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Detection of Parkinson Disease Rest Tremor

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A Thesis on the

Detection of Parkinson Disease Rest Tremor

by

Matthew Jonathan Johnson

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I would like to dedicate my thesis to those unfortunately afflicted with Parkinson's Disease, my heart goes out to you and your loved ones.

Matthew Jonathan Johnson

Washington University in St. Louis
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ABSTRACT OF THE THESIS

A Thesis on the Detection of Parkinson Disease Rest Tremor

by

Matthew Jonathan Johnson

Master of Science in Electrical Engineering

Washington University in St. Louis, 2014

Research Advisor: Dr. Arye Nehorai, Department Chair

Parkinson Disease (PD) is a debilitating and progressive movement disorder that is estimated to affect over six million worldwide. One of the most characteristic symptoms of PD is resting tremor, which involves unintentional and rhythmic muscle oscillations of an afflicted extremity while the muscles of said extremity are relaxed. This study involved measuring the rest tremor of 10 PD subjects, 10 Essential Tremor subjects, and 10 healthy control subjects using two devices. One device was an FDA approved accelerometry system to measure human tremor known as the Tremorometer™ and the other was a consumer three-dimensional camera known as the Leap Motion™ Controller. The study compares tremor characteristics calculated from both devices to compare the Leap Motion Controller to the Tremorometer System. The tremor characteristics obtained from the Leap Motion Controller were also used in an attempt to classify the subjects used in the study as either PD or non-PD subjects.

Chapter 1

Introduction

1.1 Purpose

Parkinson Disease (PD) is a debilitating and progressive movement disorder that affects over one million people in the United States alone. One of the most characteristic symptoms of PD is resting tremor, as it has been shown that the proportion of patients with resting tremor ranged from 69-100% in 3 series of patients with autopsy-proven PD.[1,2,3] Several methods currently exist to quantitatively measure tremor including accelerometry, electromyography, the spirogram, and most recently three-dimensional cameras.[4]

This study involves measuring the rest tremor of 30 human subjects, consisting of 10 Parkinson's subjects, 10 Essential Tremor subjects, and 10 healthy control subjects to classify test subjects as either Parkinson or non-Parkinson. The rest tremor was measured by recording the three-dimensional position and acceleration of their index finger while at rest over a set period of time using two devices. The first device, the Tremorometer™, has 510k clearance by the FDA to measure and quantify tremor by measuring acceleration in human patients. The second device, the Leap Motion™ Controller, is a three-dimensional camera that uses two CCD (Charged Coupled Device) cameras, three infrared Light Emitting Diodes (LEDs), and preprocessing in order to obtain position data.

The study was split into two sections. The first section, involves comparing the Leap Motion Controller to the Tremorometer by calculating different tremor characteristics and comparing them to determine if the two devices are statistically

similar. The second part of the study involves using those same characteristics in an attempt to classify subjects as either Parkinson or non-Parkinson subjects.

1.2 Motivation

Advances in three-dimensional cameras have allowed for more accurate recordings and can now be used to provide much more accurate measurements in microdisplacements of upper extremities that are involved in movements such as resting tremor. The Leap Motion Controller produced by Leap Motion, Inc., has been shown to be capable of measuring changes in position of 0.2 mm for static setup and 1.2 mm for a dynamic setup.[5] The Leap Motion Controller requires no external sensors or markers to be attached to the body unlike accelerometry, electromyography, and the spirogram. One possible disadvantage of having sensors attached to the body is that for every gram of additional mass a sensor adds, the peak frequency of finger tremor decreases by approximately 0.85 Hz and can also have an affect the amplitude of acceleration.[6] Therefore the attached sensors may change the characteristics of the tremor and thus could alter the interpretation of tremor. Attaching sensors to the body can also be inconvenient, uncomfortable, and provide a margin of error if not done correctly. Another advantage of the Leap Motion Controller over accelerometry is that it does not require calibration, eliminating possible errors caused by consistent recalibration. Unlike electromyography, the Leap Motion Controller is not affected by interference from electrical sources, mechanical artifacts, stimulus artifacts, and the electrical activity of muscles that are not of interest. It is for these reasons that the Leap Motion Controller is of interest and may be a superior method for measuring tremor.

Chapter 2

Background

2.1 Parkinson Disease

2.1.1 Prevalence

According to the National Institute of Neurological Disorders and Stroke, at least 500,000 people suffer from Parkinson Disease (PD) in the United States with about 50,000 new cases reported annually.[7] With more than 22,000 lives lost to PD in 2010, it was claimed to be the 14th leading cause of death in the United States by the United States Centers for Disease Control and Prevention (CDC).[8] As can be seen in Figure 2.1, the age-adjusted death rate for PD has steadily increased since 1958.

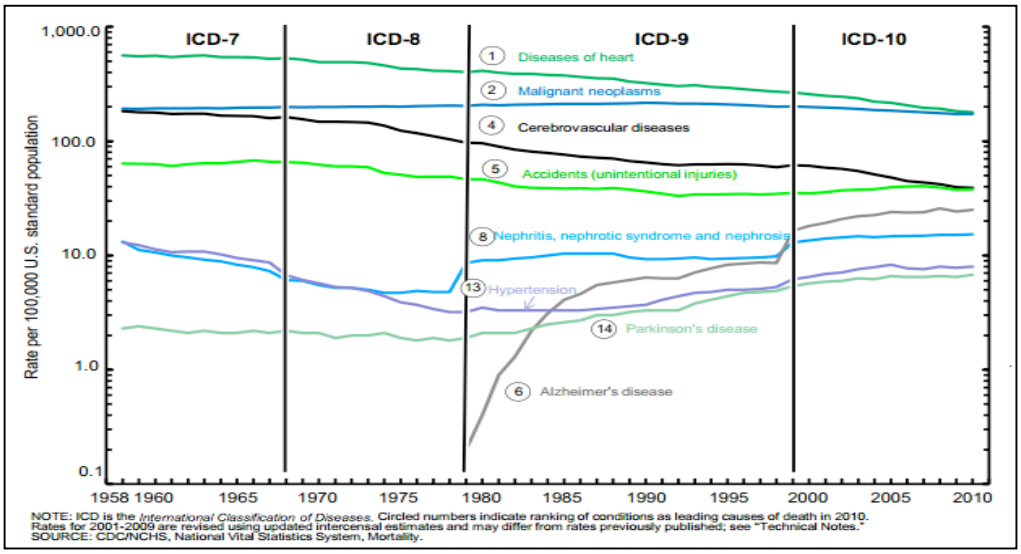

Figure 2.1 Age-adjusted death rates for selected leading causes of death in the United States between 1958 and 2010. Figure obtained from the CDC.[8]

In fact, it has been projected that the estimate of people with Parkinson's (PwPs) in 2005 is expected to double by 2030 in the world's ten most populous nations as shown in Figure 2.2.[9]

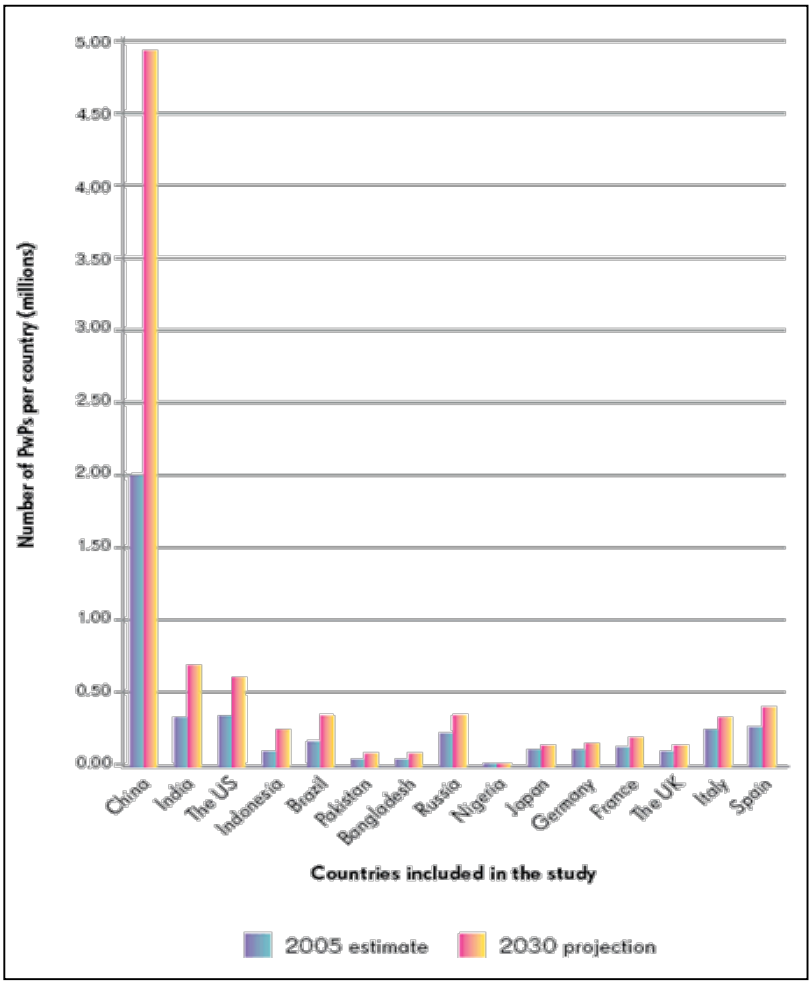

Figure 2.2 Projected number of People with Parkinson disease (PwP) in the most populous nations between 2005 and 2030. Figure obtained from Dorsey, et al (2007).

2.1.2 Symptoms

Although symptoms can vary significantly between individuals, the primary motor symptoms involved with Parkinson Disease include: rigidity, postural instability, bradykinesia and tremor.[10]

Bradykinesia Bradykinesia refers to slowness of movement and initially manifests as slowness in performing activities associated with daily living, slow movement, and reaction times.[10,11,12] Similar to other parkinsonian symptoms, bradykinesia is dependent on the emotional state of the patient and is the Parkinson characteristic that correlates best with the degree of dopamine deficiency.[10,13]

Rigidity Rigidity is described as an increase in resistance while passively stretching a muscle, causing a feeling of stiffness.[14] Rigidity is sometimes accompanied by the "cogwheel" phenomenon, which is the periodic interruption of rigidity on passive movement of the limbs.[15] Rigidity of the neck and trunk eventually leads to changes in posture and postural deformities.

Postural Instability Postural instability usually occurs during the late stages of PD and typically after the onset of the other motor symptoms.[10] It is the most common cause of falls and the late onset of falls can differentiate PD from other neurodegenerative disorders like progressive supranuclear palsy (PSP) and multiple system atrophy (MSA). [10,16]

Tremor Tremor is defined as an involuntary rhythmic oscillation of a body part. The characteristic tremor of PD, is usually a 3-6 Hz distal resting tremor, but patients with PD may also exhibit postural and kinetic tremors.[17-19] Rest tremor occurs when a body part is at rest or relaxed while postural tremor occurs when a body part is maintained at a position against gravity, and kinetic tremor occurs during the movement of a body part. Rest tremor is such a characteristic feature of Parkinson's that it has been shown that the proportion of patients with resting tremor ranged from 69-100% in three series of autopsy proven PD.[1,2,3] In fact, rest tremor is the most common and most recognizable symptom of PD, and is, by itself, a positive diagnostic criterion for PD.[10,20]

2.2 Tremor Analysis

New technologies and methods that complement the clinical neurologic evaluation are becoming more popular and useful by offering objective and quantitative data that can be analyzed. In fact, difficult medical diagnoses can even be confirmed or excluded on the basis of these additional tests. Since tremor is one of the most cardinal symptoms of PD, tremor analysis has become one of the most useful of these new methods to help differentiate tremor associated with PD from other types of tremor.[21]

Tremor analysis refers to the method of recording certain identifiable characteristics of tremor and other involuntary movements through the use of computers and other hardware. Since tremors are quasi-sinusoidal movements, they can be approached using a quantitative mathematical analysis.[21] Two of the most important characteristics of tremor in tremor analysis, are the frequency and amplitude. Tremor frequency refers to the number of oscillations per second and is usually measured in cycles per second (Hz), while tremor amplitude refers to the degree of linear or angular displacement of the limb and is typically measured in degrees or millimeters. Tremor analysis is most useful when the clinical signs are subtle, such as distinguishing between Parkinsonian tremor and essential tremor.[22]

2.2.1 Commonly Used Methods

Accelerometry Accelerometry is accomplished through the use of accelerometers that measure static or dynamic acceleration forces. Miniature accelerometers can be attached to the afflicted body part, which are typically the limbs, and usually do not interfere with voluntary or involuntary movements. Mathematical integration is needed to determine the displacement of the oscillating body part and to better perceive the sinusoidal motion of the tremor.[21]

Electromyography In electromyography (EMG), typically surface electrodes are fixed on the flexor and extensor muscles of the limb to measure the electrical

activity produced by the muscles involved in the generation of the tremor. However, EMG activity can also be measured using needle or wire electrodes.[23] The EMG signal should be processed by rectification and integration or smoothing to properly place its frequency profile into the tremor range.[24]

Spirogram Spirograms are less common than the other methods, but are performed by analyzing a drawing made by the patient of models of Archimedes' spirals. This method is based on essentially "unraveling" the two-dimensional drawn spiral to determine kinematic data. This kinematic data is collected in the X, Y, and pressure axes, which essentially provides a virtual tri-axial recording of data. By analyzing multiple trials together, tremor characteristics such as frequency, direction, and amplitude can be detected and quantified.

Optical Systems Optical systems consist of a light source and an optical sensor. Some examples of laser-based systems are displacement lasers and velocity transducing lasers and have been previously used to record kinematic data associated with tremor in PD.[25,26] Other optical systems include vision systems and essentially involve a sensor and an emitter, such as infrared cameras, which are used in many commercial motion capture systems.[27,28] These vision systems can be used to measure and record the three-dimensional position of the body part exhibiting tremor with respect to time and can then be used to calculate velocity, acceleration, and other characteristic parameters.

2.2.2 Tremorometer

The Tremorometer is an accelerometer-based system produced by FlexAble Systems, Inc. that has received FDA 510 (k) approval to measure and quantify tremor in human patients. The system consists of two major components: the TremorScope and the TremorLab.

TremorScope® The TremorScope, shown in Figure 2.3, consists of a tri-axial accelerometer integrated circuit that can measure precise changes in acceleration in three dimensions as well as a microcontroller that provides the precision timing necessary to take the measurements. These components are housed in a 15x20x9 mm plastic case, weighing approximately 4 grams, and interface to any PC via a permanently attached USB cable. The triaxial accelerometer can measure 5 milli-g resolution, however it is recommended that the selectable measurement range of ± 2g at 3 milli-g resolution is best for most tremors. The TremorScope samples at 100 Hz and the acceleration readings are converted from an analog to a digital output signal in 1 or 3 milli-g units within the accelerometer.

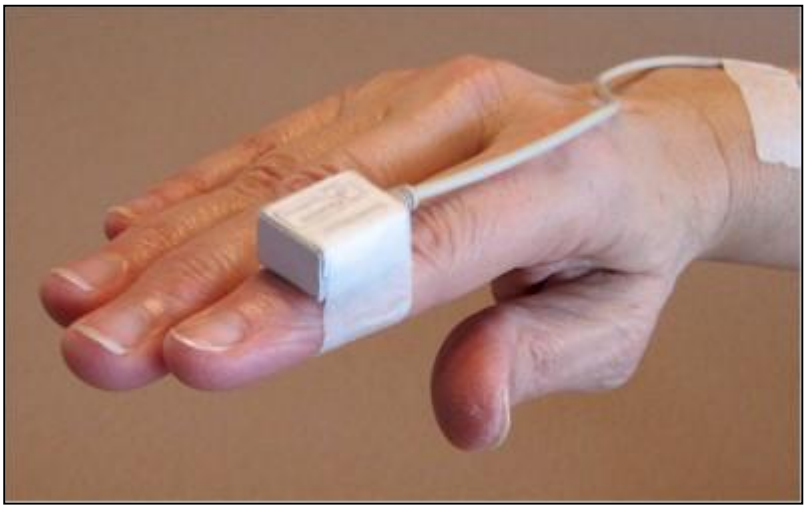

Figure 2.3 TremorScope. Image obtained from Tremorometer System Manual.

TremorLab® The TremorLab is a Windows-based PC program that reads the incoming data from the TremorScope and converts the acceleration into tremor statistics as seen in Figure 2.4, on the following page. The software is capable of running a standard set of tests for human tremor including active, resting, active with load, and intention tremor in order to obtain the frequency, amplitude, and tremor time percent among other measurements and results.

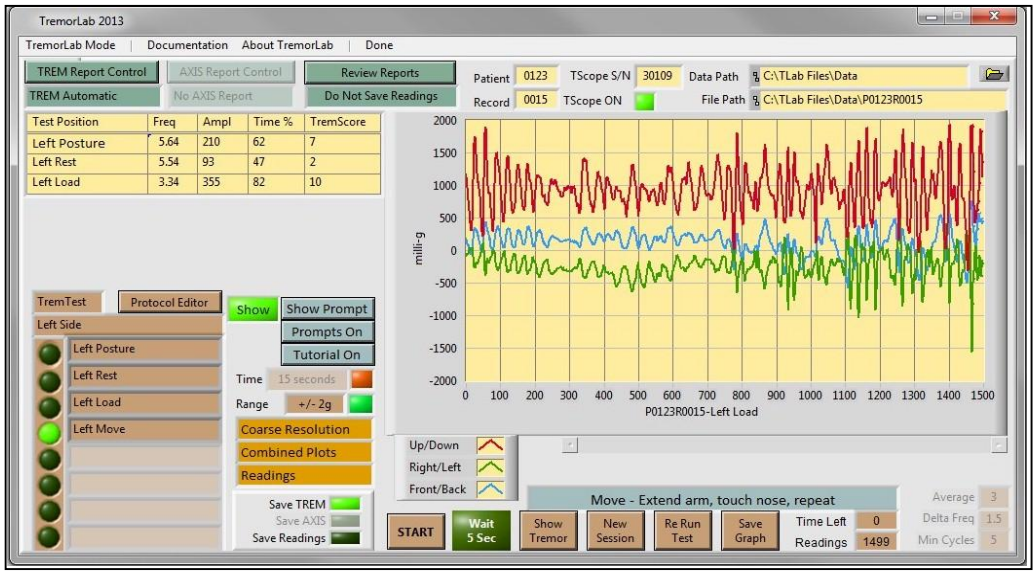

Figure2.4 Screenshot of TremorLab. Image obtained from the Tremorometer System Manual.

