

**WEARABLE BIOIMPEDANCE SENSING FOR QUANTIFYING  
KNEE HEALTH IN JUVENILE IDIOPATHIC ARTHRITIS**

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Presented to  
The Academic Faculty

by

Emily Moise

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**WEARABLE BIOIMPEDANCE SENSING FOR QUANTIFYING  
KNEE HEALTH IN JUVENILE IDIOPATHIC ARTHRITIS**

Approved by:

Dr. Omer Inan, Advisor  
School of Electrical and Computer Engineering  
*Georgia Institute of Technology*

Dr. Young-Hui Chang  
School of Biological Sciences  
*Georgia Institute of Technology*

Dr. Sampath Prahalad  
School of Medicine  
*Emory University*

Date Approved: July 14, 2022

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## LIST OF SYMBOLS AND ABBREVIATIONS

JIA	Juvenile Idiopathic Arthritis
MRI	Magnetic Resonance Imaging
EBI	Electrical Bioimpedance
US	Ultrasound
NSAID	Non-steroidal anti-inflammatory agent
IAS	Inter-articular corticosteroid
ERA	Enthesitis-related arthritis
MTX	Methotrexate
CHOA	Children's Healthcare of Atlanta
CAP	Center for Advanced Pediatrics
ESR	Erythrocyte Sedimentation Rate
CRP	C-reactive Protein
SIJ	Sacroiliac Joint
PCA	Principal Component Analysis
ILAR	International League of Associations for Rheumatology

## SUMMARY

Juvenile Idiopathic Arthritis (JIA) is chronic arthritis that impacts children under the age of 16. The lack of pediatric rheumatologists in the United States, along with the inconvenience of Magnetic Resonance Imaging (MRI) results in JIA misdiagnosis and lost care opportunities. Telehealth and virtual medicine provide the ability to monitor patients from home which can result in more insight into the current disease status. Improved technologies for assessing joint health in patients with JIA can enable personalized titration of care and lead to improved outcomes. In this work, we studied, for the first time, wearable bioimpedance measurements as a technique for quantifying joint health in JIA. Knee bioimpedance data were collected from 23 children with JIA and 8 healthy controls. Bioimpedance data were collected at 5 kHz and 100 kHz in knee flexion and extension positions. The calculated  $H_{\alpha}$  compares the changes in 5 kHz and 100 kHz resistance from flexion and extension position.  $H_{\alpha}$  showed statistically significant results ( $p < 0.05$ ) for discriminating between healthy controls and children with JIA. Additionally, electrical bioimpedance data were collected on multiple subjects ( $n=4$ ) throughout their treatment time. Over time,  $H_{\alpha}$  decreases implying a positive change in disease status. The results of this study show the potential for using wearable electrical bioimpedance to determine JIA status and treatment effectiveness.

## CHAPTER 1. INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is the most common childhood rheumatic disease and affects around 1 in 1,000 youths. Patients report that pain and tenderness impact functionality in daily life, which in turn negatively influences their quality of life [1]. Limited access to resources, including pediatric rheumatologists emphasize the need for a readily available, easily used system to track disease status [2]. In my experience, throughout this study at Children's Healthcare of Atlanta, patients often traveled for upwards of 3-4 hours to have an appointment with a pediatric rheumatologist.

Currently, the gold standard for diagnosing JIA is Magnetic Resonance Imaging (MRI) [3]. However, there are several disadvantages to MRI. For example, the high cost makes it relatively inaccessible for many families. Additionally, younger children may be afraid of the device and require sedative drugs, which is an additional burden for the family [4]. If MRI is not available to the child, the next best diagnostic tool is a clinical examination provided by a pediatric rheumatologist [5]. Following a diagnosis, the clinician may require the patient to return to the clinic every 3-6 months to track disease status and treatment effectiveness [6]. Because the closest pediatric rheumatologist may be several hours away, this requires an extra effort on the caregiver's part. For all these reasons, it is imperative to develop more optimal methods of monitoring JIA disease status in these children.

The low number of pediatric rheumatologists creates the need for additional affordable and convenient ambulatory diagnostic tools. Furthermore, accessibility to telehealth has been utilized more recently to provide patients with limited access to

pediatric rheumatologists with care [7]. However, telehealth is limited to subjective tools and patient reported symptoms. Wearable sensing hardware enabling direct measurements of joint health properties may provide a new means of obtaining objective and quantitative data outside of clinical settings, easing the burden on pediatric rheumatologists while also allowing for more frequent assessments of patient status to be obtained ubiquitously.

In this work, the first study on using Electrical Bioimpedance (EBI) to discriminate between a knee with JIA and a healthy knee was performed. Electrical bioimpedance is a tool that has been used to assess body composition, and more recently, edema in ankle injuries [8], [9]. Bioimpedance was measured in the flexion and extension position of knees with the goal of being able to use the data to separate between knees with JIA and healthy knees. This work details the results of the study that was performed at Children's Healthcare of Atlanta.

## **CHAPTER 2. BACKGROUND**

### **2.1 Overview**

Juvenile Idiopathic Arthritis (JIA) is chronic arthritis that impacts children under the age of 16. The lack of pediatric rheumatologists in the United States, along with the inconvenience of Magnetic Resonance Imaging (MRI) cause children with JIA to be frequently misdiagnosed and not given the proper care they need. Electrical bioimpedance (EBI) is a tool that can be used to help discriminate whether a knee has active JIA or is healthy.

### **2.2 Juvenile Idiopathic Arthritis**

Juvenile Idiopathic Arthritis (JIA) is a condition in which chronic arthritis of unknown etiology onsets within the first 16 years of life and occurs for at least six weeks [10]. Currently, JIA affects 1 in 1,000 adolescents with one-third having on-going active arthritis into adulthood [11]. The International League of Associations for Rheumatology (ILAR) classifies JIA into seven sub-categories, with each one presenting in different ways, including the symptoms and active joints [12]. The different sub-categories of JIA also present differently in terms of frequency of diagnosis and demographic in which the sub-category occurs [13]. The frequency of disease and demographics are described in Table 1. The seven sub-categories and the differences in symptoms between them are described in Table 2 [14], [15].

2.2.1 JIA Sub-Types

**Table 1: JIA Sub-Types: Occurrence Rate and Demographics**

<b>JIA Sub-Type</b>	<b>Percentage of Patients with Specific JIA Type</b>	<b>Female to Male Ratio</b>
Systematic juvenile idiopathic arthritis	4-17%	Female and male occur at the same frequency
Rheumatoid factor positive polyarthritis	2-7%	Females occur more frequently than male
Rheumatoid factor negative polyarthritis	11-28%	Females occur more frequently than male
Oligoarthritis	27-56%	Females occur much more frequently than male
Enthesitis-related arthritis	3-11%	Males occur more frequently than female
Psoriatic	2-11%	Females occur more frequently than male
Undifferentiated	11-21%	N/A

**Table 2: JIA Sub-Types: Affected joints and characteristic features**

<b>JIA Sub-Type</b>	<b>Number of Affected Joints</b>	<b>Characteristic Features of the JIA Sub-Type</b>
Systematic juvenile idiopathic arthritis	1 or more	Systemic features including fever and rash
Rheumatoid factor positive polyarthritis	5 or more	Thought to be like adult rheumatoid arthritis. The child will also have two positive tests for rheumatoid factor
Rheumatoid factor negative polyarthritis	5 or more	The child will have a negative blood test for rheumatoid factor
Oligoarthritis	1-4	No other features required to diagnose
Enthesitis-related arthritis	1 or more	Pain, swelling, and/or tenderness at an entheses site (ligament, tendon or joint capsule attached to bone)
Psoriatic	1 or more	The child must have arthritis and psoriasis, or they have arthritis and two of the following: <ul style="list-style-type: none"> <li>- Enlarged fingers or toes</li> <li>- Family member with psoriasis</li> </ul>
Undifferentiated	1 or more	The child receives this diagnosis if they do not specifically fall into another category

### *2.2.2 Current Methods of Diagnosis*

To be diagnosed with JIA, a thorough physical examination is conducted by a pediatric rheumatologist, in which all body joints are examined, tenderness, swelling, and pain levels are recorded, and details about patient history are taken [16].

However, to understand more about the details of the patient's disease, imaging is the preferred diagnostic tool. Rheumatologists have agreed that ultrasound (US) imaging and magnetic resonance imaging (MRI) are superior to a clinical evaluation and provide more details in terms of disease severity [17].

### *2.2.3 Limitations of Current Methods of Diagnosis*

In the United States, there is a lack of sufficient pediatric rheumatologists to meet the existing demand, which can cause patients to wait several months or years without getting the proper diagnosis or care they need. Specifically, it is estimated that there are only three pediatric rheumatologists per million children in the United States with 14 states having zero practicing pediatric rheumatologists [18]. In 2019, the mean driving distance to a pediatric rheumatologist was over 40 miles, with 18% of children being more than 80 miles away from a pediatric rheumatologist [19].

Although there are positives to imaging, there are drawbacks that make it less practical. First, the cost of an MRI can deter a patient's family from pursuing that option for diagnosis [20]. Secondly, even if a family can get an MRI scheduled, imaging a

young child can prove challenging. The child may be frightened or uncooperative, which can result in doctors using sedation methods, such as anesthesia [21].

### **2.3 Inactive versus Active JIA**

Upon clinical examination, a physician is able to classify the patient's JIA status as inactive disease or active disease. When a patient enters remission, they are considered to have inactive disease. Inactive disease is classified as meeting the following criteria:

- Documented clinical assessment of inactive disease
- No active arthritis
- No active uveitis
- No fever/rash attributed to JIA
- Normal blood marker values for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)

Inactive disease can be classified in two ways – clinical remission on medication and clinical remission off medications [22]. If a patient does not meet the above criteria, they are considered to have active disease. Periods of active and inactive disease can cycle throughout the course of disease [22], [23].

#### *2.3.1 Classification of Active Disease*

The pain and stiffness experienced in children with JIA can come and go and also get better or worse throughout the course of active disease [24]. Specific traits that were examined in the clinical examination at Children's Healthcare of Atlanta are:

- Synovial thickening: an inflamed synovium can lead to synovial thickening [25]
- Effusion: an abnormal collection of fluid in hollow spaces or between tissues of the body [26]
- Tenderness
- Limited range of motion

US can help to determine the cause of the pain: effusion size, synovial thickening, cartilage erosions and thinning. MRI determines the extent of the effusion and synovial thickening based on the individual components of the joint, which is a capability that US does not have [27].

