DEPARTMENT OF BIOMEDICAL ENGINEERING

University of Strathclyde Engineering

On the Quantification and Objective Classification of Instability in the Healthy, Osteoarthritic and Prosthetic Knee

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Declaration

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed:

Date:

ABSTRACT

Knee instability is a common complaint in osteoarthritis (OA), and a common reason for revision following total knee arthroplasty (TKA). Despite this, assessment of instability is hampered by the lack of a validated method of objective classification or quantification, with most research relying upon patient reports of frequency of symptoms. The aim of this thesis is to define a theoretical framework for instability in the knee, and to develop a protocol for the classification and quantification of instability in the native and prosthetic knee.

Instability of the knee in this thesis is understood as the failure of the joint to return to a zero-state following perturbation using all the available active and passive mechanisms available to it, resulting in system collapse. Symptomatic instability is the awareness of reaching the boundary between the stable and unstable state. The prevalence of subjective instability in the end stage OA knee was measured from a publicly available database of pre-operative knee scores from TKA patients, while the prevalence of instability as a cause of revision was assessed from case note review of TKA revision patients from a tertiary referral orthopaedic unit. A single channel, tibia mounted accelerometer was selected for assessment of frontal plane knee movement during normal walking and a protocol developed its use. This was assessed for its repeatability and compared with standard gait analysis in heathy volunteers, and subjectively stable and unstable post-operative TKA patients. Found to be repeatable with differentiation of output between subjectively stable and unstable TKA, the protocol was adapted and used to compare subjectively stable and unstable OA knees prior to TKA. Using patient subjective assessment as classifier, wavelet transforms, Principal Component Analysis

and linear regression was used to produce a classification model from the accelerometer data.

The single accelerometer was found to produce classification with an accuracy of 84.6%, sensitivity of 93.3% and specificity of 72.7%, with area under the curve (AUC) of 0.797. This classification model for instability produces the basis from which the protocol can be adapted and developed to improve performance and ultimate quantify instability in the knee for use in clinical and research settings.

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PEER REVIEWED PUBLICATIONS FROM THIS THESIS

- The Assessment of Instability in the Osteoarthritic Knee. Wallace, D. T., Riches, P., Picard, F., *EFORT Open Reviews.* 2019;4(3): 70-76

PRESENTATIONS FROM THIS THESIS

- Oral Presentation: Development of a device for the Classification and quantification of instability in the knee. *Engineering Faculty Research Presentation Day, University of Strathclyde, Glasgow,* December 2018
- Poster presentation: Wavelet analysis in the diagnosis of knee instability – Early Results from a Novel Assessment Method. *BioMedEng18, London, UK*, September 2018
- Poster presentation: Reduced Sagittal Plane Stiffness in Total Knee Replacement with Patient Reported Instability. *European Federation of Orthopaedics and Traumatology, Barcelona, Spain,* May 2018
- Oral Presentation: Reduced Sagittal Plane Stiffness in Total Knee Replacement with Patient Reported Instability. *Glasgow Meeting of Orthopaedic Research, Clydebank, UK,* March 2018
- Oral Presentation: Development of a device for the quantification of instability in the total knee replacement. *Engineering Faculty Research Presentation Day, University of Strathclyde, Glasgow,* December 2017
- Oral Presentation: Healthy Subject Validation of a Single Accelerometer for The Assessment of Knee Stability. *Glasgow Meeting of Orthopaedic Research, Clydebank, UK,* March 2017

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

TABLE OF EQUATIONS

LIST OF ABBREVIATIONS

AP	Anterior to posterior
ACL	Anterior cruciate ligament
ADLS	Activities of Daily Living Score
AFO	Ankle-foot orthosis
ANOVA	Analysis of Variance
ASIS	Anterior Superior Iliac Spine
AUC	Area Under the Curve
AVN	Avascular Necrosis
BMI	Body Mass Index
CAD	Computer Aided Design
CR	Cruciate retaining
CT	Computed tomography
CTS	Computed tomography scanogram
CWT	Continuous wavelet transform
DAIR	Debridement, Antibiotics, Irrigation and Retention of Prosthesis
DWT	Discrete Wavelet Transform
EDRIS	Electronic Data Research and Innovations Service

EKAM	External knee adduction moment
EMG	Electromyography
FB	Fixed bearing
FFT	Fast Fourier Transform
FTMA	Femoral tibial mechanical axis
GJNH	Golden Jubilee National Hospital
HSD	Honest Significant Difference
HTO	High Tibial Osteotomy
ICC	Interclass correlation
ICD	International Classification of Diseases
IMU	Inertial measurement unit
IR	Internal rotation
K-L	Kellgren-Lawrence grading for knee osteoarthritis (x-ray)
KOOS	Knee Injury and Osteoarthritis Outcome Score
KOS	Knee Outcome Survey
KSS	Knee Society score
LCL	Lateral collateral ligament
LR	Logistic Regression
MB	Mobile bearing

MCL	Medial collateral ligament
MEMS	Micro-electric Mechanical System
ML	Medial-Lateral
MRI	Magnetic resonance imaging
NHS	National Health Service
OA	Osteoarthritis
OKS	Oxford knee score
PBPP	Public Beneficiary and Privacy Panel
PC	Principal Component
PCA	Principal Component Analysis
PCL	Posterior Cruciate Ligament
PCL	Posterior cruciate ligament
PIG	Plug in Gait
PLA	Polylactic Acid
PROMS	Patient Reported Outcome Measures
PS	Posterior stabilised
PSIS	Posterior-Superior Iliac Spine
RA	Rheumatoid arthritis
RCT	Randomised Controlled Trial

REC	Regional Ethics Committee
RMS	Root Mean Square
ROM	Range of movement
ROC	Receiver Operating Characteristics
ROM	Range of Movement
SCT	Stair Climb Test
SD	Standard Deviation
SF-36	36-Item Short Form Survey
SVM	Support Vector Machine
V-V	Varus to valgus
THA	Total Hip Arthroplasty
TKA	Total knee arthroplasty
TTTG	Tibial Tubercle - Trochlear Grove
UKA	Unicompartmental Knee Arthroplasty
WOMAC	Western Ontario and McMasters University Osteoarthritis Index

CHAPTER 1 – INTRODUCTION

In knee osteoarthritis a frequently reported symptom is “instability”. It is reported as affecting more than two thirds of people with end stage arthritis of the knee (Fleeton *et al.*, 2016) and is the cause of failure requiring revision of total knee arthroplasty in up to 20% of cases (Sharkey *et al.*, 2014). “Instability” has been shown to be an independent predictor of poor performance in activities of daily living and is associated with reduced activities of daily living (Fitzgerald, Piva and Irrgang, 2004). Causes and solutions for the problem of knee “instability” have been examined and tested for decades, however there is still no consensus on what instability objectively is, how it can be measured, or how it relates to the subjective descriptions of “buckling and giving way” so often given by patients and made use of in striation of subjects for study.

Standard methods of assessment of knee “instability” include visual analysis of gait, clinical (manual) examination of the knee, hip and ankle, radiographic analysis of the limb, both two and three-dimensional, computerised mechanical quantification of ligamentous stability, 3D video gait analysis and imageless computer-based navigation systems (Chang *et al.*, 2010; Creaby *et al.*, 2013; Abdel and Haas, 2014; Vince, 2014). Despite this no test or combination of tests exists to give a quantifiable measurement of “instability” in the knee in arthritis or following arthroplasty that might be used for analysis of pathology, and planning of surgical strategy, much less one that has usability within the clinical setting.

Recent advances in micro processing and miniaturisation have popularised the

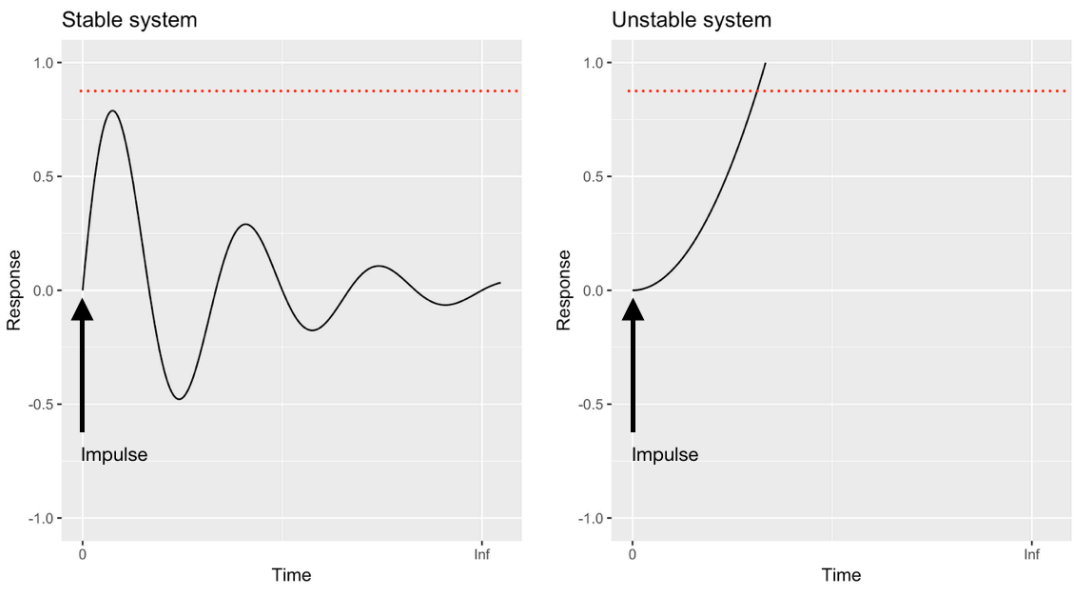

Figure 1 1 – Examples of stable and unstable systems in response to an impulse
Stable image representing dampened impulse tending towards zero – a stable system. Unstable image representing the exponential increase in impulse – an unstable system. Red dotted line indicating threshold for system collapse.

development of inertial measurement units. These as small and easy to use, dispensing with expensive, time consuming, and physically large setup. While this has begun to be translated to the field of ligamentous injury (Berruto *et al.*, 2013) little work has been done with regards to knee "instability".

For the purposes of this thesis, and a coherent discussion of instability it is necessary to create a working definition of stability. In control systems engineering a stable system is defined as one in which a system's response to an impulse returns to zero. In an unstable system, the impulse does not return to zero, but tends towards infinity (Figure 1-1.) In the context of the knee, a stable system will be one in which an internal or external influence is damped, and the can return to a state of equilibrium. An unstable knee will be one in which an external influence cannot be controlled, and the knee fails to return to its steady state. In a simple model of the knee, it is either straight and still,

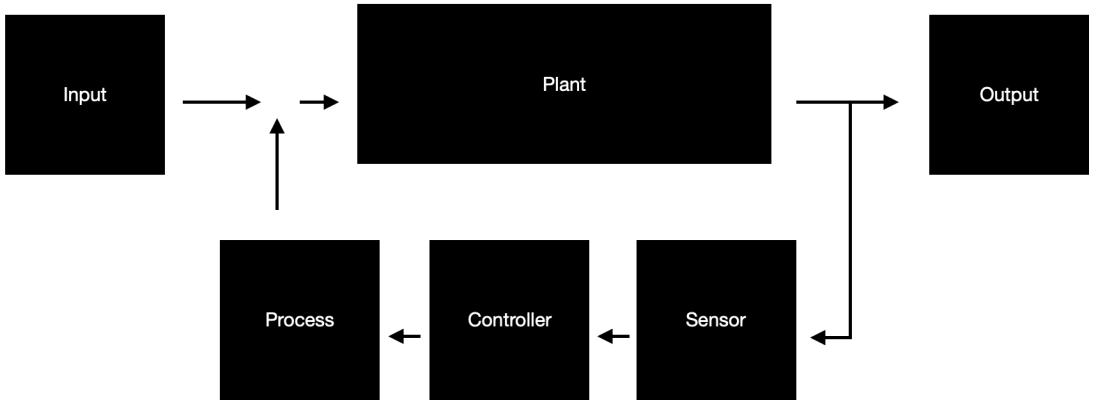

Figure 1-2 – Generic control system diagram
System flow diagram showing generic control system mode to be applied to the knee)

supporting weight, or exhibiting linear, periodic flexion and extension. A stable model here is one in which a controller receives information from an input, and orders a response, with the current system state fed back to influence the outcome (Figure 1-2). In the case of straight, weight bearing knee that may be a posterior/anterior force directed at the back of the knee causing it to flex, stretch receptors in the quadriceps tendons sensing elongation, and a neural arc response resulting in a muscle contraction to extend the knee (Figure 1-3). It is plainly evident that the stability of the system described here is dependent upon the force applied – a gentle kick to the back of the knee will be stabilised; the impact from a speeding vehicle would not be.

In reality, however, the knee does not undergo simple linear motion, but instead is subject to non-linear influences, as it is used in everyday activities. For this reason, knee motion has been examined through the model of non-linear dynamic (England and Granata, 2007). The motion and external forces acting on the knee are complex, but so too are its sensors – proprioceptors, stretch receptors, sight, balance – and control systems and actuators such as bony congruency, ligament, tendon, and muscle. The

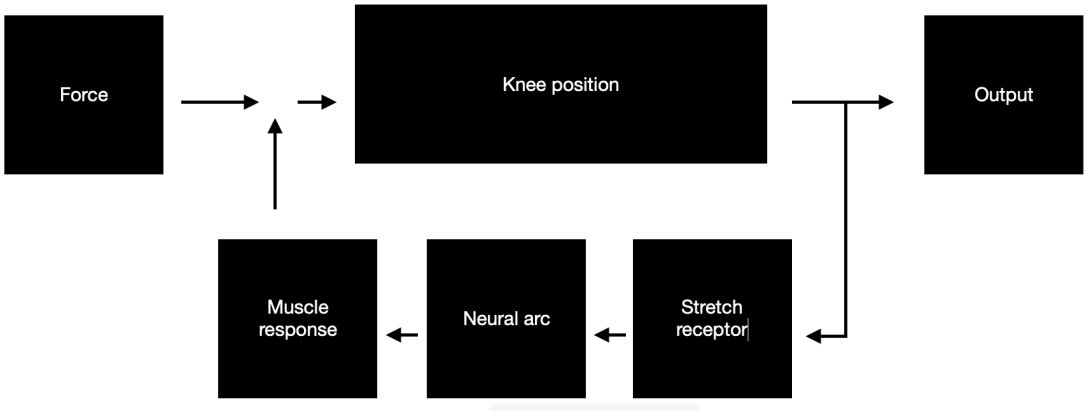

Figure 1-3 – Simplified control system diagram of knee stability in sagittal plane

investigation of specific mechanisms of sensing perturbation and correcting it are not the purpose of this thesis, but the exploration of measuring when these combined systems fail, or approach failure, during normal activities of daily living.

In such a case, an internal or external stimulus begins to exceed correction mechanism to result in an accelerating trajectory towards failure. However, in the knee, such perturbations rarely result in complete failure (where buckling or collapse results in participant collapse) so a broader approach is required. In OA instability research, several definitions revolving around subjective patient feeling about the knee are in common usage, which will be discussed at a later stage. The inherent difference here is that a joint that feels unstable may not result in complete collapse, as many homeostatic mechanisms exist to prevent this occurrence. It is the position of this thesis that, as the knee approaches the boundary of failure, the perception of this impending collapse gives rise to the patient reported feeling of "instability". It is proposed that while an "unstable" knee may not fail, the knee have increased digression from its resting state, require increased recruitment of mechanisms return to zero state, and throughout this

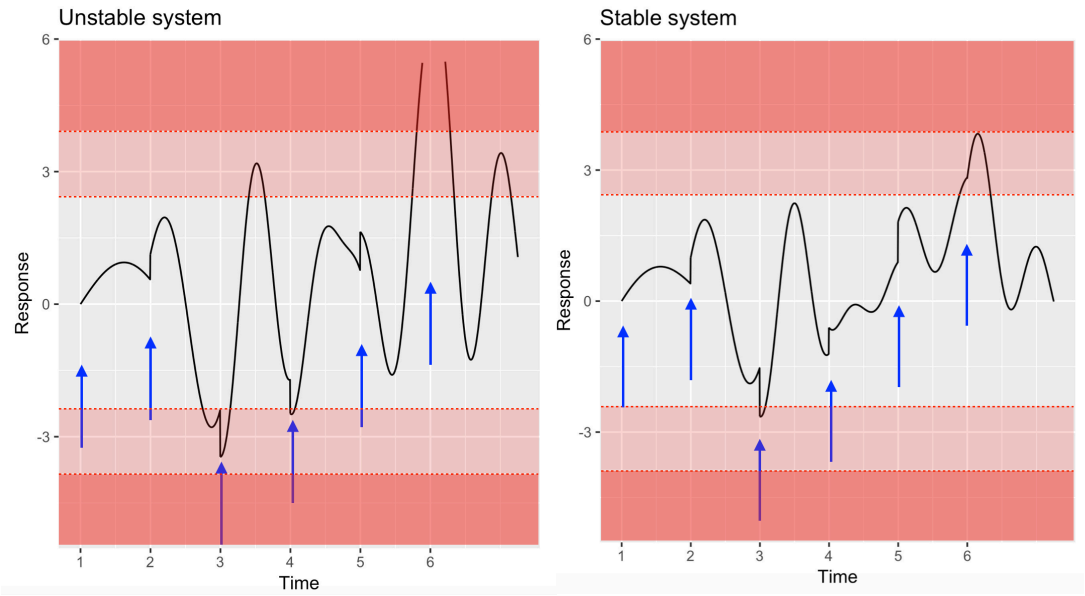

Figure 1 4 – Diagrammatic representation of the knee undergoing multiple impulses
Each blue arrow represents an impulse, light red area represents the boundary zone and the dark red zone represents system failure. In the stable and unstable systems, the impulses are damped according to the decay functions e^{-t} and $1-\left(\frac{e^{t}}{\max e^{t}}\right)$ representing greater and lesser amounts of dampening

time at the boundary between stable and unstable will activate greater conscious feedback of this state. Consequently, a symptomatically unstable knee will be one in which more time is spent in these "boundary" regions (Figure 1 4). Therefore, in this thesis the term "instability" as pertaining to the knee refers to the system failure, or approaching failure, of the knee joint to maintain its equilibrium such that it results in an actual or perceived event for the person.

No objective measurement of the frequencies or extent of these recruitments required to produce feelings of instability exist and so, for the purposes of this thesis, patient reported instability will be the metric by which subjects are categorised into "stable" and "unstable" groupings using answer to the question:

"has your knee buckled or given way in the last month?"

The aim of this study will be to provide classification and quantification of basis of these feelings of instability based upon the underlying joint movement during normal walking – a physiologically and biomechanically routine task during which the knee should act in a "stable" manner within the constraints of its feedback and control mechanisms. This will provide the bioengineer the tool to assess and quantify objectively the degree, change and response of instability to time and intervention, allowing greater understanding of the natural course of instability, and allowing the development of treatments. For the clinician and patient, and objective measuring will allow better diagnosis of pathology, selection of treatment and monitoring of progress.

1.1 PROJECT RATIONALE

The purpose of this work is to develop a device to objectively measure symptomatic instability in the knee joint, as described above. This is to allow clinical and research assessment of the frequency and extent to which a knee joint is failing to maintain functional stability during normal activities of daily living. In this thesis, arthritic and prosthetic knee joints in particular will be considered.

While much work has been done to quantify gait parameters, assessment of mechanical characteristics and measurement of outcomes in arthritis related instability of the knee little of this has translated into changes the assessment and management of symptomatic instability in the orthopaedic clinic. This may, in some part, be due to the complexity, expense and time-consuming nature of assessments performed in published research,

and the lack of direct flow from identification of parameter to change in management. Consequently, many biomechanical studies in this area are small, and the benefits of better understanding of movement on an individual level have not translated to the clinic.

The availability of lightweight portable and wearable technology allows the translation of laboratory-based study to the clinic; however, this requires clear utility in its application and validity in comparison to more expensive and expansive technologies. This project develops a device for the quantification of knee instability with the intention at the outset to be a device that can be used in the clinical environment due to its cost and ease of use. As symptomatic instability is believed to be a failure of dampening of response to impulses, and consequent increasing time in the boundary zone, the use of an accelerometer that wound measure this increased movement is proposed.

In this thesis, the current literature with regards to knee instability in arthritis and prosthetic joints will be examined, along with current methods of measuring stability, followed by an examination of the impact of the symptom in a population of patients with osteoarthritic knees.

By creating and effective objective measurement of symptomatic instability in the knee, comparison of intensity of symptoms will be achievable at differing timepoints, allowing monitoring of patient progress through treatment, assessment of tools to treat

instability in the knee, and the development of techniques, surgeries and implants to treat instability in the knee.

CHAPTER 2 – LITERATURE REVIEW

In order to transmit load from the body to the ground, the knee must function as a stable unit – that is, the various components of the knee, including intrinsic and extrinsic components, must work together to allow force to transmit from femur to tibia throughout a functional range of movement, without loss of control of the joint. In this literature review the anatomy of the knee relevant to this purpose will be described briefly as well as its physiology as it pertains to stability. The current literature describing symptomatic instability in the native osteoarthritic knee will be systematically reviewed, presented and summarised, with the gaps in knowledge and understanding highlighted. Methods of examination of the knee will be examined, with a particular focus on knee stability, finishing with an examination of symptomatic instability in the total knee replacement.

2.1 KNEE STRUTURE AND FUNCTION

The knee is a synovial joint consisting of the articulation of the distal femur and proximal tibia, augmented by medial and lateral menisci and restrained by ligaments, the largest of which are the medial and lateral collateral ligaments, and the anterior and posterior cruciate ligaments which together create a so-called “four-bar” linkage to assist stability (Figure 2-1). All this is wrapped in a joint capsule giving passive restraint. Additionally, the patella, a large sesamoid bone within the quadriceps tendon, articulates within the anterior part of the femoral condyle, known as the trochlear grove, creating a lever-arm to assist with extension at the knee. The hamstring muscles cross the knee joint postero-medially (semimembranosus, semitendinosus) and laterally (biceps femorus) to provide flexion moment, and the popliteus muscle sits posteriorly within the popliteal fossa giving medial rotation of the tibia. These elements act in

synergy to produce a functional knee joint, but each element will be discussed separately.

2.1.1 OSTEOLOGY

The distal femur sits superiorly on the proximal tibia creating what is primarily a hinge joint. The distal femur has two condyles, medial and lateral, consisting of cartilage covered prominences with a deep grove between them. The proximal tibia consists of a broad tibial plateau with two corresponding cartilage covered depressions, medial and lateral, with a central portion within which the menisci and cruciate ligaments attach. The articular surface of the medial and lateral tibial plateau is covered in part by the medial and lateral menisci, leaving central portions of articular cartilage to articulate with the femoral condyles.

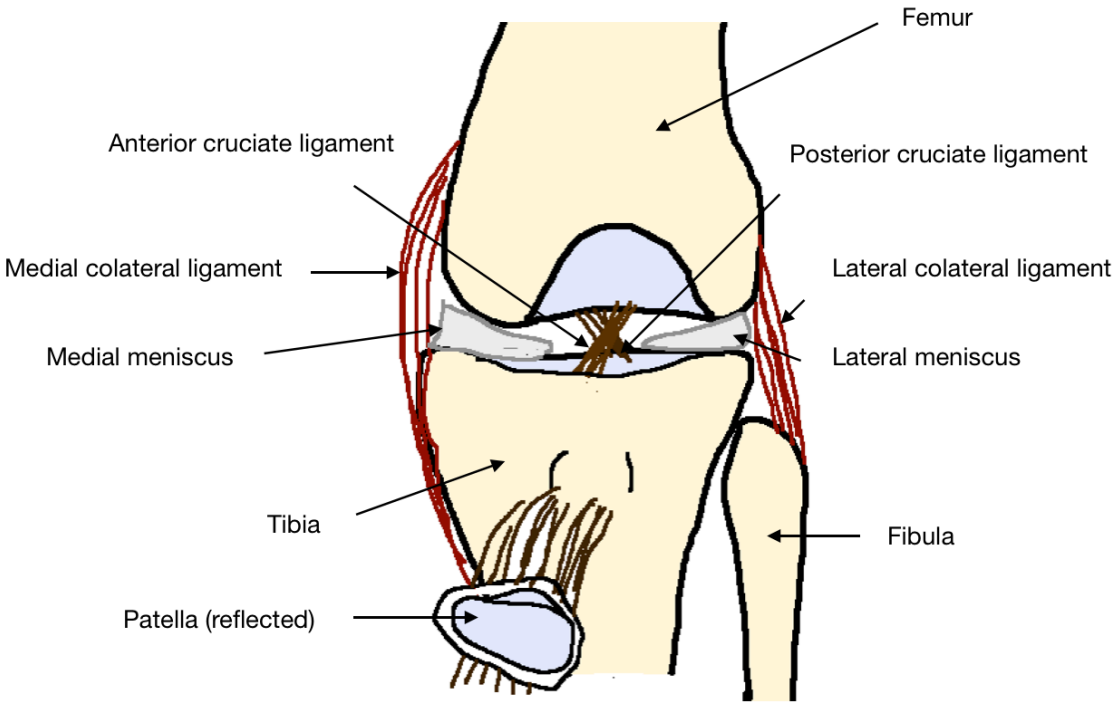

Figure 2-1– Simplified diagram of the of the knee (anterior view)

In a cadaveric MRI study examining the tibia and femoral relationship throughout flexion, Iwaki et al. (2000) describe the geometry of the femoral condyles in the sagittal plane as consisting of two intersecting circles of differing radii, the larger anteriorly, and the smaller posteriorly. These have differing centres of rotation during flexion. The portion of the medial femoral condyle that bears weight does so between full extension and 20 +/- 10 degrees of flexion through an extension facet anteriorly located on the tibial plateau. This portion of the tibia is approximately 10mm in length and drops way anteriorly where the anterior horn of medial meniscus sits. As flexion progresses, the contact area on the tibia moves posterior to the flexion facet. By full flexion, the posterior arc of the medial femoral condyle makes no contact with the tibia and articulates only with the posterior horn of the medial meniscus. On the lateral side, the size difference between the two geometric circles is less, and a single 24mm facet articulates with the femur between extension and 90 degrees of flexion. Anterior to this facet the plateau dips to accommodate the anterior horn of the lateral meniscus, and posteriorly the posterior horn. Beyond 90 degrees of flexion it is the posterior horn only with which the femoral condyle articulates.

Medial and lateral condyles of the femur move against the tibia with a combination of sliding and rolling, with greater movement of contact centre posteriorly during flexion on the lateral condyle. This results in internal rotation of the leg during flexion, with the initial 5 degrees occurring between extension and 10 degrees of flexion, and a further 15 degrees occurs after 45 degrees flexion, with little in between. A supplementary report confirmed these cadaveric findings in living knees using thirteen healthy volunteers and MRI evaluation (Hill *et al.*, 2000). In weight bearing flexion however, there was 4mm of anterior translation of medial femoral condyle between 10

and 45 degrees of flexion in comparison to the unloaded knee, with more posterior translation of the lateral condyle.

A further study by the same research group using the same methods (Nakagawa *et al.*, 2000) examined the fullest extent of active (133 degrees) and passive (162 degrees) of flexion in Japanese young men. MRI scanning showed between 90 and 133 degrees the lateral femoral condyle moves posteriorly 28 degrees, before subluxing completely by 162 degrees. Medial condyle movement is much less pronounced with only 2mm translation between 90 and 133 degrees and a further 4.5 to 162 degrees. This results in 28 degrees of tibial internal rotation between 133 degrees and 162 degrees alone.

2.1.2 SOFT TISSUE RESTRAINTS

Stability of the knee is created by a number of complementary structures, namely the collateral ligaments, cruciate ligaments, menisci and the posterior capsule (Markolf, Mensch and Amstutz, 1976). Their anatomy and function will be described as follows.

2.1.2.1 COLLATERAL LIGAMENTS

The lateral collateral ligament (LCL) arises from the lateral epicondyle of the distal femur and inserts into the head of the proximal fibula. It forms no attachment with the lateral menisci. The medial collateral ligament (MCL) in contrast arises from the medial epicondyle and inserts broadly upon the medial proximal tibia but is attached to the medial meniscus.

In a cadaveric investigation, Markolf et al. (1976) examined the function of the collateral ligaments in 35 knees. They were examined for stability on coronal, axial and sagittal planes using a custom-made device incorporating three-dimensional goniometer and force measurement. Once examinations were complete, structures were sequentially sectioned, and stability re-examined to identify the contributing portion from each component. The LCL was found to have most effect on varus movement, with small contributions to rotational stability and A-P translation. The LCL was identified as contributing 54.8% of ligamentous restraint in 5 degrees of flexion, and 69.2% in 25 degrees flexion, however this varied greatly between specimens (Grood *et al.*, 1981).

The MCL has significant contribution to varus-valgus (V-V) movement, as well as involvement in stabilising axial rotation and AP translation. It has been found to contribute 50 to 60% of terminal stiffness in valgus angulation. Superficial fibres of the MCL were identified as providing 57.4% of restraint against valgus movement in 5 degrees of flexion, and 78.2% in 25 degrees of flexion (Grood *et al.*, 1981). In both varus and valgus movement it was the relaxing of the posterior capsule in flexion that required increased contribution from the collateral ligaments.

2.1.2.2 CRUCIATE LIGAMENTS

The anterior cruciate ligament arises from the medial aspect of the lateral femoral condyle, posteriorly, and inserts anterior to the AP midline of the tibial plateau centrally. It consists of two bundles of fibres, anteromedial and a posterolateral. The posterior cruciate ligament arises from the lateral wall of the medial femoral condyle

and runs posteriorly to a broad insertion on the posterior tibia. It also consists of two bundles, here an anterolateral, and a posteromedial bundle. Broadly, this results in the ACL being tight in flexion and loose in extension, with the PCL being tight in extension and loose in flexion.

Sectioning of cruciate ligaments has shown their contribution not only AP stability, but also to frontal plane control (Markolf, Mensch and Amstutz, 1976). 14% of valgus restraint was found to be due to the combined action of PCL and ACL in both 5 and 25 degrees of flexion. For varus restraint the cruciate ligaments contributed 22.2% and 12.3% of restraint at 5 and 25 degrees of flexion, however this was subject to considerable variability between specimens examined (Grood *et al.*, 1981).

In combination with MCL, the ACL plays a role in rotational stability of the knee, but not terminal stiffness. In the absence of the ACL in the context of total knee replacement, the PCL acts as a restraint on axial distraction (Zalzal *et al.*, 2004).

2.1.2.3 MENISCI

Menisci were not found to make a contribution to laxity in knee in any plane (Markolf, Mensch and Amstutz, 1976), however in a study of stiffness in the knee following medial meniscectomy found that operated patients had reduced midrange stiffness in the frontal plane, and increased passive V-V range in partial flexion as measured using an isokinetic dynamometer (Thorlund *et al.*, 2014).

2.1.2.4 POSTERIOR CAPSULE

In association with the MCL, the posterior capsule plays a role in resisting rotational movement in the axial plane (Markolf, Mensch and Amstutz, 1976). In addition, it plays a role in resisting V-V laxity, and terminal varus stiffness. The medial half of the posterior capsule provides 17.5% of valgus restraint at 5 degrees flexion, and this contribution increased by 2.7% per mm as joint opening increases (Grood *et al.*, 1981). When flexed to 25 degrees however, the contribution dropped to only 3.6%. The lateral half of the capsule provides 17.2% and 8.8% of restraint respectively at 5 and 25 degrees against varus movement.

2.1.3 ALIGNMENT

The coronal alignment of the knee is the defined by the connecting axis of the hip joint centre to knee joint centre, and knee joint centre to ankle join centre. Where this creates a continuous axis, this in known as neutral alignment of the mechanical axis of the leg, and a zero-degree femoral tibial mechanical axis (FTMA). A review of the current literature with regards to concepts of normal alignment of the knee identified that while traditional understanding has assumed neutral alignment in the normal knee, this has been challenged by recent studies, as well as describing the evolving concept of a varying alignment dependent on stance (Deep et al. 2015).

Several studies have employed long leg radiographs to identify the normal range of FTMA, usually measured as intersection of the lines connecting centre of the femoral head to the tibial spines or intercondylar notch, and the tibial spines to the centre of the ankle (Bellemans *et al.*, 2012; Babazadeh *et al.*, 2013). An early radiographic study of 25 male healthy volunteers between 25 and 45 utilised long leg radiographs to assess

the FTMA using centre of the femoral head, knee centre, and ankle centre. A mean valgus angle of 1.5^0 of varus on the right and 1.5^0on the left was identified (Moreland, Bassett and Hanker, 1987). Unipedal standing long leg radiographs of 100 healthy Caucasian subjects aged 17-62 were assessed to find FTMA. A mean angle of 1.4 degrees varus was found, with a range of -5 to 12^0, and standard deviation of 2.8^0 (Jenny, Boeri and Ballonzoli, 2005).

A study of 250 healthy volunteers evenly distributed in gender, aged 20-27, showed an average FTMA of 1.87^0 varus in men and 0.79^0 in women using long leg radiograph (Bellemans *et al.*, 2012). This showed significant variation, with a standard deviation of 2.34^0 across the whole population. It was noted that 32% and 17% of men and women respectively were in varus of $>3^0$, described as constitutional varus.

A study of 40 patients awaiting high tibial osteotomy for medial knee OA compared FTMA in long leg radiographs between supine, bipedal stance and single leg stance (Specogna *et al.*, 2006). Here it was shown that varus alignment of the FTMA increased significantly between supine and bipedal standing, and again between bipedal and single leg stance. An assessment was made of lying and standing alignment in 20 patients with osteoarthritis using long leg radiographs (Brouwer *et al.*, 2003). Carefully controlling for foot position, unipedal stance was compared to supine and FTMA calculated. Between weight bearing and non-weightbearing a 2^0 increase in varus alignment was found.

CT scanning has also been used to show changes in lying and standing FTMA (Hirschmann *et al.*, 2015). They compared supine CT of the knee with a novel standing scan (single leg stance) in 26 patients, finding changes in femorotibial rotation, tibial tubercle - trochlear grove (TTTG) measurement, lateral patellar tilt angle and medial joint space between supine and standing. This is consistent with findings of changes in FTMA between lying and standing using navigation tools (Deep et al. 2015; Clarke et al. 2012), with a likely suggestion being that the change from unloaded to loaded stance changes the dynamic placement of the limb.

Dynamic, non-radiological methods have also been employed in assessing alignment. In a study of 267 healthy knees, a non-invasive infrared computer navigation device (Orthopilot, BBraun Aesculap) was used to identify a resting FTMA in the supine patient of 1.2^0 varus with a standard deviation of 4^0 (Deep, 2014). Supine and standing alignment in cohorts of healthy (30) and osteoarthritic (31) patients before and after TKA using a similar device and setup. Here FTMA was found to be 0.1^0 varus, 2.5^0 varus, and 0.7^0 varus in the three groups respectively supine, and 1.1^0 varus, 3.6^0 varus and 2.5^0 varus respectively in the three groups, demonstrating both a preponderance to valgus alignment, and the further deviation from neutral on weight bearing (Clarke et al. 2012). In a much larger study of 264 health knees supine and standing FTMA were compared using the same method (Deep et al. 2015). Here, the earlier finding of 1.2^0 of varus supine were confirmed, with a standard deviation of 4^0, and only 59% of subjects within 3^0 of neutral. Further, it is shown that if knees were within 2.5^0 of neutral while supine, the FTMA moved varus on weight bearing, on average 2.2^0 in bipedal stance, and 3.4^0 in monopedal. Where the knee was more than 2.5^0 valgus supine, it moved further valgus weightbearing. It was noted that men had a FTMA of 1.7^0 varus while

women were 0.4^0 varus. Additionally, it was noted that a mean hyper extension in the sagittal plane of 3.2 supine was increased by 5.6 degrees on weight bearing.

2.1.4 SUMMARY OF STRUCTURE AND FUNCTION

It may be therefore summarised that normal, constrained motion of the knee is structurally, and passively, maintained by a combination of bony congruence (Hill *et al.*, 2000; Iwaki, Pinskerova and Freeman, 2000; Nakagawa *et al.*, 2000), meniscal support (Thorlund *et al.*, 2014), ligamentous restraint and capsular enclosure (Markolf, Mensch and Amstutz, 1976; Grood *et al.*, 1981; Zalzal *et al.*, 2004). Alignment of the lower limbs shows a large variation, with standard deviation of up to 4^0 reported (Deep 2014; K. Deep et al. 2015), and standing alignment tending towards varus (Moreland, Bassett and Hanker, 1987; Jenny, Boeri and Ballonzoli, 2005), more prominent in men(Bellemans *et al.*, 2012; Deep, Eachempati and Apsingi, 2015). Furthermore it has been demonstrated that alignment tends toward increasing varus as standing force is applied, unless supine alignment was greater than 2.5^0 of valgus (Brouwer et al. 2003; Hirschmann et al. 2015; Clarke et al. 2012; Deep et al. 2015).

2.2 STABILITY IN THE KNEE

To discuss the stability of the knee, a working definition of "stability" is required. A stable system is one in which, when an external impulse is applied, the system returns its initial state (Figure 1 1). In a complex and dynamic system like the knee, stability is conferred by a range of bony and soft tissue structures acting both actively and passively. This results in a joint that maintains its alignment and congruence in both active and passive situations, such as sitting, standing or walking. "Instability" of the joint would therefore occur when the system (the knee) fails to return to its zero state (controlled congruence of the joint allowing transmission of force through from the body) The result of this may be either a fall, or actions taken to prevent this (Figure 2-2). It is self-evidently clear that the stability of the joint will be dependent upon the forces applied: stability during simple stance requires less effort than stability during running. Further, non-physiological forces such as those in road traffic accidents may overcome the normal restraints in the knee that are sufficient for normal daily living.

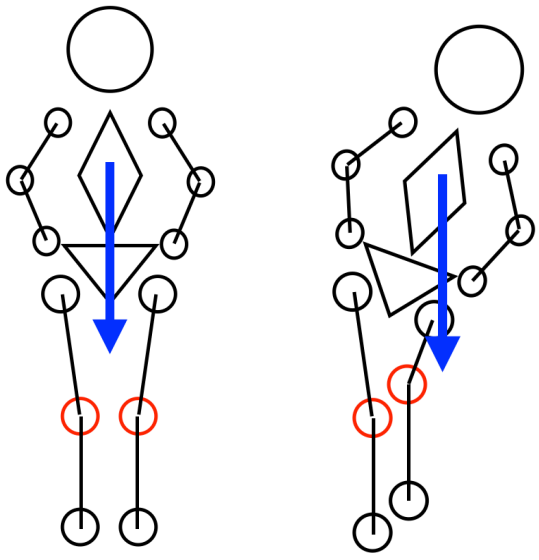

Figure 2-2 – Simplified diagram of stable and unstable stance. The first figure is standing balanced as both knees are stable. In the second, the knee is not stable resulting in the figure losing balance

For the purposes of this section, the various anatomical and physiological systems within the knee that create conditions tending towards a stable system will be discussed. Where relevant, their limits will be discussed. Further, the changing limits of stability throughout the physiological range of the joint will be discussed.

Stability in the knee is marked both by its range of movement in each plane, and by its resistance to such movement beyond a set point. Zalzal et al. (2004) have demonstrated the non-linear stress-strain relationship of the whole soft tissue envelope in a study of osteoarthritic knees undergoing TKA. Here, soft tissue balance was carried out using a ligament tensioning device (Stryker, Howmedica Osteonics, NJ). As tension increased, stiffness of the envelope increased both in flexion and extension. The authors postulate that this is due to the varying resting lengths of the multiple tissues involved in this tensioning process.

Markolf et al. (1976) identified the point of greatest coronal stability as being in full extension where “midrange stiffness is maximum and laxity is minimum”, however in the sagittal plane with increased knee flexion comes increased anterior stiffness, but decreased posterior stiffness. Furthermore, it was identified that when one stabilising structure was removed, a second structure provided terminal stiffness to an examined movement. Noyes et al. (1980) describe concepts of stability with regards to the interplay of bony, soft tissue and muscular forces, in addition to those joint forces created in the weight bearing environment. With regards to soft tissue stabilisers they describe a system of primary and secondary stabilisers, each contributing a portion of restraining force. During weight bearing activities it has been shown that the

instantaneous centre of pressure within the knee moves differently than during non-weightbearing activities, indicating that the path of movement of the knee is governed by the interplay of bone, soft tissue, muscle force and body weight, with the soft tissue envelope and system stability resulting in some variation internal contact mechanics in different circumstances (Dyrby and Andriacchi, 2004). The three planes will be discussed with emphasis on the coronal, the most pertinent to this study.

2.2.1 CORONAL PLANE

The normal knee in the coronal plane is known to exhibit a variable amount of V-V rotation. Markolf et al. (1976) identified that coronal laxity was increased by the sectioning of either MCL, LCL, ACL or posterior capsule, while terminal stiffness in valgus was most notably affected by the posterior capsule. Grood et al. (1981) noted that flexion of knee relaxed the posterior capsule, increasing the dependence on the collateral ligaments during V-V rotation. During unloaded V-V testing it was noted that the axes of rotation are located above the opposite femoral condyles with respect to joint opening, and there is a corresponding slide of the tibia on the condyle with the applied force, representing a shear on the joint surface, during V-V movement.

Attempts have been made to quality the range of V-V rotation within population groups and using different methods. A radiographic analysis of older healthy volunteers examined knee coronal laxity in extension and 70 degrees flexion (Heesterbeek, Verdonschot and Wymenga, 2008). Radiographs were taken at full extension and at 70 degrees of flexion using a custom-made rig. Mean valgus laxity in extension was recorded as 2.3^0 (range 0.0^0 to 6.0^0) and varus laxity of 2.8^0 (range 0.6^0-5.4^0), while in

flexion valgus laxity was 2.5^0 (range $0.0\text{-}6.0^0$) and varus laxity was 3.1^0 (range $0.1\text{-}7.0^0$).

A large study of 267 healthy volunteers aged 19-35 years old examined the varus-valgus laxity in the knee joint using a non-invasive infra-red navigation device and a hand held dynamometer (Deep, 2014). In this manner, a standard moment of 10Nm was applied to the knee in both full extension and fifteen degrees of flexion in the sagittal plane. At zero degrees extension a varus displacement of 3.1^0, rising to 6.9^0 in 15^0 flexion, with values displacement of 4.6^0 rising to 7.9^0 in 15^0 flexion, all measured from the resting FTMA.

Coronal stability is created by the interplay of several stabilisers as detailed above. Wilson et al. (2013) have examined the mechanical properties of the collateral ligaments in clinical and mechanical testing. Ultimate tensile strength of both medial and lateral collateral ligaments was found to be orders of magnitude higher than those applied in simple clinical assessment. Ultimate tensile strength revealed displacement of only 20mm in the medial collateral ligament suggesting that even at very high lateral forces, the medial collateral ligament would apply a strong stabilising restraint.

2.2.2 SAGITAL PLANE

Markolf et al. (1976) have shown stability in the sagittal plane to be affected by collateral ligaments, cruciate ligaments, menisci and posterior capsule. The greatest effects were from the ACL in extension and the PCL in flexion, however there appeared to be significant synergistic effects in A-P stability between the ACL and both LCL and

MCL. While these primary stabilisers act to create passive stability, a recent review of the physiology of knee stability described the interplay of several muscle groups around the knee as acting as secondary stabilisers, including particularly the effects of the main flexor and extensor groups at the knee (Abulhasan and Grey, 2017).

2.2.3 AXIAL PLANE

Markolf et al. (1976)) showed that only the MCL had independent involvement in rotational stability in the axial plane, with sectioning of it increasing torsional movement 12 degrees. In combination with either posterior capsule or ACL release there was a further increase by 18-20 degrees.

2.2.4 SUMMARY OF STABILITY IN THE KNEE

It may be concluded that the normal knee exhibits stability in V-V motion through a combination of bony and soft tissue restraints. Excesses of sagittal movement are similarly controlled while axial motion is dependent on soft tissue restraint only. In V-V motion some movement is allowed from the FTMA, however this varies with flexion. Clinical examination of the knee is limited by the force that may reasonably be placed across the knee by the examiner being far below those that might arise in normal walking.

2.3 OSTEOARTHRITIS AND INSTABILITY

Osteoarthritis of the knee is a common complaint, with increasing realisation of the importance of symptomatic instability on physical function (van der Esch *et al.*, 2012; Fleeton *et al.*, 2016). Here the pathophysiology of osteoarthritis will be described

briefly, along with a review of the literature on symptomatic knee instability in osteoarthritis. While extensive literature exists on gait patterns and biomechanical changes in osteoarthritis the literature on symptomatic instability is sparse. Here described, symptomatic instability is the perception by the patient that the knee joint is about, or actually, gives way or buckles. While the latter case may represent true instability of the joint, in that it fails to return to normal parameters following an impulse, it may also represent the feeling that this is about to happen, being within the boundary zone requiring further recruitment of muscle power to stabilise the joint, or even an extrinsic action such as the use of a stick, hand or muscle force in the contralateral leg to prevent collapse (Figure 1 4). The nature of the patient reported symptom is such that it does not of its self describe the mechanism of instability, only its perception.

Instability - reported as a feeling of buckling or giving way - is a commonplace symptom in OA knees, being found in up to 72% of subjects (Fitzgerald, Piva and Irrgang, 2004; Knoop *et al.*, 2012; Nguyen *et al.*, 2014; Sharma *et al.*, 2015; Fleeton *et al.*, 2016). In attempting to understand and treat instability, either through total knee arthroplasty (TKA), osteotomy or through physical therapies, it is important to define what is characteristic about the unstable knee in comparison to the stable osteoarthritic (OA) knee. Since the first published incidence of instability in the OA knee (Fitzgerald, Piva and Irrgang, 2004), factors with potential association to instability have been examined such as joint laxity, muscle strength, proprioception, knee joint stiffness, disease severity and gait parameters, with several significant associations found (Farrokhi *et al.*, 2012, 2015; Knoop *et al.*, 2012; Creaby *et al.*, 2013; Gustafson *et al.*, 2015). This is of importance as recent findings make clear that instability in the native

knee has associations with poor function, both in terms of objective measurement (Get-up and Go testing and times stair climb) and subjective assessment with questionnaires on star climbing, walking and getting up from sitting (van der Esch *et al.*, 2012; Fleeton *et al.*, 2016), and this instability may persist post operatively after TKA with an increased fear of falling by nearly double, and significantly increase the limiting of activities (Nguyen *et al.*, 2014). Currently "patient reported instability" is the benchmark used in clinical studies as well as in clinical assessment.

Extensive research has been done into the prevalence of instability following arthroplasty surgery with several recent papers reviewing the nature of instability postoperatively (Augustine, 1956; Yercan *et al.*, 2005; Kelly G Vince, Abdeen and Sugimori, 2006; Parratte and Pagnano, 2008; Vince, 2016). However, such an extensive body of literature does not exist for the native knee. Recent research has attempted to provide an objective description of instability by investigating various kinematic and biomechanical factors that may describe it (van der Esch *et al.*, 2008; Schmitt *et al.*, 2008; Farrokhi *et al.*, 2012, 2014, 2015; Kavchak *et al.*, 2012; Creaby *et al.*, 2013; Sanchez-Ramirez *et al.*, 2013; Gustafson *et al.*, 2015, 2016; Van Der Esch *et al.*, 2016; Freisinger *et al.*, 2017). While these studies are heterogeneous in design, and do not lend themselves to meta-analysis, a qualitative overview of this work can give insight into understanding instability. Therefore, this review aims to explore current definitions and prevalence's of self-reported instability, before examining various components of knee structure and function that have been examined in an attempt to quantify instability. The results of these studies will be examined together to form conclusions as to the biomechanical nature of self-reported instability, and to suggest further direction for research to produce a quantifiable marker for knee instability.

PubMed and Medline searches using the terms “knee”, “osteoarthritis”, “unstable”, “instability”, “stability” and “buckle” were performed to identify relevant studies. Abstracts were reviewed for relevance to patient reported instability and osteoarthritis. Papers were then reviewed in full for methodology and relevance to the measurement of instability in the osteoarthritic knee, with their references used to identify additional sources. While earlier work has explored subjective instability as a co-variable in knee arthritis (van der Esch *et al.*, 2007; Schmitt *et al.*, 2008; Sanchez-Ramirez *et al.*, 2013), more recent work has look directly at the association between subjective instability and objective measures of assessment (van der Esch *et al.*, 2008; Farrokhi *et al.*, 2012, 2014; Kavchak *et al.*, 2012; Knoop *et al.*, 2012; Gustafson *et al.*, 2015, 2016; Van Der Esch *et al.*, 2016). These measures will be discussed in turn.

2.3.1 PATHOPHYSIOLOGY OF OSTEOARHTITIS

While the details of the pathophysiology of osteoarthritis are beyond the scope of this literature review, suffice it to say that osteoarthritis of the knee is characterised by symptoms of stiffness, swelling and pain in the joint, with pathological changes in synovium, hyaline cartilage and, eventually, bony erosions. The exact mechanisms of this process are complex and debated, but the consequences for the joint can be summed up in the commonly used Kellgren-Lawrence (K-L) classification of osteoarthritis, grading radiographic features on a scale of increasing severity from 0-4, from “no joint space narrowing or reactive changes” to “large osteophytes, marked joint space narrowing, severe sclerosis, definite bone end deformity” (Kohn, Sassoon and Fernando, 1999).

2.3.2 EPIDEMIOLOGY OF INSTABILITY

The importance of patient reported outcomes, and subjective assessment has become increasingly clear in the pre-assessment of arthroplasty. Several commonly used patient-reported outcome measures (PROMS) look at functional components of knee health e.g. (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Oxford Knee Score (OKS), (Knee Outcome Survey – Activities of Daily Living Score (KOS-ADLS)), but it is only the OKS and KOS-ADLS that specifically question subjective instability. With answers scored on a five- and six-point Likert scale, they ask respectively: "have you felt that your knee might suddenly 'give way' or let you down?"; and "to what degree do each of the following symptoms affect your level of daily activity" with "giving way, bucking or shifting of the knee" as an option.

Defining instability as a self-reported feeling of buckling, slippage or giving way in the knee during activities of daily living (Fitzgerald, Piva and Irrgang, 2004), a study of 105 subjects with knee osteoarthritis reported symptomatic instability in 63% with 44% of subjects reporting that instability impaired their activities of daily living. Knoop et al. (2012) found a similar rate of 64% reporting symptoms of buckling, shifting or giving way in their cohort of 283 patients with osteoarthritis recruited from the Amsterdam Osteoarthritis Cohort. Another group of 248 patients from the Amsterdam Osteoarthritis Cohort was assessed by van der Esch et al. (2012) finding self-reported instability in 65% of patients. This was found to be associated with worse Western Ontario and McMasters University Osteoarthritis Index (WOMAC) scores, poorer stair climb, and "Get up and Go" tests. This group was re-examined at two years with 64% of those with instability at baseline retained it, and 29% of patients stable at baseline

developed instability (Van Der Esch *et al.*, 2016). Nguyen et al. (2014) report on a cohort of 2120 subjects with osteoarthritis or risk factors for osteoarthritis. 36% of subjects are shown to have either buckling, feelings of instability without buckling, or a combination of both. While this figure is significantly lower than the other studies it is notable that the rates of instability were significantly higher in subjects with worse radiographic osteoarthritis. Of those with symptoms, 40% report reducing their activity as a result. Sharma et al. (2015) found 35.8% incidence of buckling alone in their cohort of 212 subjects with knee osteoarthritis. Fleeton et al. (2016) examined 388 patients awaiting total knee replacement (TKA), and found a prevalence of 72% self-reported instability in the 1-2 days prior to administration of the activities of daily living questions from the Knee Outcomes Score.

2.3.3 JOINT LAXITY

One proposed difference between subjectively stable and unstable knees has been joint laxity – the "looseness" of the joint – however the evidence does not support this suggestion. It has been hypothesised that increased laxity in the joint would more likely result in a feeling of instability (van der Esch *et al.*, 2008; Freisinger *et al.*, 2017). While joint laxity is routinely assessed in any knee examination, quantitative examination has been assessed using stress x-rays (10,24), isokinetic dynamometry (Knoop *et al.*, 2012; Creaby *et al.*, 2013), non-invasive image free navigation (Clarke *et al.*, 2017) and under anaesthetic using bone anchored computer navigation (Freisinger *et al.*, 2017). These methods allow a repeatable measurement of joint laxity in a static situation to be assessed. Dynamically, varus-valgus (V-V) movement during walking has been assessed using optoelectronic gait analysis, in particular analysing the stance

phase between foot strike and the point of maximum weight acceptance (van der Esch *et al.*, 2007, 2008; Schmitt and Rudolph, 2008; Skou *et al.*, 2014). However, despite an expectation of increased V-V laxity in subjectively "unstable" knees in comparison to "stable", none of these studies has found any connection.

2.3.4 MUSCLE STRENGTH

A further hypothesis as to the cause of subjective knee instability is that it is a consequence of decreased muscle strength in comparison to subjectively stable knees (Table **2-2**). Several methods exist to quantitatively assess muscle strength, and varying results have been found with regards to muscle strength comparison between "stable" and "unstable" knees (table 1). When measuring power independent of function, no difference was found in quadriceps strength between "stable" and "unstable" subjects with knee OA in several small studies (Schmitt and Rudolph, 2008; Schmitt *et al.*, 2008; Farrokhi *et al.*, 2015; Gustafson *et al.*, 2016). Whilst weaker quadriceps muscle power was found in "unstable" vs "stable" knees in several studies (Schmitt and Rudolph, 2008; Schmitt *et al.*, 2008; Farrokhi *et al.*, 2015; Gustafson *et al.*, 2016), none were statistically significant. However, in a larger study of 283 well matched subjects (191 "unstable" vs 92 "stable" OA knees) subjectively unstable knees were found to be significantly weaker in quadriceps extension in comparison to subjectively stable knees when examined using an isokinetic dynamometer at 60 degrees/second and normalised for patient weight (Knoop *et al.*, 2012). It is notable that in this larger study the unstable group contains 5% more women, is slightly older, more painful and with a longer duration of symptoms, and while none of these parameters reached statistical significance individually, the combined effect of these factors may have had an

influence on the outcome. In a study of 388 patients undergoing TKA, Fleeton et al. (2016) showed no association between quadriceps strength post operatively at 6 weeks and 6 months following surgery and the persistence of pre-operative knee instability. However, when the more functional stair climb test is used, reduced power – calculated as a function of weight, speed, and height of stair climb - was found to be an independent predictor of instability post operatively.

A lack of muscular co-contraction may contribute to instability. This hypothesis has been tested when comparing OA to healthy knees, but only in small subgroup analysis comparing stable and unstable OA (Lewek *et al.*, 2005; Schmitt and Rudolph, 2008). Contradictorily, while greater co-contraction in vastus medialis and medial hamstring was found in the symptomatically unstable group (Schmitt and Rudolph, 2008), greater co-contraction was also identified in the symptomatically stable group (Lewek *et al.*, 2005). It may be, however, that this increase in co-contraction represents an attempt to provide increased stiffness in an unstable knee joint to counteract its inherent instability.

Whilst many studies failed to reach significance, it is noteworthy that all had non-statistically significant weakness in the unstable compared to stable group, suggesting an association of weaker quadriceps in with symptomatic knee instability. Some confounding factors, such as the effect pain and the influence of gender need further exploration, and although an association potentially exists, whether quadriceps weakness is a cause, or an effect of the instability is unclear. Further studies involving knee power measures and muscular co-contraction are warranted to clarify potential links and mechanisms of instability.

2.3.5 PROPRIOCEPTION AND POSTURAL CONTROL

One hypothesis is that instability in the OA knee is due to an impairment in either proprioception or postural control, with the patient unable to clearly identify the position of, and thereby control, the knee joint in space. However, this hypothesis has not been proven.

Impaired proprioception was not associated with self-reported instability in 283 patients when tested with regards to passive knee flexion sensitivity (Knoop *et al.*, 2012), however, the same group did find that impaired proprioception was associated with the retention of instability at 2 years (Van Der Esch *et al.*, 2016). However, impaired proprioception was found to be associated with excessive V-V movement during gait in 63 patients with OA, but the participants were unfortunately not stratified into "stable" and "unstable" categories (van der Esch *et al.*, 2008). Instability was found not to be associated to the ability to perform a one-legged unsupported balance in 284 patients with knee OA, once confounding variables of BMI, pain, muscle strength and range of active flexion were removed in the regression analysis (Sanchez-Ramirez *et al.*, 2013). Further, no difference was found between strength training and a combination of strength and proprioception training in reducing the incidence of instability in an RCT of 159 patients (Knoop *et al.*, 2013).

Normal proprioception in the subjectively unstable knee (Knoop *et al.*, 2012; Sanchez-Ramirez *et al.*, 2013) may lead to patient recognition of feelings of buckling and instability that may or may not lead to falls, leading to the voluntary reduction of

activity (Fitzgerald, Piva and Irrgang, 2004; Nguyen *et al.*, 2014). Three studies reported results of differing physiotherapy intervention in knee OA subjects with and without knee instability using self-reported knee instability as their stratification point (Fitzgerald *et al.*, 2011; Knoop *et al.*, 2013, 2014). Outcomes of these studies were limited to qualitative self-reported function with regards to instability. While two studies showed no improvement in outcome with additional training for proprioceptive feedback in addition to strength training alone (Fitzgerald *et al.*, 2011; Knoop *et al.*, 2013), the third reported a subgroup analysis showing that for those subjects with already good quadriceps strength and instability, the addition of stability training did improve outcome (Knoop *et al.*, 2014). This may suggest that while quadriceps strength alone is not the cause of the instability, and proprioception is not lost, the strengthening of those abilities may allow subjects to better control their instability: in a joint undergoing increasing tendency towards disorder, increased muscular strength may be required to prevent buckling and giving way that may otherwise be prevented by intrinsic joint stiffness. Overall, proprioception does not appear to be associated with subjective instability, nor does proprioceptive training improve symptoms.

2.3.6 KNEE JOINT STIFFNESS

A hallmark of osteoarthritis is the symptom of stiffness. This is felt by the patient as a difficulty in easily bending the knee. However, in gait analysis, stiffness is defined and measured as the moment required to produce an angular rotation at the knee. This is a defining characteristic of OA of the knee, which has also been investigated as a factor of stability in the OA knee in both the frontal and sagittal plane; non-weight bearing and while walking. This is different from laxity in that it records the effort required to

produce angular change while laxity, in the context of frontal plane movement, commonly refers to the range of movement.