2.2.3 Leap Motion Controller

The Leap Motion Controller, shown in Figure 2.5, is a USB 3D camera that connects to a computer and is claimed to measure positional data accurate to within 0.01 mm. The device, made by Leap Motion, Inc., is very small with a height of 1.27 cm, a width of 3.05 cm, a depth of 7.62 cm, and only weighs 45.36 g. The Leap Motion Controller uses two CCD (Charged Coupled Device) cameras and three infrared LEDs to obtain depth information. As illustrated in Figure 2.6, on the following page, the device is capable of detecting a roughly hemispheric area of about 0.23 cubic meters.

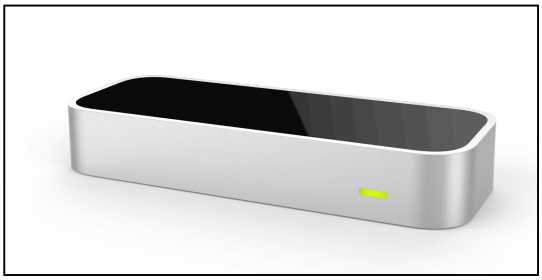

Figure 2.5 The Leap Motion Controller. Image obtained from Leap Motion, Inc.[29]

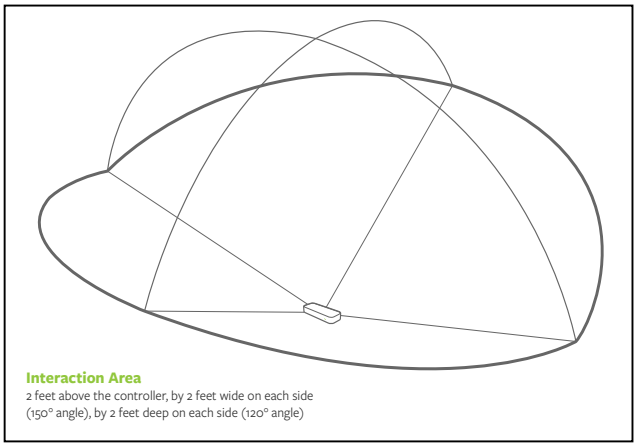

Figure 2.6 Interaction Area of Leap Motion Controller. Image obtained from Leap Motion, Inc.[29]

Output The Leap Motion Controller is capable of detecting and tracking hands, fingers, and tools in its field of view. The device captures data one frame at a time and the rate at which this occurs, or frame-rate, can vary based on the lighting conditions, but typically occurs at approximately 100 frames per second (fps). The device is capable of recording the three dimensional fingertip positions, which is done in millimeters relative to the device's origin. The Leap Motion Controller follows a right-handed Cartesian coordinate system, with the origin centered at the top and middle of the Leap Motion Controller as shown in Figure 2.7. The data from the Leap Motion Controller is accessible using the Leap SDK and a supported programming language such as C++, C#, Objective-C, Java, JavaScript, and Python.

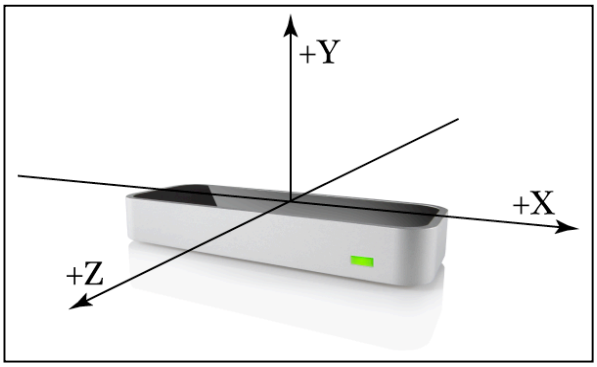

Figure 2.7 The Leap Motion Controller right-handed coordinate system. Image obtained from the Leap Motion Developer Portal.[29]

Chapter 3

Methodology

A description of the methodology will include information about the setup required for the devices used, the subject groups, the recruitment and consent process, as well as the ethical considerations involved. A more in-depth methodology of the study can be seen in the attached Protocol, located in the Appendix.

3.1 Device Setup

The two devices that were used in this study were the Tremorometer and Leap Motion Controller. These devices required an initial setup, which will be described in this section.

3.1.1 Tremorometer

For the purposes of this study, the Custom module of the TremorLab 2013 Software Program was used. This module allows the user to use the system for custom controlled tremor experimentation and supports different lengths of recording (from 5 to 180 seconds) as well as custom test protocols.

One custom test protocol was developed for this study, which involved measuring rest tremor of the index finger of the hand that exhibited the most severe rest tremor. This protocol consisted of two separate trials, each lasting for thirty seconds, and was run once for each participant. Once the protocol was run, the data was labeled to identify the participant number and whether the participant was part of

the healthy, Parkinson, or Essential Tremor group. This data was then saved to a HIPAA compliant secure flash drive for later analysis.

3.1.2 Leap Motion Controller

To use the Leap Motion Controller for the purposes of this study, a stand-alone Java program was written in order to access and record the positions detected by the Leap Motion Controller. The Leap Motion Skeletal V2 Beta SDK for Java, obtained through the Leap Motion Developer Portal, was used in writing the program to provide more robust hand tracking even if the fingers or hands were partially occluded. The Leap Motion Java SDK utilizes a standard Jar file for Leap Motion API class definitions as well as a set of native libraries that allow the Leap-enabled Java program to exchange data with the Leap Motion Controller. The Eclipse platform was used to write the code necessary to access and record the data obtained from the device for thirty seconds.

The stand-alone Java program that was written, recorded the position of each fingertip on the hand that exhibited the most tremor. The code was run twice for each participant and each time it was run, it saved a separate comma delimited CSV file to a HIPAA compliant secure flash drive with a filename that identified an arbitrary participant number, the trial number, and whether the data was from a participant from the Healthy Control, Parkinson Disease, or Essential Tremor group.

The Leap Motion Controller itself was also attached to the ramp used to support the participants' arm during the recordings. It was positioned approximately 6 cm below where the base of the hand rested. The Leap Motion Controller was oriented such that the Z-axis was vertical and increased in the upward direction; the Y-axis was parallel with the horizon and increased moving away from the ramp.

3.2 Subject Selection

There were a total of thirty individuals who participated in this study. These thirty individuals were divided up into the different groups as follows: 10 patients with Parkinsonism with tremor based on diagnostic criteria[30], 10 patients with Essential Tremor based on diagnostic criteria[31], and 10 healthy subjects. All potential participants had to be over the age of 18, could be either male or female, could be of any race or ethnicity, and had to have the ability to give informed consent. A history of stroke, cerebral palsy, additional neurological disorders, severe upper limb tremor, and cognitive impairment (A Mini-Mental State Score less than 19) were set as exclusion criteria for all participants since the possible inclusion of these criteria could negatively affect the data.

3.3 Subject Recruitment and Consent Process

Participants were recruited from the Movement Disorders Center at Washington University School of Medicine as well as the Volunteer for Health initiative of Barnes-Jewish Hospital, an affiliate of the Washington University School of Medicine with a pool of over 8,000 volunteers. The clinical database in the Washington University Movement Disorders Clinic follows a large number of patients that met the criteria set for the study, making it a practical choice for recruitment.

Participants were recruited in person during their clinic visits with their physician or nurse. If the potential participant expressed interest in the study and fit all inclusion/exclusion criteria, informed consent materials were provided. A study team member reviewed the document with the potential participant, which gave the participant an opportunity to ask questions. Potential participants were then given time to read the document in its entirety, ask questions, and speak with friends/family members if they desired. If the potential participants agreed to participate in the study,

they signed the informed consent, and were offered a signed copy of the consent after both parties signed the document.

3.4 Study Procedures

All participants, including the control participants, followed the same procedure. Each participant was measured individually, twice with the Tremorometer and twice with the Leap Motion Controller. This occurred behind the closed doors of an examination room. First, a study member taped the accelerometer (from the Tremorometer system) to the index finger on the hand that they believe to exhibit the most symptomatic tremor. Each participant then rested their arm on a small slanted ramp and was asked to relax their fingers and hands. The acceleration of their index finger was then recorded for 30 seconds, while the participant counted down from 100. After the first Tremorometer recording, the subject was asked to re-adjust their arm on the slanted ramp and again relax their fingers. The participant was again asked to count down from 100 while the 30-second recording takes place for the second time. Once the second recording was complete, the accelerometer was removed.

The participant was then asked to place the same arm on the small slanted ramp with their fingers relaxed, this time in front of the Leap Motion Controller. The position of each finger on the testing hand was then recorded for 30 seconds, while the participant again counted down from 100. After the first recording with the Leap Motion Controller, the subject was asked to re-adjust their hand and again place it on the slanted ramp with their fingers relaxed. Then the second 30-second recording with the Leap Motion Controller took place, while the participant again counted down from 100. It was estimated that the time commitment for each participant was approximately 10 minutes.

3.5 Ethical Considerations

Each participant was an adult equal to or greater than 18 years of age and gave informed consent. To ensure all participants had the ability can give informed consent all participants had to have a Mini-Mental State Score greater than or equal to 19 and could not have any serious medical or psychiatric condition.

3.5.1 Risks and Benefits

The potential risks that were determined for the participants were mild and considered unlikely. The predetermined potential risks included: discomfort from attempting to hold one hand still, boredom or frustration during the recordings, and stress if the patient exhibits too severe of upper limb tremor to record the data. In order to reduce the potential risk to the subjects, a physician was present throughout all studies.

The two devices that were used in this study, the Leap Motion Controller and the Tremorometer, met the Food and Drug Administration (FDA) definition of a Non-Significant Risk Device (NSR). This is because neither device was used as an implant, used in supporting or sustaining human life, was of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health, and neither presented a potential for serious risk to the health, safety, or welfare of a subject.

The Leap Motion Controller is a consumer three-dimensional camera and was used in accordance with its purpose: to measure and record hand and finger motions. The Tremorometer has 510k clearance for measuring and quantifying tremor in human participants, which was its only use in this study. As a result, it can be concluded that the use of these devices in the study was safe for all those who participated in the study.

3.5.2 Early Withdrawal of Subjects

None of the participants chose to or were withdrawn from the study. However, all of the participants were informed that they could withdraw from the study at any point and would not be penalized or lose any benefits that they would otherwise qualify for. In this case, the recordings would end and the data collected from the participant would have been deleted and not used in the study. Participants could have also been withdrawn from the study if they had exhibited upper limb tremor that was too severe to be recorded or if the participant could not spread their fingers enough to be detected by the Leap Controller. This withdrawal would have been based on the judgment of the study team member at the time of recording. Any data collected by a subject who had decided to withdraw or was withdrawn during the recording would not have been used and would have been deleted.

3.5.3 Confidentiality and Security

In order to protect the confidentiality of the patients, only study team members had access to the medical record of any of the potential and enrolled subjects. These records are password protected in the clinical movement disorders database (MARS) of Washington University in St. Louis, which is HIPAA compliant. This is the clinical database for which clinical information is entered for all patients seen in the movement disorders division of neurology. The collected data did not contain any identifiers and was stored on a LOK-IT Secure Flash Drive, which was automatically encrypted with military-grade 256-bit AES hardware encryption and is also HIPAA compliant.

Chapter 4

Analysis

4.1 Leap Motion Data Conditioning

In order to calculate the necessary characteristics from the data of the Leap Motion Controller, a preliminary conditioning of the position data was performed. This position data was conditioned to reduce noise and eliminate errors in order to obtain the filtered displacement, which was later used to classify the Parkinson subjects. The displacement was then further conditioned to derive the acceleration, in order to compare it to the acceleration from the Tremorometer.

Upon collection of the Leap Motion Controller data, it was noticed that the Leap Motion Controller would not detect the hand unless the hand was moved into the field of view of the device after the test had begun. Although the code was written so that no data was recorded until the hand was detected, this still caused the first second or so of each data set to be recording the subject purposefully moving their hand into a relaxed position into the view of the Leap Motion Controller. It was determined that the removal of the first three seconds of the data from each recording was sufficient to eliminate any intentional movement of placing the hand in view of the Leap Motion Controller from the data.

4.1.1 Positions

The Leap Motion Controller provides three-dimensional coordinates of position for each finger in its field of view. The position of the index finger is recorded with

respect to the origin of the Leap Motion Controller, which is centered at the top and middle of the surface of the Leap and is assumed to remain stationary.[29] Examples of these positions can be seen on the following pages for subjects with Parkinson Disease in Figure 4.1, Essential Tremor in Figure 4.2, and for a Healthy Control in Figure 4.3.

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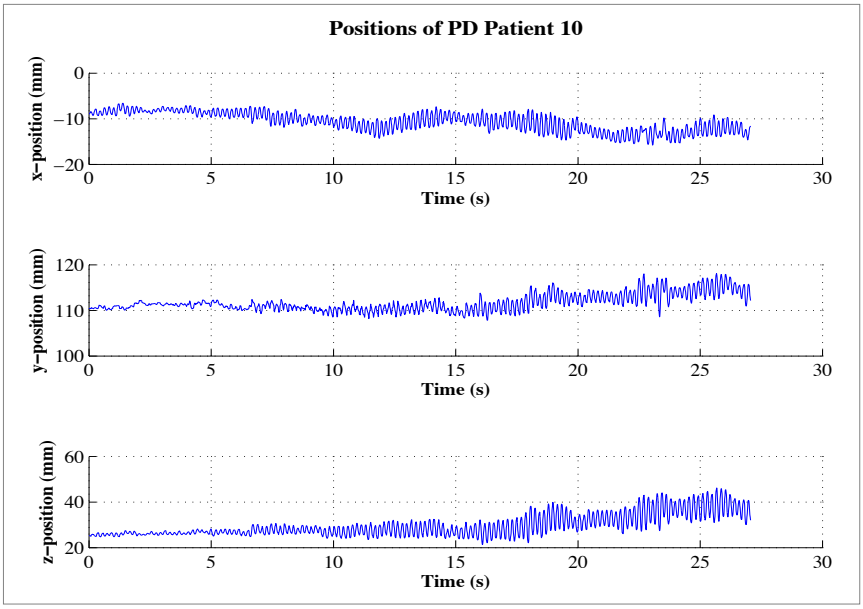

Figure 4.1 Recorded positions in millimeters with respect to time for each axis (x,y, and z) of Patient 10, who has Parkinson Disease (PD).

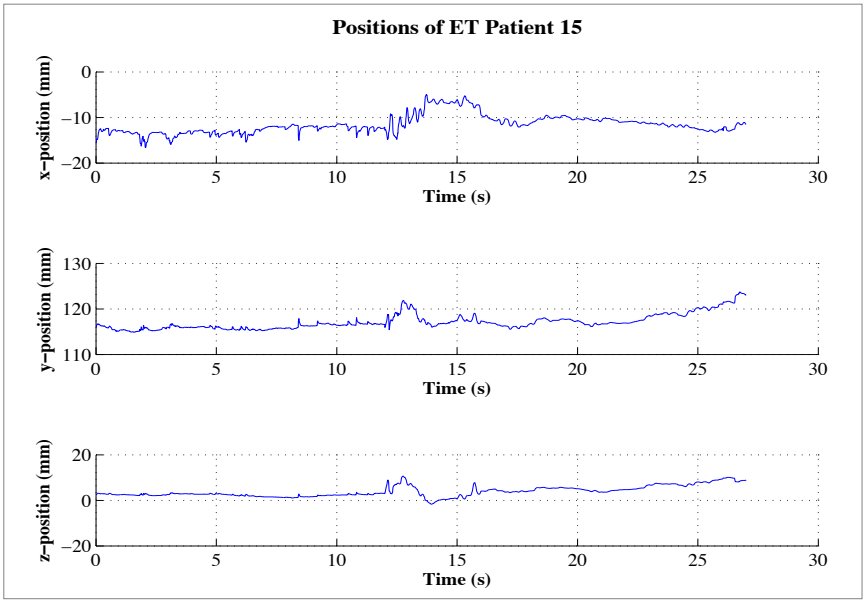

Figure 4.2 Recorded positions in millimeters with respect to time for each axis (x,y, and z) of Patient 15, who has Essential Tremor (ET).

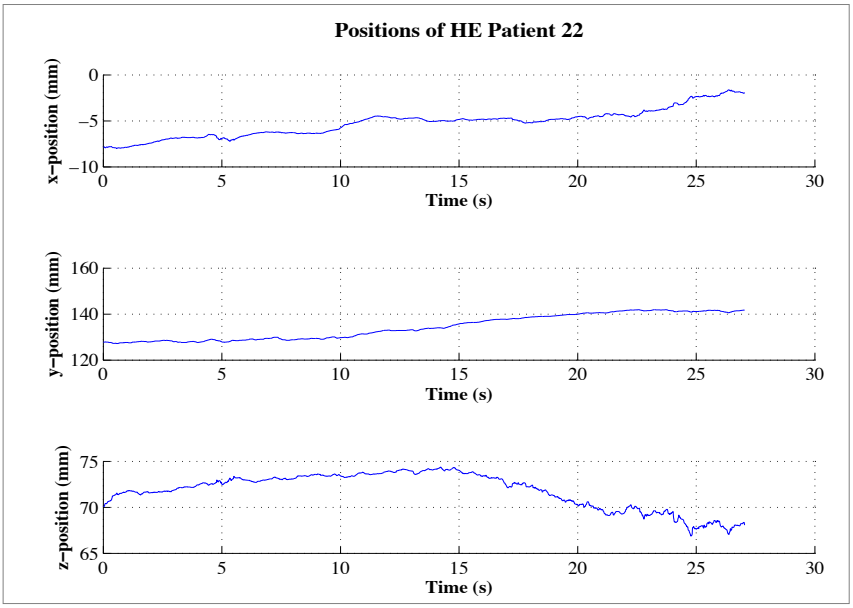

Figure 4.3 Recorded positions in millimeters with respect to time for each axis (x,y, and z) of Patient 22, who is a Healthy (HE) Control.