## **2.4 Treatment Options**

Being able to diagnose and treat JIA is critical to the patient for several reasons. First, children with JIA are often in pain and it is crucial to find a method to alleviate the pain they experience. Second, it is important to diagnose and treat early so that the repercussions of the disease are minimal. If JIA goes without treatment, soft-tissue and joint damage may become irreversible [28]. *Stoll et al.* reports that prescribing aggressive treatment early in the disease diagnosis may provide the best opportunity for remission [29].

JIA treatment options can be separated based on whether a child has active or inactive arthritis. In both cases, the overall goal is to suppress all physical symptoms [30]. Treatment varies slightly depending on the type of JIA that is presented in the patient. *Wallace et al.* describes the treatment options as described below [31].

### 2.4.1 *Oligoarthritis*

In most cases of Oligoarthritis, with mild disease there are options for non-steroidal anti-inflammatory agents (NSAIDs) or intra-articular corticosteroid injections (IAS). With IAS, synovial thickening should decrease. In the case that the thickening does not decrease, or the reduction is temporary, a follow-up IAS may be administered. If remission is achieved with an NSAID, the NSAID will be continued for 3-6 months before use is no longer required.

### 2.4.2 *Polyarticular Arthritis*

Patients with mild disease have the option for NSAIDs and hydroxychloroquine. In most cases, there is a need for rapid treatment with methotrexate (MTX) and either oral steroids or IAS. There is no known optimal dose of MTX; however, once remission is achieved, the dose is lowered as an aggressive treatment is no longer needed.

### 2.4.3 *Systemic JIA*

Patients with systemic JIA normally have other symptoms, in addition to joint swelling, pain and tenderness. The severity of these additional symptoms (fever spikes, rash, etc.), dictate the course of treatment. With moderate fevers not requiring hospitalization, NSAIDs normally suffice for the beginning of treatment. If the disease is more severe, high dose corticosteroids are required. Medications such as methylprednisolone, and prednisone are used in an attempt to minimize systemic features. For systemic JIA, blood work is critical to monitor the fluctuations in disease severity.

#### 2.4.4 *Enthesitis-Related Arthritis*

Patients with Enthesitis-Related Arthritis (ERA) are treated similar to patients with oligoarthritis. The options for ERA include either NSAIDs, IAS or a combination of both. In the case of severe disease, oral steroids may be required.

## 2.5 **Bioimpedance**

### 2.5.1 *Introduction to the Work that Will Be Presented*

As a result of the lack of pediatric rheumatologists and inefficient imaging practices, a better method to diagnose and track treatment progress of JIA must be established. The method that will be discussed in this work is bioimpedance.

### 2.5.2 *What is Bioimpedance?*

Electrical bioimpedance (EBI) is a non-invasive method of assessing tissue composition that may provide such a wearable tool for assessing joint health objectively and quantitatively for patients with JIA. However, EBI has never been explored for this purpose. EBI is measured by injecting a small alternating current into a volume of tissue and measuring the resulting voltage drop across the tissue using electrodes placed distally and proximally, respectively, to the tissue of interest. The ratio of the measured voltage to the injected current yields the bioimpedance value for that segment of the tissue [32]. The difference in impedance results from the ability of ions to mobilize within and outside of cellular matrices. For example, ions can be present outside of a material (e.g., extracellular fluid), inside the material (e.g., intracellular fluid), fluid between outside and inside a material, or a combination [33]. Historically, bioimpedance has been primarily

used to assess body composition [8]. However, more recently, bioimpedance has been used to assess hydration levels, blood glucose levels, and edema in injuries [34]–[36]. Impedance can be measured using two-electrode systems; however, for this study and the prior work completed in the Inan Research Lab, a four-electrode system was used to eliminate the skin-electrode impedance interface [36].

### 2.5.3 *Overview of Prior Work Done in Lab with Bioimpedance*

Previous work in the Inan Research Lab has shown that bioimpedance can quantify edema in ankle injuries [36], [9]. The information about impedances of biological materials can allow insight into the state of the segment that is being measured. *Mabrouk et al.*, developed a novel data capture system that used bioimpedance to detect changes in ankle edema and structural integrity of the joint by examining the effects of movement on low and high frequency bioimpedance measurements. The capturing and processing of these data allows physicians to make a more informed decision about injury rehabilitation and return to play for a sports injury [9]. Recent work has also demonstrated that wearable EBI measures can help classify disease activity in patients with rheumatoid arthritis [37]. In a similar manner, this work addresses the hypothesis that edema and structural properties of a knee joint with JIA will yield different EBI values as compared to a healthy knee joint with no history of JIA. More importantly, we anticipate that changes in knee joint health associated with treatment for a patient with JIA will yield improvements in EBI parameters trending closer to the normal healthy values.

## **CHAPTER 3. PROJECT OVERVIEW**

### **3.1 Objective**

The objective of this project is to determine the utility of EBI to identify the existence or absence of JIA in a child's knee. As a first step toward this goal, EBI data has been collected on children with both JIA and children who have healthy knees.

#### *3.1.1 Hypothesis*

It has been shown that EBI can quantify edema in ankle injuries [9]. Because of this, the hypothesis in this thesis is that EBI will be able to provide insight on the status of JIA in children. The following sections present the breakdown of the experiment and tools used to conduct the research.

### **3.2 Methods**

In order to investigate the efficacy in using EBI for JIA detection, a clinical study was designed in which subjects were recruited at Children's Healthcare of Atlanta. The study had several objectives, (1) determine the best placement of EBI electrodes for EBI data collection around the knee, (2) collect data from similar demographic populations of healthy children and children with JIA, and (3) analyze the data to determine whether differences occur in knees of children with JIA versus knees of children who are healthy.

#### *3.2.1 Materials*

The wearable device used for data has been previously described in the literature and will be described in detail in section 3.3 [9]. Briefly, the device uses the AD5940

bioimpedance front-end created by Analog Devices (Norwood, MA). The firmware of the system was programmed to collect impedance data from a range of frequencies varying from 5 kHz to 100 kHz. However, for post-processing analysis, only 5 kHz and 100 kHz were chosen for analysis based on prior work with ankle health assessment [36], [38]. The 5 kHz frequency captures the changes in extracellular fluid and the 100 kHz frequency captures the changes in both intra and extra cellular fluid content. For each subject, the data were saved on a local memory card and then transferred to a computer for analysis.

Subjects sat on an adjustable stool, shown in Figure 1, which was positioned high enough to prevent the subjects' foot from contacting the ground and potentially introducing artifacts into the signal.



**Figure 1: Height-adjustable stool that allowed for subjects to sit without contacting the ground**

### 3.2.2 Subject Recruitment

This study was approved by the Georgia Institute of Technology Institutional Review Board (IRB H15383) and the Emory Institutional Review Board (IRB00081670). All subjects' parents provided written consent. For this study, 23 subjects with JIA and 8 healthy controls were recruited. The average age of the JIA subjects was 13 +/- 3.9 and the average age of healthy subjects was 12.1 +/- 2.5. The average BMI of the JIA subjects was 20.1 +/- 5.2 and the average BMI of the healthy subjects was 18.6 +/- 2.6. 70% of the JIA subjects were female and 63% of the healthy controls are female. Table 1 highlights the demographics of the subjects.

**Table 3: Subject demographics for healthy controls and subjects with JIA**

	<b>Demographics</b>			
	<i>Number of Subjects</i>	<i>Average Age</i>	<i>Average BMI</i>	<i>Percent Female</i>
Healthy	8	12.1	18.6	63%
JIA	23	13	20.1	70%

All data were collected at either Children's Healthcare of Atlanta (CHOA) – The Center for Advanced Pediatrics or the Georgia Institute of Technology. Clinical research coordinator, Lori Ponder, of CHOA consented each subject. JIA subject inclusion criteria included: children aged 5-21 who met the International League of Associations for Rheumatology (ILAR) criteria for JIA based on an evaluation with a CHOA physician. For this study, each subject with JIA had prior knee involvement over the course of their

active JIA disease. Healthy subject inclusion criteria included: children aged 5-21 with no previous JIA diagnosis and no prior known knee injury.

Subjects were recruited at the time of their scheduled visit with a clinician. At the time of each individual visit, subjects were asked by their clinician if they were interested in participating in research. If the child was under 18, both the parent and the child needed to provide consent. For children aged 11-17, written assent was needed in addition to the parental consent. For children aged 6-10, verbal assent was needed in addition to the parental consent.

In addition to the signed consent forms, each corresponding clinician was provided with a document to detail the severity of the current disease status. An example current disease status form is provided in the Appendix of this thesis. The details of the clinician form are as follows:

- Did the child have active or inactive JIA at the time of the visit?
- What is the subtype of JIA?
- How severe is the JIA in the recording location?

