TRACKING OSTEOARTHRITIC GAIT USING WEARABLE SENSORS

TRACKING REAL-WORLD CHANGES IN OSTEOARTHRITIC GAIT PATTERNS USING WEARABLE SENSORS

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TITLE: Tracking real-world changes in osteoarthritic gait patterns using wearable sensors

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Lay Abstract

Wearable sensor-based gait analysis is becoming increasingly popular for studying knee osteoarthritis (OA). Unfortunately, this work involves highly controlled and short walking protocols that represent a single snapshot of one's walking, which is not indicative of the fluctuations that occur in the real-world. Therefore, to use wearable sensors for understanding knee OA gait, it is essential to understand normal fluctuations in gait and differentiate them from meaningful changes. We utilized knee injections as a model to determine the sensitivity of wearable sensors to identify meaningful changes in gait. Three gait trials were insufficient in describing typical gait patterns and post-injection atypical strides were not significantly different from pre-injection. Changes in pain following the injection were not correlated to atypical strides. This study was the first to use wearable sensors for multi-week knee OA gait monitoring out-of-lab, but suggests more work is needed to understand these complex real-world fluctuations in gait.

Abstract

Intra-articular corticosteroid knee injections (ICIs) were used as a tool to determine the sensitivity of wearable inertial sensors and machine learning algorithms in identifying meaningful changes in gait patterns amidst day-to-day fluctuations in out-of-laboratory gait. Specifically, three overarching aims were proposed; I) Determine if three gait trials could define an everyday typical gait pattern, II) investigate if post-injection atypical strides are significantly different from pre-injection atypical strides and III) explore the relationship between changes in pain and atypical strides. Nine knee OA patients (7M/2F) were recruited from St. Joseph's Healthcare Hamilton. Participants completed a total of four walking trials prior to the ICI and three following. Participants were fitted with two wearable sensors on each shank just below the knee, and one sensor on the lower back during every trial. Data from these sensors were processed to train and test a one-class support vector machine (OCSVM). Individual gait models were created based on three out of the four pre-injection trials. Each trained model was tested on a withheld pre-injection trial and three post-injection trials to determine the number of typical and atypical gait cycles. Self-reported pain was analyzed throughout the study and compared to the percent of atypical strides seen during each walk. It was found that three gait trials could not define a typical gait model and that post-injection atypical strides were not significantly different from with-held pre-injection atypical strides. Finally, large variations and fluctuations in self-reported pain were observed on a week-to-week basis, which were not significantly correlated to atypical strides observed. This study was the first to investigate the sensitivity of wearable inertial sensors and machine learning algorithms to detect changes in real-world gait patterns and provides foundational work for using wearable sensors to monitor and triage knee OA patients.

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List of Abbreviations and Symbols

OA: Osteoarthritis

ICI: Intraarticular Corticosteroid Knee Injection

SVM: Support Vector Machine

OCSVM: One-Class Support Vector Machine

PCA: Principal Component Analysis

IMU: Inertial Measurement Unit

NPRS: Numerical Pain Rating Scale

KOOS: Knee Osteoarthritis Outcome Score

TKA: Total Knee Arthroplasty

6MW: 6-Minute Walk

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

RMS: Root Mean Square

K/L Grade: Kellgren and Lawrence Grade

Declaration of Academic Achievement

I, Zaryan Masood, hereby declare that I am the sole author of this thesis. The study was conceived by Zaryan Masood and Dr. Dylan Kobsar. Edits and revisions were conducted by Zaryan Masood, based on feedback from Dr. Dylan Kobsar, Dr. Peter Keir, and Dr. Janie Wilson.

Chapter 1: Introduction

Osteoarthritis (OA) is a degenerative joint disease resulting in pain, stiffness, impaired mobility, and a reduced quality of life (Henriksen et al., 2012). Currently, nearly 5 million Canadians are diagnosed with OA, making it the most prevalent musculoskeletal disease and the leading cause of physical disability in adults (Bombardier, 2011; Cross et al., 2014). Knee OA is the most common form of OA (Chehab et al., 2014) and is characterized by the loss of cartilage, change in bone, and abnormal lower limb movement patterns (Chu & Andriacchi, 2015). As such, gait analysis provides a non-invasive approach to study the mechanics and loading of the lower limbs that can provide valuable information on the etiology, progression, and treatment of knee OA (Davis, 1997). Unfortunately, conventional gait analysis laboratories involving motion capture cameras and in-ground force platforms are expensive and confined to laboratory settings thus limiting their accessibility and clinical practicality. Further, the use of conventional gait analysis technology can only assess a limited number of gait cycles in a controlled environment which may not effectively define one's typical gait pattern that is occurring every day in the real-world (Benson et al., 2019; Hillel et al., 2019).

Fortunately, the advent of wearable sensors has revolutionized gait analysis by making it more accessible and affordable, while also providing the unique ability to collect data out-of-lab. Research has shown that wearable inertial sensors or inertial measurement units (IMUs) can collect detailed and reliable biomechanical data (Ahmad et al., 2013; Kobsar et al., 2014) in a laboratory setting. Further, these wearable sensor-based gait analyses have the potential to support clinical decisions for common musculoskeletal disorders such as OA (Kobsar et al., 2016; Na & Buchanan, 2021; Turcot et al., 2008). For these reasons, wearable sensors are

becoming increasingly popular for the study of OA, with more research utilizing them in out-of-lab gait collections (Ahamed et al., 2019; Ahmad et al., 2013; Halilaj et al., 2018; Kobsar, Masood, et al., 2020). Unfortunately, much of this work still involves highly controlled and short (e.g., 20 m) walking protocols (Kobsar et al., 2020) that represent a single snapshot of gait and may not be indicative of the fluctuations occurring daily in more real-world gait patterns (Hillel et al., 2019).

Therefore, if future research aims to use wearable sensors more effectively in tracking changes with respect to OA disease progression or treatment, there is not only a need to better understand day-to-day fluctuations in real-world gait patterns, but to place them in the context of meaningful changes overtime. Doing so will allow us to better understand the sensitivity of these devices by determining whether meaningful changes can be identified amongst these variable, out-of-lab gait patterns in older adults with knee OA. As such, we utilized a common clinical intervention for reducing pain as a method to evoke and assess these meaningful changes in gait. Specifically, individuals with knee OA are commonly given intra-articular corticosteroid injections (ICI) to both treat the affected joint as well as reduce pain. This reduction in pain from ICI has been shown to provoke individual changes in gait patterns (Mehta et al., 2011). Therefore, the overarching aim of this project is to use ICI as a model to assess the ability of wearable inertial sensors and machine learning algorithms to identify changes in gait, amidst the day-to-day fluctuations in out-of-lab gait patterns. More specifically, our goal is to use a principal component analysis (PCA) to capture key gait features and a one-class support vector machine (OCSVM) to holistically define and represent changes in individual gait models, particularly with respect to changes in pain.

This current document consists of a Literature Review (Chapter 2), as well as Thesis Research Questions (Chapter 3), Methodology (Chapter 4), Results (Chapter 5) and Discussion (Chapter 6). The Literature Review highlights and analyzes studies that are in the field of knee OA biomechanics specifically utilizing IMUs and machine learning for gait analysis. The methods, results, and discussion outline the study design, sample, and key findings from the thesis "Tracking real-world changes in osteoarthritic gait patterns following intra-articular corticosteroid knee injections".

Chapter 2: Literature Review

The purpose of this Literature Review is to first briefly outline background topics such as knee OA (2.1) and the importance of gait analysis in adults with knee OA (2.2), followed by a more in-depth examination of current literature on wearable sensors (2.4), knee injections (2.5) and machine learning (2.6) all in knee osteoarthritic populations. Specifically, this review critically highlights the importance of using inertial measurement units (IMUs) and machine learning techniques to understand knee OA gait.

2.1 Knee Osteoarthritis

Osteoarthritis (OA) is a deteriorating joint disease characterized by structural changes and pain in synovial joints (Henriksen et al., 2012). OA can affect the hands, hips, feet and spine, however, OA is most commonly found at the knee (Chehab et al., 2014). Knee OA is diagnosed by assessing structural damage or reduction of the knee joint space via magnetic resonance imaging or a radiograph (Altman et al., 1991). Common structural changes include the presence of osteophytes, bone sclerosis, or malalignment (Michael et al., 2010). These structural damages can be graded using the Kellgren and Lawrence (K-L) criteria where grade 0 is no structural damage and grade 4 is classified as severe. The most common feature of knee OA is the presence

of joint pain, which can accompany other symptoms such as limited mobility, joint stiffness and swelling (Guccione et al., 1994). Further, knee OA can be characterized by its location within the knee joint. Locations include the medial tibiofemoral compartment, the lateral tibiofemoral, and the patellofemoral compartment. The medial tibiofemoral compartment, or medial compartment for short, is the most common location for knee OA and is most commonly studied in current literature (Neumann et al., 2009).

Although knee OA has previously been described as a wear and tear disease, current literature focuses on the interaction between biology and physiology, structure or alignment, and gait mechanics in the development and progression (Asay et al., 2018). Specifically, the changes to the articular cartilage are highly complex and involve mechanical, biological and structural pathways (Figure 1) (Andriacchi et al., 2004). Andriacchi and colleagues (2014) created a two-part framework (Initiation and Progression), which describe the degradation of articular cartilage that contributes to the worsening of knee OA. The initiation phase is associated with biological or mechanical changes that shift load-bearing to infrequently loaded regions, which the cartilage cannot accommodate and support. The progression phase follows cartilage breakdown, where knee OA progresses more rapidly with increasing load. Further, there is no single risk factor that can define the etiology of OA but rather several systemic and local factors. Factors include obesity, sex, age, exercise status, and menopause, which can influence the onset or progression of knee OA by activating the initiation phase. Additionally, Silverwood et al., (2015) conducted a systematic review and meta-analysis in order to determine the most common risk factors, which influence the onset of knee OA. Although age, genetics, BMI, muscle strength, and alignment play a considerable role in the development of knee OA, Silverwood and colleagues (2015) concluded obesity and female sex were the most common risk factors for the onset of

knee OA. As knee OA becomes more prevalent in our aging population, understanding the functional, anatomical, and biological interactions further will assist in optimizing treatments for this highly prevalent and debilitating disease. Specifically, this review analyzes the functional aspect through investigating gait, where the knee joint is subject to high loads.

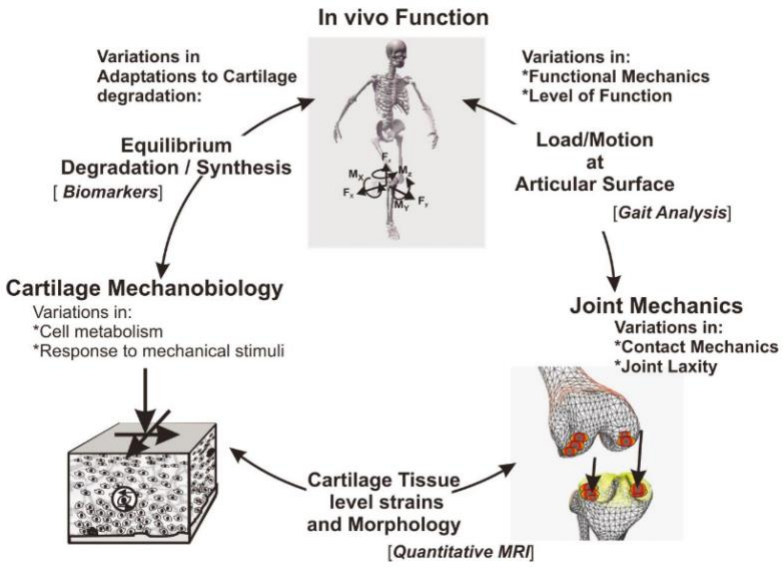


Figure 1: Outlining the relationship between joint mechanics, cartilage mechanobiology and *in vivo* function in knee OA all influencing articular cartilage degradation. Gait analysis, quantitative MRI and biomarkers are valuable tools in understanding this pathway. (Andriacchi et al., 2004)

2.2 Knee Osteoarthritic Gait

2.2.1 Introduction to Gait Analysis

Walking is the most common form of locomotion and has the ability to describe an individual's overall health (Roberts et al., 2017). The gait cycle is divided into two phases, stance and swing. Stance is used to designate the entire period the foot is on the ground and begins with initial contact. Swing applies to the time when the foot is in the air and is essential for limb advancement (Kharb et al., 2011). The swing phase is initiated when the foot is first lifted from the surface which is also known as toe-off. Within the gait cycle, there are seven major events, four of which occur in the stance phase and three which occur in swing (Figure 2).

The major events include loading response, mid-stance, terminal stance, pre-swing, initial swing, mid-swing, and terminal swing. Dividing the gait cycle into these specific events allows for a more specific gait analysis.

Gait analysis has become widely used as a means to diagnose specific pathologies, monitor prognosis, and establish treatment plans (Roberts et al., 2017). In more clinical settings, gait analysis is often conducted through visual observation due to its ease in measurement; however, this method remains highly subjective. Optical motion capture analysis systems, wearable sensors, and force plates allow researchers to understand gait pathologies further as well as analyze specific objective gait parameters. Gait parameters that are commonly studied in healthy and clinical populations are spatiotemporal parameters, ground reaction forces (GRF), joint kinematics, and joint moments (Kobsar et al., 2020; Tyburski & Gage, 1991; Winter et al., 1990). Gait analysis is a meaningful way to study the mechanical environment of the lower limbs non-invasively and can allow researchers to further understand gait pathologies such as knee osteoarthritic gait, and to design specific prevention and treatment plans.

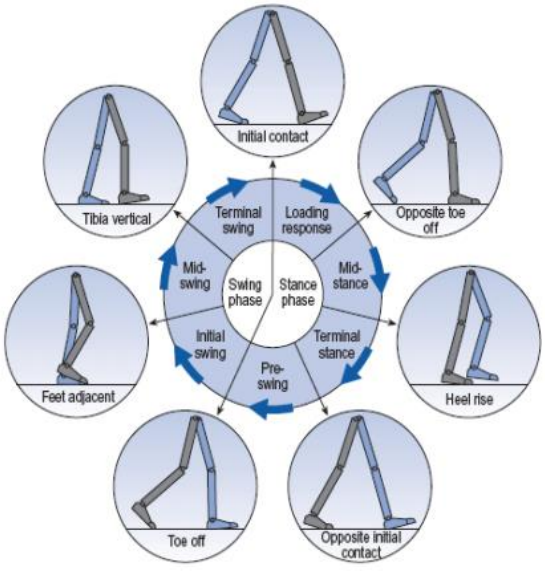


Figure 2: Highlighting the stance and swing phase as well as the major events within the gait cycle. (Whittle, 1991)

2.2.2 Knee Osteoarthritis Gait Metrics

Adults with knee OA adopt a wide variety of patterns and deviations of gait depending on their disease severity, sex, or compartment (Zeni & Higginson, 2009). First, gait speed and other spatiotemporal parameters are critical metrics used to characterize gait in knee OA populations. Numerous studies have reported slower gait speeds in OA patients compared to healthy controls and slower gait speeds in more severe OA as compared to less severe OA patients (Astephen et al., 2008; Julien Favre & Jolles, 2016). Astephen et al., (2008) found individuals with severe knee OA had smaller stride lengths, increased stride time and increased stance time as compared to moderate knee OA and asymptomatic participants. While spatiotemporal patterns are effective and efficient parameters to describe the overall knee OA gait, they are often not sensitive enough to detect underlying differences in knee biomechanics (Julien Favre & Jolles, 2016). Therefore, it is necessary to further analyze three-dimensional kinetic and kinematic gait patterns in individuals with knee OA.

While there is a near-infinite number of potential parameters which could be assessed with respect to walking gait kinetics and kinematics, knee OA research has most often focused on three key parameters. First, the knee adduction moment (KAM) undoubtedly receives the most attention and analysis as it provides a proxy for the medial to lateral distribution of loading through the knee and has been linked to OA severity, progression, and symptoms (Astephen Wilson et al., 2017; Brisson et al., 2017; Julien Favre & Jolles, 2016; Hurwitz et al., 2002; Maly et al., 2015; Mündermann et al., 2005; Sharma et al., 1998). Another important kinetic variable assessed in osteoarthritic gait is the knee flexion moment (KFM). Similar to KAM, KFM is thought to be highly related to compartmental loading and has been shown to play an important

role in knee OA severity and progression (Bennell et al., 2014; Henriksen et al., 2010; Astephen et al., 2008; Huang et al., 2008). Finally, the knee flexion angle (KFA) has been an essential variable in the analysis of knee OA biomechanics. Current literature has highlighted the smaller ranges of motion over the entire gait cycle which are consistently reported with increasing disease severity and outline the importance of KFA in the biomechanical analysis of knee OA (Baliunas et al., 2002; Favre et al., 2014).

Although this section highlights spatiotemporal, kinetic (KAM & KFM), and kinematic (KFA) parameters separately, these variables are not entirely independent, and all play a vital role in describing and understanding knee osteoarthritic gait. Further, while KAM, KFM, and KFA are characteristic measures of knee OA gait, they are time-consuming to measure, making it difficult to collect large amounts of longitudinal research data and almost entirely impractical to collect in a clinical setting. Further, their sensitivity to change with respect to pain or exercise is limited (Bennell et al., 2014; Khalaj et al., 2014) and they are often not assessed repeatedly over time or reported on a day-to-day basis where fluctuations in pain can occur. Although these metrics will likely remain the gold-standard variables due to their relationship with knee OA severity and progression, we know that these cannot be fully representative of everyday real-world gait patterns where such day-to-day fluctuations in these parameters is ever-present (Hillel et al., 2019). One solution to tracking everyday gait patterns that may be sensitive enough to changes in pain, is to use wearable inertial sensors in out-of-laboratory settings along with machine learning algorithms to manage and track gait patterns over time.

2.3 Wearable Sensors in Knee Osteoarthritis

The purpose of this section is to highlight the importance of wearable sensors, specifically inertial measurement units (IMUs), to conduct gait analysis in knee OA patients.

This section will start with a general overview of IMUs and then take a comprehensive approach to examine and analyze current studies that use wearable sensors for gait analysis where spatiotemporal variables, impact accelerations, and gait symmetry are studied in knee osteoarthritic patients.