4.1.2 Displacements

In order to analyze the data from the Leap Motion Controller, displacements of the positions (Eq. 4.1) and new associated times (Eq. 4.2) were calculated for each axis.

$$\Delta p_n = p_{n+1} - p_n \qquad (4.1)$$

$$T_n = t_{n+1} \qquad (4.2)$$

Where:

n is the frame number,

p is the x, y, or z coordinate associate with frame n,

t_{n+1} is the time associated with frame $n+1$,

T_n is the new time associated with p_n.

The displacements are indicative of the magnitude of movement in each axis of the index finger. A comparison between the positions and calculated displacements for Patient 22 are shown in Figure 4.4. As expected, the increase in oscillations of the position in the z-axis starting at around 20 seconds can be shown by the increases in magnitude of the displacements. The displacements were calculated, in part, to eliminate any large spikes in the position data, which will be discussed next.

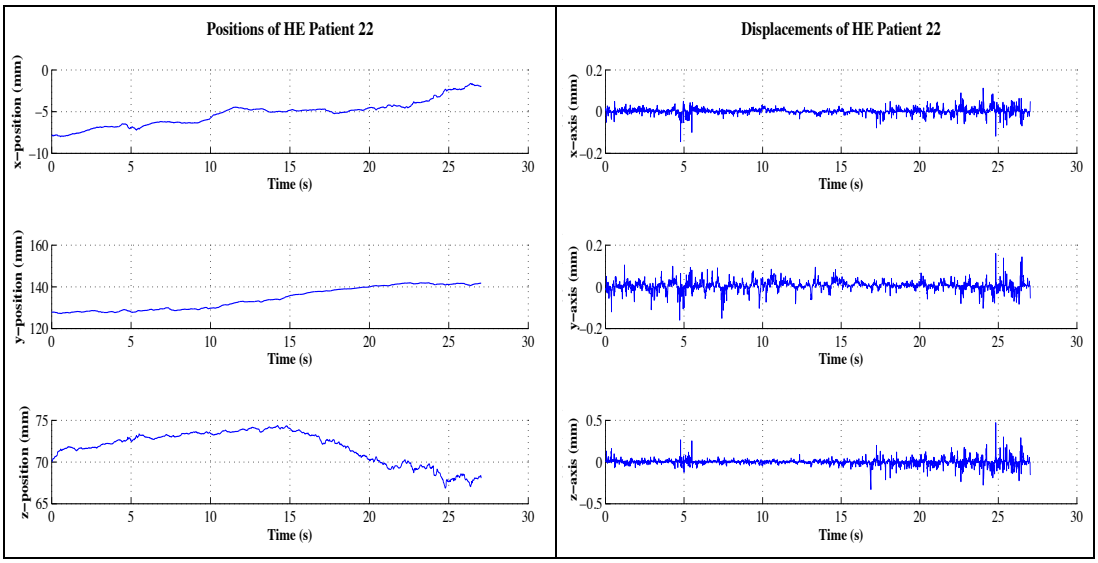

Figure 4.4 A side by side comparison of the positions and displacements for each axis of Patient 22, who is a Healthy (HE) control.

4.1.3 Spike Removal

Upon inspection of both the position and displacement data it was noticed that there were occasionally large spikes in the recorded positions and as a result, large magnitude spikes in the calculated displacements from the Leap Motion Controller.

An example of data containing these spikes can be seen in the position data and displacement data from Patient 18 with Essential Tremor in Figures 4.5, on the following page. As expected, a spike can be seen to occur on multiple axes and often can be seen more easily in one axis than another for both positions and displacements. It is apparent by observing the y-axis and z-axis positions that there are significant

spikes around 5 seconds, but these spikes are not as visible in the x-axis. As shown below, it is much easier to visualize these spikes by observing the displacement data rather than just observing the position.

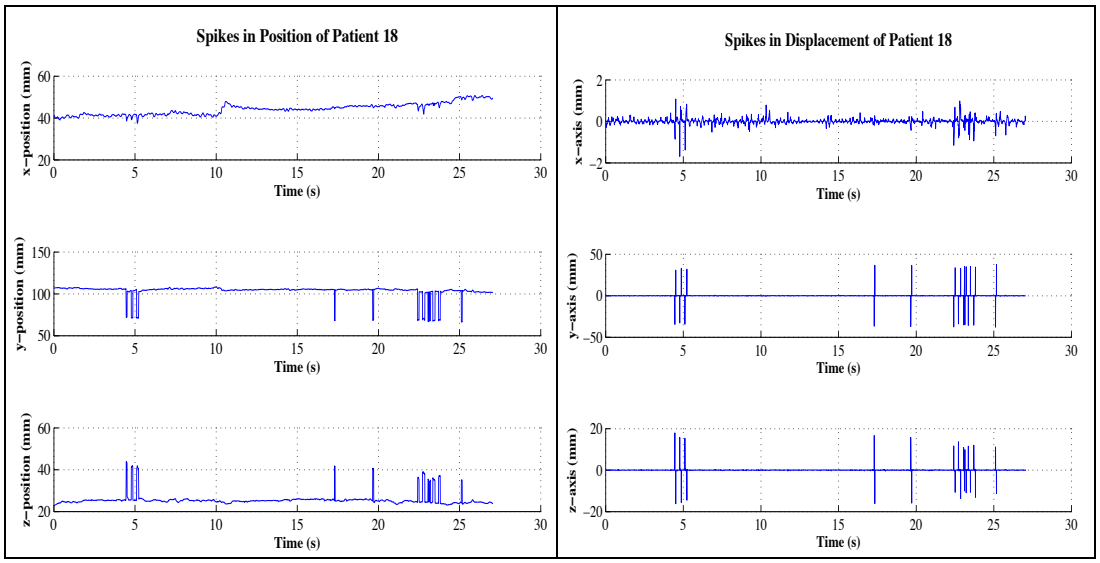

Figure 4.5 The positions and displacements for each axis of Patient 18, who has Essential Tremor (ET).

The skeletal tracking V2 Beta Version of the SDK that was used in this study uses an anatomical model of the human hand to track 26 feature points of each hand. If one finger is not seen for a frame it is interpolated and considered as curled beneath the palm or the map of the entire hand is incorrectly recorded for that frame, returning an incorrect position. Another possible cause of these spikes could be a quick shift in the arm of the subject during the recording, such as a quick readjustment or a twitch, which would also return an erroneous position. When this occurs, the data was shown to have large magnitude spikes in the position, and more visibly in displacement as shown above in Figure 4.5.

To compensate for this, any displacement with a magnitude of 4 mm or above was discarded. This value was chosen on the basis that a displacement of 4 mm between two frames approximately 0.01 milliseconds apart is too large of a magnitude for rest tremor since the magnitude of displacement from PD subjects has been shown to be

below 4 millimeters for similar sampling rates of high-amplitude rest tremor.[32] Nearly all of the large magnitude spikes in the data that were larger than 4 millimeters between two frames were at least several magnitudes larger than 4 millimeters, supporting the argument that these large magnitude spikes are not a result of abnormally high-amplitude tremor, but are incorrect readings. Therefore, it was concluded that displacement magnitudes greater than 4 mm between two frames on any axis indicated an incorrect reading and were thus removed from the data set. Eliminating these large displacement magnitudes from every axis ensured the removal of incorrect readings from an axis even when incorrect readings were not visible on that axis. Unfortunately, elimination of these data points does not exclude the possibility that an incorrect finger or an incorrect finger position could be tracked for several frames before the Leap Motion Controller returns the correct finger position. However, it was determined that the elimination of these large magnitude spikes in displacement was a better alternative than using a median filter since these spikes lasted for a different number of frames in different data sets. Therefore, in one data set a median filter using a given number of adjacent data points might work well while the same filter in another data set would not. A median filter would also face the same issue in that it would also not eliminate the possibility of an incorrect position reading for several frames. As a result, it was concluded it would be best to simply set a threshold with a displacement of 4 millimeters between any two frames and remove any large magnitude spikes that were larger than this threshold.

Figure 4.6, on the following page, shows a side-by-side comparison of the displacement data for Patient 18 before and after the removal of these large magnitude spikes. It can be seen that all of the spikes shown were several magnitudes larger than 4 mm and are clearly incorrect recordings. It can easily be seen that after the removal of these large magnitude spikes, the data is cleaner and more reasonable.

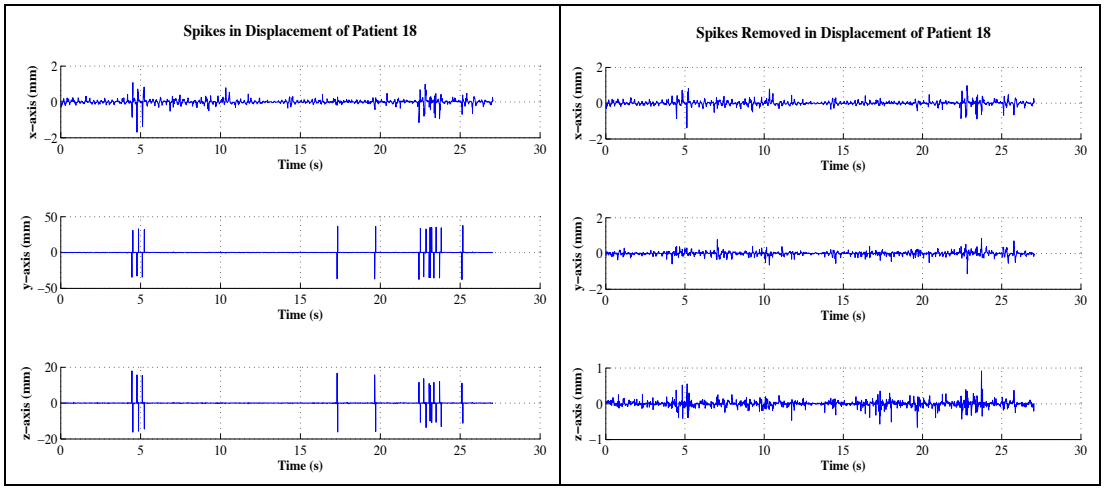

Figure 4.6 A side by side comparison of the displacements with respect to each axis of Patient 18, who has Essential Tremor (ET), before and after the large magnitude spikes were removed.

4.1.4 Euclidean Distance

Once the spikes were removed from the displacement data, the Euclidean distance (Eq. 4.3) was calculated between the three-dimensional sampled position and the origin of the Leap Motion Controller.[33] As previously mentioned, the origin of the coordinate system of the Leap Motion Controller is centered at the top and middle of the surface of the Leap and is assumed to remain stationary.[29] The change in Euclidean Distance (Eq. 4.4) was calculated for each recorded frame in order to determine the magnitude of the change in distance of the index finger with the new associated time (Eq. 4.5).

$$d_n = \sqrt{x_n^2 + y_n^2 + z_n^2} \qquad (4.3)$$

$$D_n = d_{n+1} - d_n \qquad (4.4)$$

$$T_n = t_{n+1} \qquad (4.5)$$

Where:

n is the frame number,

d_n is the Euclidean distance,

(x_n, y_n, z_n) are the positional coordinates associated with frame n,

d_{n+1} is the Euclidean distance associated with frame $n+1$,

t_{n+1} is the time associated with frame $n+1$,

T_n is the new time associated with D_n.

D_n is the new Euclidean distance associated with frame n.

This new metric takes into account the magnitude of movement from each axis. As expected, if the spikes had not been removed they would have had a significant impact on the change in Euclidean Distance. The impact of the spikes can be seen in Figure 4.7, where a comparison between the change in Euclidean Distance with and without spike removal for Patient 18 with Essential Tremor is shown. When the spikes were removed, the actual magnitude of movement of the index finger can be seen much more clearly.

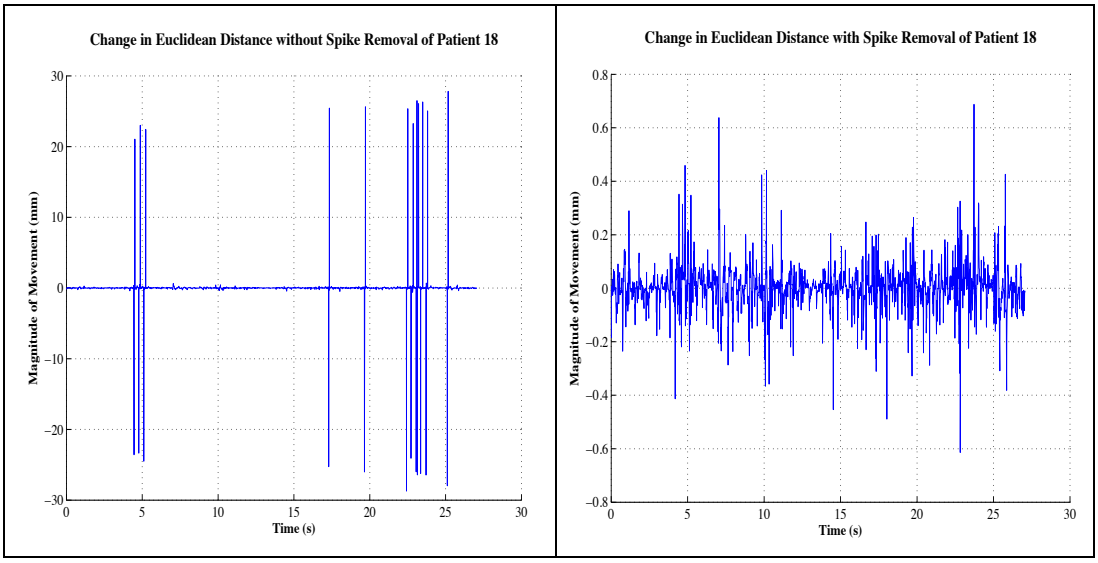

Figure 4.7 A side by side comparison of the change in Euclidean Distance of Patient 18, who has Essential Tremor (ET), before and after the large magnitude spikes were removed.

4.1.5 Non-Uniform Sampling

As previously mentioned, the Leap Motion Controller has an inconsistent frame rate and so the collected data is non-uniform with respect to time. According to the Shannon sampling theory for non-uniform sampling, a band-limited signal can be reconstructed from its samples if the average sampling rate satisfies the Nyquist condition.[34] The average sampling rate of the Leap Motion Controller during the study was approximately 100 Hz, which satisfies the Nyquist condition since the upper limit of the frequency that is of interest is no more than 25 Hz. As a result, the change in the Euclidean distance was interpolated with a cubic spine and resampled at a frequency of half of the average sampling rate, 50 Hz.

4.1.6 Band-pass Butterworth Filter

The magnitudes of the Euclidean distance for the data from the Leap Motion Controller were then filtered using a 4^{th}-Order band-pass Butterworth Filter. The Butterworth Filter that was used had a low-pass cutoff frequency of 20 Hz and a high-pass cutoff of 2.5 Hz to eliminate frequencies that were not of interest, such as those due to physiological factors like breathing and heartrate.[35] This approximation of the change in magnitude of displacement after band-pass filtering was used to classify Parkinson subjects, discussed later.

4.1.7 Savitzky-Golay Filter

A 4^{th} order Savitzky-Golay FIR filter, with a frame size of 11 points, was implemented in MATLAB using the *sgolay* function to smooth and perform a 2^{nd} order differentiation on the band-pass filtered Euclidean distance.[36] This allowed for an approximation of the change in magnitude of the acceleration while removing higher frequency noise that was amplified from differentiation. In Figure 4.8, the effects of the

Savitzky-Golay FIR filter can be seen on the magnitude of displacement, change in velocity, and change in acceleration of Patient 10, with Parkinson Disease.

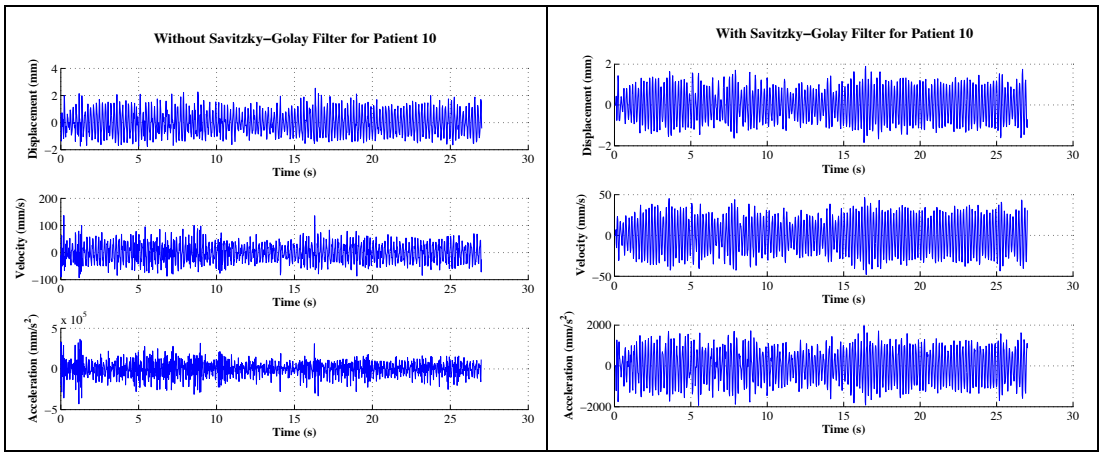

Figure 4.8 The displacement, change in velocity, and change in acceleration of Patient 10, who has Parkinson Disease, with and without the Savitzky-Golay FIR filter.

It can be more clearly seen that the amplification of higher frequency noise is greatly reduced when the Savitzky-Golay filter is applied in the frequency domain. Figure 4.9 shows Welch's one-sided power spectral density estimate for acceleration with and without the Savitztky-Golay Filter using a Hanning window, averaging twenty sections with no overlap for Patient 10, with Parkinson Disease.