Regarding the last question, for each possible recording site (knee joint, Sacroiliac joint, Achilles tendon), the treating physician was asked about specific qualities of each site. Because the knee is the highlighted joint in this work, the specific qualities that the physician noted will be discussed. Firstly, in the clinic, each knee is treated as a separate entity. Each knee has four scores that are entered into our database containing all data from the recordings to be later used in the signal processing pipeline. The four knee scores are as follows:

- Fluid
- Synovial Thickening
- Tenderness
- Limited Range of Motion

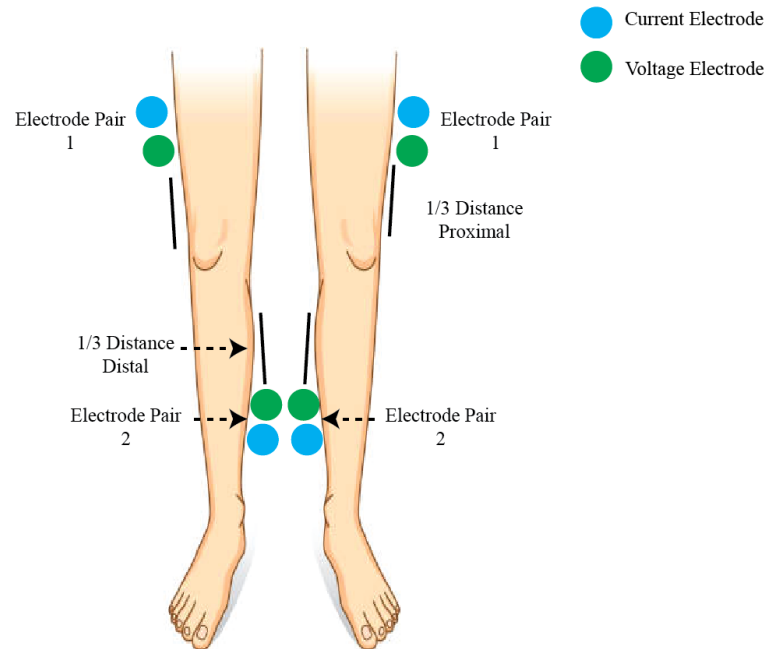
For each metric, the clinician scores a value from 0-3. For example, if the subject did not have fluid in their right knee, they would be given a score of 0. If the subject had extreme fluid in their right knee, they would be given a score of 3. The same scale applies for synovial thickening, tenderness, and limited range of motion. Each knee is given an individual set of scores.

### *3.2.3 EBI Recording Location*

After each subject has been consented, they are briefed on the recording process. This work focuses on the EBI results that were obtained during the data collection at CHOA, but other sensors were also recording during the collection process. Because of this, each recording protocol had to be streamlined to be as efficient as possible.

To collect bioimpedance data from the knee joint, we needed to ensure that the electrodes cover the entire joint area on each child. In addition, because we were recruiting subjects with a wide age range, a standardized distance from the knee could not be used to place the electrodes. To enable a systematic method of electrode placement, we measured two segments of the leg: from the hip joint to the knee joint and the knee joint to the ankle joint. Then, for each joint we measured one-third of the distance proximal and distal from the knee joint. This location was marked, and the electrodes were placed in the marked locations. For the EBI system, *Mabrouk et al.*, created a four-

electrode system [9]. There are two current electrodes and two voltage electrodes. The current electrodes were placed on the outside of the markings and the voltage electrodes were placed on the inside of the markings. Additionally, the electrodes proximal to the knee joint were placed on the lateral side of the leg and the electrodes distal to the knee joint were placed on the medial side of the leg. Figure 2 illustrates the placement of the electrodes.



**Figure 2: Relative placement of EBI electrodes on subject leg. To account for the varied lengths of the subject's legs, each leg was measured from the hip joint to the knee joint and the knee joint to the ankle joint. Electrodes were placed one-third distance proximal from the knee joint and one-third distal from the knee joint.**

joint were placed on the medial side of the leg. Figure 2 illustrates the placement of the electrodes.

### 3.3 Protocol

#### 3.3.1 Experiment Set-Up

Once the subject gave consent to the experiment protocol, the electrodes for the EBI recording were placed as described in section 3.2.3. Subjects were asked to wear shorts or tie their pants high enough to ensure that the electrodes could be placed in the required position without clothing artifacts interfering. Children’s Healthcare of Atlanta provided shorts (MediShorts Disposable Exam Shorts, Medline Industries) to subjects who did not bring shorts to their appointment. The one-third leg distance was recorded using a standard tape measure. Electrodes were placed on the leg using 3M gel electrodes (3M Electronics, Minnesota). Because each EBI system only has four electrodes, only one leg could be recorded at a time. The electrodes were placed on the right leg first; the protocol was completed, then the electrodes were moved to the left leg where the protocol was completed again.

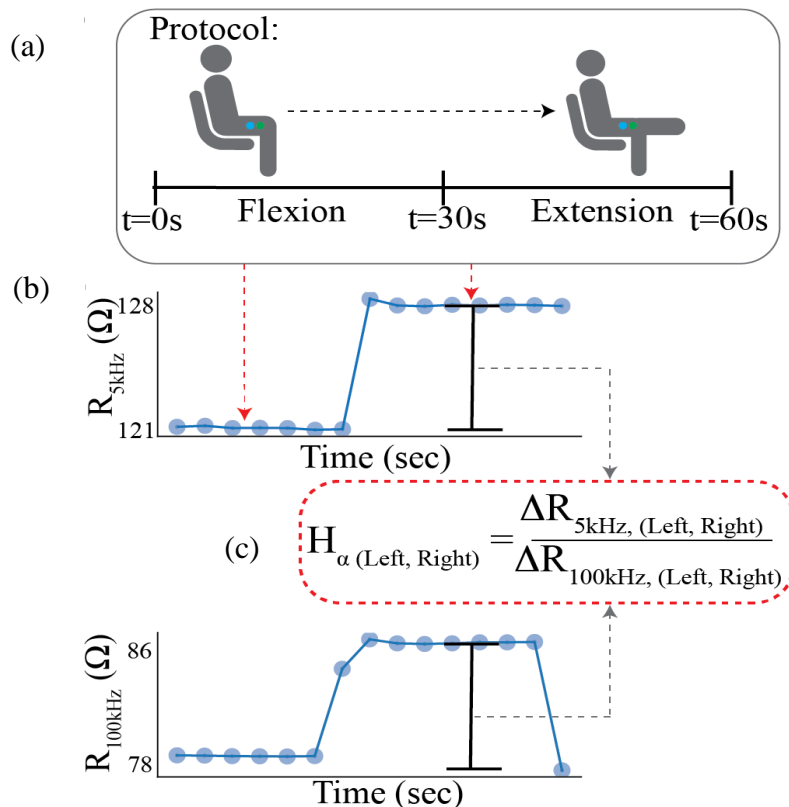
### *3.3.2 Data Collection*

Following the wearable EBI system being placed on the subject’s right leg, subjects were briefed on the recording protocol. The data collection protocol is: 30 seconds of knee flexion (keeping the knee bent at 90 degrees), 30 seconds of knee extension (straightening the leg to the best of the subject’s ability), and 11 flexion-extension cycles at a 4 seconds/cycle frequency. Fig 3 outlines the protocol that was followed by each subject.

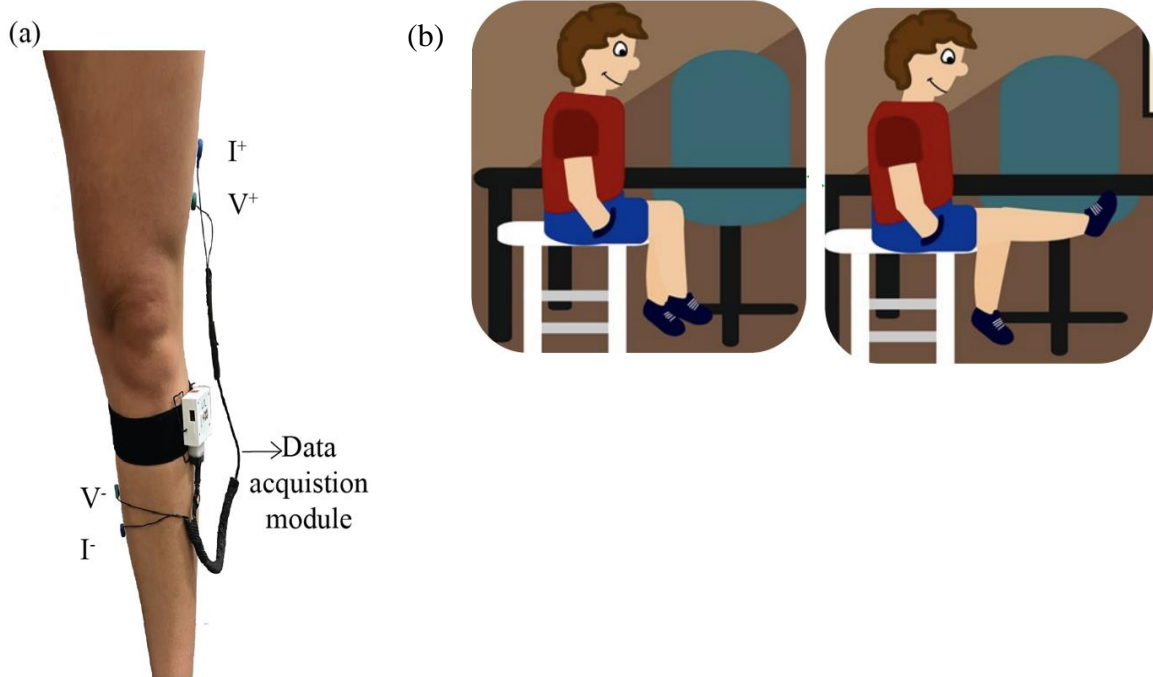
For most subjects, EBI was recorded at the same time as passive acoustic signals on the lateral and medial sides of the patella tendon. Because of this, the EBI protocol was combined with the passive knee acoustic recording protocol. The 30 seconds of knee flexion followed by 30 seconds of knee extension provided the data that was necessary

for the EBI analysis. The 11 flexion-extension cycles were required for the passive knee acoustic recording. For this part of the protocol, an animation created by Daniel Whittingslow was used for subjects to follow along. The animation guided the flexion-extension cycles with a 4 seconds/cycle frequency. To streamline the process, these two recordings were completed back-to-back.

After this process was completed on the right leg, the sensors were moved to the left leg and the same process was repeated. If at any point the subject felt uncomfortable or did not want to continue the protocol, they were able to stop without question. Following the protocol, regardless of whether the entire protocol was completed, subjects were given a \$20 gift card to their choice of Target or Amazon. Fig 4 shows an image of the electrodes on the leg along with screenshots of the flexion and extension animation that subjects used to follow along.



**Figure 3: Experiment protocol. (a) Details the 30s of knee flexion followed by 30s of knee extension. The protocol is completed for the right leg and then the left leg. (b) Shows sample 5 kHz and 100 kHz data collected from the subject. (c) The equation used to analyze the data.**



**Figure 4: (a) Example electrodes on subject legs and data acquisition module that locally stores the collected data. (b) Screenshots of flexion and extension animation to guide subjects during the flexion and extension protocol.**

### 3.4 Signal Processing

At the completion of the data collection process, there were a total of 23 subjects with JIA and 8 healthy controls. Each leg was counted as a separate entity due to the way that the clinician scores each leg's disease status independently; therefore, there was a total of 46 legs with JIA and 16 healthy legs.