2.3.1 Inertial Measurement Units (IMUs)

Inertial Measurement Units (IMUs) first became popular in the 1930s where they were primarily used for aircraft navigation (Zhao & Wang, 2012). In the past, IMUs were large, costly, inefficient, and required large power consumption which in turn restricted the use of IMUs in small devices and consumer applications (Ahmad et al., 2013). The recent development of micro-electromechanical system (MEMS) technology has made it possible to manufacture more affordable IMUs which are compact and require low processing power. Recently, the demand for IMUs has been growing exponentially and sparked many new applications, especially within scientific research, specifically human movement analysis (Avrutov et al., 2017).

IMUs consist of accelerometers, gyroscopes, and sometimes magnetometers, and are designed to measure linear acceleration, angular velocity, orientation, or gravitational force (Figure 3). Specifically, accelerometers measure linear acceleration by measuring force and using Newton's second law (i.e., Force = Mass x Acceleration). Accelerometers are currently built with a variety of different mechanisms. Commonly, a mass is attached to a spring which is suspended inside an outer casing. When the sensor is accelerating, the mass is left behind due to inertia, and the spring is stretched with a force relative to the outer casing which relates to the acceleration (Ahmad et al., 2013). The distance the spring is stretched can be used to measure the force, and subsequently acceleration. Some accelerometers use changes in electrical or magnetic

signals to determine acceleration. If a moving mass alters the distance between two parallel metal plates, measuring the change in capacitance can give insight into the total force on the sensor. Finally, in piezoresistive accelerometers, the mass is attached to a potentiometer which adjusts the electric current depending on the size of the force (Ahmad et al., 2013). Triaxial accelerometers provide measurements in three orthogonal directions or dimensions (x,y,z) for a more detailed understanding of the total acceleration on the unit.

Gyroscopes can measure the angular velocity and orientation of an object. Angular velocity is the change in the rotational angle of the object per unit of time. Gyroscopes assist in determining the pitch, roll, and yaw (Figure 3). Similar to accelerometers, gyroscopes are based on Newton's second law and transform the Coriolis force to angular velocity. The Coriolis force is a fictitious force which applies to the movement of rotating objects. It is determined by the mass of the object and the rate of rotation. Gyroscopes measure force using a mass and spring, similar to accelerometers, combined with Coriolis sensing fingers. As the mass within the gyroscope moves and as the surface that the gyroscope lies on rotates, the mass experiences the Coriolis force which translates the mass and frame 90 degrees from the movement. Further, as the rate of rotation increases, the displacement of the masses changes which creates a change in capacitance (Watson, 2016).

Finally, magnetometers are used to detect and measure magnetic fields which assist in orientation. Magnetometers commonly function under the effects of detecting the Lorentz force which measures the change in voltage or resonant frequency electronically. The exact mechanisms and applications of magnetometers are out of the scope of this review as they are less commonly used for gait applications. The advancement of accelerometers, gyroscopes, and

IMUs together are promising as they continue to spark and improve newer applications such as gait analysis, which has become more accessible, affordable, and real-world relevant.

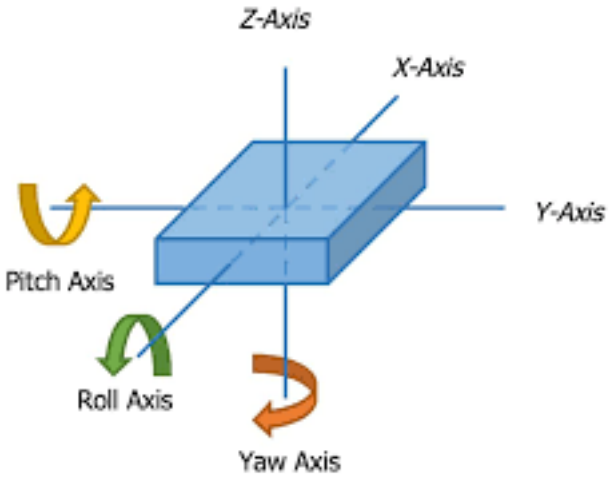


Figure 3: Inertial Measurement Unit (IMU) where accelerometer can measure linear acceleration in the X, Y, and Z axis while gyroscope can measure pitch, roll, and yaw (Javier & Ortega, 2017)

2.3.2 IMUs in Gait Analysis

IMUs continue to become more popular in scientific research and have a variety of applications such as stabilometry, instrumented clinical tests, upper body mobility assessment, daily-life activity monitoring, tremor assessment and gait analysis (Iosa et al., 2016). Specifically, gait analysis, as discussed in section 2.2, can provide important lower limb biomechanical data which can be useful in understanding the development and progression of knee OA. Gait analysis is most often done via laboratory-based optical motion capture however, this gold-standard remains inaccessible to most clinicians, can be expensive and require lengthy setup and post-processing. While using laboratory based gait analysis is beneficial as the environment can be controlled, there is also a need to collect gait data in out-of-laboratory settings where gait patterns are more representative of the patients natural gait (Hillel et al.,

2019). Wearable sensors or IMUs can be used as an affordable and accessible alternate for conventional motion capture gait analysis systems, and they offer the unique ability to track out of-laboratory gait. A recent scoping review outlined the exponential growth of studies using wearable sensors to assess knee OA gait (Kobsar et al., 2020) (Figure 4).

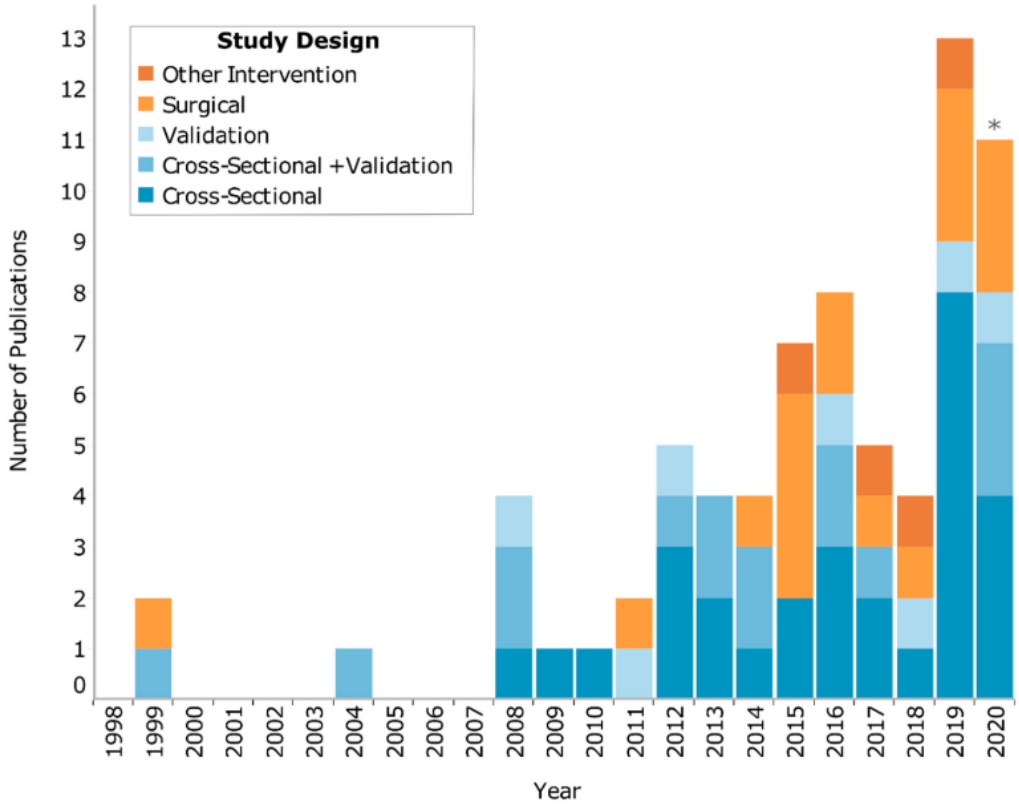


Figure 4: Number of wearable sensor studies published each year for gait analysis in knee OA populations. Colours indicate the study design (Kobsar et al., 2020).

Previous literature has highlighted the reliability and accuracy of wearable sensors for gait analysis (Benson et al., 2019; Kobsar et al., 2016). To this point, wearable sensors offer the versatility to be placed in a variety of locations to derive valid and reliable spatiotemporal,

kinematic, or even kinetic metrics of a specific body segment (Kobsar et al., 2020; Charlton, et al., 2020). Common locations include the foot, ankle, knee, hip, shank, thigh, and lower back. Although previous literature has used wearable sensors to measure joint moments, joint and segment angles, impact accelerations and gait symmetry accurately, spatiotemporal parameters remain the most common metric measured among health and knee OA populations (Kobsar et al., 2020; Mills et al., 2013; Hunt, et al., 2013).

2.3.3 IMUs for Spatiotemporal Metrics

Spatiotemporal metrics are highly reported in gait analysis as they are easy to measure and understand, while holding important clinical information (Iosa et al., 2016). Most generally, walking speed has been used as an indicator of locomotor deficits, prolonged stance phase is associated with instability and shorter steps are characteristic of pathological gait (Iosa et al., 2016). Spatiotemporal metrics are commonly reported in current literature as the mean value or presented as variability metrics where they are calculated by standard deviation or coefficient of variation for a given spatiotemporal variable.

2.3.3.1 Mean Spatiotemporal Metrics

Mean spatiotemporal metrics as measured by IMUs have also been correlated to knee OA severity. Bolink et al., (2012) used mean spatiotemporal metrics to differentiate knee OA patients from healthy controls. Bolink and colleagues (2012) found knee OA patients had a significantly slower walking speed (0.85 m/s) as compared to healthy subjects (1.29 m/s). Further, knee OA patients also had a significantly slower cadence (98.1 steps/min), shorter step length (0.52m) and slower step time (0.62s) as compared to the healthy control group (112 steps/min; 0.69m; 0.54s). Intuitively, these findings make sense as individuals with severe knee OA are less confident and comfortable in their gait due to changes in pain, increased stiffness, and decreased range of

motion which could lead to shorter step lengths and slower walking speeds. Similar results were found by many other studies utilizing a single IMU on the lower back (Andrade et al., 2017; Clermont & Barden, 2016; Fransen et al., 2019). Moreover, increased stride time has shown the strongest and most common deviation in adults with knee OA, as compared to healthy controls (Mills et al., 2013; Hunt, et al., 2013). Chopra & Crevoisier (2019) used a 5-sensor system with sensors on the tibia, ankle and metatarsals and found that adults with moderate to severe OA have increased stride time and decreased stride length as compared to healthy controls. Many studies have found similar results to Mills et al., (2013) and Chopra & Crevoisier (2019), however, the majority of current literature highlights mean spatiotemporal parameters following surgical interventions (Kobsar et al., 2020).

2.3.3.2 Spatiotemporal Variability

Although less reported in current literature compared to mean values, variability of spatiotemporal metrics is important in describing knee OA gait. Spatiotemporal variability is often used to assess health status, mobility, function or fall risk as variability measures are more sensitive to neurological and musculoskeletal changes than mean spatiotemporal metrics (Herssens et al., 2018; Lord et al., 2011). Bolink et al., (2012) found that severe knee OA patients had a significantly higher step length and step time variability when compared to healthy controls as measured by the coefficient of variation. Additionally, Andrade et al., (2017) found step and stride time coefficient of variations much greater in knee OA patients, similar to Bolink et al., (2012).

Although measuring the mean and variability of spatiotemporal can be important in describing knee OA gait, tracking lower limb or segment motions using acceleration signals can

provide a more in-depth and unique perspective to individual gait patterns (Na & Buchanan, 2021).

2.3.4 IMUs for Lower Limb Accelerations

In addition to monitoring changes in spatiotemporal variables, IMUs offer the ability to measure unique kinematic variables such as impact accelerations, which are the peak impacts during heel strikes. Depending on the placement of the IMU, segmental accelerations can be determined using a variety of methods such as multi-axis accelerations (e.g., mean, root mean square; RMS), impact peaks, or waveform analyses (Kobsar et al., 2020). These acceleration variables measured by wearable sensors have been shown to be reliable in both healthy adults (Kobsar et al., 2020; Charlton et al., 2020) and in patients with knee OA (Turcot et al., 2008). Commonly, acceleration patterns measured by wearable sensors are used to study pathological gait but can also be used in both post-surgical and sport applications. A more recent focus has been placed on clinical gait applications, specifically differentiating between healthy and OA gait.

Barrois et al., (2016) used a four IMU based protocol to understand differences between healthy and osteoarthritic gait and determined if IMUs could provide simple features that could correlate with knee osteoarthritis severity. IMUs were attached to the head, lower back (L3-L4) and both feet. The foot IMUs showed a discrimination capacity between different knee OA severity groups for mean and RMS in peak impact acceleration in the horizontal or mediolateral plane. These results remained statistically significant with BMI and age as covariates however the authors did not determine if the changes in impact accelerations were due to the slower walking speed found in OA cohorts. Nevertheless, the Barrois et al., (2016) findings are

noteworthy in clinical settings as only two lower-limb IMUs were used to differentiate impact accelerations in OA and healthy patients. Additionally, Turcot & Aissaoui, et al., (2008) were also able to discriminate between an OA and healthy group based on accelerations. Turcot & Aissaoui, et al., (2008) found differences in tibial and femoral mediolateral and anteroposterior accelerations between asymptomatic and OA groups exclusively in the loading phase of the gait cycle (Figure 5).

Impact and segmental accelerations are also useful in determining knee OA patient gait stability. Na & Buchanan (2021) examined whether impact accelerations measured by IMUs could discriminate between knee OA patients who self-reported higher instability throughout gait. Self-reported instability was measured by the Survey-Activities of Daily Living Scale (KOS-ADLS). Twenty-six participants with moderate to severe medial compartment knee OA and 13 control participants were recruited. IMUs were strapped bilaterally on the femur and tibia as well as a single IMU was placed on the PSIS. Na & Buchanan (2021) found peak RMS tibial impact acceleration to show excellent discriminant validity between the OA and control group as the OA group had significantly higher tibial accelerations during midstance. Also, within the OA group, greater tibial acceleration during midstance was associated with worse self-reported instability. The authors suggested two major findings from this study: 1) wearable sensors are a valid and appropriate tool for objectively quantifying and detecting self-perceived instability and 2) patients with knee OA are at a higher risk of these instabilities due to greater accelerations at the shank during midstance. However, Na & Buchanan (2021) did conduct the study in a cross-sectional manner and reported that knee OA patients did not have any episode of instability during data collection. Future studies may look to examine similar variables over time and through many gait trials to holistically understand gait patterns and changes.

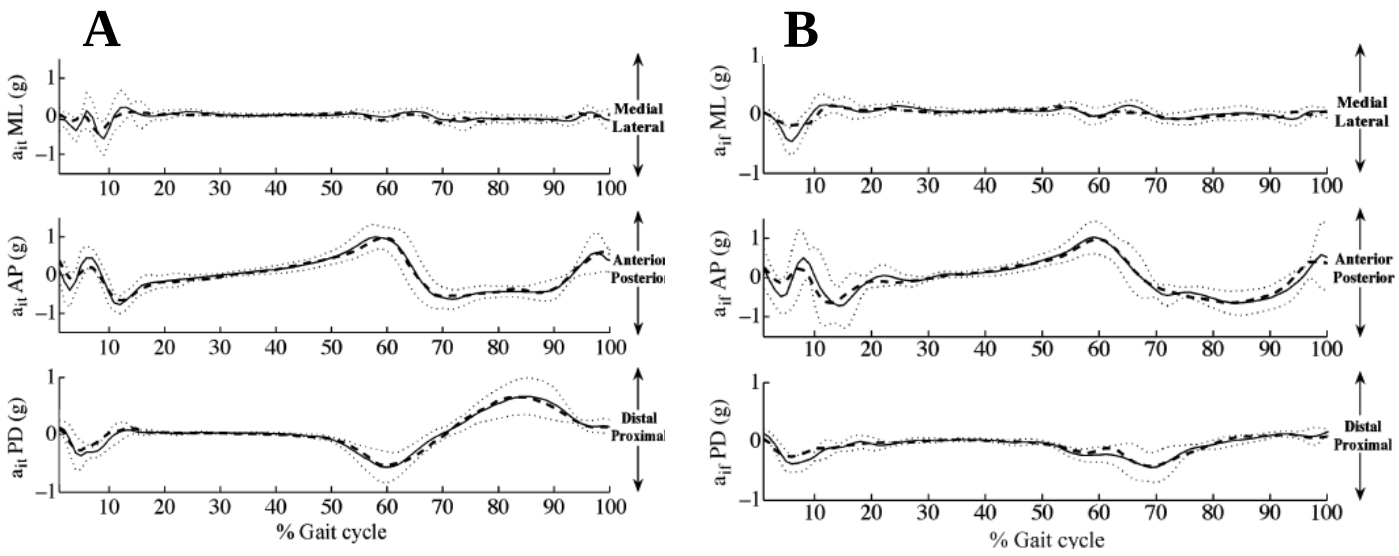


Figure 5: (A) Internal tibial and **(B)** internal femoral accelerations in mediolateral, anteroposterior, and distal-proximal directions for knee OA (mean in solid line, standard deviation in dotted line, N=9) and asymptomatic (mean in dashed line, N=9) subjects (Turcot et al., 2008).

Not only have acceleration magnitudes been shown to be sensitive enough to differentiate between knee OA patients and healthy controls, but they have also been shown to be correlated to knee OA severity. Ishii et al., (2020) divided 44 knees from 44 patients into two groups: early-stage knee OA (K-L grade = 2) and severe knee OA (K-L > 3). The mediolateral thrust during gait, which was measured by the mediolateral acceleration immediately after heel strike, was recorded by IMUs placed on each tibia and each foot. The severe knee OA group had a significantly higher mediolateral impact acceleration (0.76 G's) as compared to the less severe group (0.58 G's). These increases in the mediolateral impact accelerations could be attributed to varus alignment and or varus thrust gait patterns. However, it is important to note, that mediolateral accelerations using wearable sensors have been previously shown to demonstrate poor reliability.