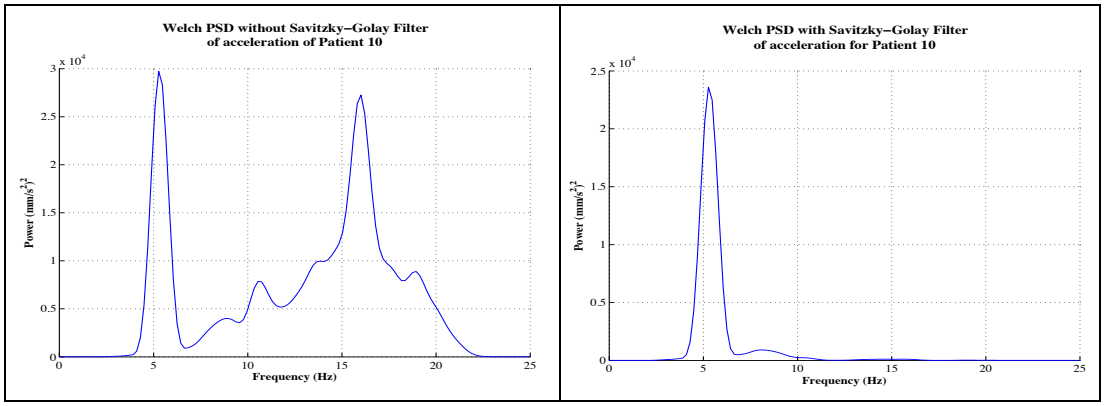

Figure 4.9 Welch's one-sided Power Spectral Density (PSD) estimate of Patient 10 who has Parkinson Disease, with and without the Savitzky-Golay FIR filter.

4.2 Tremorometer Data Conditioning

Since the Tremorometer provides a uniform sampling rate of 100 Hz, the data from the Tremorometer did not have to be resampled since this rate is sufficient to analyze the frequencies of interest, those below 25 Hz.

4.2.1 Change in Acceleration

The Tremorometer provides changes in acceleration in three dimensions measured in milli-g ($1/1000^{th}$ of the acceleration due to gravity), with respect to time measured in seconds. Examples of these recorded accelerations can be seen on the following pages for subjects with Parkinson Disease in Figure 4.10, Essential Tremor in Figure 4.11, and for a Healthy Control subject in Figure 4.11.

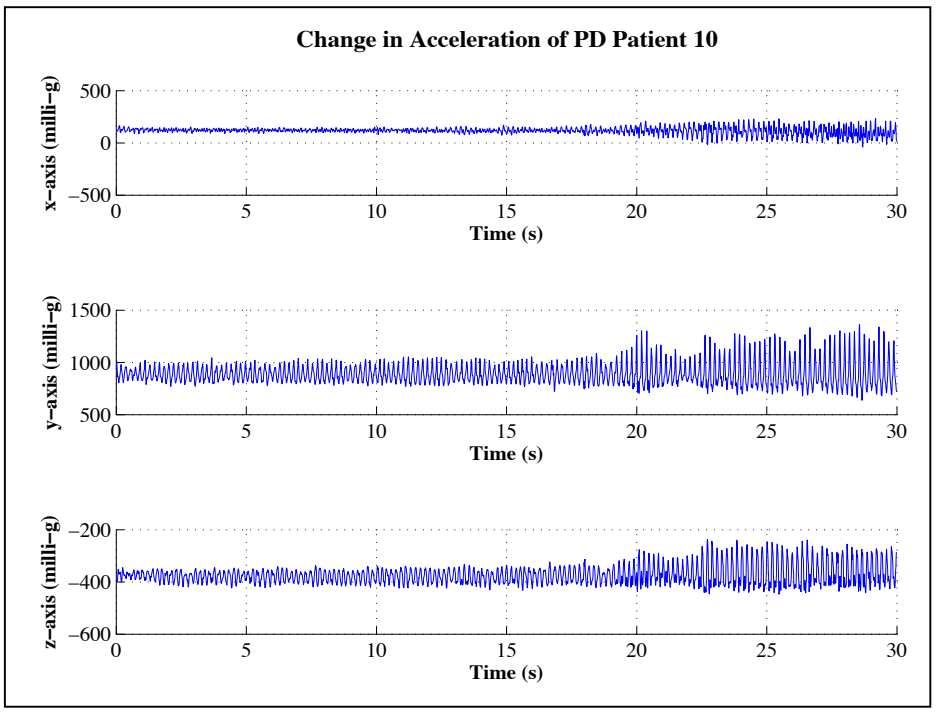

Figure 4.10 Recorded changes in acceleration (milli-g) with respect to time for each axis (x,y,z) of Patient 10, who has Parkinson Disease (PD).

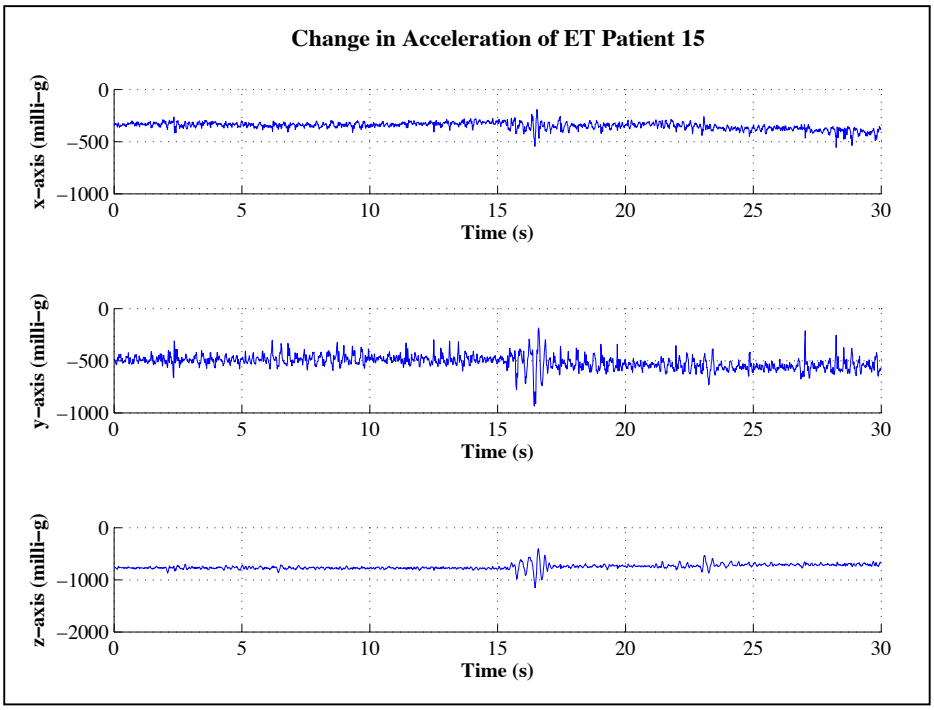

Figure 4.11 Recorded changes in acceleration (milli-g) with respect to time for each axis (x,y,z) of Patient 15, who has Essential Tremor (ET).

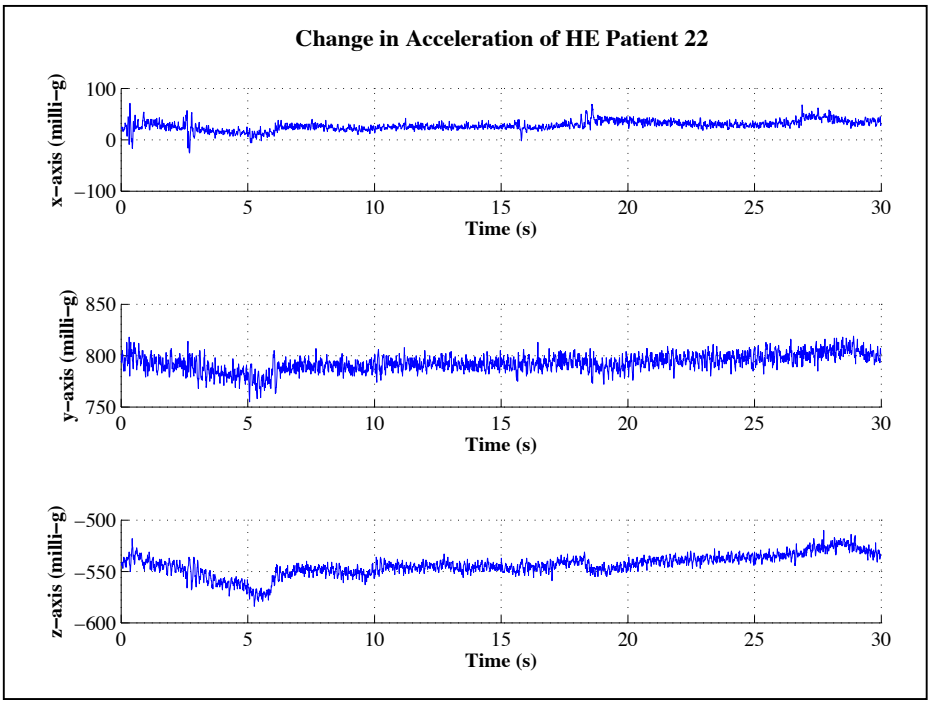

Figure 4.12 Recorded changes in acceleration (milli-g) with respect to time for each axis (x,y,z) of Patient 22, who is a Healthy (HE) Control.

4.2.2 Magnitude of Acceleration

As previously mentioned, the Tremorometer records changes in acceleration in three different dimensions. These dimensions were used to calculate the total magnitude of the acceleration shown below, in Equation 4.6.

$$||a_n|| = \sqrt{a_x^2 + a_y^2 + a_z^2} \quad (4.6)$$

Where:

n is the frame number,

$||a_n||$ is the magnitude of the acceleration associated with frame n,

(a_x, a_y, a_z) are the changes in acceleration in each dimension with their associated frame n,

An example of the calculated magnitude of acceleration for the three different axes can be seen in Figure 4.13 for Patient 10 who has Parkinson Disease (PD). It can be seen that in this case the largest changes in acceleration occur in the y-axis, which causes the greatest influence on the total magnitude of acceleration. However, it should be noted that the changes in acceleration from the other axes are also important and also contribute to the result of the total magnitude of the acceleration.

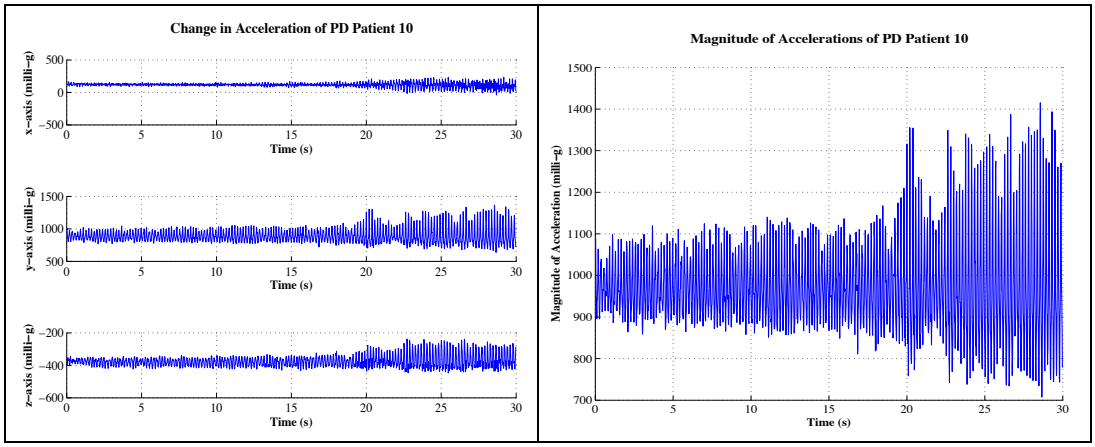

Figure 4.13 The accelerations (milli-g) for three axes of Patient 10, who has Parkinson Disease (PD) and the magnitude of acceleration (milli-g) calculated from the three axes.

4.2.3 Offset

Although the accelerometer from the Tremorometer system was properly calibrated before the data was recorded, there was a significant offset in the data. As a result, the offsets in the data were removed by subtracting the mean value of each data set from the respective data set. The removal of a large offset can be seen in Figure 4.14, where the magnitude of acceleration for Patient 10, who has Parkinson Disease, had an offset of approximately 1000 milli-g.

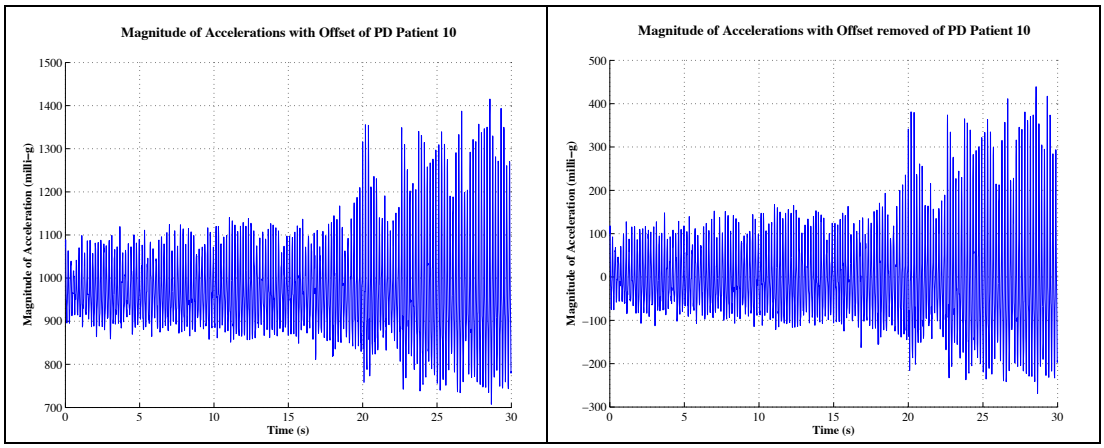

Figure 4.14 The magnitude of acceleration (milli-g) of Patient 10, who has Parkinson Disease (PD) with and without the offset.

4.2.4 Band-pass Butterworth Filter

The magnitudes of acceleration for each trial were also filtered using the same 4th-Order band-pass Butterworth Filter with the same parameters used for the Leap Motion Controller. Again, the filter had a low-pass cutoff frequency of 20 Hz and a high-pass cutoff of 2.5 Hz to eliminate frequencies that are not of interest.[35]

4.2.5 Savitzky-Golay Smoothing

Once the frequencies not pertinent to the study were removed from the data obtained from the Tremorometer, the data was then smoothed using a Savitzky-Golay

smoothing filter. The same 4th order Savitzky-Golay FIR smoothing filter, with a frame size of 11 points that was used for the data from the Leap Motion Controller was used for the data from the Tremorometer in order to apply the same smoothing filter to the two devices.

4.3 Frequency Domain Characteristics

Once the data from the Leap Motion and Tremorometer were properly conditioned, various frequency domain characteristics were calculated. This was done in order to analyze and compare the derived acceleration data from the Leap Motion Controller to the acceleration data of the Tremorometer. The derived accelerations from the Leap Motion Controller, measured in millimeters per second squared, and the acceleration from the Tremorometer, measured in milli-g, were converted into meters per second squared. These same frequency domain characteristics were also used in an attempt to classify Parkinson subjects using the position data obtained from the Leap Motion Controller in Section 4.16, before the Savitzky-Golay 2nd order differentiation filter was applied.

The Welch's one-sided power spectral density estimate was calculated using a Hanning window averaging twenty sections with no overlap with the necessary correction factors applied.[35] The following frequency domain characteristics were then determined based on this estimated power spectral density.

4.3.1 Proportional Power between 4-6 Hz

This characteristic quantifies the proportional power that is contained in the frequency range between 4-6 Hz and quantifies the approximate amount that this range contributes to the tremor. In typical parkinsonian tremor, it is expected that there is a significant peak in this range, thus causing a large proportion of the power of the spectrum to also exist in this range.[35] An example of this peak can be seen in Figure

4.15, which shows a large peak for the accelerations of both the Leap Motion Controller and the Tremorometer of Patient 10, who has Parkinson Disease. Although the peaks are seen to have slightly different magnitudes, it is clear that due to these peaks there is a large proportion of power in the 4-6 Hz range for Patient 10.

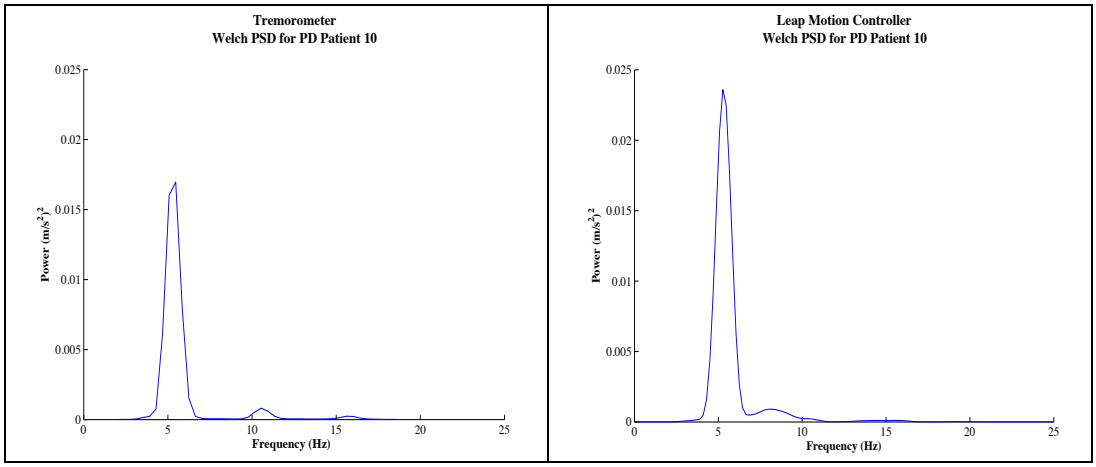

Figure 4.15 The Power Spectral Density (PSD) of Patient 10 with Parkinson Disease (PD). The large peaks in the 4-6 Hz range cause a large proportion of power to also exist in this range.

As shown in Figure 4.16, it was found that many of the Healthy Controls also exhibited a large peak in both the Tremorometer acceleration data and the calculated accelerations from the Leap Motion Controller. This peak also caused an increase in the proportional power in the 4-6 Hz range for the Healthy Controls.