First, EBI data gathered by the wearable device were converted to actual tissue impedances using the novel calibration scheme designed by Mabrouk et al. [36]. From this point on, the actual tissue impedances are used throughout the analysis. With the

tissue impedances, the first step in the analysis was to visually inspect the data to verify clean, easily identifiable sections of knee flexion and extension. Each knee was analyzed independently as it was scored individually by the clinician. Once identified, the flexion-extension data were extracted for additional analysis. Data with non-identifiable flexion-extension segments were excluded from the analysis. Next,  $\Delta R_{5\text{kHz}}$  and  $\Delta R_{100\text{kHz}}$  values were filtered to include ranges greater than 3 ohms. As we take the  $H_\alpha$  ratio, if the resistance is too small ( $< 3$  ohms), small changes that are within the system noise floor can affect the ratio substantially.

### 3.4.1 Analysis – $H_\alpha$

The main metric used to analyze the data was  $H_\alpha$ , which is a measure of the range of 5 kHz resistances divided by the range of 100 kHz resistances (as described in Equation 1.0). This value was utilized based on the existing literature [36].  $H_\alpha$  provides insight into the overall swelling of the joint. The 5 kHz signal travels primarily through extracellular fluid, while the 100 kHz signal is able to travel through the extracellular and intracellular fluid. The flexion and extension recording positions allow changes in fluid movement to be captured. Because children with JIA have more swelling, edema, and synovial thickening in their knees than healthy children, the fluid in their knees has greater movement than healthy knees. Thus, the predicted  $\Delta R_{5\text{kHz}}$  value when compared with  $\Delta R_{100\text{kHz}}$  for JIA subjects is higher than for healthy subjects due to the superfluous fluid in the diseased knees. Therefore, it was predicted that  $H_\alpha$  would be higher for subjects with JIA and lower for healthy subjects. This information was utilized to compare properties of knees with JIA versus healthy knees.

$$H_{\alpha} = \frac{\Delta R(5k)_{extension-flexion}}{\Delta R(100k)_{extension-flexion}} \quad \text{Equation 1.0}$$

Once it was determined that  $H_{\alpha}$  would provide the most meaningful result,  $H_{\alpha}$  was calculated for each independent leg. From there, values less than 3 ohms were filtered out to account for system error.

Following the segmentation of flexion-extension cycles and filtering ranges less than 3 ohms, there were 10 healthy legs and 41 JIA legs remaining. The statistical analysis was performed on this subset of data.

### *3.4.2 Analysis – Demographic Information*

In addition to comparing  $H_{\alpha}$  values between healthy knees and diseased knees,  $H_{\alpha}$  was compared to the demographic information of the subjects. Because the experiment included a wide range of ages, it was important to verify that the  $H_{\alpha}$  values did not correspond to age. In addition, because the children encompassed a wide range of ages, that also meant that their height and weight encompassed a wide range. Refer back to Table 1 for reference. It was equally important to verify that  $H_{\alpha}$  values did not correspond to subject BMI. For these analyses, standard regression plots were used. The relationship between  $H_{\alpha}$  and demographics is described in detail in Section 4.3.

### 3.4.3 Analysis – Other JIA characteristics

To determine whether the  $H_\alpha$  comparison between healthy and JIA knees was the only meaningful characteristic to investigate, other JIA characteristics were looked at as well. These traits included JIA type, inactive/active JIA disease at the time of recording, the score that was given for swelling, synovial thickening, limited range of motion, tenderness, and the blood values for ESR and CRP.

The ESR and CRP values were provided to the study when they were available. The clinician provided them as ‘normal’ or ‘high’. These values were only provided when a blood test was recommended by the physician during their clinical visit. No part of the experiment that we conducted required subjects to have their blood tested.

With all the listed traits, the goal was to determine whether  $H_\alpha$  would be different depending on the specific trait. For example, one of the questions asked was: for subjects with a higher swelling score, does  $H_\alpha$  also reflect this? A similar question was asked pertaining to all the traits listed above.

## 3.5 Statistical Analysis

All statistical analysis for the  $H_\alpha$  score was performed in Python. The goal is to verify that the  $H_\alpha$  difference in JIA subjects versus healthy subjects was statistically significant. To see if a T-test was able to be performed, normality and equality of variances had to be checked. First, the data (Healthy and JIA) were checked for normality using the Shapiro-Wilk test [39]. Next, equality of variances between the two datasets using the Levene test were checked [40]. Because the Shapiro-Wilk test failed for the JIA

dataset, the Mann-Whitney non-parametric test was used to test for statistical significance [41], [42].

### 3.6 Longitudinal Subjects

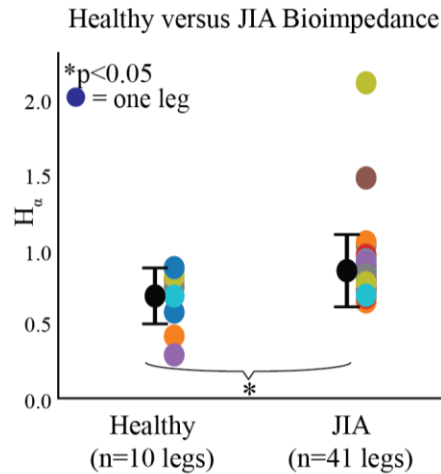
EBI measurements can also be utilized to track disease activity during treatment. Four JIA subjects had EBI recorded at least twice over the study period. For each of these visits, the same EBI protocol was collected from the subjects.  $H_\alpha$  was analyzed for each subject's active leg(s) for each visit. Because  $H_\alpha$  represents the change in extracellular fluid over the change in total fluid content, we can infer that an overall decrease in  $H_\alpha$  signifies the reduction in inflammation in the knee joint with active JIA. For a clinician, this can then help guide the direction that treatment follows.

Overall,  $H_\alpha$  was the main value used through all the analysis. The main challenge was deciphering what was important to compare to  $H_\alpha$ .

## CHAPTER 4. RESULTS

The results for this study were encouraging because a statistical difference was observed in the  $H_\alpha$  value between healthy and JIA knees. However, additional research with a larger, controlled population is necessary to maximize the signal difference and to develop a robust clinical tool. In this section, the specific results for the analyses described above will be highlighted. The main result of this work is the healthy versus JIA  $H_\alpha$  score, which is highlighted in a recent IEEE sensors conference publication submission [43].

### 4.1 Healthy versus JIA

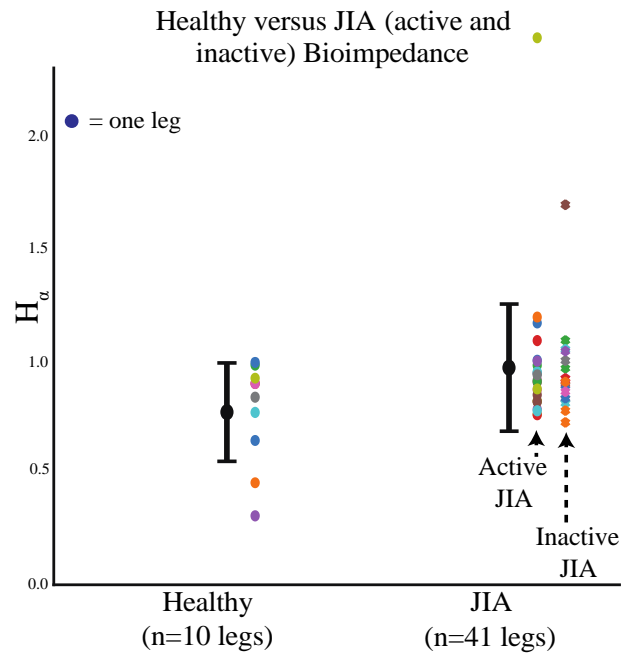


**Figure 5: Healthy versus JIA bioimpedance differences in  $H_\alpha$  indicating that  $H_\alpha$  increases for knees with JIA.**

The results for the healthy versus JIA  $H_\alpha$  bioimpedance score can be seen in Figure 5. The healthy  $H_\alpha$  average was taken on 10 legs and came out to be 0.72. The JIA  $H_\alpha$  average was taken on 41 legs and came out to be 0.91. The healthy and JIA datasets failed the requirements for testing with a T-test. The Shapiro-Wilk test was used to assess normality. The healthy group was normal, while the JIA group was not normal. The next step was to test for equality of variances. The Levene test showed that the two groups did not have an equality of variances. From that point, the Mann-Whitney test was used because the two groups were non-parametric. Using the Mann-Whitney test, the p-value between the two groups was statistically significant ( $p < 0.05$ ). Additionally, the result is not driven by the two outliers (seen in Figure 5) and those outliers were verified to be a result of a physiological condition.

#### *4.1.1 Inactive versus Active JIA*

It's worth noting that when analyzing the healthy knees versus knees with JIA, the disease status was looked at as well. The active JIA group did not differ significantly from the inactive JIA group in terms of the  $H_\alpha$  score, as shown in Figure 6. This suggests that even when JIA is considered 'inactive' in a specific joint, the overall body response to the disease produces chronic inflammation – which can be seen in the higher  $H_\alpha$  score. Therefore, when analyzing the results from the study, the inactive and active JIA groups were combined into one 'JIA' group.