Passive mechanical stiffness in the frontal plane at 20 degrees of flexion was found to be reduced for those with symptomatic instability in a study of 73 patients with medial knee OA (Creaby *et al.*, 2013) leading the authors to hypothesise that increased V-V stiffness was a mechanism for stability. Moreover, those with self-reported instability have been characterized as walking with reduced sagittal plane stiffness (Gustafson *et al.*, 2016). While these appear to be the only studies examining the effect of stiffness on knee stability there appears to be a clear pattern of reduced stiffness in both sagittal and coronal plane associated with subjective instability in the OA knee.

2.3.7 OTHER FACTORS IDENTIFIED IN GAIT ANALYSIS

Several parameters of gait have been found to differ between subjectively stable and unstable knees. While extensive investigation has been performed comparing normal and OA gait, until recently less attention has been to the differences between stable and unstable OA gait. Three studies have commented on walking speed, all noting that those OA patients with instability in the knee walk with slower self-selected speed in comparison to those with no reported instability (Schmitt and Rudolph, 2008; Farrokhi *et al.*, 2015; Gustafson *et al.*, 2016). Increased knee flexion range of motion during stance phase is noted by two studies (Farrokhi *et al.*, 2015; Gustafson *et al.*, 2016) but no agreement is found with regards to knee flexion angle at heel contact (Farrokhi *et al.*, 2014; Gustafson *et al.*, 2016). Internal contact mechanics of the knee has been assessed in three studies through the use of dynamic stereo x-ray. A 3D bony model of the knee joint was created from a CT scan, and matched with high frequency bi-planer x-rays of

the knee taken during treadmill walking to determine the internal joint motion and contact points (Farrokhi *et al.*, 2012, 2014; Gustafson *et al.*, 2015). Comparisons were made between healthy subjects, and those with knee OA and subjective instability, during downhill treadmill walking. OA subjects were noted to have greater V-V movement in the weight acceptance phase in comparison to controls, as well as a decreased flexion range of motion. It had been hypothesised that instability in the OA knee would result in increased movement of the tibia with respect to the femur during loading in comparison with healthy controls, however this was not found to be the case, with no significant differences found between groups. (Farrokhi *et al.*, 2012) However, the medial tibiofemoral contact point was found to move a greater distance and at greater velocity in those with OA and "instability", in comparison to those with OA and no instability and to those without OA, with no differences found between controls and those with OA and no instability.(Farrokhi *et al.*, 2014). Variability, defined as the average of the standard deviations at each recorded time point across weight acceptance phase, was examined for both knee joint rotation, and tibiofemoral contact point (Gustafson *et al.*, 2015). Anterior-posterior (AP) contact point mobility was higher in the OA unstable group in comparison to stable OA and control groups, while stable OA patients exhibited the least stance phase sagittal plane variability with unstable OA patients the most variable. Gait in subjectively unstable knee OA differs from the subjectively stable with slower self-selected pace, increased knee flexion range of motion during stance and greater knee joint internal contact point variability (Schmitt and Rudolph, 2008; Farrokhi *et al.*, 2012, 2014, 2015; Gustafson *et al.*, 2015, 2016). Together, these findings agree with the hypothesis presented of an unstable knee system existing with increasing positional variability due to a failure of dampening mechanisms (Figure 1 4). Increased tibiofemoral contact variability may represent an inability to

control internal movement, while reduced walking speed may be a mechanism to reduce this variability.

2.3.8 ANTERIOR CRUCIATE LIGAMENT IN OSTEOARTHRITIC KNEE INSTABILITY

While work has been performed identifying the deficient nature of the anterior cruciate ligament (ACL) in OA, it's relationship with subjective instability has not been established. The anterior cruciate ligament is known to be the primary stabiliser of the knee in anterior translation of the tibia against the femur (Noyes *et al.*, 1980; Grood *et al.*, 1981). Traumatic anterior Cruciate Ligament (ACL) rupture is known both to cause instability in the knee, and to predispose to OA (Kessler *et al.*, 2008; Kiapour and Murray, 2014); and OA is known to cause degeneration and rupture in the ACL (Ishii *et al.*, 2016; Mont *et al.*, 2016). Macroscopic ACL deficiency of any aetiology has been observed in between 6% and 22% of OA knees at TKA (Trompeter *et al.*, 2009; Berend *et al.*, 2016; Ishii *et al.*, 2016; Mont *et al.*, 2016). However, histological appearance of the remaining ACL has been found to be abnormal, even in the macroscopically normal ACL (Cushner *et al.*, 2003; Trompeter *et al.*, 2009; Douglas, Hutchison and Sutherland, 2010; Mont *et al.*, 2016). Worse macroscopic and histological appearance has been associated with severity of arthritis, higher BMI, increasing age, and increased coronal deformity (Mullaji *et al.*, 2008; Berend *et al.*, 2016; Mont *et al.*, 2016). Varying abnormalities have been found in the ACL of OA knees, including myxoid degeneration, vascular proliferation, chondroid metaplasia, cystic changes and reorientation of fibres (Cushner *et al.*, 2003; Mullaji *et al.*, 2008; Trompeter *et al.*, 2009; Mont *et al.*, 2016), with more significant abnormality found in the posterolateral bundle in comparison to the anteromedial (Watanabe *et al.*, 2011). Correlation between ACL

deficiency and OA scoring systems has been mixed with no association found with Oxford Knee Score (Douglas, Hutchison and Sutherland, 2010), but a lower Knee Society score found with ACL deficiency (Berend *et al.*, 2016). In conclusion, in the osteoarthritic knee it seems probable that the ACL may function inadequately even where present. This is likely to result in increasing joint translation and movement of contact points. This may contribute to subjective feelings of instability in the knee joint.

2.3.9 DISEASE SEVERITY

The influence of OA severity of subjective instability has been examined in a study of 192 patients with OA, in which instability was stratified using a four point Likert scale, with the results dichotomised (Leichtenberg *et al.*, 2017). Severity was assessed using joint space narrowing, osteophyte formation, and the Kellgren and Lawrence (K-L) scale from an anterior posterior and lateral standing radiograph. No associations were found between severity of OA and subjective instability (29). An association between worsening varus alignment and instability has been shown in one small study (Farrokhi *et al.*, 2014), but not replicated in another (Schmitt *et al.*, 2008). Taken together, and to date, there is no evidence of a link between disease severity and instability.

2.3.10 SUMMARY FROM CURRENT LITERATURE ON INSTABILITY

While it may seem intuitive that instability and increased laxity go hand-in-hand, several studies have found that neither V-V laxity in non-weight-bearing conditions

(Schmitt and Rudolph, 2008; Schmitt *et al.*, 2008; Knoop *et al.*, 2012; Creaby *et al.*, 2013; Gustafson *et al.*, 2015) nor during movement (van der Esch *et al.*, 2007, 2008) are related to instability. Similarly, it may be reasonably postulated that a knee is unstable due to inadequate strength. However, most studies looking for associations between strength and instability are not conclusive, (Schmitt and Rudolph, 2008; Schmitt *et al.*, 2008; Farrokhi *et al.*, 2015; Gustafson *et al.*, 2016). In the one study that found a significant difference, it was unclear whether weakness was a cause of instability or the effect of reduced activity caused by the instability (Nguyen *et al.*, 2014). As impaired proprioception has not been shown to be associated with instability in the OA knee (van der Esch *et al.*, 2012; Sanchez-Ramirez *et al.*, 2013), it must be concluded that the cause of symptomatic instability may be found in aetiologies other than V-V laxity, muscular weakness and one's sense of joint position.

Stiffness is one of the cardinal features of OA, and it is therefore unexpected to find that stiffness in the knee is reduced in instability (Creaby *et al.*, 2013; Gustafson *et al.*, 2016). However, the reduced passive stiffness in the knee in the frontal plane in the first few degrees around the neutral axis (Creaby *et al.*, 2013) and in the sagittal plane during walking (Gustafson *et al.*, 2016) presents a picture of a knee that is more difficult to control, lacking the restraining characteristic that stiffness brings to perturbation under small load. This seems consistent with subjects with unstable knees walking slower (Schmitt and Rudolph, 2008; Farrokhi *et al.*, 2015; Gustafson *et al.*, 2016), with increased knee flexion (Farrokhi *et al.*, 2015; Gustafson *et al.*, 2016) and with an increased movement and variability of contact points within the knee (Farrokhi *et al.*, 2012, 2014; Gustafson *et al.*, 2015) . Contradictorily, these characteristics, taken together, point to a knee that, while not objectively loose with regards to supine

ligamentous laxity (Schmitt and Rudolph, 2008; Schmitt *et al.*, 2008; Knoop *et al.*, 2012; Creaby *et al.*, 2013; Gustafson *et al.*, 2015) nonetheless displays the characteristic of a joint lacking passive control during gait.

The lack of correlation between K-L grading and symptomatic instability points to an aetiology beyond simply bone and cartilage damage, to a whole joint process (Leichtenberg *et al.*, 2017). The ACL in the OA knee has been shown to be absent or damaged frequently in OA knees (Cushner *et al.*, 2003; Trompeter *et al.*, 2009; Douglas, Hutchison and Sutherland, 2010; Berend *et al.*, 2016; Ishii *et al.*, 2016; Mont *et al.*, 2016), and while the coloration between subjective instability in OA and ACL status has not been examined, it is clear to see how a dysfunctional or absent ACL may contribute to a more internally mobile and unstable joint. Further work, to identify both the relationship between macroscopic ACL condition and symptomatic instability, but also to characterise the biomechanical function of the ACL in the OA knee, is warranted.

One clear limitation in any study examining instability in the knee is lack of consensus over the definition of subjective instability. As discussed previously, several methods of description exist, but all are based upon a single questionnaire giving an ordinal result, often transformed dichotomously. Validation of this method is not possible due to the lack of comparison; however, it is widely accepted throughout the literature. Due to the nature of biomechanical studies, several involve small subject numbers (Schmitt and Rudolph, 2008; Kavchak *et al.*, 2012; Gustafson *et al.*, 2016). It is important, particularly with regards to subgroup analyses, to interpret their results with caution due to sample size and multiple comparisons.

To overcome the shortfall of self-reported instability and to determine a more quantified measure, biomechanical characteristics of unstable movement must be identified. The hypothesis of this thesis is that symptomatic instability is the awareness of the knee approaching failure, even if not actually reaching it. The feeling of instability is the time spent in this boundary area, representing a point where additional action is taken under increasingly conscious control, to counteract the effects of internal joint movement. It has been shown that the OA unstable knee is less stiff (Creaby *et al.*, 2013; Gustafson *et al.*, 2016), has increasing internal contact variability (Farrokhi *et al.*, 2012, 2014; Gustafson *et al.*, 2015), and results in increasing co-contraction of muscles (Schmitt and Rudolph, 2008). Testing of this symptomatic instability could therefore be directed at measuring this increased oscillation within the knee.

To make testing of this of practical, clinical relevance requires the development of a portable device capable of demonstrating small, rapid movements at the knee during movement. Recent work has been ongoing to develop portable gait analysis devices using accelerometers, with some success(Dejnabadi *et al.*, 2006; Khan *et al.*, 2013; Roberts *et al.*, 2013), while the use of accelerometer in examining varus thrust has well established foundations (Yoshimura *et al.*, 2000, 2003; Yoshimura, Naito and Zhang, 2002). Computational analysis techniques such as Fast Fourier Transform (FFT) (Soeno *et al.*, 2018) or wavelet filtering using a discrete wavelet transform (DWT) (Clark, Bartold and Bryant, 2010) of accelerometer data allow exploration of frequency domain in knee movement. This will allow the exploration of fast knee vibration and oscillation that is suggested by reduced stiffness and increased contact point variability

in the subjectively unstable knee in comparison to stable. While no successful results of these technologies have yet been demonstrated, the known characteristics of instability in the knee lends itself this method and therefore work should be directed towards such practically useful technologies.

There is potential for more understanding between the behaviour of the restraining ligaments of the knee and knee instability. Much of our understanding of the biomechanical characteristics of ligaments derives from cadaveric work (Markolf, Mensch and Amstutz, 1976; Noyes *et al.*, 1980; Grood *et al.*, 1981). Devices to determine in vivo ligament stiffness' are required to understand healthy, pathological and OA ligamental contributions to knee stability (Sohirad *et al.*, 2017).

In conclusion, the subjective sensation of instability and buckling in the OA knee has been linked to reduced stiffness, reduced walking speed, increased flexion and increased internal contact point movement variability in comparison to the stable OA knee. Work should be undertaken to assess the impact of ACL function on subjective instability in the OA knee. It appears that the subjectively unstable OA knee exists in a state of unpredictability and reduced stiffness both during walking and while static, in contrast to the classic symptom of OA stiffness. Practical methods of quantifying this reduced stiffness should be pursued in an effort to quantify knee instability in patients with knee OA in the orthopaedic clinic

2.4 KNEE ADDUCTION MOMENT

Knee adduction moment (KAM) describes the rotational forces acting on the frontal

plane of the knee and has been found to be associated with various parameters of osteoarthritis. The importance of the passive frontal plane knee stiffness has already been discussed in relation to subjective knee stability (Mark W Creaby *et al.*, 2010). Sagittal plane stiffness, described as the change in flexion moment required to produce an angular change, has been examined in its relationship to self-reported instability, (Gustafson *et al.*, 2016), but not in the frontal plane where the ankle of movement is examined is less. However, as KAM is the acting moment in the frontal dynamic knee stiffness equation, its relationship to knee instability should be considered. The knee adduction moment is calculated using the ground reaction force during stance, the force associated with the body in movement, and the lever arm produced by the knee position with regards to the point of ground contact. Calculation of knee adduction moment is through an optoelectronic gait analysis system using at least three infra-red video cameras, allied with one or more force plates integrated into the ground. A subject of known height, body mass and anthropometry, and fitted with reflective tracking markers corresponding to pre-determined anatomical locations, walks through a measurement area. The three-dimensional position of the markers is then transformed using a process of inverse dynamics to formulate a rigid body model. Using force plate data, joint moments are be calculated. Knee adduction moment is represented as a graph of moment over time. The interpretation of this has been examined as it pertains to gait in osteoarthritis.

2.4.1 METHODS OF REPORTING KAM

When presenting and comparing KAM data, normalisation of moments in the lower limb allows reduction of the effect of subject size from the analysis. Normalisation by

bodyweight and height has been shown to reduce variation due to height and weight to less than 6% in healthy subjects in a study of 158 healthy subjects (Moisio *et al.*, 2003)

The parameter of knee adduction angular impulse is examined in a study of 117 subjects comprising healthy volunteers and those with varying grades of OA (Thorp *et al.*, 2006). Knee adduction angular impulse is measured as the integral of knee adduction moment, calculated by inverse dynamics and normalized for height and weight, and with respect to duration of stance. This is then subdivided by phases of stance, with 0-16% early stance, 17-50% midstance, 51-83% midstance and 84-100% preswing. For the whole stance phase, differences were found between K/L grades 2 and 3 for impulse but not peak KAM, with higher grades showing higher impulse. Further, in terminal stance phase, a difference was identifiable between K-L grades 0 and 1, and 2 and 3. The authors note the importance therefore in this terminal stance phase in measuring OA characteristics. It seems therefore reasonable to present KAM as normalised for weight and height, as well as examining peak KAM and KAM impulse data.

2.4.2 KAM IN OSTEOARTHRITIS

Knee adduction moment and osteoarthritis has been examined extensively as a means of identifying severity of OA measured both objectively and subjectively (Kim *et al.*, 2004; Foroughi, Smith and Vanwanseele, 2009; M. W. Creaby *et al.*, 2010; Kean *et al.*, 2012; Maly *et al.*, 2015). A review of knee adduction moment in osteoarthritis reported that as severity of OA increases, so does KAM (Foroughi, Smith and Vanwanseele, 2009). Hover there is no definitive evidence that mild OA results in greater KAM than in healthy subjects. The relationship between laxity and alignment indicates increasing

varus is associated with increasing KAM. The authors however question whether increased KAM is cause or effect. It was noted that there is a lack of consistency in methods of describing KAM, as well as methods of normalisation.

In a study of 14 patients with medial knee OA and 14 controls, KAM during single leg stance was assessed for correlation with symptoms on the WOMAC score (Kim *et al.*, 2004). Peak, minimum and mean KAM were adjusted for weight but not height and a difference was seen between OA and healthy subjects. Pearson's correlation showed some correlation between pain and physical function subscores of the WOMAC in the OA group.

A comparison of knee adduction moment and knee adduction impulse sought to identify the predictive value of each in identifying OA severity as measured by K-L grading (Kean *et al.*, 2012). Data from 169 patients recorded using a VICON 8 camera system at 120Hz using the VICON PIG during flat walking at self-selected pace. After co-variate adjustment, a difference between peak KAM and alignment group only was found, however for KAM impulse there was also a difference between K-L grade. No difference was found for either marker against pain. The authors conclude that KAM impulse is a better tool for the identification of OA severity and alignment in knee OA. In the prediction of bone marrow lesions (found on MR imaging) peak KAM and KAM were equally effective.

In a study of 180 subjects with medial knee OA of K/L grade 2 or 3, the relationship

between KAM and cartilage defects was assessed through gait analysis and MRI of the affected knee (Creaby et al. 2010). Both KAM and KAM impulse were examined over the entirety of stance, both showing association with increasing cartilage defects but not with total cartilage volume. The relationship however was stronger with KAM impulse than with KAM. An association between increased KAM and increased subchondral bone cross-sectional area was also found. The authors conclude that there is an association between the mechanical force across the knee and both the cartilage damage, and the increased bone volume in the medial tibial plateau. There is an acknowledgement that there is no clear relationship between the mechanical loads and total cartilage volume however.

A similar study examining 40 female subjects with knee OA using MRI and motion capture observed meniscal pathology and KAM (Vanwanseele *et al.*, 2010). Here, comparison between peak KAM and KAM impulse was made with meniscal height, presence of tear and cartilage thickness. KAM values are normalized for height and weight. Association was found between medial tear and peak KAM and KAM impulse, with increases in those with medial tears, and decreases in those with lateral. Statistically significant correlations were found between KAM impulse and peak KAM and meniscal extrusion; however, no correlation was found with cartilage thickness or denuded areas. The authors conclude that there is a relationship between KAM and KAM impulse and cartilage damage but indicate little correlation with cartilage thickness. However, the limitations of the study size (40 subjects) and the inclusion of a heterogeneous group including both medial and lateral tears must be taken into account. Furthermore, the presentation of the results made clear analysis of the descriptive findings difficult.

A cross-sectional study of subjects with knee OA examined the difference between peak KAM, KAM impulse and loading frequency on knee cartilage morphology (Maly *et al.*, 2015). Cartilage was analysed by MRI, KAM by gait analysis and loading frequency on body-worn tri-axial accelerometers, averaged over 5 days. No relationship between loading frequency and thickness was found, however both peak KAM and KAM impulse were found to be related.

A recent study has assessed the reliability of peak knee adduction values in patients awaiting HTO for medial knee OA (Birmingham *et al.*, 2007). Here, 31 patients had two gait analysis sessions several days apart measuring peak KAM averaged over 5 sessions. A Bland-Altman calculation was performed to show and interclass coefficient of 0.86. this suggests that in this group of patients it is reasonable to use peak knee KAM as a reliable method of assessing an intervention designed to alter KAM.

2.4.3 SUMMARY OF KAM IN INSTABILITY AND OA

From the above studies it has been shown that peak KAM is a reliable measurement in an OA population (Birmingham *et al.*, 2007), is of greater value in detecting variation in moments rather than inter-subject differences when normalised for body height and weight (Moisio *et al.*, 2003), and that there is a relationship of increasing KAM with increasing severity of OA as measured by K/L grade (Foroughi, Smith and Vanwanseele, 2009). In an attempt to better explain the nature of knee adduction moment Thorp et al. (2006) described the use of time/moment product they described as

KAM impulse, and this was found to be more sensitive in identifying the differences between grades of K/L OA. This was confirmed in a further study which also identified both peak KAM and KAM impulse as being able to predict bone marrow lesions identified on MR (Kean *et al.*, 2012). Two studies identified a link between KAM parameters and cartilage damage, however neither was able to find an association with cartilage volume or depth(M. W. Creaby *et al.*, 2010; Vanwanseele *et al.*, 2010).

No study has been found comparing KAM and self-reported instability. However, Dixon et al. (2010) examined walking knee stiffness in the sagittal plane an compared this with KAM. 37 patients with knee OA and 11 controls were compared using a 6-camera VICON system collecting at 120Hz, and 1080Hz AMTI force plates (Advanced Mechanical Technology, Watertown, MA.) Dynamic knee joint stiffness is described as the "change in sagittal plane joint angle in response to the applied joint moment from initial ground contact to peak joint flexion". In their study, walking joint stiffness was greater in OA than in controls, with mean 10.1+/-4.4 Nm/degree/kg vs 5.6+/-1.5 Nm/degree/kg. However, no correlation was found between reported stiffness and actual stiffness in the OA group. The study hypothesised a positive correlation self-reported knee stiffness and knee adduction moment; however, the eventual correlation was inverse. The authors propose that this stiffness may in fact be a reduction of instability. Should this be the case, it would suggest that self-reported instability may be associated with increased knee adduction moment.

2.5 EXPERIMENTAL DETERMINATION OF INSTABILITY

Extensive literature exists on methods of identifying biomechanical abnormalities responsible for subjective feelings of pain, instability and malfunction in the limbs and activities of daily living. Collectively, this literature can be explored to identify how instability in the knee may be quantitively assessed. This section reviews the literature with regards to examination of the knee - both clinical and radiological - and the evidence behind effective and illuminating techniques, with the emphasis on the use of these techniques to determine instability.

2.5.1 CLINICAL EXAMINATION

Clinical examination of the knee is used routinely for diagnosis and management planning of knee pathology. However, this is reliant on the clinical acumen of the examiner in identifying clinical differences by feel and interpreting small changes to which clinical meaning can be attributed. The validity of varying clinical skills has been examined by several authors. In their review of knee examination tests Noyes et al. (1980) describe the difficulty of assessing failure of the primary stabiliser of a joint when the force required to displace the secondary stabiliser may be greater than that applied in a clinical examination. While clinical examination usually involves the elimination of weight bearing forces to allow a more controlled application of pressure, this is often far below those forces experienced in daily activity. Grood et al. (1981) examined clinical examination for V-V stressing of cadaveric knees before and after cutting of the respective collateral ligaments. Here, under clinical examination forces at 5 degrees of flexion 0.84mm and 1.24mm of increase in laxity was found in varus and

valgus testing, and 2.56mm and 3.9mm at 30 degrees of flexion – amounts of laxity that may be very difficult to pick up clinically. Additionally, it was noted that tibial rotation occurred consistently during V-V testing which could be mistaken for joint laxity. The difficulties in assessing laxity are further discussed in a recent study of laxity under anaesthesia (Freisinger *et al.*, 2017). Here, testing was carried out using bone anchored navigation just prior to TKA. The authors describe this method as reducing the expected laxity produced during knee flexion, mimicking intraoperative testing usually performed during TKA, and the 3D local co-ordinate system applied at the tibia reducing error associated with rotation.

Watkins et al. (1991) compared intra and inter observer reliability in assessment of knee flexion and extension between a plastic goniometer and free hand examination. While intraobserver reliability was good for the goniometer in flexion and extension, inter tester interclass correlation co-efficient fell to 0.86 for extension, and was only 0.83 for visual estimate extension and 0.82 for visual estimate flexion. This results in significant risk of error in repeated visual measurements.

A cadaveric study assessed clinical examination of coronal laxity in the knee with respect to the mechanical properties of the collateral ligaments (Wilson *et al.*, 2013). Standard manual examination of collateral ligaments was performed to a firm endpoint in 3^0 of flexion. Using dynamometer attached to the tibial shaft, manual testing of the knee revealed an applied force of 10+/-3N. Mechanical assessment of the ligaments found their ultimate tensile strength to be averaging 376N for lateral and 780N for medial. Consequently, it can be assuming that clinical examination of collateral

ligaments only identifies the point of instantaneous stiffness of the ligament.

One study examined the clinical assessment of knee V-V movement as knee position over foot during min-squats in single leg stance (Ageberg *et al.*, 2010). While they identify good agreement between assessed knee V-V alignment in flexion when compared to 2-D gait analysis, the 3-D analysis shows that what is being observed is hip rotation only.

A recent study shows the consequence of this difficulty in generating quantitative results from what are effectively qualitative examination (Shetty *et al.*, 2011). The authors examined the accuracy of 52 orthopaedic surgeons in estimating lower limb alignment using a sawbones femur and tibial connected by elastic bands simulating collateral ligaments, the femoral head, and connected to a computer navigation system (Brain lab, Munch, Germany). Blinded to the navigation data, surgeons were asked to place the limb in full extension, 10^0 flexion and 90^0 flexion, and neutral sagittal alignment, and 5^0 varus and valgus, all with respect to the FTMA. Overall, only 25% of surgeons could place the knee within both 5^0 of desired flexion, and 3^0 of varus valgus. No association was found between accuracy in placing the limb and length of time as an orthopaedic surgeon, experience in TKA or experience in navigated TKA. This work shows clear limitations in manual clinical assessment.

2.5.2 QUANTIFIED MECHANICAL TESTING

The use of quantified mechanical testing is intended to remove the qualitative aspect of

clinical examination from the assessment of knee stability. However, in the absence of clear definitions of what symptomatic knee instability is, the nature of these assessments are broad, and what they actually measure varied. To this end a computer navigation system for total knee replacement (Orthopilot, BBraun Aesculap) was adapted to use a non-invasive attachment of arrays, to assess the repeatability of the system for in vivo assessment of FTMA in healthy volunteers (Clarke et al. 2012). This showed coronal alignment agreement of +/- 1.6^0 for coronal examination, and +/- 2.4^0 for sagittal taken supine, between measurements. Standing alignment seems to have been less repeatable with +/-2.9^0 and +/- 5.0^0 for coronal and sagittal FTMA respectively, however it is acknowledged by the authors that stance was less well controlled. Standardised coronal laxity testing with this system was tested using a custom made force application device to measure coronal laxity in a standardised manner, at known knee flexion (Clarke et al. 2012). They showed sagittal alignment precision within 1^0 of that measured with an electrogoniometer, and good intra-observer variability in measuring coronal alignment in extension.

A series of studies looked to compare the results of bony attachment of trackers to non-invasive attachments using cadaveric models. A study examined 12 knees, comparing the same non-invasive infrared system with a validated standard operative navigation system (Orthopilot, BBraun Aesculap) with tracker arrays fixed to bone (Russell *et al.*, 2013). Acceptable correlation was found between the invasive and non-invasive system in assessing AP translation of the tibia on the femur from full extension to 40^0 of knee flexion. A further report from this experimental setup showed this non-invasive system to be reliable to in calculating coronal laxity with an applied 15Nm moment between 0^0 and 30^0 of knee flexion (Russell *et al.*, 2014a). A final report studied repeatability and

reliability in rotational laxity. The non-invasive device was found to be repeatable and reliable on comparison to the invasive device, although the investigators highlighted the limitations of a simple rotation test in identifying knee pathology (Russell *et al.*, 2014b). The mounting of non-invasive passive trackers has been examined in further cadaveric work (Russell et al. 2014c). Here, six cadaveric knees were examined for coronal laxity in varying degrees of flexion using bone screw attachments, fabric straps and rubber straps. It was observed that through the examined range of flexion bone fixed and strap fixed systems were precise, however rubber strapping resulted in unacceptable repeatability beyond 40^0 flexion. Where coronal force was applied, all strapping materials showed a tendency towards imprecision with increasing flexion.

Isokinetic dynamometry has been used to show both varus and valgus laxity at a set force, as well as identifying mechanical stiffness in the coronal plane (Creaby et al. 2010; Creaby et al. 2013; Thorlund et al. 2014). Using the Kim-com 125-AP dynamometer and a custom-made attachment, V-V motion was tested in 20^0 of flexion. A set force was applied in varus and valgus movement and a quantified laxity can be determined. Furthermore, stiffness has been assessed by measuring the force required to produce a given deviation from neutral alignment over the initial degree of deviation. This has already been shown to be associated with self-identified instability of the knee, differentiating the knee stiffness over its frontal plane movement from the available range of frontal plane movement (Creaby *et al.*, 2013).

2.5.3 IMAGING

Several imaging modalities have been examined to look at their contribution to objective assessment of the knee, most notably FTMA (Stähelin *et al.*, 2003; Cooke, Sled and Scudamore, 2007; Yaffe, Koo and Stulberg, 2008; Gbejuade *et al.*, 2014; Holme *et al.*, 2015; Yoshihara *et al.*, 2015). While none of these studies examine the symptom of instability, they do explore the frontal plane alignment of the knee and its dynamic nature. This is of relevance to the forces required to maintain a stable joint, both in terms of active and passive restraint, however and is therefore instructive towards an understanding of knee physiology, however appears to offer little towards a diagnostic understanding of subjective instability.

2.5.4 DYNAMIC TESTING

Imaging studies examined in section 2.5.4 dealt entirely with static analysis, while instability, as previously discussed, is a dynamic problem occurring as the knee undergoes varying forces and obstacles throughout the gait cycle. In order to assess the knee under such conditions, analysis of the knee during movement must be performed. While several methods have already been discussed that involve passive movement, where the knee is brought through its movement range by the examiner, this section is concerned with active movement where normal physiological effects such as gravitational force, knee flexion moment etc. are included, namely gait analysis. Various methods and their application to instability will be discussed.

2.5.4.1 VARUS THRUST

Varus thrust is a term used to describe the lateral movement of the proximal tibia with regards to the distal tibia taking place at the point of weight acceptance in the stance phase. While this does not appear to be synonymous with instability or perceived instability, it suggests greater movement in the knee joint that requires greater control to prevent instability. According to our hypothesis of instability in the knee, it may therefore be presumed that increased varus thrust may result in greater risk of instability where counteracting forces are weakened or absent or may even be a consequence of mechanisms designed to prevent this phenomenon. Varus thrust may be observed visually or using instrumentation. Several authors have examined this parameter to identify whether it is consistent with osteoarthritis and instability.

One study describe varus thrust, observed qualitatively during walking, as predictive of worsening of OA in an observational study of 237 patients with OA (Chang *et al.*, 2004). 64 participants went on to have gait analysis. The authors established that in varus aligned patients there was three-fold increase in progression of OA in those with varus thrust in comparison to those without. Those with varus thrust had an increase in adduction moment. There was also a correlation with poorer function. Another study attempted to quantify the varus thrust of patients using a gait analysis system with markers positioned on the iliac ring, greater trochanter, lateral joint line, lateral malleolus, lateral calcaneus and head of fifth metatarsal, using a three camera system recording at 120Hz (Kuroyanagi *et al.*, 2012). Measurements were taken during normal walking on a flat surface. Varus thrust was identified as the change in varus angle between heel strike and varus peak. They conclude that this quantifies the instability in the knee and that this could also be done with a single camera recording in clinic.

However, the ability of a single camera to take account of multidimensional movement must be questioned.

A large scale study to look at the prevalence of varus thrust between Caucasian and African-American subjects with OA or at risk of OA used trained examiners to assess the presence or absence of thrust during walking (Chang *et al.*, 2010). In 1566 subjects with, and 2026 subjects without radiographic signs of arthritis, varus thrust was observed in 32.1% of subjects without and 36.7% with OA. As this was assessed visually there was no quantification of this and was presented therefor as a binary outcome.

A further study by the same group compared visually assessed varus thrust to observational parameters in gait analysis in 440 knees with OA, 82 with visually assessed varus thrust (Chang *et al.*, 2013). It was identified that those with varus thrust had a higher tibial rotational velocity in early stance.

In a study examining KAM in medial knee osteoarthritis shank angle throughout the stance phase was examined (Foroughi *et al.*, 2010). This study compared 17 women with medial knee OA with 17 controls. Shank adduction angle and mean angular velocity was found to be higher in the OA group, peaking at 30% of stance phase. This peak corresponds with the peak KAM. It seems probable that this peak shank angle is analogous to the varus thrust observed in medial knee OA.

In 40 patients with one ACL injured knee, and 25 post ACL reconstruction patients varus thrust was assessed (Yoshimura *et al.*, 2000). An accelerometer (type 1823, NEC

San-ei, Tokyo, Japan) was fixed over the tibial tubercle with tape, and pre-loaded. In 40 healthy knees, an initial lateral peak was found in 30 knees, followed by a medial peak. Four knees showed the opposite and 6 had no classifiable pattern. In ACL injured patients the lateral thrust was significantly higher in 36 knees, with a medial thrust in the remaining 4 knees.

A similar study examined accelerations in ACL and PCL deficient subjects in comparison to healthy, noting that it was only in the ACL deficient subjects that the increase in thrust existed (Yoshimura, Naito and Zhang, 2002).

The same group examine the effect of wedged insoles on varus thrust in ACL deficiency (Yoshimura *et al.*, 2003) drawing on earlier work looking at accelerometer and varus thrust (Ogata, Yasunaga and Nomiyama, 1997). Here it is shown in 35 ACL deficient knees in comparison to 60 age matched controls that varus thrust is greater, using a tibial mounted uniaxial accelerometer. A wedge insole is used in the ACL patients and the peak thrust decreases. This is analogous to the patterns reported by Ogata et al. (1997).

While none of the above studies comment upon self-reported instability in the knee, they concern rapid movement of the knee in the frontal plane during, and shortly after, weight acceptance. This requires a counter force to prevent ongoing lateral movement and collapse of the knee. These mechanisms may be present and functioning in the healthy knee making varus thrust a controllable and benign phenomenon, but that to control this thrust may be associated with instability in the knee and may be a target for assessment of instability.

2.5.4.2 OPTOELECTRONIC GAIT ANALYSIS

In 2.3.8 the use of gait analysis was discussed in relation to the diagnosis and quantification of osteoarthritis. However, optoelectronic gait analysis has also been used in knee replacement patients to assess post-operative function. A systematic review of gait analysis in total knee replacement examined what activities of daily living had been described in reviews of movement analysis in post-operative total knee replacement patients. 87 studies were reviewed showing walking, sit-to-stand, stair ascent, stair descent, turning task, lunge task and obstacle course. Knee adduction however was investigated in only 29 of the articles. (Komnik *et al.*, 2015)

A systematic review on gait analysis compares post-operative TKA patients at least 6 months from surgery to control populations (McClelland, Webster and Feller, 2007). They identify 11 studies meeting acceptable criteria for review. Significant heterogeneity of method and results are identified. Consistently however there is a reduction in knee total ROM in TKA in comparison to controls, with reduced knee flexion. This is shown with reduction in the numbers within the TKA population producing a biphasic knee flexion pattern in gait in comparison to the normal group. Interestingly, it is noted that only one study explained at the coronal plane data.

2.5.4.4 JOINT STIFFNESS AND INSTABILITY

Two studies have examined the use an isokinetic dynamometer to establish passive mechanical stiffness in the knee, and how it relates to patient reported symptoms of instability (Creaby et al. 2013; Thorlund et al. 2014). With the knee in 20^0 of flexion a

medio-lateral force is applied to the relaxed knee around a pre-set range of movement. The required force to produce an angulation is described as the passive mechanical stiffness. Reduced mechanical stiffness in movement of 1 degree from the neutral axis has been shown to be associated with self-reported instability (Creaby *et al.*, 2013) and is also found to be present subjects following meniscectomy (Thorlund *et al.*, 2014).

In the dynamic setting walking stiffness has been extracted from optoelectronic gait analysis data by computing the change in moment by the change in knee angle in the sagittal plane (Dixon *et al.*, 2010; Gustafson *et al.*, 2016). Similar calculations for the coronal plane have not been performed due to difficulties measuring angular change over such a narrow range. However, in the dynamic situation, normal muscle and joint forces applied to the knee will be more representative of daily living. If stiffness is reduced in the knee, then a given force will cause a greater acceleration that must be countered to allow the knee to return to its steady state. Where the impulse is too large, or the dampening mechanisms insufficient, the subject may perceive the knee as about to fail (symptomatic instability), or it may fail in reality. It may be that measuring this parameter dynamically could be of use in measuring symptomatic instability

2.5.4.5 DYNAMIC STEREO X-RAY

Knee joint movement has been visualised using x-ray visualisation. Several studies report on the findings of knee movement assessed using bi-planar x-rays performed during walking. High frequency bi-planar x-ray images are combined to create a 4D representation of bony movement during walking (Farrokhi *et al.*, 2012, 2015, 2016), with the pattern of bony contact point measured for the gait cycle (*see section 2.3.7*

Other factors Identified in Gait analysis). Comparison of variability and total excursion have been performed using this technique with the intension of identifying instability. This technique allows for the examination of contact point movement in the knee between groups with and without symptomatic instability hypothesising that subjects with symptomatically unstable knees have greater movement in contact point which results in their symptoms. This hypothesis fits with the understanding of symptomatic instability in the knee set out here, however the specialised, expensive and cumbersome methodology of stereo x-ray assessment makes it unsuitable for routine clinical use.

2.5.4.3 INERTIAL MONITORING AND ACCELEROMETERY

One more recent methodology for assessing gait and knee movement is accelerometery and inertial measurement. Designed as a portable, worn instrument, an accelerometery unit measures instantaneous acceleration at the attached point. Inertial monitoring units (IMU) comprise accelerometers, gyroscopes and magnetometers to identify not only the acceleration, but the orientation of the unit. This has been utilised by several authors to examine differences in healthy and OA gait (Turcot *et al.*, 2009), differences between differing designs of total knee replacement (Jolles *et al.*, 2012), and to examine the effect of symptomatic instability on accelerations about the knee (Khan *et al.*, 2013; Soeno *et al.*, 2018).

Broadly, accelerometers or IMUs can be used either in place of standard opto-electronic gait analysis to provide standard gait analysis parameters such as joint angles, cadence and velocities in portable format (Dejnabadi, Jolles and Aminian, 2005; Dejnabadi *et al.*, 2006; Cooper *et al.*, 2009; Jolles *et al.*, 2012), to examine for accelerations during a

specific examination such as the pivot shift test (Delasotta *et al.*, 2012; Lopomo *et al.*, 2012; Berruto *et al.*, 2013; Zaffagnini *et al.*, 2014) or to examine the accelerations about the joint itself during specific tasks (Turcot, Aissaoui, Boivin, Hagemeister, *et al.*, 2008; Turcot, Aissaoui, Boivin, Pelletier, *et al.*, 2008; Turcot *et al.*, 2009, 2011). Early use of accelerometers to assess impulses around the knee involved bone mounted accelerometers (Light, McLellan and Klenerman, 1980; Lafortune, 1991) with more recent study groups externally mounting the accelerometer and IMU devices using tape (Ogata, Yasunaga and Nomiyama, 1997; Yoshimura *et al.*, 2000, 2003; Yoshimura, Naito and Zhang, 2002), straps (Dejnabadi, Jolles and Aminian, 2005; Khan *et al.*, 2013; McCarthy *et al.*, 2013; Roberts *et al.*, 2013; Monda *et al.*, 2015; Rahman *et al.*, 2015) or custom made exoskeletons (Turcot, Aissaoui, Boivin, Hagemeister, *et al.*, 2008; Turcot, Aissaoui, Boivin, Pelletier, *et al.*, 2008; Turcot *et al.*, 2009, 2011).

Three studies directly address the issue of symptomatic instability in the knee following total knee replacement (Khan *et al.*, 2013; Roberts *et al.*, 2013; Soeno *et al.*, 2018). Kahn et al. (2013) examined TKA patients differentiated into those with and without symptomatic instability in the knee as reported using subsections of the WOMAC and Knee Society Evaluation form, and control patients without TKA. A tri-axial accelerometer was mounted on the proximal tibia using a strap and magnitude of peak and trough AP readings were compared between groups during various stepping activities. Acceleration magnitudes were increased in the TKA group in comparison to controls. No data was presented between symptomatically stable and unstable groups, but it was noted that magnitude was not always higher when instability was reported with a particular task.

The group modified their methodology in a subsequent study to include gyroscope, magnetometer and time stamping along with accelerometery to allow correction of accelerometer output to the global axis using a rotation matrix, and the calculation of jerk as the time derivative of acceleration (Roberts *et al.*, 2013). Groups were compared as before (TKA and control) and instances of symptomatic instability recorded during tasks. Step up and down activities were most associated with symptomatic instability, and those tasks had greatest differences in acceleration magnitudes in AP and axial directions between TKA and control groups. Differences between symptomatically unstable and symptomatically stable TKA patients were not presented, however the authors conclude that a single IMU used in this manner may be developed for use in identifying "instability" in the knee.

Another study compared two implant designs of TKA during gait, differentiating subjects using a self-reported instability score asking about "buckling, shifting or giving way" in the previous 3 months (Soeno *et al.*, 2018). With a tri-axial accelerometer mounted following the protocol of Kahn *et al.* (2013) accelerations in three planes were measured stance phase and the whole gait cycle both as the root mean square (RMS) of acceleration, and in the frequency domain using the Fast Fourier Transform (FFT). No significant differences between groups were found between groups in either of these parameters. The use of frequency-based analysis of acceleration in this study is novel, however the use of FFT limits this to measurement over the whole time base. This approach does present an opportunity however to examine accelerations in the knee as a means to identify symptomatic instability in a new way.

Accelerometers provide a portable, inexpensive and easy to use measure of knee

movement in the clinical environment (Roberts *et al.*, 2013). So far, they have not been used to successfully quantify or differentiate the symptomatically stable and unstable knee, however the in theory, the accelerations seen in the knee during activities could form the basis for this (Khan *et al.*, 2013; Roberts *et al.*, 2013). While one study has examined a frequency-based analysis of knee acceleration using FFT as a method of determining symptomatic stability with no success, other methods of frequency-based analysis could be performed. Our hypothesis of "symptomatic instability" in the knee being due to time spent in the boundary zone between dampened knee impulse and uncontrolled knee impulse could benefit from accelerometery to determine the movement of the accelerations of the knee, and a frequency-based approach to this may reveal further information of relevance to an understanding based on failure to dampen uncontrolled movement. Further, the use of limited measures of maximum, minimum, mean and range of acceleration magnitude is studies (Khan *et al.*, 2013; Roberts *et al.*, 2013) may limit the interpretation of the accelerometer output.

2.5.5 SUMMARY ON ASSESSMENT FOR INSTABILITY

Methods of identifying symptomatic instability, and therefore its causative pathology, are wide ranging in both design and success. Most involve considerable size, expense and user skill, such as gait analysis, and bi-planar x-ray analysis. It is proposed that such limitations have held back development and implementation of these devices beyond biomechanical trail. Increasingly, the advantages of cheap, portable and usable accelerometers have been utilised in the study of instability (Table **2-3**). The use of these devices to attempt to represent gait, quantify varus thrust and measure accelerations associated with symptomatic instability appears to be path that will reach

the destination of a cheap and usable device quantify the conditions leading to symptoms of impending instability, and therefore better understanding of their causative factors. In the opinion of the author, none of these studies have reached this goal as yet because they have largely focused on sagittal plane movement (Dixon *et al.*, 2010; Khan *et al.*, 2013; Roberts *et al.*, 2013; Gustafson *et al.*, 2016), and statistical methods which reduce the dimensionality of available data to a summary measures only such as peaks, trough and values averaged over the gait cycle (Khan *et al.*, 2013; Roberts *et al.*, 2013; Soeno *et al.*, 2018).

Simple statistical tools for the evaluation of biomechanical signals relies on summary data, however other methods of analysis examining the whole dataset exist (Chau, 2001b, 2001a). While FFT analysis has been used to examine accelerometer frequency across the data signal as a whole (Soeno *et al.*, 2018), the whole signal can be examined using other techniques. The wavelet transform allows measurement of discrete points within the signal, in both time and frequency. Its use Continuous wavelet transform (CWT) has been used to analyse EMG signals in the frequency/time domain, allowing frequency analysis of the signal throughout its repeating cycles (Dantas *et al.*, 2010), as well as to measure the effects of shoes on ground reaction force (Fischer, 2010). This approach has been used to measure accelerometer signals in non-biomechanical fields (Chuang, Wu and Wang, 2013)(Silva *et al.*, 2018) and more recently in detecting accelerometer measured vibrations at biomechanical interphases (Błażejewski, Głowiński and Maciejewski, 2019). This approach has not been found in the literature for examining symptomatic knee instability, but it is proposed that by examining the signal in this manner throughout the cycle, more information may be gathered. With

analysis of the frontal plane and a time/event analysis hoped that classification and quantification of symptomatic instability will be possible.

2.6 INSTABILITY AND THE TOTAL KNEE REPLACEMENT

"Instability" is a commonly described mode of failure following total knee replacement (Sharkey *et al.*, 2014; Pitta *et al.*, 2017). However, while other common modes of failure such as infection have clearly defined definitions (Parvizi *et al.*, 2018), no such definition exists in the total knee replacement. Reported modes of failure are often assessed by reviewers through review of clinical notes comprising radiological and laboratory investigations, on consort with clinician letters and patient reported outcome measures (Pitta *et al.*, 2017), but no clear understanding of the "unstable" knee is described. As an example, discussion of "mid-flexion instability" has become popular in the literature lately, with definitions revolving around ligamentous laxity between 20 and 90 degrees of flexion (Petrie and Haidukewych, 2016), however this definition, and the entity its self, is debated (Vince, 2016). However, as most studies of failure rely on revision surgery as an endpoint (*see Table 11-6 – Reasons for revision TKA - Review of the literature*.) and such surgery would not be carried out in the absence of symptoms, it seems that a definition of symptomatic knee instability is required. Further, a simple method of assessment by which it may be quantified is needed, as currently no standard method of biomechanical assessment exists, with clinicians instead relying on a combination of patient reported symptoms, clinical examination and simple radiological examination.

2.6.1 FAILURE AND THE CAUSES OF FAILURE

Reasons for failure following total knee replacement, using revision as a surrogate marker of failure, has been an extensively studied over the years (Table 11-6, Appendix

A, p233), with several reviews examining the changing nature of the revision burden (Lombardi, Berend and Adams, 2014; Lum, Shieh and Dorr, 2018). One particular challenge in comparing the causes of failure are the lack of consensus as to their definition. Several studies have aligned themselves with the definitions provided by Sharkey et al. giving reasons as infection, instability, aseptic loosening, periprosthetic fracture, malalignment, retro-patellar arthritis and unexplained pain, AVN of patella and extensor mechanism failure (Sharkey *et al.*, 2014). However, here the diagnosis of cause of failure is often from surgeon diagnosis without clear definition. Further, the largest review study classified reasons for revision using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) which has little cross compatibility with other studies (Delanois *et al.*, 2017).

It is notable that the causes of failure have changed over time. While aseptic loosening, infection and instability are found in the top four cases in almost all studies covering revisions between 1991 and 2016 (Sharkey *et al.*, 2002, 2014; Gioe *et al.*, 2004; Schroer *et al.*, 2013; Le *et al.*, 2014; Thiele *et al.*, 2015; Pitta *et al.*, 2017; Postler *et al.*, 2018), polyethylene wear has fallen from the most common and second most common reasons respectively in the earlier studies (Sharkey *et al.*, 2002; Gioe *et al.*, 2004) to much lower cause today (Table 11-6). This is most likely due to improvement in the manufacturing process of the polyethylene insert resulting in greater longevity (Lombardi, Berend and Adams, 2014; Sharkey *et al.*, 2014; Lum, Shieh and Dorr, 2018). Instability has remained a common cause, despite improvement in manufacturing and operative technique. Difficulty exists in classifying this method of failure however due to the lack of definition. In one study, for example, instability was assessed based upon reported symptoms and clinical examination, however what symptoms and examination findings

were not defined (Le *et al.*, 2014).

Within the discussion of TKA failure, definition has centred around defining differing modes of instability. These may classified as flexion, extension (V-V), mid-flexion, recurvatum or global instability (Augustine, 1956; Yercan *et al.*, 2005; Kelly G Vince, Abdeen and Sugimori, 2006; Parratte and Pagnano, 2008; Vince, 2016). In an earlier review time is spent discussing instability as a result of polyethylene wear (Rorabeck, 2001) however as this is seen much less frequently in revision situations today it will not be addressed here.

Seah et al. (2012) examined patient satisfaction as it relates to V-V stability within the knee. A cohort of 1500 patients with 1507 TKAs were examined 2 years following surgery. Knee Society Score (KSS), Oxford Knee Score (OKS) and SF-36 were administered along with a clinical assessment of V-V laxity at 30 degrees of knee flexion. Better outcomes were found in general health, pain, vitality, mental health and function in those with V-V laxity of <5 degrees compared to those with >10 degrees, and in body pain, general health and vitality between those with <5 degrees V-V laxity and 6-9 degrees laxity. Sagittal ROM was better with increasing laxity. A significant limitation of this study however was the clinical examination of laxity.

Nakahara et al. (2015) assessed KSS compared to condylar lift-off and patient satisfaction in 94 PS fixed bearing TKA performed by a single surgeon in 68 patients. Long leg standing radiographs were used for pre-and post-op alignment, and a Telos device was used to assess varus and valgus laxity at 10 degrees flexion. In 19 patients, condylar lift-off was measured during treadmill walking using a continuous sagittal

radiograph at 10Hz. Lift-off distance on each condyle was measured. No correlation was found between extension laxity and either KSS score, or condylar lift-off. Varus-valgus laxity was reported as 5.9 +/- 2.7 and 5.0+/-1.6 respectively.

Fleeton et al. (2016) examined self-reported instability in the knee before and after TKA using self-reported measure of questions from the Activities of Daily Living Scale of the Knee Outcome Survey. Here, instability in the previous 1-2 days was assessed. At 6 months following TKA 22.9% of 323 subjects and retained symptomatic instability from a baseline of 72%, with an additional 3.1% developing symptomatic instability.

From this collection of studies, it can be seen that no single definition of instability exists, ranging from conclusions drawn from the patient record, varus-valgus movement and patient reported outcomes. However, in all studies with revision as an end point, some element of patient reported "instability" is necessarily used as the knee would not be revised without symptoms. For the purposes of this thesis, the previous model of instability being the inability of stabilising mechanisms to return the knee to zero state following an impulse received during physiological activity, and symptomatic instability being increased time spent in the boundary between "stable" and "unstable" conditions, will be applied to prosthetic knees (Figure 1 4 – Diagrammatic representation of the knee undergoing multiple impulses).

2.6.2 ALIGNMENT

A full examination of the hotly debated topic of knee alignment is beyond the scope of this review, but a recent review discusses the controversy of alignment in TKA (Allen

and Pagnano, 2016). Ongoing dissatisfaction rates of up to 20% following TKA are noted, and the reliance both on short radiograph for post-operative alignment checking is commented on. It is suggested here that ideal alignment may be patient specific, and not merely dependent on maintaining the traditional neutral +/- 3^0 alignment. Another review of the current debate identify that much of the historical literature involves the use of short leg radiographs and often small study numbers (Abdel *et al.*, 2014). They note a movement from neutral alignment in the mechanical axis to so called kinematic alignment based upon patient specific instrumentation. However, they conclude that neutral alignment is still supported by the literature at present.

2.6.3 EXTENSION INSTABILITY

Ligament balance during total knee replacement is vitally important in producing a stable TKA. This requires resection to produce a collateral ligament in equal tension both in flexion and in extension, both medially and laterally (Figure 2-3). In Extension instability can be described as either symmetrical or asymmetrical (Parratte and Pagnano, 2008; Abdel and Haas, 2014). Symmetrical instability is caused by over resection of the femur resulting in a large extension gap in relation to flexion gap, resulting in an undefiled joint in extension only. This can be corrected by augmenting the femur to restore length. If excessive tibia has been cut this will give extension instability as well as flexion instability unless the tibia is augmented to compensate for the loss of bone. Care must be taken not to elevate the joint line as this has classically been linked to the production of mid-flexion instability.

Asymmetrical instability is caused by functional collateral ligamentous failure or

angular deformity in the coronal plane. This is described as more common than symmetrical instability and is often iatrogenic. The varus knee with medial OA collapses medially due to cartilage and bone loss on at the medial femoral condyle and tibia with subsequent tightening of the medial collateral ligaments and stretching out of the lateral. Insufficient release of the tightened medial ligament results in a post-operative deforming varus force. This can result in damage to the restraining ligament on subsequently convex (lateral) side of the joint (Browne, Parratte and Pagnano, 2012). This may be exacerbated by malalignment of the components, further driving instability and failure. In the valgus knee the converse is true, with the stretched medial collateral

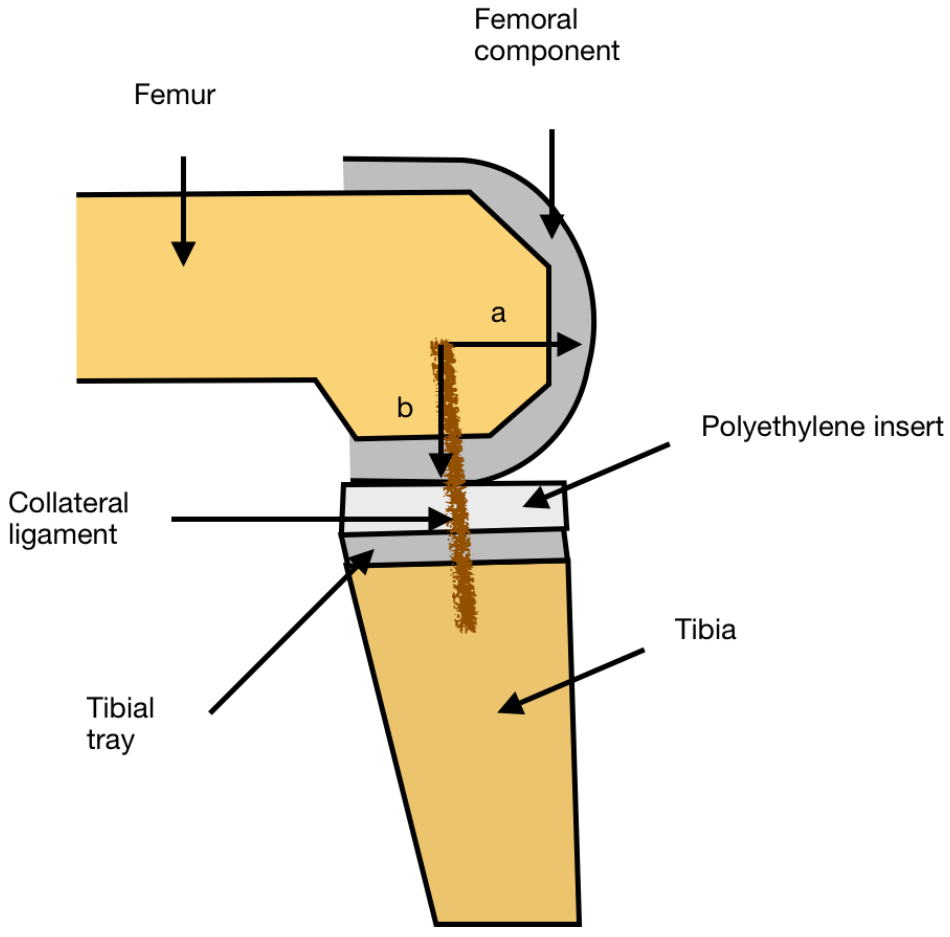

Figure 2-3 – Diagrammatic representation of a sagittal section of a TKA.
While a & b remain equal sizes, rotation of the femur against the tibia will maintain tension in the collateral ligaments. Asymmetry through over or under resection of either femoral cut results in changing tension through the flexion arc.

ligament continuing to be redundant following insufficient release of the lateral side with subsequent valgus deforming force (Parratte and Pagnano, 2008).

2.6.4 FLEXION INSTABILITY

Flexion instability is an unstable knee in flexion, caused by a large flexion gap relative to the extension gap, subsequently undefiled by the components (Browne, Parratte and Pagnano, 2012; Abdel and Haas, 2014; Vince, 2014) or rupture of the PCL in CR implants (Parratte and Pagnano, 2008). This is historically under recognised, and can occur in well fixed, well aligned knees. Clinically this results in AP instability in 90 degrees of flexion, met by a hard stop either direction as the two components interact. This may present as an ill-defined instability. In severe cases, the knee may dislocate (Vince, 2016). The patient without frank dislocation may instead complain of difficulty climbing and descending stairs, as well as recurrent or persistent knee effusion, and anterior knee pain and instability between 30 degrees and 60 degrees of flexion, as well as experiencing difficulty rising from a chair (Yercan *et al.*, 2005). Examination reveals posterior sag and a positive anterior drawer test (Parratte and Pagnano, 2008).

2.6.5 MID-FLEXION INSTABILITY

A recent review describes the concept of mid-flexion instability as a mis-diagnosis of posterior capsule tightness and extension instability (Vince, 2016). While it has been demonstrated in cadaveric studies by Martin & Whiteside (1990) it has been argued that it has yet to be proven in patients, and what is being encountered is in fact continuing fixed flexion deformity as a result of posterior capsular stiffness, not addressed at the time of surgery. This results in subtle reduction in extension gap with a normal flexion

gap, and the fitting of components to produce a knee looser in flexion - the scenario of flexion instability. It is postulated that as the knee flexes, the posterior capsular relaxation results in sudden loss of V-V stability, resulting in the feeling on mid-flexion instability.

One cadaveric study managed to replicate the mid-flexion instability obtained with a raise in joint line by artificially tightening the posterior capsule (Cross *et al.*, 2012). Seven cadaveric specimens with no knee pathology were selected and a PS TKA performed using a navigation system (Praxim, La Tronche, France) using a Genesis II TKA (Smith and Nephew, Memphis, TN) and a standard midline incision and medial arthrotomy. Using the navigation system coronal laxity was tested in varying flexion using a standardised 9.8Nm moment applied to the tibia. Following this, the components were removed, and the posterior capsule sutured to create a 10-degree flexion contracture when the components were re-inserted. An additional 2mm of distal femoral cut was then made with a robotic cutting guided to simulate a bony cut to overcome a tight flexion gap. Measurements were made again of coronal laxity at varying flexion, before a second 2mm was removed and tests re-performed. Cross et al (2012) identified a statistically significant increase in coronal laxity at 30 and 60 degrees of flexion, when resecting an additional 4mm, and a statistically significant increase at 30 degrees flexion when increasing by 30 degrees. However, this had disappeared at 90 degrees flexion in both scenarios. This suggests that raising the joint line by 2mm results in an increase of approximately 2.5 degrees for every 2mm resected at 30 and 60 degrees of flexion, with the most marked change at 30 degrees.