Based on a recent review by Kobsar et al., (2020), lower-limb accelerations have been a reliable measure in healthy adults, however, mediolateral accelerations, especially in OA cohorts can exhibit poor reliability. In healthy adults, Moe-Nilssen (1998) found the mediolateral axis demonstrated good reliability with an intraclass correlation coefficient (ICC) of 0.79, however it was still the lowest ICC as compared to the anteroposterior (ICC = 0.93) and vertical axis (ICC = 0.91). Further, Kobsar et al., (2016) compared the reliability of the three axes (e.g., vertical, anteroposterior and mediolateral) in a cohort of knee OA patients. Kobsar and colleagues (2016) also found the mediolateral axis to demonstrate the lowest reliability (ICC = 0.82-0.95) whereas the vertical and anteroposterior axis had excellent reliability (ICC = 0.97-0.99). Lastly, similar results were found by Lyytinen et al., (2016) in knee OA patients where the mediolateral axis demonstrated the lowest reliability (ICC = 0-0.75), while the vertical and anteroposterior axis demonstrated good to excellent reliabilities (ICC = 0.69-0.94). Mediolateral accelerations can still prove to be useful in understanding gait patterns in knee OA patients, however, should be used cautiously given the low reliability found by Moe-Nilssen (1998), Kobsar et al., (2016) and Lyytinen et al., (2016).

2.3.5 IMUs for Gait Symmetry

Between-limb differences in gait can reflect functional differences in the limbs and, as such, these metrics have been commonly studied in healthy and OA gait using IMUs. Staab et al., (2014) placed sensors on the back (L3) of 12 knee OA diagnosed patients and found the knee OA group to be significantly more asymmetrical in mediolateral trunk accelerations and spatiotemporal parameters such as step and stance time. Similar asymmetries were detected by Chopra & Crevoisier (2019) in patients with ankle OA and by Rapp et al., (2015) in hip OA patients who underwent hip arthroplasty.

Christiansen et al., (2015) analyzed tibial acceleration symmetry in severe knee OA patients who underwent a total knee arthroplasty (TKA) and a healthy control group. The knee OA patients who underwent TKA had a greater between limb asymmetry for tibial initial peak acceleration asymmetry index during a stair climbing intervention and a 6-min walk test 5 weeks after TKA. This increased asymmetry is characterized by decreased loading of the surgical limb compared to the non-surgical limb which has been related to the higher incidence of knee pathologies after TKA (Christiansen et al., 2015). The authors suggested that improving asymmetry could be an important approach to improving rehabilitation outcomes after TKA. Measuring acceleration asymmetry can be useful for clinicians in providing patient feedback during gait retraining following surgery. Christiansen and colleagues (2015) demonstrated that tibial acceleration asymmetry can be a valuable tool in understanding knee OA progression, especially after TKA and that acceleration-based symmetry patterns show similar results to limb loading and other kinetic parameters. Finally, gait symmetry has also been an important tool in assessing gait differences between unilateral and bilateral knee OA groups. Messier et al., (2016) compared the gait symmetry between a unilateral and bilateral knee OA group and interestingly found no significant differences in any spatiotemporal, kinematic, or kinetic symmetries between the two groups. Therefore, Messier et al., (2016) hypothesized that biomechanical gait changes are systemic and not exclusively based on physiological changes in the affected limb.

Although gait symmetry is becoming increasingly popular in current literature, many studies do not assess between limb gait symmetry in longitudinal designs or out-of-laboratory gait. This may be because many studies still utilize IMUs in combination with force plate or optical motion capture cameras. Assessing these asymmetries in more real-world, out-of-

laboratory settings where gait patterns may be more indicative of an individual's natural or real-world gait pattern would be an important addition to the literature.

2.3.6 Bridge to Section 2.4

IMUs have the capability to accurately measure a variety of biomechanical gait variables including spatiotemporal, kinematic or symmetry-based. Lower limb accelerations have shown a lot of promise and are increasing in popularity to further understand gait patterns (Kobsar et al., 2016). Accelerations in the vertical and anteroposterior axis demonstrate good-to-excellent reliability however, the mediolateral axis has continued to exhibit poor reliability, especially in OA cohorts (Kobsar et al., 2016; Lyytinen et al., 2016; Moe-Nilssen, 1998). However, gait biomechanical variables including accelerations are continuously subject to change as knee OA progresses and patients experience fluctuating changes in pain. Patients with knee OA can have random variations in pain which can influence biomechanical gait variables on a day-to-day basis. These changes due to pain may be more pronounced in out-of-lab gait patterns, where individuals may experience a pain flare at any time and are more likely to walk similar to their typical gait pattern. Therefore, understanding a patient's regular day-to-day fluctuations and analyzing how pain influences gait parameters can be useful to further comprehend knee OA gait as well as foster preventative technologies and treatments aimed to slow the progression of knee OA. One method to study changes in pain is to analyze intra-articular knee injections, an exceedingly common intervention given to knee OA patients to reduce pain and control knee OA advancement.

2.4 Intra-articular Injections for Knee Osteoarthritis

The most common injection types administered in Canada include corticosteroid derived and hyaluronic acid injections (Kopka et al., 2019). Synthetic corticosteroids have been used in clinical practice for over 50 years and provide an anti-inflammatory effect due to their ability to modulate the expression of lymphocytes and cytokines. Corticosteroids increase the viscosity of the synovial fluid however their primary purpose is to reduce inflammation and alleviate pain (Hollander, 1951). The most common form of corticosteroid administered includes methylprednisolone and triamcinolone, however, these are usually combined with local anaesthetics to decrease the incidence of a post-injection flare up (Kopka et al., 2019). Further, hyaluronic acid is a naturally occurring polymer which increases the viscosity of the synovial fluid as well as strengthens the articular cartilage. Like corticosteroids, hyaluronic acid injections can have anti-inflammatory effects.

Although they seem to have similar effects, many studies have compared the efficacy of corticosteroids versus hyaluronic acid. A recent Cochrane review highlighted that corticosteroids are more beneficial in reducing pain and improving function within 6 weeks post-injection with no benefit observed after 6 months (Jüni et al., 2015). Hyaluronic acid provides improvement in pain, function and stiffness however has a significant delay post-injection before positive effects are felt and can last up to a year (Jüni et al., 2015). Similar results were found by a systematic review and meta-analysis by Bannuru et al., (2009) where from baseline to week 4, corticosteroids appear to be more effective for pain but beyond week 8, hyaluronic acid has greater efficacy (Figure 6). Therefore, intra-articular corticosteroids may offer similar benefits in pain, stiffness, and function as hyaluronic acid but in a faster and shorter term (4-6 weeks).

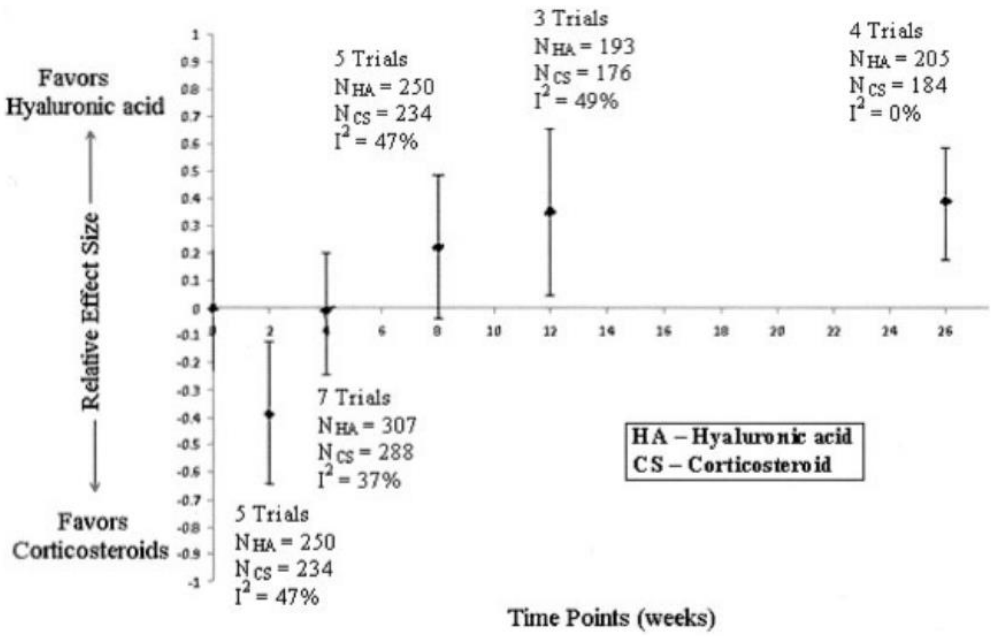


Figure 6: Relative effect size for corticosteroids and hyaluronic acid (95% Confidence Interval) (Bannaru et al., 2009). N represents the total number of studies and I^2 represents the level of heterogeneity across the studies.

2.4.1 Corticosteroid Injection Applications in OA Gait

Pain can have varying effects on gait mechanics. Henriksen et al., (2010) demonstrated that induced pain in healthy subjects led to reduced peak moments in the frontal and sagittal planes. However, what are the effects of pain reduction via intra-articular corticosteroid knee injections on spatiotemporal, kinetic, and kinematic gait variables in knee OA patients? Shrader et al., (2004) compared the gait of 19 medial compartment knee OA patients before and immediately after pain-relieving intra-articular corticosteroid knee injections with 21 healthy controls. Shrader and colleagues (2004) found gait velocity to increase by 5.8% and cadence to increase by 4.6% after injection. Further, peak KAM significantly increased with pain relief to a level not significantly different from that of the control group. No significant differences were found in joint angles in flexion-extension, abduction-adduction, or internal-external rotation, at the knee, hip, or ankle after the injection. A notable limitation of this study is that the researchers

did not ask participants to complete a self-reported pain questionnaire or survey and thus did not measure the degree of pain relief from the corticosteroid injection. This would mean that the authors results could be due to other confounding variables and not from direct pain-relief itself. Similar results were found by Pinto & Birmingham (2018) where the gait, numeric pain rating scales (NPRS) for pain, and Knee Injury and Osteoarthritis Outcome Scores (KOOS), before and 3 weeks after a corticosteroid injection was examined. NPRS pain decreased post-injection and peak KFM and KOOS subscale increased post-injection, where an increase in KOOS is related to less knee OA symptoms, pain, and a better daily living score. Increases in gait speed and reductions in NPRS pain were associated with greater peak KFM highlighting the relationship between changes in pain and knee joint moments.

Although corticosteroids have been shown to reduce pain in the short-term, many knee OA patients still experience increases in knee pain post-injection (Jüni et al., 2015) Additionally, although no study has directly assessed the effect of knee injection on segmental accelerations and gait symmetry, authors Bolink et al., (2015), Turcot et al., (2009) and Christiansen et al., (2010) have demonstrated that pain can influence accelerations and gait symmetry in knee OA patients. Therefore, we may expect similar results after decreases in pain following knee injections. Bolink et al., (2015) discovered a moderate correlation between self-reported pain levels and acceleration magnitudes in knee OA patients with a single IMU on the lower back. Contrary to their hypothesis, Bolink et al., (2015) found knee OA patients who had less pain or a lower WOMAC score had lower mean acceleration magnitudes in the anteroposterior and mediolateral directions. Similar results were found by Turcot et al., (2009) after examining mild-to-moderate knee OA patients following a rehabilitation treatment aimed to reduce knee OA pain and strengthen the knee joint. Self-reported pain, as assessed by WOMAC, significantly reduced

following the rehabilitation program. With this reduction in pain, Turcot and colleagues (2009) found reduction in mean tibial accelerations in the mediolateral and anteroposterior direction. These findings by Bolink et al., (2015) and Turcot et al., (2009) were not expected, as many studies have demonstrated that the reduction of pain symptoms in knee OA could lead to increase of knee loading and accelerations as patients feel more comfortable in their gait as seen by an increase in walking speed (Henriksen et al., 2012; Hurwitz et al., 2002; Shrader et al., 2004). Perhaps these differences in pain-response are attributed to sample size, compartment, severity, or unilateral/bilateral status.

Bolink et al., (2015) and Turcot et al., (2009) had knee OA patients with varying severity, had bilateral knee OA and were not specified to the medial compartment. Nonetheless, while changes in pain are seen to influence impact accelerations in mild-to-moderate knee OA patients, the exact mechanism of change is still unknown. Moreover, Christiansen et al., (2010) found a strong correlation between Numerical Pain Rating Scale (NPRS) and weight-bearing asymmetry where individuals with higher NPRS scores had a more asymmetrical gait. These findings by Christiansen et al., (2010) may be specific to individuals with severe unilateral knee OA and future research should explore the relationship between knee OA severity and symmetry.

Although many studies have found changes in spatiotemporal, kinetic, kinematic and symmetry variables following changes in pain or post-injection, many studies have not tracked these gait variables, especially symmetry and accelerations, in longitudinal and out-of-laboratory settings. Many studies have assessed pain before and after TKA, however, they frequently report frontal-plane loading. Studies need to examine multiple gait assessments due to the unpredictable nature of pain flares and take advantage of IMUs to track acceleration and symmetry variables out-of-lab.

Bridge to Section 2.5

Many studies have found changes in biomechanical gait variables with changes in pain (Henriksen et al., 2010; Jüni et al., 2015; Pinto & Birmingham, 2018; Shrader et al., 2004). How the changes in pain influence lower-limb accelerations and gait over time is still relatively unknown. Further, it is essential to account for changes in pain to define and understand typical gait patterns over time. By doing so, meaningful changes in gait can be better distinguished from everyday typical gait patterns. However, differentiating a typical gait pattern from a meaningful change (e.g., reduction in pain, improvement in function, disease progression, etc.) over multiple gait assessments in out-of-lab settings can be difficult, especially due to the large datasets that are provided by wearable sensors that quickly become complex and hard to interpret. Within these large datasets, there remains a vast amount of data that goes unanalyzed which can limit many study findings (Kobsar & Ferber, 2018). One method of sorting, processing, analyzing, and differentiating these large datasets is through the growing field of machine learning.

2.5 Machine Learning Methodology

2.5.1 Support Vector Machines

Support Vector Machines (SVMs) are machine learning models that are utilized for regression and classification of data (Chen, 2009). Multi-class SVMs are one of the most robust prediction machine learning methods and are primarily used for the classification of two distinct groups. Given a set of training data (e.g., data with input variables and known class labels), an SVM training algorithm classifies new data into one of the two groups making it a non-probabilistic binary linear classifier (Hastie et al., 2013). To separate data into two groups, multi-

class SVMs construct a hyperplane (a line for 2-Dimensional data), which is used to classify new data and separate it into groups. A hyperplane is designed using support vectors, which are the data points in each group that are used to calculate the orientation of the hyperplane and are usually the closest for both groups (Decoste & Schölkopf, 2002). A maximal marginal classifier technique is used when designing a classification boundary or hyperplane, where the distance from the support vectors is maximized to reduce errors for new unclassified data (Figure 7).

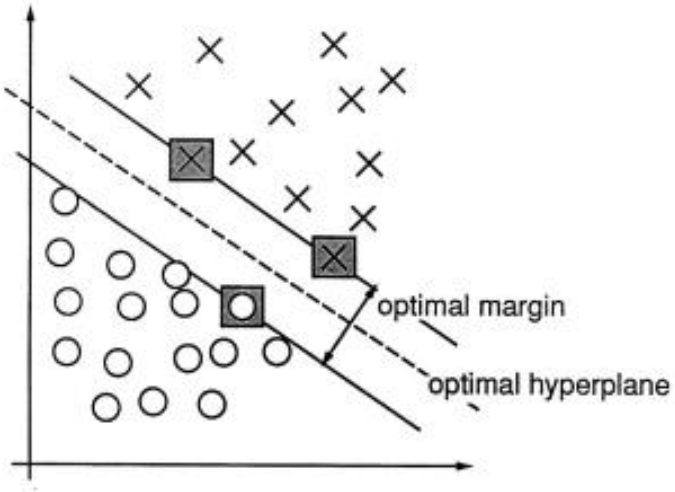


Figure 7: SVM example in 2-dimensional space. Support vectors, marked with grey squares, define the optimal hyperplane used to separate two groups (X and O)(Chen, 2009).

In more complex data with no easily recognizable pattern, multi-class SVMs can increase the dimensionality of the data using specific kernel functions to create an effective hyperplane (Figure 8). Common kernels include polynomial, gaussian radial basis, and hyperbolic (Chen, 2009). In data with low dimensionality, a kernel is applied before deciding on an optimal hyperplane. Using SVM-specific models has many advantages such as high dimensionality, where they are effective in high dimensional spaces ($>10^6$) and memory efficiency, meaning they only require a small subset of training points to create an efficient decision process. Finally, SVMs can be extremely versatile, where many kernels can be applied in highly non-linear data

making SVMs flexible and highly accurate (Statnikov et al., 2006). SVMs also carry some disadvantages such as a high risk of generalization and overfitting error which can lead to incorrect classifications. Further, SVMs give no direct probability interpretation for each group or new featured data (Lee et al., 2004). While training data is often labelled for binary classification, if training data is unlabelled (i.e., data is not specified as one group or another), the process relates to an unsupervised learning approach that can be used to find a natural cluster(s) in the data.