**Figure 6: Results figure, with the JIA column split into active versus inactive disease. The active and inactive group did not have a statistically significant difference in their  $H_\alpha$  score and was thus combined into one ‘JIA’ group**

## 4.2 Longitudinal Subjects

The four longitudinal subjects had data collected during at least two clinical visits. The clinical diagnosis was noted for each visit as well as the  $H_\alpha$  score. Figures of the change in all four subjects are shown below. The first plot for each subject shows the change in  $H_\alpha$  from one visit to another. The second plot for each subject shows the change in  $R_{5k}$  from one visit to another. The importance in adding this plot is to show

whether the change in  $H_\alpha$  is attributed to a change in fluid in the specific leg or overall inflammation in the body

#### 4.2.1 Subject 1

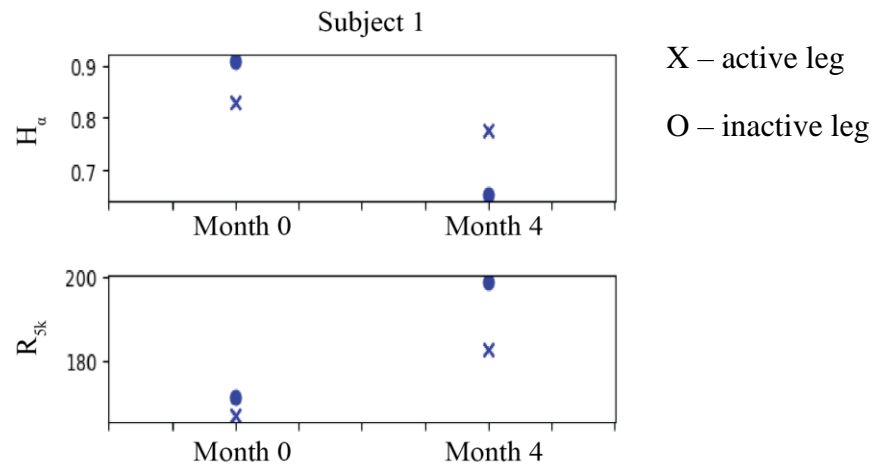
- Clinical Evaluation

- Visit 1: At this visit, the right leg had active JIA and the left leg had inactive disease. The subject had a fluid score of 1, a synovial thickening score of 1, a limited range of motion score of 1, and a tenderness score of 0 for the right leg. The left leg had scores of zero for each metric. At this visit, his CRP value was 6.6.
- Visit 2: At this visit, the right leg was still active, and the left leg was still inactive. The subject had a fluid score of 1, a synovial thickening score of 1, a limited range of motion score of 1, and a tenderness score of 1 for the right leg. The left leg still had scores of zero. At this visit, his CRP value was 0.3. Although a CRP value greater than 8 is considered out of normal range, the decrease in CRP value from visit 1 to visit 2 shows the overall decrease in inflammation in the subject's body.

-  $H_\alpha$ :

- As shown in Figure 7,  $H_\alpha$  decreased for both legs, but for the inactive decreased substantially more, which possibly means that overall inflammation is down, but affected leg is still swollen.
- The baseline bioimpedance (R5k) increased for both legs, but increased substantially more for the unaffected leg, which again confirms the decrease in CRP but still swollen on affected leg.

- When comparing the change in impedance (R5k and 100k) between visits, the unaffected leg had a 2x increase in R5k when compared to 100k, but affected leg had the same change in R5k and R100k.



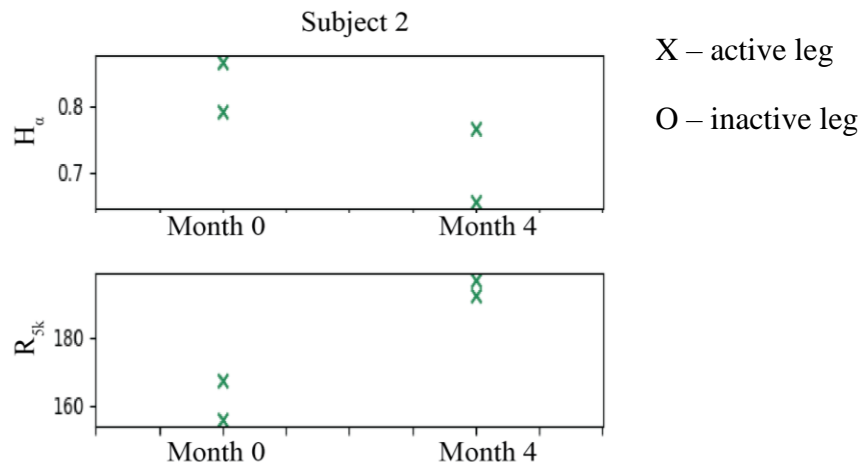
**Figure 7: Subject 1: Longitudinal subjects throughout the course of treatment. The top plot shows how  $H_{\alpha}$  changes per visit. The bottom plot shows the changes in  $R_{5k}$  per visit.**

#### 4.2.2 Subject 2

##### - Clinical Evaluation

- Visit 1: At this visit, both the right and left leg had active JIA disease. The right leg had a fluid score of 0, a synovial thickening score of 1, a limited range of motion score of 0, and a tenderness score of 1. The left leg had a fluid score of 0, a synovial thickening score of 1, a limited range of motion score of 0, and a tenderness score of 1. At this visit, the subject was prescribed medication for the first time in 6 weeks.

- Visit 2: At this visit, both the right and left leg still had active JIA disease. The right leg still had a fluid score of 0, a synovial thickening score of 1, a limited range of motion score of 0, and a tenderness score of 1. The left leg had a fluid score of 0, a synovial thickening score of 0, a limited range of motion score of 0, and a tenderness score of 1. No blood values were provided at either visit.
- $H_\alpha$ :
- As depicted in Figure 8, Both legs active, swollen and tender on first visit, but no tenderness on second visit.  $H_\alpha$  for both legs decreased equally, and baseline bioimpedance increased equally as well. The change in R5k compared to R100k between visits for both legs was higher which also indicates a reduction in overall fluid.



**Figure 8: Subject 2: Longitudinal subjects throughout the course of treatment. The top plot shows how  $H_\alpha$  changes per visit. The bottom plot shows the changes in  $R_{5k}$  per visit.**

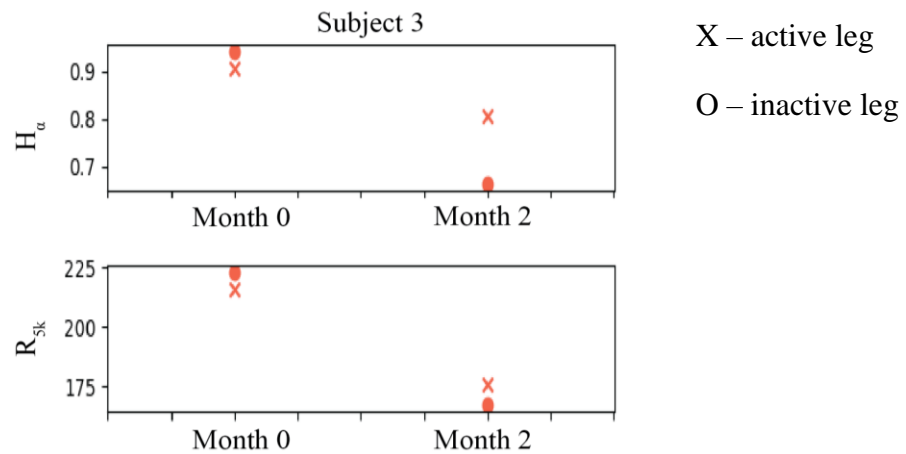
### 4.2.3 Subject 3

- Clinical Evaluation

- Visit 1: At this visit, the right leg had active JIA and the left leg was inactive. The right leg had a fluid score of 1, a synovial thickening score of 1, a limited range of motion score of 0, and a tenderness score of 0. The left leg had scores of zero for each metric.
- Visit 2: At this visit, the right leg was still considered to have active JIA with a fluid score of 1, a synovial thickening score of 1, a limited range of motion score of 0, and a tenderness score of 0. The left leg remained inactive with scores of 0. Between visit 1 and visit 2, the clinical assessment remained the same and the prescribed medication did not change.

- $H_\alpha$ :

- As displayed in Figure 9,  $H_\alpha$  was less for both legs, like the first patient: the change was bigger in unaffected leg. However, there was a substantial decrease in impedance (R5k) between both visits, but that drop was the same at both R5k and R100k, signifying that there is a change in the tissue, but not due to fluid.



**Figure 9: Subject 3: Longitudinal subjects throughout the course of treatment. The top plot shows how  $H_\alpha$  changes per visit. The bottom plot shows the changes in  $R_{5k}$  per visit.**

#### 4.2.4 Subject 4

##### - Clinical Evaluation

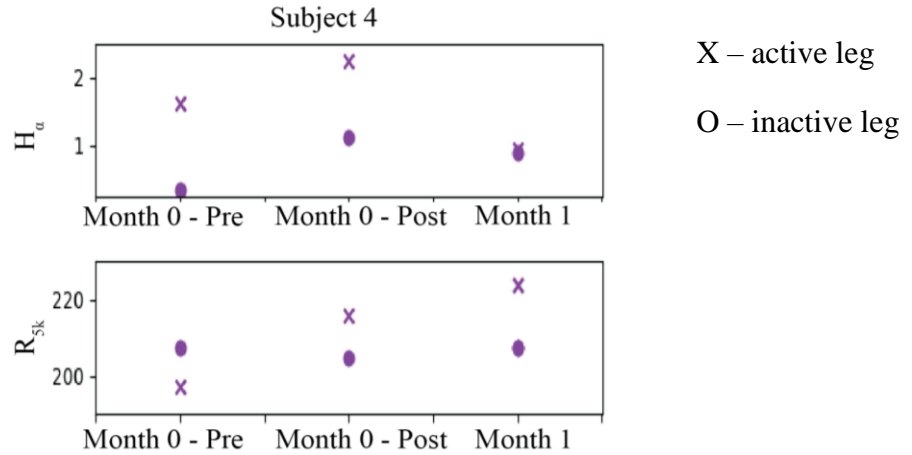
- Visit 1: At this visit, the right leg had active JIA while the left leg was inactive. The goal of the visit was to extract fluid from the subject’s right knee and inject medication. In the figure below, the ‘pre’ set of data points show the EBI measurements prior to fluid extraction. At this point in the visit, the right leg had a fluid score of 3, a synovial thickening score of 2, a limited range of motion score of 2, and a tenderness score of 2. The left leg had a score of zero for all four metrics. The clinician was able to extract 30 mL of fluid. Immediately following the fluid extraction, the right leg had a fluid score of 2, a synovial thickening score of 2, a limited

range of motion score of 2, and a tenderness score of 2. The ‘post’ set of data points show the measured EBI following the fluid extraction and steroid injection. The left leg had scores of zero for all four metrics. At this visit, the subject’s prescribed medicine was switched from Naproxen to Meloxicam.