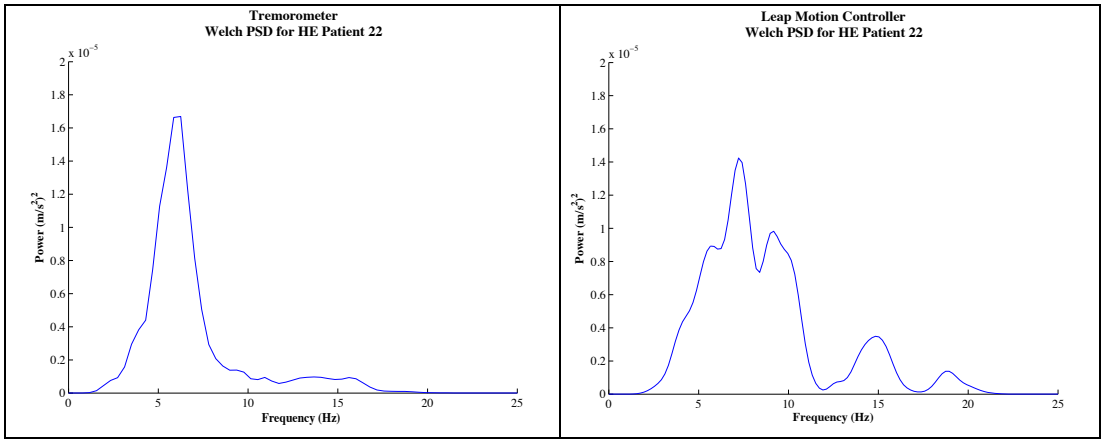

Figure 4.16 The Power Spectral Density (PSD) of Patient 22, a Healthy (HE) Control. The large peaks in the 4-6 Hz range causes a larger proportion of power to also exist in this range, but the peaks are less significant and have less power than those in the PD subjects.

However, the peaks of the Healthy Controls were proportionally smaller with respect to the power spectrum, than the peaks of the Parkinson subjects. This typically resulted in a smaller proportional power in the 4-6 Hz range for Healthy Controls than Parkinson subjects. The peaks from the Healthy Controls also tended to exist at a higher frequency than those of the Parkinson subjects, again resulting in a decreased proportional power in comparison to the Parkinson subjects.

4.3.2 Proportional Power between 8-12 Hz

This characteristic quantifies the proportional power that is contained in the frequency range between 8-12 Hz and quantifies the approximate amount that this range contributes to the tremor. Since normal physiological tremor is typically concentrated in the 8-12 Hz range, it was expected that the proportion of power in this range would be high in the absence of any low-frequency pathological tremor.[35] As mentioned in the previous section, some Healthy Controls did exhibit a peak in the 4-6 Hz range but this peak was proportionally smaller for the Healthy Control subjects than for the Parkinson subjects, typically resulting in a larger proportional power in the 8-12 Hz range for the Healthy Control subjects than subjects with Parkinson Disease. An example of this can be seen by visually comparing the proportional power in the 8-12 Hz range for subjects with Parkinson Disease in Figure 4.15 to Healthy Control subjects in Figure 4.16.

4.3.3 Median Frequency

This characteristic is indicative of the frequency at which there is a median of the area below the power spectrum, where there exists 50% of the power in the spectrum above and 50% below this frequency and has previously been used to characterize tremor.[35,36] For power spectrums with one significantly large peak, the median frequency typically coincides with this peak as shown in Figure 4.17, on the following page.

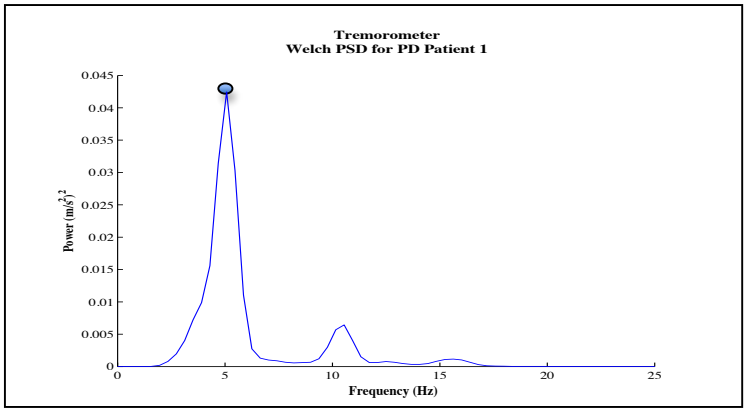

Figure 4.17 The Power Spectral Density (PSD) of Patient 1 with Parkinson Disease (PD). The large peak in the 4-6 Hz range is so significant that the median frequency coincides with this peak, shown by the blue dot.

4.3.4 Frequency Dispersion

The frequency dispersion measures the width of an interval centered at the median frequency that contains 68% of the power in the spectrum and has also been previously used to characterize tremor.[35,36] This characteristic can be used to quantify the harmonicity of oscillations. Typically, for regular oscillation such as parkinsonian or essential tremor the dispersion bandwidth is small due to a large peak while irregular tremors like physiological tremor, which usually have several peaks, tend to have a larger dispersion.[35,38]

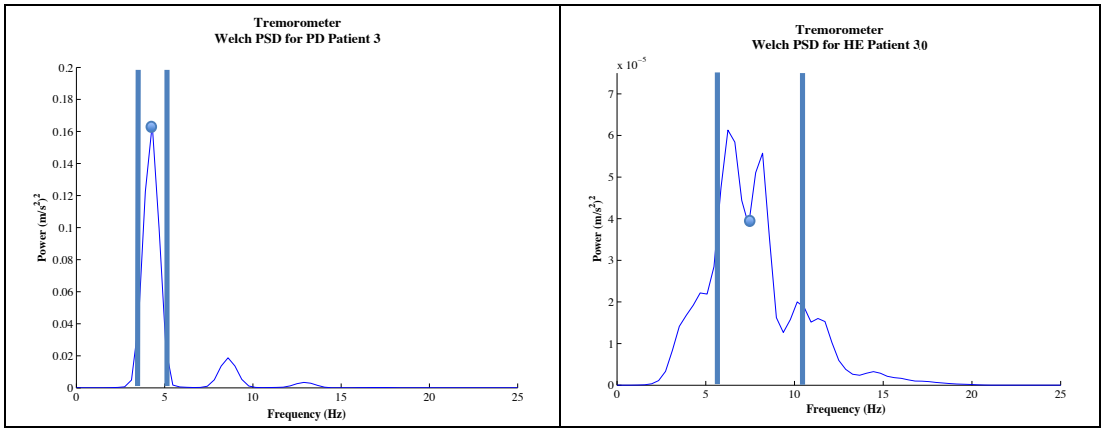

Figure 4.18 The Power Spectral Density (PSD) of Patient 3 with Parkinson Disease (PD) and Patient 30, a Healthy (HE) Control. As shown by the blue bars, the frequency dispersion for the subject with PD is narrower than that of the Healthy Control. The blue dot indicates the median frequency.

Figure 4.18, on the previous page, illustrates the difference in frequency dispersions by comparing Patient 3, with Parkinson Disease, and Patient 30, a Healthy Control, using the Tremorometer. The lower end of the frequency dispersion for Patient 3 is shown by the blue bar at 3.91 Hz, the blue bar at 5.08 Hz shows the upper end, and the median frequency is marked by a blue dot at 4.29 Hz. Whereas Patient 30 has a frequency dispersion with a lower end of 5.47 Hz, an upper end of 10.16 Hz, and a median frequency of 7.43 Hz. As shown, this results in a much more narrow frequency dispersion for Patient 3 who has Parkinson Disease, than Patient 30 who is a Healthy Control.

4.3.5 Peak Frequency between 0-25 Hz

This characteristic indicates the frequency of the highest peak power in the estimated power spectrum and also has been used to characterize tremor.[35] It was expected that the frequency of this peak would be lower for typical parkinsonian tremor, typically between 4-6 Hz, and was expected to be higher for Healthy Controls, while subjects with Essential tremor would exist throughout the spectrum. Although this was not the case for all subjects, an example of a higher peak frequency in a Healthy Control subject compared to a Parkinson subject with a peak in the 4-6 Hz range, can be seen in Figure 4.18.

4.3.6 Peak Power between 0-25 Hz

The peak power between 0-25 Hz is indicative of the power at the highest peak in the estimated spectrum. It was expected that this peak would be larger for those with visible high-amplitude tremor, and significantly lower for Healthy Control subjects. This in seen by comparing the peak power of a subject with Parkinson Disease in Figure 4.15 to the peak power of a Healthy Control subject in Figure 4.16.

4.3.7 Proportional Power of Peak between 0-25 Hz

The proportional power of the peak between 0-25 Hz represents the proportion of power in the peak frequency of the estimated spectrum. It was expected that this peak would be larger for those with visible high-amplitude tremor such as Parkinson subjects and Essential Tremor subjects, and significantly lower for Healthy Control subjects.

4.3.8 Total Power between 0-25 Hz

This characteristic is indicative of the total power of the tremor that exists in the 0-25 Hz range of the estimated spectrum. Those with high-amplitude tremor were expected to exhibit a larger value than those with low-amplitude or no visible tremor. This can be in Figure 4.18, where the magnitude of the area under the power spectrum for a Parkinson subject, Patient 3, is much larger than that of a Healthy Control, Patient 30.

Chapter 5

Results

5.1 Device Comparison

In order to compare the Leap Motion Controller to the Tremorometer, first the characteristics were tested in order to determine if the devices could be considered repeatable across trials. Once it was shown that both devices were not statistically different across trials, the two devices were compared. To do this, the trials and subject groups were combined for each device and a statistical analysis was performed to compare the resulting characteristics from each device. Then, a statistical analysis was performed separately on each subject group, again with combined trials, to determine if there was a difference in characteristics between devices for each subject group.

5.1.1 Repeatability

To determine the repeatability of each device, a statistical analysis was performed across trials for each device on each characteristic. It was found that for both devices, the distributions of each characteristic for both trials did not follow a normal distribution as was expected.[36,39] Therefore, the two trials for each device were first compared directly using the following nonparametric methods: the Wilcoxon Signed Ranks Test and the Sign Test.

The Wilcoxon Signed Ranks Test was used as a two-sided test for the null hypothesis that the differences between trials come from a distribution with zero median. The Sign Test was also used to test the hypothesis that the differences in the

trials had a distribution with zero median against the alternative that the distribution did not have zero median. Again, the test failed to reject the null hypothesis of zero median in the differences of the trials for both devices for all, but one characteristic. The only null hypothesis that was rejected was the Peak Frequency between 0-25 Hz for the Leap Motion Controller using the Sign Test. The Wilcoxon Signed Ranks Test, however, did not reject the null hypothesis that the Peak Frequency between 0-25 Hz for the Leap Motion Controller between trials had a distribution with a zero median. The results of these two tests can be seen in Tables 5.1 and 5.2. Those characteristics with highlighted p-values are shown to have no significant difference between trials.

Table 5.1 The results of the Wilcoxon Signed Ranks Test and the Sign Test for the difference between the two trials of the Leap Motion Controller. Highlighted p-values indicate that there was no significant difference.

Leap Motion Controller	*Wilcoxon Signed Ranks Test*		*Sign Test*	
Differences between Trial 1 and Trial 2	*Z*	*p value*	*Z*	*p value*
Proportional Power between 4-6 Hz	-0.072	0.943	0	1
Proportional Power between 8-12 Hz	-0.751	0.453	-0.183	0.855
Median Frequency	-0.671	0.502	-	0.523
Frequency Dispersion	-0.688	0.491	-0.588	0.556
Peak Frequency between 0-25 Hz	-1.435	0.151	-	0.023
Peak Power between 0-25 Hz	-0.504	0.614	-0.548	0.584
Proportional Power of Peak between 0-25 Hz	-1.08	0.28	-1.278	0.201
Total Power between 0-25 Hz	-0.956	0.339	-0.913	0.361

Table 5.2 The results of the Wilcoxon Signed Ranks Test and the Sign Test for the difference between the two trials of the Tremorometer. Highlighted p-values indicate that there was no significant difference.

Tremorometer	*Wilcoxon Signed Ranks Test*		*Sign Test*	
Differences between Trial 1 and Trial 2	*Z*	*p value*	*Z*	*p value*
Proportional Power between 4-6 Hz	-1.45	0.147	-0.548	0.584
Proportional Power between 8-12 Hz	-0.278	0.781	-0.183	0.855
Median Frequency	-0.409	0.682	-	1
Frequency Dispersion	-0.258	0.797	-	1
Peak Frequency between 0-25 Hz	-0.653	0.514	-	1
Power of peak between 0-25 Hz	-1.162	0.245	-0.913	0.361
Proportional Power of Peak between 0-25 Hz	-0.792	0.428	-0.183	0.855
Total Power between 0-25 Hz	-0.442	0.658	-0.183	0.855

The differences between trials were also tested to determine if they followed a normal distribution. To do so, a Kolmogorov-Smirnov One-Sample Test with Lilliefors' Significance and a Shapiro-Wilk Test was run to test the null hypothesis that the differences in characteristics between trials for each device come from standard normal distributions against the alternative that they do not, at the 0.05 significance level. The results are shown in Table 5.3 and Table 5.4 on the next page, where highlighted p-values indicate that the null hypothesis was not rejected and that the distribution was assumed to follow a normal distribution. As shown, not all characteristics were revealed to follow a normal distribution. However, for those characteristics that were shown to follow a normal distribution by just one of the normality tests, a one-sample t-test was performed.

A one-sample t-test was used to test the null hypothesis that the differences in the trials come from normal distributions with means equal to zero and unknown variance for those characteristics that were assumed to follow a normal distribution from the normality tests. The alternative hypothesis was that the distributions of the differences in trials do not have means equal to zero. The results for the one-sample t test can be seen below, in Table 5.3 below and Table 5.4 on the following page, with highlighted p-values again indicating that there was no significant difference in the means of the two trials.

Table 5.3 The results of the Kolmogorov-Smirnov Test with Lilliefors' Significance, Shapiro-Wilk Test, and t-test for the differences between trials for the Leap Motion Controller. Highlighted p-values for the Kolmogorov-Smirnov Test and the Shapiro-Wilk Test suggest that the characteristic follows a normal distribution. Highlighted p-values for the t-test indicate that there was no significant difference in the means of the two trials.

Leap Motion Controller	***Normality***		***t-test***	
Differences between Trial 1 and Trial 2	***Kolmogorov-Smirnova***	***Shapiro-Wilk***	***t***	***p value***
Proportional Power between 4-6 Hz	0.052	0.007	0.065	0.949
Proportional Power between 8-12 Hz	0.200	0.235	-1.098	0.281
Median Frequency	0.112	0.424	0.767	0.449
Frequency Dispersion	0.200	0.497	-0.518	0.608
Peak Frequency between 0-25 Hz	0.000	0.001	-	-
Peak Power between 0-25 Hz	0.000	0.000	-	-
Proportional Power of Peak between 0-25 Hz	0.013	0.005	-	-
Total Power between 0-25 Hz	0.000	0.000	-	-

Table 5.4 The results of the Kolmogorov-Smirnov Test with Lilliefors' Significance, Shapiro-Wilk Test, and t-test for the differences between trials for the Tremorometer. Highlighted p-values for the Kolmogorov-Smirnov Test and the Shapiro-Wilk Test suggest that the characteristic follows a normal distribution. Highlighted p-values for the t-test indicate that there was no significant difference in the means of the two trials.

Tremorometer *Differences between Trial 1 and Trial 2*	*Normality*		*t-test*	
	Kolmogorov-Smirnova	*Shapiro-Wilk*	*t*	*p value*
Proportional Power between 4-6 Hz	0.026	0.095	-1.868	0.072
Proportional Power between 8-12 Hz	0.2	0.637	0.244	0.809
Median Frequency	0.006	0.123	0.356	0.725
Frequency Dispersion	0.2	0.304	-0.476	0.638
Peak Frequency between 0-25 Hz	0	0.002	-	-
Power of peak between 0-25 Hz	0	0	-	-
Proportional Power of Peak between 0-25 Hz	0.119	0.036	-1.161	0.255
Total Power between 0-25 Hz	0	0	-	-

5.1.2 Combined Subject Groups

Both trials and all subject groups were combined for each device and the differences between devices were calculated. Similar to the analysis between trials, the two devices were first compared directly using nonparametric methods. Again, the Wilcoxon Signed Ranks Test and Sign Test were used to test the null hypothesis that the differences between devices come from a distribution with a zero median. The results of the tests are shown in Table 5.5, where highlighted p-values indicate that the differences between the devices were not significant.

Table 5.5 The results of the Wilcoxon Signed Ranks Test and the Sign Test for the difference between the Leap Motion Controller and the Tremorometer. Highlighted values indicate that there was no significant difference.

Differences between Leap Motion Controller and Tremorometer	*Wilcoxon Signed Ranks Test*		*Sign Test*	
	Z	*p value*	*Z*	*p value*
Proportional Power between 4-6 Hz	-2.591	0.010	-1.678	0.093
Proportional Power between 8-12 Hz	-2.952	0.003	-2.969	0.003
Median Frequency	-2.397	0.017	-2.806	0.005
Frequency Dispersion	-2.756	0.006	-2.649	0.008
Peak Frequency between 0-25 Hz	-1.328	0.184	-0.530	0.596
Peak Power between 0-25 Hz	-4.483	0.000	-5.035	0.000
Proportional Power of Peak between 0-25 Hz	-6.729	0.000	-7.359	0.000
Total Power between 0-25 Hz	-2.812	0.005	-2.969	0.003

The differences between the two devices were then tested to determine if they followed a normal distribution. The Kolmogorov-Smirnov One-Sample Test with Lilliefors' Significance and Shapiro-Wilk Test were run to test the null hypothesis that the differences in characteristics between the two devices come from a standard normal distributions against the alternative that they do not, at the 5% significance level. The results of these tests can be seen in Table 5.6, where highlighted p-values indicate that the null hypothesis was not rejected and that the differences were assumed to follow a normal distribution. The one-sample t-test was then performed on those characteristics that were assumed to follow a normal distribution. This test was run in order to test the null hypothesis that the differences in the devices come from normal distributions with means equal to zero and unknown variance. The results for the one-sample t test are shown in Table 5.6, with highlighted p-values indicating that there was no significant difference in the means of the difference between the two devices.

Table 5.6 The results of the Kolmogorov-Smirnov Test with Lilliefors' Significance, Shapiro-Wilk Test, and t-test for the difference between the Leap Motion Controller and the Tremorometer. Highlighted p-values for the Kolmogorov-Smirnov Test and the Shapiro-Wilk Test suggest that the characteristic follows a normal distribution. Highlighted p-values for the t-test indicate that there was no significant difference in the means of the two trials.