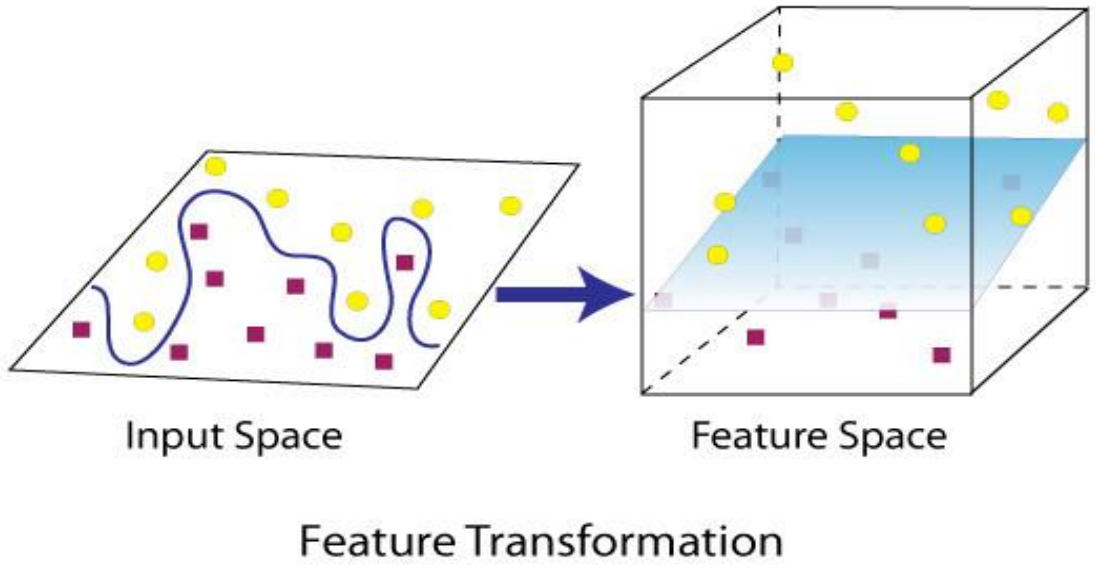


Figure 8: Dataset has no easily recognizable pattern and thus no linear hyperplane. A kernel is used to increase the dimensionality of the data and allows for a 3D hyperplane to optimally separate the data into two groups (Yu et al., 2010).

SVMs can be multi-class or one-class depending on the dataset and goal of the model. Multi-class models separate each group or class by a hyperplane whereas in one-class, the classification is not defined by either side of a hyperplane, but rather a "typical" boundary is created. Then, new test data can be classified as outliers if they fall outside of the "typical" boundary and inliers if they fall within (Mourão-Miranda et al., 2011). One-class SVM's have become increasingly popular in a variety of applications and are used for facial detection,

bioinformatics, image and text classification, and more recently for gait biomechanics to classify typical and atypical changes in movement patterns (Hawley et al., 2022; Kobsar & Ferber, 2018).

2.5.2 Support Vector Machines in Gait Analysis

Recently, Halilaj et al., (2018) conducted a review highlighting machine learning in human movement biomechanics. In this review, the authors identified an exponential growth of using machine learning models over the last 20 years and found SVM's to be the most common machine learning method. Further, wearable sensors were the most common data source over the last 10 years and osteoarthritis, stroke, and Parkinson's disease were among the leaders in pathologies studied. Overall, it was found that the most common area of application was classification of movement patterns, with many studies focusing on distinguishing pathological kinematics from healthy kinematics during gait.

Multi-class SVM models are used often for studying knee OA gait and can be useful tools in distinguishing OA patients from healthy controls. Laroche et al., (2014) used an SVM approach on kinematic metrics during gait in hip OA patients and were able to successfully distinguish between OA patients and healthy controls with a mean success rate of 88%. Similarly, Moustakidis et al., (2010) distinguished between healthy and knee OA patients as well as assessed OA severity using GRF measurements in an SVM based machine learning model. SVM models are also extremely versatile and have been used in more clinical settings to assess improvement from TKA or exercise interventions. Levinger et al., (2009) used a SVM model to classify gait patterns indicative of knee OA before TKA based on spatiotemporal gait parameters and investigated whether SVMs could successfully predict gait improvement 2 and 12 months following TKA. The authors concluded that the SVM could be used to distinguish between OA gait and healthy control using spatiotemporal parameters with an accuracy of 88.89%. Further,

the SVM model was also able to predict and detect improvement in gait function post-TKA in all but three subjects, which coincided with the WOMAC scores and clinical assessment of the knee. Levinger and colleagues (2009) suggested that spatiotemporal patterns contain important discriminative information which could be used for identifying knee OA improvement using an SVM classifier. Laroche et al., (2014), Moustakidis et al., (2010) and Levinger et al., (2009) all used multi-class supervised machine learning models for gait pattern analysis which is a more common method in current literature (Halilaj et al., 2018). Alternatively, one-class SVM models for gait analysis has been a more recent focus for classifying changes in typical gait patterns over time and after interventions.

Kobsar & Ferber (2018) provide an interesting example where a subject-specific one-class SVM was used to evaluate whether knee OA patients exhibited changes in their gait after a 6-week exercise intervention program. They found that patients who benefited most from the exercise intervention also demonstrated the greater overall change in gait patterns as detected by the SVM and a significant association between outlier gait cycles post-intervention and clinical outcome improvement. This study was the first to use wearable sensors and pattern recognition algorithms to define subject-specific biomechanical metrics related to clinical improvements. Kobsar and Ferber (2018) also discuss the clinically relevancy of this methodology as a percentage score from 0% to 100% could be used in the future by clinicians to define meaningful changes in gait patterns. Although this study was one of the first to classify gait patterns using one-class SVM's and track improvement using IMUs, some notable limitations are still present in this work. The study had a very small sample size (8 subjects) and had classified a typical gait pattern for subjects in only two 2.5 minute in-laboratory gait trials. As a next step, authors could have focused on quantifying a baseline or typical gait pattern with more training data and have

administered data collection in out-of-lab settings where gait patterns are more indicative of real-world gait. More recently, Benson et al., (2019) utilized a one-class SVM model using wearable sensors, in out-of-laboratory settings, to determine how many trials were required to classify a typical pattern in runners. Benson and colleagues (2019) determined 4 running trials could define a typical running pattern which was defined by models with less than 5% anomalies or atypical data. Although this research by Benson et al., (2019) was novel and highly relevant, many key limitations were present in the study. Only one IMU was placed on the lower back thus limiting their analysis to six spatiotemporal and kinematic parameters with varying levels of validity. More importantly, Benson et al., (2019) did not have any perturbation to accurately verify meaningful change from typical running pattern. By not having any perturbation, the authors are subject to overfitting of their SVM and the sensitivity to change is unclear. For instance, their typical gait model may cast a very wide net and they are then unable to detect large enough changes in gait to fall outside of these ranges. Lastly, although not for gait, Hawley et al., (2022) utilized a similar OCSVM approach to classify fatigue in lifting kinematics. Hawley and colleagues (2022) utilized 35% of the first lifting sets as training to data to define the OCSVM boundaries and found a positive correlation between self-report fatigue (i.e., rate of perceived exertion) and the percent of outliers (i.e., outlier lifting kinematic sets). This study really highlights the unique applications in which SVMs can be applied to understand typical human movements and detect meaningful changes.

The versatility of SVMs in conjunction with wearable sensors allows for researchers to not only track out-of-lab gait patterns but also provide a feasible method to understand knee OA progression and treatment. Using an approach like Kobsar and Ferber (2018), Benson et al., (2019), and Hawley et al., (2022), gait analysis using machine learning and wearable sensors has

the ability to become clinically feasible and meaningful. Measuring variables such as gait symmetry and impact accelerations using wearable sensors and an SVM approach can allow for clinicians to track gait progress in more longitudinal settings, especially when changes in pain can significantly change gait patterns on a day-to-day basis. Therefore, the combination of wearable sensors and machine learning can allow us to track real-world changes in gait patterns, all while differentiating between day-to-day fluctuations and clinically meaningful changes in knee OA patients.

2.6 Summary of Literature Review

Osteoarthritis is a progressive joint disease which results in the breakdown of cartilage and bone leading to pain and limited mobility. It currently affects nearly 5 million Canadians and has a significant impact on long-term disability and the Canadian labour force (Bombardier et al., 2011). Biomechanical gait analysis is commonly used to analyze and understand specific gait pathologies such as lower-limb OA. While the gold standard for gait analysis includes optical motion capture equipment and force plates, these methods are expensive and are limited as they only assess in-laboratory gait. The advancement of IMUs has made gait analysis more affordable and real-world relevant as they can analyze gait in out-of-lab settings. Commonly, knee OA onset, progression, and treatment are understood by analyzing gold-standard metrics such as KAM, KFM, and joint angles. However, these gold-standard metrics are often measured cross-sectionally or at large intervals to depict disease progression, and are not feasible or easily transferable to clinical or out-of-lab settings (Asay et al., 2018). Thankfully, lower limb accelerations and gait symmetry have also been correlated with knee OA onset and progression and remain more practical as they can be measured accurately out-of-lab with wearable sensors. Additionally, wearable sensors offer the opportunity to track these changes longitudinally in real-

world settings, yet this remains something that has yet to be fully realized. Machine learning techniques, such as SVM's, may provide the link to actualize this prophecy and maximize the impact of human movement analysis (Halilaj et al., 2018). Preliminary research has highlighted the use of subject-specific biomechanical models (e.g., one-class SVM) to track typical movement patterns in runners (Benson et al., 2019), adults with knee OA (Kobsar & Ferber, 2018), and weightlifting (Hawley et al., 2022). Understanding the stability of these individual biomechanical models in the context of clinically relevant changes in gait will support the longitudinal tracking of adults with knee OA using wearable inertial sensors.

Chapter 3: Research Question and Hypotheses

The overarching aim of this project was to use intra-articular corticosteroid injections (ICI) as a model to assess the ability of wearable inertial sensors to identify changes in gait, amidst the day-to-day fluctuations in out-of-lab gait patterns. To address this, I used multiple pre-injection, real-world wearable sensor gait collections in a one-class support vector machine to individually define typical gait models for older adults with knee OA. Individually defined typical gait models were generated using three pre-injection gait trials. These models were then compared to withheld test data collections from before and after the ICI to determine the level of deviation (i.e., percent of atypical strides) that occurred for each in their gait pattern.

Research Questions

Specifically, I proposed 3 research questions:

i) Will withheld pre-injection gait trials display a similar pattern (<10% atypical strides) when compared to the individually defined typical gait models in patients with knee OA.

ii) Will post-injection gait trials display a deviant pattern (e.g., significantly greatly proportion of atypical strides) when compared to the pre-injection gait trials in the individually defined typical gait models in patients with knee OA?

iii) Will the level of pattern deviance (i.e., proportion of atypical strides) in post-injection gait trials be significantly correlated with the self-reported changes in pain in knee OA patients?

Hypotheses

Based on the previous findings by Kobsar & Ferber (2018), Benson et al., (2019), and Ahamed et al., (2019), I hypothesized that three pre-injection gait trials will allow for the definition of a stable gait pattern amongst typical day-to-day fluctuations in gait. As such, I expect any held-out pre-injection gait collections will represent a similar multivariate profile and display, on average, less than 10% atypical strides, thus forming a stable gait pattern (RQi). Additionally, I hypothesized that following the ICI, individual gait patterns will deviate and result in a significantly greater number of atypical strides, in comparison to the pre-ICI stable gait pattern (RQii). However, it is unlikely that the ICI will have the same effect on all patients and as such some may experience greater changes in pain than others. Therefore, I hypothesized that the deviation in post-injection gait patterns, as defined by the proportion of atypical strides, will display a significant positive correlation with self-reported changes in pain (RQiii).

Chapter 4: Methods

4.1 Study Design

The study is a within-subjects, longitudinal prospective design, with data collected at seven total time points (Figure 9). Participants scheduled for an ICI in at least five weeks were recruited by the physician assistant or junior resident at St. Joseph's Healthcare Hamilton (SJHH). ICIs were chosen over hyaluronic acid injections as they provide fast-acting pain relief and have a shorter course of action (Section 2.4). Participants who fit within the inclusion criteria and agreed to participate completed 4 trials before their injection and three following their injection. Only one trial was completed per week leading up to the scheduled injection day (trial 1-4), followed by three more trials (1/week) post-injection (trial 5-7). Each trial consisted of a 6-min walk and completion of knee OA pain questionnaires, such as the Knee Osteoarthritis Outcome Survey (KOOS) and Numerical Pain Rating Scale (NPRS).

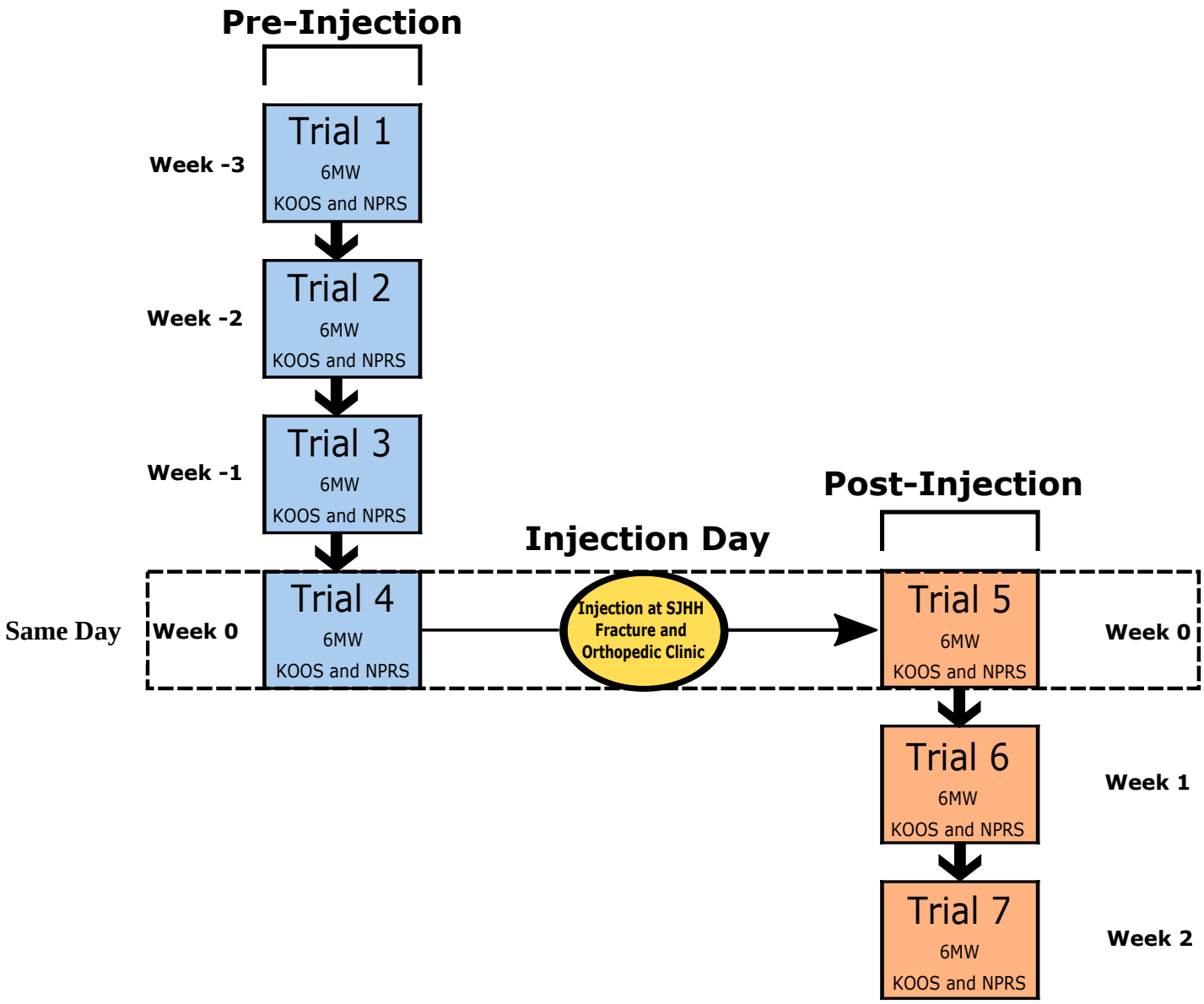


Figure 9: Study protocol outlining the schedule for each participant. Abbreviations: 6MW; 6-Min Walk, KOOS; Knee Outcome and Osteoarthritis Survey, NPRS; Numerical Pain Rating Scale, SJHH; St. Joseph's Healthcare Hamilton.

4.2 Sample

This study was approved by the Hamilton Integrated Research Ethics Board (HiREB) #13247 and informed consent was obtained prior to testing. Adults diagnosed with knee OA who were scheduled for an ICI at St. Joseph's Healthcare Hamilton (SJHH) in Hamilton, Ontario, were recruited. We collaborated directly with the clinicians and physician's assistants administering the injections for recruitment. The inclusion criteria consisted of participants scheduled to receive an ICI in 5 or more weeks, have knee pain greater than 3/10 on the NPRS when screened, and are able to walk 6 minutes without stopping and without using any gait aids. Exclusion criteria included previous lower limb joint replacement surgery, systemic inflammatory arthritis (e.g., rheumatoid arthritis), any neuromuscular conditions which could affect gait, recently or soon to be in new physiotherapy or exercise rehabilitation program, or the inability to provide informed consent.

The study was powered for a within-subject design (repeated measures analysis of variance). Based on previous work using similar methods in healthy adults (Benson et al., 2019), our recommended sample size was 15 individuals with knee OA (medium effect size with an α = 0.05 and β = 0.20; Faul et al., 2007). However, due to challenges in recruitment with COVID-19 restrictions and weather considerations, we were able to recruit a total of 9 participants (7 male, 2 female). The cohort had an average age of 64(8), a BMI of 30.9(5.3) kg/m^2, and KL grades ranging from 2-4 (See Table 1 for individual participant demographics).

Table 1: Participant characteristics of all subjects.

Subject (Sex)	Age (years)	BMI (kg/m^2)	K/L Grade	Average Pre-Injection NPRS Pain	Average Post-Injection NPRS Pain	Average Stride Time Pre-Injection	Average Stride Time Post-Injection	Average Strides Over 7 Trials
1 (F)	55	24.4	4	5	4	1.0	1.0	345
2 (M)	60	30.7	3	6	6	1.1	1.1	334
3 (F)	64	35.9	2	8	3	1.3	1.2	272
4 (M)	69	26.8	3	6	3	1.2	1.2	284
5 (M)	70	30.1	3	0	2	1.0	1.1	328
6 (M)	56	22.9	2	5	5	1.1	1.1	325
7 (M)	80	36.4	3	3	4	1.3	1.3	281
8 (M)	62	32.8	3	6	1	1.2	1.2	309
9 (M)	62	38.0	2	9	3	1.2	1.2	314
Mean (Std.)	64.2(7.7)	30.9(5.4)	2.8(0.6)	5.3(2.7)	3.4(1.5)	1.2(0.1)	1.2(0.08)	310.2 (25.8)

M; Male. F; Female. BMI; Body Mass Index. K/L; Kellgren-Lawrence. NPRS; Numerical Pain Rating Scale.