- Visit 2: At this visit, the right leg still had active JIA while the left leg was still inactive. The right leg now had a fluid score of 0, a synovial thickening score of 1, a limited range of motion score of 0, and a tenderness score of 0. No blood values were provided for either visit.

-  $H_{\alpha}$ :

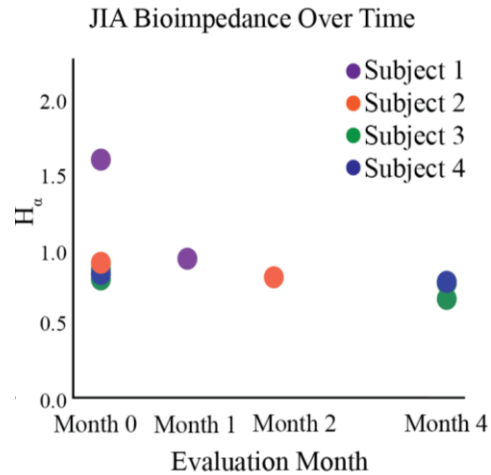
- As shown in Figure 10, R5k for the unaffected leg had no change at all from all measurements (<2 ohms). The affected leg’s R5k increased by more than 20 ohms due to aspiration and another 10 ohms on follow up. This increase in R5k was expected as with less fluid in the knee, the impedance is higher as there is less extracellular fluid content for the signal to flow through.  $H_{\alpha}$  decreased from the first recording to the follow-up, signifying a reduction in overall fluid.



**Figure 10: Subject 4: Longitudinal subjects throughout the course of treatment. The top plot shows how  $H_\alpha$  changes per visit. The bottom plot shows the changes in  $R_{5k}$  per visit.**

#### 4.2.5 Combined Results

Overall, we would expect the  $H_\alpha$  value to decrease each time we measure the subject's EBI. The reason for this is that as their treatment progresses, we would theoretically see less edema and fluid in the knee. With less fluid and swelling, the  $\Delta R_{5kHz}$  value would decrease, yielding a smaller  $H_\alpha$  as a result. As shown in Figure 11, on average, all four subjects'  $H_\alpha$  decreased throughout treatment. This provides the clinicians with insight on the progression of the subject's JIA.

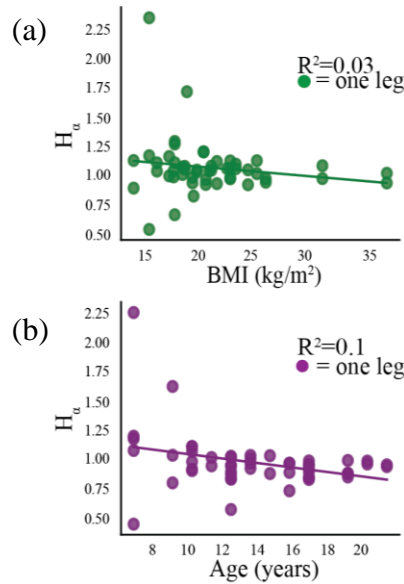


**Figure 11: Changes in  $H_\alpha$  during disease for four subjects. Each subject was recorded at their clinical exam. Decreases in  $H_\alpha$  signify positive changes in disease status.**

### 4.3 Other Characteristics

In addition to the main healthy versus JIA  $H_\alpha$  result, other characteristics were analyzed and are able to strengthen the result shown in Figure 5. As described in the analysis section, demographic information and other clinical information were analyzed and compared to  $H_\alpha$  to determine if any other information was correlated to  $H_\alpha$ .

### 4.3.1 Demographic Information



**Figure 12: Regression Plots. (a)  $H_\alpha$  in relation to BMI. (b)  $H_\alpha$  in relation to age.**

Figure 12 strengthens the results shown in Figure 5 by showing how the  $H_\alpha$  score is not driven by subject age or BMI. All  $R^2$  values do not imply significance between  $H_\alpha$  and the dependent variables of age and BMI. This shows that we can have confidence that  $H_\alpha$  is depicting physiological joint health measures and is not strongly dependent on demographics.

### 4.3.2 Other JIA Characteristics

For the other JIA characteristics, the goal was to determine whether the specific clinical scores would be able to decipher the active from the inactive JIA group when

comparing their  $H_\alpha$  score. Splitting the JIA group into high fluid scores, high synovial thickening scores, high limited range of motion scores, and high tenderness scores and then comparing it to the inactive JIA group did not show any separation.

Following the testing of clinical scores (active and inactive knees) versus  $H_\alpha$ , the next JIA characteristic to be tested was blood value. The active JIA group was split by high CRP or ESR value and compared to the inactive JIA group. Once again this showed no separation from the inactive group. Because none of the clinical markers showed any difference between active and inactive JIA groups, the decision to keep inactive and active JIA together as one group remained.

#### **4.4 Discussion**

First, the result between healthy controls and JIA subjects is positive and has much room to extend upon. It is encouraging that recording a subject's legs for a data collection session of approximately 5 minutes can produce positive results. The EBI technique provides the potential opportunity for a true addition to clinical practices. If an extra 5 minutes can provide insight to clinicians on disease status of their subjects, that is an invaluable complement to existing practices. Additionally, combining the results of Figures 5 and 12, could provide clinicians with a baseline  $H_\alpha$  value for their subjects and then the longitudinal values could be measured at each follow-up visit. Based on the results for this study, the follow-up recordings would give the clinician a good indication of whether the medication or treatment method of choice is working as expected. For example, as seen in Figure 11, all four subjects had lower  $H_\alpha$  scores for their active leg during the follow-up visit when compared to the  $H_\alpha$  score for the first visit. This could

signify to the clinician that the current method of treatment is working effectively. On the opposing side, if there is a significant increase in  $H_{\alpha}$  during a follow-up recording, this could signify a regression in disease status or indicate that the current treatment plan is not working as expected.

The time between recordings for the longitudinal subjects must be brought up as well. As seen in Figure 11, the four subjects were recorded at their next follow-up visit; however, those clinical visits were spread out across different time periods. This time between initial recording and follow-up recording for this study was set by the clinician and when they requested to see the subject again. For future studies, it would be worthwhile to have set time durations between the recordings to limit the variables.

One trait that was not looked at during this time was how long each subject had JIA – whether they still had active disease or were in remission. Inactive versus active disease status was investigated greatly; but within each group, how long each subject had JIA would have been interesting to investigate as well. For example, does JIA remission time impact the overall body inflammation? Perhaps as the subject is in remission longer, the overall whole-body response to JIA is less, which would cause the  $H_{\alpha}$  score to appear closer to a healthy control.

With regards to the healthy controls, the inclusion criteria for each subject were that they were aged between 5-21 and had no previous major knee injuries or JIA diagnosis. The activity levels of each subject were not brought into question. One reason why this may be important is because if someone is highly active in high-impact sports, they might have extra inflammation in their knee joint from extensive contact. This extra

inflammation may cause the  $H_\alpha$  score to appear closer to a JIA score. Our lab has done work on classifying exercise-induced fatigue with bioimpedance, and it has been found that fatigue and inflammation from sports does impact the resulting EBI [38]. By separating each healthy subject by activity level and also separating each JIA subject by disease length, there may have been a possibility to further the separation shown in Figure 5.

Another point worth discussing is the large age range of the subjects. Because the study was in the pediatric population, inclusion criteria for the study included children aged from 5 to 21. The subjects on the younger side of that range were overall much smaller (height and weight) than the older children. This posed the question of whether the results were directly related to the size of the subject and not necessarily due to the physiological markers of their knee. Figure 12 was important in showing that age and BMI were not driving the results between the healthy subjects and the subjects with JIA. To build upon this, within the JIA group, it was important to see that the  $H_\alpha$  JIA result was a product of JIA and not necessarily active JIA. To verify this, the inactive group was split from the active group on the JIA side. As shown in Figure 6, there is no statistical significance in the difference between the two groups, signifying that the  $H_\alpha$  result that is shown in Figure 5 is a result of the physiological damage done to the knee joint as a result of having JIA.

Even though there is statistical significance between the healthy group and the JIA group, there is an overlap that is seen in Figure 5. With a larger number of subjects, the reason for this overlap would become clearer, but there are currently some hypotheses as to why this overlap is occurring. First, the JIA group is made up of subjects who are

experiencing a wide variety of symptoms along with their JIA. Some of the JIA subjects are experiencing few to zero symptoms and are considered to have ‘inactive’ disease. These subjects cannot be grouped with the healthy subjects though because their clinical diagnosis still says JIA. Furthermore, the activity levels of both groups of subjects were not considered when recruiting subjects. Some of the healthy subjects participate in various activities, which could increase their joint inflammation level inadvertently [38]. With a greater number of subjects, we would hope to see the overlap become less noticeable.

The most challenging part of this entire study is the fact that each subject is an independent human, with JIA affecting them each in a unique way; and because of that, each clinical exam is subjective. In the clinical sense, this means that every time a subject has an exam with a physician, the physician conducts a thorough exam of every joint, inquires about the patient’s pain and tenderness levels, recent activity levels, and overall, how they are feeling and then at the conclusion of the exam provides the study with the fluid, synovial thickening, tenderness, and limited range of motion scores for each leg. There is currently no objective measure of quantifying JIA disease status, aside from a clinical exam so the values scored by the clinician are taken as gold standard. The subjectivity in the study and the scores that were received for each subject come from the fact that multiple clinicians at CAP are conducting these exams. Each clinician may have a slightly different approach which can yield slightly different scores depending on who the clinician is that gave the exam. In the appendix, I provide an example of the form given to the clinician – notice the specific spaces for each clinician to fill out the fluid, synovial thickening, limited range of motion, and tenderness scores. Because of this, the

best metric and the main one used in this study was whether the subject had JIA or was considered a healthy control. For this study, even if the subject did not have active JIA in the knees, they were excluded from being a healthy control due to the fact that at one point they had a JIA diagnosis.

