	
Responders Study Participant	RNR
Response Code: Responder	R
Response Code: Non-Responder	NR

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Table B.14: Misclassifications of Post-SMT Responder Status as a result of LCRA Clustering

Post-Treatment Curves		LCRA 2-Class		LCRA w/ Cov	
Subject	**True Classification**	**Class**	**Misclass.**	**Class**	**Misclass.**
RNR-1	R	NR (1)	Y	NR (1)	Y
RNR-2	NR	NR (1)		NR (1)	
RNR-3	R	NR (1)	Y	NR (1)	Y
RNR-4	NR	R (2)	Y	R (2)	Y
RNR-5	NR	NR (1)		NR (1)	
RNR-6	R	NR (1)	Y	NR (1)	Y
RNR-7	NR	NR (1)		NR (1)	
RNR-8	NR	NR (1)		NR (1)	
RNR-9	R	R (2)		R (2)	
RNR-10	R	R (2)		R (2)	
RNR-11	R	NR (1)	Y	NR (1)	Y
RNR-12	NR	NR (1)		NR (1)	
RNR-13	NR	NR (1)		NR (1)	
RNR-14	NR	NR (1)		NR (1)	
RNR-15	R	NR (1)	Y	NR (1)	Y
RNR-16	NR	R (2)	Y	R (2)	Y
RNR-17	NR	NR (1)		NR (1)	
RNR-18	R	NR (1)	Y	NR (1)	Y
RNR-19	R	R (2)		R (2)	
RNR-20	NR	NR (1)		NR (1)	
RNR-21	R	NR (1)	Y	NR (1)	Y
RNR-22	NR	R (2)	Y	R (2)	Y
RNR-23	R	R (2)		R (2)	
RNR-24	NR	NR (1)		NR (1)	
RNR-25	R	NR (1)	Y	NR (1)	Y
RNR-26	NR	NR (1)		NR (1)	
RNR-27	NR	R (2)	Y	R (2)	Y
RNR-28	R	NR (1)	Y	NR (1)	Y
RNR-29	NR	NR (1)		NR (1)	
RNR-30	R	NR (1)	Y	NR (1)	Y
RNR-31	NR	R (2)	Y	R (2)	Y
RNR-32	R	R (2)		R (2)	
Total:	*32*	*Total:*	*15*	*Total:*	*15*
		Misclass.:	*47%*	*Misclass.:*	*47%*

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Appendix 3: Conferences

The work detailed in this thesis has thus far been presented in the following ways:

- Casciaro, Y., Prasad, N., Kawchuk, G. (2016). *Latent class regression analysis for clustering spinal stiffness curves: An exploratory analysis*. Poster session presented at the DC2017 Conference, World Federation of Chiropractic (WFC), Association of Chiropractic Colleges (ACC) and American Chiropractic Association (ACA), Washington, D.C. — March, 2017
- Casciaro, Y., Prasad, N., Kawchuk, G. (2016). *Latent class regression analysis for clustering spinal stiffness curves: An exploratory analysis*. Poster session presented at the Alberta Biomedical Engineering Conference, Calgary, AB. — October, 2016
- Casciaro, Y., Kawchuk, G., Prasad, N. (2018). *Spinal Stiffness Evaluation Using Latent Class and Functional Data Analyses*. Poster session presented at the 45th International Society for the Study of the Lumbar Spine (ISSLS) Annual Meeting, Banff, AB. — May, 2018

End