4.3 Protocol

Participants participated in seven total gait trials (Figure 9). Each trial consisted of a 6-min walk around the spiritual gardens at SJHH. Before each trial, participants were fitted with wearable inertial sensors (IMeasureU, ±16g, 250Hz) embedded in semi-elastic straps under the knee and on the lower back (Figure 10). The IMeasureU sensor is commercially available and one of the most robust and valid sensors for assessing lower limb accelerations ($r>0.9$) during walking and running gait (Andrews, 2019; Johnson et al., 2020). Participants were asked to wear their regular shoes and walk at a comfortable and self-selected pace.

During each trial, participants completed two questionnaires to describe their pain and function in the previous week, as well as their pain before and after the 6-min walk. Specifically, the Knee Injury and Osteoarthritis Outcome Score (KOOS) was administered to describe their

pain, symptoms, function, and quality of life in the previous week. The KOOS has been shown to be a reliable measure in this population (ICC = 0.8-0.97; Alviar et al., 2011), with subscale sensitive to change following surgical or non-surgical interventions such as those in the current study design (Collins & Roos, 2012). Additionally, participants completed an 11-item Numeric Pain Rating Scale (NPRS) immediately prior to and following their 6-min walk. The NPRS is the most accepted and commonly used measure of pain intensity and allows for a simple and immediate assessment of the current level of pain in the participant's knee at the time of the collection (Hawker et al., 2011).

Standing full-length weight-bearing lower limb radiograph images and reports were used to determine disease severity for all participants. These were obtained from the orthopedic and fracture clinic at SJHH following participant consent to access these data. In addition to the severity and compartment of OA identified in the radiographic report, for the purposes of this study the Kellgren-Lawrence classification of OA was assessed by an orthopaedic surgeon (Kohn et al., 2016) and contralateral limb OA status was obtained from patient records.

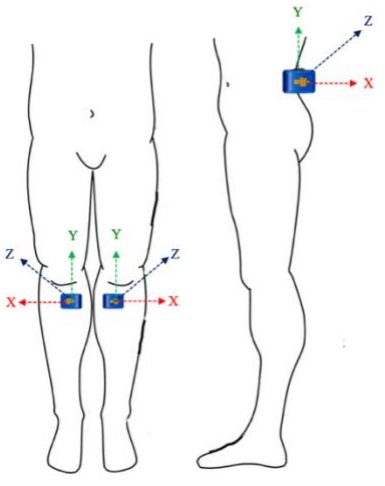


Figure 10: Sensor placement and axis orientation during the 6-min walk.

4.4 Data Analysis

4.4.1 Data Pre-Processing

The study design involves significant amounts of data being collected and as such, there are significant pre-processing requirements to be outlined. Specifically, the 3 sensors collecting 6 channels of data (i.e., 3D accelerometer and gyroscope) at 250Hz for 6 minutes generate 1.62 million data points per collection and over 100 million in total across all participants. These data are stored within the sensors before being exported using the iMeasureU software (CaptureU, Vicon, Oxford, UK) following each data collection. The exported data are the calibrated accelerometer and gyroscope signals which are time-synchronized between sensors at sampling frequency of 250 Hz. These data are tri-axial, but given their placement on the anteromedial shank, they are not aligned with the local coordinate systems of the shank and require further pre-processing to do so. Specifically, a previously developed method utilizing angular velocity data and a principal component analysis (PCA) was implemented to correct this orientation (Hafer et al., 2020). The PCA generated coefficients which defined rotations based on the principal motion occurring during walking (i.e., sagittal plane angular rotation). Tri-axial aligned data were then generated by applying the coefficients generated by the PCA to the previously unaligned data (Hafer et al., 2020). Additionally, all inertial data were filtered with a 40Hz low-pass 4^{th} order Butterworth filter before this rotation (Fong & Chan, 2010). Recent research has demonstrated both the validity (coefficient of multiple correlation = 0.94-0.99 for 3D data) and reliability (coefficient of multiple correlation > 0.9 for vertical and anteroposterior signals and > 0.8 for mediolateral signals) of this method in healthy adult walking gait (Ruder et al., 2022).

Following sensor alignment, gait event detection and time-normalization were implemented to segment the 6 minutes of walking data into separate gait cycles. Gait event

detection was completed using the mediolateral angular velocity data, where key gait events were clearly evident due to the large sagittal plane rotation the shank undergoes during gait. Specifically, the mid-swing peak in the mediolateral angular velocity data was used to provide event detection "search windows" from the mid-swing of one gait cycle to the mid-swing of the subsequent gait cycle. Following this mid-swing event, initial contact was estimated as the zero-crossing preceding the stance phase, relating to the change in rotation direction of the shank immediately preceding initial contact (Mariani et al., 2013; Trojaniello et al., 2014). Alternatively, toe-off was identified as the negative peak concluding the stance phase, as this represents the initiation of the swinging shank (Mariani et al., 2013; Trojaniello et al., 2014). By determining these gait events, gait cycle segmentation and time-normalization of the identified gait cycles was set to 60% stance and 40% swing, which is a common ratio used in previous studies for OA gait (Messier et al., 1992) (Figure 11). The average number of gait cycles per 6-minute walking session was 309.7(27.6).

4.4.2 Data Reduction

The resulting segmented and time-normalized inertial data still represented an unreasonably large amount of data describing the motion for each gait cycle, and as such further data reduction was required. First, only the vertical acceleration, anteroposterior acceleration, and mediolateral (sagittal plane) angular velocity of the bilateral shank sensors were retained based on their proximity to the injection site and their consistently superior reliability as compared to the other signals (Kavanagh et al., 2006; Kobsar et al., 2016; Kobsar et al., 2020; Lyytinen et al., 2016; Moe-Nilssen, 1998; Ruder et al., 2022). These signals were then concatenated into a single 600-point vector (i.e., three 100-point signals from each shank sensor) and combined into an *s x 600* matrix for each trial, where *s* represents the number of gait cycles

in the 6-minute walk. Second, given these 600 data points represent correlated information describing a gait cycle, a PCA was applied to further reduce these data to a subset of linearly uncorrelated variables. This method is commonly utilized in biomechanical gait data to generate a smaller number of features which still retain the majority of the variance in an original dataset (Astephen Wilson et al., 2015; Ibrahim et al., 2020; Robbins et al., 2013). The current application of the PCA involved retention of PCs that explained at least 90% variance across the entire cohort. Therefore, these newly generated PC scores more efficiently described gait cycles than the original 600 data points and were subsequently implemented in the OCSVM to define each individual's typical gait (Figure 11).

84.4.3 One-Class Support Vector Machine (OCSVM)

An OCSVM aims to define a hypersphere where most of the data lie within, thereby creating a definition of "typical" values within the hypersphere and "atypical" values which lie outside the hypersphere. In the current application, this method was used to model an individual's multivariate gait pattern based on PC scores from three pre-injection gait trials. Thereafter, the model could be compared to any pre- or post-ICI trial held out from the training of the model to determine the percentage of gait cycles that fell outside of the hypersphere. Specifically, individual gait pattern models were developed using the "fitcsvm" function in MATLAB2020A (The MathWorks INC., Natick MA, USA) to create an OCSVM trained on combinations of three of the four pre-injection trials. A Gaussian kernel function was used to model the hypersphere or decision boundaries, with a regularization parameter ("Nu") to optimize how many support vectors would be used to create a decision boundary. Generally, the more complexity in the data, the more support vectors and ultimately the more flexible decision boundary is required (depicted with a larger Nu value). An additional parameter

("OutlierFraction") was also implemented in the OCSVM to which account for potential outliers in the training data (Dagher & Azar, 2019)

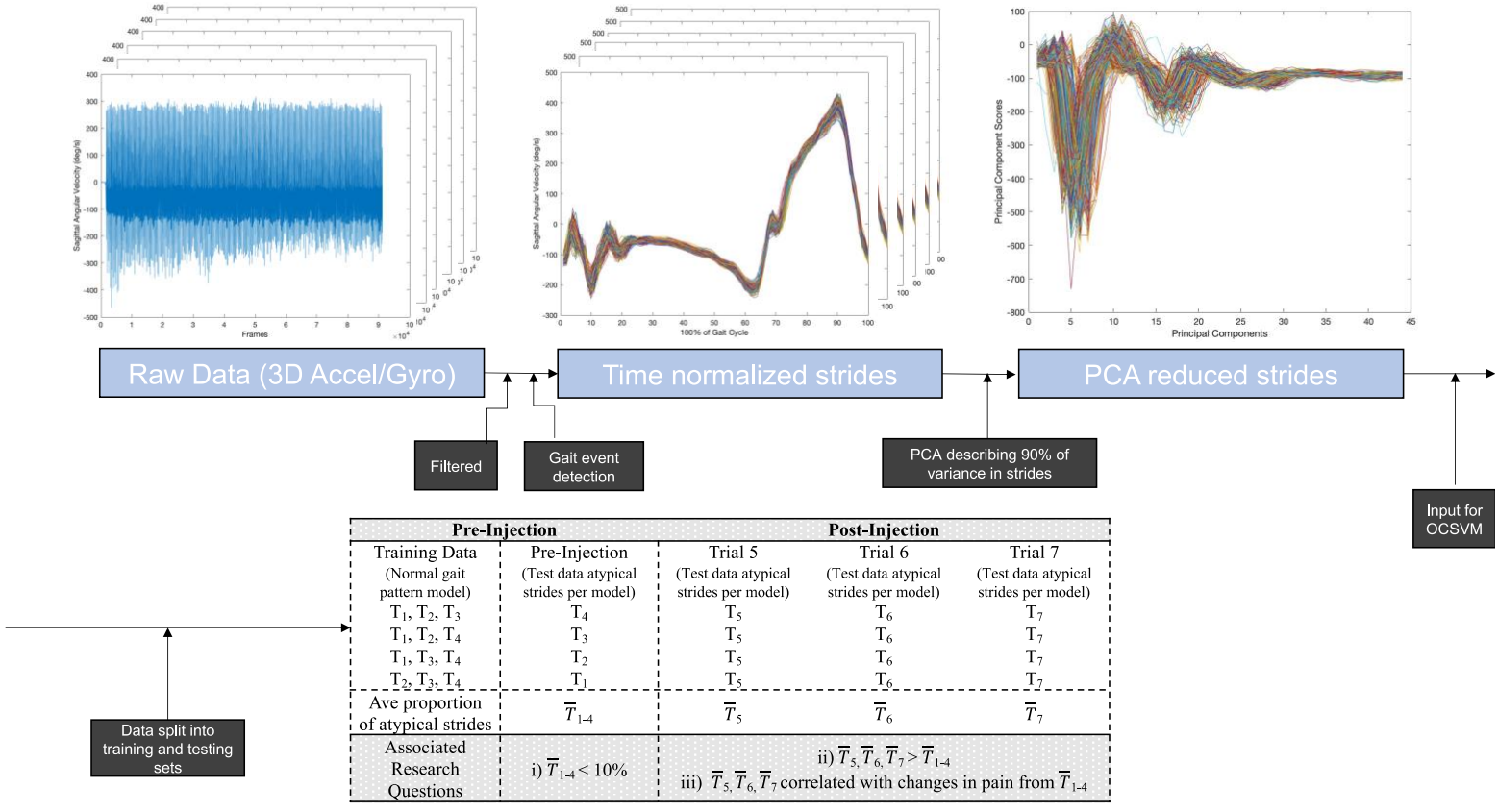
Given the average number of gait cycles per trial was 309, the resulting training sets were, on average, 927 gait cycles (i.e., 927 gait cycles each defined by the PC score features). Training data were randomly subdivided into 80% training and 20% cross-validation for defining individual models and decision boundaries. Further, based on these training and cross-validation data a "Nu" of 0.9 and an "OutlierFraction" of 1% were determined use for all models. Refer to tables 3-8 in the appendix for other iterations of hyperparameters for the OCSVM.

Following the training and cross-validating of each model, pre-injection data unseen to the model (one of the Trials 1-4) could be tested on a single, held-out pre-injection trial to determine the number of gait cycles defined as typical or atypical (Table 2). Concerning the first research question, all combinations of pre-injection training sets and test sets were examined, with the average proportion of atypical gait cycles from all four held-out pre-injection trials (T_{1-4}) used to examine the stability of this model (i.e., the proportion of atypical strides <10%). A 10% value was selected as it has been used in previous literature to define anomalies or atypical values in similar machine learning methodologies (i.e., one-class support vector machine, anomaly detectors) (Breunig et al., 2000; Shyu et al., 2003).

Additionally, I examined if ii) post-injection trials displayed a significantly greater proportion of atypical strides than the average pre-injection proportion. Post-injection trials (Trials 5-7) underwent the same processing defined in 4.4.1 and 4.4.2 before being compared to the individual gait pattern model developed from pre-injection data to determine the proportion of atypical strides (Table 2). It was hypothesized that post-injection trials would demonstrate a greater proportion of atypical trials than observed in the trial's pre-injection. This was

statistically assessed using one-way repeated measures analysis of variance (ANOVA) at an alpha level of 0.05.

Finally, I examined iii) the potential association between the number of atypical strides from a given post-injection gait trial with the change in self-reported pain for that gait trial. This change in pain score measured at each post-injection trial was calculated compared to the average pre-injection pain level, using the NPRS before walking. A Pearson's Correlation Coefficient, with significance at an alpha level of 0.05, was used to determine if the proportion of atypical strides observed was correlated with changes in pain following the ICI.



Pre-Injection		Post-Injection		
Training Data (Normal gait pattern model)	Pre-Injection (Test data atypical strides per model)	Trial 5 (Test data atypical strides per model)	Trial 6 (Test data atypical strides per model)	Trial 7 (Test data atypical strides per model)
T_1, T_2, T_3	T_4	T_5	T_6	T_7
T_1, T_2, T_4	T_3	T_5	T_6	T_7
T_1, T_3, T_4	T_2	T_5	T_6	T_7
T_2, T_3, T_4	T_1	T_5	T_6	T_7
Ave proportion of atypical strides	$\overline{T}_{1\text{-}4}$	$\overline{T}_5$	$\overline{T}_6$	$\overline{T}_7$
Associated Research Questions	i) $\overline{T}_{1\text{-}4} < 10\%$	ii) $\overline{T}_5, \overline{T}_6, \overline{T}_7 > \overline{T}_{1\text{-}4}$ iii) $\overline{T}_5, \overline{T}_6, \overline{T}_7$ correlated with changes in pain from $\overline{T}_{1\text{-}4}$		

Figure 11: Pipeline highlighting the transformation of raw data into time normalized waveforms, and then reduced via PCA before entering the OCSVM. This pipeline was followed for each participant.

Chapter 5: Results

Participant demographic and gait trial information is presented in Table 1. The total number of gait cycles measured across all participants was 19,410, relating to an average of 310 (25.89) per trial. The PCA data reduction method reduced the number of gait variables from 600 (i.e., time-normalized vertical acceleration, anteroposterior acceleration, and mediolateral angular velocity of the left and right sensors) to 44 linearly uncorrelated PCs which described 90% of the total variance in this sample. Further, on average, the number of observations in the training sets was 933.7(34.9), while the withheld test sets had 309.9 (31.0). Therefore, dimensions of the input data used to define typical gait models in the OCSVMs were, on average, 934 x 44 (i.e., gait cycles x PC scores), and withheld test sets (pre- or post-ICI) used to determine the proportion of atypical gait cycles were 310 x 44.

Regarding the first research question, an average of 17.7% atypical strides were found across all participants pre-injection trials when compared to three-trial built typical models (Table 2). Further, when comparing post-injection trials to those typical models for the second research question, an average of 6.9%, 16.9%, and 26.6% were observed for trials 5, 6, and 7, respectively (Table 2). Based on these data, no significant difference was found between the average post-injection atypical strides and pre-injection atypical strides between all participants ($p = 0.390$; Figure 12). The effect of these atypical strides can clearly be seen on a case-by-case basis. For example, the participant in Figure 13 has test waveforms that fall within the boundaries created by the training sets (purple), resulting in a low percentage of atypical strides for this participant. On the contrary, Figure 14 has test waveforms that fall outside the boundaries created by the training sets (purple), resulting in a high percentage of atypical strides for this participant.

The NPRS data showed variability week-to-week across the cohort across the entire study (Figure 15). The average pain reported in the pre-injection trials was 5.5(2.7) and 3.7(1.4) post-injection, for an average reduction in pain of -1.8(1.3). However, this reduction in pain was not significant ($p = 0.20$; Cohen's $d = 0.43$). Notably, in the pre-injection period, pain levels varied up to 5 points between adjacent weeks with an average of 2.2 over this time. Similarly, in the post-injection period, pain levels varied up to 8 points between adjacent weeks with an average of 3.9 over this time. Finally, for the third research question, no significant correlation was found between changes in the NPRS (or KOOS) post-injection and atypical strides ($r = 0.15$, $p = 0.70$) Figure 16).

Table 2: Overview of one-class SVM training and testing models for each individual's pre-injection and post-injection collections, with associated research questions. The average proportion of atypical strides are shown for all subjects.

Pre-Injection		**Post-Injection**		
Training Data (Normal gait pattern model)	Pre-Injection (Test data atypical strides per model)	Trial 5 (Test data atypical strides per model)	Trial 6 (Test data atypical strides per model)	Trial 7 (Test data atypical strides per model)
T_1, T_2, T_3	T_4	T_5	T_6	T_7
T_1, T_2, T_4	T_3	T_5	T_6	T_7
T_1, T_3, T_4	T_2	T_5	T_6	T_7
T_2, T_3, T_4	T_1	T_5	T_6	T_7
Ave proportion of atypical strides (Std.)	$\overline{T}_{1\text{-}4}$ = **17.7 (9.4) %**	$\overline{T}_5$ = **6.9 (9.2) %**	$\overline{T}_6$ = **16.9 (28.1) %**	$\overline{T}_7$ = **26.6 (36.3) %**
Associated Research Questions	i) $\overline{T}_{1\text{-}4} < 10\%$	ii) $\overline{T}_5, \overline{T}_6, \overline{T}_7 > \overline{T}_{1\text{-}4}$ iii) $\overline{T}_5, \overline{T}_6, \overline{T}_7$ correlated with changes in pain from $\overline{T}_{1\text{-}4}$		

Abbreviations: T; Trial.Std.; Standard Deviation Subscript denotes the test trial. $\overline{T}$ denotes the average seen across all subjects and respective trials.