## CHAPTER 5. CONCLUSION AND FUTURE WORK

### 5.1 Conclusion

Overall, this study demonstrated the capability of bioimpedance in the realm of JIA for the first time. Before this study, the only work that used bioimpedance on subjects with JIA was in assessing the nutritional status of the children [44], [45]. As a result of this study, there is an opportunity to use bioimpedance in understanding physiological parameters of children with JIA. Additionally, there is now a great possibility for future work to expand upon this study and be able to provide patients suffering with JIA and clinicians a much more streamlined method to understand disease status and treatment effectiveness.

#### 5.1.1 Resulting Dataset

The resulting dataset from this study contains EBI recordings from 23 subjects with JIA and 8 healthy controls. The dataset also has 4/23 subjects with more than one EBI recording. This dataset can be utilized in the future for further investigations on longitudinal effects of treatment and JIA status. With a greater number of subjects with  $n>1$  recordings, more concrete results could be made regarding how EBI provides insight into treatment status.

Additionally, expanding the number of subjects in the dataset can allow researchers to investigate how EBI relates to more traits of JIA. Currently, with the 23 JIA subjects in the dataset, not many of them have high fluid scores or high synovial thickening scores. Specifically obtaining data from the subjects with higher fluid scores or higher synovial

thickening scores could provide insight into how fluid and synovial thickening impacts EBI. Furthermore, obtaining more data from these specific subjects can provide insight on how the electrical current travels through fluid as opposed to synovial thickening and can hopefully guide physicians on assigning subjects accurate scores on future clinical examinations.

## **5.2 Limitations**

While the results from this study are positive, it is important to make note of the limitations. With regards to the healthy versus JIA  $H_{\alpha}$  results, the main limitation is the smaller dataset for the healthy subjects. Future work can expand upon these results by recruiting a larger number of healthy age-matched controls. Second, regarding the longitudinal result, a limitation is also the  $n=4$  sample size. Recruiting subjects for multiple visits is difficult is limited by the appointments scheduled and should be addressed for future work. Additionally, the inconsistency in follow-up time should be addressed for future work. Ideally, follow-up recordings should occur at standardized times.

The biggest limitation in this study is the fact that each subject has had their own individualized experience with JIA. Because of this, there is no standardized approach to treatment options, medications and follow-up visits. For the purpose of recording data, this individualized experience adds significant variability to the study. Each subject has their own swelling and pain experience and throughout the course of their active JIA disease, the medication and treatment could vary greatly. Another variable that was not considered during this study was the duration of which the subject has had JIA. For some

subjects in the dataset, EBI was recorded at the initial JIA diagnosis. For other subjects, they had been diagnosed at age two and been undergoing treatment for JIA for years. In addition, the wide range of ages and BMIs in the study adds variables to the data. Future work would include recruiting enough subjects with similar JIA status in order to be able to accurately classify the data.

### **5.3 Related and Future Work**

As briefly mentioned above, one of the main limitations of the EBI work was the small sample size of the healthy control group and additionally the small sample size of the longitudinal measurement group. Future work for the EBI study would include collecting more data from healthy controls. Also, collecting more data from children with JIA who visit the clinic more than once would be useful. From there, collecting data from children with a wide variety of JIA diagnoses is important to understanding the capabilities of the EBI measuring system. For example, can EBI detect whether the pain in a subject's knee is caused by synovial thickening or excess fluid? It is necessary to collect data from multiple subjects with the same fluid, synovial thickening, tenderness, and limited range of motion scores in order to provide concrete results. Future work should focus on this aspect of the data collection.

Future work could also incorporate MRI and US results and correlate those with EBI. Leveraging MRI and US results could help researchers better understand the EBI results, which could then add to the capability of EBI. Of course, the limitation here is that conducting MRI and US on subjects is an additional cost; however, if those

examinations are already required for the subject's disease, utilizing the information to correlate with EBI would provide increased benefits.

The work in this thesis focused on gathering data on knees of children with JIA and healthy controls. However, this work can be extended to other joints. Other work in the lab focused on recording acoustic signals from the knee joint and comparing those signals from healthy controls and subjects with JIA [46], [47]. Despite the knee being the most common joint affected in JIA, there are opportunities to gather data on other joints to further aid in helping children with JIA. I had the opportunity to begin working on monitoring the sacroiliac joint and the Achilles tendon as described in the next two sections.

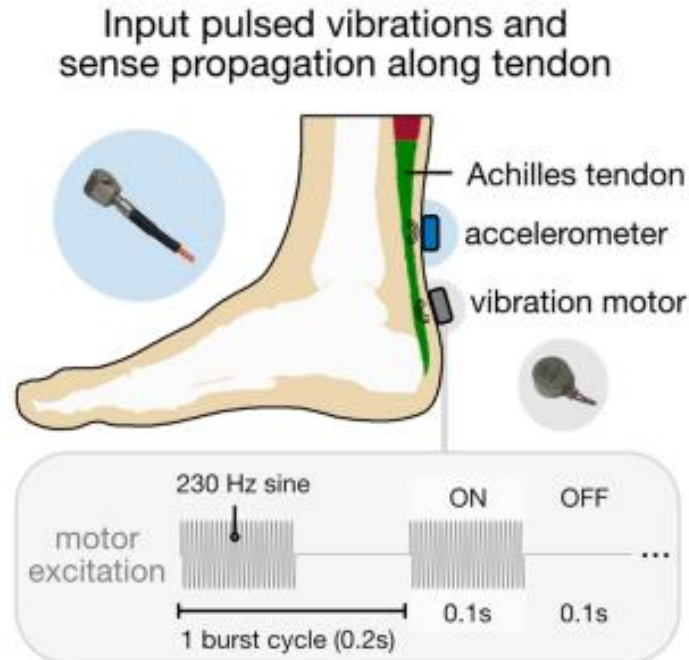
### *5.3.1 Active Sensing of Achilles Tendon*

Another commonly affected body part of children with Enthesitis-Related Arthritis is the Achilles tendon [48]. In a similar sense of recording EBI and passive acoustics from the knee, recording active acoustics from the Achilles tendon was also performed. The goal of recording active acoustics was along the same lines as the other joints: does an Achilles tendon with ERA behave differently than an Achilles tendon from a healthy subject?

Recording active acoustic signals is slightly different than the passive acoustic signals that were recorded from the SIJ. Recording active acoustic signals entails sending an active vibration signal through the tendon and then passively recording the response with a small contact accelerometer [49], [50]. It has been shown that the response recorded from the Achilles tendon can be used to non-invasively measure muscle-tendon

loading capabilities [51]. Because ERA can cause thickening of the tendon, it was predicted that the response from a tendon with ERA would behave differently than a healthy tendon [52].

The experimental protocol was designed based on the work previously done in the Inan Research Lab. Based on *Bolus et al.*, tendon loading was assessed using a vibration motor and an accelerometer placed approximately 2 cm apart from each other on the skin. The sensors were placed superficial to the Achilles tendon along the middle of the tendon. The linear resonance actuator (LRA) motor was placed distal to the accelerometer, as shown in Figure 13. Both the motor and the accelerometer were attached to the skin using a double-sided adhesive pad (23-mm Stickie, Rycote, Gloucestershire, UK) and Medipore tape (3M, Minnesota). The LRA (G0832012, Jinlong Manufacturing, China), was driven by a 3V AC voltage at its resonance frequency of 230 Hz. The 230 Hz sine wave was multiplied with a 5 Hz square wave to produce continuous burst vibrations. The burst vibrations were important as the “on-off” behavior of the burst changed characteristically with Achilles tension [49]. The response to the burst vibrations were measured with the same Dytran accelerometer used to passively measure the sacroiliac joint (SIJ). Previous work in the Inan Research Lab collected Achilles tendon data using a benchtop system with a function generator. For this project, all data acquisition, including the output of the burst vibrations and the input of the Dytran accelerometer was connected to a data acquisition unit (USB-4432, National Instruments, Austin, TX, USA). The data acquisition unit was connected to a laptop collecting the data via MATLAB and the acquisition of accelerometer data was sampled at 10 kHz.

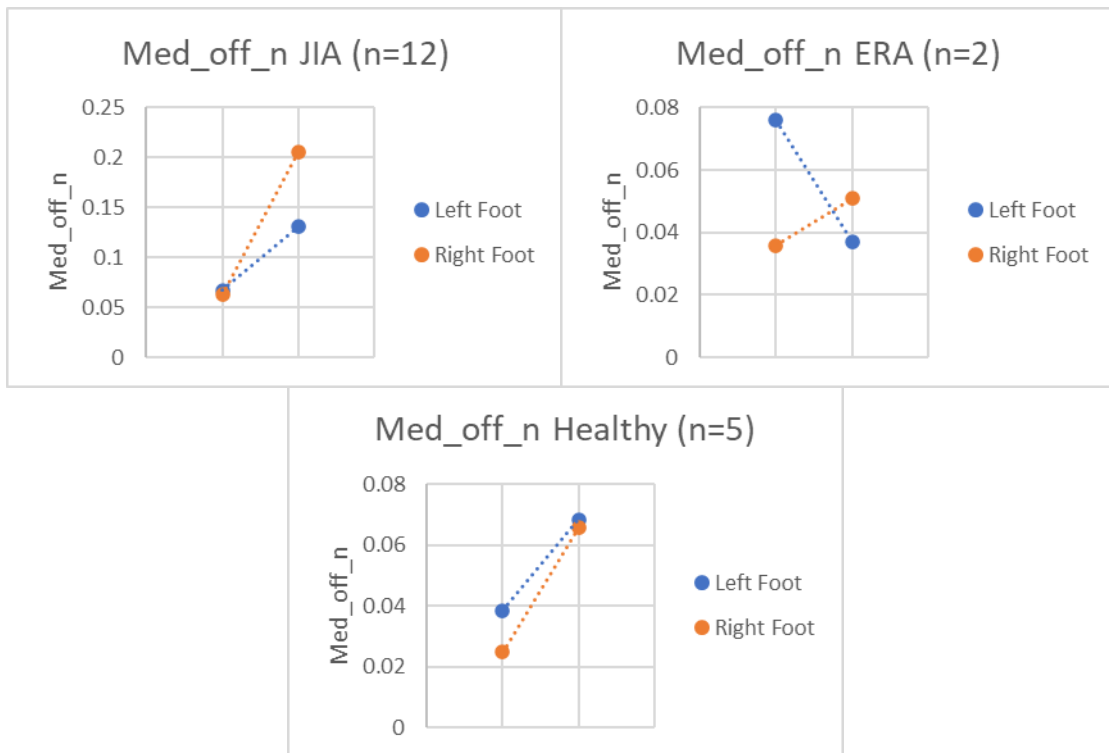


**Figure 13: Image detailing the placement of the motor and accelerometer in relation to the Achilles tendon [49].**

For this part of the project, data from five healthy subjects, 12 subjects with general JIA, and two subjects with the ERA sub-type of JIA were collected. Based on the prior work completed in the Inan Research Lab, I collected data from these subjects in four postures: sitting, standing flat on two feet, standing tip-toe on two feet, and calf raises [49]. The active signal output to the LRA was the same signal as described in the previous paragraph.