Differences between Leap Motion Controller and Tremorometer	***Normality***		***t-test***	
	Kolmogorov-Smirnova	***Shapiro-Wilk***	***t***	***p value***
Proportional Power between 4-6 Hz	0.069	0.034	-2.919	0.005
Proportional Power between 8-12 Hz	0.007	0.003	-	-
Median Frequency	0.065	0.070	2.083	0.042
Frequency Dispersion	0.200	0.098	2.745	0.008
Peak Frequency between 0-25 Hz	0.082	0.258	1.170	0.247
Peak Power between 0-25 Hz	0.000	0.000	-	-
Proportional Power of Peak between 0-25 Hz	0.017	0.004	-	-
Total Power between 0-25 Hz	0.000	0.000	-	-

5.1.3 Separate Subject Groups

To compare the differences between the two devices, the same series of statistical analyses that were performed for all subjects in the previous section were also performed for each subject group. The results of the Wilcoxon Signed Ranks Test and the Sign Test are shown in Table 5.7 for the Parkinson Group, Table 5.8 for the Essential Tremor Group, and Table 5.9 for the Healthy Control Group. Following the same convention as before, highlighted p-values indicate that the differences between the devices were not significant for that characteristic.

Table 5.7 The results of the Wilcoxon Signed Ranks Test and the Sign Test for the difference between the Leap Motion Controller and the Tremorometer for the Parkinson Group. Highlighted values indicate that there was no significant difference.

Parkinson Group: Differences between Leap Motion Controller and Tremorometer	*Wilcoxon Signed Ranks Test*		*Sign Test*	
	Z	*p value*	*Z*	*p value*
Proportional Power between 4-6 Hz	-1.760	0.079	-1.118	0.264
Proportional Power between 8-12 Hz	1.083	0.279	0.671	0.502
Median Frequency	0.371	0.711	0.236	0.814
Frequency Dispersion	1.269	0.205	1.376	0.169
Peak Frequency between 0-25 Hz	-0.666	0.505	-1.376	0.169
Peak Power between 0-25 Hz	-2.053	0.040	-1.565	0.118
Proportional Power of Peak between 0-25 Hz	-3.883	0.000	-3.801	0.000
Total Power between 0-25 Hz	-1.083	0.279	-0.224	0.823

Table 5.8 The results of the Wilcoxon Signed Ranks Test and the Sign Test for the difference between the Leap Motion Controller and the Tremorometer for the Essential Tremor Group. Highlighted values indicate that there was no significant difference.

Essential Tremor Group: Differences between Leap Motion Controller and Tremorometer	*Wilcoxon Signed Ranks Test*		*Sign Test*	
	Z	*p value*	*Z*	*p value*
Proportional Power between 4-6 Hz	-1.717	0.086	-0.671	0.502
Proportional Power between 8-12 Hz	3.808	0.000	3.354	0.001
Median Frequency	3.468	0.001	3.064	0.002
Frequency Dispersion	1.955	0.051	1.835	0.066
Peak Frequency between 0-25 Hz	2.660	0.008	1.650	0.099
Peak Power between 0-25 Hz	-3.733	0.000	-3.354	0.001
Proportional Power of Peak between 0-25 Hz	-3.920	0.000	-4.249	0.000
Total Power between 0-25 Hz	-3.136	0.002	-2.460	0.014

Table 5.9 The results of the Wilcoxon Signed Ranks Test and the Sign Test for the difference between the Leap Motion Controller and the Tremorometer for the Healthy Control Group. Highlighted values indicate that there was no significant difference.

Healthy Control Group: Differences between Leap Motion Controller and Tremorometer	***Wilcoxon Signed Ranks Test***		***Sign Test***	
	Z	***p value***	***Z***	***p value***
Proportional Power between 4-6 Hz	-0.747	0.455	-0.671	0.502
Proportional Power between 8-12 Hz	0.149	0.881	0.671	0.502
Median Frequency	0.412	0.681	1.118	0.264
Frequency Dispersion	1.250	0.211	0.918	0.359
Peak Frequency between 0-25 Hz	0.112	0.911	0.671	0.502
Peak Power between 0-25 Hz	-2.763	0.006	-3.354	0.001
Proportional Power of Peak between 0-25 Hz	-3.920	0.000	-4.249	0.000
Total Power between 0-25 Hz	-1.045	0.296	-2.012	0.044

The differences between the two devices for each group were then tested to determine if they followed a normal distribution using the Kolmogorov-Smirnov One-Sample Test with Lilliefors' Significance and Shapiro-Wilk Test. A one-sample t-test was performed on those characteristics that were assumed to follow a normal distribution. The results of the these tests are shown on the following pages in Table 5.10 for the Parkinson Group, Table 5.11 for the Essential Tremor Group, and Table 5.12 for the Healthy Control Group. Again, following the same convention as before, highlighted p-values for the normality tests indicate that the differences were assumed to follow a normal distribution and a highlighted p-value for the t-test indicates that there was no significant difference in the means of the difference for that characteristic between the two devices. P-values with an asterisk for the Kolmogorov-Smirnov indicate that the value was a lower bound of the true significance.

Table 5.10 The results of the Kolmogorov-Smirnov Test with Lilliefors' Significance, Shapiro-Wilk Test, and t-test for the difference between the Leap Motion Controller and the Tremorometer for the Parkinson Group. Highlighted p-values for the Kolmogorov-Smirnov Test and the Shapiro-Wilk Test suggest that the characteristic follows a normal distribution. P-values with an asterick indicate the value is ta lower bound of the true significance. Highlighted p-values for the t-test indicate that there was no significant difference in the means of the two trials.

Parkinson Group: Differences between Leap Motion Controller and Tremorometer	*Normality*		*t-test*	
	Kolmogorov-Smirnov	*Shapiro-Wilk*	*t*	*p value*
Proportional Power between 4-6 Hz	0.200*	0.776	1.835	0.082
Proportional Power between 8-12 Hz	0.200*	0.673	-0.916	0.371
Median Frequency	0.200*	0.841	-0.322	0.751
Frequency Dispersion	0.200*	0.581	-1.117	0.278
Peak Frequency between 0-25 Hz	0.077	0.105	0.195	0.848
Peak Power between 0-25 Hz	0.000	0.000	-	-
Proportional Power of Peak between 0-25 Hz	0.200*	0.647	7.114	0.000
Total Power between 0-25 Hz	0.000	0.000	-	-

Table 5.11 The results of the Kolmogorov-Smirnov Test with Lilliefors' Significance, Shapiro-Wilk Test, and t-test for the difference between the Leap Motion Controller and the Tremorometer for the Essential Tremor Group. Highlighted p-values for the Kolmogorov-Smirnov Test and the Shapiro-Wilk Test suggest that the characteristic follows a normal distribution. Highlighted p-values for the t-test indicate that there was no significant difference in the means of the two trials.

Essential Tremor Group: Differences between Leap Motion Controller and Tremorometer	*Normality*		*t-test*	
	Kolmogorov-Smirnova	*Shapiro-Wilk*	*t*	*p value*
Proportional Power between 4-6 Hz	0.200*	0.058	2.341	0.030
Proportional Power between 8-12 Hz	0.200*	0.987	-7.435	0.000
Median Frequency	0.078	0.159	-4.493	0.000
Frequency Dispersion	0.200*	0.073	-2.278	0.034
Peak Frequency between 0-25 Hz	0.200*	0.136	-3.037	0.007
Peak Power between 0-25 Hz	0.000	0.000	-	-
Proportional Power of Peak between 0-25 Hz	0.200*	0.195	8.577	0.000
Total Power between 0-25 Hz	0.000	0.000	-	-

Table 5.12 The results of the Kolmogorov-Smirnov Test with Lilliefors' Significance, Shapiro-Wilk Test, and t-test for the difference between the Leap Motion Controller and the Tremorometer for the Healthy Control Group. Highlighted p-values for the Kolmogorov-Smirnov Test and the Shapiro-Wilk Test suggest that the characteristic follows a normal distribution. Highlighted p-values for the t-test indicate that there was no significant difference in the means of the two trials.

Healthy Control Group: Differences between Leap Motion Controller and Tremorometer	*Normality*		*t-test*	
	Kolmogorov-Smirnova	*Shapiro-Wilk*	*t*	*p value*
Proportional Power between 4-6 Hz	0.200*	.438	1.034	0.314
Proportional Power between 8-12 Hz	0.144	.093	0.013	0.990
Median Frequency	0.009	.010	-	-
Frequency Dispersion	0.139	.406	-1.585	0.129
Peak Frequency between 0-25 Hz	0.018	.009	-	-
Peak Power between 0-25 Hz	0.000	.000	-	-
Proportional Power of Peak between 0-25 Hz	0.200*	.266	11.767	0.000
Total Power between 0-25 Hz	0.000	.000	-	-

5.2 Classification of Parkinson Subjects

To classify Parkinson Subjects, the band-pass filtered displacement data of the Leap Motion Controller from Section 4.1.6 were used. Only the Healthy Control group and the Parkinson Disease group were used in the classification of Parkinson subjects, due to the statistical differences found between devices that are discussed later in Section 6.1.3. Also based on the statistical differences between devices for the Parkinson and Healthy Control groups, only six of the eight characteristics were used to classify the Parkinson subjects. These six characteristics were used for both supervised and unsupervised learning and include: Proportional Power between 4-6 Hz, Proportional Power between 8-12 Hz, Median Frequency, Frequency Dispersion, Peak Frequency between 0-25 Hz, and the Total Power between 0-25 Hz. For unsupervised learning, a K-means cluster analysis was performed to determine how well underlying patterns or groupings in the characteristics separated the subjects. For supervised learning, a Support Vector Machine (SVM) was used to train and classify the Parkinson subjects.

5.2.1 K-means Cluster Analysis

To determine how well underlying patterns and groupings in the characteristics separated subjects into their respective groups, K-means cluster analysis was used to partition the subjects into 2 clusters. First both trials from both subject groups were combined and normalized. Then the K-means cluster analysis was performed using the city-block distance measure, where each centroid was the component-wise median of the points in that cluster. Since the true clinical diagnosis for each subject was known, the validity of the clustering was verified by comparing the true diagnosis to the cluster results. The results for each subject can be seen in Table 5.13, where Cluster 2 was chosen to be representative of the Parkinson group and Cluster 1 was representative of the Healthy group. The green highlight indicates a correct classification and a red highlight indicates an incorrect classification. It was found that there were 9 misclassifications out of the 40 subjects, an error rate of 0.225.

Table 5.13 The results of the K-means cluster analysis using the city-block distance measure for the Parkinson Disease (PD) Group and Healthy (HE) Control Group.

Patient Group	Subject	Trial	Cluster
PD	1	1	2
		2	2
	2	1	2
		2	2
	3	1	2
		2	2
	4	1	1
		2	2
	5	1	1
		2	1
	6	1	2
		2	2
	7	1	1
		2	1
	8	1	2
		2	1
	9	1	1
		2	1
	10	1	2
		2	2
HE	21	1	1
		2	1
	22	1	1
		2	1
	23	1	1
		2	1
	24	1	1
		2	1
	25	1	1
		2	1
	26	1	1
		2	1
	27	1	1
		2	1
	28	1	1
		2	2
	29	1	1
		2	1
	30	1	1
		2	1

5.2.2 Support Vector Machine

In an attempt to classify Parkinson subjects, the binary support vector machine (SVM) classifier function *fitcsvm* within MATLAB was used. Both trials from the two subject groups were combined, normalized and labeled with their respective class. The default parameters of the function were used to train the classifier using a linear kernel for the six standardized predictors. Once trained, the model was cross-validated using the leave-one-out method and the cross-validation loss of the model was calculated using the function *kfoldLoss*, which was found to be 0.2. This SVM classifier was then tuned by adjusting the box constraint and kernel scale parameters to optimize this performance estimation. The best parameters for the kernel scale and the box constraints were found to be 0.1 and 1, respectively. The tuned SVM classifier was again cross-validated using the leave-one-out method and the new cross-validation loss was recalculated to be 0.15. The predicted response for the cross-validated classification model was then calculated and the resulting predicted class labels are shown in Table 5.14. Again, the green highlight indicates a correct classification and a red highlight indicates an incorrect classification.

Table 5.14 The predicted response for the tuned cross-validated SVM classification model for the Parkinson Disease (PD) Group and Healthy (HE) Control Group.

Patient Group	Subject	Trial	SVM Model
PD	1	1	PD
		2	PD
	2	1	PD
		2	PD
	3	1	PD
		2	PD
	4	1	HE
		2	PD
	5	1	HE
		2	HE
	6	1	PD
		2	PD
	7	1	HE
		2	HE
	8	1	PD
		2	PD
	9	1	PD
		2	PD
	10	1	PD
		2	PD
HE	21	1	PD
		2	HE
	22	1	HE
		2	HE
	23	1	HE
		2	HE
	24	1	HE
		2	HE
	25	1	HE
		2	HE
	26	1	HE
		2	HE
	27	1	HE
		2	HE
	28	1	HE
		2	HE
	29	1	HE
		2	HE
	30	1	HE
		2	HE

Chapter 6

Discussion and Conclusion

6.1 Device Comparison

To compare the Leap Motion Controller to the Tremorometer, several analyses were performed. First each device was tested to determine if the trials were statistically different or if they could be repeatable, then statistical analyses of the differences between devices for all subject groups were performed, and finally statistical analyses of the differences between devices for each separate subject group was presented. A discussion and the conclusions drawn from the results of these analyses are presented in this section.

6.1.1 Repeatability

The first step in comparing the two devices was to determine if they provide characteristics that could be repeatable. It was found that the Leap Motion Controller and Tremorometer were both shown to not statistically different across trials for all characteristics, which suggest that the devices could be repeatable. This is supported by results of the Wilcoxon Signed Ranks Test, which indicated that there were no significant differences between trials. The results of the Sign Test also indicated that there were no differences between trials for all characteristics in the Tremorometer and all but one characteristic in the Leap Motion Controller, the Peak Frequency between 0-25 Hz. However, it can be argued that the Wilcoxon Signed Ranks Test was a stronger indicator since it took into account the magnitudes and signs of the observations rather than just the signs. As a result, if there was a discrepancy between the results of the

Wilcoxon Signed Ranks Test and the Sign Test, the results of the Wilcoxon Signed Ranks Test were used to determine statistical difference. Since the Wilcoxon Signed Ranks Test suggested that there was no significant difference between trials for the Peak Frequency between 0-25 Hz for the Leap Motion Controller, it was concluded that this characteristic was also not different between trials for the Leap Motion Controller. The difference between trials were also tested for normality to see if a more powerful parametric test, such as the t-test, could also be used to determine if there was a statistical difference between the trials for each device. The results of the t-test supported the results of the Wilcoxon Signed Ranks Test, where all those characteristics shown to follow a normal distribution were shown to not be statistically different between trials for either device. As a result, the results of the t-test also support the argument that the two devices could be repeatable for measuring all eight characteristics and that the two trials are not statistically different for either device. In conclusion, it was found that the two devices could be considered repeatable for the purposes of this study.

6.1.2 Combined Subject Groups

The results of combining subject groups and comparing the devices revealed that characteristics for the two devices were statistically different for all but one characteristic. The only characteristic that was shown to not be statistically different between devices from the Wilcoxon Signed Ranks Test and Sign Test was the Peak Frequency between 0-25 Hz. This result was confirmed by the t-test, which indicated that out all of the characteristics that were shown to possibly follow a normal distribution by the normality tests, the only one that was not significantly different was, in fact, the Peak Frequency between 0-25 Hz. The end results of the relevant statistical tests are summarized on the following page in Table 6.1 where the characteristics highlighted in green indicate that they are not statistically different between devices, while a red highlight indicates that the characteristic is statistically different between devices. In conclusion, only the Peak Frequency between 0-25 Hz was shown to not be

statistically different between the Leap Motion Controller and Tremorometer when testing the combined subject groups.

Table 6.1 Summary of characteristics that are not statistically different between devices for the combined subject groups. Green indicates not statistically different. Red indicates statistically different.

Combined Subject Groups: Summary of characteristics not statistically different between devices
Proportional Power between 4-6 Hz
Proportional Power between 8-12 Hz
Median Frequency
Frequency Dispersion
Peak Frequency between 0-25 Hz
Peak Power between 0-25 Hz
Proportional Power of Peak between 0-25 Hz
Total Power between 0-25 Hz

Initially this was a little discouraging, but it is also very important to note. The statistical differences are most likely due to the consequences of pre-processing of the data previously mentioned in Chapter 4. When comparing the Leap Motion to the Tremorometer, the displacement data from the Leap Motion Controller had to be differentiated to calculate acceleration and was then filtered to eliminate the amplification of the high frequency noise. The differentiation and filtering likely affected many of the characteristics that depended on the power in the higher frequencies, such as the Total Power between 0-25 Hz. This most likely resulted in the distortion of many of these characteristics resulting in a statistical difference between devices. It is also possible that upon calculating the Welch's one-sided power spectral density estimate with the Hanning window averaging twenty sections, the shape of the power spectral density for some of the trials were not preserved and could influence some of these resulting characteristics such as the Median Frequency and Frequency Dispersion. Unfortunately, some of these pre-processing issues were very difficult to avoid because the data from each trial would have to be conditioned individually, which would be incredibly time-consuming and could introduce bias into the results since the study was not blinded. Several methods to improve the pre-processing of the data are discussed in more detail in the Future Works Section.

6.1.3 Separate Subject Groups

Once it was found that there was only one characteristic that was not significantly different between devices for all subject groups, the groups were separated and reexamined to determine if there were any differences for particular groups. The trials were combined per subject group due to the small sample size of each group. A summary of the conclusions drawn from the results can be seen on the following pages in Table 6.2 for the Parkinson group, Table 6.3 for the Essential Tremor group, and Table 6.4 for the Healthy Control group. In the summaries, characteristics highlighted in green indicate that they were not statistically different between devices, while characteristics with a red highlight indicate that they were statistically different between devices.

Parkinson Group The results of the Wilcoxon Signed Ranks Test indicated that there was no significant difference between devices for the majority of characteristics. The only two characteristics that were shown to be statistically different between devices were the Peak Power between 0-25 Hz and the Proportional Power of Peak between 0-25 Hz. The results of the t-test were shown to support these results for those characteristics that were shown to follow a normal distribution. It was therefore concluded that all of the characteristics were shown to not be statistically different between devices except for Peak Power between 0-25 Hz and Proportional Power of Peak between 0-25 Hz for the Parkinson group.