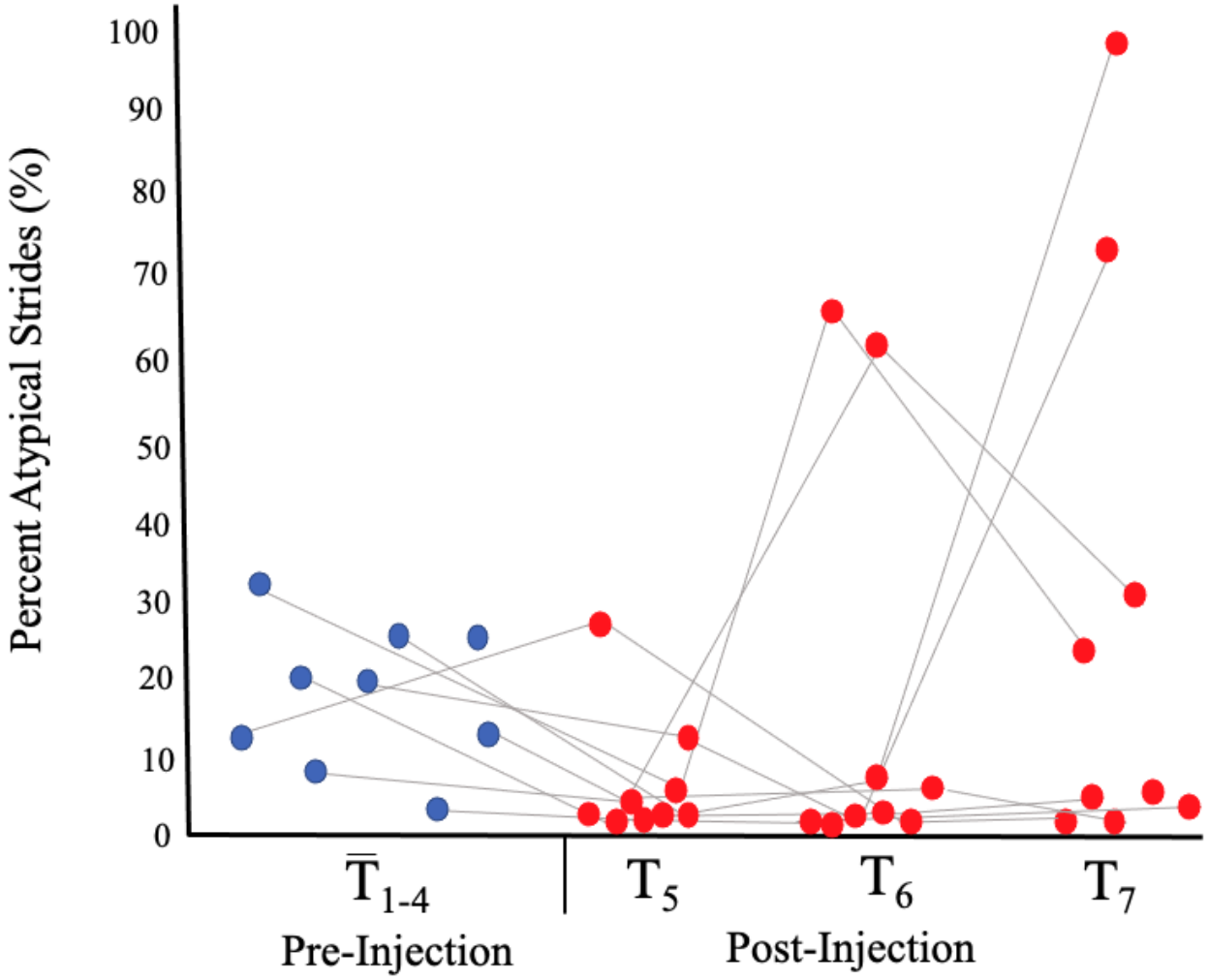
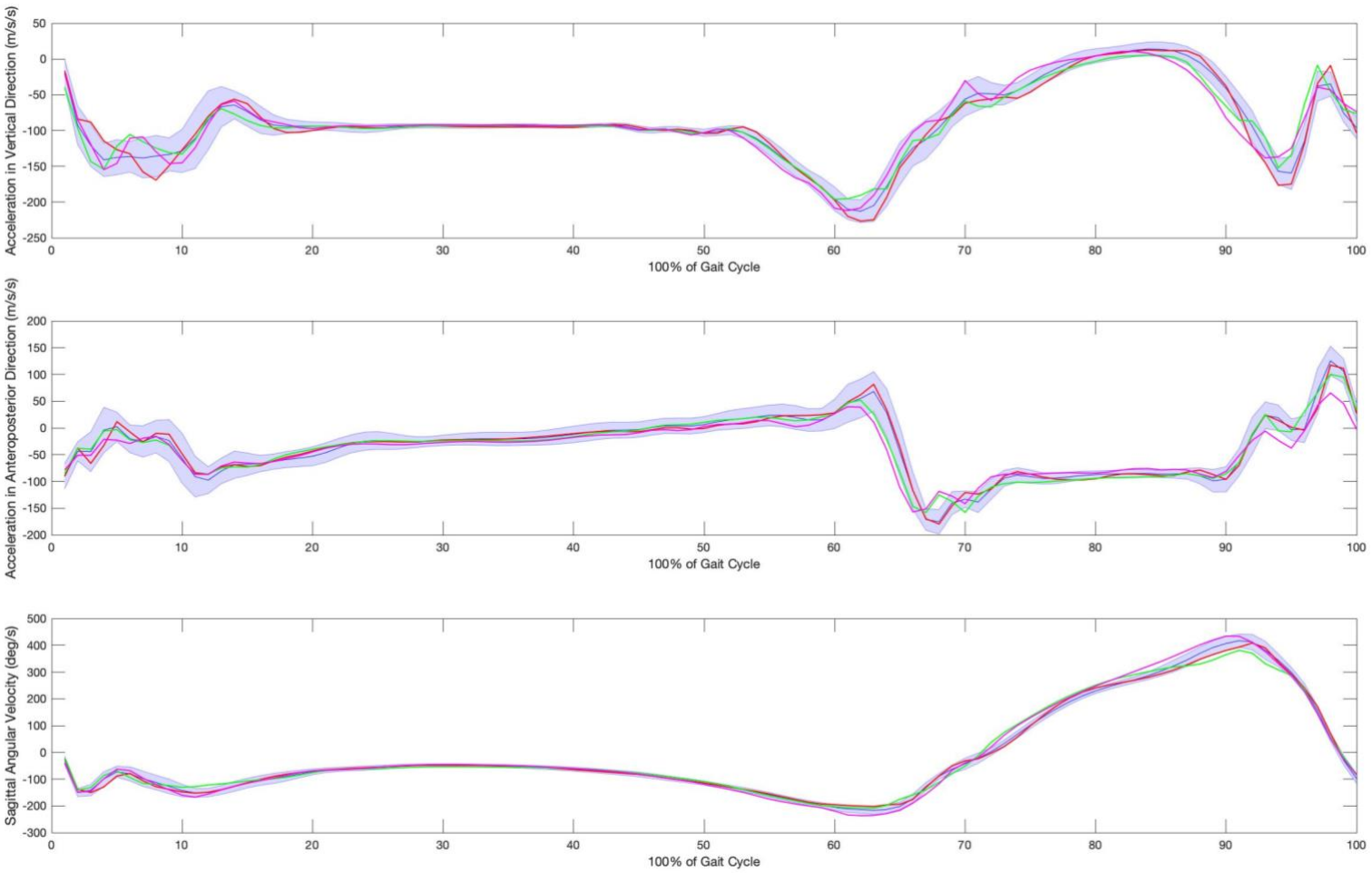
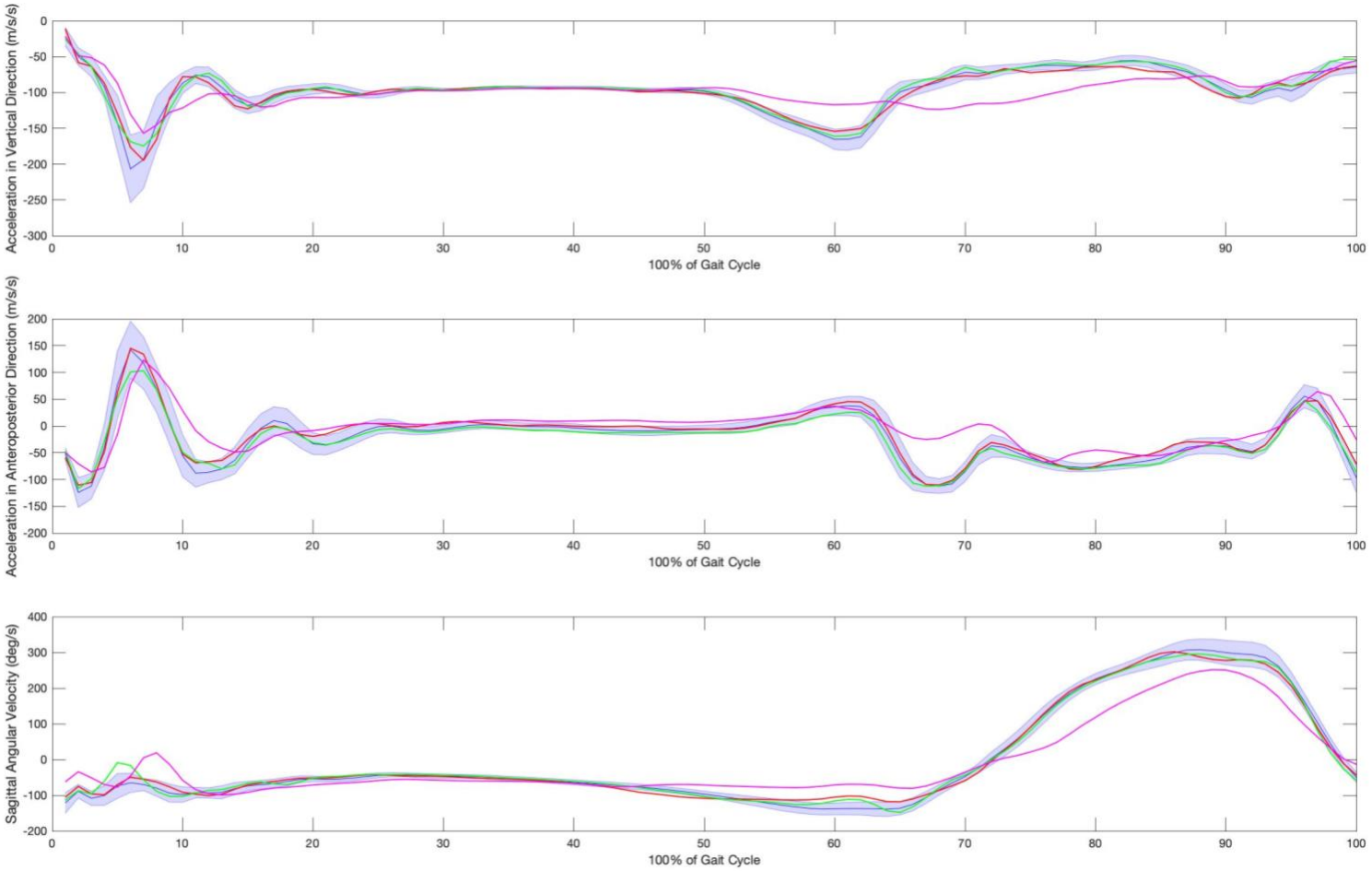


Figure 12: Atypical strides for each participant across pre-injection and post-injection trials. Each circle represents the atypical strides (%) for each participant and the grey line shows the change in pre- and post-injection that is occurring within individual participants. No significance ($p = 0.390$) was found when comparing post-injection atypical strides to pre-injection atypical strides.



Pre-Injection		**Post-Injection**		
Training Data (Normal gait pattern model)	Pre-Injection (Test data atypical strides per model)	Trial 5 (Test data atypical strides per model)	Trial 6 (Test data atypical strides per model)	Trial 7 (Test data atypical strides per model)
T_1, T_2, T_3	T_4	T_5 = 1.24%	T_6 = 3.14%	T_7 = 2.44%
T_1, T_2, T_4	T_3	T_5 = 1.55%	T_6 = 3.46%	T_7 = 3.66%
T_1, T_3, T_4	T_2	T_5 = 0.93%	T_6 = 5.35%	T_7 = 4.27%
T_2, T_3, T_4	T_1	T_5 = 1.24%	T_6 = 3.14%	T_7 = 4.57%
Ave proportion of atypical strides	$\overline{T}_{1\text{-}4}$	$\overline{T}_5$ = **1.24%**	$\overline{T}_6$ = **3.77%**	$\overline{T}_7$ = **3.73%**

Figure 13: Representative example of one participant (subject 6) demonstrating a low percentage of atypical strides. Ensemble mean and standard deviation strides of training sets in purple, with ensemble mean of atypical strides overlayed for test data in red (trial 5), green (trial 6) and magenta (trial 7).



Pre-Injection		**Post-Injection**		
Training Data (Normal gait pattern model)	Pre-Injection (Test data atypical strides per model)	Trial 5 (Test data atypical strides per model)	Trial 6 (Test data atypical strides per model)	Trial 7 (Test data atypical strides per model)
T_1, T_2, T_3	T_4	T_5 = 1.94%	T_6 = 2.96%	T_7 = 100%
T_1, T_2, T_4	T_3	T_5 = 1.29%	T_6 = 4.93%	T_7 = 100%
T_1, T_3, T_4	T_2	T_5 = 1.94%	T_6 = 3.62%	T_7 = 100%
T_2, T_3, T_4	T_1	T_5 = 2.90%	T_6 = 6.25%	T_7 = 100%
Ave proportion of atypical strides	$\overline{T}_{1\text{-}4}$	$\overline{T}_5$ = **2.02%**	$\overline{T}_6$ = **3.77%**	$\overline{T}_7$ = **100%**

Figure 14: Representative example of one participant (subject 9) demonstrating a high percentage of atypical strides. Ensemble mean and standard deviation strides of training sets in purple, with ensemble mean atypical strides overlayed for test data in red (trial 5), green (trial 6) and magenta (trial 7).

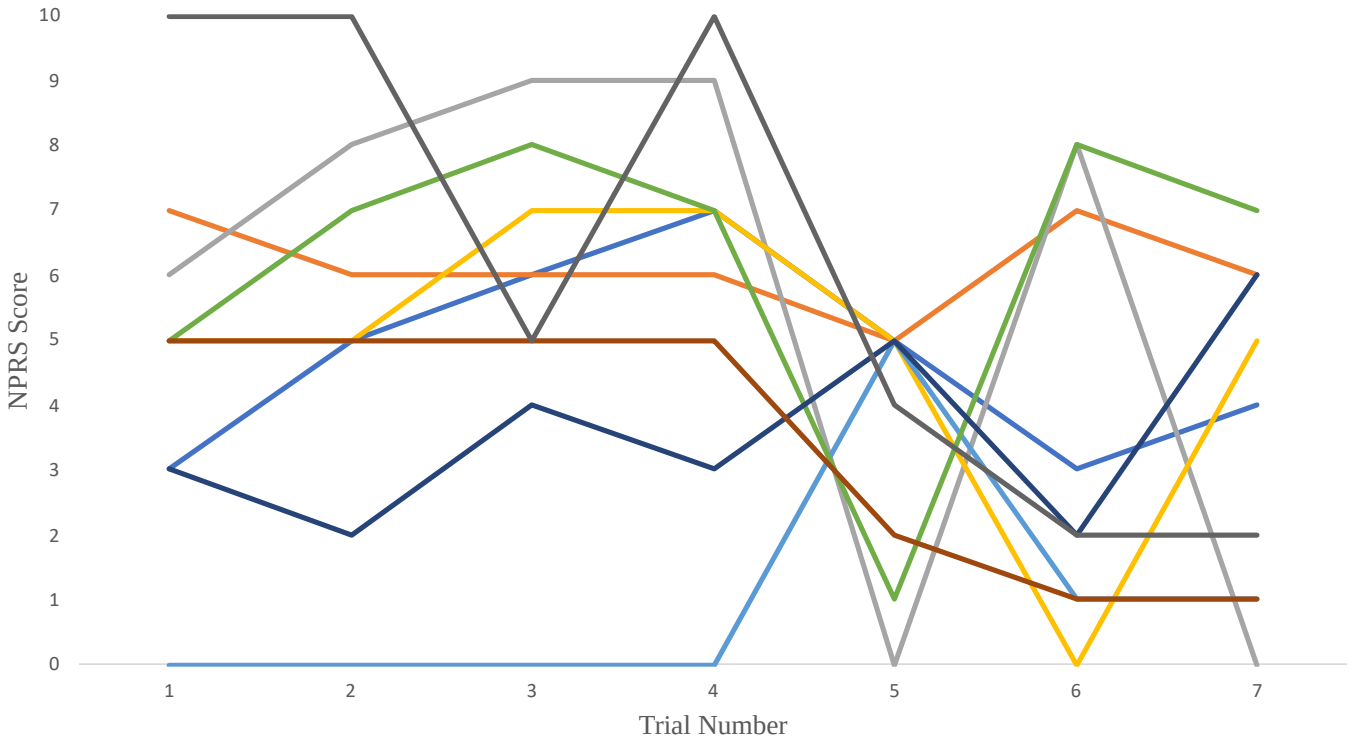


Figure 15: NPRS score for all participants over the course of seven trials. Each colour represents a different participant.