Another study described mid-flexion instability as an entity existing between 45 and 90

degrees of flexion, requiring revision with joint line restoration. It is noted however that this is poorly understood in the literature (Petrie and Haidukewych, 2016). Another study assessed the degree of mid flexion stability at time of implantation in a mobile bearing PS TKA (Vanguard RP, Biomet Japan, Tokyo, Japan.) in 259 patients with osteoarthritis (Minoda *et al.*, 2014). A custom-made device to tension the joint was used during the trial implant phase of surgery to assess joint gap during flexion. Greatest joint gap was found at 30 degrees of flexion, falling as flexion increased. The peaking of joint laxity through the flexion arc, rather than a continuous laxity throughout flexion, was seen as indicative of mid flexion instability. A further study on the same cohort of patients compared the flexion and extension gaps cut prior to implantation to the laxity following implantation (Minoda *et al.*, 2015). Divided between equal gaps, flexion - extension >1mm, and flexion -extension <-1mm, a statistically significant reduction in the joint gap in the <-1mm and >1mm groups was found at 60, 90, 120 and maximum flexion. Statistically significant reductions in joint gap were found between >1mm and both other groups at 60 and maximum flexion. However, no significant difference was found at 30 degrees, suggesting that this is not caused by inappropriate gap balancing.

Another group considered mid flexion stability comparing posterior stabilised (PS) and PCL retaining (CR) implants (Hino *et al.*, 2013). In a study of 34 patients with varus FTMA, an alternating sequence of CR and PS implants (NexGen CR-Flex and NexGen LPS-Flex, Zimmer) were implanted using computer navigation (Precision Knee, Stryker). Navigation readings were taken prior to removal of ACL, osteophytes of menisci every 10 degrees of flexion with manual V-V force applied. A capsular incision used to assess AP axis of the tibia was also sutured closed. Once implanted

and the joint closed, the readings were taken again. In all groups (Pre-TKA and Post-TKA) maximal V-V laxity was seen at 30 degrees flexion, with greatest increase being between 0 and 10 degrees. Overall, CR TKA was more stable, with significant differences between 10 and 30 degrees. It is postulated that the PCL has a contribution to V-V stability in this range.

2.6.6 LITERATURE REVIEW SUMMARY, & ONGOING RATIONALE FOR STUDY DESIGN

Total knee arthroplasty (TKA) is an increasingly common procedure, with one recent study predicting an increase in primary procedures by 117% by 2030, and 332% in the case of revision (Patel *et al.*, 2015). While revision rates are low, volume will make such procedures increasingly frequent. With improvement in technique and materials, methods of failure have changed, with polythene wear decreasing in significance, while infection, instability and remaining significant causes (Sharkey *et al.*, 2002, 2014; Le *et al.*, 2014; Lombardi, Berend and Adams, 2014; Thiele *et al.*, 2015; Wilson *et al.*, 2017). While detection of infection and loosening can be made simply using radiographs microbiology testing, currently no standard method of assessment for instability exists, with clinicians instead relying on a combination of patient reported symptoms, clinical examination and simple radiological examination (Yercan *et al.*, 2005; Parratte and Pagnano, 2008; Abdel and Haas, 2014; Petrie and Haidukewych, 2016; Vince, 2016; Wilson *et al.*, 2017). Attempts have been made to quantify instability in the native knee (Farrokhi *et al.*, 2012, 2014; Creaby *et al.*, 2013; Thorlund *et al.*, 2014; Gustafson *et al.*, 2016), and following TKA (Hamilton *et al.*, 2014); however no simple, repeatable device currently exists for the objective identification to instability in TKA. Instability

is therefore most usefully understood as a symptom – from the feeling of requiring increasing conscious control to counter an impulse across the knee to that of actually exceeding the existing control mechanisms – and is classically evaluated through a questionnaire asking about "giving way", "buckling", "insecurity" or "letting down" of the knee (Fitzgerald, Piva and Irrgang, 2004; Murray *et al.*, 2007; Wilson *et al.*, 2017). In the unstable osteoarthritic knee (OA) one key measure of instability is reduced stiffness (Creaby *et al.*, 2013; Thorlund *et al.*, 2014; Gustafson *et al.*, 2016), however this has not been investigated in TKA.

2.7 CONCLUSIONS ON THE NATURE OF INSTABILITY IN THE KNEE

A common complaint in the osteoarthritic knee is the symptom of instability, described variously as loss of confidence, feelings of buckling or giving way (Fitzgerald, Piva and Irrgang, 2004; Fleeton *et al.*, 2016). This may or may not be associated with actual falls, but is associated with decreased activities (Nguyen *et al.*, 2014; Nevitt *et al.*, 2016), most likely due to patient concern about falling. In the prosthetic knee, again without a clear definition, "instability" , which must be symptomatic or it would not result in further surgery, is a common cause for revision surgery (Sharkey *et al.*, 2014; Pitta *et al.*, 2017). The exact pathological process for this "instability" has not been fully determined, but the effect of passive structures, such as bone, ligament, menisci, and capsule, in counteracting destabilising forces have been (Markolf, Mensch and Amstutz, 1976; Grood *et al.*, 1981; Zlotnicki *et al.*, 2016) as well as the use of active restrain such as muscle contraction (Schmitt and Rudolph, 2008; Knoop *et al.*, 2012, 2013).

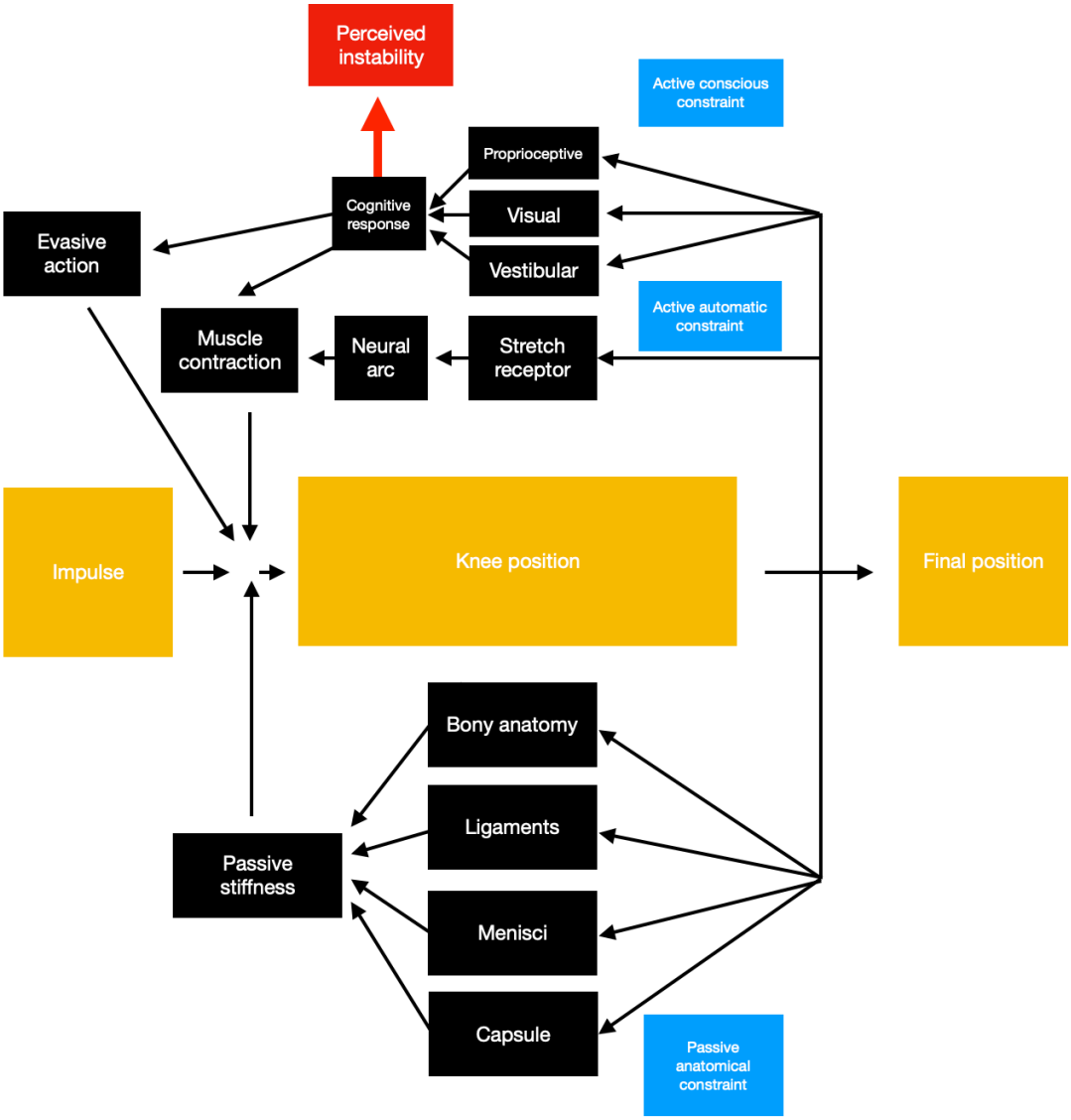

Figure 2-4 – Diagrammatic representation of the control system of the knee
Diagram showing three layers of response to a destabilising impulse in the knee: passive anatomical control, active automatic constraint and active conscious constraint. The conative response to the aberrant knee position results in both active measures to stabilise the knee, and a conscious perception of that instability
.

Osteoarthritis involves damage many of these passive structures, while TKA removes some of them (menisci, ACL, often PCL) completely. Patients with symptomatic instability have been shown to have decreased passive stiffness around the neutral axis of the knee (Creaby *et al.*, 2013), as do patients following medial meniscectomy

(Thorlund *et al.*, 2014), a procedure often with similar results to the medial meniscal damage in OA. It is proposed that symptomatic instability in the knee is the conscious appreciation of the destabilising of the knee by physiological impulse. The effects of osteoarthritis or TKA render the passive mechanical responses less effective, requiring active responses, possibly including conscious control (Figure 2-4).

It is proposed that the symptomatic instability points to a reduced capacity of the earlier mechanisms to control destabilising impulses leading to greater internal movement in the knee (Farrokhi *et al.*, 2014). From review of methods of experimental determination, it is proposed that an accelerometer mounted at the knee joint can be used to measure this movement and correlate it to symptomatic instability in the knee.

Table 2-1 – Summary of Studies Examining Instability

Author, date	Study type	Study subjects	Instability striation	Study method	Primary findings
Fitzgerald et al. 2004	Regression analysis biomechanical data	105 OA (66 with instability)	6-point scale adapted from Knee Outcome Survey-Activities of Daily Living Scale	2 groups based on stability, regression analysis of biomechanical data	63% subjects report instability, instability associated with poor physical function (WOMAC)
Schmitt et al. 2008	Regression analysis biomechanical data	52 OA (32 with instability)	6-point Likert scale (Fitzgerald 2004)	3 groups based on stability, regression analysis of biomechanical data	Instability not associated with laxity, associated with poor function (KOOS, SCT)
Knoop et al. 2012	Regression analysis biomechanical data	283 OA (191 with instability)	"sensation of an episode of buckling, shifting, or giving way of the knee in the previous 3 months", dichotomised (Felson 2007)	2 groups based on stability, regression analysis of biomechanical data	strength associated with instability, laxity and proprioception not
Kavchak et al. 2012	Regression analysis biomechanical data	16 OA, 16 Controls	6-point Likert scale (Fitzgerald 2004)	2 groups, step-over test causing feeling of instability, regression analysis	increased vibration perception threshold correlates with instability
Van Der Esch et al. 2012	Regression analysis biomechanical data	248 OA patients	"sensation of an episode of buckling, shifting, or giving way of the knee in the previous 3 months",	regression analysis of self-reported knee pain as a variable for activity limitation	self-reported instability associated with limitations in activity

			dichotomised in various activities (Felson 2007)		
Creaby et al. 2013	Regression analysis biomechanical data	73 OA (52 with instability)	6-point Likert scale (Fitzgerald 2004)	Striated instability, modified isokinetic dynamometer for varus-valgus stiffness, linear regression modelling	passive mechanical stiffness associated with instability, reduced in few degrees about neutral axis
Sanchez-Ramirez et al. 2013	Regression analysis biomechanical data	284 OA (81 with instability)	Dichotomised scale (Felson 2007)	Postural control assessed with one leg stance test, dichotomised. Regression analysis with instability as a variable	Instability not associated with postural control
Nguyen et al. 2014	Regression analysis biomechanical data	2120 OA	New Likert scale asking for buckling or giving way in past 3 months/12 months	Poisson regression with robust variance for instability relationship to variables	Instability associated with fear of falling, low balance confidence, activity limitation, and poor physical function
Skou et al. 2014	Regression analysis biomechanical data	100 OA (76 with instability)	5-point Likert scale	Knee confidence (5-point scale from Knee Injury and Osteoarthritis Outcome Score) dependent variable for regression analysis with instability as a variable	Lower knee confidence associated with increased knee instability
Van Der Esch et al. 2016	Regression analysis biomechanical data	201 OA patients	“sensation of an episode of buckling, shifting, or giving	regression analysis of self-reported knee pain, isokinetic muscle strength,	Pain and poor proprioception (detection

			way of the knee in the 6 weeks", dichotomised	proprioception, exercise programs at baseline, and 2 years on.	of knee flexion) related to retained instability.
Schmitt & Rudolph 2008	Gait analysis	20 OA (10 with instability)	6-point Likert scale (Fitzgerald 2004)	Gait analysis, perturbed walking	Limb alignment and laxity not associated with instability, higher muscle activation after perturbation
M. van der Esch et al. 2008	Gait analysis	63 with OA	no striation	Gait analysis varus-valgus movement, with regression analysis	Varus-valgus movement not associated with strength, proprioception, laxity or alignment
Farrokhi et al. 2015	Gait analysis	53 OA (17 with instability)	Dichotomised based on 6-point Likert scale (Fitzgerald 2004) (≤3 indicating instability)	Gait analysis comparing stable and unstable OA knees	Difference in gait parameters between stable and unstable
Gustafson et al. 2016	Gait analysis	52 subjects with OA (17 with instability)	Dichotomised based on 6-point Likert scale (Fitzgerald 2004) (≤3 indicating instability)	Walking knee joint stiffness compared between stable and unstable OA patients	reduced knee joint stiffness associated with knee instability
Sharma et al. 2015	Longitudinal study with baseline gait analysis	212 OA	Dichotomised scale (Felson 2007)	Logistical regression of outcome variables over two years and gait analysis variables	knee instability associated with poor outcome at 2 years in advanced tasks only

Farrokhi et al. 2012	Dynamic Stereo X-ray	14 OA and instability 12 healthy controls	OA subjects only included if ≤3 on 6-point Likert scale (Fitzgerald 2004)	2 groups, dynamic stereo x-ray with 3D CT modelling during treadmill walking. Joint sizes normalised for comparative analysis between groups	reduced flexion and rotation compared with healthy, abduction/adduction increased. No comparison with OA no instability
Farrokhi et al. 2014	Dynamic Stereo X-ray	25 control, 18 OA (11with instability)	Dichotomised based on 6-point Likert scale (Fitzgerald 2004) (≤3 indicating instability)	2 groups, dynamic stereo x-ray with 3D CT modelling during treadmill waking downhill. Joint sizes normalised for comparative analysis between groups	Longer medial contact points and velocities in unstable knees in comparison to osteoarthritis without instability.
Gustafson et al. 2015	Dynamic Stereo X-ray	24 control, 19 OA (11 with instability)	Dichotomised based on 6-point Likert scale (Fitzgerald 2004) (≤3 indicating instability)	Analysis of variance to identify variability of internal knee motion comparing three groups	Increased knee motion variability in patients with OA and instability
Knoop et al. 2013	RCT	159 OA	Inclusion only if instability on dichotomised scale (Felson 2007), or "biomechanically assessed (low bodyweight adjusted hamstring strength, impaired	Randomised controlled trial of physiotherapy protocols in OA with instability, standard therapy vs specific knee stabilisation strategies	No additional value of knee stabilisation training

			proprioception, height, laxity)		
Fleeton et al. 2016	Longitudinal study with regression analysis biomechanical data	388 pre-op OA (281 unstable)	Activities of Daily living from Knee outcome survey	Biomechanical data taken before and after total knee replacement to assess risk factors for ongoing instability following TKA	Stair climb power predictive of instability. Prevalence of instability before and after surgery identified
Freisinger et al. 2016	Gait analysis/intraoperative testing	30 knees (29 patients	KOS activities of daily living score	Regression analysis of factors associated with V-V laxity tested under anaesthesia.	No relationship between instability and V-V laxity in full extension measured under anaesthesia
Soeno et all 2018	Accelerometery	92 Medial pivot TKA	Buckling, shifting, giving way in last three months	ANOVA of RMS of acceleration, ANOVA of FFT of acceleration	No differences between groups

Table 2-2 – Muscle Strength Data

Author, date	Study size	Measurement protocol	Study design	Result
Schmitt et al.2008[19]	52	isokinetic dynamometer, isometric, knee flexed to 90, electrode monitoring, normalised for height, quadriceps only, monitored with EMG	comparison of strength between stable and unstable	no relationship between muscle power and instability
Schmitt and Rudolph 2008[18]	20	isokinetic dynamometer, isometric, knee flexed to 90, electrode monitoring, normalised for height, quadriceps only, monitored with EMG	baseline data taken between stable and unstable subjects	no statistical difference between stable and unstable group
Knoop 2012[2]	283	isokinetic dynamometer, flexion and extension at 60 degrees/s, normalised for body mass	regression analysis for multiple variables in subjects with OA instability vs no instability	reduced muscle strength associated with self-reported instability
Skou 2014[21]	100	isokinetic dynamometer, isometric, 60 degrees flexion, normalised for body mass, quadriceps only	regression analysis for multiple variables between OA patients looking at knee *confidence*	association between worse knee *confidence* and lower quadriceps power
Farrokhi 2015[22]	53	isokinetic dynamometer, isometric, 60 degrees flexion, normalised for body mass, quadriceps only	baseline data taken between stable and unstable subjects	no statistical difference between stable and unstable group
Gustafson 2016[23]	35	isokinetic dynamometer, isometric, 60 degrees flexion, normalised for body mass, quadriceps only	baseline data taken between stable and unstable subjects	no statistical difference between stable and unstable group
Fleeton 2016[6]	388	handheld dynamometer mounted on a jig, isometric, 60 degrees flexion, normalised for body mass, knee flexion and extension	pre- and post-operative testing between stable and unstable knees undergoing TKA, regression analysis for multiple variables	no association between muscle strength and groups of stable, unstable, and resolving instability

Table 2-3 – Accelerometers used in Gait Analysis

Study	Type of accelerometer	Attachment	Parameters measured
Light 1980	"Light weight transducer of extended frequency response"	2 K-wires in proximal tibia, compared with "moulded spreader plate of expanded polyethylene	axial vibrations
LaFortune 1991	triaxial piezo resistive accelerometer (Etran model: EGA3-25D) 6g weight, resonant frequency 1kHz, range ± 25g	4.7mm Steinmann Pin to anterolateral border of tibia in posteromedial direction, 3cm below tibial plateau	3 axes aligned with tibia
Ogata 1997	unidirectional accelerometer (Type 1823, NEC San-ei, Tokyo) (no datasheet available)	adhesive tape to skin overlying the subjects' tibial tubercle	horizontal medial- lateral component of acceleration whilst walking
Yoshimura 2000, 2002, 2003	unidirectional accelerometer (Type 1823, NEC San-ei, Tokyo) (no datasheet available)	adhesive tape to skin overlying the subjects' tibial tubercle	ML accelerations during walking ACL patients
Turcot 2008a,Turcot 2008b, Turcot 2011	two triaxial accelerometers (ADXL320, 5 g) and two triaxial gyroscopes (Murata, ENC-03J,) (both now discontinued) housed in rigid body	Two straps proximally and distally, but also femoral exoskeleton	3d accelerations
Cooper 2009	three orthogonally aligned single axis rate gyroscopes (7 1200 deg/s) and a three-axis accelerometer (7 5 g	not stated. Possibly fabric straps to lateral thigh and shank	flexion-extension at the knee (assumed to be a hinge)

Dejnabadi 2005, Dejnabadi 2006, Jolles 2012	sensor modules containing dual axis accelerometer chips ADXL202/210 and yaw rate gyro chips ADXRS150/300	mounted on thigh and shank using straps, sensor axes adjusted to AP plane	virtual assessment of knee joint centre
Khan 2013	tri-axial accelerometer (GLI interactie LLC, Seattle, WA) 2g, 100Hz	Rubber strap to proximal tibia at tibial tubercle aligned to axis of tibia. (Compared with "rigid fixation to plastic tibia").	AP direction accelerations
Roberts 2013	triaxial accelerometer, tri-axial gyroscope, tri-axial magnetometer.	Strap, with 5mm rubber pad between skin and IMU, located over tibial tuberosity.	"Jerk" movement in 3 planes
McCarthy 2013	IMU - 3 orthogonal gyroscopes and 3 orthogonal accelerometers, as used by Cooper et al. in an earlier study on joint angles	straps - on the calf at the level of belly of gastrocnemius muscle, lateral side of the calf. The strap was then fastened securely over the pocket.	knee joint flexion-extension
Monda 2015	an IMU system containing three orthogonal gyroscopes and three orthogonal accelerometers (GaitSmart, ETB, UK)	Velcro thigh and shank straps with attachment from thigh to belt. IMU located in pocket in elastic strap.	Range of movement only in knee flexion-extension
Rahman 2015	GaitSmart, ETB, UK three tri-axial accelerometers and three tri-axial gyroscopes (as Monda 2015)	Velcro straps, one to each thigh and shank with belt round the waist (as Monda 2015)	knee flexion

CHAPTER 3 – AIMS AND OBJECTIVES

This thesis will explore the topic of instability in the osteoarthritic and prosthetic knee, from the stand point of our described framework, namely that instability is the failure of countering mechanism – bony architecture, ligaments, menisci, tendons, capsule, muscles etc. – to return the knee to its resting point following a physiologically relevant impulse across the knee, and that symptomatic instability in the knee is the state in which the knee is frequently approaching the boundary between impulses that can and cannot be controlled such that the patient is increasingly conscious of the danger of exceeding limitations. The frequency of such patient reported symptoms will be examined in OA knees and prosthetic knees, as well as an examination of frequency of instability as a reason for revision in the TKA in a local population. Further, a method of measuring instability in the knee will be devised and explored in both TKA and OA populations.

Research has demonstrated the reduced stiffness in the symptomatically unstable knee (Dixon *et al.*, 2010; Mark W Creaby *et al.*, 2010), increased contact point variability (Farrokhi *et al.*, 2014; Gustafson *et al.*, 2015) and the potential of accelerometery in measuring this aberrant movement (Khan *et al.*, 2013; Roberts *et al.*, 2013). The hypothesis of this study is that the accelerations of the knee in the frontal plane during normal walking used to distinguish symptomatically stable and unstable knees in the prosthetic and OA situation.

The aim of this study is to develop and validate a protocol for the objective

classification and quantification of instability in the arthritic and prosthetic knee that is applicable to an outpatient clinic setting.

In attempting to achieve this aim, the following objectives will be approached:

1. Define the extent of pre-operative symptomatic instability in a pre-operative OA knee population
2. Define the proportion of TKA revised for instability
3. Develop a new protocol for the assessment of knee instability in osteoarthritic and post-arthroplasty patients using existing technologies, specifically the accelerometer
4. Validate its use on a healthy subject group
5. Identify differences between symptomatically stable and unstable post-operative TKA patients using a new protocol
6. Objectively classify OA knees as stable or unstable based upon the new protocol.

CHAPTER 4 - PREVELANCE OF INSTABILITY IN AN OSTEOARTHRITIC POPULATION – DATA FROM NHS DIGITAL PATIENT REPORTED OUTCOME MEASURES DATASET

4.1 INTRODUCTION

In this section, the prevalence of symptomatic instability in the OA knee is examined, along with the association between pre- and post-operative symptomatic knee instability. As previously described, symptomatic instability in the knee is where the patient feels that the knee may be about to, or actually does, give way. Often described as a feeling of "buckling", "slipping" or "loss of confidence," it is a common complaint in arthritis of the knee (Fitzgerald, Piva and Irrgang, 2004; Knoop *et al.*, 2012; van der Esch *et al.*, 2012; Nguyen *et al.*, 2014; Fleeton *et al.*, 2016) and commonly assessed through Patient Reported Outcome Measures such as the Oxford Knee Score (OKS) or Knee Outcome Survey (KOS). However, its prevalence in an osteoarthritic population has not been described. Its importance as a symptom is well documented, associated with reduced levels of activities of daily living (Fitzgerald, Piva and Irrgang, 2004; Nguyen *et al.*, 2014) and increased risk of falls (Nevitt *et al.*, 2016), and thus the improvement of stability is an important outcome for arthroplasty patients (Lange *et al.*, 2017). Further, post-operative instability is a common source of dissatisfaction and revision in total knee arthroplasty (Sharkey *et al.*, 2002, 2014; Yercan *et al.*, 2005; Kelly G Vince, Abdeen and Sugimori, 2006; Kelly G. Vince, Abdeen and Sugimori, 2006; Le *et al.*, 2014; Lombardi, Berend and Adams, 2014; Thiele *et al.*, 2015; Vince, 2016; Wilson *et al.*, 2017), yet the associated between pre- and post- operative symptomatic instability has also not been described.

In total knee replacement, the pathological joint surfaces are resected and replaced with synthetic components in an attempt to create a stable, well balanced joint. However, this addresses a limited number of components only in within the knee control system (*see Figure 1-3 – Simplified control system diagram of knee stability in sagittal* plane). Should the mechanisms present to dampen destabilising impulses around the knee be sufficiently disrupted it may be that restoration of a congruent joint surface, correct alignment and well-balanced ligaments from a well performed total knee replacement are insufficient in creating a "stable" joint. The hypothesis of this study is that there is an association between pre-operative symptomatic instability of the knee with end stage osteoarthritis, and symptomatic instability of the knee following total knee replacement.

To assess instability, the lack of objective, quantitative measures of instability has led to the use of either a single question being asked, e.g. "have you had an episode in the past 3 months where your knee buckled or gave way?" (Felson *et al.*, 2007; Knoop *et al.*, 2012, 2013; van der Esch *et al.*, 2012; Sharma *et al.*, 2015), or a Likert scale created from the activities of daily living items from the KOS (Fitzgerald, Piva and Irrgang, 2004; Schmitt and Rudolph, 2008; Farrokhi *et al.*, 2012, 2015; Kavchak *et al.*, 2012; Creaby *et al.*, 2013). These latter items are similar in nature to the question "during the past 4 weeks have you felt that your knee might suddenly "give way" or let you down?", found in the widely-used OKS. Therefore, this chapter aims to describe the prevalence of symptomatic knee instability in end stage osteoarthritis, as determined by question 10 of the OKS, and the association between this and post-operative symptomatic instability following TKR.

4.2 PATIENTS AND METHODS

Retrospective data from the was taken from the NHS digital Patient Reported Outcome Measures dataset available under the Open Government Licence v.2.0 (http://www.nationalarchives.gov.uk/doc/open-government-licence/version/2/) for all patients undergoing primary total knee replacement in England in the financial year 2015-2016 (NHS Digital, 2016). This data is freely available from NHS digital for analysis and was chosen as it represents a large volume, population level dataset of patients with end stage osteoarthritis of the knee. The data is anonymised in its published form but includes limited demographic data such as patient age category and gender, as well as pre- and post-operative Patient Reported Outcome Measure data in the form of the OKS. This data was recorded pre-operatively, and at least six-months post-operatively. Where demographic data could allow identification of specific patients the data was redacted prior to database publication and therefore not available. Included patients had completed an OKS pre-operatively, and at least six-months post-operatively.

Distributions of all OKS question responses were determined pre- and post-TKA and individual patients were identified as better, the same, or worse following the procedure, based on the change in pre- and post-op scores. Subsequently, knee stability was dichotomised from the OKS five-point Likert scale question "during the past 4 weeks have you felt that your knee might suddenly "give way" or let you down?". Patients were categorised as unstable if they answered using one of the three most affirmative responses (i.e. often, most or all of the time), and stable otherwise (i.e. never, rarely or sometimes). Statistical analysis was carried out using RStudio software (R Core Team,

2017). Correlation between ordinal data was compared using Spearman's rank correlation coefficient, with dichotomised data compared using chi squared test and odds ratios. Probability of post-operative stability grouping was determined by relative rate of grouping for each pre-operative group.

4.3 RESULTS

45094 patient records were examined. 509 and 602 records did not capture pre-TKA and post-TKA OKS scores respectively, providing 43994 records for analysis. Age and gender information had been redacted from the record in 2746 patients (6%), with more females than males, and a skewed distribution of age ranges, with most of patients aged between 60 and 79 (Table **4-1**).

Table 4-1 – Demographic details of dataset

Demographic	Number (%)
Redacted	2746 (6.24)
40-49	51 (0.12)
50-59	3873 (8.80)
60-69	15216 (34.59)
70-79	17204 (39.11)
80-89	4904 (11.15)
Male	17512 (39.81)
Female	23736 (53.95)

Table 4-2 – Comparison between % respondents indicating best score for each category pre- and post- operatively

Criteria	Pre-op	Post-op	Change
Felt the knee might suddenly give way or let you down	8.2%	60.6%	52.5%
How long could you walk before pain becomes severe	8.0%	56.2%	48.1%
Could you do household shopping on your own	10.0%	52.2%	42.2%
Limping when walking	1.3%	40.1%	38.7%
Pain in the knee interfered with usual work	1.4%	37.4%	36.0%
Could you walk down a flight of stairs	3.7%	37.2%	33.6%
Standing up from a chair	1.9%	34.5%	32.5%
Pain in your knee at night in bed	7.2%	39.3%	32.1%
Trouble washing and drying yourself	33.5%	64.9%	31.5%
Trouble getting in and out of a car or using public transport	7.2%	34.0%	26.8%
Pain you usually have in your knee	0.2%	24.4%	24.2%
Kneel down and get up again	0.5%	7.5%	7.0%

Pre- and post-TKA OKS scores show significant improvements across all areas but to varying degrees: knee “instability” achieves the greatest improvement with a 52.5% point increase in the top response, whilst kneeling showed the least improvement, with a 7% point increase, albeit from a very low (0.5%) pre-TKA prevalence (Table **4-2**). Changes in other categories were also positive, with population statistics improving in each category (figure 4.1, 4.2), however, at the individual level, patients achieved better outcomes for all items at least 50% of the time (figure 4.3).

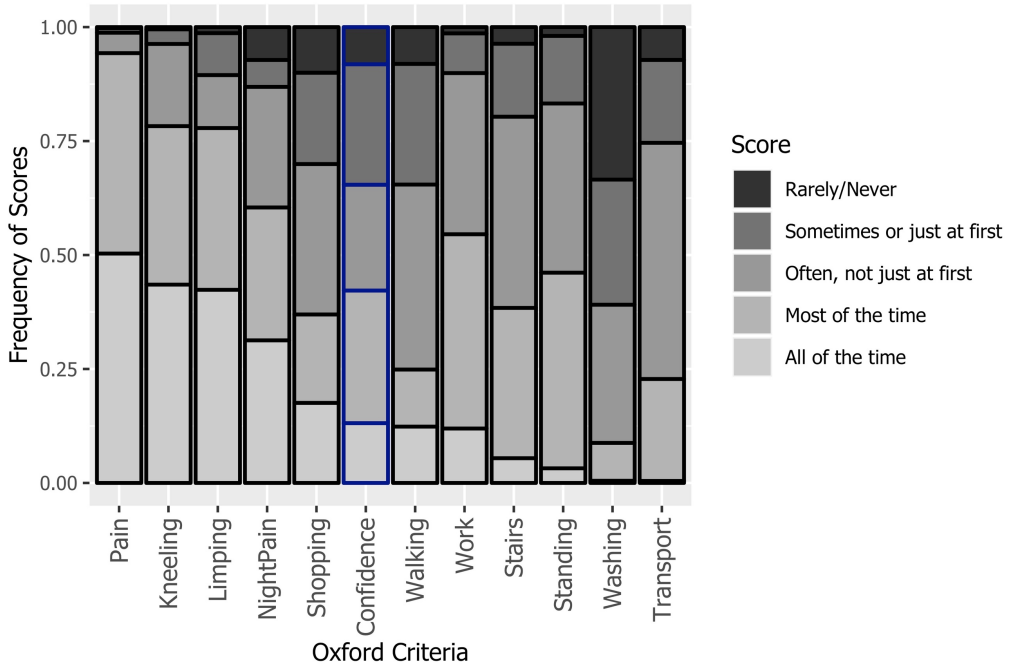

Figure 4-1 – Pre-TKA OKS scores

Results of the OKS in pre-operative subjects, divided into each question, by frequency of responses in population groups. Question 10 result highlighted in blue. Increased severity of symptom indicated by lightened colour.

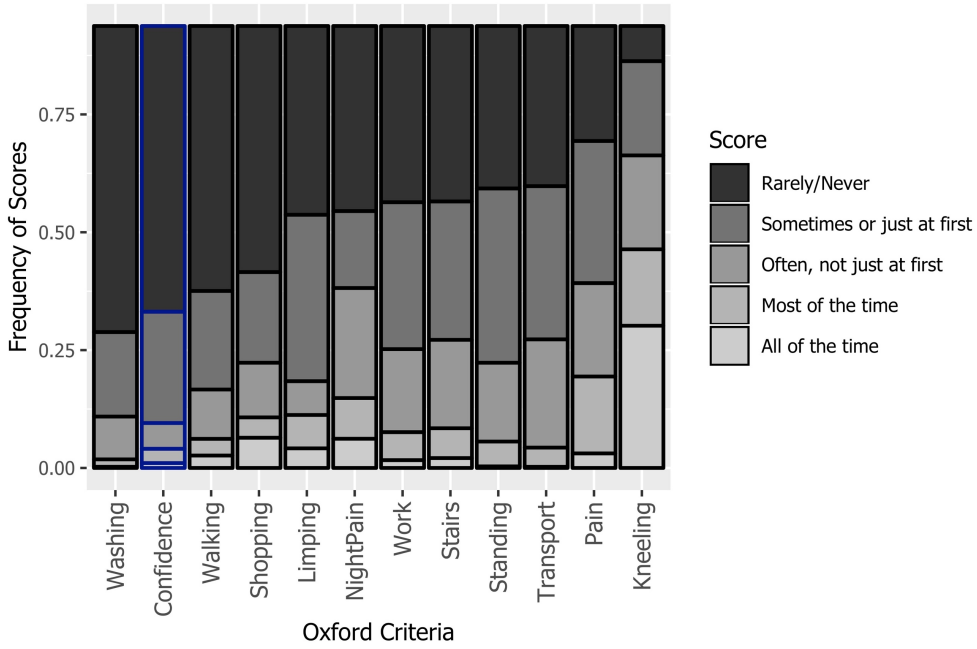

Figure 4-2 – Post-TKA OKS scores

Results of the OKS in post-operative subjects, divided into each question, by frequency of responses in population groups. Question 10 result highlighted in blue. Increased severity of symptom indicated by lightened colour.

Whilst patient-reported stability ("*Have you felt that your knee might suddenly give way or let you down?"*) was the most improved measure overall following TKA, improvement was dependent upon pre-operative score ($\rho = 0.234$, $p < 0.001$, Table 4-5). Most patients reported a post-operative answer of "rarely/never", however the proportion of patients reporting more instability increased with pre-operative instability ($p<0.001$) (figure 4.4). For those with pre-operatively unstable knees "All of the time", the probability of post-operative instability "Rarely/Never" was approximately 50%. However, for those with pre-operative instability "Rarely/Never", the same outcome arose 85.7% of the time (figure 4.4). For the worst post-operative outcome (instability "all of the time), the probabilities were 11.7% and 0.7% respectively for those with the worst and best pre-operative scores (figure 4.4).

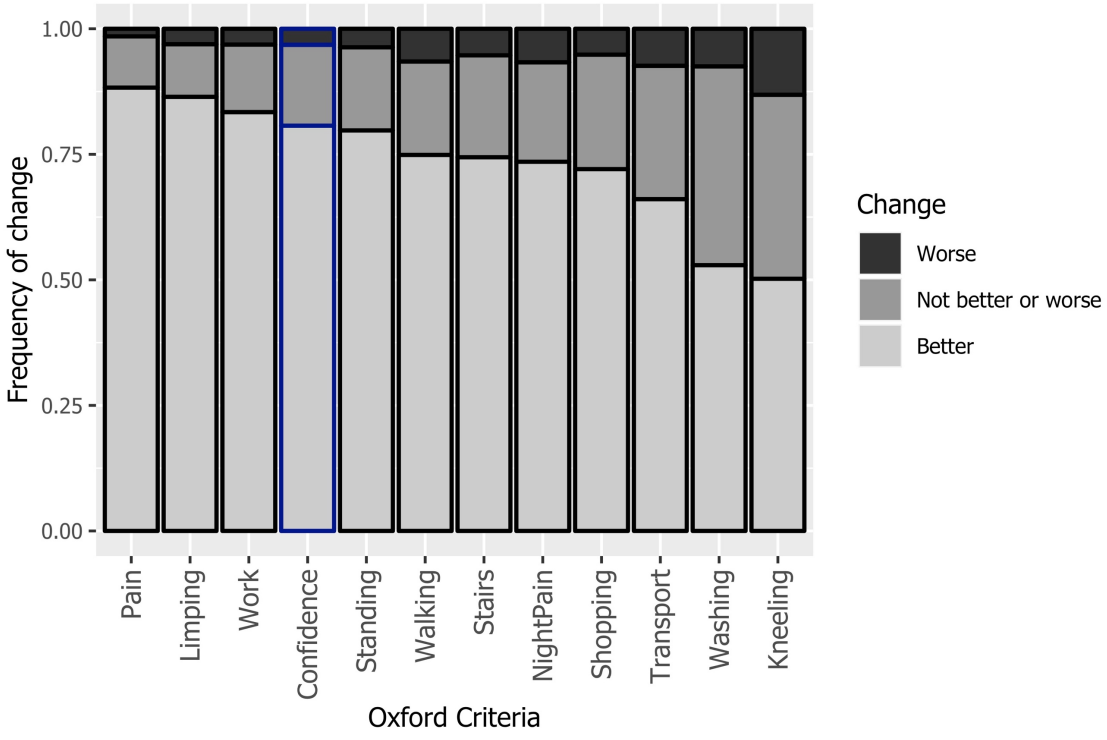

Figure 4-3 – Change in item score following TKA, in terms of better, the same, or worse
Confidence highlighted in blue

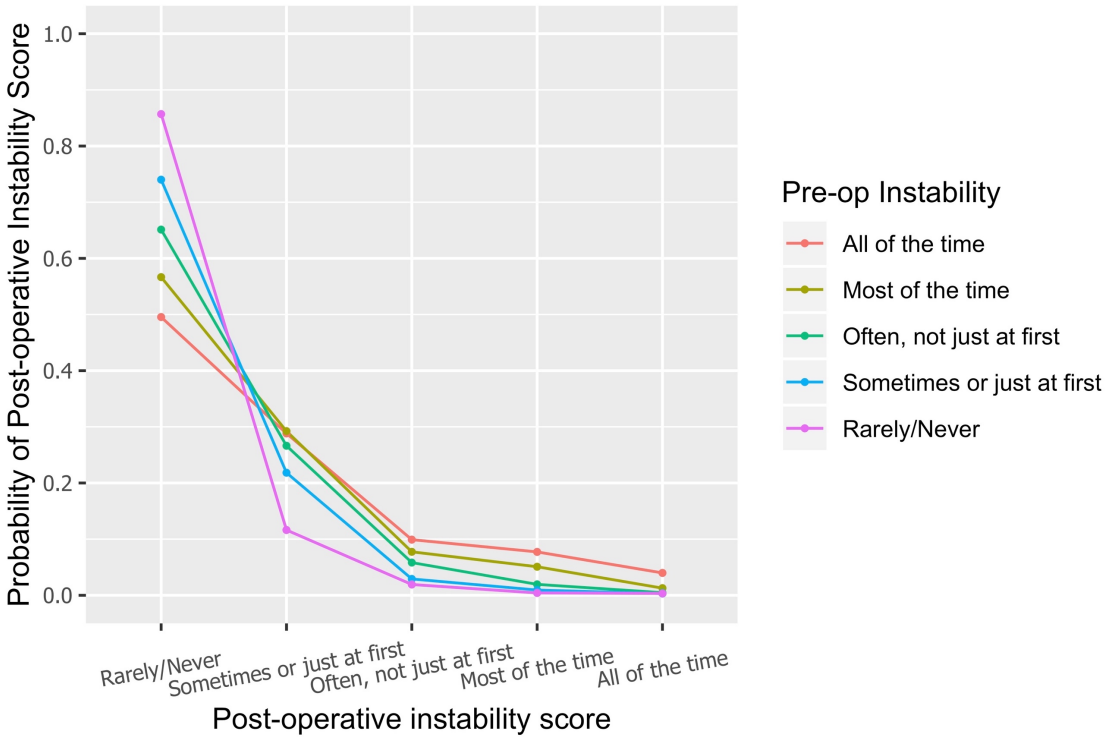

Figure 4-4 – Frequency of post-TKA instability score by pre-TKA instability score. Probability of post-operative instability classification calculated as rate of post-operative instability in each pre-operative instability group in our dataset

As defined by the described dichotomous measure of instability, 65.4% of patients have pre-TKA instability, reducing to 10.2% post-TKA, while only 8.2% of pre-op patients describe the best score, rising to 64.6% post-operatively (Table 4-3). For the dichotomised groupings, 86.5% of unstable pre-TKA knees became stable, whilst 3.8% of stable knees were unstable post-TKA Table 4-5 Post-operative stability was

Table 4-3 – Percentage distribution of pre- and post-operative knee instability scores

Score	Pre-TKA %		Post-TKA %	
All of the time	13.1		1.1	
Most of the time	29.1	65.4	3.2	10.2
Often, not just at first	23.2		5.8	
Sometimes or just at first	26.4	34.6	25.2	89.8
Rarely/Never	8.2		64.6	

Table 4-4 – Percentage dichotomised post-operative knee instability in each category of pre-TKA knee instability score

	Pre-TKA				
Post-TKA dichotomised stability	**All the time**	**Most of the time**	**Often, not just at first**	**Sometimes or just at first**	**Rarely /never**
unstable	21.6	14.1	8.2	4.2	2.7
stable	78.4	85.9	91.8	95.8	97.3

significantly more likely in pre-operatively stable patients (OR 3.95 (3.61, 4.32)), males (OR 0.87 (0.82, 0.93)), and those over 60 (OR 2.06 (1.88, 2.25), Table 4-5).

Of those unstable "all of the time" pre-TKA, 78.2% achieved stability post-TKA; conversely there was a 2.7% prevalence of having an unstable knee post-TKA if the

Table 4-5 – Dichotomised post-TKA knee stability counts by pre-TKA categories. Percentages reflect percentage of post-TKA outcome in each pre-TKA category

		Post-TKA dichotomised stability			
Pre-TKA dichotomised stability		**unstable**	**stable**	**p**	**OR (95% CI)**
stability	Stable	580 (3.8%)	14633 (96.2%)	<0.001	3.95 (3.61, 4.32)
	Unstable	3895 (13.5%)	24886 (86.5%)		
Gender	Male	1636 (9.3%)	15876 (90.7%)	<0.001	0.87 (0.82, 0.93)
	Female	2505 (10.6%)	21231 (89.4%)		
Age	>60	2250 (11.8%)	16890 (88.2%)	<0.001	1.42 (1.34, 1.52)
	<60	1891 (8.6%)	20217 (91.4%)		

Table 4-6 – Change in stability by pre-operative instability

OKS	Better	Not better or worse	Worse	Total
All of the time	5542 (96.0%)	230 (4.0%)	0	5772
Most of the time	11985 (93.6%)	651 (5.1%)	163 (1.3%)	12799
Often, not just at first	9368 (91.8%)	595 (5.8%)	247 (2.4%)	10210
Sometimes or just at first	8606 (74.1%)	2538 (21.8%)	484 (4.2%)	11628
Rarely/Never	0	3072 (85.7%)	513 (14.3%)	3585

knee was "rarely/never" unstable pre-TKA (Table 4-3). At an individual, patient level, there was a 96% likelihood of having a better instability score if the knee was unstable "all of the time", and a 14.3% likelihood of having a worse instability score if the knee was "rarely/never" unstable (Table 4-6).

4.4 DISCUSSION

As far as is known, this is the largest data analysis to present the results of individual Oxford Knee score criteria for patients attending TKA. This study has quantified the problem of symptomatic instability in the knee, with 65.4% of patients attending for total knee replacement in a national population having an unstable knee by the study definition. As feelings of instability correlate with patients' activities of daily living (Fitzgerald, Piva and Irrgang, 2004; Nguyen *et al.*, 2014), this suggests that there is a significant morbidity associated with knee instability at a population level. Further, this data underlines the effectiveness of total knee replacement in improving subjective knee instability in total knee replacement, as this prevalence reduces to 10.2%.

However, it is notable that there is a cohort of patients who continue to experience severe instability in the knee following total knee replacement (Figure 4-3). As post-operative instability is a recognised cause of failure in total knee replacement (Sharkey *et al.*, 2002, 2014; Yercan *et al.*, 2005; Kelly G Vince, Abdeen and Sugimori, 2006; Kelly G. Vince, Abdeen and Sugimori, 2006; Le *et al.*, 2014; Lombardi, Berend and Adams, 2014; Thiele *et al.*, 2015; Vince, 2016; Wilson *et al.*, 2017) it is useful both to the surgeon and the patient that the risk of post-operative symptomatic instability may be determined from pre-operative scoring. Our data analysis show that preoperative instability, female gender, and younger age all correlate with increased odds of post-operative symptomatic instability. This data is consistent with previous studies findings of lower fulfilled expectations in female patient (Baker *et al.*, 2007; Gandhi *et al.*, 2009), and high rates of symptom retention in younger patients (Parvizi *et al.*, 2014). Correlation between pre-and post-operative severe instability may be due to an inability to correct all defective stabilising mechanisms through a joint replacement procedure in severely symptomatically unstable patients. Arthroplasty aims to restores joint alignment, ligament balance and improve joint congruence, however other aspects such as proprioception or muscle strength are not addressed. Female gender correlates with decreased muscle strength, and this is a possible contributing to the association here with retained instability for the same reason. It is proposed that likely increased severity of disease process in those undergoing TKA at a younger age may correlate to increased difficulty in reconstructing well balanced, well aligned joint, leading to increased difficulty in providing stability.

These data may be used in patient pre-operative education as they will allow realistic goal setting for expectations such as kneeling, using transport and being completely pain free. A recent Delphi consensus study examined which outcomes were deemed necessary for a successful operation (Lange *et al.*, 2017). Of those results deemed necessary by patients for operation success, six are similar to those examined in the Oxford score: Physical function (OKS question "does pain in the knee interfere with your usual work"), pain ("do you have pain in your knee at night", "How severe is the pain you usually have in your knee"), walking distance ("how long could you walk before the pain becomes severe"), walking stairs ("could you walk down a flight of stairs"), physical activity ("how long could you walk before the pain becomes severe") and knee stability ("how often do you feel the knee might suddenly give way or let you down"). From this data analysis it is clear that symptom reduction can be expected across all categories in the Oxford Knee Score (Figure 4-3). However, in this subject group the best OKS category ("rarely or never" experiencing symptoms) can be expected by more than half of patients in only knee confidence, walking distance and household shopping (Figure 4-2).

This statistic has significant implications for pre-operative counselling as fulfilment of patient expectation has been shown to be strongly associated with satisfaction (Scott *et al.*, 2012). It is notable that while a recent study indicated ability to walk down stairs and get on and off public transport/and or drive as being among the most important expectations for pre-operative TKA patients (J. Smith *et al.*, 2016) this analysis suggests that for most patients these symptoms will not be completely relieved in 66.4% and 73.2% of cases respectively (Table 4-2), and may not have improved at all in 20.3%

and 33.9% of cases respectively (Figure 4-2). These results also have relevance to the understanding of knee instability. Should instability be caused by alignment, cartilage morphology or another knee structure-specific mechanism, it would be likely that TKA would remove this variability. The low correlation ($\rho = 0.234$) between pre and post-operative instability scores across the 5-point scale, suggesting that just over 5% of the variability in post-operative score is explained by the pre-operative score, and since TKA made an unstable knee stable in 86.5% of cases (table 4), one could say that instability is well-addressed by the intra-operative biomechanical adjustment of the knee by the surgeon. However, with 13.5% of unstable knees remaining unstable, and with post-operatively symptomatic instability occurring more commonly with pre-operative instability with an odds ratio of 3.95, further analysis of these cases is warranted to ascertain the reasons for this. It is suggested therefore that other factors beyond those within the knee joint itself may be responsible for feelings of instability or loss of confidence, and that those are not addressed at the time of surgery. More concerning is the 3.8% of stable knees that became unstable post-operatively. The population level database examined here does not allow assessment as to possible surgical reasons for this, such as prosthesis choice, resection level or soft tissue balancing, however the relatively high level of this complication in a previously stable knee is significant and requires further investigation. Nevertheless, there remains the possibility that instability has an aetiological element which is not addressed by arthroplasty, with some knees being inherently unstable for some other anatomical or physiological reason. This may relate to other mechanisms within the control system of the knee such as proprioception, muscle strength and patterning which are not addressed by the procedure. While failure to address these mechanisms is not in itself a failing of the surgical technique, recognition of the broader context of symptomatic knee

instability is important. From the data analysis here, it suggests that a patient with the most sever symptomatic knee instability pre-operatively must be counselled as to the increased risk of post-operative symptomatic instability. Further, this extrinsic element to the instability may have impact upon level of constraint required in revision surgery for instability.

Several limitations exist within this study due to the use of registry data. Firstly, it relies on the accuracy of its recording. While this could not be verified by the authors, its authoritative source is recognised. The data set contains no information on implant type, surgical approach or surgeon technical skill, and some aspects of demographics such as age and gender have been partially blinded for reasons of data protection limiting the scope of the analysis. However, the analysis presented still allows overview data of outcome at a population level. Another limitation is that the study analysis has dichotomised the 5 possible responses to question 10 of the OKS into unstable and stable, opting to choose the best two responses as stable (rarely/never and sometimes) and the other three defining an unstable knee. It may be argued that having a knee that is "sometimes" unstable, or unstable "at first", should be classified as unstable. Thus, the classification is necessarily somewhat arbitrary, which may be linked to the lack of quantitative measures of instability.

4.5 CONCLUSIONS

The findings of this study demonstrate the improvement of patient symptoms in the categories of the Oxford knee score following TKA. This should allow better patient

expectation management by clinicians at pre-operative assessment. Further, the frequency of pre-operative symptomatic instability has been shown, with 65.4% of patients reporting feelings of instability at least “often”. It has been shown that pre-operative symptomatic knee instability is predictive of post-operative symptomatic knee instability (OR 3.95, $\rho = 0.234$, $p < 0.001$), suggesting that patients with significant preoperative symptomatic instability must be warned of the risk of ongoing post-operative symptoms. This suggests that symptomatic instability in the knee is multifactorial and must be accounted for beyond just the knee joint, lending evidence to our understanding of knee stability as a system of controls, failure of which results in perceived risk of, or absolute, failure (Figure 1 4 – Diagrammatic representation of the knee undergoing multiple impulses).– Diagrammatic representation of the knee undergoing multiple impulses

CHAPTER 5 – EXPLORATION OF AN ACCELEROMETER DEVICE

This chapter describes the choice and exploration of the use of an accelerometer device for the assessment of symptomatic instability in the knee. As previously described, this is based on the understanding of "instability" in the knee as a system control problem. An impulse acts upon the knee, this destabilises the normal course of movement, and it is countered by a restraint – active or passive, conscious or unconscious. It is proposed that the use of an accelerometer will allow detection of the increased movements at the knee joint that result in this perception of instability. In this section, the selection and early work examining the use of an accelerometer device will be described, ending with a developed method for testing its use in the assessment of knee movement.

5.1 DEVELOPMENT OF ATTACHMENT

Various different types of accelerometer have been used for gait analysis, either custom made or commercially bought (Table **2-3** – Accelerometers used in Gait Analysis). A convenience choice of an accelerometric node of a body sensor network was made (G-Link, LORD Microstrain, Williston, VT) This comprised an external housing of 58 mm x 43 mm x 26 mm, and weight of 46 grams containing two dual axis, orthogonally mounted ADXL210 MEMS accelerometers (Analogue Devices, Norwood, MA) operating at a range of +/-10g, low pass filtered using a 0.022 uF capacitor, and broadcast using a 2.4GHz radio frequency transceiver from an omnidirectional antenna with a line of site range of 2000m. The signal is received through a USB connected 2.4GHz radio frequency transceiver connected to a personal computer and processed using proprietary Node Commander® software (G-Link, LORD Microstrain, Williston,

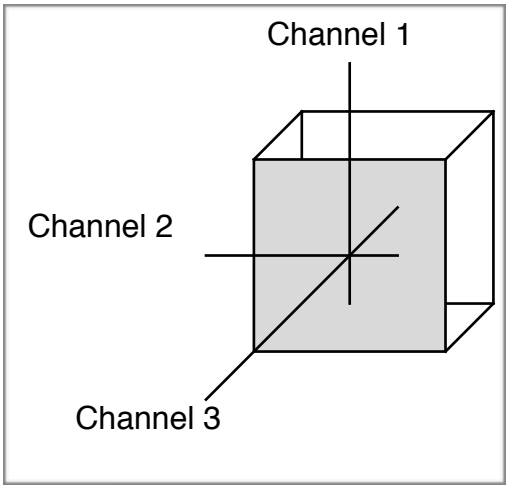

Figure 5-1 - Diagrammatic representation of accelerometer channel

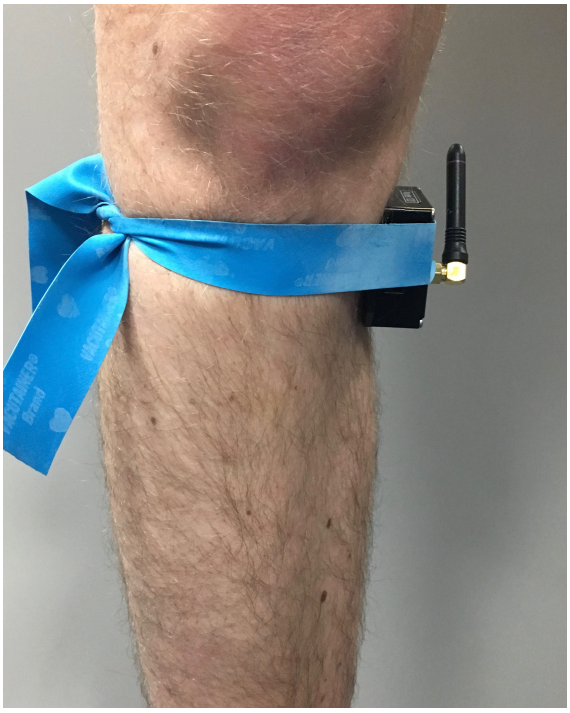

Figure 5-2 – Accelerometer secured with rubber band

VT). Axial and coronal output channels were selected for analysis, giving an output frame rate of 679Hz.

$$m = \frac{2 \times g}{\bar{n} - \bar{p} - \bar{f}}$$

Equation 5-1 – Accelerometer slope calculation
Where m = slope, g = gravitational force = 9.81m/s^{-2},
$\bar{n}$= inverted accelerometer reading, $\bar{p}$ = correctly orientated accelerometer reading,
$\bar{f}$ = flat accelerometer reading

$$c = \bar{f} \times (-m)$$

Equation 5-2 – Accelerometer offset calculation
Where c = offset, $\bar{f}$ = flat accelerometer reading, m = calculated slope

```
function  accelerometer_callibration(inputfile)

%% ACCELEROMETER_CALIBRATION calculates slope and offset for the
accelerometer
% based upon an output file created when M=1 and C=0.  Data must be
% recorded for 5 SECONDS flat, 5 SECONDS vertical and 5 SECONDS
% horizontally on the antenna.  Outputs for the function are M, the slope,
% and C, the offset.  INPUTFILE is given as the .csv file created in nodecomander

x = csvread(inputfile, 21,1);
gravitational_force = mean(x(1000:3000));
zero_gravity = mean(x(5000:7000));
negative_gravity = mean(x(9000:11000));
m = -1 *(2* (-9.81) - 0 - 9.81)/ (2 * negative_gravity - zero_gravity -
gravitational_force);
c = zero_gravity * (-m);
output = [m;c];
fprintf('slope of accelerometer is %d\n offset of accelerometer is %d\n',m,c)
dlmwrite('calibration file.csv',output,'precision',6)
```

Equation 5-3 – MATLAB code to calibrate accelerometer

The accelerometer gives outputs in three channels, each corresponding to a face of the housing (Figure 5-1). Channel 1 gives a gravitational force and Channel 3 gives frontal plane

movement when the accelerometer is mounted medially or laterally on a vertical tibia. A calibration protocol for the accelerometer was developed using a routine of collecting

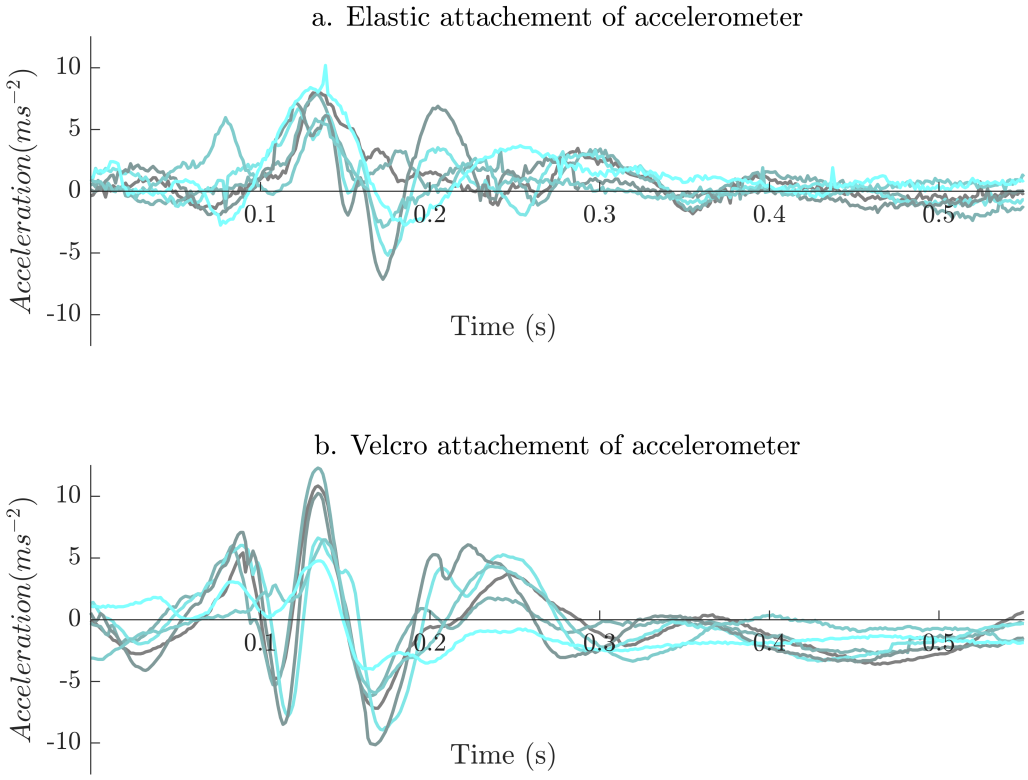

Figure 5-3 – Comparison of fixation methods.
Graph (a) shows six manually extracted steps in one subject during flat walking using the elastic attachment, with graph (b) showing the modified mount using a metal backing and Velcro straps. Visual review shows a clear reducing in 'noise', understood to be movement of the accelerometer against the skin, with the modified attachment. Time synchronised to peak acceleration

data from the vertical channel 1 for 5 vertical, 5 seconds 90 degrees from vertical, and 5 seconds 180 degrees from vertical with slope set to 1 and offset to 0. The data was then assessed with a custom-made MATLAB program to calculate slope and offset, using data sampled for the central 2000 frames for each orientation, and the slope calibrated as in equation 5.1 and offset as in equation 5.2, and the accelerometer rechecked with the values inputted (Equation 5.3).