Table 6.2 Summary of characteristics that are not statistically different between devices for the Parkinson subject group. Green indicates not statistically different. Red indicates statistically different.

Parkinson Subject Group: Summary of characteristics not statistically different between devices
Proportional Power between 4-6 Hz
Proportional Power between 8-12 Hz
Median Frequency
Frequency Dispersion
Peak Frequency between 0-25 Hz
Peak Power between 0-25 Hz
Proportional Power of Peak between 0-25 Hz
Total Power between 0-25 Hz

Essential Tremor Group The Essential Tremor group, however, only had two characteristics that were not statistically significant based on the results of the Wilcoxon Signed Ranks Test. These two characteristics were the Proportional Power between 4-6 Hz and Frequency Dispersion. It was noted that these two characteristics were also not statistically different for the Healthy Control group and the Parkinson Group, suggesting that these characteristics may be most similar between devices for the different groups. The Essential Tremor group was also shown to have many of the characteristics follow a normal distribution, but the t-test revealed that all of these characteristics were also shown to be statistically different between devices. Therefore, it was found that all of the characteristics were concluded to be statistically different between the Tremorometer and Leap Motion Controller for the Essential Tremor group.

Table 6.3 Summary of characteristics that are not statistically different between devices for the Essential Tremor subject group. Green indicates not statistically different. Red indicates statistically different.

Essential Tremor Subject Group: Summary of characteristics not statistically different between devices
Proportional Power between 4-6 Hz
Proportional Power between 8-12 Hz
Median Frequency
Frequency Dispersion
Peak Frequency between 0-25 Hz
Peak Power between 0-25 Hz
Proportional Power of Peak between 0-25 Hz
Total Power between 0-25 Hz

Healthy Control Group The Wilcoxon Signed Ranks Test for the Healthy Control Group indicated that there were no significant differences between devices for most of the characteristics. Similar to the Parkinson group, the only two characteristics that were shown to be statistically different between devices were the Peak Power between 0-25 Hz and the Proportional Power of Peak between 0-25 Hz. Again like the Parkinson group, the t-test supported the results from the Wilcoxon Signed Rank Test for the normally distributed. It was concluded that all of the characteristics were shown to not be statistically different except for Peak Power between 0-25 Hz and

Proportional Power of Peak between 0-25 Hz for the Healthy Control group, which were the same results as the Parkinson group.

Table 6.4 Summary of characteristics that are not statistically different between devices for the Healthy Control subject group. Green indicates not statistically different. Red indicates statistically different.

Healthy Control Groups: Summary of characteristics not statistically different between devices
Proportional Power between 4-6 Hz
Proportional Power between 8-12 Hz
Median Frequency
Frequency Dispersion
Peak Frequency between 0-25 Hz
Peak Power between 0-25 Hz
Proportional Power of Peak between 0-25 Hz
Total Power between 0-25 Hz

It is clear that the results for the Parkinson group and Healthy Control group agree, where the same six characteristics are shown to not be statistically different between devices. This supports the claim that for these six characteristics, the two devices are not statistically different. However, these six characteristics were revealed to not be statistically similar for the Essential Tremor group. The statistical differences in the characteristics measured from the Essential Tremor group could be due to the nature of the disorder. It is known that the amplitude of Essential Tremor tends to be fairly variable and thus changes in the amplitude of the tremor between device recordings may have influenced the results, especially since many of the characteristics depend on the amplitude of this tremor. Another possibility for the statistical difference in characteristics for the Essential Tremor group is that during the pre-processing of the data, such as during the differentiation and filtering of the displacement data from the Leap Motion Controller, the characteristics unique to subjects with Essential Tremor were more greatly affected than the Parkinson and Healthy Control subjects. Similarly, upon calculating the Welch's one-sided power spectral density estimate using a Hanning window with an average of twenty sections, the shape of the power spectral density for the Essential Tremor subjects could have been more distorted than the Healthy Control subjects or the Parkinson subjects due to features unique to Essential Tremor.

6.2 Classification of Parkinson Subjects

Due to the statistical differences in characteristics between devices for the Essential Tremor group, only the Healthy Control and Parkinson groups were used for the classification of Parkinson subjects. Likewise, only those six characteristics that were not shown to be statistically different between the Leap Motion Controller and the Tremorometer were used as features to classify the Parkinson subjects. Again, those six characteristics were Proportional Power between 4-6 Hz, Proportional Power between 8-12 Hz, Median Frequency, Frequency Dispersion, Peak Frequency between 0-25 Hz, and the Total Power between 0-25 Hz. Since these characteristics were not statistically different by device for the Healthy Control group and Parkinson group, it was assumed that the characteristics provided by the Leap Motion Controller were correct and that they would be the most useful features to classify the Parkinson subjects.

6.2.1 K-means Cluster Analysis

The K-means Cluster analysis, as a method of classifying Parkinson subjects from Healthy Control subjects, was found to be fairly successful. It was found that there were 9 misclassifications out of the 40 subjects, an error rate of 0.225. To evaluate the performance of the classification, a confusion matrix was created and is shown in Table 6.5. The label True Positive represents the subjects that were from the Parkinson group, True Negative represents the subjects that were from the Healthy Control group, the label Predicted Positive represents the subjects that were classified as Parkinson subjects, and the Predicted Negative label represents the subjects that were classified as Healthy Control subjects.

Table 6.5 The confusion matrix for the K-means cluster analysis as a means of classification.

	True Positive	True Negative
Predicted Positive	12	1
Predicted Negative	8	19

Based on the confusion matrix, the accuracy, sensitivity, and specificity were calculated and are shown in Table 6.6. The precision is indicative of the percentage of the positive cluster labels that were correct, the recall/sensitivity represents the percentage of True Positive subjects that were correctly clustered, the specificity represents the percentage of True Negative subjects that were correctly clustered, and the accuracy represents the percentage of the clustering that were correct. The overall accuracy for classifying Parkinson subjects from Healthy Control subjects using K-means Clustering was found to be 77.5%.

Table 6.6 The precision, recall/sensitivity, specificity, and accuracy to evaluate the K-means cluster analysis as a means of classification.

	K-means Clustering
Precision	92.3%
Recall/Sensitivity	60%
Specificity	95%
Accuracy	77.5 %

A visualization of the K-means cluster analysis was also created for several of the characteristics and can be seen in Figure 6.1 on the following page. Blue data points indicate the data that were classified into Cluster 1 and red data points are those that were classified of Cluster 2. The data points labeled with an asterisk are diagnosed Parkinson Disease subjects and the data points labeled by a circle are Healthy Controls. Those points labeled with an "X" represent the centroid of the cluster. This figure allows for a better visualization of the performance of the K-means cluster analysis in terms of classifying the Healthy Controls and Parkinson subjects. It also allows one to visually compare the characteristics of individual subjects per subject group. It can be seen that some of the Parkinson subjects exhibited a higher Proportion of Power between 4-6 Hz as expected and it is hypothesized that these Parkinson subjects had visible or high-amplitude tremor. This is supported by the fact that the same Parkinson subjects had a much higher Proportional Power of Peak between 0-25 Hz than other Parkinson subjects. However, other Parkinson subjects were shown to have a lower

Proportional Power between 4-6 Hz that were more similar to the Healthy Controls. This most likely indicates that these subjects did not exhibit any visible high amplitude tremor and were possibly being treated using Deep Brain Stimulation (DBS) or were taking medications to suppress the severity of the tremor.

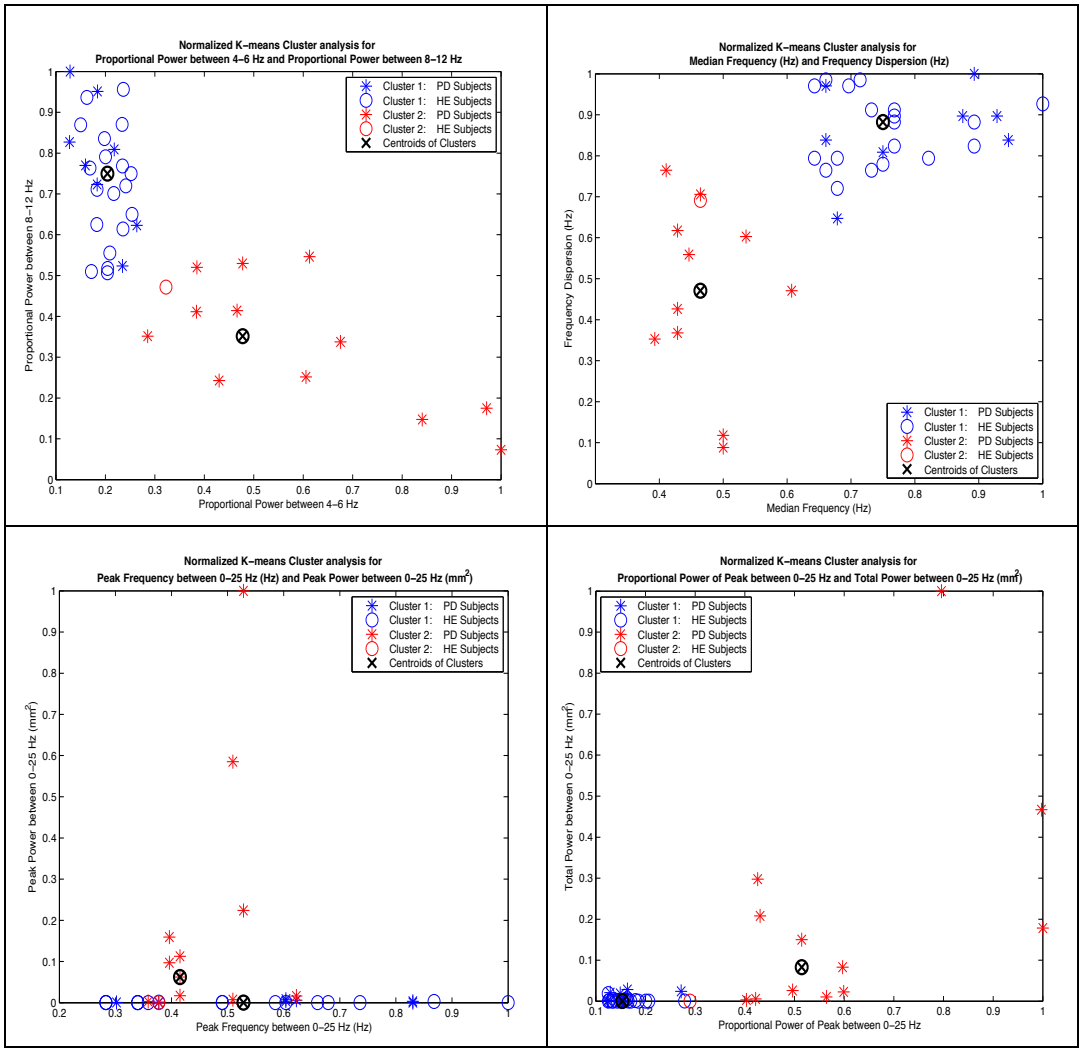

Figure 6.1 The K-means cluster analysis for several characteristics. The data points in blue represent Cluster 1, the red data points represent Cluster 2. The data points labeled with an asterisk are Parkinson Disease (PD) subjects and those labeled with a circle are Healthy (HE) Controls. The points labeled with an "X" represent the centroid of the cluster.

6.2.2 Support Vector Machine

The original SVM classifier was also found to be fairly successful in classifying the Parkinson subjects. When cross-validated using the leave-one-out method, the misclassification rate was calculated to be 0.2, which was slightly better than the error rate of 0.225 from the K-means cluster analysis. However, once the SVM classifier was tuned, the misclassification rate was reduced from 0.2 down to 0.15. To evaluate the performance of this classification the confusion matrix was created and the accuracy, sensitivity, and specificity were calculated and can be shown in Table 6.7 and Table 6.8, respectively. The same labels used in the K-cluster analysis confusion matrix were used for the SVM confusion matrix. As shown, the precision, recall/sensitivity, and accuracy were all higher for the tuned SVM classifier than for the K-means clustering, while the specificity remained the same. The resulting overall accuracy of the tuned SVM classifier for classifying Parkinson subjects from Healthy Controls was found to be 85%.

Table 6.7 The confusion matrix for the predicted response of the cross-validated SVM classification model

	True Positive	True Negative
Predicted Positive	15	1
Predicted Negative	5	19

Table 6.8 The precision, recall/sensitivity, specificity, and accuracy for the tuned SVM Classifier.

	SVM Classifier
Precision	93.75%
Recall/Sensitivity	75%
Specificity	95%
Accuracy	85%

6.3 Concluding Remarks

In conclusion, the study was fairly successful in comparing the Leap Motion Controller to the Tremorometer. All eight characteristics were found to not be statistically different across trials for either device, suggesting that both devices may be repeatable. It was concluded that when comparing the differences between devices for the combined subject groups, only the Peak Frequency between 0-25 Hz was found to not be statistically different. This suggests that the Leap Motion Controller may be capable of obtaining the same Peak Frequency between 0-25 Hz as the Tremorometer for subjects with Parkinson Disease, subjects with Essential Tremor, and Healthy subjects. However, for all other characteristics, the characteristics between devices were shown to be statistically different. These statistically different characteristics could be attributed to the pre-processing of the Leap Motion Controller displacement data that was performed to obtain acceleration. When the devices were compared within each subject group, evidence was found that the Leap Motion Controller could be capable of obtaining the same Proportional Power between 4-6 Hz, Proportional Power between 8-12 Hz, Median Frequency, Frequency Dispersion, Peak Frequency between 0-25 Hz, and Total Power as the Tremorometer in Parkinson subjects as well as Healthy Control subjects. However, it was found that the Leap Motion Controller did not obtain similar characteristics to the Tremorometer for the Essential Tremor subjects. This could also be attributed to the pre-processing of the data, where perhaps characteristics unique to subjects with Essential Tremor were more greatly affected than the Parkinson and Healthy Control subjects. It has also been shown that some accelerometers do not correspond well to the data obtained from devices that record displacement, except for cases of high-amplitude tremors even though the devices that measure displacement are shown to be fairly precise.[32] Possible improvements to the pre-processing methods are discussed in the next section. It was noted that in subjects with high-amplitude tremor, consisting of a very large peak with small frequency dispersion, the resulting characteristics of the Tremorometer and Leap Motion Controller were very similar. The power spectral density estimate of such a subject can be seen in Figure 4.15.

Although only Parkinson subjects and Healthy Controls were used for classification, the study was still successful in that Parkinson subjects were accurately differentiated from the Healthy Controls. The Proportional Power between 4-6 Hz, Proportional Power between 8-12 Hz, Median Frequency, Frequency Dispersion, Peak Frequency between 0-25 Hz, and the Total Power between 0-25 Hz were all used as features for classification, based on the results of the statistical differences between the Leap Motion Controller and Tremorometer for the Parkinson and Healthy Control groups. The K-means cluster analysis, as a method of classification, was found to have an accuracy of 77.5%, while the tuned cross-validated SVM classifier was found to have an accuracy of 85%. It should be noted that another SVM classifier was also trained using all eight characteristics and while the results are not mentioned in this study, it was interesting to find that using all eight decreased the overall accuracy even after tuning. This suggests that perhaps the Peak Power between 0-25 Hz and the Proportional Power of Peak between 0-25 Hz are either not good predictors or are not consistent across recordings. Although not perfect, the SVM classifier reported in this study was more successful in classifying Parkinson subjects than simply using K-means clustering. Based on these results, it can be concluded that overall the study was successful in classifying Parkinson subjects from Healthy Control subjects.

It is important to keep in mind that not all of the Parkinson and Essential Tremor subjects displayed high-amplitude tremor. Many of the subjects were likely taking medication or undergoing Deep Brain Stimulation (DBS) that could have greatly suppressed their tremor. This would most likely detriment the accuracy of the classifications, making it much more difficult to discern subjects Parkinson from Healthy Controls. Methods to account for cases where patients are undergoing treatment for their disorder are mentioned in Future Works.

6.4 Future Works

In future works, it would be interesting to investigate a variety of different methods to go about comparing the Leap Motion Controller with the Tremorometer to measure human tremor. It is suggested that rather than performing two separate trials with the two devices individually, to perform one trial with the two devices simultaneously as done in other similar studies.[32] This would ensure that the same tremor was recorded rather than tremor from the same individual at two different points in time. Since tremor can significantly vary at different times, especially for those with movement disorders, it would be ideal to perform the recordings of both devices simultaneously. It is also recommended that postural tremor be recorded rather than rest tremor, since it is less likely that the Leap Motion Controller will incorrectly record the index finger. This is because if the hand is outstretched, fingers are more spread apart than they would be at rest. When the Leap Motion Controller can distinguish individual fingers as is the case when fingers are more spread apart, it is much more likely to obtain an accurate recording of the index finger. It would also be useful to implement the confidence level method, available in the Leap Motion Skeletal V2 Beta SDK for Java, in the code used to record the Leap Motion data. This method rates how well the internal hand model fits the observed hand and would be useful to ensure that the recordings are as accurate as possible.

It is suggested that to improve the pre-processing of the data an alternative approach be taken to estimate the spectra on the data. One method is to blind the study to eliminate bias and pre-process each tremor signal individually, applying different filters and windowing to best estimate the power spectral density. This would eliminate the possibility of distorting the shape of power spectral density estimate by applying the same filtering and windowing to all tremor signals. Another method would be an adaptive approach specifically for tremor, such as the one suggested by Timmer, Lauk, and Deuchl (1996).[40] In future works, a Kalman Filter could also be implemented during the pre-processing of data.

Although not performed in this study, it would have been interesting to determine how well the Parkinson subjects could be classified, if the Essential subjects had been included in the classifications. Likewise, it would also be interesting to determine if abnormal tremors could be correctly classified out of the Healthy Control subjects, Parkinson subjects, and Essential Tremor subjects. It is also suggested that more subjects and possibly more trials be recorded in future works. This would increase the power of the study and add more validity to the results. It would also be beneficial to include the UPDRS score at the time of the recording, recorded by a clinician. This would provide better true indication of the severity of tremor and determine if similar scores can be derived based on the tremor measurements and characteristics. Comments as to whether the subjects are currently taking medication or if they are undergoing treatment for the tremor would also be useful as this could greatly affect the presence of tremors characteristic to Parkinson Disease and Essential Tremor. The identification and calculation of more potential features could also prove to be useful along with an implementation of a feature selection algorithm to identify the most deterministic features that could be used in the classification. Although only one unsupervised and one supervised learning methods were implemented in this study, it is suggested that others alternatives may provide better results.