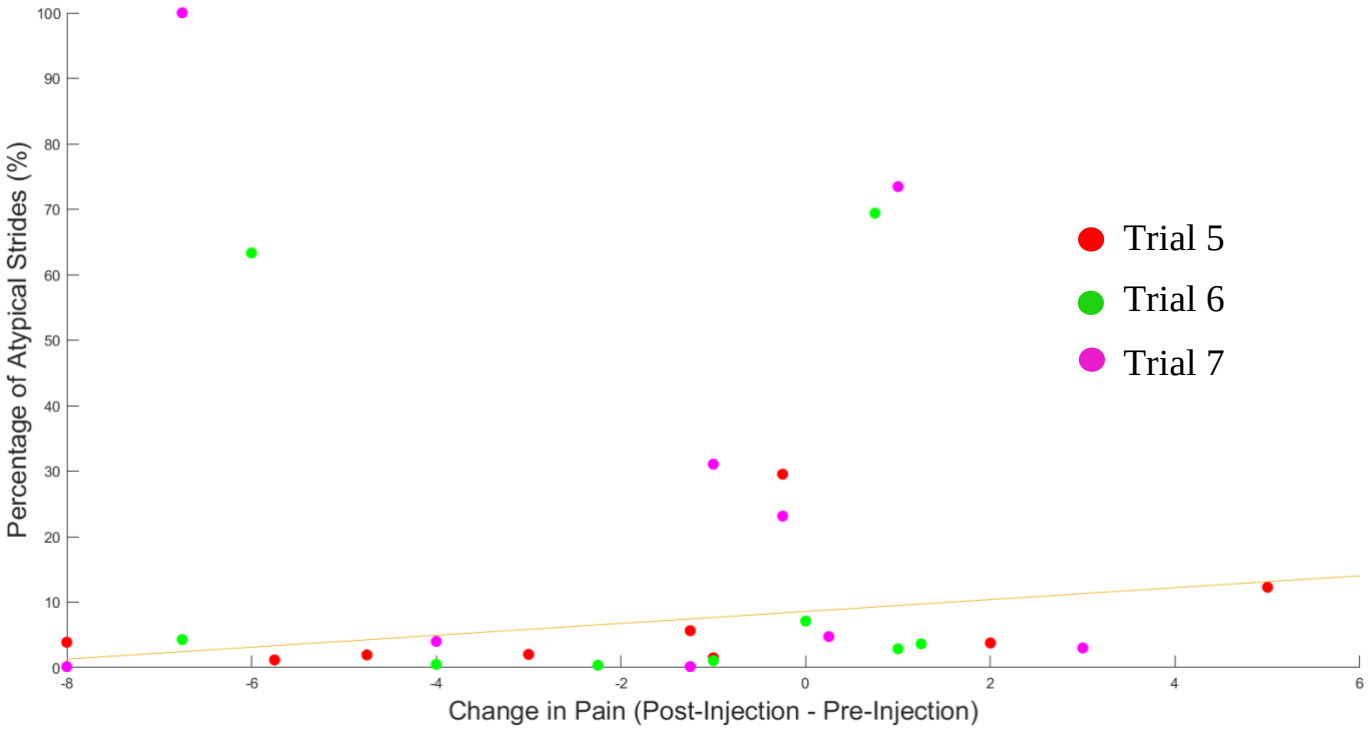


Figure 16: Change in pain compared to atypical strides in post-injection trials. Red circles highlight trial 5 while green and magenta circles highlight trial 6 and 7, respectively. A change in pain was defined as the difference between each post-injection trial (5,6 or 7) compared to the average pain levels seen in pre-injection collections (trials 1,2,3 and 4).

Chapter 6: Discussion

The purpose of the study was to use ICIs as a model to determine if wearable inertial sensors and machine learning algorithms can identify changes in gait, amidst the day-to-day fluctuations in out-of-lab gait patterns of older adults with knee OA. First, I hypothesized that three pre-injection gait trials would create stable patient-specific typical gait models, such that most strides from a fourth pre-injection gait trial would fall within this model (e.g., <10% atypical strides). Contrary to this initial hypothesis, I observed a grand mean of 17.7% atypical strides in the withheld pre-injection trials. Further, contrary to my second hypothesis, I found the percent of atypical strides observed in post-injection trials were not significantly different from atypical strides seen in withheld pre-injection trials. Finally, large differences in self-report pain levels were observed within-subjects on a week-to-week basis. While I hypothesized changes in pain from an ICI would be positively correlated to the proportion of atypical strides, no correlation was found in this cohort. Although these results did not support my hypotheses, important findings can be taken from this work as it was not only the first study to examine gait and pain together on a week-to-week basis, but it was done using wearable sensors in an out-of-lab setting. Specifically, both pain and gait can be highly variable on even a week-to-week basis in older adults with knee OA and this may limit our ability to identify potential intervention effects, especially when those data observed out of lab. The remaining sections of this discussion will address these issues of weekly fluctuations of both pain and gait with respect to defining a stable gait pattern model, as well as the effect of the ICI on this relationship.

6.1 Fluctuations of Pain and Gait in Defining Typical Gait Models

The goal of the study was to individually define a typical gait pattern using wearable sensor data from three pre-injection trials using in an out-of-laboratory setting. While week-to-

week fluctuations were expected during this pre-injection period with respect to both pain and gait, it was also expected that these would be limited in comparison to changes occurring with the ICI. Unfortunately, the fluctuations observed pre-injection may have limited the ability to define a stable, yet sensitive typical gait model. With respect to pain, many individuals displayed highly variable NPRS data in weeks prior to the ICI (Figure 15). These findings are in accordance with Parry and colleagues (2019) who found that pain intensity was highly variable for some and stable for others. While this may be due to unpredictable pain flares, random bouts of inflammation, and varying knee soreness, the underlying reason for this heterogeneity remains unclear (Atukorala et al., 2021; Parry et al., 2019). Together with the current findings, there is a clear literature gap identified in our understanding of multi-week assessments of pain in knee OA cohorts. Moreover, this variability could be at least partially responsible for the difficulty in defining stable gait pattern models in current study.

The desired stability of the typical gait models with respect to pre-injection gait trials did not achieve the desired 10%. In fact, only two of the nine participants demonstrated an average stable typical gait pattern below the predefined 10%. The exact reason for this finding can be multifactorial, however, it can be hypothesized to have a relation to the variability in pain. Previous literature has found that changes in pain can influence gait patterns (Wang et al., 2021; Shrader et al., 2004), specifically impact accelerations which were heavily utilized as key features in our OCSVM. Further, Asay et al., (2013) found that while KAM was repeatable with varying changes in pain over a multi-week study, but gait speed, stride length, cadence and first peak ground reaction forces (proxy to impact accelerations) had large variations between visits and were more sensitive to variations in pain. Therefore, the findings by Asay and colleagues (2013) could be one explanation as to why we are seeing such variability in gait within

individuals as impact accelerations may be less reliable week-to-week and more sensitive to changes in pain. Moreover, when integrating such gait data into a machine learning algorithm aimed at identifying high-dimensional relationships, the lack of stability from three out-of-lab gait trials is not surprising.

6.2 Determining Typical Gait Patterns from a Modeling Perspective

The current findings suggest that three collections may be insufficient to define a typical gait pattern among the ever-present variations in out-of-lab gait. Nevertheless, this lack of a typical pattern from three trials is specific to the current OCSVM and features, and as such further advancements may be made on these data. Firstly, a different feature selection method may be important to identify a smaller and more stable subset of gait parameters. In the current study, PCs that explained 90% of the variance in the original data were selected as features to define typical gait models. Other studies have had similarities in feature selection where Kobsar & Ferber (2018) and Hawley et al., (2022) used a 95% threshold. However, these applications were conducted in-lab, with Kobsar & Ferber (2018) relating to highly consistent treadmill walking. Alternatively, Benson et al. (2019) utilized a similar model in out-of-lab running data, but only had access to six simplified parameters. Therefore, increased variability with out-of-lab gait (Hillel et al., 2019) may require a smaller subset of highly specialized and/or clinically-relevant features, rather than larger, more holistic sets of gait pattern data utilized in the current study.

Further, even with other advanced feature selection methods, there can still be a high degree of variability due to the number and direction of turns made within each collection as participants were told to walk freely. This was evident in a recent study by Hillel et al., (2019) where step length and gait speed were significantly different in out-of-lab "free-living" gait as

compared to in-lab. Further, stride regularity was far lower in out-of-lab "free-living" gait versus in-lab gait, thus highlighting the variability present in out-of-lab gait data. Additionally, the direction and number of turns between each subject and within trials can be highly variable in out-of-lab gait which increases the complexity of defining typical gait patterns. Participants could also be rounding corners, turning in different directions, or not walking in a straight line which could make defining typical gait patterns difficult. By having to turn in the protocol alone, participants can have large variations in stride lengths, swing times and double-support times as compared to a straight-line walk (Gulley et al., 2020). However, to control for the large variation in "free-living" gait data, event detection pre-processing algorithms could be utilized to only analyze straight walking bouts (Hickey et al., 2017).

To also combat the variability and irregularities that can be present in out-of-lab "free-living" data, different machine learning models can be implemented to better define typical gait models. An unsupervised K-means clustering model can be applied to this dataset where data is clustered based on specific patterns and new test data is sorted into a cluster with the nearest mean (Sinaga & Yang, 2020). For example, one can sort the combinations of three trials (training data) into one large cluster and then determine the distance of new test data to determine the magnitude of atypical strides. Further, a semi-supervised anomaly detector has been used previously to predict fall risk (Yang et al., 2016) but can be similarly implemented to define a typical gait model. A small portion of the three trial training data can be labelled to define overall boundaries while a large portion of the data can be unlabeled to define overall gait clusters. Future work should consider these approaches along with other machine learning models and determine a way to optimize parameters without over or underfitting.

6.3 Atypical Strides following an ICI

There was no significant difference in the percent of atypical strides observed between post-injection and pre-injection strides across our cohort (Figure 15). Further, we found no significant differences in atypical strides between trials 5, 6 and 7. However, there was a general trend observed between subjects where following the ICI, the percent of atypical strides decreased from 17.7% to 6.8% in trial 5 and then steadily increased to 16.9% and 26.6% in trials 6 and 7, respectively. This pattern can be attributed to the varying effects of pain relief following an ICI where increases in pain contributed to greater percentages of atypical strides, however, this was not found statistically in the current study. Interestingly, trial 5 occurred immediately following the ICI and as such had the immediate effects of a "numbing agent" (lidocaine) and it resulted in the most typical gait patterns. While this is contrary to what may be expected, there may be a safer or more consistent pattern adopted that has a reduced chance of atypical strides. Immediately following an ICI, Shrader et al., (2004) and Asay et al., (2013) found significant changes in gait such as increased gait speed, gait cadence and KFM. To our knowledge, no study has assessed gait biomechanics weekly following an ICI however, Pinto & Birmingham also found an increased gait speed and KFM (Pinto & Birmingham, 2018) 3-weeks after the ICI. The exact timeline of these gait changes with respect to the ICI is unknown and can be one explanation as to why no significant differences are found between participants in atypical strides post and pre-injection.

Importantly, the increase in average atypical strides in trials 6 and 7 are largely driven by a few anomalous subjects. An example of this can be seen in Figure 14 where the average and standard deviation of pre-injection trials are plotted in purple for the three channels used in our

feature selection and OCSVM. While the purple waveforms are not equivalent to that of the typical gait pattern model developed for this one patient, they do provide an adequate visual representation of differences from this typical pre-injection baseline. The red, green, and magenta trials represent trials 5, 6, and 7, respectively. Figure 15 clearly shows the deviation of trial 7 from the pre-injection trials thus resulting in an average of 100% atypical strides for this individual. Most subjects in the study demonstrated waveforms similar to those seen in Figure 14, where many of the post-injection trials fit within the boundaries of the pre-injection trials, resulting in a lower percentage of atypical strides post-injection. Nonetheless, these two case study examples not only highlight our methodology in determining atypical strides but also the variability observed within knee OA gait patients, especially after an ICI.

6.4 Correlation between changes in pain and atypical strides

We found that the proportion of atypical strides in post-injection gait trials was not significantly correlated with self-reported changes in pain after an ICI (Figure 16). The change in pain was calculated by taking the difference between the average pre-injection pain levels (trials 1-4) and the pain reported in each trial following the ICI (trial 5, trial 6, and trial 7). Generally, we found that with even large changes in pain (i.e., 5 points) the percentage of atypical strides was still low in trial 5. However, this was not the case for trials 6 and 7 where any changes in pain resulted in larger percentages of atypical strides. Interestingly, the largest proportions of atypical strides were found at very low and high levels of changes in pain, however, this finding may be attributed to the low sample size in the study. Although our results were not hypothesized, there are a few reasons to why this was observed. Firstly, self-reported pain is a subjective measure and measuring through the NPRS is not highly sensitive (Spadoni et al., 2004). Pain can be perceived by individuals very differently and other biopsychosocial factors

(mental, emotional, and physical wellbeing) can interplay in this pain score (Meints & Edwards, 2018). Additionally, previous research has demonstrated that not all gait features are sensitive to pain (Asay et al., 2013; Henriksen et al., 2010) and, as previously discussed, there may be a need to identify more pain-specific gait features that can be implemented in such a models.

6.5 Limitations

The study has some limitations regarding the PCA waveform reduction and the selected OCSVM parameters. First, only the vertical and anteroposterior accelerations along with the sagittal angular velocities were selected for the PCA due to their high reliability between days. However, by selecting these three channels, we could be missing out on the natural variability within the data, which could help differentiate typical gait models. Perhaps we are missing valuable gait characteristics by neglecting mediolateral accelerations which have been related to KAM. Further, due to the high variability within the data, we selected PCs, which described 90% of the variance, thereby casting a wider "net" for typical strides by reducing the overall variability of strides as compared to Kobsar & Ferber (2018) and Hawley et al., (2022) who used a 95% threshold. However, it is essential to note that this threshold can be an arbitrary value but should be accounted for when optimizing models. Further, another limitation with our PCA feature selection method was that a PCA was built across all nine subjects and not applied for each individual separately. In doing this, the features selected may underrepresent gait patterns for some participants. However, by alternatively building PCA models individually, features would be derived based on the aspects of gait patterns, which, by definition, have the greatest variability within or between days. Therefore, this within-participant PCA method could thereby potentially make it even more difficult to define consistent gait patterns within individuals. Nevertheless, future research may examine optimal practices for defining these features and

models. Next, another limitation with many machine learning models can be selecting parameters without over or underfitting. The regularization or "nu" parameter of 0.9 can be considered a large hypersphere as "nu" spans from 0 to 1, perhaps resulting in overfitting and decreased percent atypical values. Nonetheless, this value was determined as it based on learning curves relating to the training and cross-validation atypical rates. Naturally, real-world gait data where participants can walk "freely" and make varying turns can have larger variability between trials (Hillel et al., 2019; Asay et al., 2013), potentially adjusting the timing of gait cycles and/or event detection algorithms, and thus the results from the OCSVM. Further, the sample size in the current study was small; however, based on our within-subject model, this did not impact our main research question of defining typical gait models for each knee OA patient. In other words, a larger sample would be required to compare the percentage of atypical strides between-subjects more effectively in post-injection and pre-injection trials, but not generate individual results below 10% atypical strides. Additionally, the small sample size could also skew the relationship between changes in pain and atypical strides, as the correlation occurs between-subjects. Finally, to define typical gait models more accurately, it may be ideal to increase the number of sensors and have varying sensor placements (i.e., foot, thigh, torso). However, the goal with the current sensor set-up was to capture knee motion during gait minimally and to eventually have clinicians implement this set-up to monitor knee OA patients' progression following ICIs.

6.8 Future Directions

The overarching aim of this study was to define typical gait patterns using wearable sensors in a real-world, out-of-lab setting and to use ICIs to perturb gait patterns to determine if meaningful changes can be detected. However, based on our findings, clear future directions are

needed to progress this critical area of research further. Firstly, future studies may need to utilize different perturbation methods apart from ICIs to elicit meaningful changes. Changes in pain and the week-to-week fluctuations are clearly driving these unpredictable changes in gait. Therefore, a simpler and more predictable perturbation would be beneficial for detecting changes. Perturbations could include neuromuscular tasks such as serial subtraction, which have previously been shown to perturb gait (Hillel et al., 2019), exercise programs, 2-week immobilization or more severe changes such as joint arthroplasty. Further, future studies should aim to monitor patients for more extended periods to create more robust training and testing sets for the OCSVM. In the future, these wearable sensors can have similar applications to ECG-Holter monitoring, where knee OA patients who are recommended ICIs can be given wearable sensors and tracked in "free-living" situations for a longer duration. To do this, future work should also develop efficient data pipelines and event-detection algorithms to monitor these patients more accurately. These event detection algorithms could first process only straight-line walking data to reduce the within-subject variability in gait patterns seen with turning, perhaps making it easier to define typical gait patterns (Hickey et al., 2017). This would also require more robust and sensitive feature selection methods. Further, with these larger datasets, it is essential to understand the best way to select the ideal machine learning models and, more specifically, hyperparameters needed for optimization. Finally, future work should validate our findings and experiment with different sensor set-ups to determine the ideal number of sensors and locations required to define typical gait models. Nonetheless, these studies should be aware of the clinical practicality of using a more minimal and affordable sensor setup.

Chapter 7: Conclusion

In summary, we found that three gait trials with our wearable sensor set-up and machine learning algorithm could not define a typical gait pattern in knee OA patients. Further, we noticed no differences between post-injection and pre-injection atypical strides between subjects and found no significant correlation between changes in pain and atypical strides. We believe many discrepancies in atypical strides within participants and between trials could be attributed to pre-injection changes in pain observed on a week-to-week basis. The current study is the first to assess gait and pain over multiple weeks using wearable sensors in out-of-lab settings and is the first to monitor changes in gait following an ICI. With such a large and diverse dataset, our method integrates using wearable sensors and machine learning algorithms to understand the complex gait patterns of knee OA patients.