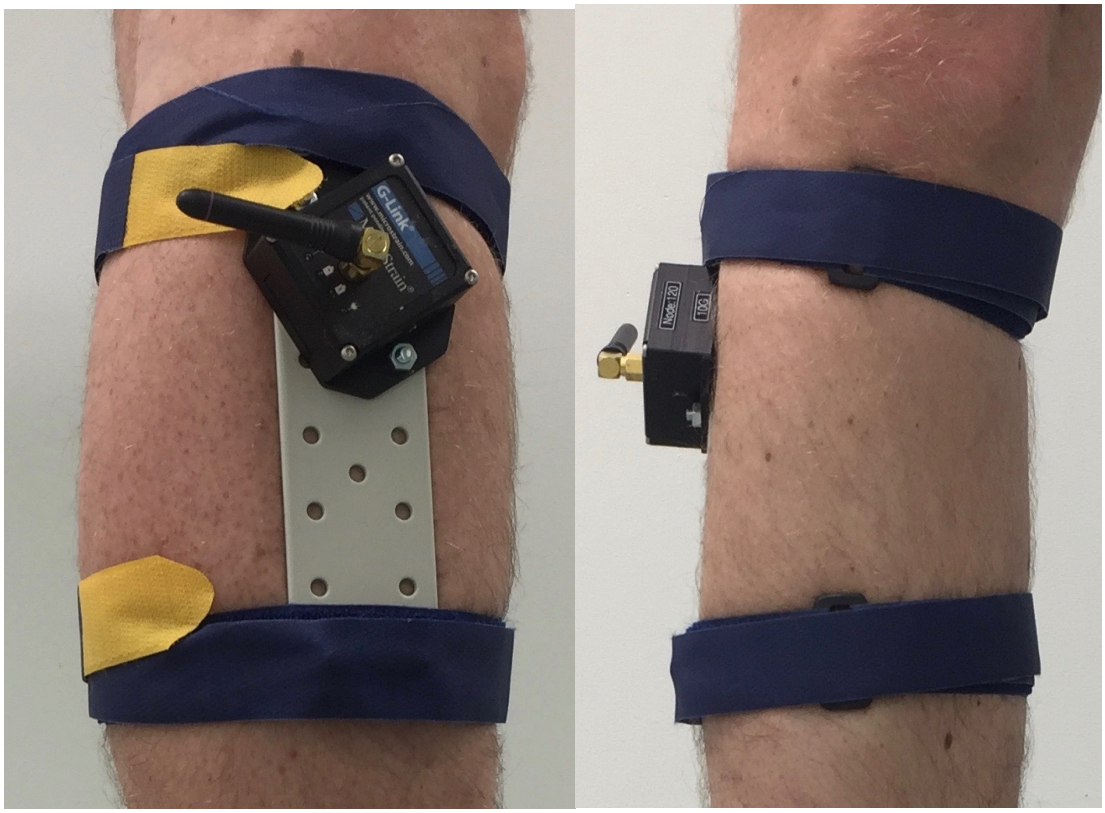

Figure 5-4 – Accelerometer with mount in situ

Several different methods of attachment have been described including tape, elastic, Velcro and exoskeleton construction (Table **2-3** – Accelerometers used in Gait Analysis). Initial testing of the accelerometer was therefore carried out using an elastic band (Stretch, BD, USA) holding the accelerometer to the medial aspect of the researcher's tibia, 2cm distal to the joint line (Figure 5-2)

Preliminary walking tests were carried out in the laboratory to assess the effectiveness of this attachment, with high speed video recording of accelerometer movement during gait (iPhone 6, Apple, CA). Initial walking tests showed movement of the accelerometer separate to the skin. Output from the accelerometer was reviewed and

manually reconstructed to show individual strides by identifying the negative peak of the graph corresponding to heel strike. Review showed significant vibration throughout the gait cycle, thought to be a representation of this movement of accelerometer against the skin seen on video analysis of the steps.

Further, initial tests showed that while the medial surface of the tibia gave a flat surface for attachment of the accelerometer, it was liable to interfere with the swing phase of normal walking. Despite the difficulties inherent with lateral placement (prominence of the lateral aspect of the head of fibula), the decision was made to attach the device laterally. The accelerometer unit was mounted on a pre-drilled 140mm x 60mm metal base plate (B&Q), secured with proximal and distal Velcro straps attached to the plate using screws and washers, and attached to the proximal tibia with the measurement unit sitting 2cm under the lateral joint line, under flare of tibial plateau, at 90 degrees to the frontal plane (Figure 5-4)

Output from the two attachments were examined graphically looking solely at the frontal plane in one subject (DTW), with each trial consisting of six manually extracted steps from normal walking on a flat surface. Visual comparison of the wave forms reveals significantly reduced noise using the Velcro and baseplate setup with lateral attachment in comparison to rubber band and medial attachment (Figure 5-3). Consequently, Velcro setup was adopted for subsequent testing.

5.2 DESCRIPTION AND ANALYSIS OF OUTPUT

The aim of creating a clinic-applicable system resulted in the need to develop a system to identify gait events from accelerometer output only. This requires the identification of a repeatable pattern of accelerometer output and with a matching of the pattern to gait events. This pattern be tested against known quantifications of gait parameters. While frontal plane movement is unaltered by sagittal plane rotation during gait, axial and sagittal outputs from an accelerometer attached to the shank are vulnerable to altered output during gait cycle. From heel strike to toe off the accelerometer rotates in the sagittal plane through 77 degrees (Figure 5-5). Consequently, in the absence of gyroscopic correction, the vertical and horizontal channels produce data that is hard to interpret as incline alters the magnitude of both the gravitational force and of forwards acceleration with respect to the horizontal plane. The decision was therefore taken to identify information from the single channel only

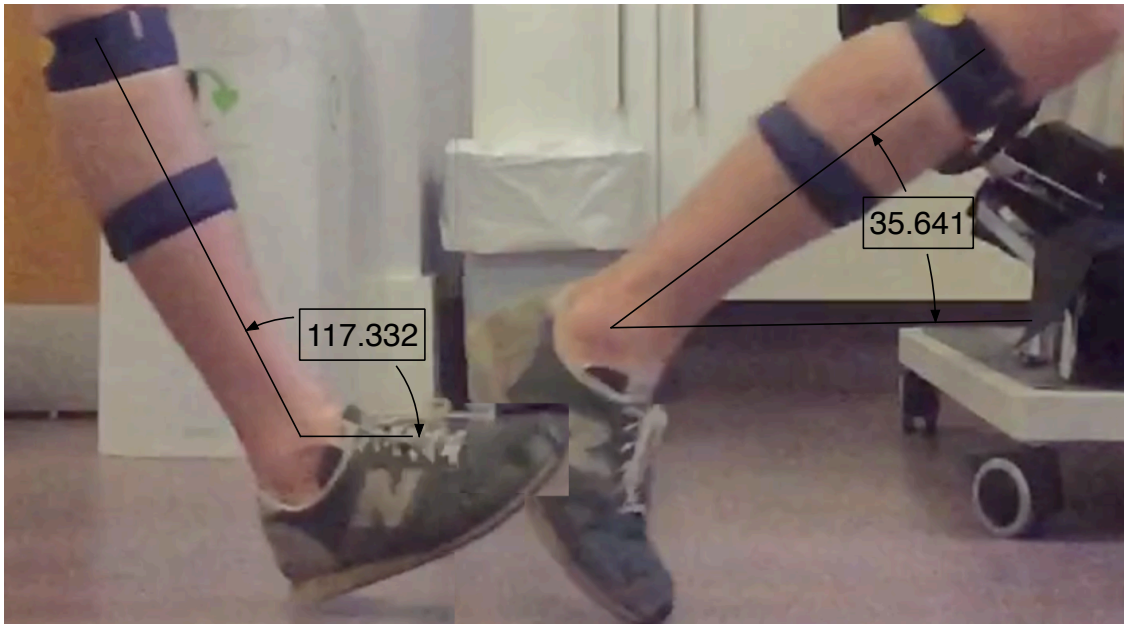

Figure 5-5 – Shank position change during stance phase

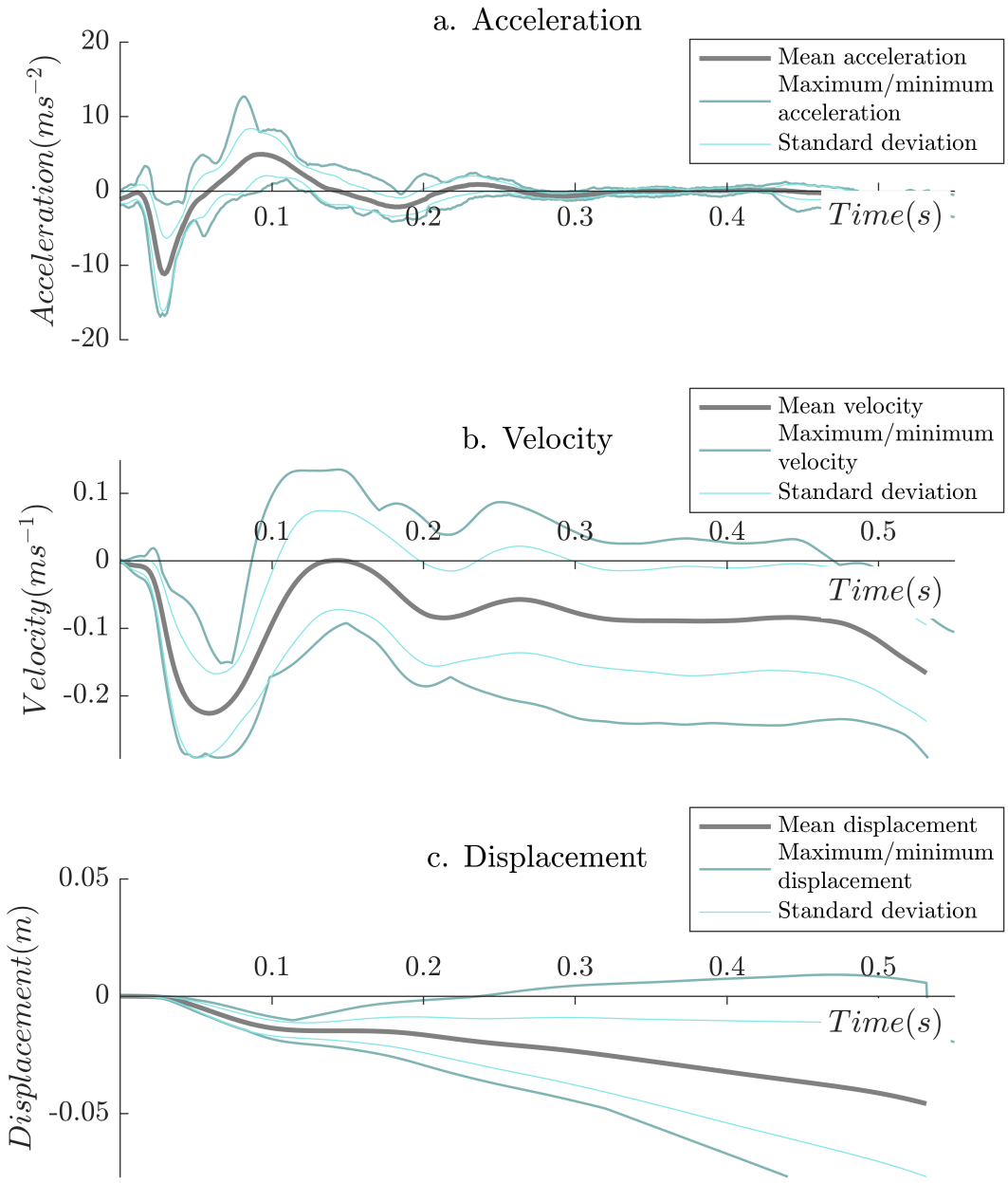

Figure 5-6 – Acceleration, relative velocity and displacement averaged over 11 steps. Each graph shows mean, standard deviation, maximum and minimum tracing. Positive Y-axis movement indicates lateral values, with negative indicating medial. Initial velocity at time zero taken as zero.

Preliminary data output for medial lateral movement over 4 test runs comprising 11 steps sampling at 679 Hz was compared for stance phase. This was identified using

data from channel 3. As previously, a maximal transient impulse was present at the start of each stride, corresponding to the jerk of heel strike, and seen in all three planes during earlier testing. This was used to synchronise all strides. Results are shown in Figure 5-6 from 20 frames prior heel strike 0.5s, corresponding to stance phase, moving towards swing. Medial lateral accelerations with their standard deviations are shown in Figure 5-6a. This data shows a clear pattern of acceleration early in stance phase. While the relative velocity and displacement with regards to starting velocity and displacement were calculated by finding the integral of this data (Figure 5-6b) with its double integral representing displacement (Figure 5-6c), the absence of recorded time zero velocity gives limited value to this calculated value, as noted by its heteroscedastic characteristic as time increases, indicative of cumulative error.

The repeatable nature of this acceleration over multiple steps indicates the promise of this method in the analysis of gait. The output implies hard impact associated with heel strike, followed by a lateral acceleration.

5.3 DEVELOPMENT OF A PROCEDURE FOR DATA RECORDING, EXTRACTION AND ANALYSIS

In order to test the repeatability of the device for use in preliminary trials, an initial trial protocol and analysis was devised.

Repeatability of attachment was tested over 4 walking trials conducted on one individual on one day, each comprising approximately ten steps with the Velcro and baseplate configuration. The accelerometer was not removed between acquisitions. The trial was repeated the following day with a five-step test. The trial was repeated

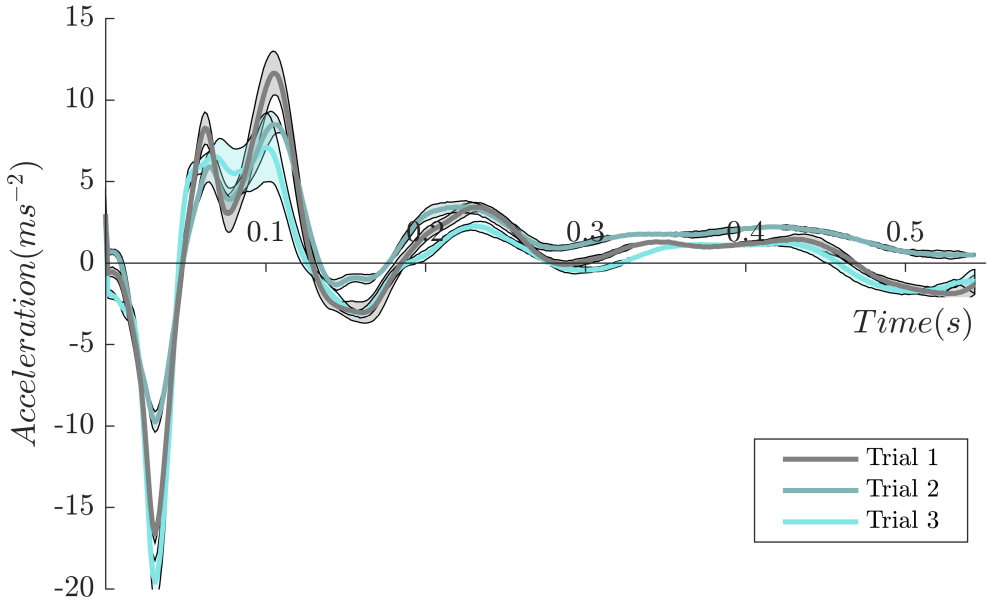

Figure 5-7 – Accelerometer repeatability test.
Three trials conducted over two days on one subject demonstrating repeatability of the waveform between applications of accelerometer. Each line represents one trial, with the shaded area indicating the standard deviation.

after 1 hour and re-application of accelerometer without re-calibration

To facilitate data extraction a custom-made MATLAB program was written by the researcher to extract steps based on peak minimum acceleration (Appendix F – STEP SELECT ACCELEROMETER MULTIFILE). Data was filtered for accelerations >30m/s^2, then peaks corresponding to heel strike are identified as peaks of minimum acceleration. Distance between each peak was calculated to find a stride length, with stance phase assumed to be 60% of total stride. Each stride was extracted from 20 frames prior to peak minimum acceleration to the end of stance phase. Peak acceleration in stance phase and stride length were calculated and averaged to overall strides. Calculated data was saved to a MATLAB data structure as averages of each trial, before the next accelerometer data file was automatically loaded for analysis. This

Table 5-1 – Stride characteristics from single volunteer repeatability trials

Name	Stride Length (s)	Max Acceleration (ms^{-2})	Max Velocity (ms^{-1})	Max Displacement (m)
Trial 1 stride 1	0.992	8.296	0.156	0.007
Trial 1 stride 2	0.955	6.602	0.146	0.007
Trial 1 stride 3	0.953	9.111	0.157	0.002
Trial 1 stride 4	0.954	7.518	0.127	0.000
Trial 1 stride 5	0.962	8.676	0.158	0.007
Trial 2 stride 1	0.988	9.666	0.415	0.127
Trial 2 stride 2	0.975	11.453	0.419	0.126
Trial 2 stride 3	0.977	12.684	0.438	0.124
Trial 2 stride 4	0.975	13.064	0.402	0.116
Trial 2 stride 5	0.960	11.656	0.402	0.105
Trial 3 stride 1	0.855	8.605	0.794	0.199
Trial 3 stride 2	0.835	8.577	0.755	0.176
Trial 3 stride 3	1.015	9.440	0.893	0.284
Trial 3 stride 4	0.897	7.899	0.768	0.212
trial 1 mean ± SD	0.963 (±0.016)	8.040 (±0.995)	0.149 (±0.013)	0.004 (±0.003)
trial 2 mean ± SD	0.975 (±0.010)	11.705 (±1.326)	0.415 (±0.015)	0.120 (±0.009)
trial 3 mean ± SD	0.900 (±0.080)	8.630 (±0.631)	0.802 (±0.062)	0.218 (±0.047)
Mean ± SD	0.949 (±0.052)	9.518 (±1.964)	0.431 (±0.272)	0.107 (±0.092)

allowed rapid analysis of multiple walking trials.

For the combined 14 walking trials the mean with standard deviation, maximum and minimum were examined (Figure 5-7, Table 5-1). This showed similarities between stride length and accelerations with narrow standard deviation, however with velocity

and displacement, identified by integrating and double integrating the acceleration, the standard deviation rises, as does the difference between each trial. Further, the velocities and displacements shown do not hold with simple understanding of the gait process. This may be due to lack of zero-time velocity and displacement data, and cumulative error associated with the integration process creating exponentially increasing velocity and displacement outputs (Figure 5-6). Consequently, acceleration only was used for subsequent work.

5.4 PROGRAM DEVELOPMENT

In order to automate and standardise the analysis of accelerometer output a MATLAB computer program was designed by the researcher to extract acceleration data around each stride rather than from manual data review in a spreadsheet. The program was designed to allow up to six strides to be extracted from each file. The strides were defined as occurring from one heel strike transient to the next. In order to identify strides, the total accelerometer output graph was displayed to the program user with data point number displayed on the x-axis. The user was then asked to input an estimate of the x-value for initial heal strike based on this visual review of the accelerometer graph, along with an estimation of stride duration. The estimated heel strike point is then further explored by identifying the lowest trough location in the surrounding frames and designating this the heel strike point. The estimated stride length is then used to identify subsequent heel strike transients and split the file into strides for analysis. The program was altered to allow examination and analysis different features of the strides such as acceleration and stride length.

5.5 CONCLUSIONS

Following the initial development testing, an accelerometer recording from a single channel, mounted on the proximal tibia has been established as providing a consistent stride pattern with a clear pattern of heel strike transient designating the beginning of stance. This can be used to divide the output into different strides for analysis. In testing of the device on the researcher, the output of the accelerometer appeared to be consistent in stride length and acceleration in multiple testing over different days. Results of integrated signal for velocity and displacement were not found to be useful due to a lack of information on zero-time velocity for the integrative process.

The custom MATLAB program has been developed to allow the researcher to estimate heel strike and stride length and calculate peak acceleration and stride duration. This provides a base for further analysis of collected data. Following this development, it is necessary to collect normal data and show the repeatability on normal knees. To this end, the next chapter will detail the testing of the accelerometer on a healthy participant group.

CHAPTER 6 – HEALTHY SUBJECT TESTING – REPEATABILITY ANALYSIS

6.1. STUDY AIMS AND OBJECTIVES

Symptomatic instability in the knee is common in osteoarthritis and following TKA but has no objective assessment(Fleeton *et al.*, 2016; Pitta *et al.*, 2017). Rather, the frequency of symptoms such as buckling, giving way, and loss of confidence are reported on Likert scales (Fitzgerald, Piva and Irrgang, 2004). We have previously described our hypothesis that symptomatic instability is a result of conscious appreciation of the failure to closely control impulses acting around the knee, and the consequent increased time in the boundary between recoverable and irrecoverable deviation from normal motion. The populations in which this situation arises are likely to have altered knee joint morphology in terms of bony, ligamentous and cartilaginous construction, and this is known to result in altered joint biomechanics (M. W. Creaby *et al.*, 2010). Further, there is experimental evidence to support increased internal contact point variability during walking as measured by 3D fluoroscopy of the joint in patients with symptomatic instability in the knee (Farrokhi *et al.*, 2015; Gustafson *et al.*, 2015), as well as reduced passive stiffness in the frontal plane about the neutral axis (Creaby *et al.*, 2013), and reduced sagittal plane walking stiffness (Gustafson *et al.*, 2016). This adds up to symptomatic instability the knee resulting from reduced passive restraint in the knee resulting in increased internal movement. Several researchers have examined the possibility of using accelerometers to determine increased internal knee movement and link them to symptomatic instability following TKA (Khan *et al.*, 2013; Roberts *et al.*, 2013; Soeno *et al.*, 2018). These utilised a device that is cheap and portable, as well as being easy to use, in contrast to the more time consuming and expensive technologies

involved in the previous studies. While these studies have concentrated on AP motion of the knee (the ACL is sectioned during TKA), our study examines frontal plane movement , shown to be associated with decreased stiffness in OA instability (Creaby *et al.*, 2013). As in these studies, we use an accelerometer unit mounted on the proximal tibia.

This initial healthy subject study seeks to show the accelerometer device to be repeatable in measuring accelerations in the proximal tibia during normal walking. In this regard, our hypothesis is that basic measurements of gait taken by the accelerometer, namely mean stride duration and mean lateral knee peak frontal plane acceleration, will be a recordable and repeatable parameter. Further, we compare the acceleration in the frontal plane to other biomechanical parameters associated with frontal plane movement (KAM) and subjective knee instability (frontal plane stiffness). Our hypothesis is that increasing accelerations in the frontal plane will be associated with increased KAM and decreased sagittal plane stiffness. In the former this is due to accelerations representing increased movement requiring compensation, and the later that greater frontal plane accelerations are a consequence of the same internal joint circumstances that lead to decreased stiffness in the sagittal plane of the knee. This healthy subject work is intended for form the basis for further study in those experiencing instability in the OA knee and the TKA.

6.2. METHODS AND MATERIALS

Ethical approval for this study was granted by the University Departmental Ethics Committee (Figure 11-9). In this early study examining the repeatability of a new device and protocol, a convenience sample of subjects was recruited from amongst university students. Healthy subjects were recruited by departmental e-mail. Inclusion criteria were heathy subjects aged over 18. Exclusion criteria were neurological or orthopaedic disorders relating to balance, the lower limb, or walking; any history of knee or hip pain or instability; any history of surgery to the hip, knee or foot; any history of giving way or bucking of the knee, or unexplained falls; use of walking aids; pregnancy. Informed consent was obtained in writing at least 24 hours following the receipt of the participant information sheet.

Participants were invited to attend the gait analysis laboratory for testing. Following changing into lycra shorts and comfortable shoes the following protocol was followed: Baseline data were recorded for height, body mass, leg length, knee width, ankle width and inter ASIS distance. Clinical examination of the subject was performed with the subject lying supine of the examination couch. Screening examination of hip, ankle and foot was performed, and the knee was examined for bruising or tenderness, effusion, integrity of collateral and cruciate ligaments and meniscal pathology. Range of motion was examined supine, and alignment was visually assessed supine and standing. Gait was visually assessed for any obvious abnormality prior to instrumented testing.

6.2.1 OPTOELECTRONIC GAIT ANALYSIS

Data were recorded in three phases. Firstly, 14mm reflective markers were attached to the subject following the Vicon "Plug-In-Gait" model, with 16 markers attached to ASIS, PSIS, thigh segment, lateral condyle of the knee, shank segment, lateral malleolus, calcaneus and 2nd metatarsal, bilaterally. All markers were attached using double sided tape.

Gait analysis was performed using a 12-camera optoelectronic gait analysis system (Vicon, Oxford, UK) recording at 100Hz. 4 integrated force platforms (Kistler, NY, USA) recorded kinetic data at 1000Hz. Data was recorded using Vicon Nexus software (Vicon, Oxford, UK).

A static trial was performed to allow the creating of a skeleton model. Walking trials were then performed along the laboratory walkway and visually reviewed to ensure thee clean strikes from each foot on a force plate were captured.

Data were filtered using a 4th order Butterworth filter, and inverse dynamic calculations were performed using the Vicon Nexus Plug-in-Gait software (Vicon, Oxford, UK) and, with each step normalised for stride duration using a custom written MATLAB programs (MathWorks, Mas, USA.) Each step was analysed for knee adduction moment, sagittal plane knee moment, and KAM impulse. These criteria were chosen as the KAM is the required to be countered in order to maintain the knee position, and similarly, KAM impulse represents the sustained impulse to be resisted. Sagittal knee

stiffness is the moment required to oppose an angular change in the knee joint in the sagittal plane and is therefore associated with our hypothesis of instability in the knee being failure of the mechanisms designed to counteract aberrant knee movement. All values were normalised by dividing by height and body mass (Moisio *et al.*, 2003). Sagittal plane stiffness was computed as the change in angle/ change in moment (normalised for weight and height) in the sagittal plane between the point of minimum knee moment and the earlier of maximum knee flexion or maximum knee moment (Gustafson *et al.*, 2016). This was compared using a two-tailed t-test of the gradient of the regression line of each participant.

6.2.2 ACCELEROMETER

The second phase of recording involved accelerometer data. An accelerometric node of a body sensor network was used (G-Link, LORD Microstrain, Williston, VT). This comprised an external housing of 58 mm x 43 mm x 26 mm, and weight of 46 grams containing two dual axis, orthogonally mounted ADXL210 MEMS accelerometers (Analogue Devices, Norwood, MA) operating at a range of +/-10g, low pass filtered using a 0.022 uF capacitor, and broadcast using a 2.4GHz radio frequency transceiver from an omnidirectional antenna with a line of site range of 2000m. The signal was received through a USB connected 2.4GHz radio frequency transceiver connected to a personal computer and processed using proprietary Node Commander® software (G-Link, LORD Microstrain, Williston, VT). As previously described, the accelerometer was calibrated using a custom written MATLAB program (MathWorks, Mas, USA (see section 5.1). The accelerometer node was mounted on a metal baseplate with Velcro strapping as previously described (Figure 5-4 – Accelerometer with mount in situ) and placed in line with the axis of the knee in the sagittal plane. A single channel was

selected giving recording in the frontal plane only, with positive output indication lateral acceleration for both right and left leg, and the attachment adjusted to give an output close to zero during natural stance indicating vertical alignment of the accelerometer with regards to the ground, as the zero output indicated no effect from gravitational acceleration. Accelerometer output was displayed using Node Commander software (LORD Microstrain, VT, USA).

Walking data from three trials was recorded, with each trial containing at minimum of six strides. The accelerometer was then repositioned on the opposite leg and data recording repeated. Following completion of this first testing session participants returned at an interval of no less than 1 week for retesting with the accelerometer only.

6.2.3 STATISTICAL ANALSIS

For this early exploratory work, a sample size calculation has not been performed as the expected correlation between accelerometer and gait analysis is not known. A convenience sample has been taken in order to explore the test methodology and setup and provide information for further testing. Analysis of the results were performed in two parts: firstly, to assess the repeatability of the accelerometer method; secondly, to compare lateral accelerations to the gait analysis parameters of KAM and sagittal plane stiffness.

Table 6-1 – Demographic summaries of healthy participants

Name	Height (m)	Body mass (kg)	BMI ($kg.m^{-2}$)	Age (years)
H1	1.82	64.20	19.49	22
H2	1.57	66.90	27.31	26
H3	1.73	78.10	26.25	32
H4	1.65	62.00	22.77	26
H5	1.57	54.10	21.95	20
H6	1.66	63.40	22.87	19
H7	1.60	55.30	21.52	20
H8	1.75	76.00	24.68	21
H9	1.91	84.20	22.96	20
H10	1.79	77.00	23.90	24
Mean (±SD)	1.71 (±0.12)	68.12 (±10.2)	23.37 (±2.29)	23 (±4)

Accelerometer data was extracted using a custom written program (MathWorks, Mas, USA) as described in Chapter 5.5, and shown in Appendix F. Heel strike was approximated by the negative peak on the tracing that occurred with the associated sudden jerk. All strides were extracted, and mean values found stride duration and lateral acceleration parameters for first and second test session for comparison. The accelerometer was assessed for repeatability using the initial peak lateral acceleration in the first 30% of the stride following heel strike, averaged over all strides in each walking test. Interclass Correlation was calculated using an average of random raters (Shrout and Fleiss, 1979) with this parameter chosen (ICC 2,k) as in similar studies (Turcot, Aissaoui, Boivin, Hagemeister, *et al.*, 2008), to and Bland-Altman plots were used to visually represent the repeatability of the test with limits of agreement calculated at 1.96 time the standard deviation of the difference between the paired results (Bland and Altman, 1986).

Table 6-2 – Accelerometer healthy subject output

Name	Stride Duration 1 (s)	Stride Duration 2 (s)	Acceleration 1 (ms^{-2})	Acceleration 2 (ms^{-2})
H1L	1.01	1.01	4.76	4.91
H1R	1.02	1.00	6.38	9.30
H2L	0.97	0.97	10.40	10.15
H2R	1.01	1.04	11.47	11.28
H3L	0.77	0.94	5.88	7.81
H3R	0.92	0.93	9.38	10.35
H4L	1.12	0.97	9.47	6.99
H4R	1.13	1.13	6.02	6.52
H5L	1.03	1.12	3.86	4.75
H5R	1.08	1.06	6.69	5.00
H6L	0.90	0.85	7.05	6.15
H6R	1.00	0.94	7.71	10.45
H7L	1.04	1.03	10.22	8.94
H7R	1.03	1.04	11.06	6.50
H8L	1.00	0.89	6.63	4.99
H8R	0.95	0.97	7.32	5.37
H9L	1.15	1.13	6.76	7.02
H9R	1.09	1.19	10.05	7.22
H10L	0.85	0.98	4.87	5.75
H10R	0.78	0.83	9.30	7.67
Mean (±SD)	0.99 (±0.11)	1.00 (±0.09)	7.76 (±2.25)	7.36 (±2.08)

Accelerometer readings were compared with normalised KAM, normalised KAM impulse and normalised sagittal walking stiffness using a linear regression model to identify R^2 and p-values for goodness of fit between the two measures.

6.3. RESULTS

10 subjects were recruited for analysis and full data sets were available for all, with each subject tested in both knees, giving 20 knees. Demographic details for each subject are shown in Table **6-1**.

6.3.1 ACCELEROMETER REPEATABILITY

Accelerometer outputs all followed a repeatable pattern of 1) heel strike transient, 2) lateral (positive) acceleration, quickly damped, 3) medial (negative) acceleration just beyond 50% of stride (corresponding with swing phase) and 4) repeat for the next stride (Figure 6-1). This is thought to be associated with 1) the jerk of heel strike being represented by a spike of acceleration positive and negative, 2) a lateral thrust of the knee, dampened by stabilising mechanisms, 3) a perceived medial acceleration as the knee externally rotates into swing phase, and the hip flexes, changing the axis of the accelerometer and creating a "medial-lateral" reading from an forwards movement.

Following extraction of strides form trials, a mean of 22.3 strides (range 15-28) were available for each subject over both days of testing. Mean values with standard deviations showed consistent stride durations of about 1 second (Table 6-2). Peak acceleration showed an average rater ICC of 0.75 (0.54-0.87) and a stride length average rater ICC of 0.84 (0.60-0.94) indicating good reliability for both, although with fewer than the suggested number of data points (Koo and Li, 2016). Bland-Altman plots are shown for acceleration and stride length (Figure 6-2,Figure 6-3). All subject

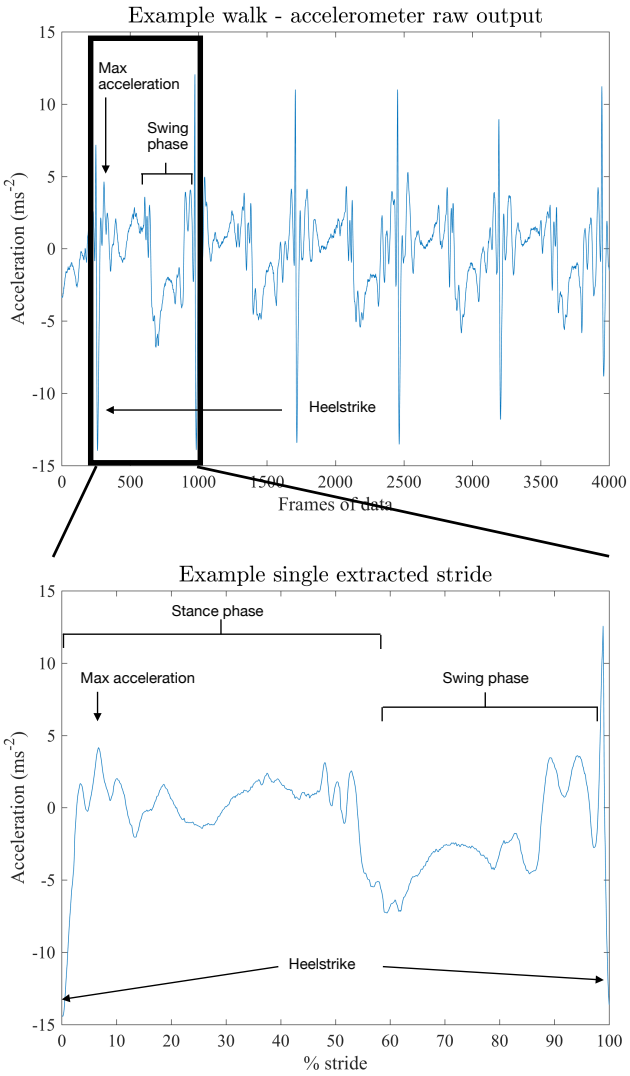

Figure 6-1 – Example of stride extraction

Raw output of mediolateral acceleration in the knee. Upper box represents several strides in succession. Characteristic patterns of heel strike transient, immediate lateral (positive) acceleration quickly dampened through stance phase, medial (acceleration) during swing followed be heel strike. The second box shows the extracted, x-axis changed to normalised to % stride, and the estimated division into stance and swing.

based data are means for each testing session, with overall mean and standard deviation shown.

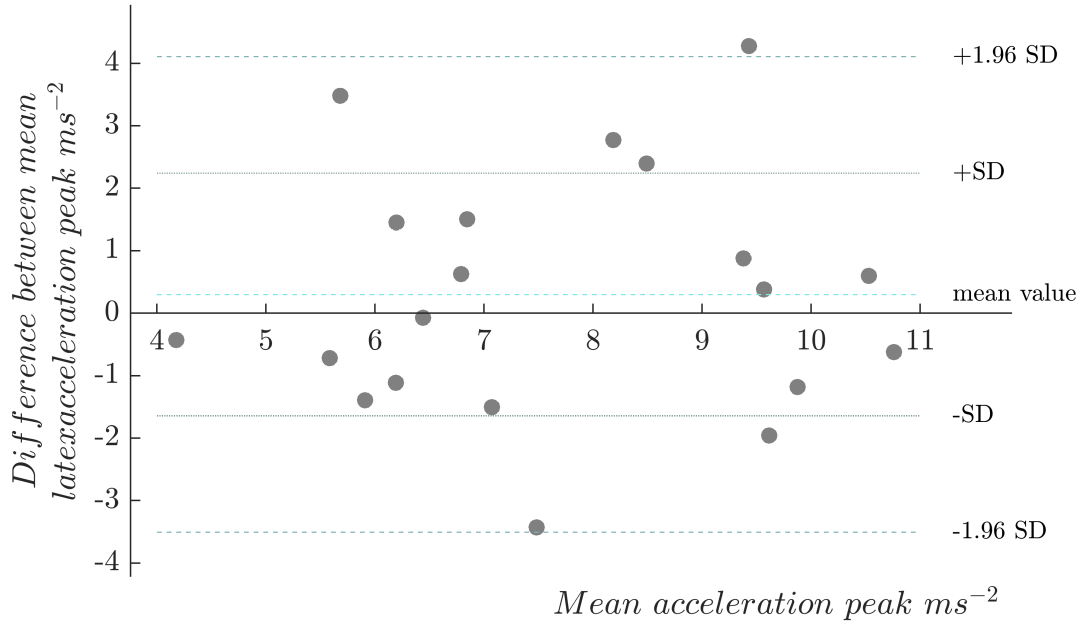

Figure 6-2- Bland-Altman plot showing repeatability for Acceleration

Figure 6-3 – Bland-Altman plot of stride duration repeatability

6.3.2 COMPARISIONS WITH GAIT ANALYSIS

Gait analysis data was acquired from all 10 subjects for each side, giving results for 20 knees (Table 11-4). Comparison between normalised KAM, normalised KAM impulse showed a weak positive relationship ($R^2 = 0.150$, $R^2 = 0.120$), with sagittal walking stiffness showing a weak negative relationship ($R^2 = 0.134$), however none of these associations reach statistical significance ($p = 0.092$, $p = 0.135$, $p = 0.112$) (Figure 6-4). Retrospective power calculation using an R^2 of 0.150 shows that the study would have required a sample size of 346 to detect a statistically significant correlation at this level with β of 0.8 and α of 0.05, so any possible association here must be treated with caution but may provide data for future work.

6.4 DISCUSSION

Healthy subject testing of the accelerometer unit and protocol showed that repeatable outputs could be recorded for stride duration and lateral knee peak acceleration on two different days (Figure 6-2, Figure 6-3), with ICC of 0.75 and 0.84 respectively. This confirms the hypothesis that these measures would be repeatable, and measurable using this technique. The repeatable nature of the measurement device is a necessary starting point for the development of a device for clinical use. No statistically significant correlation was found between KAM parameters and peak accelerations.

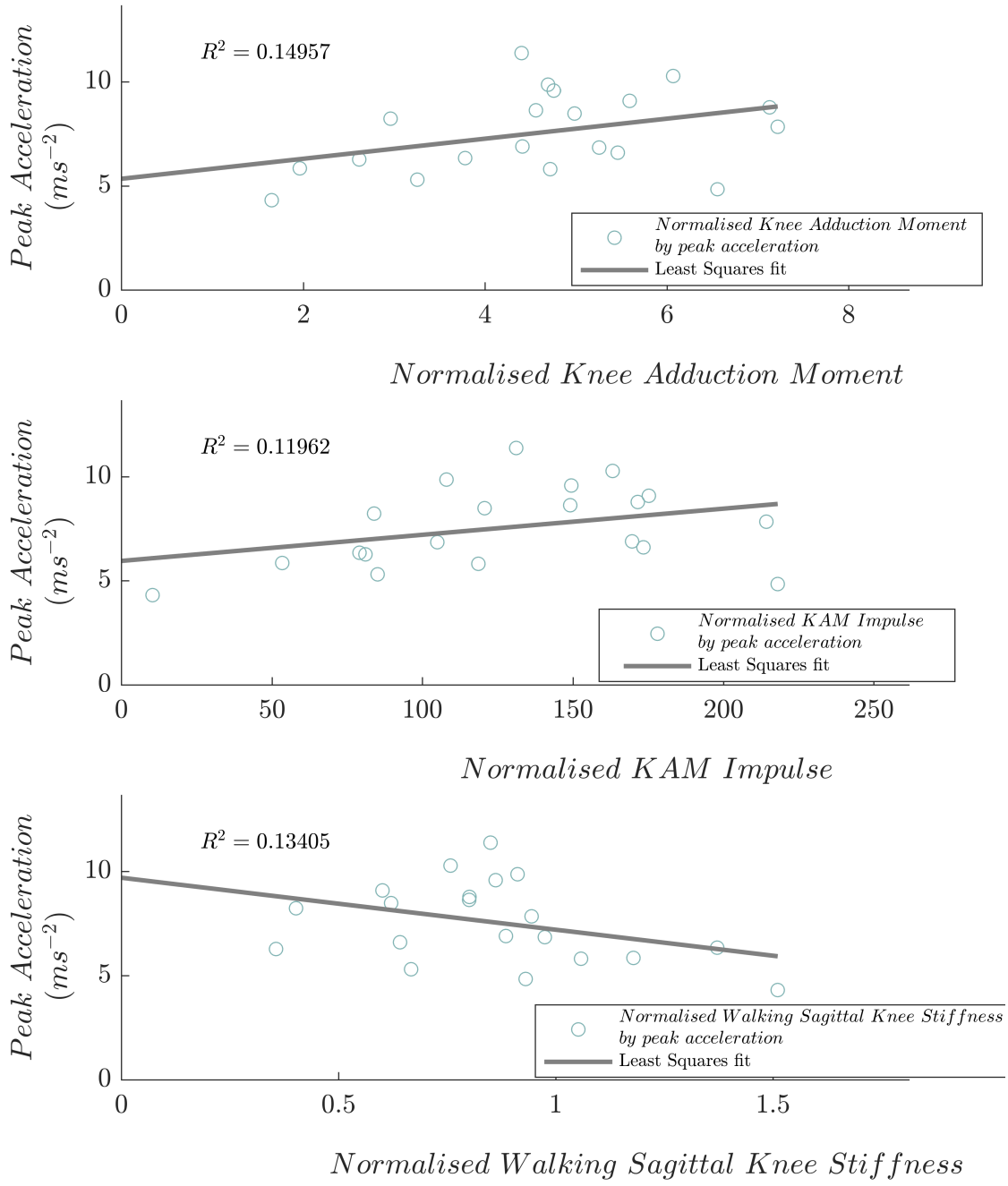

Figure 6-4 – Regression analysis of accelerometer parameters and gait analysis parameter

This preliminary study was designed to assess the ability to measure lateral accelerations in the knee repeatably using a custom-made unit of accelerometer node and mount, attached to the lateral shank using Velcro. In this convenience sample of young and healthy subjects, it was hypothesised that stride duration could be extracted from the accelerometer tracing and measured repeatably over two different sessions. Our study has shown that this parameter has been repeatably extracted. As was hypothesised, it has been shown that the early lateral acceleration found in the healthy knee by previous authors (Yoshimura *et al.*, 2000) can be recorded with our device, and that this parameter is repeatable. The repeatability of these when recorded by the accelerometer unit and protocol is necessary if it is to be used as a clinical measurement device. While some variation does exist, the discovered ICC for lateral acceleration and stride duration can be classified as "good" (Koo and Li, 2016). However, it must be noted that the sample size in this early testing was chosen for rather than following a sample size calculation due to the exploratory nature of the work, and therefore falls below suggested number of subjects for Bland-Altman calculation. Following this early work, further study in different age groups will be required, with larger populations, to confirm this device.

A weak association between rising normalised KAM and normalised KAM impulse suggest that increased acceleration is associated with increased medial adduction force, however this did not reach statistical significance. The hypothesis of the lateral acceleration is that following heel strike, the knee undergoes a sudden lateral thrust, with a corresponding increase in force through the medial knee. This is consistent with the findings of Yoshimura et al. (2000) who showed increased lateral accelerations in

ACL deficient knees using a tibial mounted accelerometer, and with suggestions that varus thrust is associated with increased tibial frontal plane angular velocity (Foroughi *et al.*, 2010; Chang *et al.*, 2013). Our accelerometer measured acceleration in the same frontal plane, with a consistent finding of lateral acceleration following heel strike. This acceleration was subsequently dampened rapidly leading to a quiescent period during stance before the following swing period. Consequently, the laterally mounted accelerometer appears to record a value analogous to varus thrust following heel strike that has been previously demonstrated by various authors. Our instability hypothesis is that it is the failure to dampen frontal plane accelerations in the knee that results in symptomatic instability. Reduced stiffness in the knee is associated with instability, both in passive frontal plane testing (Creaby *et al.*, 2013) and in sagittal walking stiffness (Dixon *et al.*, 2010; Gustafson *et al.*, 2016). This is due to the protective effect of stiffness in dampening jerk in the knee joint. The study showed a weak negative correlation between increased peak acceleration following heel strike and decreased sagittal walking stiffness, but again it failed to reach statistical significance. Further, there is no statistically significant association with the magnitude of KAM and KAM impulse. It is of note again that the sample size in this technology demonstration was low, and therefore underpowered to find any correlation.

In this healthy subject testing no participants reported any history of knee instability, had any prior knee pathology, or had undergone any knee surgery. The results found showed repeatability of the accelerometer node and protocol in both stride duration and lateral accelerations over two different testing sessions. In order to identify whether the accelerometer can be used to identify knee instability it will be necessary to test it in a

population exhibiting these symptoms and measure again its repeatability. This is done in the following chapters.

6.5 CONCLUSIONS

The accelerometer device for recording lateral knee accelerations during flat walking is repeatable in a healthy population. Some association between lateral peak acceleration and KAM, KAM impulse and stiffness have been found in healthy subjects consistent with the hypothesis that lateral knee accelerations can be used as a method of assessing instability, however they failed to reach statistical significance. Further work is required to test this system on a population with symptomatic knee instability.

CHAPTER 7 – TKA SUBJECT TESTING

The preceding chapters have discussed the prevalence of instability following TKA and its importance as a cause for revision surgery. Further, the difficulties in objectively identifying and quantifying that instability have been discussed (Chapter 2.6). Following review of the literature concerning measurement of instability (Chapter 2.5) an accelerometer was chosen as a device that may developed to quantify instability, while being portable, cheap and quick enough to use to be a viable tool for the orthopaedic clinic. Following early development (Chapter 6) it has been shown that the device is repeatable in the healthy population (Chapter 7) however it requires testing against those with symptoms of instability since the primary objective of the device is to discriminate between these two populations. The initial analysis found in Chapter 7 examined only amplitude data from the accelerometer analysis. However, the use of wavelet transform, discrete or continuous, typically used to filter and smooth data (Ismail and Asfour, 1999; Clark, Bartold and Bryant, 2010), the whole stride data can be compared in both time and frequency domains, which may provide additional insight into knee instability.

7.1 STUDY AIMS AND OBJECTIVES

This section sets out the testing of subjectively unstable knees with subjectively stable knees. These are compared to the control subjects described in detail in Chapter 7 and leads on from the successful repeatability testing of the new accelerometer device and testing protocol. It is the objective of this chapter to determine the repeatability of the accelerometer in a population of subjects following total knee replacement surgery, and to identify any differences in characteristics of lateral knee acceleration between

participants with and without subjective knee instability in both time and frequency domains.

7.2 METHOD

7.2.1 ETHICS AND SUBJECT SELECTION

Following ethical approval from NHS Scotland A Ethics Committee (16/SS/0171), participants were recruited for the assessment of knee instability over a period from January 2016 to August 2017. TKA patients were recruited from those attending a high-volume arthroplasty centre for either routine knee post-arthroplasty follow-up, or for pain and instability following TKA.

Prosthetic joints were categorised as "unstable" if TKA patients answered "yes" to the question: "Has your knee buckled or given way in the last month?", and "stable" otherwise. Volunteers were excluded if they had any history of any neurological or orthopaedic disorders relating to balance, the lower limb, or walking or joint infection, previous knee injury or ligamentous reconstruction surgery

7.2.2 OPTOELECTRONIC GAIT ANALYSIS

Gait analysis was performed using a 12-camera optoelectronic gait analysis system (Vicon, Oxford, UK) recording at 100Hz. Four integrated force platforms (Kistler, NY, USA) recorded kinetic data at 1000Hz. 14mm reflective markers were attached to the

subject following the Vicon lower limb "Plug-In-Gait" model (VICON), with 16 markers attached to ASIS, PSIS, thigh segment, lateral condyle of the knee, shank segment, lateral malleolus, calcaneus and 2nd metatarsal, bilaterally. Walking trials were performed along the laboratory walkway and visually reviewed to ensure three clean strikes from each foot on a force plate were captured

7.2.3 ACCELEROMETER

A single 10g triaxial accelerometer (LORD Microstrain, VT, USA). was attached to the lateral aspect of the proximal tibia using a custom-made jig, secured using Velcro (Figure 5-4 – Accelerometer with mount in situ). The accelerometer was calibrated using a custom written MATLAB program (MathWorks, Mas, USA.) Accelerometer output was displayed using Node Commander software (LORD Microstrain, VT, USA). Data was recorded in the frontal plane at 736Hz (accelerometer default setting for single channel use) during, and output manually checked to confirm placing and orientation prior to first data collection. Prior to data collection, the participant had a trial walk to ensure no restriction in movement was caused by the placing of the accelerometer.

Walking data from three trials was recorded, each trial containing at least six strides. Accelerometer recordings were repeated at a minimum of one week to assess repeatability.

7.2.4 DATA ANALYSIS – OPTOELECTRONIC GAIT ANALYSIS

Marker trajectory data were low-pass filtered using a zero-lag, 4th order Butterworth filter with a cut-off frequency of 6 Hz, with force plate data low-pass filtered using a zero-lag 4th order filter with cut-off frequency of 300 Hz. Inverse dynamic calculations were performed using the Vicon Nexus Plug-in-Gait software (Vicon, Oxford, UK) with each stride normalised by its duration using a custom written MATLAB programs (MathWorks, Mas, USA.). Knee adduction moment, knee flexion moment, knee flexion angle and knee adduction angle were determined in stance. Moments were non-dimensionalised by dividing by the product of body mass and height (Moisio *et al.*, 2003). Sagittal plane stiffness was computed as the least squares gradient of the normalised flexion moment with respect to the flexion angle (Moisio *et al.*, 2003; Thorp *et al.*, 2006) during weight acceptance, defined as between the point of minimum knee moment and either the maximum knee flexion or the maximum knee moment, whichever came first (Gustafson *et al.*, 2016). Differences between groups were calculated using non-parametric analysis using the Kruskal-Wallis test, with post-hoc Bonferroni test for multiple comparisons.

7.2.5 DATA ANALYSIS -ACCELEROMETER

The accelerometer produces a waveform that may be divided into peaks, troughs and means, reducing its high dimensionality to a series of discrete measurements. This has been the standard method of assessing accelerations in the knee (Yoshimura, Naito and Zhang, 2002; Khan *et al.*, 2013). However, this results in the loss of temporal characteristics, and may lose resolution of transient accelerations. The use of the

continuous wavelet transform, a mathematical transform of a signal in time and amplitude dimensions to one of time and frequency, allows visualisation of the time-frequency domains of the accelerometer, similar to those methods used in EMG analysis (Dantas *et al.*, 2010; Koenig *et al.*, 2018), allowing time resolution in beyond that found with standard Fourier Transform (Chau, 2001b). For this reason, it has been used to identify peaks and transient activities within accelerometer signals in various engineering applications (Chuang, Wu and Wang, 2013; Silva *et al.*, 2018) and more recently in biomechanics(Błażejewski, Głowiński and Maciejewski, 2019), and is a recognised technique for time series analysis in biomechanics that avoids the loss of temporal resolution in Fast Fourier Transform (FFT) (Edwards, Derrick and Hamill, 2017). The continuous wavelet transform examines the accelerometer signal, x, at each time point, t, using the wavelet function $\psi(t)$ where the wavelet is a time limited, zero meaned wave form of known geometry. This is given by the function:

$$X(a,b) = \int_{-\infty}^{\infty} x(t)\, \psi_{a,b}(t)\, dx$$

Equation 7-1 – Continuous wavelet transform

Where x = accelerometer trace, t = time, ψ = wavelet function in both time and frequency domain, X(a,b) = outputted signal in time (a) and frequency(b) domain

This transform gives further information on the accelerometer output characteristics but increases the data dimensionality by giving outputs in time, frequency and power, instead of time and amplitude only. This is accomplished using a "matching" of the wavelet shape with the pattern of the waveform being analysed at varying time points t for all possible periods of the wavelet. Consequently, the wavelet can differentiate

frequency differences at higher resolution at the low range, sacrificing temporal discrimination, while allowing better time approximation and lower frequency resolution at a higher range (Figure 7-1, Figure 7-2). The Morlet wavelet was chosen as it is most commonly used within similar biomechanical tasks (Fischer, 2010; Błażejewski, Głowiński and Maciejewski, 2019). While this technique has not previously been used in accelerometer measurements in the knee examining for instability, the concept of a time series analysis approach has been previously tried using FFT (Soeno *et al.*, 2018), but it is proposed that the discrete impulse based understanding of symptomatic instability that we have postulated might be better assessed using a wavelet analysis allowing for temporal resolution.

Data were analysed using custom written MATLAB programs (MathWorks, Mas, USA.) Each stride was extracted from the walking data by automatic identification of negative peaks corresponding to heel strike, giving a total stride between two heel strikes (Figure 7-3). Quality of data was visually reviewed to confirm strides prior to data transform. Each stride was resampled to 1000 frames for comparative analysis. Repeatability analysis was performed by comparing mean maximum acceleration following heel strike in the first 30% of each stride between first and second trials.

Spectrograms were extracted using the CWT decomposition for each time-normalised individual stride for each participant (appendix F) using a 5 level wavelet decomposition using the discrete wavelet transform (DWT) and 3rd order coiflets (Clark, Bartold and Bryant, 2010). A continuous wavelet transform using the Morlet wavelet was performed to produce a time/frequency analysis. The resultant

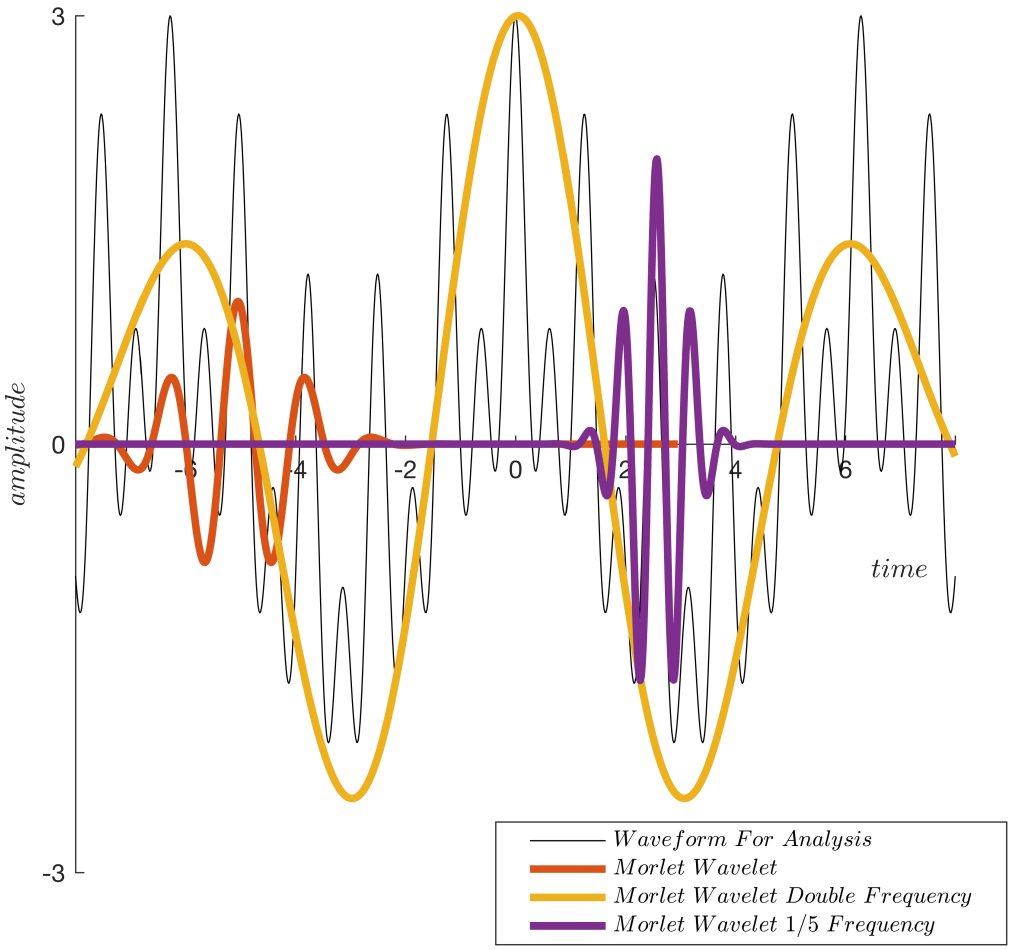

Figure 7-1 – CWT example.