Following data collection, I wrote a script to compute the main feature described in *Bolus et al.*'s work, *med\_off\_n*. This feature, *med\_off\_n*, is defined as the median value of the “off” portion of the burst envelope normalized to the burst window's maximum amplitude [49]. This feature emphasizes the changes in the falling edge of the burst

signal, which is representative of physical changes in the state of the Achilles tendon. Figure 14 shows the *med\_off\_n* value for the three population groups. Although the ERA graph appears to have a different trend, this may solely be dependent on the specific subjects that data were collected from. The two ERA subjects had active JIA, but neither had active swelling, pain, or tenderness in their Achilles. Future work would include



**Figure 14: *Med\_off\_n* feature for the JIA group, the ERA group, and the healthy group.**

collecting data from subjects who currently had active disease in their Achilles.

Although I collected some data for this part of the project, much more data must be collected from all 3 populations (healthy, JIA, ERA sub-type of JIA). The *med\_off\_n* value currently does not show much difference between the 3 groups – which could be a

result of the small subset of data or the specific subjects that have been recruited. Collecting more data would clarify the impact of the *med\_off\_n* value. Following data collection, designing a fully wearable system would benefit the project, as the data acquisition unit was cumbersome and was not an efficient method of data collection. Having a fully wearable system would allow the process to be streamlined and allow for multiple joints to be recorded in one session. Currently with the set-up of the data acquisition unit and wire system, set-up, collection, and take-down take too much time to the point where recording other joints (SIJ, knee, etc.) is not practical. Streamlining this system would allow more time for other recordings to take place. Lastly, extracting other features, aside from *med\_off\_n*, could provide more impact than *med\_off\_n* and should be explored.

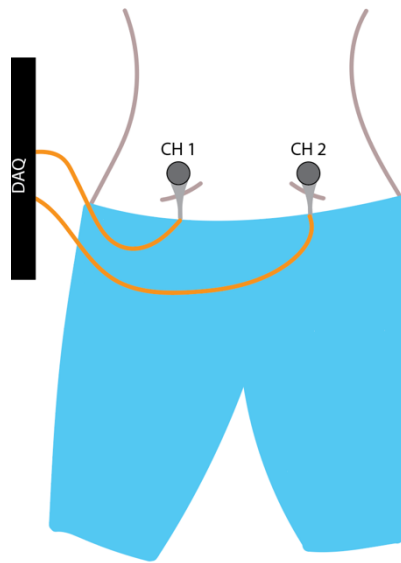
### 5.3.2 *Passive Sensing of Sacroiliac Joint*

The sacroiliac joint (SIJ) is a commonly affected joint for children with enthesitis-related arthritis (ERA) [53]. In a similar way that the bioimpedance sensing was able to differentiate between a healthy knee and a knee with JIA, part of the project I worked on involved sensing acoustic signals from the SIJ.

Passive acoustics were recorded from the SIJ during the same data collection session as the bioimpedance. Two uniaxial accelerometers (Series 3225F7, Dytran Instruments Inc., CA, USA) were attached to the two back dimples located at the bottom of the spine by double-sided sticky pads (Series 65530, Rycote Microphone Windshields Ltd, Stroud, Gloucester, GL5-IRN, UK) to collect the joint acoustic emissions as they acted as microphones for this study. The joint vibrations were sampled at 100 kHz via a

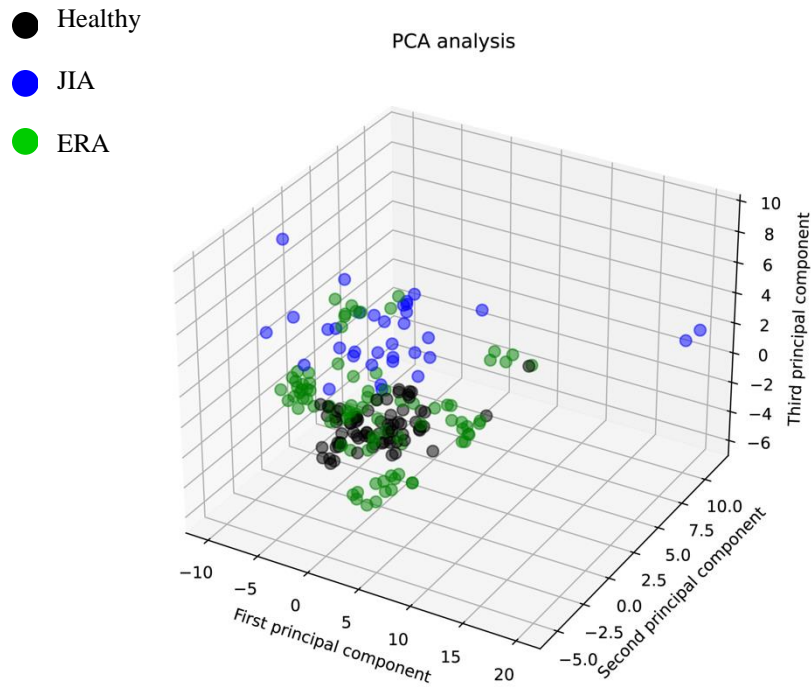
data acquisition system (USB-4432, National Instruments, TX, USA) and analyzed using MATLAB (MathWorks, Natick, MA, USA) and Python laptop software [54].

The experimental efforts included selecting the appropriate sensing location (shown in Fig. 15), collecting data from children, and initial data analysis using Python. In total, data were collected from five children with the ERA sub-type of JIA, two children with generic JIA, and four healthy children. Data analysis involved extracting the flexion-extension cycles from the data segment and extracting features for each cycle. All cycles were averaged to yield one large feature matrix per subject. The feature extraction work was done in MATLAB and then the feature matrices were moved to Python for analysis. I ran a Principal Component Analysis (PCA) on the feature matrices to determine if there was separation between the three classes – healthy, JIA without ERA, and JIA with ERA. Fig. 16 shows the PCA result from python. PCA is generally useful in showing whether separation occurs in the features of the groups that are being input to the analysis. In this case, the three groups being input were: healthy subjects, subject with JIA that did not have ERA, and subjects with JIA that had ERA. Figure 16 shows the results from running a PCA – with black being the healthy subjects, blue being JIA (no ERA), and green being JIA (with ERA). As seen in the figure, there is not a wide range of separation. Some reasons for this could be a lack of meaningful features or because of the small sample size.



**Figure 15: Image detailing the placement of Dytran accelerometers on the subject's back dimples. Each individual accelerometer was placed on one of the back dimples using a double-sided Rycote sticker. The accelerometers were connected to a National Instruments Data Acquisition Unit.**

These initial evaluations were supported by the Terwilliger Foundation. Future work in this project involves collecting much more data on children with different types of JIA and healthy controls. With more data, building and running classifiers will be a useful next step in determining if the acoustic signature that comes from the SIJ of someone with JIA and ERA versus the SIJ of a healthy control is significantly different. In addition, the feature extraction code that I was running, used the same features that were extracted from the knee acoustic data. Future work may also involve selecting the most appropriate features for the SJI and perhaps adding other features that show more value.



**Figure 16: PCA for the Sacroiliac Joint. The three groups involved in the analysis are: healthy, JIA (no ERA), and JIA (with ERA). Most of the separation can be seen separating the JIA subjects from the other two groups. Future work would expand upon appropriate feature selection.**

#### 5.4 Closing Remarks

In this work, we present a method for discriminating between knees with JIA and healthy knees. To the best of our knowledge, this is the first time EBI data has been collected and analyzed on knees of children with JIA to discern physiological properties of the knee joint. We believe that this work can be used as a foundation for additional evaluations in JIA diagnosis using wearable technology. As a future clinical tool, EBI has the potential to evaluate disease, monitor treatment effectiveness and reduce patient suffering.

# APPENDIX

Example clinical form that is given to clinicians for every subject:

Subject Seen for **JAMS** Study:  Baseline  Follow-Up

## Clinical Presentation via MD Exam



**On Exam Today.....**

FORM TO BE FILLED OUT BY **TREATING PHYSICIAN**

**1.)** Does the patient have clinically active JIA disease?

YES  NO  N/A-not JIA

**2.) Please classify JIA as one of the following:**

- New JIA** (dx'd within 6 months)
- Established JIA** (7 months to 5 yrs)
- Chronic JIA** (dx'd for over 5 yrs)
- Inflammatory Arthritis (not JIA)**

Other Condition: \_\_\_\_\_

**3.) JIA Subtype for my pt is:**  N/A, not JIA  sJIA (1)  PolyRFpos (2)

PolyRFneg (3)  OligP (4)  ERA (5)  PsorJIA (6)  UndiffJIA (7)  OligE (8)

**4.) Knee Exam today:**

	RIGHT	LEFT
Fluid	0 / F1 / F2 / F3	0 / F1 / F2 / F3
Synovial Thickening	0 / S1 / S2 / S3	0 / S1 / S2 / S3
Tenderness	0 / T1 / T2 / T3	0 / T1 / T2 / T3
Limitation	0 / L1 / L2 / L3	0 / L1 / L2 / L3

N/A, neither knee affected.

**5.) SIJ Exam today:**

	RIGHT	LEFT
Tender	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
	PERFORMED	RESULT
Schober	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____

**6.) Achilles Exam today:**

	RIGHT	LEFT
Tender	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No



**7.) PGA:**

MD Global Assessment of Disease										
0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
mild			moderate				severe			

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