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Chapter 8: Appendix

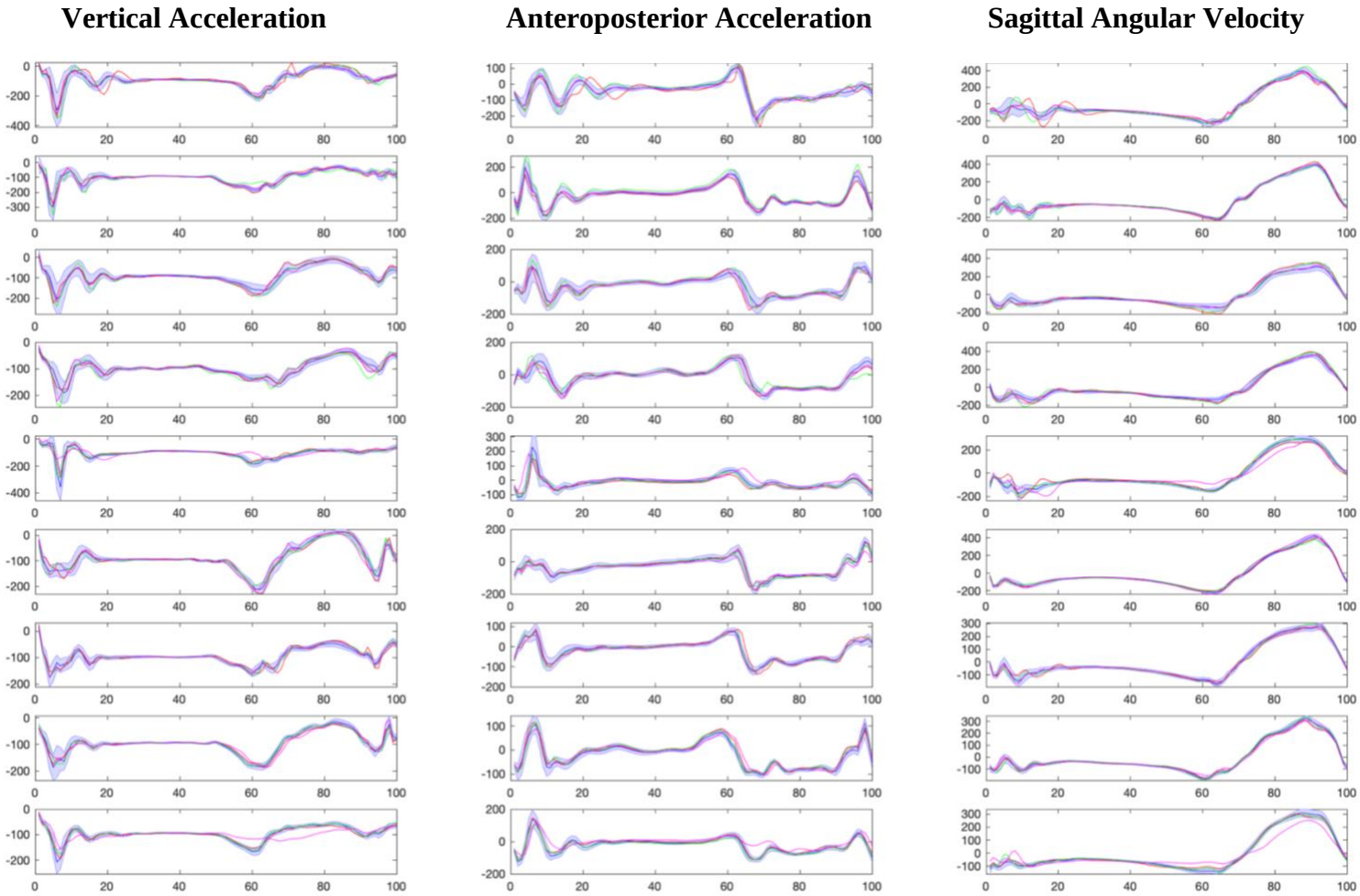

Figure 17 (Appendix): All waveforms from right shank sensor for all 9 subjects. Each row represents one subject. Ensemble mean and standard deviation strides of training sets in purple, with ensemble mean atypical strides overlayed for test data in red (trial 5), green (trial 6) and magenta (trial 7).

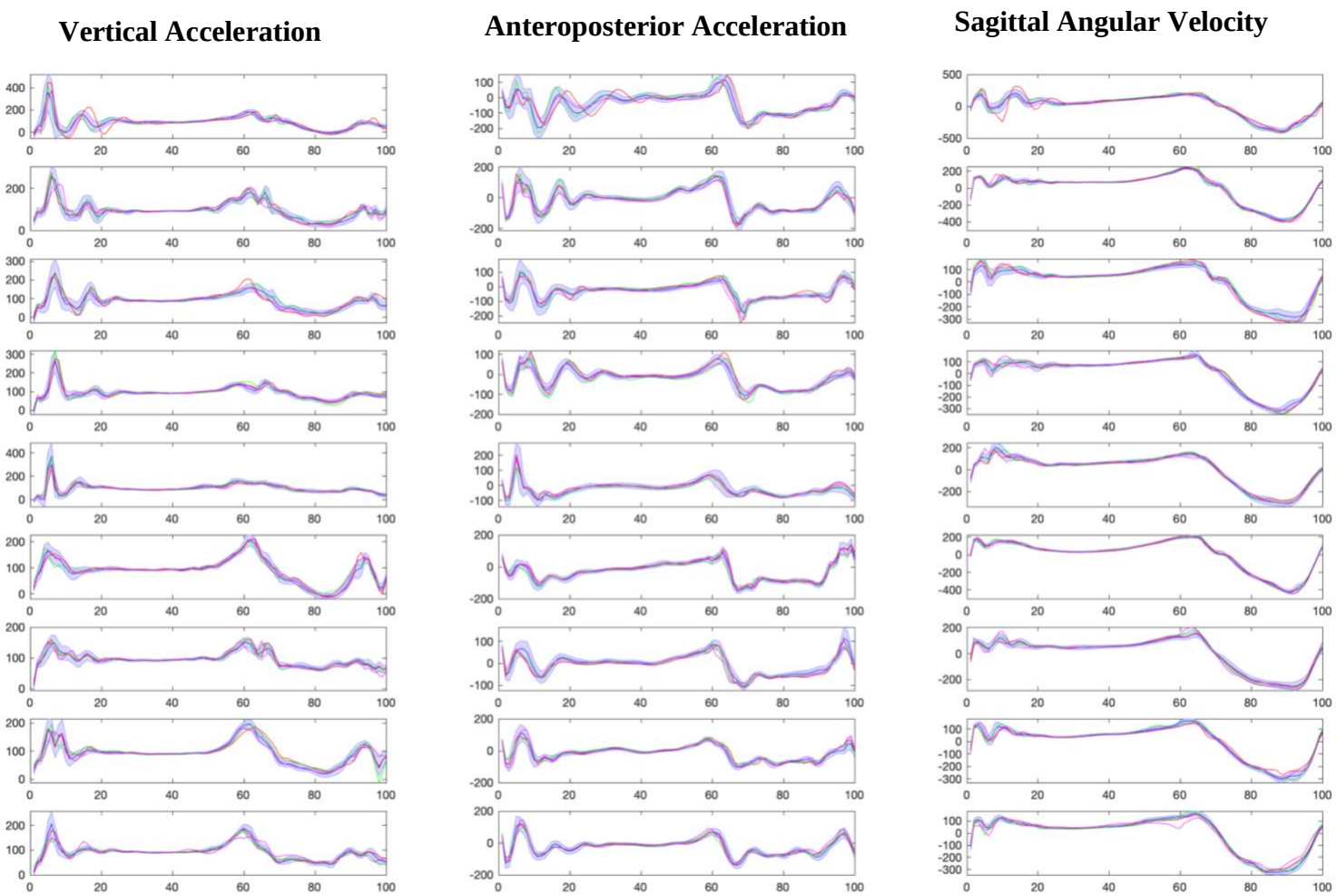

Figure 18 (Appendix): All waveforms from left shank sensor for all 9 subjects. Each row represents one subject. Ensemble mean and standard deviation strides of training sets in purple, with ensemble mean atypical strides overlayed for test data in red (trial 5), green (trial 6) and magenta (trial 7).

Table 3: Average atypical strides when using the three most reliable channels and a PCA reduction. *Methodology used in current study.

Pre-Injection		**Post-Injection**		
Training Data (Normal gait pattern model)	Pre-Injection (Test data atypical strides per model)	Trial 5 (Test data atypical strides per model)	Trial 6 (Test data atypical strides per model)	Trial 7 (Test data atypical strides per model)
T_1, T_2, T_3	T_4	T_5	T_6	T_7
T_1, T_2, T_4	T_3	T_5	T_6	T_7
T_1, T_3, T_4	T_2	T_5	T_6	T_7
T_2, T_3, T_4	T_1	T_5	T_6	T_7
Ave proportion of atypical strides (Std.)	$\overline{T}_{1\text{-}4}$ = **17.7 (9.4) %**	$\overline{T}_5$ = **6.9 (9.2) %**	$\overline{T}_6$ = **16.9 (28.1) %**	$\overline{T}_7$ = **26.6 (36.3) %**
Associated Research Questions	i) $\overline{T}_{1\text{-}4} < 10\%$	ii) $\overline{T}_5, \overline{T}_6, \overline{T}_7 > \overline{T}_{1\text{-}4}$ iii) $\overline{T}_5, \overline{T}_6, \overline{T}_7$ correlated with changes in pain from $\overline{T}_{1\text{-}4}$		

Abbreviations: T; Trial.Std.; Standard Deviation Subscript denotes the test trial. $\overline{T}$ denotes the average seen across all subjects and respective trials.

Table 4: Average atypical strides when using the three most reliable channels and no PCA reduction.

Pre-Injection		**Post-Injection**		
Training Data (Normal gait pattern model)	Pre-Injection (Test data atypical strides per model)	Trial 5 (Test data atypical strides per model)	Trial 6 (Test data atypical strides per model)	Trial 7 (Test data atypical strides per model)
T_1, T_2, T_3	T_4	T_5	T_6	T_7
T_1, T_2, T_4	T_3	T_5	T_6	T_7
T_1, T_3, T_4	T_2	T_5	T_6	T_7
T_2, T_3, T_4	T_1	T_5	T_6	T_7
Ave proportion of atypical strides (Std.)	$\overline{T}_{1\text{-}4}$ = **20.3 (14.3) %**	$\overline{T}_5$ = **14.8 (23.6) %**	$\overline{T}_6$ = **20.7 (34.4) %**	$\overline{T}_7$ = **25.9 (39.2) %**
Associated Research Questions	i) $\overline{T}_{1\text{-}4} < 10\%$	ii) $\overline{T}_5, \overline{T}_6, \overline{T}_7 > \overline{T}_{1\text{-}4}$ iii) $\overline{T}_5, \overline{T}_6, \overline{T}_7$ correlated with changes in pain from $\overline{T}_{1\text{-}4}$		

Abbreviations: T; Trial.Std.; Standard Deviation Subscript denotes the test trial. $\overline{T}$ denotes the average seen across all subjects and respective trials.

Table 5: Average atypical strides when using all six channels and a PCA reduction.

Pre-Injection		**Post-Injection**		
Training Data (Normal gait pattern model)	Pre-Injection (Test data atypical strides per model)	Trial 5 (Test data atypical strides per model)	Trial 6 (Test data atypical strides per model)	Trial 7 (Test data atypical strides per model)
T_1, T_2, T_3	T_4	T_5	T_6	T_7
T_1, T_2, T_4	T_3	T_5	T_6	T_7
T_1, T_3, T_4	T_2	T_5	T_6	T_7
T_2, T_3, T_4	T_1	T_5	T_6	T_7
Ave proportion of atypical strides (Std.)	$\overline{T}_{1\text{-}4}$ = **57.9 (25.1) %**	$\overline{T}_5$ = **44.0 (23.5) %**	$\overline{T}_6$ = **48.4 (33.1) %**	$\overline{T}_7$ = **55.1 (38.3) %**
Associated Research Questions	i) $\overline{T}_{1\text{-}4} < 10\%$	ii) $\overline{T}_5, \overline{T}_6, \overline{T}_7 > \overline{T}_{1\text{-}4}$ iii) $\overline{T}_5, \overline{T}_6, \overline{T}_7$ correlated with changes in pain from $\overline{T}_{1\text{-}4}$		

Abbreviations: T; Trial.Std.; Standard Deviation Subscript denotes the test trial. $\overline{T}$ denotes the average seen across all subjects and respective trials.

Table 6: Average atypical strides when using all six channels and no PCA reduction.

Pre-Injection		**Post-Injection**		
Training Data (Normal gait pattern model)	Pre-Injection (Test data atypical strides per model)	Trial 5 (Test data atypical strides per model)	Trial 6 (Test data atypical strides per model)	Trial 7 (Test data atypical strides per model)
T_1, T_2, T_3	T_4	T_5	T_6	T_7
T_1, T_2, T_4	T_3	T_5	T_6	T_7
T_1, T_3, T_4	T_2	T_5	T_6	T_7
T_2, T_3, T_4	T_1	T_5	T_6	T_7
Ave proportion of atypical strides (Std.)	$\overline{T}_{1\text{-}4}$ = **68.9 (20.7) %**	$\overline{T}_5$ = **53.1 (27.2) %**	$\overline{T}_6$ = **54.4 (38.3) %**	$\overline{T}_7$ = **56.6 (34.1) %**
Associated Research Questions	i) $\overline{T}_{1\text{-}4} < 10\%$	ii) $\overline{T}_5, \overline{T}_6, \overline{T}_7 > \overline{T}_{1\text{-}4}$ iii) $\overline{T}_5, \overline{T}_6, \overline{T}_7$ correlated with changes in pain from $\overline{T}_{1\text{-}4}$		

Abbreviations: T; Trial.Std.; Standard Deviation Subscript denotes the test trial. $\overline{T}$ denotes the average seen across all subjects and respective trials.

Table 7: Average atypical strides when using a regularization parameter ("Nu") of 0.1 and the three most reliable channels with a PCA reduction.

Pre-Injection		**Post-Injection**		
Training Data (Normal gait pattern model)	Pre-Injection (Test data atypical strides per model)	Trial 5 (Test data atypical strides per model)	Trial 6 (Test data atypical strides per model)	Trial 7 (Test data atypical strides per model)
T_1, T_2, T_3	T_4	T_5	T_6	T_7
T_1, T_2, T_4	T_3	T_5	T_6	T_7
T_1, T_3, T_4	T_2	T_5	T_6	T_7
T_2, T_3, T_4	T_1	T_5	T_6	T_7
Ave proportion of atypical strides (Std.)	$\overline{T}_{1\text{-}4}$ = **80.3 (19.1) %**	$\overline{T}_5$ = **68.6 (31.0) %**	$\overline{T}_6$ = **69.4 (25.5) %**	$\overline{T}_7$ = **70.2 (37.0) %**
Associated Research Questions	i) $\overline{T}_{1\text{-}4} < 10\%$	ii) $\overline{T}_5, \overline{T}_6, \overline{T}_7 > \overline{T}_{1\text{-}4}$ iii) $\overline{T}_5, \overline{T}_6, \overline{T}_7$ correlated with changes in pain from $\overline{T}_{1\text{-}4}$		

Abbreviations: T; Trial.Std.; Standard Deviation Subscript denotes the test trial. $\overline{T}$ denotes the average seen across all subjects and respective trials.

Table 8: Average atypical strides when using an "OutlierFraction" of 5% and the three most reliable channels with a PCA reduction.

Pre-Injection		**Post-Injection**		
Training Data (Normal gait pattern model)	Pre-Injection (Test data atypical strides per model)	Trial 5 (Test data atypical strides per model)	Trial 6 (Test data atypical strides per model)	Trial 7 (Test data atypical strides per model)
T_1, T_2, T_3	T_4	T_5	T_6	T_7
T_1, T_2, T_4	T_3	T_5	T_6	T_7
T_1, T_3, T_4	T_2	T_5	T_6	T_7
T_2, T_3, T_4	T_1	T_5	T_6	T_7
Ave proportion of atypical strides (Std.)	$\overline{T}_{1\text{-}4}$ = **49.4 (22.4) %**	$\overline{T}_5$ = **27.7 (24.1) %**	$\overline{T}_6$ = **37.1 (39.0) %**	$\overline{T}_7$ = **50.9 (42.2) %**
Associated Research Questions	i) $\overline{T}_{1\text{-}4} < 10\%$	ii) $\overline{T}_5, \overline{T}_6, \overline{T}_7 > \overline{T}_{1\text{-}4}$ iii) $\overline{T}_5, \overline{T}_6, \overline{T}_7$ correlated with changes in pain from $\overline{T}_{1\text{-}4}$		

Abbreviations: T; Trial.Std.; Standard Deviation Subscript denotes the test trial. $\overline{T}$ denotes the average seen across all subjects and respective trials.

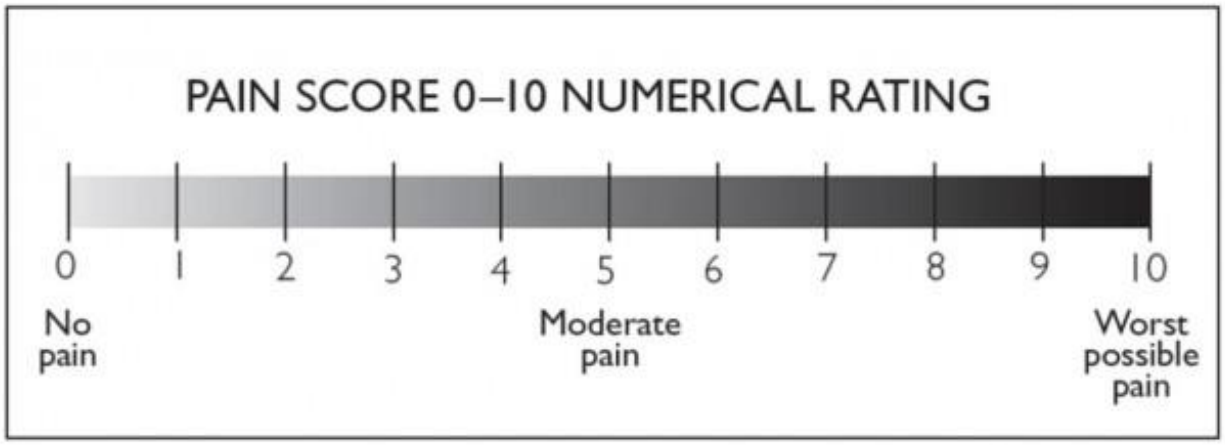

Figure 19: Numerical Pain Rating Scale (NPRS) used in the current study.