Analysis of waveform $y = \cos x + \cos x \times 2 + \cos x \times 10$. Wavelet is displayed at three different periods and time points, identifying frequency components of the underlying waveform at different time points.

spectrogram was thresholded between 4 and 32 Hz in 30 bins of differing frequency (Figure 7-2) with each pixel representing a bin of frequency resolution over 1/1000 of a stride. The CWT produces a complex number for intensity, converted to its modulus, or absolute number for analysis, with each pixel colour representing the absolute CWT co-efficient: the brighter the colour, the greater the intensity of signal at that particular frequency time point.

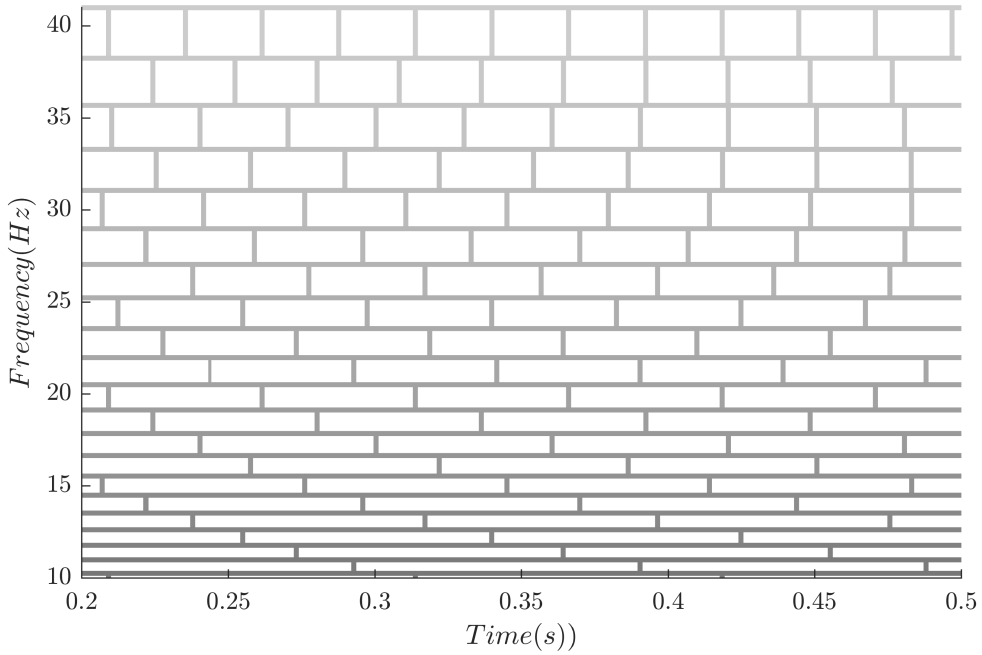

Figure 7-2 – Pictographic demonstration of frequency-time resolution for CWT
Each rectangle represents a time/frequency resolution revealed by the wavelet. At lower frequencies, resolution is more precise at the expense of temporal accuracy, whereas at higher frequencies this is reversed.

All spectrograms were grouped with regards to self-reported stability group membership and each one of the 30000 pixels averaged for the group, creating an average frequency intensity at each point in the gait cycle. The 95% confidence interval for each pixel was also determined.

For each of the 979 strides, each of the 30000 pixels were compared to the 95% confidence interval for each of the three groups. For each pixel, if 90% of the strides were within the 95% confidence interval of all three groups, then that pixel was categorised as one that could not differentiate between strides, as the pixel intensity was similar in all conditions. These pixels were removed from further analysis. The remaining pixels may be labelled as pixels of interest, or POI

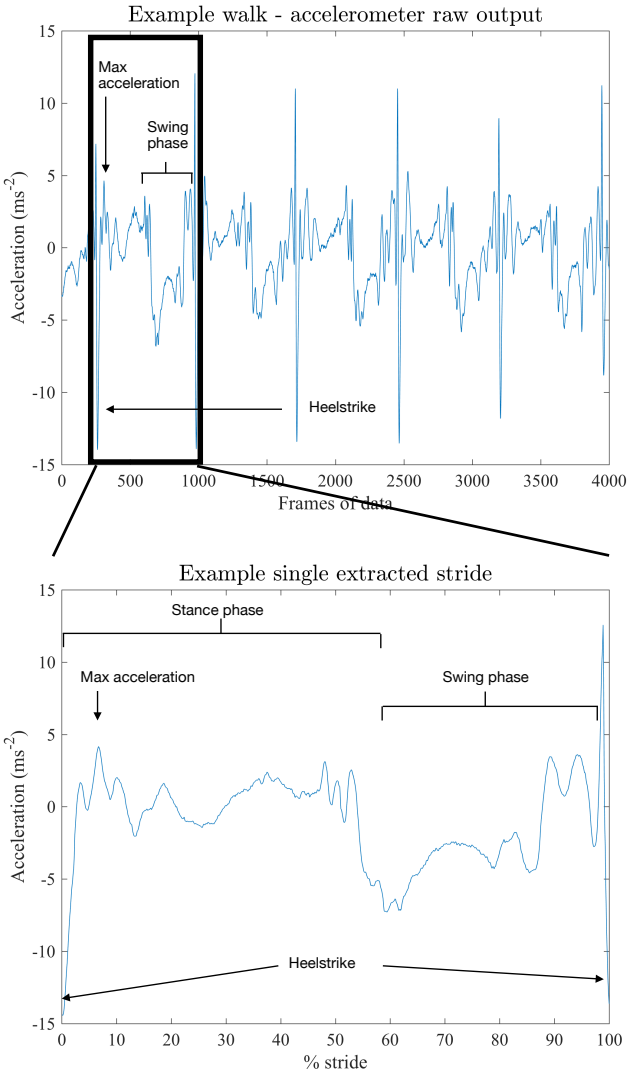

Figure 7-3 – Example of stride extraction

Raw output of mediolateral acceleration in the knee. Upper box represents several strides in succession. Characteristic patterns of heel strike transient, immediate lateral (positive) acceleration quickly dampened through stance phase, medial (acceleration) during swing followed be heel strike. The second box shows the extracted, x-axis changed to normalised to % stride, and the estimated division into stance and swing.

Each stride in the unstable group was then assessed to determine whether the stride was mechanically different to the stable group by comparing the stride intensity at each time/frequency point with the 95% confidence interval of all strides in the stable group. If > 95% of the intensities of the POI of a stride were within the subjectively stable stride confidence intervals, then the stride was classified as stable. The stride was

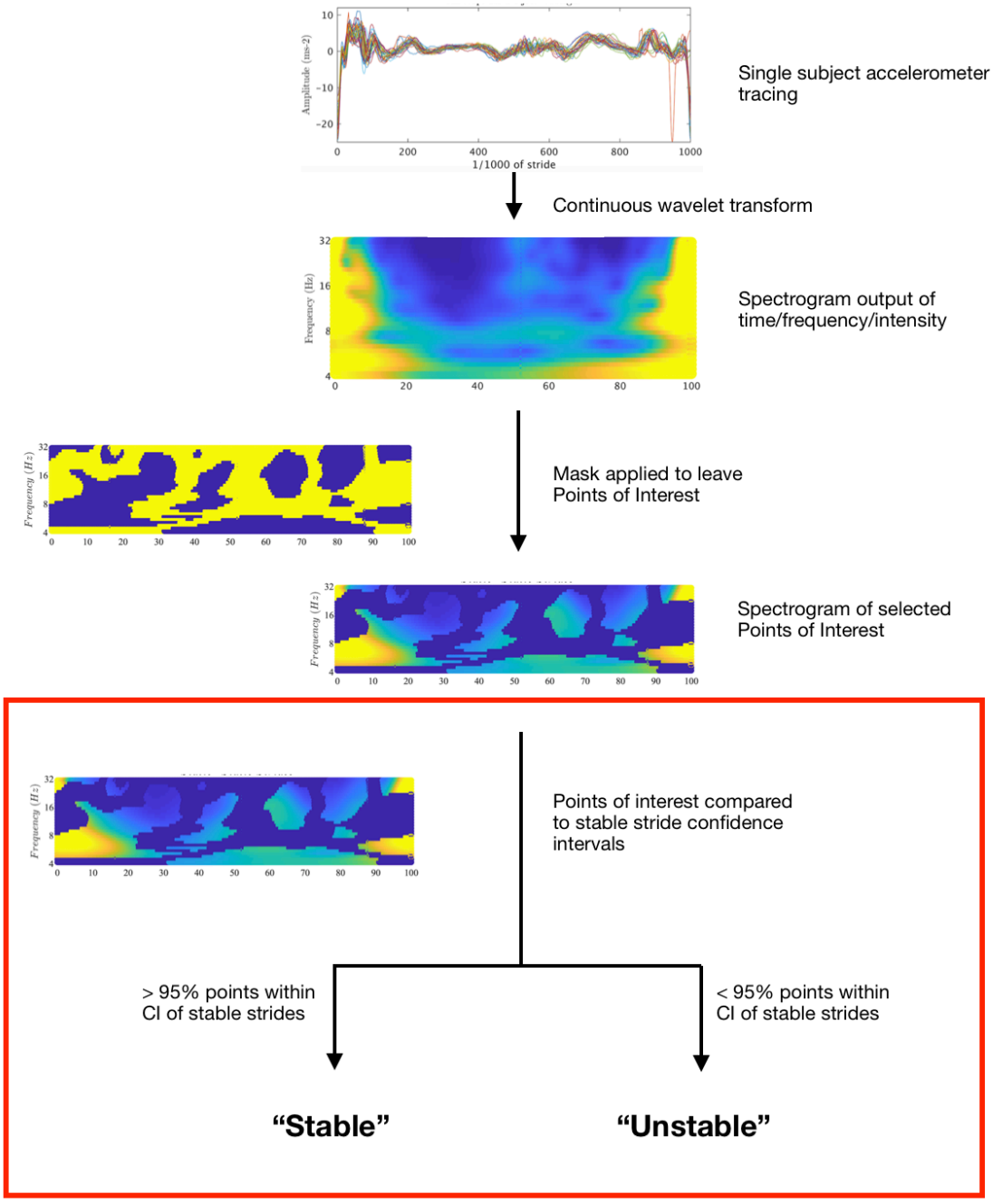

Figure 7-4 – Flow chart for classification of strides into "stable" or "unstable". Each accelerometer tracing, representing a single stride, is transformed using CWT to give a time/frequency/power matrix, displayed here as a spectrogram. A mask is then applied to remove all data points where no difference was found between groups. The masked stride was then compared to the confidence intervals of the symptomatically stable group. If >95% of the strides were within those CIs, then the stride was classified as "stable". Otherwise it was classed "unstable"

classified as unstable otherwise (Figure 7-4). The resultant divisions of the stable and unstable group were then used to produce new confidence intervals of "stable" and

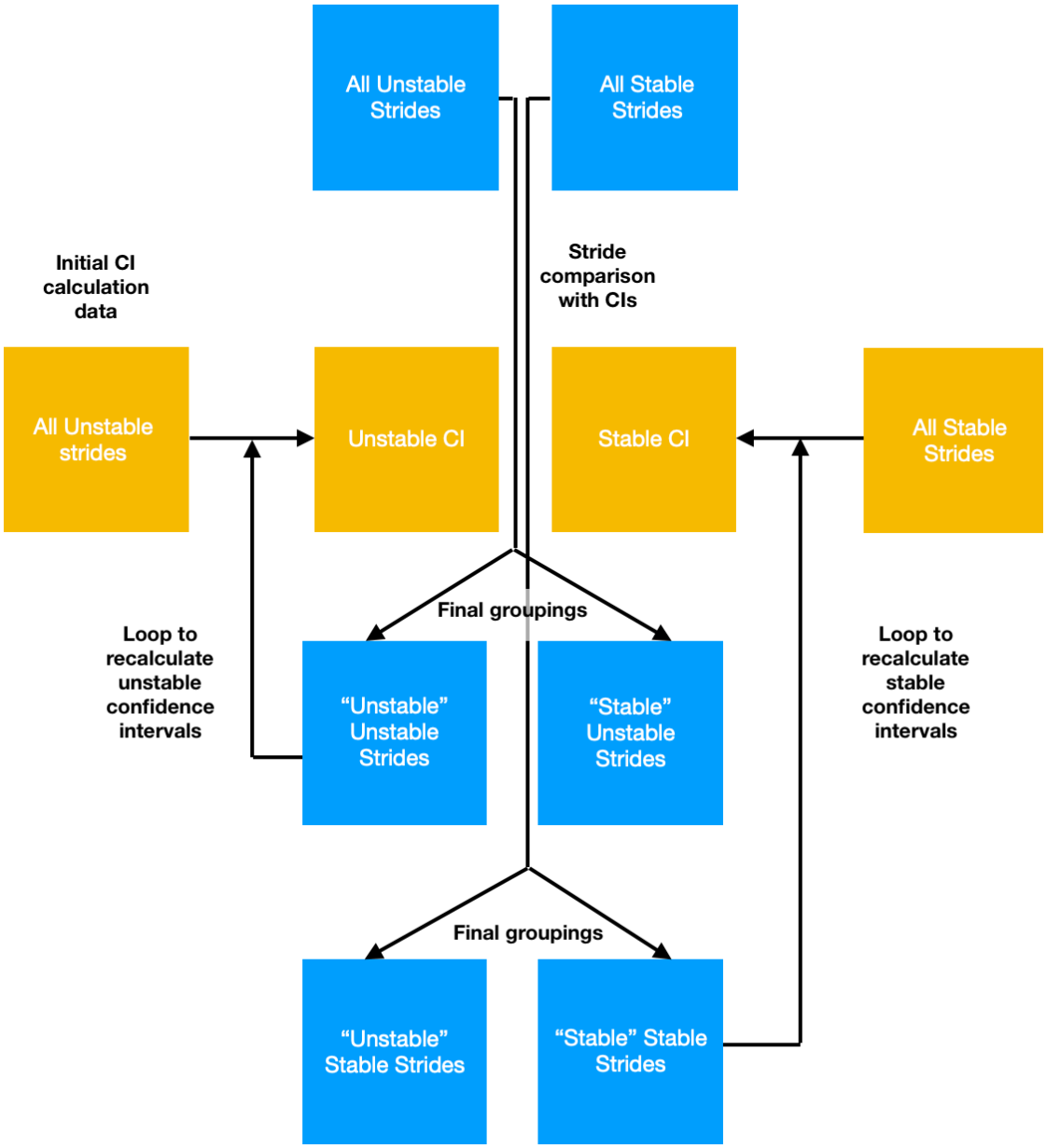

Figure 7-5 – Iterative algorithm for producing final divisions
An initial consideration of stride division is made using confidence intervals from all strides within each patient group (yellow boxes). Strides from stable and unstable subject groups are divided into "stable" and "unstable" according to their conformity. These new groups are then used to create new Cis for an iterative loop, each time reprocessing the whole subject group against the new Cis.

"unstable" strides, and an iterative process of selection used to create a final mask as per the algorithm in Figure 7-4. This mask was then used to redefine mechanically "stable" and "unstable" patterns of strides based upon the confidence intervals at the POIs and divide all strides from stable and unstable subjects again. A chi-squared test

was used to test the null hypothesis that the distribution of "unstable" strides was equal between self-reported stable and unstable groups.

Strides which were identified by this method to be mechanically different to the stable group, i.e. potentially unstable strides, were grouped and a mean spectrogram created. The remaining strides, i.e. those not different to the self-reported stable group, were combined and an average spectrogram created. These two spectrograms of stable and "unstable" strides were visually compared. Unstable here is in quotations since whilst these strides have been identified as mechanically different to the self-reported stable group, they may not be unstable strides per se. However, it is hypothesized that the differing intensities of points of interest in the "unstable" strides will point to differences in acceleration within the knee due to a failure of dampening mechanism in comparison to "stable" strides. This fits with our model of symptomatic instability being due to failure to control impulses in the knee using passive and automatic active control mechanisms, and therefore the increased accelerations are a result of control failure felt as instability.

7.3 RESULTS

7.3.1 STANDARD GAIT ANALYSIS

Sixteen post-operative TKA patients volunteered (Table **7**-) due to difficulties in recruiting subjects willing to travel to a different institution. At recruitment, nine patients declared instability, however when recording their subjective stability at the time of data collection, two indicated they had no instability and were reclassified to the

"stable" group, leaving 9 stable and 7 unstable TKA patients. Data were collected on both knees of the asymptomatic group. Controls were younger ($p < 0.001$) and lighter ($p = 0.003$) than TKA patients but no difference existed between stable and unstable TKA (Table 7-). There was no difference in alignment between the stable and unstable TKA groups. One participant (unstable TKA group) moved their knee into extension following heel strike. Results for measured parameters in each subject are shown (Table 11-5). Otherwise, all participants in all groups flexed the knee in the early stance phase.

Table 7-3 – Comparison of parameters between groups.

All values displayed as mean ± SD. Kruskal-Wallis comparison between groups. Post-hoc testing using Bonferroni test.

Grouping	Sagittal Flexion Angle at Heel strike	Sagittal Flexion during Weight Acceptance	Adduction Angle at Heels trike	Adduction Angle at max Weight Acceptance	Maximum Adduction Moment during Weight Acceptance	Sagittal Stiffness
Healthy	4.92 (±3.66)	13.46 (±4.80)	0.89 (±2.80)	2.77 (±5.06)	5.96 (±2.83)	0.85 (±0.29)
Stable	4.46 (±6.99)	12.08 (±4.62)	3.32 (±5.19)	0.38 (±5.95)	4.99 (±3.71)	0.70 (±0.52)
Unstable	0.79 (±4.52)	9.20 (±6.03)	2.66 (±3.78)	1.73 (±4.71)	1.52 (±2.36)	0.57 (±0.26)
p-value	0.125	0.205	0.211	0.677	0.020	0.040
Post-hoc testing		Unstable vs healthy			0.016	0.098
		Stable vs healthy			0.831	0.165
		Stable vs Unstable			0.358	1.000

Table 7-2 – Participant characteristics.
All values displayed as mean ± SD

Group	Height (m)	BMI (kg.m^{-2})	mass (kg)	Age (years)	Alignment (°)
Healthy	1.71 ± 0.12	23.4 ± 2.3	68.1 ± 10.2	23 ± 4	N/A
Stable TKA	1.65 ± 0.09	32.1 ± 3.9	88.0 ± 18.8	64.4 ± 7	1.74 ± 3.84
Unstable TKA	1.68 ± 0.06	30.2 ± 3.2	85.6 ± 12.4	64.6 ± 7	-0.31 ± 2.54

Overall knee stiffness was lower in the unstable group compared to the healthy group but this did not reach statistical significance (p = 0.098), with no difference between stable and healthy or unstable and stable groups (Figure 7-6, Table 7-) Maximum

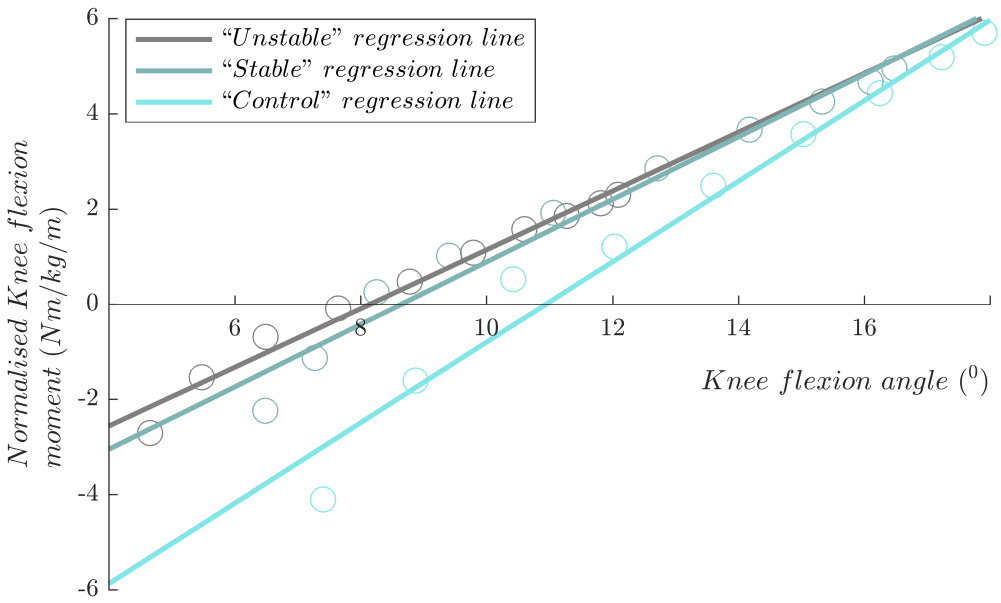

Figure 7-6 – Knee flexion angle against knee flexion moment during weight acceptance phase.
For each subject, weight acceptance phase is normalised to 10 frames for comparison. The average knee flexion angle and knee flexion moment at each frame is plotted for each group, with the least squares regression line representing average sagittal stiffness for each group.

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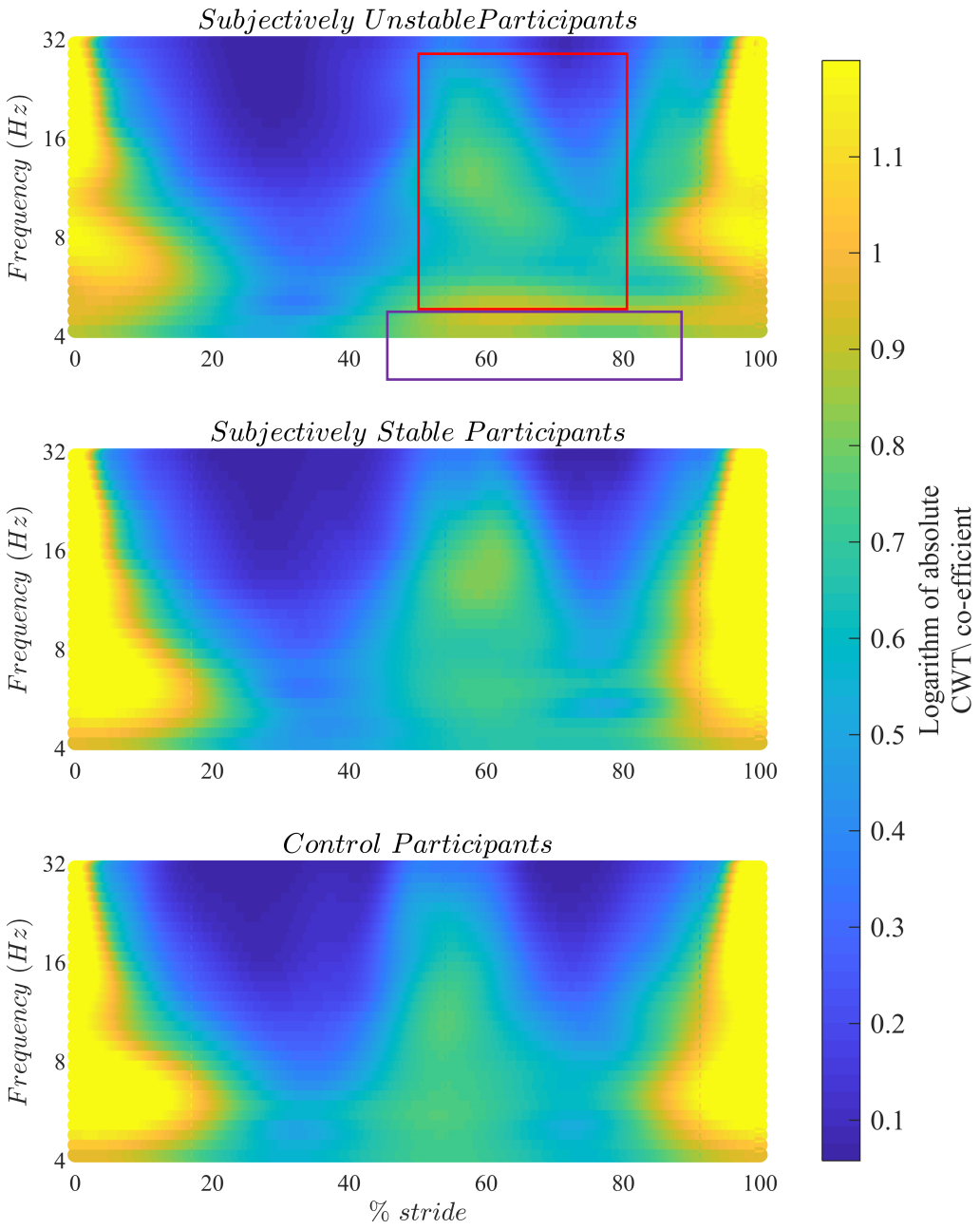

Figure 7-7 – Frequency intensity across stride range for each group.
Colour intensity indicates absolute CWT for each frequency/time area. Mean across all strides taken. Red and purple boxes indicate visually identified as different between unstable group and other groups, therefore identified as areas for initial comparison. Purple box corresponds to transition from terminal stance through swing phase of the gait cycle

adduction moment during weight acceptance was also lower during weight acceptance for the unstable participants in comparison to the healthy volunteers (p = 0.016).

7.3.2 ACCELEROMETER

979 strides were available for the analysis, divided between groups (Table **7-1**). Visual review of the spectrograms of all strides in each group showed increased power, or modulus of co-efficient of CWT, during swing phase in the subjectively unstable group in the 4-8Hz range (Figure 7-7). Classification, through confidence intervals (Figure 7-4) resulted in 144 strides from "unstable" subjects (58.5%) showing less than 95% agreement with the "stable" pattern, while 101 strides from the "stable" subjects (38.1%) showed less than 95% agreement ($p<0.001$) (Figure 7-8). Following the ten-cycle iterative algorithm and application of the final mask (Figure 7-5), subjectively unstable subjects were more likely to lack conformity with the stable pattern, with 88 (33%) of the subjectively stable subject strides classified as "unstable" compared to 49.8% of subjectively unstable strides ($p<0.001$, Figure 7-9, Table 7-2) .

Table 7-1 – Accelerometer strides analysis

Comparison of groups using Chi-squared test. Mean number of strides is the mean number of strides recorded for analysis in each subject group

Group	Total Number of Strides	Mean Number of Strides	"Stable" pattern	"Unstable" pattern	p
Healthy	468	23.4 ± 2.2			
Stable	265	29.4 ± 6.9	164	102	<0.001
Unstable	246	35.1 ± 14.4	101	144	

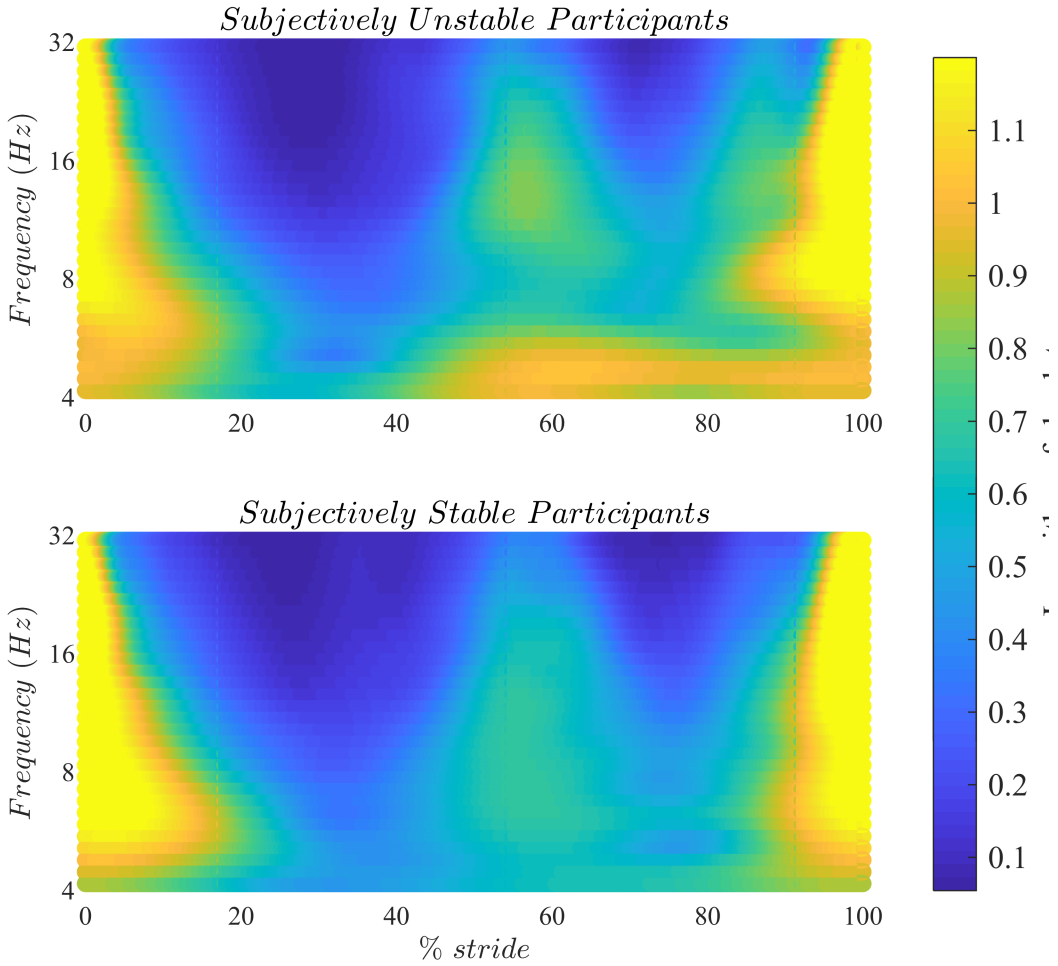

Figure 7-8 – Selected strides following conformity algorithm.
First subplot shows 144 strides from subjectively unstable participants not conforming with the "stable" type, while the second subplot shows 164 strides from subjectively stable participants conforming with the "stable" type. The previously highlighted area is now more clearly defined indicating increased low frequency accelerations in the knee during swing phase

Table 7-2 – Accelerometer strides analysis – Final mask
Final classification of strides in stable and unstable group following 10 loop iterative process. Significant difference found between division of stable and unstable subject groups using comparison of groups using Chi-squared test

Group	Total Number of Strides	"Stable" pattern	"Unstable" pattern	p
Stable	265	178	88	<0.001
Unstable	246	124	123	

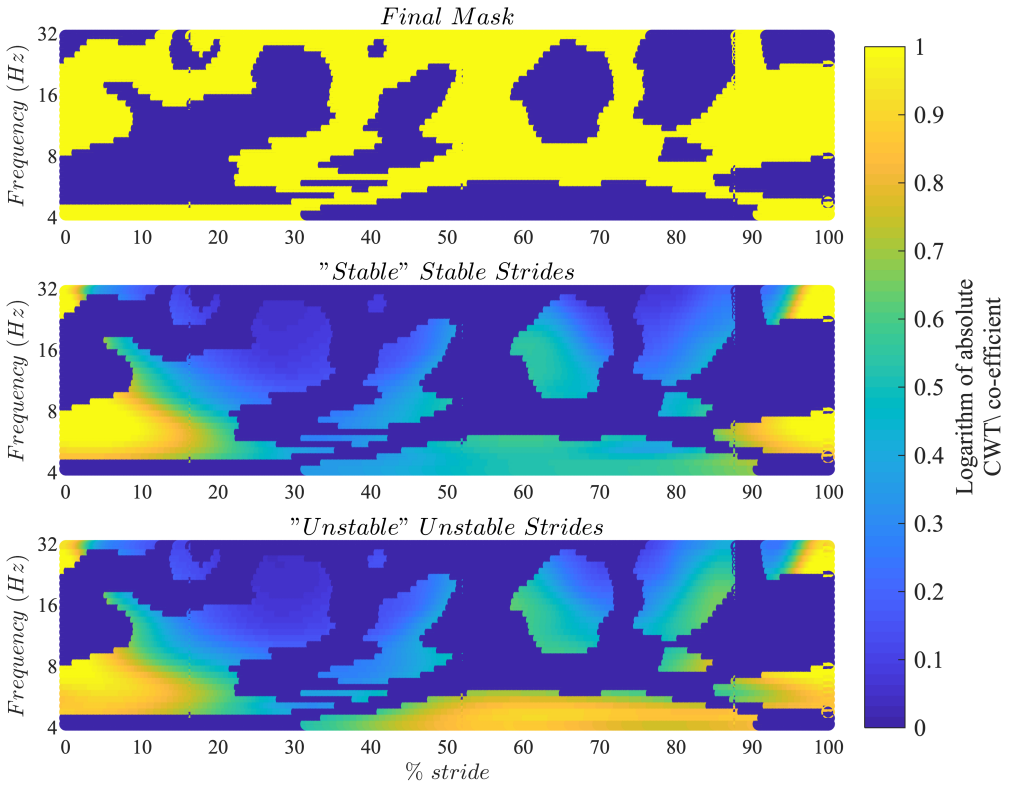

Figure 7-9 – Final mask and divisions

Upper panel – final mask following ten cycles of algorithm with removed areas in yellow. Middle panel – strides from subjectively stable subjects classified as stable with mask applied. Bottom panel – strides from subjectively unstable subjects classified as un stable with mask applied.

7.4 DISCUSSION

Instability in the knee following total knee replacement, subjectively defined here as "giving way" or "buckling" in the previous month, is a significant source of dissatisfaction and cause for revision (Sharkey et al. 2002; Sharkey et al. 2014; Kelly G Vince et al. 2006; Kelly G. Vince et al. 2006; Yercan et al. 2005; Vince 2016). However, the lack of quantitative analysis of this phenomenon has left assessment to subjective clinical assessment and patient reported symptoms (Parratte and Pagnano, 2008; Browne, Parratte and Pagnano, 2012; Abdel *et al.*, 2014; Petrie and Haidukewych, 2016). Following a similar methodology to previous studies (Dixon *et al.*, 2010; Gustafson *et al.*, 2016), this study has used standard gait analysis techniques to identify biomechanical differences between patients reporting instability in the knee following TKA and healthy controls during walking. Specifically, the unstable group had reduced peak knee adduction moment in comparison to healthy knees during the weight acceptance phase of walking, (Table 7-). While it did not reach statistical significance level, sagittal plane stiffness was also trended lower in the unstable group (Figure 7-6)

Further, a new technique has been shown have the potential to differentiate subjectively stable and unstable knees (Figure 7-7). The accelerometer analysis shows a distinctive pattern of increased absolute co-efficient of CWT between 4 and 6Hz in the range of 35-90% of stride in some strides in subjectively unstable TKA patients in comparison to healthy. This coincides with double-stance to the end of stride - as weight is being removed from, then becoming absent from the knee, leading to a transition from compressive forces at the knee causing increased stiffness (Marouane, Shirazi-Adl and

Adouni, 2015), to the compressive forces arising from co-contraction of the limb during swing phase. This change of forces across the knee is likely to be the point of greatest vulnerability in the knee due the intersection of falling compression as the knee ceases weight bearing, muscular contraction takes over, and ligament tension rises (Woo *et al.*, 1999) . This accelerometer finding is suggestive of reduced control of movement in the knee and hence feelings of instability. Our model of knee instability is that the control system of the knee acts to maintain a steady periodic trajectory during normal gait, with active and passive mechanisms, automatically and consciously controlled, acting to counter deviations from this. When the automatic mechanisms are insufficient, the subject becomes conscious of the aberrant knee movement as a risk of buckling or giving way – symptomatic instability. These accelerometer findings show high low-frequency accelerations in the frontal plane in early swing phase in symptomatically unstable patients. This fits with our hypothesis of increased movement in the knee being associated with symptomatic instability. Whilst this is associated with the unloaded and load-transitioning knee, PROMs for self-reported instability tend to be related to issues with knee loading. In light of this temporal understanding of biomechanical differences between stable and unstable strides, it may be necessary to rephrase questions to reflect this.

While accelerometers are increasingly being used for gait analysis in the laboratory setting (Turcot, Aissaoui, Boivin, Hagemeister, *et al.*, 2008; Turcot, Aissaoui, Boivin, Pelletier, *et al.*, 2008; Clark, Bartold and Bryant, 2010) and in clinic (Ogata, Yasunaga and Nomiyama, 1997; Kuroyanagi *et al.*, 2012), these have primarily relied on raw and filtered output of acceleration to determine kinematic parameters. Although discrete

wavelet transform has been used previously as a method of filtering accelerometer signal for kinematics (Ismail and Asfour, 1999) and tibial acceleration (Clark, Bartold and Bryant, 2010), this is the first time the continuous wavelet transform has been used for the accelerations in the knee. The use of time-series analysis has previously been examined using FFT to assess symptomatic instability (Soeno *et al.*, 2018) however this lacks the ability to differentiate activity throughout the periodic movement (Edwards, Derrick and Hamill, 2017). Our study identifies a particular point within the gait cycle where movement of the knee differs between the symptomatically stable and unstable TKA. This occurs at transition point where the forces acting upon the knee change. The study hypothesis that a subjectively unstable knee would be "loose", "wobbly" or more difficult to control requires an assessment that is both sensitive to small frontal plane movements (Mark W Creaby *et al.*, 2010; Creaby *et al.*, 2013; Thorlund *et al.*, 2014), has resolution in time (Edwards, Derrick and Hamill, 2017), and has the portability for office based assessment. The accelerometer CWT analysis shows differentiation of subjective stability in a compact quick data collection device.

Since reduced stiffness in the sagittal plane has been associated with patient-reported instability in OA (Gustafson *et al.*, 2016), we have hypothesised that a similar reduction in stiffness in the symptomatically unstable TKA may play a part in the reduced knee control. We did not find a statistically significant reduction in stiffness, however, the trend of reduced stiffness patient reported unstable TKA provides data that may allow a powered study to find such a difference.

Measured walking stiffness in the sagittal plane and TKA subjective stiffness has not previously been measured. However the relationship between subjective instability and stiffness in OA knees has been examined previously (Creaby *et al.*, 2013; Gustafson *et al.*, 2016) with authors finding a reduction in stiffness both in frontal and sagittal plane. Internal contact point variability has also been shown to increase in unstable OA knees during walking (Farrokhi *et al.*, 2012, 2014, 2016; Gustafson *et al.*, 2015). Together, these characteristics suggest that the OA unstable knee is "loose", or poorly controlled, during functional movement, resulting in the perception of instability. The suggestion of decreased sagittal plane stiffness during the weight acceptance phase of gait in the subjectively unstable TKA, also suggests a joint that is under less control. However, it was during the transition to swing phase that our accelerometer reading was most different. This would be consistent with finite element analysis findings of reduced stiffness at rapidly changing load, suggesting it is in these unloaded situations that the knee is least controlled (Marouane, Shirazi-Adl and Adouni, 2015). In OA, several studies have suggested no link between subjective instability and increased varus-valgus movement (van der Esch *et al.*, 2007, 2008; Schmitt *et al.*, 2008; Skou *et al.*, 2014), and passive varus-valgus stiffness has only been shown to be related to instability within a few degrees of neutral (Creaby *et al.*, 2013; Thorlund *et al.*, 2014), with an exponential increase in stiffness occurring with increasing soft tissue tension within the knee (Zalzal *et al.*, 2004). While multiple primary and secondary passive restraints exist in the knee to limit knee movement in the varus-valgus and sagittal plane, these are most effective when under tensile strain (Markolf, Mensch and Amstutz, 1976; Noyes *et al.*, 1980; Grood *et al.*, 1981; Zalzal *et al.*, 2004). One may therefore hypothesise that if ligaments are under low strain and bony restraints under low load conditions, little passive restraint on the knee exists. Since active joint restraint through muscular co-contracture

show no consistent picture in OA stable vs unstable knees (Lewek, Rudolph and Snyder-Mackler, 2004; Schmitt and Rudolph, 2008), it is the proposition of this thesis that it is within these changing load, low strain conditions that the knee is of greatest risk as these stabilising and countering mechanism fail to fully act.

The second finding from the gait analysis is the association between instability and decreased knee adduction moment (KAM) in the weight acceptance phase (Table 7-). KAM has been extensively studied as a tool to define the characteristics of OA. While increasing KAM and KAM impulse are associated with increasing varus (Foroughi, Smith and Vanwanseele, 2009) cartilage defects and bone marrow lesions, and KAM impulse with OA severity (M. W. Creaby *et al.*, 2010; Kean *et al.*, 2012) and cartilage damage (Vanwanseele *et al.*, 2010), the relationship with sagittal stiffness and KAM is more complex .

In the total knee replacement, an increase in KAM post-operatively has been reported (Nagura *et al.*, 2017; Niki *et al.*, 2018), while others have demonstrated a reduction (Hatfield *et al.*, 2011). In this study, although no pre-operative data was available, the unstable TKA group had a reduced KAM in comparison to healthy controls, whilst the stable TKA group was not different to the control group. This is noteworthy since there was no difference in alignment between stable and unstable TKA groups in this study. KAM indicates the distribution of load to the medial condyle (Komnik *et al.*, 2015). It may therefore be postulated that the unstable patient's reduced KAM could indicate a reduced medial knee contact force. Without this, the passive restraints of the medial condyle may be underutilised, resulting in feelings of instability. This contributes to

our model of instability where symptomatically unstable subjects are not able to counteract impulses across the knee in the as well as symptomatically stable.

This study gives confirmation to the presence of biomechanical differences between subjectively stable and unstable TKAs which can be detected using standard optoelectronic gait analysis. The presence of differences in these same groups using a novel method of assessment is promising for the development of a quick, cheap and portable device for the analysis of instability.

A strength of this study is its use of techniques previously documented to differentiate subjectively stable and unstable OA knees to study TKAs. A further strength is its use of techniques previously documented to differentiate subjectively stable and unstable OA knees to study TKAs. This has shown differences in data collected by the new accelerometer technique between these groups, suggesting that further work could be done to identify whether this can be used to train an algorithm to classify and even quantify differences here.

One significant limitation of the study is the small number of subjects. This is due to the restrictive nature of the exclusion criteria for the study patient population that was deemed necessary to fairly validate this technology, as well as the difficulty in finding subjects able to travel to a separate centre for analysis. This led to the study being underpowered for some aspects of the gait analysis and it is proposed that further work with a greater subject size may identify differences in sagittal walking stiffness. Several

different methods of assessing subjective instability have been used previously, based largely on the Knee Outcome Study Activities of Daily Living subscale (KOS-ADL) (Fitzgerald, Piva and Irrgang, 2004) and (Felson *et al.*, 2007). These produce an ordinal outcome which has sometimes been dichotomised in several biomechanical studies to facilitate comparison (Sanchez-Ramirez *et al.*, 2013; Gustafson *et al.*, 2016). The study attempts to ascertain subjective instability also dichotomises the participants into simple groups based upon stability in the last month, at the cost of differentiating between the severity of instability. Quantifying stability is the subject of the following chapter.

7.5 CONCLUSION

To conclude, subjectively unstable TKA patients exhibited a pattern of reduced KAM during weight acceptance, indicating in a reduced force required to produce a perturbation in either frontal or sagittal plane. A trend of reduced sagittal plane walking stiffness was also identified in the symptomatically unstable subject. Accelerometer data has shown in symptomatically unstable subjects an increase in low frequency accelerations in the transition between stance and swing phases. In combination this provides evidence for our model of instability as being the failure to control aberrant movement about the knee joint as the optoelectronic data suggests reduction in the stabilisation mechanisms while the accelerometer shows an increase in knee movement in symptomatically unstable subjects. , The use of a single accelerometer recording in the frontal plane combined with continuous wavelet has shown differences in signal between “unstable” and “stable” strides. This should be developed to allow a classification and quantification of instability in the TKA in the clinic setting without the need for expensive laboratory setup.

CHAPTER 8 – METHOD MODIFICATION AND OSTEOARTHRITIC KNEE TESTING

This chapter will discuss the progress from initial pilot testing (Chapter 7), to redevelopment of the mount, assessment algorithm, and testing on an OA population. Following initial testing on healthy and TKA subjects several conclusions were drawn. Firstly, the method was found to show differences accelerometer in signal during normal gait in the frontal plane between subjectively stable and unstable TKA patients. This was consistent with changes in dynamic sagittal stiffness also found in patients with subjectively unstable osteoarthritic knees (Gustafson *et al.*, 2016). Consequently, it was decided to continue to test the device on OA patients with and without subjective instability of the knee to see whether similar differences could be found. Further data would be used to modify the analysis method in order to seek a quantification of instability. During pilot testing, several areas for improvement were noted in the initial setup of the accelerometer and an ultimately unsuccessful attempt was made to address these with a redesigned accelerometer mount (see Appendix D). Ultimately the original mount was maintained but augmented with a crepe bandage to preload the accelerometer.

QUANTIFICATION OF INSTABILITY IN THE ARTHRITIC KNEE

8.1 INTRODUCTION

As previously discussed, instability - reported as a feeling of buckling or giving way - is a commonplace symptom in OA knees, being found in up to 72% of subjects (Fitzgerald et al. 2004; Knoop et al. 2012; Fleeton et al. 2016; Sharma et al. 2015;

Nguyen et al. 2014), and in 65.4% of pre-operative subjects in the OKS study group (chapter 4, Table 4-3). Self-reported knee instability has been associated with reduced levels of activities of daily living (Fitzgerald, Piva and Irrgang, 2004; Nguyen *et al.*, 2014) and increased risk of falls. Despite this, instability remains a symptom only, identified through several commonly used patient-reported outcome measures (PROMS) such as the Oxford Knee Score (OKS) and Knee Outcome Survey – Activities of Daily Living Score (KOS-ADLS). Attempts have been made to quantify instability in the native knee (Farrokhi *et al.*, 2012, 2014; Creaby *et al.*, 2013; Thorlund *et al.*, 2014; Gustafson *et al.*, 2016), and following TKA (Hamilton *et al.*, 2014); however no simple, repeatable device currently exists for the objective identification of instability. The pilot study demonstrated a difference in lateral knee accelerations between subjectively stable and subjectively unstable TKA subjects. This study seeks to identify any differences in lateral knee accelerations between subjectively stable and unstable OA knee patients and develop the accelerometer algorithm to provide a useful quantification of instability. Several recent studies have attempted to use computer learning methods to classify pathological and non-pathological gait (Laroche *et al.*, 2014; Figueiredo, Santos and Moreno, 2018). This study will use similar techniques to classify a symptom of pathological gait in the OA knee.

8.2 METHODS

8.2.1 ETHICAL APPROVAL

Ethical approval was received from Edgbaston Research Ethics Committee (17/WM/0457), and locally from the Golden Jubilee National Hospital Research and Development office (Appendix E, Study documentation).

8.2.2 STUDY DESIGN AND HYPOTHESIS

This study is designed to explore the hypothesis that biomechanical differences in the gait of symptomatically stable and unstable OA knee patients can be classified using an accelerometer unit and protocol. This is based upon the previously described model that symptomatic instability in the knee is a consequence of excessive and uncontrolled movement in the knee. No power calculation was performed as the purpose of this study was to explore a new method of data analysis and classification with no a priori data from which to determine an effect size.

8.2.3 PATIENT SELECTION AND RECRUITMENT

Pre-operative TKA patients were approached at pre-operative clinics at a national orthopaedic referral centre. If listed for total knee replacement, and willing to speak to the investigator, and deemed suitable by the operating consultant who was familiar with the study inclusion and exclusion criteria, potential volunteers were approached by the investigator. Patients were excluded if they had any history of neurological or orthopaedic disorders relating to balance, the lower limb, or walking or joint infection, previous knee injury or ligamentous reconstruction surgery, or joint replacement within the last year. If interested, the patient was given a patient information leaflet, and when reattending for surgery were approached and recruited if happy to participate. Participants were divided into “stable” and “unstable” groups based upon their answer to the question “has your knee buckled or given way in the last month?”.

Due to the nature of pre-admission process (patient factors of availability, and clinical factors of medical suitability for operation), many patients approached and willing to be involved in the study did progress to surgery within the time period of the study.

8.2.4 DATA COLLECTION

The same accelerometer and setup were used as in Chapter 7. However, due to observation during the first study of varying tightness of the Velcro attachment between subjects, an overwrapped tight crepe bandage was added to further reduce any movement between accelerometer and shank. This bandage ended below the knee, and prior to first waking test, each participant practiced a short walk to ensure they felt unencumbered by the presence of the bandage. Each participant was instructed to complete four unsupported, self-paced walks of at least six strides along a well-lit corridor. Participants were invited to sit between each walk if necessary and given the opportunity to withdraw at any point if required.

8.2.5 DATA ANALYSIS

Each walking trial data containing the accelerometer output for each patient was reviewed using a custom written MATLAB application (Figure 8-1). For each trial, the whole trace was displayed and the approximate beginning and end of the first stride was selected using the cursor, with the user asked to confirm the selected positions (Figure 8-2). The computer program identified the greatest minimum in the vicinity of the identified point and designated this as the heel strike point. The same was done with the maximum. The program attempted to identify subsequent strides based upon the initial stride length and positions of negative peaks in the data. If no clear points were identified, an area deemed to contain a stride was displayed and the user asked to

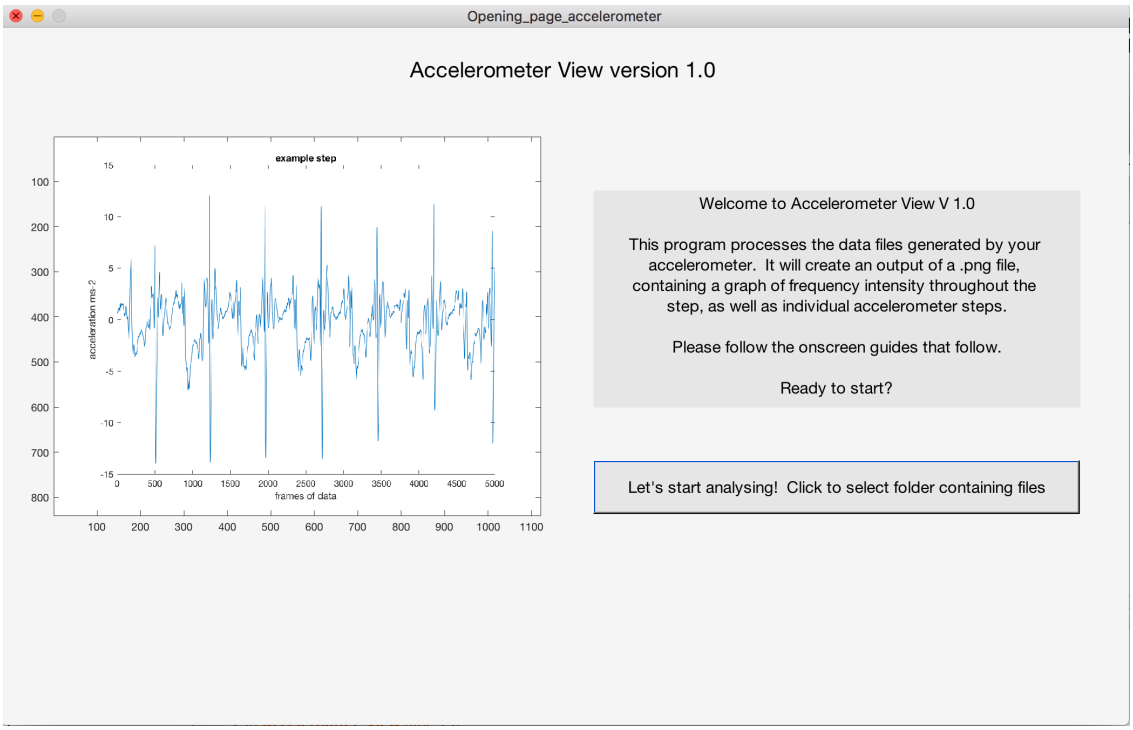

Figure 8-1 - Accelerometer App opening page

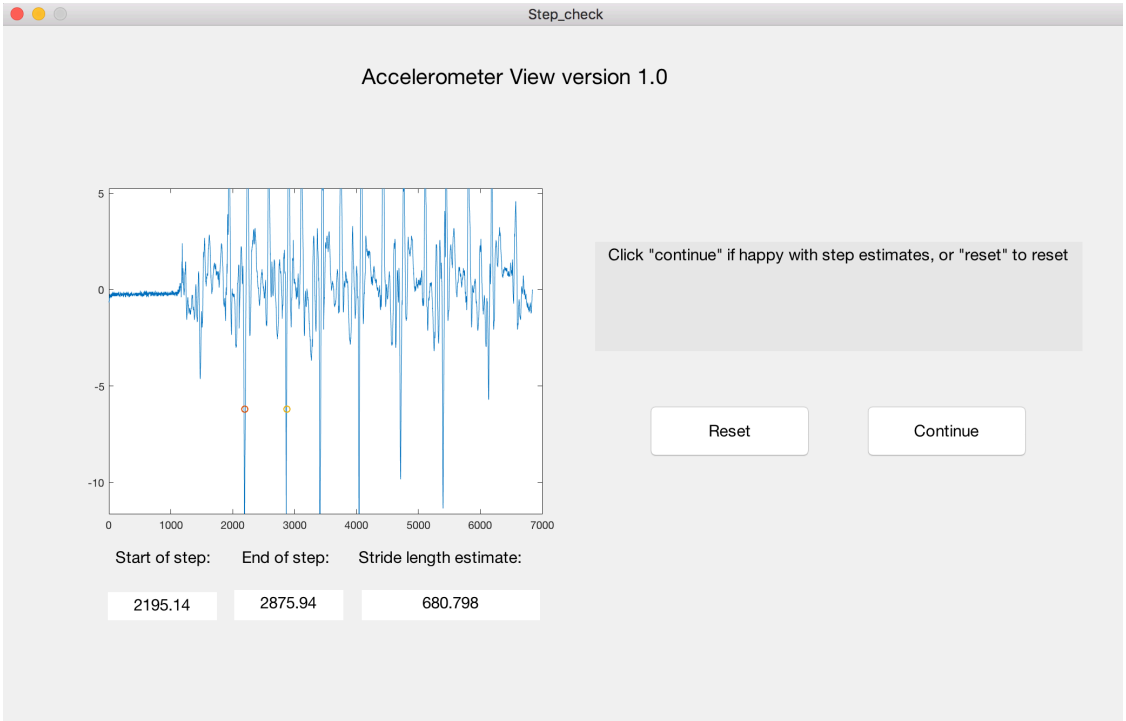

Figure 8-2 – Accelerometer app with user selected points displayed (red and yellow markers).
Calculated stride length is displayed in the box below the image.

identify a heel strike point (Figure 8-3). Once a maximum number of strides had been identified, the heel strike points were plotted on the complete tracing and displayed for confirmation by the user (Figure 8-4).

Following stride identification, the strides were extracted and processed, resampling each stride to 1000 frames to allow comparison across a common time reference. Each stride was compared the overall subject stride variance and any deviating stride displayed for confirmation of its correct extraction (Figure 8-5). Once all suspect strides have been highlighted, the program asks for confirmation that all strides look valid before continuing (Figure 8-6). Should any non-stride output be miss labelled it can be removed at this point.

The stride data was transformed as described in Chapter 8.2.5, using a wavelet transform, on a stride by stride basis. Each wavelet is saved as a 2D matrix containing the absolute value of the wavelet co-efficient for each time/frequency point.

The subject study group is entered for the purposes of classification, before the program creates output files containing the raw stride data, wavelet transform data and a spectrogram of the output for visual analysis, and adding the subject in turn to the Masterfile of all subjects (Figure 8-7, Figure 8-8).

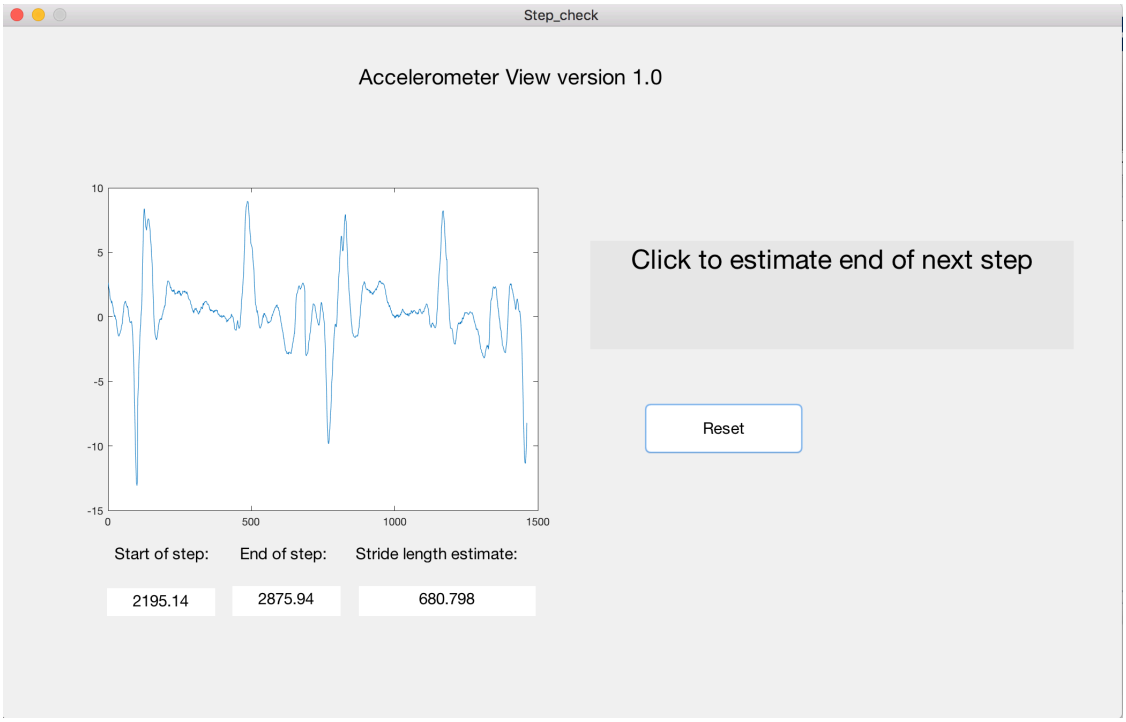

Figure 8-3 – Accelerometer application requesting a manual allocation of heel strike

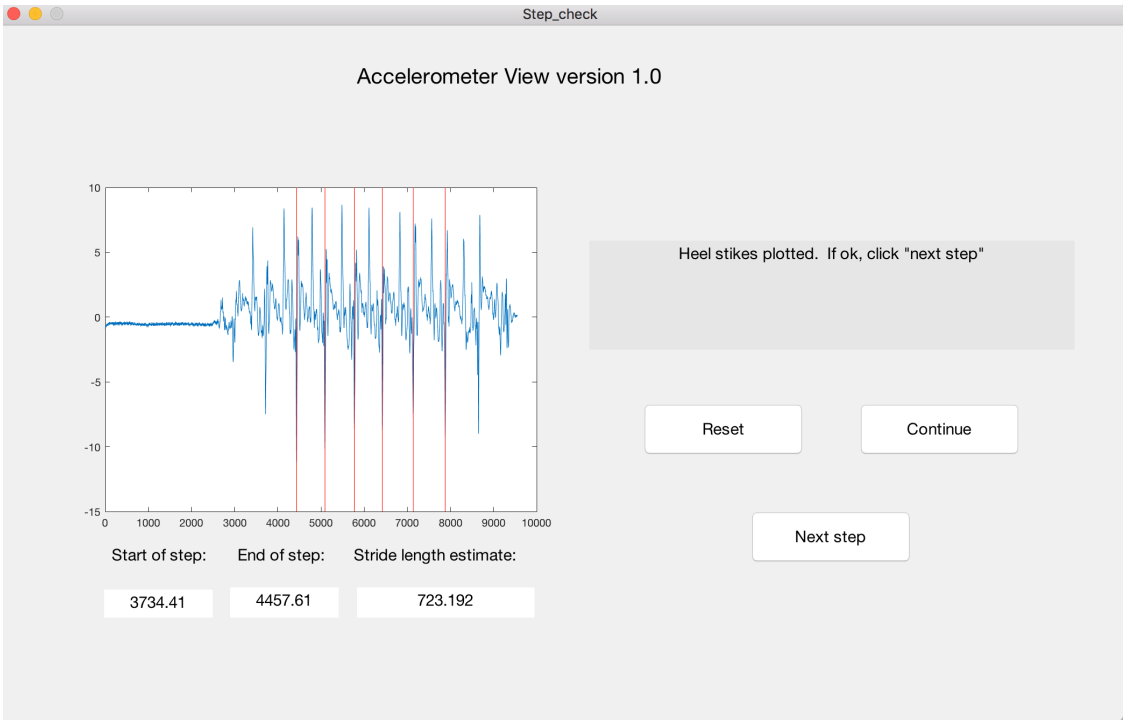

Figure 8-4 – Plotted heel strikes for confirmation by user

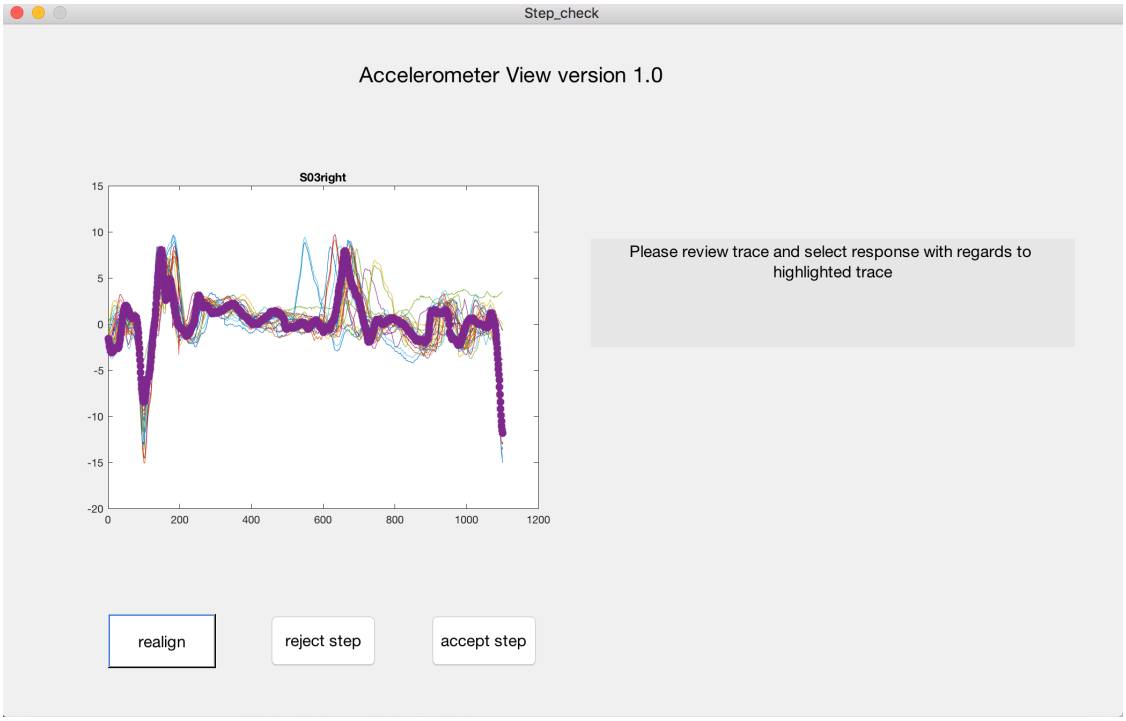

Figure 8-5 – Accelerometer identifying suspect stride and asking for confirmation

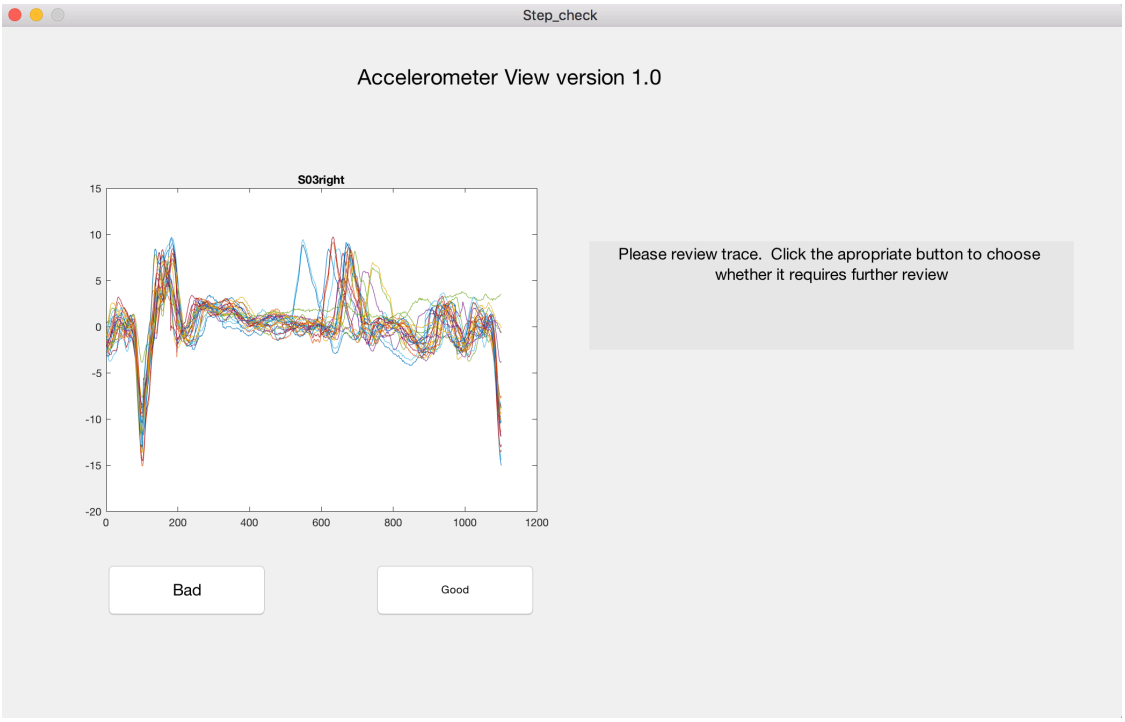

Figure 8-6 – Accelerometer App asking for confirmation of stride data extraction

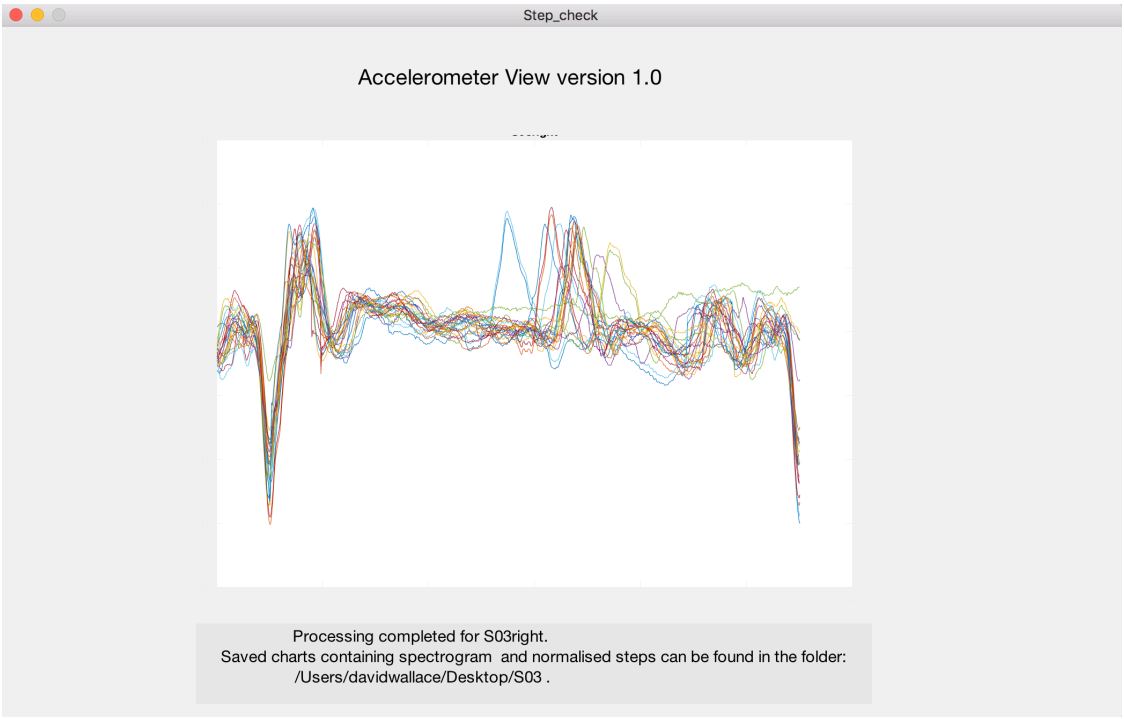

Figure 8-7 – Accelerometer App confirming completion of process

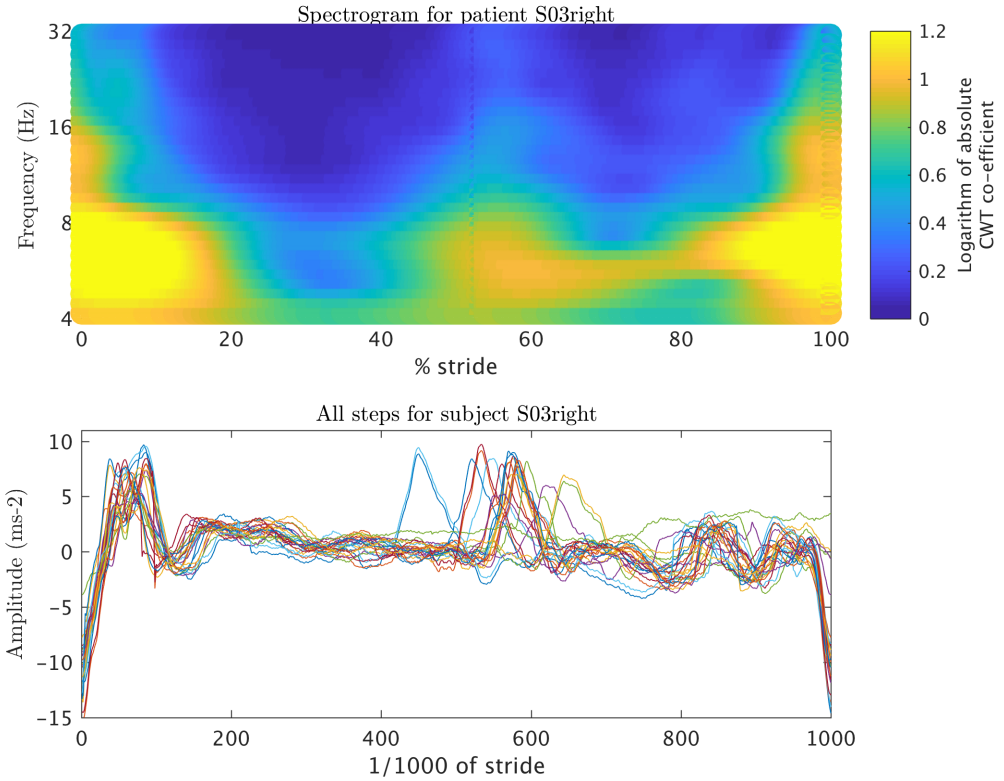

Figure 8-8 – Spectrogram file output for single subject

Output from accelerometer program showing wavelet transform (top) with overlaid accelerometer stride patterns (below). Initial acceleration is seen a 0% corresponding to heel strike, with a second spike corresponding to toe off between 45% and 65%.

8.2.6 HIGH DIMENSIONAL ANALYSIS, LEARNING AND CLASSIFICATION

Studies examining instability in the knee have generally focussed on identifying a specific characteristic that differentiates symptomatic stability and instability (Knoop *et al.*, 2012; Farrokhi *et al.*, 2014; Hamilton *et al.*, 2014). This involves *a priori* selection of specific parameters to assess, and the use of summary statistical tools. However, the goal of this study is to classify and quantify a phenomenon rather than explain its underlying pathophysiology. The use of various statistical and learning tools can therefore be employed to analyse movement at the knee.

The use of the CWT has been discussed in section 8.2.5. While this method allows appreciation of the accelerometer signal in both frequency and time domains, the resultant signal has a very high number of variables. This requires more than standard statistical analysis techniques.

Principal Component Analysis is a technique used to extract maximum amount of variance from a data set of observations of a group of participants in the lowest number of dimensions through the transform of multiple variables to a series orthogonal components, the sum of which contains the total variance of the dataset (Chau, 2001a). Co-efficients of the dataset are computed and used to find components where P_i is the *i*th Principal component found by the transform of variables *v* using the co-efficient *c*:

$$P_i = c_{i,1}v_{i,1} + c_{i,2}v_{i,2} \dots c_{i,n}v_{i,n}$$

Equation 8-1 – Calculation of principal component from co-efficient and original variables

Each component can be linearly combined to reproduce the produce an estimate of the original dataset as each component is uncorrelated, where $\hat{X}_n$ is the PCA estimation of the *n*th participant:

$$\hat{X}_n = P_{n,1} + P_{n,2} + \cdots P_{n,i}$$

Equation 8-2 – PCA estimation from principal components

however, the majority of variation in the dataset can usually be extracted from a small number of components, reducing the dimensionality of the data for analysis (Deluzio *et al.*, 1997). While interpretation of the meaning of each individual components can prove difficult (Deluzio and Astephen, 2007; Brandon *et al.*, 2013), in the case of classification, the components representing the highest variance can be used as variables for regression and learning models without the need to link to specific biomechanical events or characteristics, and is therefore commonly used as a feature selection tool for classification (Cabitza, Locoro and Banfi, 2018; Figueiredo, Santos and Moreno, 2018).

Consequently, in this study an attempt has been to use a simple gait acquisition by utilising a single joint in a single plane, while maximising the gait information obtained through a wavelet transform of acceleration data, principal component analysis and classification.

8.2.7 CLASSIFICATION MODEL

For each stride, the corresponding spectrogram was examined using an overlapping moving window. The size of the window was 2.5% (25 pixels) of the gait cycle horizontally and five frequency divisions. The window was moved over the

spectrogram, overlapping, providing 125 windows throughout the gait cycle (horizontally) and 25 windows through frequency (vertically), giving 4625 windows in total. The intensity within each window was averaged, and then a z-score for the stride was calculated by subtracting the mean window intensity over all 718 strides of all groups and dividing by the standard deviation of that window over all strides.

Thus, each spectrogram was converted to 4625 z-scores. Principal component analysis was used to create orthogonal, linear combinations of these 4625 z-scores that best explained 95% of the variance of the z-scores. This method of feature selection provided a dimensional reduction of the high dimensional CWT data while maintaining its variability for analysis, thereby preserving the variability inherent thought the waveform (Deluzio and Astephen, 2007; Figueiredo, Santos and Moreno, 2018).

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Using the principal component scores as predictors and self-reported stability class as response variable (1 = unstable, 0 = stable) a logistic regression linear classification model for binary learning was produced. This was validated using a k-fold partition with "leave one out" method, from which classification error was identified. K-folding divides the data into *k* "folds" where, for each fold of data, the remainder of the data set is used for algorithm training before testing on the held-out data. This is repeated *k* times and the classification results for each fold added together to calculate the specificity and sensitivity of the algorithm. By k-folding the data, the tested data is held out from the training data to create the classifier, avoiding over fitting where the classifier is trained on the same data it will be tested on, but all data can still be used. A "leave one out" method uses *n* folds of data, where *n* is the number of data points

available, thereby classifying each data point using a classifier trained on the remainder of the data. Each stride was classified using this method from the wavelet transform PC, with model classification being analysed based upon the results for all strides. Using predicted classification as an integer value, mean stability across all strides was then identified for each subject. The hypothesis was that increased "unstable" type strides would be associated with an increased awareness of aberrant knee movement and therefore greater awareness of instability in the knee. This predicted instability value was then plotted against self-reported stability to determine separation.

8.2.8 MODEL COMPARISON

When analysing stride data for a learning model there is a risk of model biasing where some of one subject's data is used in a training set to validate on the remaining strides. This can lead to the specific subject features rather than the characteristic features predicting the target parameter (Halilaj *et al.*, 2018) In order to avoid this, the learning algorithm was re-run using a subject-hold-out validation technique where all subjects minus one were used for training, then the algorithm used for testing, with this repeated for each subject. Various normalisation parameters were attempted for the wavelet transform using subject height and weight with classification error used to determine the most useful. Demographics details (age, height, body mass) and mean stride time were introduced into the model in all combinations, with varying numbers of principal components to a maximum of 85% of wavelet variance. Due to the ultimate low dimensionality of the data following reduction techniques, two commonly used classification techniques: linear regression, and support vector machine (SVM) (Laroche *et al.*, 2014; Wu *et al.*, 2016; Cabitza, Locoro and Banfi, 2018; Figueiredo, Santos and Moreno, 2018; Halilaj *et al.*, 2018; Lapp *et al.*, 2018). SVM learning works

by finding the hyper-plane within the predictor variables that produces the maximum discrimination between classification. The learning model was optimised using classification error as a metric to the number of principal components and demographic details giving the best classification of individual strides. The model was then analysed for its performance using accuracy, sensitivity and specificity to detecting instability, and the area under the curve (AUC) from the receiver operating characteristics (ROC) (Cabitza, Locoro and Banfi, 2018; Halilaj *et al.*, 2018). Instability classification was examined at the cut-off producing the greatest sensitivity and specificity (Wu *et al.*, 2016).

Table 8-1 – OA stability demographics.
Comparison using two tailed t-test and Chi squared test as appropriate

Stability group	Age (years)	Male/Female	Height (m)	Body mass (kg)	BMI (km/m^{-2})
Stable (±SD)	68 (±6)	4 / 7	1.68 (±0.09)	87.35 (±16.39)	30.74 (±4.62)
Unstable (±SD)	73 (±5)	6 / 9	1.66 (±0.07)	85.47 (±13.98)	31.37 (±6.15)
p-value	0.039	0.851	0.377	0.756	0.775

8.3 – RESULTS

8.3.1 DEMOGRAPHICS

72 subjects were approached by the primary investigator and met the inclusion criteria between March 2018 and August 2018, and 26 subjects were recruited from the Golden Jubilee national hospital. Reasons for non-recruitment of subjects meeting the inclusion criteria included refusal to take part (2) surgery cancelled or delayed (27), attending for surgery when the investigator was not available (13), and last-minute scheduling to cancelled slots with no time for investigation (3). Comparative age and gender of those recruited and those not recruited can be found in Table 8-2. Of the 26 recruited patients, 11 responded that they had not experienced their knee buckling or giving way in the previous month. Demographic details of both groups are shown in (Table 8-1).

Table 8-2 – Demographics of recruited vs non-recruited subjects

Variable	Recruited	Not recruited	p-value
Age	70.6	68.2	0.079
Gender	23M/ 22F	11M/ 15F	0.474

8.3.2 DATA ANALYSIS

From 26 subjects, 718 strides were extracted (mean 27.6, std 4.8, range 17-35). Wavelet analysis graphing showed no clear increase in frequency in the 4-8Hz range during swing phase for unstable OA knees as was seen in TKA subjects with subjective instability (Figure 8-9). PCA resulted in 717 components with 95.11% of the variance was explained with the initial 37 principal components, with the first 4 explaining more than 50% of the variance of the whole data (Figure 8-10).

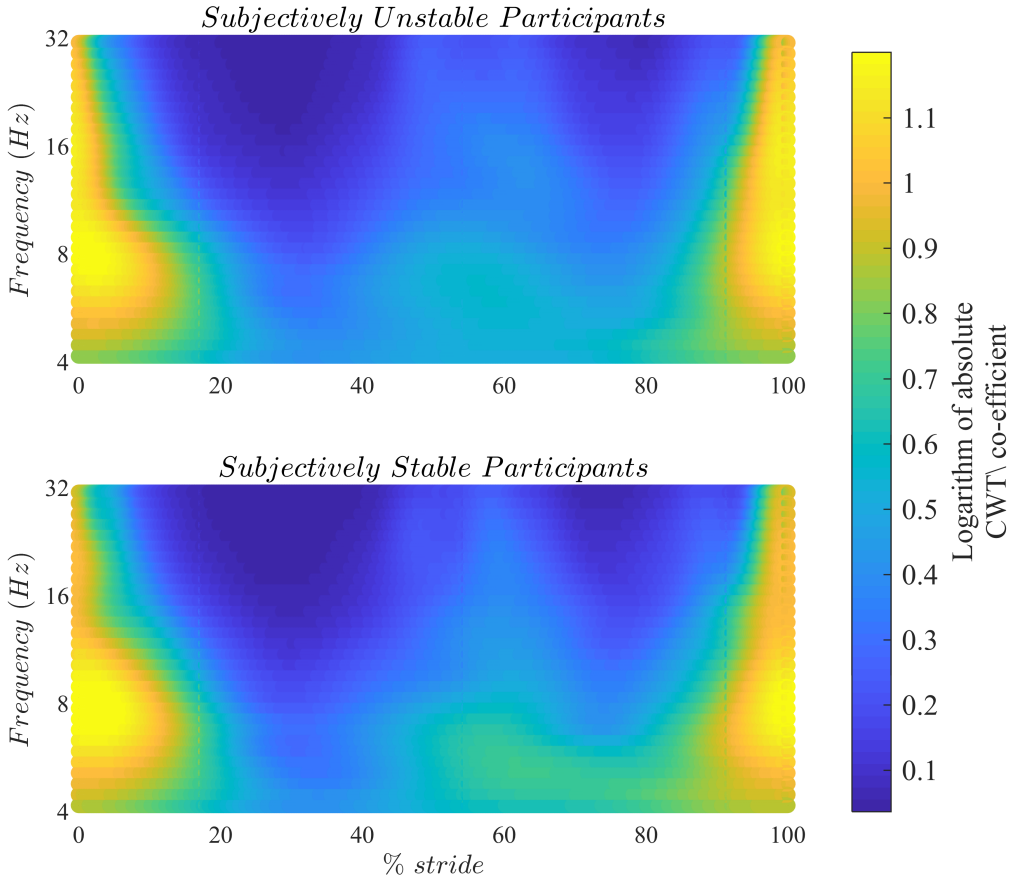

Figure 8-9 - Wavelet transform for OA knees.
Colour denotes absolute value of CWT for each time/frequency point. Each graph shows mean of mean wavelet for each subject within each group

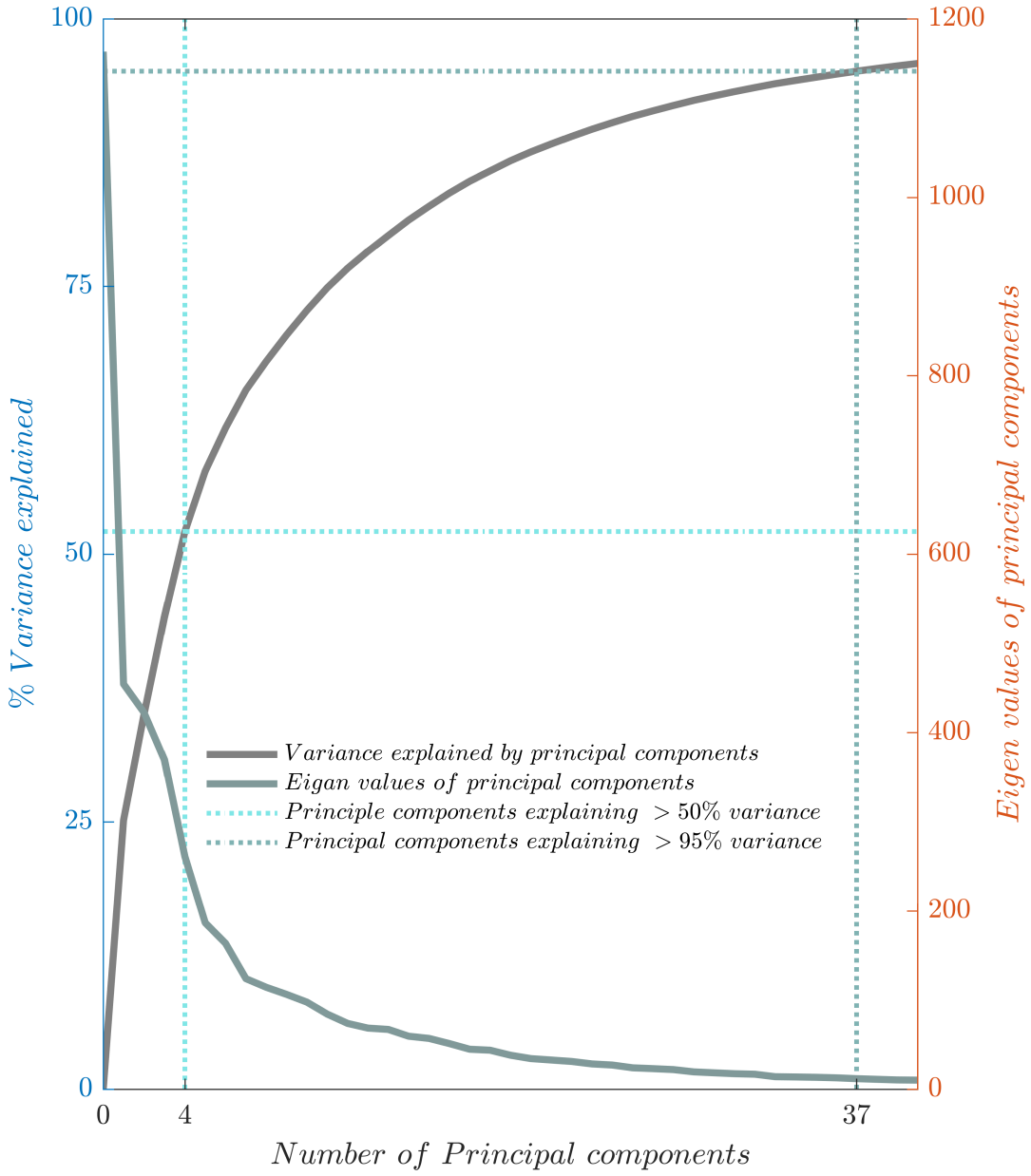

Figure 8-10 – Scree plot showing variance and Eigen values across principal components

Logistic regression using k-fold validation showed a classification error of 0.2131 on stride by stride analysis. With predicted stability per stride averaged for each subject, the two groups separated, with 96% of subjects correctly classified at an instability prediction cut-off of 0.5 (Figure 8-11).

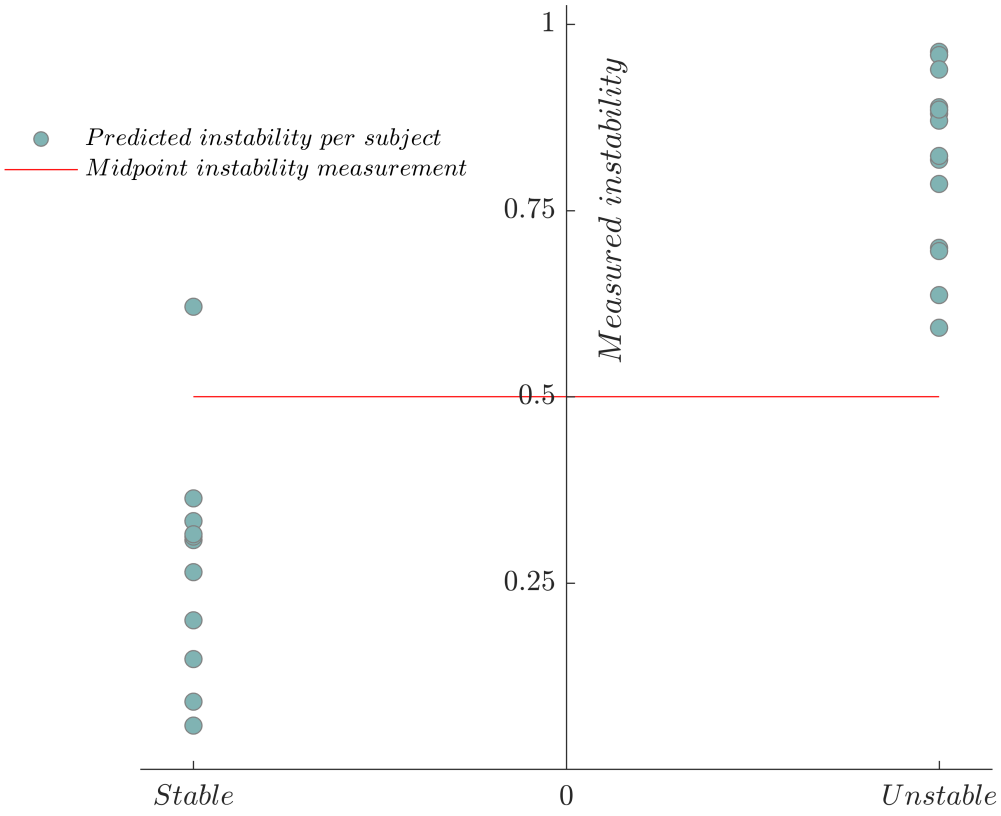

Figure 8-11 – Predicted vs self-reported instability.
Each dot represents a subject. Self-reported stability is shown on the x-axis as a binary classification, while predicted instability is shown as a continuous variable from the mean of all classified stride for each subject. The arbitrary classification cut-off is shown in red at 50% instability.

8.3.3 SUBJECT-BY-SUBJECT LEARNING

For subject-by-subject learning, the learning model resulted in the wavelet being normalised by dividing by body mass squared. After optimisation, age was the only remaining demographic in the calculation for the logistic regression model (Figure 8-14). The first 10 principal components were included, giving a classification error for the strides 0.273. For the SVM, age, height and stride duration were included, as well as the first 21 principal components, giving a classification error of 0.230. The strides were reconstituted into subjects with instability grading defined as the mean of the binary classifications of all strides. Using optimal cut-offs, a sensitivity of 72.7% and a specificity of 93.3% was calculated (Table 8-3, Figure 8-12,Figure 8-13).

Table 8-3 – Performance of learning model.
Diagnostic table for algorithm with sensitivity, specificity and area under the curve (AUC) for receiver operating characteristics

	Class positive		Class Negative	
	LR	SVM	LR	SVM
Test positive	14	12	3	3
Test negative	1	3	8	8

	Linear regression	SVM
Accuracy	84.6%	73.1%
Specificity	72.7%	63.6%
Sensitivity	93.3%	80.0%
AUC	0.797	0.712

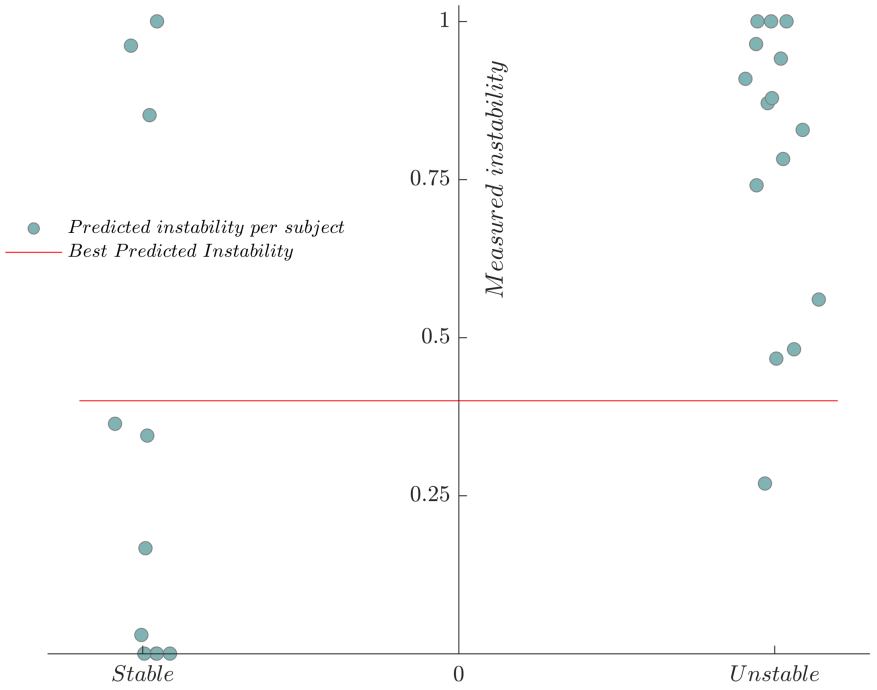

Figure 8-12 – Subject classification using subject-by-subject algorithm. Each point represents a subject. X axis denotes subject identified instability, Y axis denotes classification through algorithm. A jitter has been added to the x-axis to prevent point overlap for easier reading. A best cut-off of 40% of strides classified as unstable has been plotted.

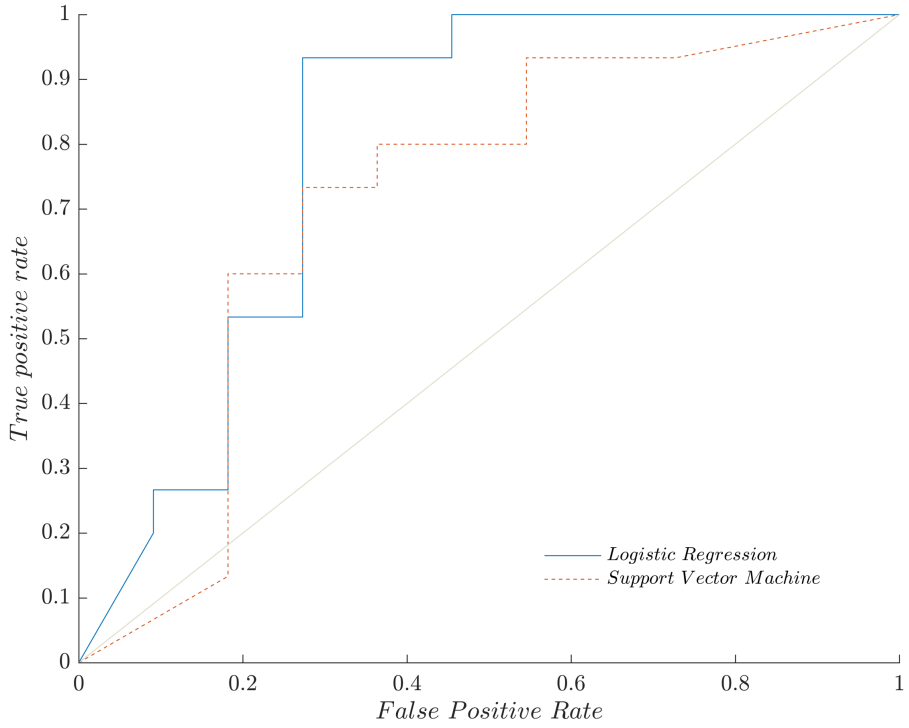

Figure 8-13 – ROC curve for logistic regression and support vector machine methods

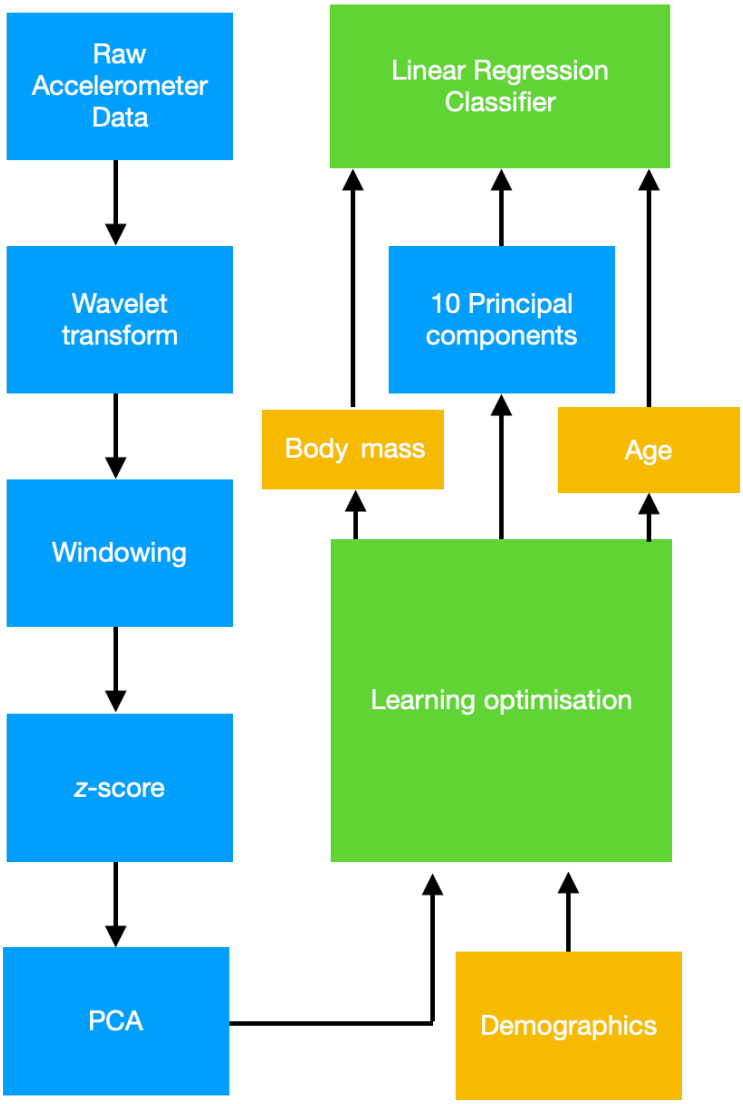

Figure 8-14 – Flow diagram of data analysis and classification
Raw data transformed to principal components of wavelet transform. Demographic details added such as age, height and body mass. Learning models tested and optimized using SVM and LR in varying combinations of number of principal components and demographics. K-fold test-training of data using leave-one-out and subject hold-out. Final combinations chosen based on classification accuracy

8.4 DISCUSSION

Instability in the OA knee is a common symptom, subjects (Fitzgerald, Piva and Irrgang, 2004; Knoop *et al.*, 2012; Nguyen *et al.*, 2014; Sharma *et al.*, 2015; Fleeton *et al.*, 2016). However, lack of quantitative analysis of this phenomenon has left assessment to subjective clinical assessment and patient reported symptoms (Parratte and Pagnano, 2008; Browne, Parratte and Pagnano, 2012; Abdel *et al.*, 2014; Petrie and Haidukewych,

2016). This study shows that a simple, unidirectional accelerometer, mounted on the proximal tibia, can be used to differentiate the strides of subjectively stable and unstable patients with osteoarthritis of the knee (Figure 8-11, Figure 8-12).

In this study, an unstable knee is defined as one where the patient reported the sensation of "giving way" or "buckling" in the knee in the previous month. Following the distinctive pattern was shown of increased absolute co-efficient of CWT between 4 and 16Hz in the range of 35-90% of stride in some strides in subjectively unstable TKA patients in comparison to stable TKA subjects using a wavelet analysis (Figure 7-8), a difference in pattern between subjectively stable and unstable patients searched for in osteoarthritic knees. This pattern has not been repeated in osteoarthritic knees (Figure 8-9), suggesting a difference in mechanism for instability in the OA knee. This is consistent with the suggestions of instability in the knee being a consequence of poor intraoperative ligament balancing (Browne, Parratte and Pagnano, 2012; Abdel and Haas, 2014; Vince, 2014) – a problem that would not be present in the native knee. However, it does not counter the hypothesis that it is the overall failure of ability to neutralise a destabilising impulse the knee that results in symptomatic instability, only that the particular point of maximal instability is different. However, the ability to classify with high specificity indicates differences in knee movement between OA unstable and stable groupings, confirming the proposed hypothesis (Table 8-3). Should this classification be quantifiable, it may be possible to measure the effect of strategies to improve knee stability, such as physiotherapy, previously only possible using subjective PROMs assessment (Knoop *et al.*, 2014), or even to provide pre-operative

risk stratification to patients undergoing TKA due to the association between pre- and post-operative subjective instability previously shown (Chapter 4).

This study differs in approach to previous researcher who have examined the unaltered acceleration output from the knee (Khan *et al.*, 2013), or Fast Fourier Transform (Soeno *et al.*, 2018) in an attempt to differentiate between subjectively stable and unstable total knee replacements. Although discrete wavelet transform has been used previously as a method of filtering accelerometer signal for kinematics (Ismail and Asfour, 1999) and tibial acceleration (Clark, Bartold and Bryant, 2010), this is the first time the continuous wavelet transform has been used for the accelerations in the knee. This allows the measurement of frequency data that may be associated with increased movement or vibration that may not be detected in acceleration alone.

Use of machine learning techniques allows relationships between high dimensional data to be identified where traditional statistical methods cannot be used (Halilaj *et al.*, 2018). Examination of the wavelet transform in association with PCA has allowed us to retain the variation of the high dimensional data during its assessment using while reducing the variables for analysis, rather than reducing it to summary measures (Chau, 2001a; Halilaj *et al.*, 2018). This method of feature selection has been used previously to analyse and classify gait data, to differentiate between those with and without OA (Deluzio and Astephen, 2007; Laroche *et al.*, 2014). Further, machine learning algorithms were used to classify subject's instability, comparing to self-described instability. Previous studies have used 3D gait analysis and support vector mechanism (SVM) learning to classify OA in the hip (Laroche *et al.*, 2014), and regression tree

modelling for OA knee classification (Mezghani *et al.*, 2017), but as far as can be identified, this is the first time that learning techniques have been used to identify biomarkers for a specific OA symptom classification. Moreover, this is the first to rely on a portable, inexpensive device.

Our data shows a classification error in 0.27% of strides, with a final subject accuracy of 84.6%, sensitivity of 72% and specificity of 93.3%, with an AUC of 0.797 using a linear regression model. Previous studies classifying OA using gait analysis have found higher accuracy (Mezghani *et al.*, 2017), however this is the first time that a learning algorithm has been used to classify an OA knee symptom. The low number of subjects and relative effectiveness of the learning model suggests that there is merit in this approach and method. Further subject testing will be required to optimise the model further, but this early work confirms effectiveness of the technique.

One limitation of this study is the change in method between first and second parts of this accelerometer study (chapter 8 and chapter 9), with the application of a compression bandage over the accelerometer in the second part (chapter 9). While this limits the cross-study comparison, extensive review of methodology following the first part required the addition of the crepe bandage to remove any suggestion that the oscillations recorded were due to inadequate loading of the accelerometer. It is notable that there is clear pattern of high low frequency intensity in the swing phase of unstable TKA participants that was not present in the OA participants (compare Figure 7-7, Figure 8-9). While it may be a possibility that the pattern detected was merely an artefact eliminated by the application of a crepe bandage, it seems more likely that the

clear distinction between stable and unstable waveforms in TKA participants is a genuine phenomenon, with a differing underlying pathophysiology in the OA knee. The increased signal was clearly visible in a particular portion of the spectrogram in unstable TKA subjects only. This would be consistent with the markedly different anatomical, physiological and biomechanical environments present in the OA and prosthetic knee, and with the proposed mechanism of mid flexion laxity as a contributor to instability that would be most prominent within the swing phase of gait (Minoda *et al.*, 2014). Instead, the CWT technique appears to be robust to detect differences in both biomechanical environments, as clear differences exist in the spectrograms in the TKA context between symptomatically stable and unstable knees (Chapter 7), and a classifiable difference between symptomatically stable and unstable in OA. Further investigation with higher subject numbers should be undertaken to confirm this finding in the TKA subject group with the new methodology. A further limitation is the small number of subjects in this study. While the total number of assessed strides is high, (718) this only represents 26 individual subjects. Clinic and surgical scheduling resulted in lower recruitment that expected, however the performance of the classifier on this small data set gives grounds for validation on a larger data set.

In order to implement a useful clinical device an easy application and data retrieval process is required. Further development will be required to improve mount and data processing for clinical use. Short acquisition time already has allowed ease of use in recording data, but a more automated post-process will be required to translate this method into the clinic. However, the utility of a device to classify and then quantify instability within the knee is of value in both the clinical and research context. An

objective measurement of instability will allow the directed treatment of methods to enhance stabilisation in the knee, such as physiotherapy to enhance muscle function or bracing, as well as allowing the monitoring of response. Further, in chapter 4 the association between pre-operative and post-operative TKA instability was determined. It may be possible to give bespoke risk assessment of post-operative instability with the ability to quantify pre-operative instability. This could be of value in determining operative technique and decisions to use increasingly constrained prosthesis based upon pre-operative stability.

8.5 – CONCLUSIONS

This study has shown that a single accelerometer mounted on the lateral tibia can be used to differentiate between OA knee patients with subjectively stable and subjectively unstable knees during walking. The detection of such a clear and measurable difference between the two subject groups demonstrates a clear biomechanical between subjectively stable and unstable groupings. The ease of use and comparative affordability of the device makes it ideal for clinic use where a quantifiable measurement of instability may be of benefit in prescribing and monitoring treatment or making decisions about surgical technique. Further development will allow useful quantification of subjective instability in the orthopaedic clinic.

CHAPTER 9 – DISCUSSION

9.1 DEVELOPMENT OF A PROTOCOL FOR THE QUANTIFICATION OF KNEE STABILITY IN NATIVE AND ARTHRITIC KNEES

The overarching aim of this project is the development of a protocol to quantify instability in the knee, in both the osteoarthritic and prosthetic population based upon the model of instability set out in the introduction. Previous studies have given some indication as to the prevalence of self-reported instability in the osteoarthritic knee Fitzgerald et al. 2004; Knoop et al. 2012; Fleeton et al. 2016; Sharma et al. 2015; Nguyen et al. 2014) and prosthetic knee (Sharkey *et al.*, 2002, 2014; Le *et al.*, 2014; Lombardi, Berend and Adams, 2014; Thiele *et al.*, 2015; Delanois *et al.*, 2017). It is notable in all of these studies that the method of assessment of instability is subjective – either that of the patient or the investigating surgeon – with no method of objective quantification.

Several authors have attempted to quantify instability using standard methods of gait analysis in OA knees (Creaby *et al.*, 2013; Farrokhi *et al.*, 2014; Gustafson *et al.*, 2015), and following TKA (Hamilton *et al.*, 2014). While some early success in differentiation of subjectively stable and unstable subjects has been demonstrated through the development of these devices, it is notable none have resulted in devices useful in the clinic. In each instance the device used is cumbersome and time consuming to use.

In this project a quantification of the problem on knee instability has been carried out

through use of the NHS digital Patient Reported Outcome Measures dataset allowing an examination of OKS pre-and post-operatively in thousands of patients attending of primary TKA. The results of this study will be examined in section 9.1.1. To determine the instance of instability as a cause of revision, case notes for all revision knee replacements carried out at a National Referral centre over a six-year period were examined, with the results here discussed in section 9.1.2. The literature on frontal plane dynamics will be discussed in section 9.1.3, examining the rational for selecting a single channel accelerometer in section 9.1.4, followed by the first and second trial using the selected device.

9.1.1 INSTANCE OF INSTABILITY IN OSTEOARTHRITIC POPULATION

Our study of data from the NHS digital Patient Reported Outcome Measures dataset showed the prevalence of symptomatic instability in the OA population attending for TKA (Chapter 4, Figure 4-1). This showed that not only did 65% of patients report feelings of buckling or giving way in the knee often or more frequently before TKA, more than 10% reported those feelings after TKA (Table 4-3). Furthermore, some subjects reported knee stability worsening following TKA surgery (Figure 4-3). This is the first study to show the extent of subjective instability in the knee prior to, and following TKA, in such a large patient cohort (43994 subjects). The use of the OKS as the measure is opportunistic due to its availability in the available database, however the final result is similar studies using an adapted KOS-ADL (63% in 105 participants), KOS-ADL (72% in 390 participants) (Fitzgerald, Piva and Irrgang, 2004; Fleeton *et al.*, 2016). This high proportion of subjects with pre-existing subjective instability, and the prevalence of instability post-operatively highlights the importance of this symptom, and therefore of being able to objectively classify it.

9.1.2 INSTANCE OF INSTABILITY AS A CAUSE FOR REVISION

Our data retrospective data analysis of the indications for revision from primary TKA in a tertiary orthopaedic unit showed instability as the third most common reason for revision (appendix A). This is consistent with previous studies suggesting that, despite improvement in techniques and materials, knee instability is a persistent cause of failure (Pitta *et al.*, 2017; Postler *et al.*, 2018). Further, this study has shown that instability as a cause of revision is much lower in a navigated TKA group (see appendix A, Figure 12-2). This is consistent with both meta-analysis findings that navigated knee replacement improves precision in mechanical axis alignment, femoral and tibial component alignment (Fu *et al.*, 2012; Hetaimish *et al.*, 2012), and the hypothesis that it is poor balance and alignment that contributes to instability (Parratte and Pagnano, 2008; Abdel and Haas, 2014; Vince, 2014). A significant limitation in the study of instability as a cause of failure is the lack of objective measurement. Consequently, a mixture of patient reported symptoms, clinical examination and simple radiological examination have been used to examine and determine instability (Yercan *et al.*, 2005; Parratte and Pagnano, 2008; Abdel and Haas, 2014; Petrie and Haidukewych, 2016; Vince, 2016; Wilson *et al.*, 2017). In defining and managing infection in TKA – another "top 3" cause of failure (Table 11-6) - much work has been done in creating an agreed definition of periprosthetic joint infection in order to better research and treat this condition (Parvizi *et al.*, 2011, 2018; Parvizi and Gehrke, 2014). The prevalence of instability as an aetiology demands a similar classification and measurement.

9.1.3 STANDARD GAIT ANALYSIS AND INSTABILITY IN THE KNEE

Beyond the subjective identification of instability through patient reported outcome measures much effort has been expended in attempting to quantify instability in the

knee (Table 2-1 – Summary of Studies Examining Instability). Various parameters in the gait cycle have been considered as measures of instability including varus-valgus movement (van der Esch *et al.*, 2008), walking stiffness (Gustafson *et al.*, 2016), and internal contact point movement (Farrokhi *et al.*, 2015), as well as novel techniques such passive stiffness (Creaby et al. 2010) or fly wheel power (Hamilton *et al.*, 2014).

The limitations of standard gait analysis in the classification of disease due to the common distillation of its high dimensional data to simple summary parameters have been discussed previously (Deluzio and Astephen, 2007; Laroche *et al.*, 2014; Mezghani *et al.*, 2017). Traditional analysis have relied on manual feature selection of means and standard deviations of a small number of gait parameters, loosing large portions of the gait features in the process (Deluzio and Astephen, 2007). Further standard methods of gait analysis are time consuming and expensive, leaving little possibility of their routine incorporation into every-day clinical care. Consequently, the aim of this study is to look beyond traditional gait analysis to a practical method of assessment that could be used in the hospital environment.

9.1.4 THE SELECTION OF THE ACCELEROMETER AND THE FRONTAL PLANE

In selecting a method of assessing knee instability, the principle goal has been portability and ease of use. To that end, an accelerometer was chosen. Accelerometers have been used extensively in gait analysis to date (Table **2-3** – Accelerometers used in Gait Analysis). Several studies have studied the frontal plane waveform during walking

to examine lateral thrust in ACL deficient knees using a tibia-mounted accelerometer (Yoshimura *et al.*, 2000; Yoshimura, Naito and Zhang, 2002), and to examine variability of lateral acceleration during phases of the menstrual cycle (Clark, Bartold and Bryant, 2010). The use of frontal plane measurements to differentiate between stable and unstable OA subjects has already been measured using an isokinetic dynamometer (Mark W Creaby *et al.*, 2010), while visual identification of various thrust has been examined as a marker of worsening OA (Chang *et al.*, 2004, 2010). Further, the discussion of causes of instability in the knee centres on the flexion-extension gap imbalance, resulting in a change of congruence in the frontal plane as the knee moves between flexion and extension (Abdel *et al.*, 2014; Vince, 2016), asymmetric gaps between flexion and extension result in varying laxity of the collateral ligaments during flexion, leading to potential instability (Figure 2-3). Consequently, the use of a tibial mounted accelerometer in the frontal plane was chosen for this study to quantify instability in the native and OA knee.

9.1.5 CONCLUSIONS

Subjective instability in the OA knee is common, occurring in 65.4% of 43994 subjects presenting for primary TKA and present in 10.2% post-operatively (Table 4-3). It was the reason for revision from primary TKA in 17.7% or cases performed at an arthroplasty tertiary referral centre between 2012 and 2017 (Table 11-2). Currently no method of objective assessment is in routine clinical use for measuring instability in the knee, however several parameters have been identified such as reduced stiffness, reduced walking speed, increased flexion and increased internal contact point movement that differentiate subjectively stable and unstable OA knees. However, these assessments require the use of bulk, expensive and time-consuming devices that have

little practical value in the clinical environment. Further, little progress has been made to classify, and eventually quantify, instability. In this study a simple portable tool has been utilised to quickly and simply record knee movement in a single plane, while employing advanced analysis techniques to maximise the retained gait information in order to classify instability effectively.

9.2 THE ACCELEROMETER AS A DEVICE FOR THE QUANTIFICATION OF KNEE INSTABILITY

Three trials have been undertaken to develop a device for the quantification of instability in the knee. Initial testing has shown the repeatability of the device using summary statistical values (Chapter 6) while the device was measured on healthy, subjectively stable and subjectively unstable TKA patients (Chapter 7). Finally, following review of the protocol and data from these initial trials, a final assessment protocol was devised and tested, using the analysis methods outlined in Chapter 8. While the TKA testing protocol and analysis gave much useful information for the development of the device, and insights into the reasons for instability in the TKA, its value was mostly as validation of the concept of a single accelerometer for the collection of gait data.

In Chapter 7 it has been shown using visual review of the data that there was a perceptible difference between the frequency-time domain outputs of lateral knee acceleration between symptomatically stable and unstable TKA patients. Using standard gait analysis, a difference in KAM between subjectively stable and unstable

TKA patients, and healthy controls was shown as well as a trend for reduced stiffness. While reduced stiffness had been used in osteoarthritis previously (Gustafson *et al.*, 2016) this has not previously been shown in TKA subjects. However, this fits with the theory of an unstable knee as a being a joint that is less controllable than a stable one. If mechanical stiffness of the joint is on preventer of excessive movement, then it makes sense that here its absence would make excessive movement easier. Notably, this is measuring in a different plane that that of the accelerometer, but Creaby et al. (2013) found a similar reduction in stiffness in the frontal plane in symptomatically unstable OA patients, under passive non-weight bearing conditions. Each of these elements are part of the control system making up a stable knee, and each missing or damaged system results in a greater risk of symptomatic instability. Previous studies attempting to objectively classify instability have also examined measures that may be interpreted as loss of knee control. In their quantitative assessment of post-operative instability Hamilton et al. (2014) showed a reduction in power during extension power testing on a flywheel using the Nottingham power rig. This is consistent with a failure to control the knee throughout flexion.

In the accelerometer study it was demonstrated that there was an increased CWT power in the low frequency swing phase of gait. In this situation, the knee, loaded by bodyweight through the stance phase, has moved to the unloaded situation, and is relatively un-compressed. The effect of compression on frontal and sagittal plane stiffness has been modelled using finite element analysis, with reduced stiffness seen in the unloaded situation (Marouane, Shirazi-Adl and Adouni, 2015). This suggests that the knee in swing phase is less stiff and therefore more easily perturbed. If, as is shown

in previous OA studies (Creaby *et al.*, 2013; Thorlund *et al.*, 2014), the subjectively unstable knee is less stiff anyway, the cumulative effect of unloading and an inherently pliant joint is increased movement during swing phase. Consequently, the knee is likely to be at less well controlled through the swing phase with increased variability in positioning at heel strike and re-loading of the joint. This, in turn, may lead to increased difficulty in achieving stable walking. Following re-loading of the joint, and the initial spike CWT intensity at heel strike, the signal decreases during stance, likely due to the dampening effects of increased knee stiffness in the loaded joint. This increased signal during swing did not occur on every stride of every symptomatically unstable subject, but rather in some strides only. This is consistent with patient experience that knee instability is not with every stride. It matches with our theory of instability as being caused by increased time spent in the boundary conditions between stable and unstable conditions, and the additive effect of uncontrolled impulses (Figure 1 4 – Diagrammatic representation of the knee undergoing multiple impulses), as not every stride requires time in boundary zone, and not every "stable" knee will be equally contained on each stride. Similarly, in the accelerometer measurement of OA knees the unstable knees were correctly classified 93.3% of the time however, as each stride was classified separately and averaged for all strides, not all subjectively unstable subjects had all strides classified as unstable.

In assessing risk of fall, research focuses on the concept of human gait as a system of diverging and correcting patterns of movement, where stability may be assessed by measures such as the short and long Lyapunov exponents, or local divergence exponents (λ_S , λ_L) (Yakhdani et al. 2010; Bruijn et al. 2013; Mahmoudian et al. 2016). Here, the

stability of the system is described as its ability to recover from perturbation. In a walking system, any variability is determined to be a perturbation, with the position of the system at a given past time is said cause the variation at the current time point (England and Granata, 2007). The divergence from a trajectory is measured, with the most stable systems having a the lowest divergence (Mehdizadeh, 2018). In the knee, the ability to control divergence is through active and passive systems of muscular, ligamentous and bony restraint. In normal gait (that is, without fall) it may be assumed that while perturbation occurs it is always within the limits of the control systems. When conditions arise to push beyond the limits of control systems, buckling or giving way of the knee may occur. It may therefore be reasonably assumed that in the unstable knee there occur many instances where movement, here measured as acceleration, is beyond that of a "normal knee" but not so much as to cause a destabilisation of the system due to the actions of control systems. Consequently, while symptom based estimation of instability are confined to instances when either conscious control of the knee is required (a feeling of giving way without actual giving way) or complete failure of control (giving way or buckling with or without fall), measurement of instability in the knee through acceleration based wavelet transform may measure the conditions through which the knee approaches higher levels of perturbation without ultimate failure. Therefore, the measurement of percentage of strides exhibiting behaviour consistent with subjectively unstable behaviour may be used as the basis of instability quantification.

The use of the medial-lateral accelerations only is used due to the previous documentation of medial-lateral stiffness and its association with instability (Mark W

Creaby *et al.*, 2010; Creaby *et al.*, 2013; Thorlund *et al.*, 2014), and the added complexity required to compensate for shank rotation in the sagittal plane, and process three times the data volume.

9.3 FUTURE DEVELOPMENT AND USABILITY

Assessment of instability in the clinic setting requires a device that gives high specificity and sensitivity, low cost and ease of application. The tested device has demonstrated aspects of all of these conditions, but with room for improvement. The data training and assessment method has been based upon the low number of subjects present. K-folding techniques were used to avoid the pitfall of classification data contaminating data, however, the total number of subjects available have prevented the use of hyperparameter tuning due to the need to divide data into train, test and validation series (Halilaj *et al.*, 2018). The acquisition of a larger dataset will allow these techniques to be employed to better effect.

Following the first accelerometer trial (chapter 8) it was identified that the interface between accelerometer and shank had been a potential area for noise. The protocol was changed to add the application of a compression bandage. Further, attempts were made to create a mount that was adjustable through three degrees of freedom to improve alignment (Chapter 9.1). Unfortunately, the design of the mount was ultimately unsuccessful with material failure prior to achieving acceptable rigidity. In the future, work should be done to design a mount allowing ease of application and control of

alignment to the knee joint. This is likely to result in better data acquisition and greater ease of application of the accelerometer.

The use of a graphical user interface (GUI) for the acquisition and pre-processing of accelerometer data improves the usability of the device significantly (figures 9-1 – 9-7). This automates significantly the process of extracting stride data, cleaning raw data, and performing wavelet transform. The current GUI shows the possibility of producing a user interface to allow easy transform of raw data to a classified outcome without the need for specialist knowledge – a process that is not possible using standard gait analysis – which could be of value in a hospital clinic environment. It is proposed that, following collection of a large database of instability data with the finalised protocol, a classification model could be built and integrated into software to output a final classification and quantification in addition to the current visual output (Figure 8-8)

One limitation in the presented data set is that between the first (chapter 8) and the second (chapter 9) investigation, the protocol for investigation was changed, resulting in improved attachment of the accelerometer between first and second trial, as well as a significant change in the analysis. While a re-analysis of the original data from chapter 8 with the new learning algorithm has been presented in Appendix B, further work will be required involving the new testing equipment and protocol to quantify instability in the TKA. Further, Hamilton et al. (2014) discuss the need to compare differing types of failure in revision situations to differentiate between classifying instability and classifying failure more broadly. The results from the presented study give strong indication from the wavelet pattern in the failure group, previously discussed in Chapter

8, that the aetiology of differing outputs is instability as the area of increased time-frequency power is that consistent with a low compression environment where control of the knee would be minimise, however now that the validity of the device has been show, larger, and broader, testing is indication. (Re-analysis of the TKA group was conducted using the data processing and classification methods of Chapter 9 finding a less satisfactory classification system (Appendix B). Repeated testing on a larger group using the new protocol would address the issues associated with the larger classification errors found here).

It is of note that while a mechanical difference in the in both OA and following TKA between patient-reported stability groups has been identified, whether this difference is a manifestation of instability or merely an association requires further experimentation. The use of the accelerometer with CWT analysis should be useful in further work to determine the specific anatomical and biomechanical meaning of differences in signal between groups.

9.4 THE ACCELEROMETER AS A DEVICE FOR THE QUANTIFICATION OF KNEE INSTABILITY

The thesis has demonstrated that, during normal walking gait, there are differences in the lateral acceleration of the proximal tibia between groups of subjectively stable and unstable TKA, OA and control groups. However, the subjectively unstable TKA group has a different frequency signature to subjectively unstable OA group (figure 7-7 and figure 8-9). Thus, this suggests that the mechanism of subjective instability is different

between these groups: the subjectively unstable TKA group demonstrated a CWT coefficient, around the 5Hz frequency in swing phase, greater than subjectively stable group, whilst in OA the opposite was apparent. Thus, a single, simplistic explanation of a “lax” or “tight” knee compared to stable, does not offer a consistent clear mechanistic hypothesis. Alternatively, these findings suggest there are two, conflicting and opposite mechanisms which may be responsible.

We have shown the utility of a single tibia-mounted accelerometer in measuring instability in the knee in both the OA and post-TKA patient using a protocol of a pre-loaded accelerometer on a mount, measuring accelerations in the frontal plane during level walking over a short distance. Repeatability in healthy and TKA subjects has been shown, with differentiation in time-frequency domain output shown between unstable and stable post-operative TKA patients. Following modification of the strategy, classification of OA patients has been presented with good initial results. The analysis of lateral acceleration only, emanated from the lateral thrust observed during early stance. However, this thesis has demonstrated that differences occur, not only in stance, but in swing; i.e. in the preparation for stance and thus the proximal tibia knee may not be in a proprioceptively-normal state. The hypothesis being that if the proximal tibia is outside proprioceptive norms, the body’s motor control system is alerted and unconscious compensatory activity is undertaken and a sense of instability is felt. This area of difference is not during the varus thrust first hypothesised and thus there is no reason why accelerations in the other degrees of freedom may not also provide evidence and further mechanistic understanding.

It is therefore of prime importance in understanding the mechanism(s) of instability that accelerometry data is acquired an analysed in all six degrees of freedom (three translational, three rotational). This complete high frequency kinematic analysis of the swing phase will provide sufficient experimental data to test many potential hypotheses. Nevertheless, one advantage of measuring lateral acceleration only is the fact that the acceleration due of gravity is of no concern. The other orthogonal directions, however, have vertical components which will vary through the gait cycle and so, in future, it is recommended than an IMU is used, including a gyroscope and magnetometer, in order to remove the effects of gravity from the recorded accelerometer data. Furthermore, if measures are taken on the proximal tibia and the distal femur, then the relative positioning of the bones in the articulation could be estimated providing a clear providing evidence in support, or not, of mechanistic hypotheses. Therefore, whilst lateral accelerations have indicated where to look for differences, many more differences may be in existence which should not go un-explored. Only then could the differences between groups, demonstrated in this thesis, be related to a single encompassing theory.

It is only once a mechanistic understanding of instability is realised that the most appropriate treatment could be devised, potentially guiding and directing the manner of surgery required. This thesis, therefore, is clearly a first step in this direction and opens the door towards a mechanistic understanding.

The quantification of instability, which this thesis has heralded, is important if it correlates with the severity of the symptoms experienced. Unfortunately, the current subjective measures are too crude and refer to frequency of occurrence, not to severity of incidence, in order to make this correlation. Different, reliable, subjective measures could be devised to correlate with CWT coefficient levels. A device such as ours could be used periodically to objectively and diagnostically assess and monitor instability, rather than relying on patient-reported measures, developing a time-history with implications for identifying surgical intervention. Excitingly, such a device could be used continuously, to assess the risk of a knee becoming unstable and alerting the wearer before this occurs. For example, if the pattern of acceleration deviates from a known “normal”, a device may offer a step or two’s warning of impending stability loss with ramifications in populations where falls are a significant risk.

The device developed in this thesis, therefore, has opened up an exciting area of research. This thesis is not proposing that the device developed herein is a finished, commercially exploitable, device. Much more experimental and theoretical work needs to be done to realise the potential for such measures in a) developing and validating a clear “engineering” understanding of knee instability in order to b) utilise this mechanistic understanding clinically in diagnosing, monitoring, and intervening in cases of knee instability.

CHAPTER 10 – CONCLUSION

This study has demonstrated the effectiveness protocol for the classification of instability in the OA knee using a single laterally mounted tibial accelerometer. The small number of subjects used here have resulted in the creation of an algorithm giving classification in OA knees with 93% sensitivity and 73% specificity. This is the first time that objective classification of instability in the knee has been demonstrated. Further work is required to improve tibia mount, before a large dataset can be collected in both OA and TKA knees to further refine the classification model for instability. This is based upon our model of instability in the knee joint as being the exceeding of the ability to control impulses around the joint, and symptomatic instability being the approach of this condition such that more active responses from the patient are required. Following an accepted and validated classification, further development of this device is likely to achieve the objectives of creating system able to quantify instability in short clinic appointments where instability in the pre-operative OA knee, or the unstable post-operative TKA patient.

CHAPTER 11 – REFERENCES

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APPENDIX A - CAUSES OF FAILURE IN TOTAL KNEE REPLACEMENTS

This section investigates the indications for revision total knee replacement based upon data from a national referral centre in Scotland. Changes in method and materials has resulted in a changing pattern of causes of failure in TKA over time (Sharkey *et al.*, 2002, 2014) The need to frequently review reasons for failure is important to detect changes in patterns arising from ongoing change of practice. This study seeks to present the causes of failure of TKA in patients presenting to a large arthroplasty referral centre.

1. INTRODUCTION

Failure of total knee replacement has been discussed extensively in section 2.6.1. The most common methods of failure are frequently cited as infection, instability, aseptic loosening, periprosthetic fracture, malalignment, retro-patellar arthritis and unexplained pain(Sharkey *et al.*, 2002, 2014; Roberts, Esler and Harper, 2007; Le *et al.*, 2014; Lombardi, Berend and Adams, 2014; Thiele *et al.*, 2015; Wilson *et al.*, 2017).

2. METHODS

After institutional review board approval, all patients undergoing revision primary TKA at a tertiary referral arthroplasty unit between January 2012 and December 2017 were included. All case records, including inpatient records, imaging, operation records, laboratory findings and clinic reviews were examined for those patients. Presence of a revision knee procedure was confirmed, and demographic details, date of admission,

length of stay, time since primary procedure details of surgery were recorded. Available details of primary implant and surgery was recorded. Indication for procedure was determined as recorded by the surgeon from clinic letters, laboratory results and operative notes. Where no clearly determined diagnosis was recorded, case notes, laboratory results and operative notes were reviewed, and a conclusion determined by two surgeons. One difficulty in comparing patterns of failure is the lack of consistency in the recording of reason for failure, often resulting in hospital coding systems rather than clinical information (Delanois *et al.*, 2017). Consequently, a standardised list of reasons for failure was used to categorise all TKA revisions carried out: infection; aseptic loosening; instability; malalignment/malrotation; retropatellar arthritis; arthrofibrosis/stiffness; unexplained pain; periprosthetic fracture; other. Early and late revision were defined as surgery before and after two years.

All patients undergoing revision of a primary TKA were included. Revision from partial knee replacement, revision knee replacement, or surgery for infection of the native knee was excluded. Patients undergoing multiple procedures as part of a planned course of treatment (i.e. 1st stage revision for infection followed by 2nd stage revision) or unplanned complication (i.e. change of polyethylene liner for instability followed by revision of joint for ongoing instability) were counted only for the first surgical procedure. All patients undergoing revision of a primary TKA were included. Revision from partial knee replacement, revision knee replacement, or surgery for infection of the native knee was excluded. Patients undergoing multiple procedures as part of a planned course of treatment (i.e. 1st stage revision for infection followed by 2nd stage revision) or unplanned complication (i.e. change of polyethylene liner for instability followed by

revision of joint for ongoing instability) were counted only for the first surgical procedure.

Descriptive statistics were used to compare patient groups by indication. Two sample comparison was by students t-test, with multiple variables compared using ANOVA Subgroup analysis of patients who had primary surgery at GJNH using a navigated implant (Columbus, BBraun Aesculap, Tuttlingen, Germany) was undertaken to assess the effect of navigation on outcome. Descriptive analysis of distribution of indication was undertaken. (Where distribution was non-normal, a log transform of the data was performed prior to ANOVA). Post-hoc testing was through HSD with a significance level of 0.01. Navigated and manual instability rates were compared using Chi Squared test.

3. RESULTS

Between 2012 and 2017, 443 revision knee procedures were carried out at the studied institution, of which 372 were from primary episodes, and 260 were revision from primary TKA. 4 patients had their second stage revision for infection within the scope of the study, but not their first. Their data was included for the purposes of group comparison, but not for subgroup analysis of the infection cases. In 166 cases (63.5%) surgery was more than 2 years following index procedure, with 94 cases (36.2%) revised within two years of primary surgery. Early revision patients were younger at time of revision ($p<0.01$) with no other details significantly different (Table 12-1).

Table 11-1 – Demographic details of all revisions

Descriptor	All revisions	Early revision	Late revision	p-value
n	260	94	166	
Age	69.3(±9.3)	66.7(±9.1)	70.7(±9.1)	<0.001
Gender M F	133 (51%) 127 (48%)	51 (54%) 43 (46%)	82 (49%) 84 (5%1	0.452
Height (m)	166 (±0.10)	1.66 (±0.10)	1.66(±0.09)	0.794
Body Mass (kg)	89.3(±19.7)	92.0(±19.7)	87.8(±19.7)	0.127
BMI (kg/m^2)	32.5(±6.6)	33.4(±6.7)	32.0(±6.5)	0.116

Table 11-2 – Reasons for revision

Variables displayed as median (min – max). Post Hoc analysis using HSD, significance level 0.01.

Reason for Revision	% All subjects	% Early	% Late	LOS	Age
Infection	33.8	47.9	25.9	22 (4-185)	68.58 (51.7-89.4)
Aseptic loosening	24.2	4.3	35.5	6(2-40)	74.38 (46.9 – 99)
Instability	17.7	19.1	16.9	5 (2-16)	67.35 (51.7 – 85.5)
Malrotation or Malalignment	8.5	6.4	9.6	5 (2-24)	65.47 (46.8-85.3)
Arthrofibrosis/stiffness	7.3	13.8	3.6	5 (3-17)	66.00 (50.9-78.9)
Retropatellar arthritis	5.4	5.3	5.4	3 (2-6)	63.62 (55.1 – 78.0)
Periprosthetic fracture	1.5	2.1	1.2	14 (4-22)	66.58 (59.3 – 83.95)
Polyethylene wear	0.8	0.0	1.2	4	62.32 (57.1 – 67.6)
ANOVA				P<0.001	P = 0.005
Group difference (post-hoc)				Infection different from all others	No differences

The primary surgery was performed at the studied institution in 165 (63.5%) cases, with the remaining 95 (36.5%) referred from other centres. The most common cause for failure was infection (33.6%) followed by aseptic loosening (24.0%), then instability (17.7%), however, failure in the first two years following arthroplasty had infection (47.4%), instability (18.9%), arthrofibrosis/stiffness (13.7%) as the most common causes of failure, with late failure caused by aseptic loosening (35.5%), infection (25.9%) and instability (16.9%).

Length of post-operative stay was highest in infection (median 22 days) while retropatellar arthritis and unexplained pain have the shortest duration (median 3 days). Post-hoc testing of log transformed length of stay showed differences between infection and all other indication only (Table 12-2).

Implant type was identified in 199 cases, of which 57 received a navigated implant. Both navigated and non-navigated groups had infection as the most common cause for failure (37.8% v 39.3%), however the navigated implants failed due to instability in 5.3% of cases in comparison to 21.8% of cases in the manual group ($p = 0.005$, Figure 12-2).

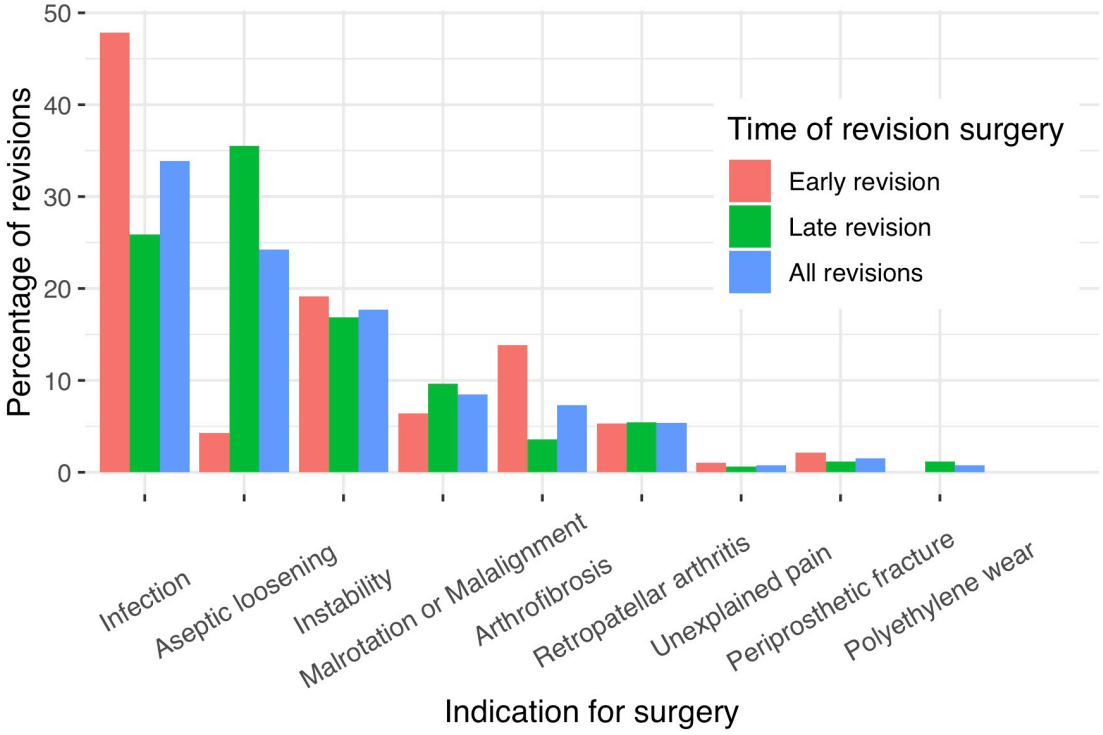

Figure 12-1 – Indication for revision TKA
Early revision <2 years from primary surgery, late revision > 2 years from primary surgery.

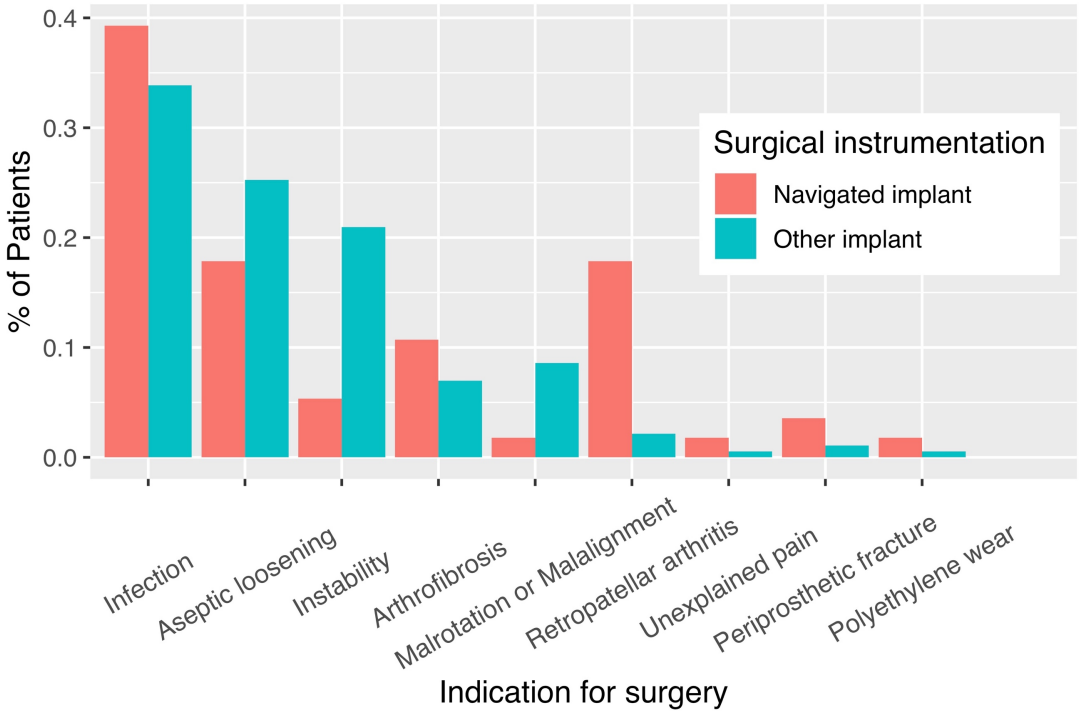

Figure 12-2 – Revision rates comparing a single navigated and manual TKA

4. DISCUSSION

Over the past twenty years much has been written discussing the common causes of failure following TKA. The most common methods of failure are frequently cited as infection, instability, aseptic loosening, periprosthetic fracture, malalignment, retro-patellar arthritis and unexplained pain (Sharkey *et al.*, 2002, 2014; Roberts, Esler and Harper, 2007; Le *et al.*, 2014; Lombardi, Berend and Adams, 2014; Thiele *et al.*, 2015; Wilson *et al.*, 2017; Postler *et al.*, 2018), however the distribution of this has changed over time. Early papers described polyethylene wear as the most common cause (Sharkey *et al.*, 2002; Thiele *et al.*, 2015) however as material technology has developed and polyethylene inserts have improved, this cause of failure has reduced in importance (Sharkey *et al.*, 2014). As wear issues have retreated, the relative importance of other causes of failure have risen, with infection and instability and instability rising in importance (Le *et al.*, 2014; Sharkey *et al.*, 2014; Postler *et al.*, 2018). Depending on the referral sources for the investigated institution, periprosthetic fracture is of more or less importance.

In this study, infection, aseptic loosening and instability have been confirmed as the top three reasons for revision surgery following primary TKA. Between them, they constitute nearly three quarters of the reasons for TKA failure requiring revision surgery (Table 11-2). It is of note that the studied institution does not accept primary trauma, and consequently the rates of periprosthetic fracture operated upon are far lower than some other published centers (Sharkey *et al.*, 2014; Postler *et al.*, 2018). This study explicitly sought to examine first cause of failure from TKA and consequently excluded

from partial knee replacement and revision of revisions. This limits direct comparison with some previous studies but allows a more detailed examination of TKA failure rates. Further, this study reports the length of stay associated with revision TKA by indication, showing significantly increased length of stay in the infection group. This is due to the need for long term antibiotic therapy following first stage therapy or DAIR. The large geographic area from which the institution's patients are drawn, and the lack of local facilities resulted in many patients having no return home prior to second stage surgery. In the early group (revision within two years) instability is the second highest finding. This high consistent with findings of others that cause of revision is time dependent, with aseptic loosening and polyethylene wear requiring time to develop, giving early instability, along with infection, a dominance in reasons for early revision (Lombardi, Berend and Adams, 2014; Sharkey *et al.*, 2014; Pitta *et al.*, 2017; Postler *et al.*, 2018).

Our study shows significantly lower frequency of revision for instability in the navigated group. One recent study has shown reduced rate of revision for navigated TKA in comparison to manual TKA in those under 65, with data presented of reasons for revision (De Steiger, Liu and Graves, 2015). However, ours is the first non-registry study to compare reasons for revision between the two groups in this manner.

The advantages of navigation surgery, specifically better alignment, have been well documented in reviews of the literature (Picard, Deep and Jenny, 2016; Jones and Jerabek, 2018), with suggestions given of improved alignment leading to reduced rates

of aseptic loosening as reduced stress is placed on the bone/implant interface (De Steiger et al. 2015). However, improving alignment, rotation and joint line placement would equally well fit with the goal of improving knee balance, and thereby reducing the proposed causes of knee instability following TKA(Parratte and Pagnano, 2008; Abdel and Haas, 2014; Vince, 2014). The results from this study suggest that instability constitutes a lower percentage of revision of navigated TKA which would logically follow from a more precise system of knee balancing.

One limitation of this study is the lack of prospective standard setting for reasons for failure. Consequently, in some instances a classification had to be determined from records retrospectively. This again highlights the need for standardized reporting of reasons for failure following TKA. Within the navigation subgroup, a significant weakness is the comparison of only one navigated implant with one non-navigated implant. However, the marked difference in rates of revision is significant, and requires further study in other implants.

5. CONCLUSIONS

The most common reason for revision of TKA in the current practice of this institution are infection, aseptic loosening and instability. In revision of navigated TKA, instability drops from the second to the fifth most common cause for revision. This study highlights the importance of instability as a cause for revisions, and the need for a focus of research in quantifying and classifying instability in the knee, as well as improving training in knee balance to reduce its occurrence.

APPENDIX B - REANALYSIS OF TKA INSTABILITY

1. INTRODUCTION & METHOD

Following the development of analysis in the OA group, TKA assessment (Chapter 8) was reassessed using the learning developed learning algorithm and the original TKA wavelet data. The wavelet data from the subjects in Chapter 8 was processed using the method used in Chapter 9. In brief, each stride was windowed using a moving window algorithm to produce 4625 intensity squares of varying time/frequency domains. The average power of each domain was taken as an intensity variable. Intensity was normalised by dividing by body mass squared. PCA scoring was performed on the Z-scored data, with the final variable set constructed from the first PCA scores to account for 95% of total data variance, and the demographic details of age, height, body mass and age.

A learning model was produced using both a linear regression classifier and an SVM classifier using a linear kernel. Data k-fold split, assessing each stride separately, but holding out one patient at a time from the training set for testing. Classification error was used to select the number of demographic and PCA score variables in the final model. In the final model, the stride classifications were reconstructed to find an average classification for each patient. Model performance as assessed using a confusion matrix, accuracy, sensitivity and specificity score of the patient level data, and the AUC of the ROC (Halilaj et al. 2018).

Table 11-3 – Diagnostic table for algorithm in TKA.
Sensitivity, specificity and area under the curve (AUC) for receiver operating characteristics

	Class positive		Class Negative	
	LR	SVM	LR	SVM
Test positive	4	5	1	3
Test negative	3	2	8	6

	Linear regression	SVM
Accuracy	75%	68.8%
Specificity	88.9%	71.4%
Sensitivity	57.1%	66.7%
AUC	0.6508	0.659

2. RESULTS

Classification differed between SVM and linear regression models, with both producing AUC of <0.7, with the linear regression model being more specific, but less sensitive that the SVM model (Table 12-3).

3. DISCUSSION

Classification models of the TKA data performed less well than those of OA data (Table 9-3, Table 12-3). This may be due to the smaller number of subjects used to create the learning model (16 vs 26) and the smaller total number of strides available for analysis (511 vs 718). Further, the change in the protocol between the first and second trial (the use of a crepe bandage to preload the accelerometer) may have resulted in a reduction in poorer correlation between model classification and subject dependent classification.

APPENDIX C – REDESIGN OF THE ACCELEROMETER MOUNT

Following initial testing the design of the accelerometer mount was reconsidered. Difficulties in aligning the device had become apparent due to differences in leg size, and the problems in identifying bony landmarks in large knees. Consideration was given to a mount design that would allow greater control over knee alignment and

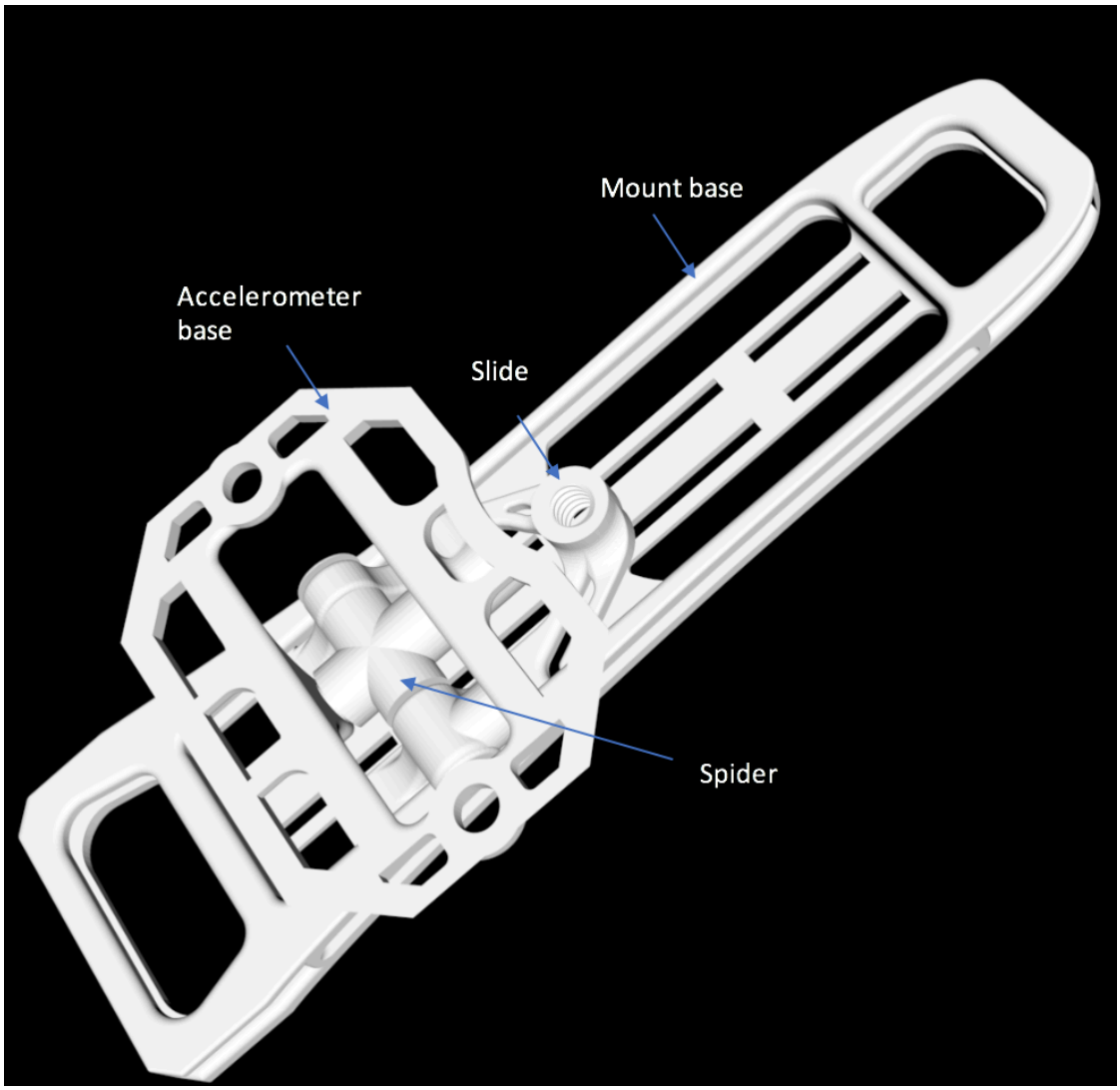

Figure 11-1 – Original CAD design of accelerometer mount

accelerometer height. The following Chapter discusses the process of design and testing, with rational for eventual rejection of a new design in favour of the original design.

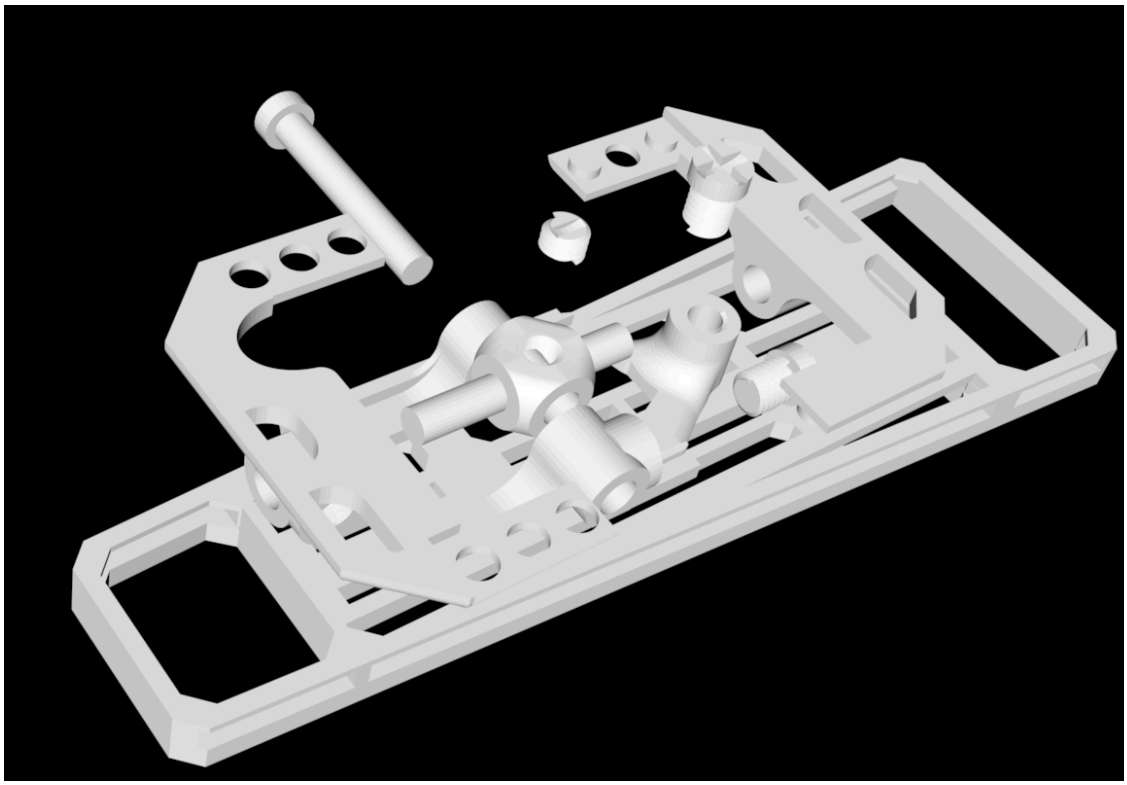

Figure 11-2 – Exploded CAD design of simplified new mount

1. INITIAL MOUNT CRITICAL ANALYSIS

The rationale for the creation of the initial mount is described in Chapter 2 part 2. It comprised of the accelerometer unit mounted on a pre-drilled 140mm x 60mm metal base plate (B&Q), secured with proximal and distal Velcro straps attached to the plate using screws and washers, and attached to the proximal tibia with the measurement unit sitting 2cm under the lateral joint line, under flare of tibial plateau, at 90 degrees to the frontal plane (Image 2). During initial phase testing of TKA patients care was taken to align the device with the axis of the knee by palpation of the joint line, femoral

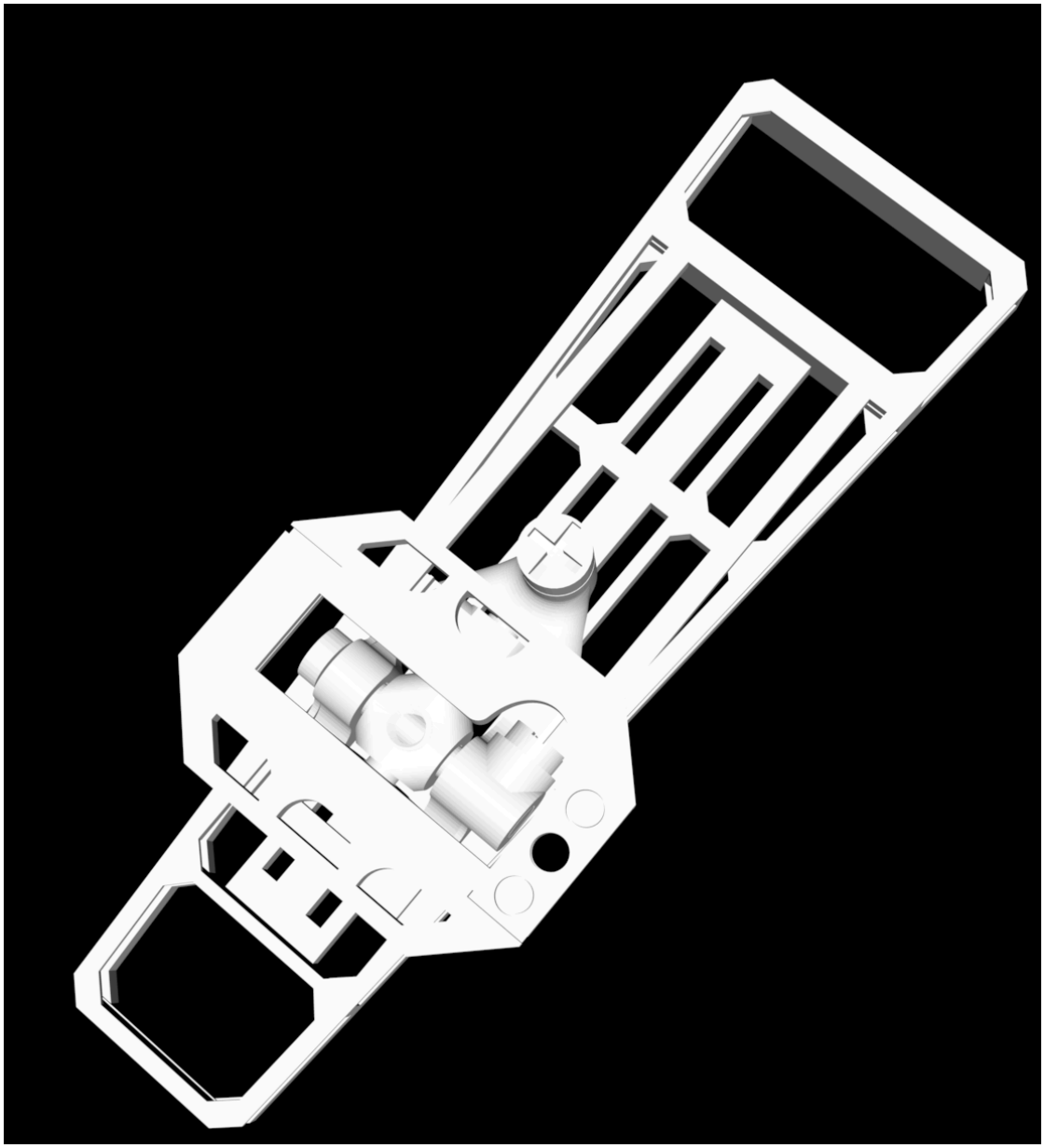

Figure 11-3 – Assembled new mount design

condyles, and observation of the accelerometer output during knee flexion. It was noted that resultant angle of the accelerometer was determined by the tibia in comparison to the ground i.e. a more varus knee would result in a varus accelerometer. Correction of these positional malalignments were made by re-siting the accelerometer in the first instance and adjusting proximal and distal strap tension in the later which gave some

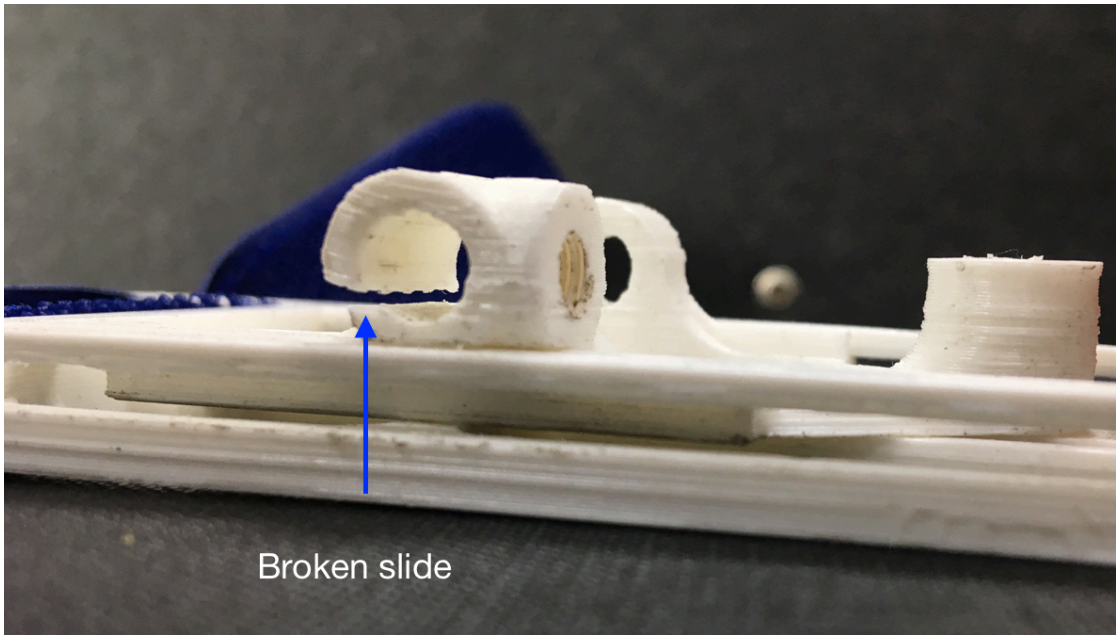

Figure 11-4 – New design with broken boss to under side

ability to correct angle. This was a time-consuming process, and still gave no ability to alter the height of the accelerometer. This was seen as a limitation in the production of a device for use in a time-constrained clinical environment. Consequently, an attempt was made to redesign the mount to allow control of accelerometer position in two planes, as well as height, so that the accelerometer position could be adjusted in situ.

2. CONCEPTS, DESIGNS, REDESIGNS AND FAILURE

Mounts were designed using Computer Aided Design (CAD) Software Creo 3.1 (PTC, MA, USA) and printed using an Ultimaker 2 Extended 3D printer (Ultimaker B.V., Utrecht, the Netherlands) using 2.85mm Poly Lactic Acid (PLA) filament. A design involving a two-axis gimbal on top of a slide was created and printed. It was designed to be as light as possible, with rounded edges to reduce skin irritation, and to be printed

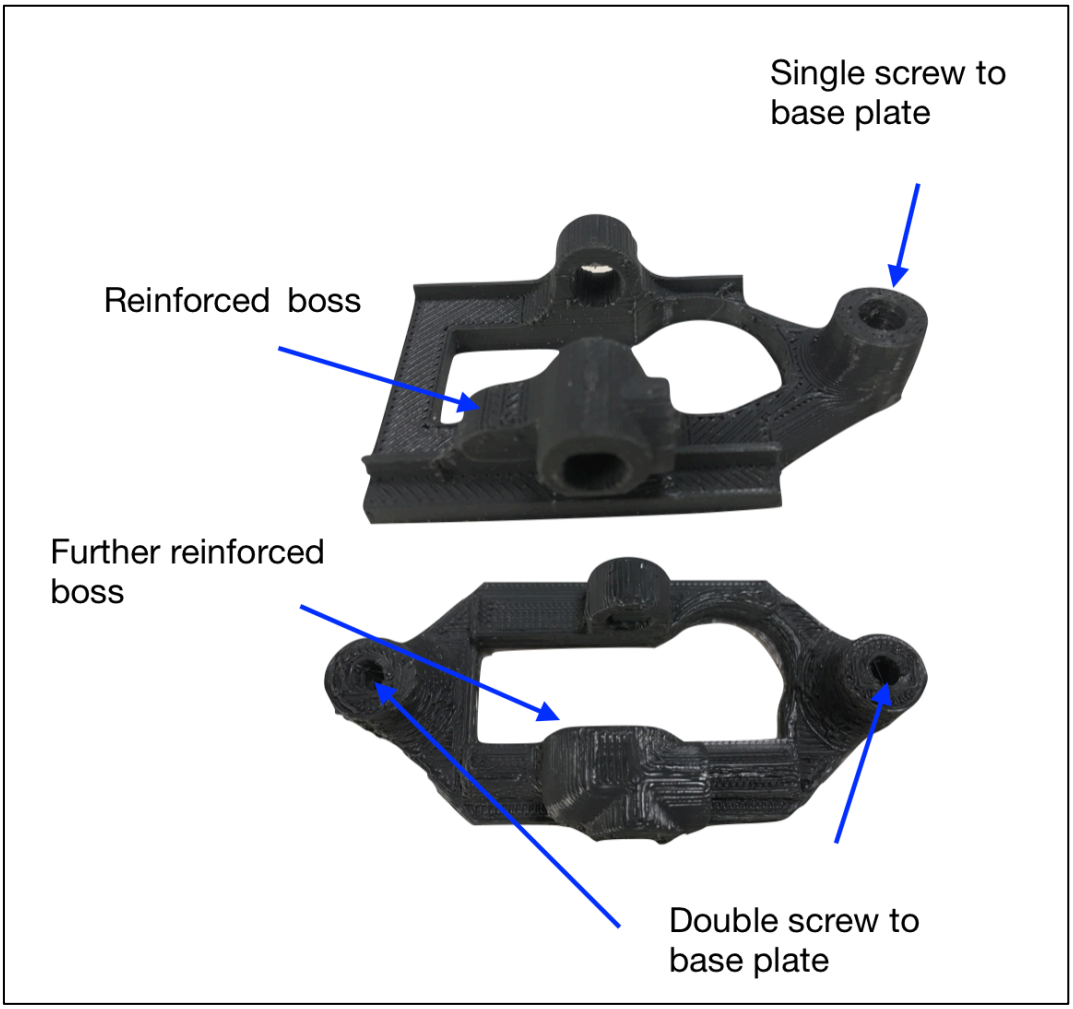

Figure 11-5 – Bottom slide prototype 3 and 4.
Note increase in boss mass, and change from single to double base screw

in its entirety (Figure 11-1). The initial design when printed lacked sufficient strength to and was therefore

redesigned to be thicker, and more robust. Further, it was redesigned to be printed in separate pieces as the spaces between moving parts were insufficient for the tolerances of the printer.

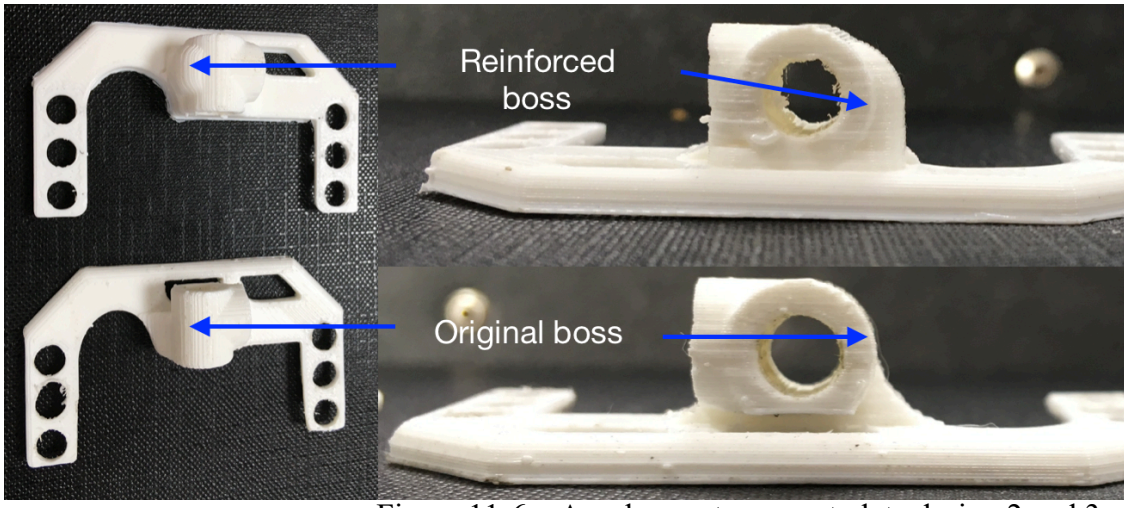

Figure 11-6 – Accelerometer mount plate design 2 and 3. Note increase in boss size

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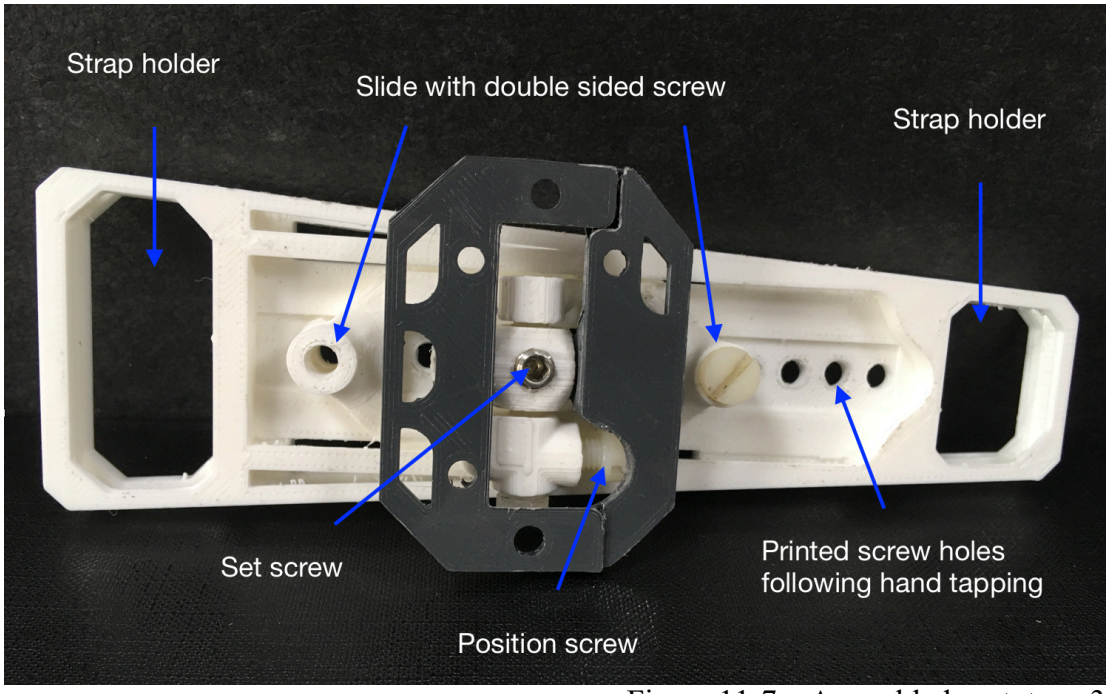


Figure 11-7 – Assembled prototype 3

Consequently, the second design was larger and less delicate. An off the shelf nylon dowel was used for the central axis dowel due to difficulties in fashioning such a small, cylindrical object. While the design involved printing a thread within the screw holes, and printing custom made screws, it was found on assembly that insufficient resolution

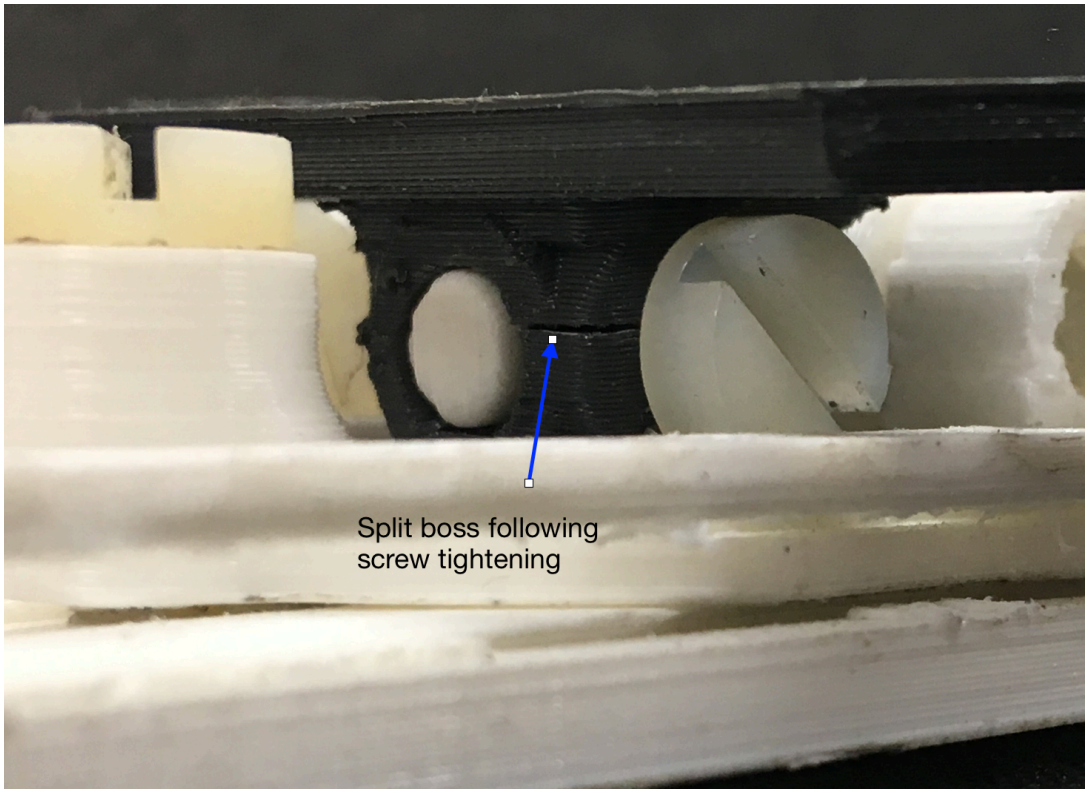


Figure 11-8 – Failure of prototype 3 due to split in accelerometer mount plate boss on tightening

in printing had rendered this unworkable, and off the shelf nylon screws were used instead, with threads re-tapped by hand (Figure 11-2, Figure 11-3). The prototype was designed to hold its position through an interference fit between blunt ended screws and the abutting part. It was noted that it was difficult to achieve a good hold, and drill holes were made part way through the base plate to improve screw hold. Unfortunately,

in an attempt to gain adequate hold between the dowel and the base plate, the slide fractured at the boss (Figure 11-4).

In an attempt to reinforce the slide, the bosses were increased in size around the fracture points (Figure 11-5, Figure 11-6) in two iterations, while the baseplate was redesigned

to incorporate a double-sided screw mechanism to lock in place, along with integrated screw-holes in the baseplate. The bosses in the accelerometer base plate were also reinforced as a precaution. Despite this, the plate once again fractured, this time at the other side of the boss.

3. CONCLUSIONS

To achieve the necessary reinforcement of the mount would be necessary to increase the height between base and accelerometer mount. Additionally, an adequate design was not produced that created sufficient stiffness at the moving parts, and the introduction of metal screws would cut into the PLA, making them use-once devices.

It was therefore concluded that with the available printing materials it would not be possible to manufacture a simple, 3D printed accelerometer mount where adequate stability of the structure could be achieved. The original mount was therefore continued, with care taken on application to ensure appropriate alignment of the device.

Table 11-4 – Gait analysis Healthy Subject output

Normal KAM is peak Knee Adduction moment divided by body mass and height, while Normal Impulse is the area under the curve of normalised KAM throughout the stance phase. Stiffness is the least squares regression of the stiffness curve during stance phase.

Name	Number of Strides	Stance duration (s)	Stiffness	Normal KAM	Normal Impulse
H1L	6	0.66	0.93	6.56	218.04
H1R	6	0.67	0.94	7.22	214.31
H2L	3	0.62	0.76	6.07	163.19
H2R	4	0.63	0.85	4.40	131.15
H3L	3	0.56	0.97	5.25	104.95
H3R	3	0.57	0.91	4.69	108.00
H4L	5	0.70	0.36	2.62	81.03
H4R	5	0.72	0.40	2.96	83.97
H5L	4	0.74	1.51	1.65	10.39
H5R	4	0.72	1.18	1.96	53.44
H6L	4	0.64	0.64	5.46	173.44
H6R	4	0.64	0.60	5.59	175.16
H7L	4	0.66	0.86	4.76	149.38
H7R	4	0.68	0.80	7.13	171.54
H8L	3	0.60	1.06	4.72	118.58
H8R	3	0.60	1.37	3.78	79.05
H9L	3	0.71	0.89	4.41	169.60
H9R	3	0.72	0.80	4.56	149.04
H10L	9	0.65	0.67	3.26	85.14
H10R	8	0.67	0.62	4.98	120.69
Mean (±SD)	4.4 (±1.7)	0.66 (±0.05)	0.86 (±0.29)	4.60 (±1.56)	128.01 (±53.54)

Table 11-5 – Post-operative TKA patient gait analysis results

Individual subject results

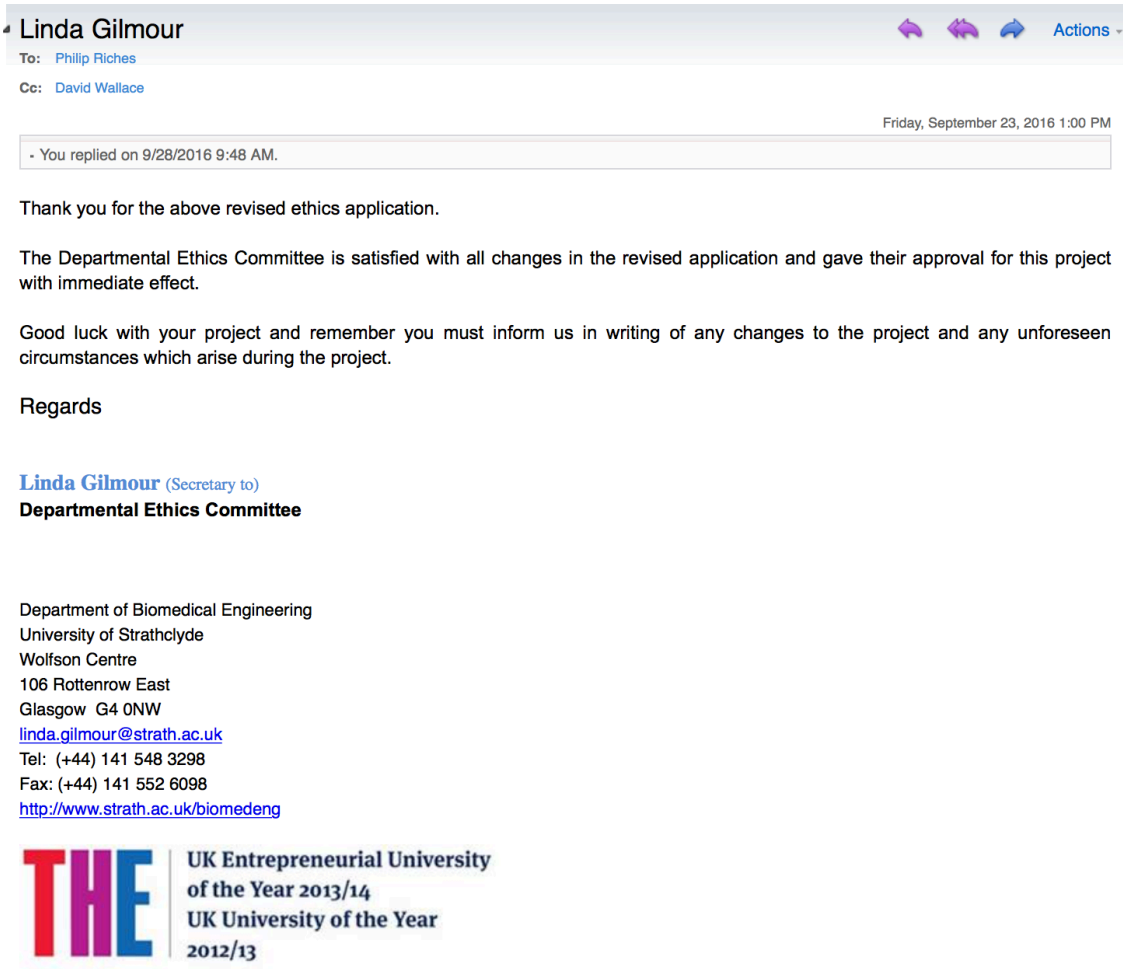
Name	Stability	Number of Strides	Stance duration (s)	Stiffness ($Nm/^0/kg/m$)	Normal KAM (Nm/kg/m)	Normal Impulse (Nm.s/kg/m)	Stiffness (unrectified) ($Nm/^0/kg/m$)
TKA1	stable	3	0.56	0.50	5.98	181.08	0.50
TKA2	stable	3	0.74	0.50	1.74	63.40	0.50
TKA3	stable	3	0.71	0.42	3.06	77.37	0.42
TKA4	Unstable	3	0.66	-0.96	4.13	176.23	0.96
TKA5	stable	3	0.63	1.96	1.94	46.42	1.96
TKA6	stable	4	0.76	0.36	2.87	132.53	0.36
TKA7	Unstable	3	0.67	0.61	2.60	94.35	0.61
TKA8	Unstable	5	0.71	0.33	2.97	128.21	0.33
TKA9	Unstable	4	0.67	0.73	2.60	88.56	0.73
TKA10	stable	4	0.64	0.49	4.30	151.88	0.49
TKA11	Unstable	3	0.79	0.38	2.39	110.20	0.38
TKA12	Unstable	4	0.70	0.23	3.00	96.70	0.23
TKA13	stable	4	0.59	1.11	2.12	66.66	1.11
TKA14	Unstable	3	0.66	0.74	4.62	177.93	0.74
TKA15	stable	3	0.62	0.52	3.93	151.50	0.52
TKA16	stable	5	0.66	0.47	9.13	173.32	0.47
Mean (±SD)		3.6 (±0.7)	0.67 (±0.06)	0.53 (±0.58)	5.2 (±0.57)	119.77 (±45.38)	0.65 (±0.42)

Table 11-6 – Reasons for revision TKA - Review of the literature.

Dates of revision surgery indicated, along with study population. Order of reported aetiology given as not all studies report percentage figures. Study population described. Notes: ¥"Other" denotes either a reported category of "other" or a revision category not otherwise reported in other studies. ‡"Progression of arthritis" (UKA to TKA 3rd most common cause, exclude from analysis. § Database review from cost coding – categories not directly comparable. *Polyethylene exchange only excluded from population by study authors. Included in numbers are revisions of revisions. $Haematoma debridement and isolated polyethylene exchange excluded from population by study authors

Study	Revision Dates	n	Population	Reasons for failure														Comments
				Infection	Instability	Aseptic loosening	Poly wear	Stiffness	Malalignment	Extensor mechanism failure	AVN patella	Periprosthetic fracture	Patellar resurfacing	Patellar loosening	Unexplained pain	Hardware failure	Other¥	
Gioe et al. (2004)	1991-2002	167	All revision Knee	4	3	1	2	-	-	-	-	6	-	-	8	5	7	‡
Sharkey et al. (2002)	1997-2000	203	All revision Knee	4	3	2	1	5	6	7	8	9	10	-	-	-	-	
Le et al. (2014)	2001-2013	253	1st revision from TKA	1	2	4	5	3	6	7	-	-	-	-	-	-	-	
Sharkey et al. (2014)	2003-2012	781	All revision Knee	2	3	1	7	5	8	9	-	4	6	7	-	-	-	
Thiele et al. (2015)	2005-2010	358	All revision Knee	4	2	1	5	7	3	9	-	8	6	-	-	-	-	
Delanois et al. (2017)	2009-2013	337,597	All revision Knee	1	-	2	-	-	-	-	-	-	-	-	-	-	-	§
Schroer et al. (2013)	2010-2011	844	1st revision from TKA	3	2	1	4	5	6	10	11	8	7	-	-	-	9	
Postler et al. (2018)	2010-2015	402	All revision from TKA*	1	4	2	6	7	-	8	-	3	-	-	5	-	-	
Pitta et al. (2017)	2012-2016	405	All revision from TKA$	1	2	3	6	4	7	12	11	5	-	9	8	-	10	

APPENDIX E – STUDY DOCUMENTATION



Linda Gilmour

Actions

To: Philip Riches

Cc: David Wallace

Friday, September 23, 2016 1:00 PM

- You replied on 9/28/2016 9:48 AM.

Thank you for the above revised ethics application.

The Departmental Ethics Committee is satisfied with all changes in the revised application and gave their approval for this project with immediate effect.

Good luck with your project and remember you must inform us in writing of any changes to the project and any unforeseen circumstances which arise during the project.

Regards

Linda Gilmour (Secretary to)
Departmental Ethics Committee

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THE UK Entrepreneurial University of the Year 2013/14
UK University of the Year 2012/13

Figure 11-9 – Confirmation of University Ethical Approval

Scotland A Research Ethics Committee

Research Ethics Service
2nd Floor Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG
Telephone: 0131 465 5680
www.hra.nhs.uk

NHS SCOTLAND

Scotland A REC
2nd Floor Waverley Gate
2 - 4 Waterloo Place
Edinburgh
EH1 3EG
Tel: 0131-465-5679

14 November 2016

Mr. David Wallace
Post-graduate Research Student
University of Strathclyde
Wolfson Building
106 Rottenrow East
Glasgow
G40NW

Dear Mr. Wallace,

Study title:	**Quantification of instability in the knee following total knee replacement using gait analysis and accelerometers - comparison between satisfactory and failed post-operative subjects**
REC reference:	**16/SS/0171**
Protocol number:	**N/A**
IRAS project ID:	**209025**

Thank you for your letter of 10th November 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Miss Manx Neill, manx.neill@nhslothian.scot.nhs.uk

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Figure 11-10 – Ethical approval for part 1 study (Chapter 8)

NHS
Health Research Authority

West Midlands - Edgbaston Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

10 January 2018

Dr. Philip Riches
Department of Biomedical Engineering
Graham Hills Building
50 George Street
G11QE

Dear Dr. Riches

Study title:	**Quantification of subjective instability in the osteoarthritic knee using an accelerometer**
REC reference:	**17/WM/0457**
IRAS project ID:	**228244**

Thank you for your letter of 8 January 2018, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Figure 11-11 – Confirmation of Ethical Approval Trial part 2 (Chapter 9)

APPENDIX F – MATLAB CODE

1. STEP SELECT ACCELEROMETER MULTIFILE

```
function step_select_accelerometer_multifile
```

STEP_SELECT_ACCELEROMETER_MULTIFILE for all data in the folder

Automatically filters accelerometer output files for aberrant spikes, and selects six steps based on maximal negative accelerations. Combined steps averaged, integrated and double integrated. Finally, an output table of peak acceleration, velocity and displacement is placed in the command window and three .csv files are produced in the root folder for acceleration, velocity and displacement

```
[~,test_subject,~] = fileparts(pwd);
source_files = dir ([pwd,'/*.csv']);
complete_file_names = cell(1,(length(source_files)));
avearage_acceleration = zeros(1000,(length(source_files)));
average_velocity = zeros(1000,(length(source_files)));
average_displacement = zeros(1000,(length(source_files)));

   for ii = 1:length(source_files)

       x = csvread(fullfile(source_files(ii).name), 21,1); %data
 selected from csv file
       selected_filename = source_files(ii).name;

       a = (find(x >30) - 20): (find(x >30) + 20);
       x(a) = NaN;  %removes aberant peaks in data
```

Calculation of step length

```
       %run nested function step_peaks for 6 peaks
       [peaks] = step_peaks(6,x);

       total_step_length = mean(diff(peaks))/736; % average step
 length in seconds

       stance_phase_length =
round(total_step_length*736*.6); %calculates stance phase length and
 rounds to nearest integer
```

Extraction of steps

```
        acceleration = zeros(stance_phase_length,6);

        for jj = 1:6
             m = x(peaks);
            [-,o] = min(m);

            y = (peaks(o)-20):(peaks(o))+(stance_phase_length - 21); %
finds steps

            z = (peaks(o)+1):(peaks(o))+(stance_phase_length +100);

            if numel(x) < max(z)
                x(min(y):numel(x)) = NaN;
                step = NaN(stance_phase_length,1);

            else %find when accelerometer reading >0 following negative
peak
                z1 = find(x(z)>0);
                z = (peaks(o)+z1(1)):(peaks(o))+(stance_phase_length +
z1(1)-1);

                step = (x(z));
                step = smooth(step); % filter

                x(y) = NaN;

            end
           acceleration(:,jj) = step;
        end
```

Integration functions

```
        z = 0:0.0014:0.0014*(stance_phase_length-1); % creates vector
of time codes based on sampling rate of 736fps for calculated stance
phase length

        mean_acceleration = nanmean(acceleration,2); % calculates
average of steps in array ACCELERATION
        velocity = cumtrapz(z,mean_acceleration); %calculates velocity
via integration of mean acceleration against time
        displacement = cumtrapz(z,velocity);  %calculates velocity via
integration of mean velocity against time
```

Acceleration

```
        zeros_acceleration = zeros((1000 - length(y)),1);
        n = find(zeros_acceleration == 0);
        zeros_acceleration(n) = NaN;
```

```
      mean_acceleration =
 vertcat(mean_acceleration,zeros_acceleration);
      avearage_acceleration(:,ii) = mean_acceleration;
```

Velocity

```
      zeros_velocity = zeros((1000 - length(y)),1);
      n = find(zeros_velocity == 0);
      zeros_velocity(n) = NaN;

      velocity = vertcat(velocity,zeros_velocity);

      average_velocity(:,ii) = velocity;
```

Displacement

```
      zeros_displacement = zeros((1000 - length(y)),1);
      n = find(zeros_displacement == 0);
      zeros_displacement(n) = NaN;
      displacement = vertcat(displacement,zeros_displacement);
      z = 0:0.0014:0.0014*((round(stance_phase_length/2)-1));
      max_acceleration(1,ii) =
 nanmean(max(acceleration(1:round(stance_phase_length/2),:),[],1));
      max_velocity(1,ii) =
 nanmean(max(cumtrapz(z,acceleration(1:round(stance_phase_length/2),:)),
[],1));
      max_displacement(1,ii) = nanmean(max(cumtrapz(z,
(cumtrapz(z,acceleration(1:round(stance_phase_length/2),:)))),[],1));
      average_displacement(:,ii) = displacement;
      step_lengths(:,ii) = total_step_length;
      complete_file_names{1,ii} = selected_filename; %cell array with
 file names in order

   end

    average_step_length = mean(step_lengths);
    max_acceleration = mean(max_acceleration);
    max_velocity = mean((max(max_velocity)));
    max_displacemenent = mean((max(max_displacement)));

    Subject = cellstr(test_subject);
    final_table =
 table(Subject,average_step_length,max_acceleration,max_velocity,max_displacemenen

    writetable(final_table,strcat(test_subject, '.csv'))
    csvwrite(strcat(test_subject,'
 acceleration.csv'),avearage_acceleration)
    csvwrite(strcat(test_subject,' velocity.csv'),average_velocity)
    csvwrite(strcat(test_subject,'
 displacement.csv'),average_displacement)
```

2. MASTER WAVELET CODE TO CREATE CWT OUTPUT

```
function [wavelets,x,f ] = baselinewavelet( heelstrikestep,subjects )
%BASELINEWAVELET Baseline calculations for wavelet analsysis
%   Analyse step using wavelet analysis.  For each step of each
 subject,
%   average absolute cwt coefficient is found and plotted using the
 MORLET
%   wavelet.  Frequencies of 4 to 256 are saved into _redrawnt_
 struct.

Fs = 736; %set sampling frequency

for kk = 1:numel(subjects) %loop for all subjects

    steps = heelstrikestep.(subjects{kk}).complete; %extract step from
 struct

    % perform wavelet analysis of  each step using MORLET wavelet,
 outputting CWT coefficient into
    % 3D matrix
    a = nan(101,1021,size(steps,2));
    for jj = 1:size(steps,2)
         step = repmat(steps(:,jj),3,1); %pad step with duplicate
 steps before and after
         step =
 wden(fillmissing(step,'constant',0),'rigrsure','s','sln',5,'coif3'); %5
 level wavelet decomposition using the DWT and 3rd order coiflets
         [wt,~]= cwt(step,Fs,'amor'); %wavelet analysis using MORLET
 wavelet, substituting any NaN for 0
         a(:,:,jj) = wt(:,990:2010); %select centre i.e. single step
    end
    [~,f]= cwt(step,Fs,'amor');
    % heelstrikestep.(subjects{kk}).maxwt =  max(max(max(abs(a))));
 %maximum wavelet transform co-efficient for subject
    wavelets.(subjects{kk}).wavelettransform = abs(a); %put wavelet
 transform coefficient into struct
    % heelstrikestep.(subjects{kk}).normalisedwavelettransform =
 nanmean(abs(a),3)/ max(max(max(abs(a)))); %put mean absolute wavelet
 transform coefficient normalised for maximum CWT into struct
    % heelstrikestep.(subjects{kk}).normalisedwavelettransformmax
 = max(abs(a),[],3)/ max(max(max(abs(a)))); %put maximum absolute
 wavelet transform coefficient normalised for maximum CWT into struct
    wavelets.(subjects{kk}).CWTfrequencies = f; %put CWT frequencies
 into struct

end
x = (1:length(a))/10-1;

end


ans =
```

Table of Contents

Live script to identify characteristics of unstable stride

```
% Analyse stride using wavelet analysis.  For each stride of each
 subject, average absolute cwt coefficient
% is found and plotted using the MORLET wavelet.  Frequencies of 4 to
 256 are saved into "redrawnt" struct.
% This has previously done using the function "masterwavelet" and the
 resultant file is loaded in the
% form of "wavelettransformlong"

load('wavelettransfomlong.mat')
load('frequencies.mat');
load('x.mat');

% "Best guess" assessment of differences: filter for frequencies
 between 4 and 32Hz using variable 'f'
wtulong = wavelettransformlong.wtu;
wthlong = wavelettransformlong.wth;
wtslong = wavelettransformlong.wts;

lowpoint = sum(f<4)+1; %find lowest point where frequency >4Hz
highpoint = sum(f<33); %find highest point where frequency <33Hz
numpoint = highpoint-lowpoint +1;
wthlongfiltered = wthlong(102-highpoint:102-lowpoint,:,:); %cut to
 only data between frequncies
wtulongfiltered = wtulong(102-highpoint:102-lowpoint,:,:); %cut to
 only data between frequncies
wtslongfiltered = wtslong(102-highpoint:102-lowpoint,:,:); %cut to
 only data between frequncies

% create variables for scatter plot

fstride = repmat(f(102-highpoint:102-lowpoint),1,1021); %repete
 frequencies for each stride point
```

```
fstride = reshape(fstride,1,(1021*numpoint)); %reshape to vector
bigx = repmat(x,numpoint,1); %repete x co-ordinate for every fequency
bigx = reshape(bigx,1,(1021*numpoint)); %recode into vector
```

Reshape find upper and lower 95% confidence intervals

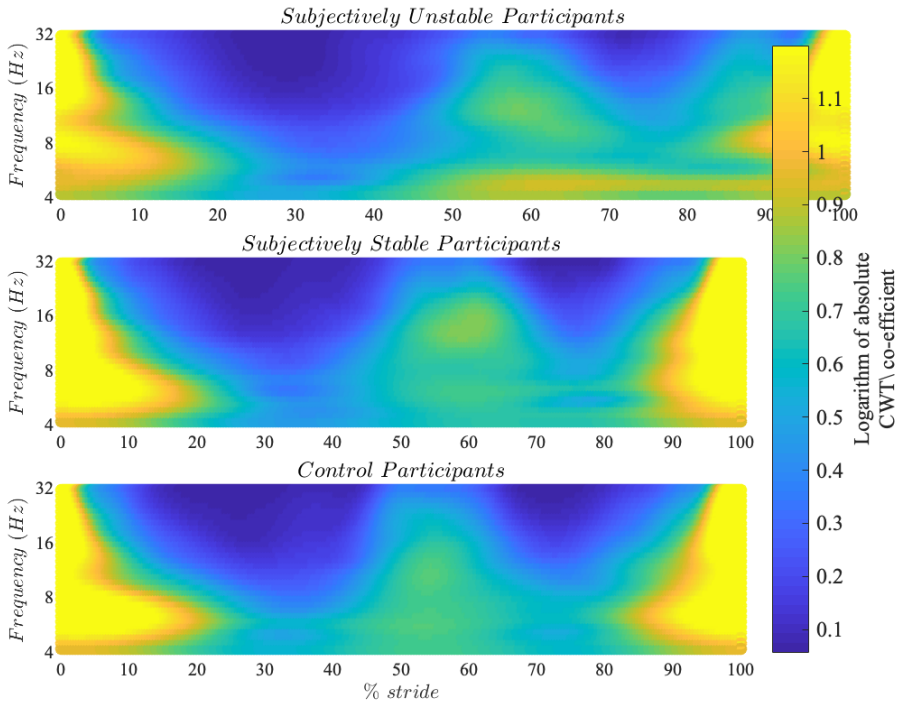
recode 3D matix of CWT into arrays, then find standard deviations for for each stride-point and frequency, in a matrix where line 1 is upper confidence range and 2 is lower confidence range, using self selected groupings

```
clearvars confidencerangesh confidencerangess confidencerangesu

%healthy
wthlong2D= reshape(wthlongfiltered,[numpoint*1021 469]);
confidencerangesh(1,:) = nanmean(wthlong2D,2)'+ 1.96*
 nanstd(wthlong2D,[],2)';
confidencerangesh(2,:) = nanmean(wthlong2D,2)'- 1.96*
 nanstd(wthlong2D,[],2)';

%unstable
wtulong2D= reshape(wtulongfiltered,[numpoint*1021
 size(wtulongfiltered,3)]);
confidencerangesu(1,:) = nanmean(wtulong2D,2)'+ 1.96*
 nanstd(wtulong2D,[],2)';
confidencerangesu(2,:) = nanmean(wtulong2D,2)'- 1.96*
 nanstd(wtulong2D,[],2)';

%stable
wtslong2D= reshape(wtslongfiltered,[numpoint*1021
 size(wtslongfiltered,3)]);
confidencerangess(1,:) = nanmean(wtslong2D,2)'+ 1.96*nanstd(wtslong2D,
[],2)';
confidencerangess(2,:) = nanmean(wtslong2D,2)'- 1.96*nanstd(wtslong2D,
[],2)';
```

Create an inital graph of CWT for each group of subjects

```
colorvectoru = log(nanmean(wtulong2D,2) +1);
colorvectoru(colorvectoru > 1.2) = 1.2;

colorvectors = log(nanmean(wtslong2D,2) +1);
colorvectors(colorvectors > 1.2) = 1.2;

colorvectorc = log(nanmean(wthlong2D,2) +1);
colorvectorc(colorvectorc > 1.2) = 1.2;

[s1,p3] =
 waveletgraph(colorvectoru,colorvectors,colorvectorc,bigx,fstride,3);
```

```
p1 = get(s1,'pos');
p1(3) = p3(3);
set(s1,'pos',p1);
```



Create logial matrix

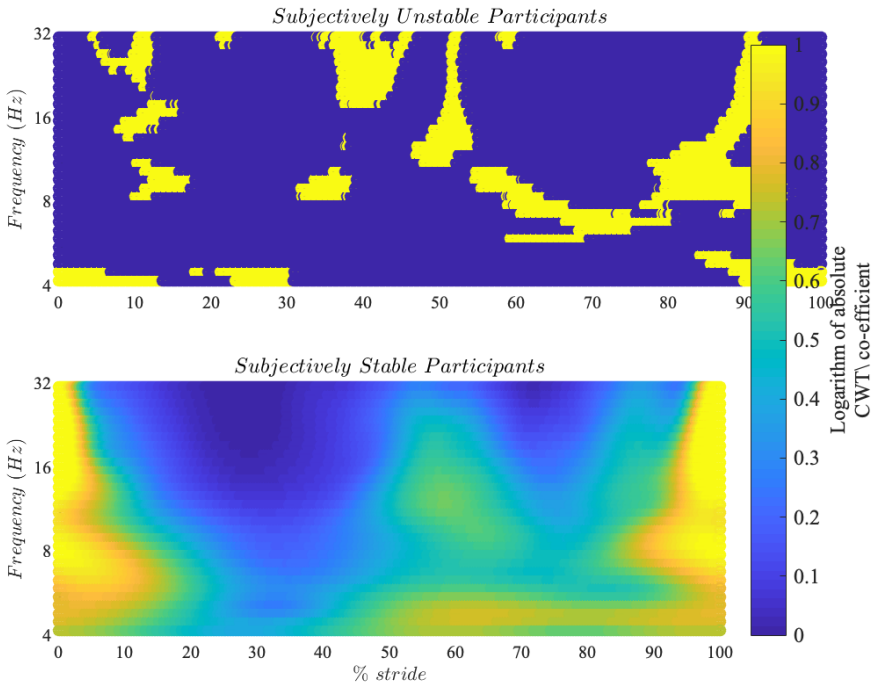
```
% Create a logical matrix identifying in each stride if time-frequency
 point
% is within confidence ratio of each group, loading into matrix where
% row 1 = healthy, 2 = unstable and 3 = stable

%Logic matrix nan templates
logiccaptureh = nan([size(wthlong2D) 3]);
logiccaptures = nan([size(wtslong2D) 3]);
logiccaptureu = nan([size(wtulong2D) 3]);

%Create logic matrices.  Find for each point if it is within 2
 standard deviations of the means of healthy, stable and unstable
%healthy
for ii = 1:size(wthlong2D,2)
logiccaptureh(:,ii,1) = wthlong2D(:,ii) < confidencerangesh(1,:)' &
 wthlong2D(:,ii) > confidencerangesh(2,:)';
logiccaptureh(:,ii,2) = wthlong2D(:,ii) < confidencerangesu(1,:)' &
 wthlong2D(:,ii) > confidencerangesu(2,:)';
logiccaptureh(:,ii,3) = wthlong2D(:,ii) < confidencerangess(1,:)' &
 wthlong2D(:,ii) > confidencerangess(2,:)';
```

```
end

%unstable
for ii = 1:size(wtulong2D,2)
logiccaptureu(:,ii,1) = wtulong2D(:,ii) < confidencerangesh(1,:)' &
 wtulong2D(:,ii) > confidencerangesh(2,:)';
logiccaptureu(:,ii,2) = wtulong2D(:,ii) < confidencerangesu(1,:)' &
 wtulong2D(:,ii) > confidencerangesu(2,:)';
logiccaptureu(:,ii,3) = wtulong2D(:,ii) < confidencerangess(1,:)' &
 wtulong2D(:,ii) > confidencerangess(2,:)';
end

%stable
for ii = 1:size(wtslong2D,2)
logiccaptures(:,ii,1) = wtslong2D(:,ii) < confidencerangesh(1,:)' &
 wtslong2D(:,ii) > confidencerangesh(2,:)'; %logic of healthy against
 healthy CI
logiccaptures(:,ii,2) = wtslong2D(:,ii) < confidencerangesu(1,:)' &
 wtslong2D(:,ii) > confidencerangesu(2,:)'; %logic of healthy against
 unstable CI
logiccaptures(:,ii,3) = wtslong2D(:,ii) < confidencerangess(1,:)' &
 wtslong2D(:,ii) > confidencerangess(2,:)'; %logic of healhty against
 stable CI
end
```

Calculate whether data point of relevance by identifying whether >90% of all datapoints within confidence intervals of all three groups

```
%calculate ratios
ratiologiccaptureh = squeeze(sum(logiccaptureh,2)./
size(logiccaptureh,2));
ratiologiccaptureu = squeeze(sum(logiccaptureu,2)./
size(logiccaptureu,2));
ratiologiccaptures = squeeze(sum(logiccaptures,2)./
size(logiccaptures,2));


%replace with NaN where >90% of strides within all 3 confidence
 windows
%healthy
for ii = 1:size(ratiologiccaptureh,1)
        if ratiologiccaptureh(ii,1) >0.90 && ratiologiccaptureh(ii,2)
 >0.90 && ratiologiccaptureh(ii,3) >0.90
           ratiologiccaptureh(ii,:) = NaN;
        end
end

%unstbale
count = 0;
for ii = 1:size(ratiologiccaptureh,1)
```

```
        if ratiologiccaptureu(ii,1) >0.90 && ratiologiccaptureu(ii,2)
 >0.90 && ratiologiccaptureu(ii,3) >0.90
            ratiologiccaptureu(ii,:) = NaN;
            count = count+1;
        end
end

%stable
count = 0;
for ii = 1:size(ratiologiccaptureh,1)
        if ratiologiccaptures(ii,1) >0.90 && ratiologiccaptures(ii,2)
 >0.90 && ratiologiccaptures(ii,3) >0.90
            ratiologiccaptures(ii,:) = NaN;
            count = count+1;
        end
end

%create mask using above relevance structs
a = squeeze(isnan(ratiologiccaptureh(:,1)));
b = squeeze(isnan(ratiologiccaptureu(:,1)));
c = squeeze(isnan(ratiologiccaptures(:,1)));
d = [a,b,c];
d = sum(d,2);
mask = d == 3;

%Create mask graph

[s1,p3] = waveletgraph(mask,
 colorvectoru,colorvectors,bigx,fstride,2);
p1 = get(s1,'pos');
p1(3) = p3(3);
set(s1,'pos',p1);
```

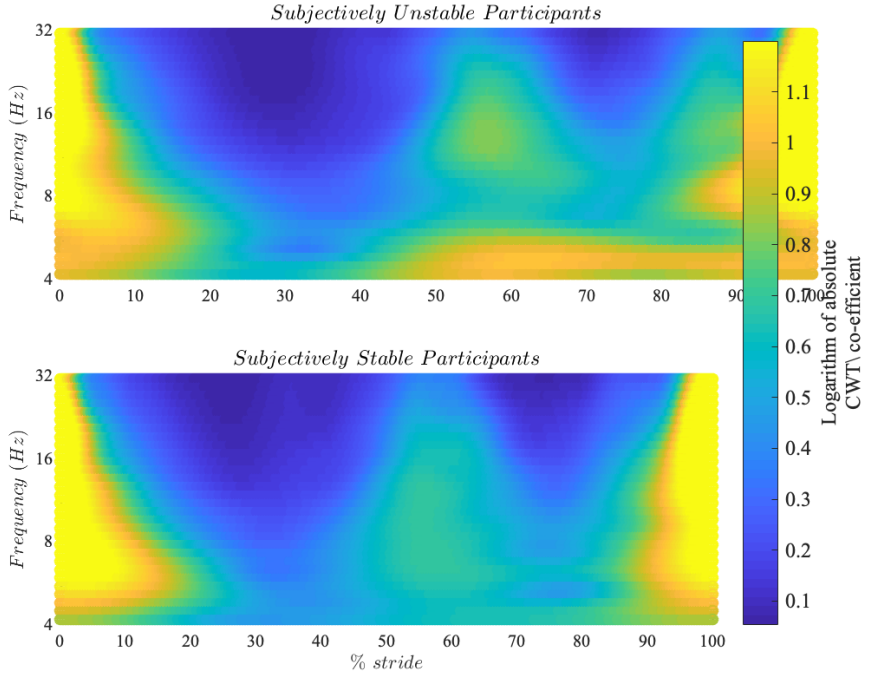


Mask eachstride. Run "unstable" strides through "stable" CIs. List "score" for each stride based on correlation, and calculate using "best guess" of 40:80% of stride phase.

```
%calculate 1 SD above and below mean
narrowconfidencerangess(1,:) = nanmean(wtslong2D,2)'+
 nanstd(wtslong2D,[],2)'; %find 1SD above mean
narrowconfidencerangess(2,:) = nanmean(wtslong2D,2)'-
 nanstd(wtslong2D,[],2)'; %find 1SD below mean


%mask unstable strides and identy all values within CI of stable trace
masku = wtulong2D;
logicmasku = nan(size(masku));
for ii = 1:size(wtulong2D,2)
    logicmasku(:,ii) = masku(:,ii) < confidencerangess(1,:)' &
 masku(:,ii) > confidencerangess(2,:)';
    temp = logicmasku(:,ii);
    temp(mask) = NaN;
    logicmasku(:,ii) = temp;
end
```

```
% Reshape matrix and use 40-80% of stride as a starting point
a = reshape(logicmasku,[numpoint,1021,size(wtulongfiltered,3)]);
a = a(:,411:810,2:end);
realnum = sum(sum(~isnan(a(:,:,1))));
a = nansum(nansum(a));
a = squeeze(a);
a = a./realnum;
numberfirstrun = sum(a>0.95);

% create logical matrix of strides with >95% agreement for remoal and
% removes strides that conform with stable strides
b = a>0.95;
selectwtu = wtulong2D;
selectwtu(:,b) = NaN;

colorvectoru = log(nanmean(selectwtu,2) +1);
colorvectoru(colorvectoru > 1.2) = 1.2;

%mask unstable strides and identy all values within CI of stable trace
masks = wtslong2D;
logicmasks = nan(size(masks));
for ii = 1:size(wtslong2D,2)
    logicmasks(:,ii) = masks(:,ii) < confidencerangess(1,:)' &
 masks(:,ii) > confidencerangess(2,:)'; %logic of unstable against
 stable CI
    temp = logicmasks(:,ii);
    temp(mask) = NaN;
    logicmasks(:,ii) = temp;
end

% create logical matrix of strides with >95% agreement for remoal and
% removes strides that conform with stable strides
a = reshape(logicmasks,[numpoint,1021,size(wtslongfiltered,3)]);
a = a(:,411:810,2:end);
realnum = sum(sum(~isnan(a(:,:,1))));
a = nansum(nansum(a));
a = squeeze(a);
a = a./realnum;
numberfirstruns = sum(a>0.95);

%create logical matrix of strides with >95% agreement and remove
 strides
%that conform with stable strides
b2 = a<0.95;
selectwts = wtslong2D;
selectwts(:,b2) = NaN;
size(selectwts)

colorvectors = log(nanmean(selectwts,2) +1);
colorvectors(colorvectors > 1.2) = 1.2;
unstablestrides = b == 0;
```

```
[s1,p3] =
 waveletgraph(colorvectoru,colorvectors,colorvectorc,bigx,fstride,2);
p1 = get(s1,'pos');
p1(3) = p3(3);
set(s1,'pos',p1);

 % Save new variables
 save('wthlong','wthlong')
 save('wtslong','wtslong')
 save('wtulong','wtulong')
 save('unstablestrides','unstablestrides')
 clearvars


ans =

        30630         266
```



Identify key differences between stable and unstable strides using selected strides by running t-test of each time-frequency point between selected unstable and selected stable. Identify those that are statistically significant.

```
load('wthlong')
load('wtslong')
load('wtulong')
load('unstablestrides')

% Reshape into 3D matrix
 wtslong2D= reshape(wtslong,[101*1021 size(wtslong,3)]);
 wthlong2D= reshape(wthlong,[101*1021 size(wthlong,3)]);
 wtulong2D= reshape(wtulong,[101*1021 size(wtulong,3)]);
 selectstridestable = wtslong2D;

 %calculate confidence ranges for whole grouping
 clearvars confidencerangesu confidencerangesh confidencerangess

 confidencerangesh(1,:) = nanmean(wthlong2D,2)'+ 1.96*
 nanstd(wthlong2D,[],2)';
 confidencerangesh(2,:) = nanmean(wthlong2D,2)'- 1.96*
 nanstd(wthlong2D,[],2)';
 confidencerangess(1,:) = nanmean(wtslong2D,2)'+ 1.96*
 nanstd(wtslong2D,[],2)';
 confidencerangess(2,:) = nanmean(wtslong2D,2)'- 1.96*
 nanstd(wtslong2D,[],2)';
```

loop for calculating most significant points

```
% __WTULONG__ - matrix of all unstable steps, __WTSLONG__ - matrix of
 all stable
% steps, __WTHLONG__ - Matrix of all healhty steps
% Nested function NEWMASKFUNCTION takes variable of __SELECTED
 STRIDES__
% along with  __SELECTEDSTRIDESTABLE__ and __WTHLONG2D__ and creates a
 new
% mask __NEWMASK__ indicating all points where no significant
 difference exists
% between all three as 1 and difference as 0
% Nested function __STEPSIGNIFICANCE__ takes __NEWMASK__,
 __WTULONG2D__ and
% __CONFIDENCERANGESS__ and identifies any steps with less than 95%
 agreement
% with __Stablesteps__ confidence intervals

count = 1;
```

```
done  = 'no';
while strcmp(done,'no')

 count = count+1;

 %select only "unstable" strides from "unstable" matrix and rehape
 matrix
 %for caluclation
 selectstrides = wtulong(:,:,unstablestrides(:,count-1));
 selectstrides = reshape(selectstrides,
[101*1021,size(selectstrides,3)]);


 %Nested function NEWMASK
 [newmask] = newmaskfunction( selectstrides, selectstridestable,
 wthlong2D);



 %recalculate confidence ranges using new unstable subjects
 clearvars confidencerangesu
 confidencerangesu(1,:) = nanmean(selectstrides,2)'+ 1.96*
 nanstd(selectstrides,[],2)';
 confidencerangesu(2,:) = nanmean(selectstrides,2)'- 1.96*
 nanstd(selectstrides,[],2)';

 confidencerangess(1,:) = nanmean(selectstridestable,2)'+ 1.96*
 nanstd(selectstridestable,[],2)';
 confidencerangess(2,:) = nanmean(selectstridestable,2)'- 1.96*
 nanstd(selectstridestable,[],2)';

%run STEPSIGNIFICANCE to identify correlation of unstable strides with
 stable at 95% level
[~,b] = stepsignificance(wtulong2D,confidencerangess,newmask,0.95);

unstablestrides(:,count) = b(2:end) == 0;
coincidingstrides =
 and(unstablestrides(:,count-1),unstablestrides(:,count));

% select 'unstable' unstable strides and remove strides that conform
 with stable strides
selectstrides = wtulong2D;
selectstrides(:,b) = [];

if sum(coincidingstrides) > 0.99*sum(unstablestrides(:,count)) ||
 count > 10
    done = 'yes';
end

%run strideSIGNIFICANCE to identify correlation of stable strides with
 healthy strides at 99% level
[~,b] = stepsignificance(wtslong2D,confidencerangesh,newmask,0.99);
```

```
%remove strides that conform with healhty strides
selectstridestable = wtslong2D;
selectstridestable(:,b) = []; end

save('selectstrides','selectstrides')
save('newmask', 'newmask')


 function  [s1,p2] =
 waveletgraph(colorvectoru,colorvectors,colorvectorc,bigx,fstride,number)

    selectfont = 'Times';
    close
    paperwidth = (21-2.54-2.54)/2.54; %A4 paperwidth - margines
    Phi = (1+sqrt(5))/2; %golden ratio
    PaperSize = [paperwidth, (paperwidth/Phi)*number*0.7];

    fig_prop(PaperSize); %run function figprop to produce properly
 sized figure

    s1 = subplot(number,1,1);
    scatter(bigx,fstride,[],colorvectoru');
    set(gca,'yscale','log','FontName',selectfont);
     ylim([4 32]);
     xlim([0 100]);
    title({'$Subjectively\ Unstable\ Participants
$'},'Interpreter','LaTeX','FontName',selectfont, 'Fontsize', 12);
     ylabel('$Frequency\
 (Hz)$','interpreter','latex','FontName',selectfont);
     yticks(2.^(1:8));
     c = colorbar;
     c.Label.String = {'Logarithm of absolute'; 'CWT\ co-efficient' };
     p1 = get(s1,'pos');
     c.Position = [0.8339 0.11 0.0357 0.8];
     c.FontSize = 12;
     set(s1,'pos',p1);

     s2 = subplot(number,1,2);
    scatter(bigx,fstride,[],colorvectors');
    set(gca,'yscale','log','FontName',selectfont)
     ylim([4 32])
     xlim([0 100])
     title({'$ Subjectively\ Stable\ Participants
$'},'Interpreter','LaTeX','FontName',selectfont, 'Fontsize', 12);
     ylabel('$Frequency\
 (Hz)$','interpreter','latex','FontName',selectfont)
     yticks(2.^(1:8))
     if number<3
         xlabel('$ \% \ stride
$','Interpreter','LaTeX','FontName',selectfont);
     end

     if number>2
         s3 = subplot(number,1,3);
```

```
            scatter(bigx,fstride,[],colorvectorc');
            set(gca,'yscale','log','FontName',selectfont);
            ylim([4 32]);
            xlim([0 100]);
            title({'$Control\ Participants
$'},'Interpreter','LaTeX','FontName',selectfont, 'Fontsize', 12);
            xlabel('$ \% \ stride
$','Interpreter','LaTeX','FontName',selectfont);
            ylabel('$Frequency\
 (Hz)$','Interpreter','LaTeX','FontName',selectfont);
            yticks(2.^(1:8))
        end

        %set positions of graphs
        p2 = get(s2,'pos');
        p2(3) = p1(3);
        set(s2,'pos',p2);
        if number>2
            p3 = get(s3,'pos');
            p3(3) = p1(3);
            set(s3,'pos',p3);
        end
        p1 = get(s1,'pos');
        p1(3) = p2(3);
        set(s1,'pos',p1);
        p1 = get(s1,'pos');
        p1(3) = p2(3);
        set(s1,'pos',p1);

    end

    function fig_prop(PaperSize)

       %Internal function to manage figure appearance
       fig = figure(1);
       fig.PaperPositionMode = 'manual';
       fig.PaperUnits = 'inches';
       fig.Units = 'inches';
       fig.PaperPosition = [0,0,PaperSize(1),PaperSize(2)];
       fig.PaperSize = [PaperSize(1),PaperSize(2)];
       fig.Position = [0.1,1,PaperSize(1)-0.1,PaperSize(2)-1];
       fig.Resize = 'off';
       fig.InvertHardcopy = 'off';
       fig.Color = 'White';
    end
```

```
Elapsed time is 0.000244 seconds.
Elapsed time is 64.586068 seconds.
Elapsed time is 0.000191 seconds.
Elapsed time is 63.027928 seconds.
Elapsed time is 0.000256 seconds.
Elapsed time is 70.627357 seconds.
Elapsed time is 0.000273 seconds.
Elapsed time is 73.125858 seconds.
```

```
function Finalgraph

% Final graph is a code to calulate the final stability grouping for
% strides based upon the previously calculated mask
```

Final graph output file

```
% Use final mask to re-calculate confidence intervals and place each
 step
% either within or without CI of stable strides.


% Calculate confidence intervals
wtulong2D= reshape(wtulong,[101*1021 247]);
wtslong2D= reshape(wtslong,[101*1021 266]);
confidencerangesu(1,:) = nanmean(selectstrides,2)'+ 1.96*
 nanstd(selectstrides,[],2)';
confidencerangesu(2,:) = nanmean(selectstrides,2)'- 1.96*
 nanstd(selectstrides,[],2)';

confidencerangess(1,:) = nanmean(wtslong2D,2)'+ 1.96*
 nanstd(wtslong2D,[],2)';
confidencerangess(2,:) = nanmean(wtslong2D,2)'- 1.96*
 nanstd(wtslong2D,[],2)';



%run STEPSIGNIFICANCE to identify correlation of unstable strides with
 stable at 95% level


[~,b] = stepsignificance(wtulong2D,confidencerangess,newmask,0.95);

% run strideSIGNIFICANCE to identify correlation of stable strides
 with stable stides strides at 95% level

[~,b] = stepsignificance(wtslong2D,confidencerangess,newmask,0.95);

% select 'unstable' and  'stable' unstable strides for unstable
 subjects
usu = wtulong2D;
usu(:,b) = [];
size(usu)
usu = nanmean(usu,2);

% select 'unstable' and  'stable' unstable strides for stable subjects
uss = wtulong2D;
uss(:,b==0) = [];
size(uss)
uss = nanmean(uss,2);
```

```
%Apply mask

for i = 1:numel(sss)

   if newmask(i) == 1
       uss(i) = 0;
       sss(i) = 0;
       usu(i) = 0;
       ssu(i) = 0;

   end
end


%Make graphs, with __fstride__ and __bigx__ created from loaded values

fstride = repmat(f,1,1021);
fstride = reshape(fstride,1,(1021*101)); %
bigx = repmat(x,101,1);
bigx = reshape(bigx,1,(1021*101));

%Set paper size
 paperwidth = (21-2.54-2.54)/2.54;
 Phi = (1+sqrt(5))/2;
 PaperSize = [paperwidth, (paperwidth/Phi)*3*0.7];

stable = log(ssu +1);
stable(stable > 1.2) = 1.2;

unstable = log(sss +1);
unstable(unstable > 1.2) = 1.2;


selectfont = 'Times';

title1 = ({'$"New"\ Mask$'});
title2 = ({'$"Stable"\ Stable\ Strides$'});
title3 = ({'$"Untable"\ Stable\ Strides$'});

[s1,p3] = waveletgraph(newmask, stable,unstable,bigx,fstride,3,
 title1, title2, title3);
p1 = get(s1,'pos');
p1(3) = p3(3);
set(s1,'pos',p1);


stable = log(uss +1);
stable(stable > 1.2) = 1.2;

unstable = log(usu +1);
unstable(unstable > 1.2) = 1.2;

title1 = ({'$"New"\ Mask$'});
title2 = ({'$"Stable"\ Unstable\ Strides$'});
```

```
title3 = ({'$"Untable"\ Unstable\ Strides$'});

[s1,p3] = waveletgraph(newmask, stable,unstable,bigx,fstride,3,
 title1, title2, title3);
p1 = get(s1,'pos');
p1(3) = p3(3);
set(s1,'pos',p1);


stable = log(sss +1);
stable(stable > 1.2) = 1.2;

title1 = ({'$Final\ Mask$'});
title2 = ({'$"Stable"\ Stable\ Strides$'});
title3 = ({'$"Unstable"\ Unstable\ Strides$'});

[s1,p3] = waveletgraph(newmask, stable,unstable,bigx,fstride,3,
 title1, title2, title3);
p1 = get(s1,'pos');
p1(3) = p3(3);
set(s1,'pos',p1);

print(gcf,'Final mask.png','-dpng','-r600')

 function  [s1,p2] =
 waveletgraph(colorvectoru,colorvectors,colorvectorc,bigx,fstride,number,
 title1, title2, title3)

    selectfont = 'Times';
    close
    paperwidth = (21-2.54-2.54)/2.54; %A4 paperwidth - margines
    Phi = (1+sqrt(5))/2; %golden ratio
    PaperSize = [paperwidth, (paperwidth/Phi)*number*0.7];

    fig_prop(PaperSize); %run function figprop to produce properly
 sized figure

    s1 = subplot(number,1,1);
    scatter(bigx,fstride,[],colorvectoru');
    set(gca,'yscale','log','FontName',selectfont);
     ylim([4 32]);
     xlim([0 100]);

 title(title1,'Interpreter','LaTeX','FontName',selectfont, 'Fontsize',
 12);
     ylabel('$Frequency\
(Hz)$','interpreter','latex','FontName',selectfont);
     yticks(2.^(1:8));
     c = colorbar;
     c.Label.String = {'Logarithm of absolute'; 'CWT\ co-efficient' };
     p1 = get(s1,'pos');
     c.Position = [0.8339 0.11 0.0357 0.8];
     c.FontSize = 12;
     set(s1,'pos',p1);
```

```
    s2 = subplot(number,1,2);
   scatter(bigx,fstride,[],colorvectors');
   set(gca,'yscale','log','FontName',selectfont)
    ylim([4 32])
    xlim([0 100])

title(title2,'Interpreter','LaTeX','FontName',selectfont, 'Fontsize',
12);
    ylabel('$Frequency\
(Hz)$','interpreter','latex','FontName',selectfont)
    yticks(2.^(1:8))
    if number<3
        xlabel('$ \% \ stride
$','Interpreter','LaTeX','FontName',selectfont);
    end

    if number>2
        s3 = subplot(number,1,3);
        scatter(bigx,fstride,[],colorvectorc');
        set(gca,'yscale','log','FontName',selectfont);
        ylim([4 32]);
        xlim([0 100]);

title(title3,'Interpreter','LaTeX','FontName',selectfont, 'Fontsize',
12);
        xlabel('$ \% \ stride
$','Interpreter','LaTeX','FontName',selectfont);
        ylabel('$Frequency\
(Hz)$','Interpreter','LaTeX','FontName',selectfont);
        yticks(2.^(1:8))
    end

    %set positions of graphs
    p2 = get(s2,'pos');
    p2(3) = p1(3);
    set(s2,'pos',p2);
    if number>2
        p3 = get(s3,'pos');
        p3(3) = p1(3);
        set(s3,'pos',p3);
    end
    p1 = get(s1,'pos');
    p1(3) = p2(3);
    set(s1,'pos',p1);
    p1 = get(s1,'pos');
    p1(3) = p2(3);
    set(s1,'pos',p1);

end

function fig_prop(PaperSize)

   %Internal function to manage figure appearance
```

```
    fig = figure(1);
    fig.PaperPositionMode = 'manual';
    fig.PaperUnits = 'inches';
    fig.Units = 'inches';
    fig.PaperPosition = [0,0,PaperSize(1),PaperSize(2)];
    fig.PaperSize = [PaperSize(1),PaperSize(2)];
    fig.Position = [0.1,1,PaperSize(1)-0.1,PaperSize(2)-1];
    fig.Resize = 'off';
    fig.InvertHardcopy = 'off';
    fig.Color = 'White';
end

end
```

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Table of Contents

Learning and classification of acceleromter

This funciton works by taking the masterfile, created by Accelerometer view, containing a countinous wavelet transform (CWT) of steps produced by subjects. The data is windowed to produce windows of intensity of absolute value of the continous wavelet transform. Principal Component analysis is then peformed.

A learning alorithm using k-fold hold out is used where each subject is witheld from each learning set. Demographic details of age, bodymass, height and stride length are added. Wavelets are normalised for bodymass squared (lowest classification error) and then calssification errors are compared for differing number of principal components and each demographic. Final result is plotted as subjects.

Load data and prepare for analysis

load('masterfile.mat') %Load complete strut of patients

```
subjects = fields(masterfile); %identify list of patients

% loop through each subject and window data

stepcount  = 0
clearvars completevars
clearvars intesity
for g = 1:numel(subjects)
    a = masterfile.(subjects{g}).wavelet; % assign each subjet
 sequentially
    s =size(a); %find the number of steps in wavelet a
    g
% find intensity at each area
    for h = 1:s(3) %loop through steps
        stepcount = stepcount+1
        StepKey(stepcount,:) = [subjects(g),stepcount,masterfile.
(subjects{g}).stability,'colour'];
        if strcmp(masterfile.(subjects{g}).stability,'Stable')
            Colourkey(stepcount,:) = [0 0 0]; %assign stable to black
        else
            ColourKey(stepcount,:) = [1 0 0]; %assign unstable to red
        end
        tic
        counti = 0;
        intensity = nan(length(1:25),length(11:5:931));
        for i = 1:25 %loop for frequency groupings
```

```
            counti = counti+1;
            countj = 0;
            for j = 11:5:931 %loop throuhg stride in 25 frame
 incriments
                b = a(:,:,h); % select appropriate step
                countj = countj + 1;
                intensity(counti,countj) = sum(sum(b(counti:counti
+5,j:j+25)));
            end
        end
        s2 = size(intensity);
        completevars(stepcount,:) = reshape(intensity,1,s2(1)*s2(2));
  %reshape into vector
        toc
    end
end

%load demographics
demos = readtable('OA instability anonymous data.xlsx');
demos = sortrows(demos);
demos.Properties.RowNames = table2cell(demos(:,1));
stepnumber  = [];
stepname = [];
for g = 1:numel(subjects)

    names = fields(masterfile); %obtain subject names
    s = size(masterfile.(subjects{g}).wavelet,3);  %find number of
 steps in wavelet a
    sub = cell2mat(names(g));
    sub = cellstr(sub(:,1:3));
    stridelength = masterfile.(subjects{g}).stridelenghts;
    stepname = [stepname;
 repmat([names(g),table2cell(demos({sub{1}},2:6)),mean(stridelength)],s,1)];
    stepnumber = [stepnumber; [names(g),s]];
end
demovars = stepname(:,[2,4,5,7]);
clearvars sub s g names
%loop through each subject
stepcount = 0;


for g = 1:numel(subjects)
    a = masterfile.(subjects{g}).wavelet; %assign each subject
 sequentially
    s = size(a); %find number of steps in wavelet a

    %create colour key
    for h = 1:s(3)
        stepcount = stepcount+1;
        StepKey(stepcount,:) = [subjects(g),stepcount,masterfile.
(subjects{g}).stability,'colour'];
        if strcmp(masterfile.(subjects{g}).stability,'Stable')
            ColourKey(stepcount,:) = [0 0 0]; %assign stable to black
        else
```

```
            ColourKey(stepcount,:) = [1 0 0]; %assign unstable to red
        end
    end
end
clearvars h s a g

%normalise completevars for height and weight

completevars = completevars./cell2mat(stepname(:,5)); %divide by
 weight
completevars = completevars./cell2mat(stepname(:,5)); %divide by
 weight
```

Principal Component Analysis

```
%conduct PCA

[coefs,scores,latent,~,explained] =
 pca(zscore(completevars(:,1:4625)),'VariableWeights','variance');

t = 0; %trial number
vardem = {};
for jj =1:4 %run throuhg all demographics
    for kk = 1:4

        if ~(kk<jj)
            t = t+1;
            vardem(t) = {num2str(jj:kk)};
        end
    end
end
for jj = 1:4
    for kk = 1:4
        t = t+1;
        p = 1:4;
        p(p==jj) = [];
        vardem(t) = {num2str(p)};
        if ~(jj==kk)
            t = t+1;
            p(p==kk) = [];
            vardem(t) = {num2str(p)};
       end
    end
end
A = unique(vardem,'rows');

ce_t = [];
ind = [];
np_t = [];

for jj = 1:length(A)
    demvarstrial = demovars(:,str2num(cell2mat(A(jj))));
     tic
```

```
    for hh = 1:40
        scorestb = [cell2mat(demvarstrial),scores(:,1:hh)];

        responseb = ColourKey(:,1);

        labelsb = [];

        p2 = [];
        stepindex = cumsum(cell2mat(stepnumber(:,2)));
        stepindex = [0;stepindex];
        num = 1:718;

        for ii = 1:26
            test = zeros(1,718);
            test(stepindex(ii)+1:stepindex(ii+1)) = 1;
            train = test == 0;
            test = test ==1;
            [Mdlb, fitinfo] = fitclinear(scorestb(train,:),
 responseb(train),'learner','logistic','ObservationsIn','rows');
            labelsb =
 [labelsb;mean(responseb(test)),mean(predict(Mdlb,scorestb(test,:),'ObservationsIn
            p2 =
 [p2;predict(Mdlb,scorestb(test,:),'ObservationsIn','rows')];
        end


        cm = confusionmat(p2,responseb);
        ce(hh) = (cm(1,2)+cm(2,1))/718;
        np_ce(hh) = hh;
    end

 ce_t = [ce_t,ce];
 np_t = [np_t,np_ce];
 ind = [ind,repmat(A(jj),numel(ce),1)];
end
```

Prepare for classification and graphing

```
[colour_palette,paperwidth,Phi] = requiredcode;
plot(ce_t);
ylim([0 1])
[~,m] = min(ce_t); %find best classification
demvarstrial = demovars(:,str2num(cell2mat(ind(m))));
scorestb = [cell2mat(demvarstrial),scores(:,1:np_t(m))];
labelsb = [];
p2 = [];
 for ii = 1:26
    test = zeros(1,718);
    test(stepindex(ii)+1:stepindex(ii+1)) = 1;
    train = test == 0;
    test = test ==1;
    [Mdlb, fitinfo] = fitclinear(scorestb(train,:),
 responseb(train),'learner','logistic','ObservationsIn','rows');
```

```
    labelsb =
 [labelsb;mean(responseb(test)),mean(predict(Mdlb,scorestb(test,:),'ObservationsIn
    p2 = [p2;predict(Mdlb,scorestb(test,:),'ObservationsIn','rows')];
 end
jitter1 = normrnd(0,0.015,[1,26]);
scatter(labelsb(:,1)+0.1+jitter1',labelsb(:,2),50,'blue','filled','MarkerEdgeColor
hold on
refline(0,0.5)
hold off
mean(ce)
m

%Classify with 0.5 cuttoff
outputlables_binary = labelsb(:,2)>0.5;
outputlables = labelsb(:,2);
truelables = labelsb(:,1);

cp = classperf(truelables,outputlables_binary);

% Plot ROC curve, adding polynomial to define "best" cuttoff
[X,Y] = perfcurve(truelables,outputlables,1);
plot(X,Y)
hold on
refline(1,0);
p =  polyfit(X,Y,2);
X2 = linspace(0,1);
Y2 = polyval(p,X2);
plot(X2,Y2)
xlim([0 1]);
ylim([0 1]);
hold off
xlabel('False positive rate')
ylabel('True positive rate')
title('ROC for Classification by Logistic Regression')
hold off
%least squares of polynomial to find "best" classification point
[~,classpoint] = min(sqrt(X2.^2+(1-Y2).^2));
outputlables_binary = labelsb(:,2)>classpoint/100;
cp = classperf(truelables,outputlables_binary);
cp.Sensitivity
cp.Specificity


jitter1 = normrnd(0,0.025,[1,26]);
[colour_palette,paperwidth,Phi] = requiredcode; %get colours, paper
 width etc
PaperSize = [paperwidth,paperwidth]; %Set paper size
xlimits = [0 1]-0.5;
ylimits = [0 1.025];

%plot
close
hold on
scatter(labelsb(:,1)-0.5+jitter1',labelsb(:,2),50,colour_palette(2,:),'filled','Ma
```

```
hline = refline(0,0.4);
hline.Color = 'red';
hold off

%add lables
xlabel('$Patient\ reported\ stabiliyt$');
ylabel('$Measured\ instability$');
xticks([-0.5 0 0.5]);
xticklabels({'$Stable$','$0$','$Unstable$'});
yticks([0 0.25 0.5 0.75 1]);
yticklabels({' ','0.25','0.5','0.75','1'})

%setup axis
ax = axis_set(xlimits,ylimits,PaperSize);
ax.YAxisLocation = 'origin';
ax.YLabel.Position = [0.0365 0.75 0.1];
axis equal

%add legends
lgd = legend('$Predicted\ instability\ per\ subject$','$Best\
 Predicted\ Instability$');
lgd.Position = [0.05,0.6,0.4,0.06];
lgd.FontSize = 10;
lgd.Box = 'off';
set(lgd, 'Interpreter','latex');

print('-dpng','-r600',strcat('Prediction graph',datestr(datetime)))
```

Code for ROC for different calculations

```
close
[colour_palette,paperwidth,Phi] = requiredcode;
PaperSize = [paperwidth,paperwidth]; %Set paper size
% Plot ROC curve, adding polynomial to define "best" cuttoff
load('LR labels.mat')
outputlables = labelsb(:,2);
truelables = labelsb(:,1);
[X,Y] = perfcurve(truelables,outputlables,1);
plot(X,Y)
hold on
load('SVM labels.mat')
outputlables = labelsb(:,2);
truelables = labelsb(:,1);
[X,Y] = perfcurve(truelables,outputlables,1);
plot(X,Y, 'LineStyle','--')
r = refline(1,0);
r.Color = [220 220 200]/255;
xlimits = ([0 1]);
ylimits = ([0 1]);

%add lables
xlabel('$False\ Positive\ Rate$');
ylabel('$True\ positive\ rate$')
```

```
%add legends
lgd = legend('$Logistic\ Regression$','$Support\ Vector\ Machine$');
lgd.Position = [0.5,0.2,0.4,0.06];
lgd.FontSize = 10;
lgd.Box = 'off';
set(lgd, 'Interpreter','latex');

%setup axis
ax = axis_set(xlimits,ylimits,PaperSize);
ax.XLabel.Position = [0.5 -0.1 0.1];
hold off
hold off


print('-dpng','-r600',strcat('ROC graph',datestr(datetime)))

% Required code


function [colour_palette,paperwidth,Phi] = requiredcode
      colour_palette = [0.5, 0.5, 0.5;
                        0.5, 0.7, 0.7;
                        0.5, 0.9, 0.9;
                        0.5, 0.6, 0.6;
                        0.5, 0.8, 0.8;
                        0.5, 1.0, 1.0;
                        0.5, 0.1, 0.1;
                        0.5, 0.3, 0.3;
                        0.5, 0.4, 0.4;
                        0.5, 0.0, 0.0;
                        0.5, 0.55, 0.55;
                        0.5, 0.45, 0.45];

    paperwidth = (21-2.54-2.54)/2.54; %A4 paperwidth - margines
    Phi = (1+sqrt(5))/2; %golden ratio
end

function ax = axis_set(xlim,ylim,PaperSize)
    fig_prop(PaperSize)
    %Internal function to manage axes
    ax = gca;
    ax.XAxisLocation = 'Origin';
    ax.Title.Interpreter = 'LaTeX';
    ax.Title.FontSize = 16;
    ax.FontName = 'LaTeX';
    ax.XLabel.Interpreter = 'LaTeX';
    ax.XLabel.VerticalAlignment = 'bottom';
    ax.YLabel.Interpreter = 'LaTeX';
    ax.YLabel.HorizontalAlignment = 'Center';
    ax.YLabel.Rotation = 90;
    ax.TickLabelInterpreter = 'LaTeX';
    ax.FontSize = 12;
    ax.Box = 'Off';
```

```
    ax.XLim = xlim;
    ax.YLim = ylim;
    ax.XLabel.Position = [20 -8 1];
    ax.Layer = 'Top';
end

function fig_prop(PaperSize)

    %Internal function to manage figure appearance
    fig = figure(1);
    fig.PaperPositionMode = 'manual';
    fig.PaperUnits = 'inches';
    fig.Units = 'inches';
    fig.PaperPosition = [0,0,PaperSize(1),PaperSize(2)];
    fig.PaperSize = [PaperSize(1),PaperSize(2)];
    fig.Position = [0.1,1,PaperSize(1)-0.1,PaperSize(2)-1];
    fig.Resize = 'off';
    fig.InvertHardcopy = 'off';
    fig.Color = 'White';
end
```

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