Appendix A

Data

Leap Motion Controller		Trial 1							
Group	Patient #	Proportional Power between 4-6 Hz	Proportional Power between 8-12 Hz	Median Frequency	Frequency Dispersion	Max. Freq. between 0-25 Hz	Power of max peak between 0-25 Hz	Proportional Power of max peak between 0-25 Hz	Total Power between 0-25 Hz
PD	Patient 1	0.718157003	0.047230623	5.468750000	1.562500000	5.468750000	0.043432726	0.129074876	0.336492491
	Patient 2	0.494700044	0.129147483	5.273437500	4.101562500	4.492187500	0.000367696	0.074963509	0.004905004
	Patient 3	0.298054658	0.244515913	7.031250000	4.492187500	7.812500000	0.003037163	0.046097740	0.065885300
	Patient 4	0.240509665	0.216167833	6.835937500	4.101562500	6.445312500	0.000223820	0.048940664	0.004573295
	Patient 5	0.163154291	0.397543853	7.812500000	4.101562500	8.398437500	0.000030801	0.048011152	0.000641542
	Patient 6	0.464242986	0.152638905	5.273437500	4.296875000	4.882812500	0.000054436	0.055259173	0.000985104
	Patient 7	0.199362996	0.290735114	7.617187500	4.687500000	7.617187500	0.000004507	0.044877746	0.000100433
	Patient 8	0.229407839	0.085742086	6.445312500	1.953125000	6.445312500	0.001036631	0.101483252	0.010214795
	Patient 9	0.278266249	0.170635175	6.640625000	4.687500000	6.640625000	0.000382394	0.058786987	0.006504744
	Patient 10	0.866497179	0.013072999	5.468750000	0.976562500	5.468750000	0.009362809	0.157165904	0.059572778
ET	Patient 11	0.449210623	0.150976390	5.859375000	3.906250000	5.468750000	0.001021449	0.053077773	0.019244391
	Patient 12	0.157759642	0.314154933	7.421875000	4.296875000	6.640625000	0.000035745	0.050386903	0.000709417
	Patient 13	0.306922904	0.228494761	6.835937500	4.101562500	5.859375000	0.000049705	0.046058161	0.001079193
	Patient 14	0.089494153	0.421897735	8.593750000	6.640625000	9.179687500	0.000053302	0.037932038	0.001405210
	Patient 15	0.227070414	0.274006783	7.421875000	6.250000000	6.054687500	0.000025204	0.035813073	0.000703786
	Patient 16	0.195201910	0.369957781	7.617187500	4.296875000	8.789062500	0.000007549	0.043754675	0.000172551
	Patient 17	0.553113743	0.091371234	4.882812500	3.320312500	4.296875000	0.001054843	0.094518968	0.011160123
	Patient 18	0.291607640	0.231831938	7.031250000	4.101562500	7.421875000	0.000048686	0.045739008	0.001064436
	Patient 19	0.748572775	0.055100047	5.468750000	1.367187500	5.468750000	0.000085866	0.136301311	0.000629973
	Patient 20	0.165982870	0.356768307	8.007812500	4.882812500	8.007812500	0.000010434	0.042593141	0.000244980
HE	Patient 21	0.154426048	0.362884801	7.812500000	4.296875000	7.421875000	0.000183941	0.040495148	0.004542297
	Patient 22	0.181373034	0.326901805	7.812500000	5.468750000	7.226562500	0.000014244	0.037229011	0.000382624
	Patient 23	0.215043190	0.360677926	7.421875000	4.101562500	8.789062500	0.000000917	0.042932528	0.000021364
	Patient 24	0.188695885	0.275123432	7.421875000	4.492187500	7.617187500	0.000000043	0.040946827	0.000001071
	Patient 25	0.217667681	0.244947460	7.031250000	4.101562500	6.640625000	0.000026941	0.046514344	0.000579197
	Patient 26	0.245120307	0.203558843	7.031250000	4.296875000	7.031250000	0.000002907	0.048743748	0.000059650
	Patient 27	0.265041140	0.294923540	7.226562500	4.492187500	6.054687500	0.000004032	0.038066900	0.000105918
	Patient 28	0.161992441	0.262174598	7.226562500	3.710937500	6.835937500	0.000002182	0.047668294	0.000045779
	Patient 29	0.172508490	0.277188282	7.421875000	3.710937500	7.617187500	0.000001164	0.051481801	0.000022624
	Patient 30	0.239263832	0.271517054	7.226562500	4.296875000	7.226562500	0.000013687	0.042982063	0.000318440

Leap Motion Controller		Trial 2							
Group	Patient #	Proportional Power between 4-6 Hz	Proportional Power between 8-12 Hz	Median Frequency	Frequency Dispersion	Max. Freq. between 0-25 Hz	Power of max peak between 0-25 Hz	Proportional Power of max peak between 0-25 Hz	Total Power between 0-25 Hz
PD	Patient 1	0.3866780	0.2547928	6.0546875	4.4921875	4.4921875	0.0024710	0.0512100	0.0482522
	Patient 2	0.5665100	0.1694586	5.0781250	4.2968750	4.4921875	0.0014137	0.0750748	0.0188308
	Patient 3	0.3284396	0.2223000	5.8593750	5.2734375	4.1015625	0.0016435	0.0614806	0.0267327
	Patient 4	0.5973380	0.1523724	5.6640625	3.3203125	5.4687500	0.0003087	0.1018742	0.0030300
	Patient 5	0.1692995	0.3030152	7.6171875	4.8828125	8.0078125	0.0000146	0.0389984	0.0003756
	Patient 6	0.3963620	0.2268910	5.8593750	4.2968750	5.2734375	0.0000329	0.0417853	0.0007880
	Patient 7	0.1364188	0.4065515	8.0078125	4.1015625	8.5937500	0.0000000	0.0426615	0.0000005
	Patient 8	0.1971898	0.2307805	6.8359375	2.9296875	6.4453125	0.0005174	0.0645624	0.0080147
	Patient 9	0.1396266	0.3631385	7.8125000	3.9062500	8.5937500	0.0002238	0.0445346	0.0050253
	Patient 10	0.8411838	0.0504775	5.4687500	1.1718750	5.2734375	0.0235972	0.1549630	0.1522761
ET	Patient 11	0.5321935	0.1811619	5.8593750	3.9062500	5.2734375	0.0043053	0.0840130	0.0512460
	Patient 12	0.2185071	0.3334472	7.6171875	5.0781250	5.8593750	0.0000570	0.0344488	0.0016554
	Patient 13	0.2199938	0.2571104	7.2265625	3.3203125	7.8125000	0.0000285	0.0504597	0.0005657
	Patient 14	0.1652737	0.4081493	8.2031250	3.7109375	8.7890625	0.0000100	0.0577935	0.0001737
	Patient 15	0.2378957	0.3410756	7.0312500	5.0781250	8.5937500	0.0000045	0.0343813	0.0001301
	Patient 16	0.2388584	0.2811318	7.4218750	4.1015625	7.6171875	0.0000103	0.0430237	0.0002391
	Patient 17	0.4346800	0.2083881	5.4687500	4.4921875	4.2968750	0.0045889	0.0590021	0.0777756
	Patient 18	0.2334817	0.2297407	7.0312500	4.1015625	7.4218750	0.0000358	0.0456488	0.0007838
	Patient 19	0.6476124	0.1217374	5.6640625	2.9296875	5.4687500	0.0000930	0.1126020	0.0008262
	Patient 20	0.1879533	0.3037330	7.6171875	4.8828125	7.8125000	0.0000125	0.0421922	0.0002957
HE	Patient 21	0.2357107	0.3092422	7.4218750	4.4921875	7.0312500	0.0000306	0.0406616	0.0007536
	Patient 22	0.2190216	0.2697444	7.2265625	4.2968750	7.2265625	0.0000043	0.0394765	0.0001089
	Patient 23	0.2326085	0.2933525	7.4218750	4.2968750	7.6171875	0.0000006	0.0414202	0.0000135
	Patient 24	0.1804642	0.2863243	7.4218750	3.9062500	7.2265625	0.0000000	0.0460995	0.0000006
	Patient 25	0.2094146	0.2362635	7.0312500	4.4921875	6.4453125	0.0000660	0.0488348	0.0013524
	Patient 26	0.2030863	0.2584315	7.0312500	5.6640625	6.6406250	0.0000032	0.0379260	0.0000837
	Patient 27	0.2469855	0.1840417	6.6406250	3.1250000	6.4453125	0.0000022	0.0592849	0.0000379
	Patient 28	0.3194359	0.2088927	6.4453125	4.6875000	5.6640625	0.0000002	0.0339593	0.0000046
	Patient 29	0.1677264	0.2928681	7.4218750	4.8828125	6.8359375	0.0000030	0.0474759	0.0000641
	Patient 30	0.2488117	0.2304057	7.0312500	4.1015625	7.0312500	0.0000164	0.0423286	0.0003872

Tremorometer		Trial 1							
Group	Patient #	Proportional Power between 4-6 Hz	Proportional Power between 8-12 Hz	Median Frequency	Frequency Dispersion	Max. Freq. between 0-25 Hz	Power of max peak between 0-25 Hz	Proportional Power of max peak between 0-25 Hz	Total Power between 0-25 Hz
PD	Patient 1	0.662898756	0.168711689	4.687500000	5.078125000	4.687500000	0.036190135	0.216915850	0.166839228
	Patient 2	0.598708708	0.041206669	5.859375000	1.953125000	5.468750000	0.000202818	0.169117390	0.001199267
	Patient 3	0.603574990	0.099730454	4.296875000	1.171875000	4.296875000	0.164428372	0.309310018	0.531597041
	Patient 4	0.200416926	0.223835262	7.031250000	3.515625000	7.031250000	0.000245489	0.107785480	0.002277539
	Patient 5	0.427382952	0.071385421	6.250000000	2.343750000	6.250000000	0.000148334	0.145017124	0.001022869
	Patient 6	0.769274566	0.052440394	4.687500000	1.562500000	4.687500000	0.002134835	0.259918587	0.008213415
	Patient 7	0.133203839	0.539032386	8.984375000	5.078125000	9.765625000	0.000004536	0.072984526	0.000062152
	Patient 8	0.132804073	0.088745389	7.031250000	1.562500000	7.031250000	0.018245964	0.236032695	0.077302496
	Patient 9	0.111090504	0.486497466	8.984375000	5.859375000	9.375000000	0.000009133	0.084547253	0.000108016
	Patient 10	0.856480613	0.049093251	5.468750000	0.781250000	5.468750000	0.016967712	0.314015256	0.054034627
ET	Patient 11	0.440837050	0.007496057	6.250000000	1.171875000	6.250000000	0.391771640	0.327519836	1.196176364
	Patient 12	0.334350383	0.060918288	6.250000000	1.953125000	6.250000000	0.000149092	0.182422641	0.000817263
	Patient 13	0.281706898	0.146672397	6.250000000	7.031250000	6.250000000	0.000211253	0.091412917	0.002310936
	Patient 14	0.175563722	0.246762788	7.421875000	6.250000000	7.812500000	0.000005242	0.094668952	0.000055371
	Patient 15	0.293197811	0.057819167	3.906250000	3.515625000	3.125000000	0.001655713	0.147906440	0.011194252
	Patient 16	0.197490222	0.317474247	7.031250000	3.906250000	6.250000000	0.000043695	0.136789286	0.000319424
	Patient 17	0.469121036	0.022960473	3.906250000	1.953125000	3.906250000	0.008292007	0.252589049	0.032828008
	Patient 18	0.535055303	0.039717415	4.687500000	2.734375000	4.687500000	0.001112017	0.131615526	0.008448965
	Patient 19	0.698532632	0.061161957	5.468750000	1.953125000	5.468750000	0.006764987	0.246581717	0.027435057
	Patient 20	0.214809747	0.027644876	6.250000000	1.171875000	6.250000000	0.000532856	0.275212948	0.001936155
HE	Patient 21	0.046460959	0.482540121	10.546875000	4.687500000	12.890625000	0.000010694	0.105050090	0.000101791
	Patient 22	0.393938815	0.090553381	6.250000000	3.515625000	6.250000000	0.000016691	0.126398975	0.000132049
	Patient 23	0.086193223	0.619810808	10.156250000	4.687500000	10.546875000	0.000015012	0.118718511	0.000126451
	Patient 24	0.104563646	0.471636612	8.203125000	3.906250000	8.593750000	0.000006063	0.112506066	0.000053884
	Patient 25	0.537190568	0.071672869	5.468750000	2.734375000	5.078125000	0.000055770	0.133051771	0.000419154
	Patient 26	0.329238115	0.180133950	6.250000000	5.468750000	5.078125000	0.000018288	0.083628360	0.000218679
	Patient 27	0.416266623	0.155343413	6.250000000	3.515625000	6.250000000	0.000054379	0.155648448	0.000349365
	Patient 28	0.165489671	0.185577894	7.031250000	3.515625000	6.640625000	0.000012222	0.132450290	0.000092270
	Patient 29	0.143306524	0.203487739	7.031250000	3.515625000	7.031250000	0.000013207	0.115649225	0.000114196
	Patient 30	0.195691573	0.317210594	7.421875000	4.687500000	6.250000000	0.000061296	0.087032386	0.000704287

Tremorometer		Trial 2							
Group	Patient #	Proportional Power between 4-6 Hz	Proportional Power between 8-12 Hz	Median Frequency	Frequency Dispersion	Max. Freq. between 0-25 Hz	Power of max peak between 0-25 Hz	Proportional Power of max peak between 0-25 Hz	Total Power between 0-25 Hz
PD	Patient 1	0.672684755	0.125659997	5.078125000	5.078125000	5.078125000	0.042454450	0.217732992	0.194982578
	Patient 2	0.740809573	0.040821762	5.468750000	1.562500000	5.078125000	0.000459365	0.221044653	0.002078145
	Patient 3	0.785542175	0.072113082	4.687500000	0.781250000	4.687500000	0.224973326	0.301747400	0.745567436
	Patient 4	0.123395765	0.332569135	7.812500000	5.078125000	7.421875000	0.000146220	0.094384801	0.001549157
	Patient 5	0.818808549	0.045136177	5.078125000	1.171875000	5.078125000	0.000357140	0.295756194	0.001207544
	Patient 6	0.601312849	0.065782174	5.468750000	2.343750000	5.468750000	0.001466413	0.195781302	0.007489995
	Patient 7	0.141014515	0.380886791	7.812500000	3.906250000	7.421875000	0.000017251	0.113996048	0.000151325
	Patient 8	0.270259334	0.116383007	6.640625000	2.734375000	6.640625000	0.012028742	0.177248317	0.067863556
	Patient 9	0.174836735	0.436066139	9.375000000	8.984375000	9.375000000	0.000007120	0.083807400	0.000084949
	Patient 10	0.889474743	0.026171007	5.468750000	1.171875000	5.468750000	0.114978839	0.304763733	0.377271878
ET	Patient 11	0.435521257	0.011900603	6.250000000	1.171875000	6.250000000	0.533550869	0.308139000	1.731524829
	Patient 12	0.240003446	0.084143894	6.250000000	2.343750000	6.640625000	0.000152531	0.179026673	0.000851982
	Patient 13	0.416674237	0.145688404	5.859375000	7.031250000	5.078125000	0.000133047	0.099205287	0.001341101
	Patient 14	0.127661723	0.294982599	7.421875000	5.468750000	7.812500000	0.000006130	0.110641640	0.000055405
	Patient 15	0.198891718	0.111229977	3.906250000	5.078125000	3.125000000	0.000591167	0.163376138	0.003618383
	Patient 16	0.190778343	0.306046388	7.421875000	4.296875000	6.250000000	0.000024683	0.105240203	0.000234537
	Patient 17	0.781076071	0.054919637	5.078125000	1.171875000	5.078125000	0.220200250	0.235908204	0.933413075
	Patient 18	0.539575483	0.081689772	5.859375000	2.734375000	5.468750000	0.000221490	0.161731859	0.001369482
	Patient 19	0.872798552	0.019882996	5.468750000	0.781250000	5.468750000	0.008210326	0.353016893	0.023257591
	Patient 20	0.258204641	0.075945087	6.250000000	1.562500000	6.250000000	0.000266671	0.239389483	0.001113959
HE	Patient 21	0.042471298	0.619398511	9.765625000	4.296875000	10.156250000	0.000008286	0.094722091	0.000087478
	Patient 22	0.325283551	0.134054200	6.250000000	4.687500000	6.250000000	0.000018182	0.162381277	0.000111967
	Patient 23	0.095406612	0.530434064	9.375000000	5.468750000	10.156250000	0.000008339	0.077629240	0.000107415
	Patient 24	0.065260770	0.511429598	8.203125000	3.125000000	8.593750000	0.000008212	0.123719237	0.000066374
	Patient 25	0.527634234	0.037593928	5.859375000	1.953125000	5.468750000	0.000185313	0.182420525	0.001015852
	Patient 26	0.312016209	0.123756980	6.250000000	3.515625000	6.250000000	0.000028807	0.128544254	0.000224099
	Patient 27	0.298518598	0.161869906	6.250000000	3.906250000	6.250000000	0.000084659	0.201496013	0.000420146
	Patient 28	0.351185158	0.136624223	6.250000000	4.687500000	5.859375000	0.000005748	0.103101113	0.000055748
	Patient 29	0.229695761	0.178013521	6.640625000	3.515625000	6.250000000	0.000039739	0.123046528	0.000322957
	Patient 30	0.307553821	0.248029242	6.640625000	3.906250000	5.859375000	0.000107824	0.099847389	0.001079882

Appendix B

IRB Application

Tremor Detection

PI: Matthew Johnson
IRB ID #: 201404034

Project Details

I. Demographics

I.1	***Project Title:*** Detection of Parkinson Disease Rest Tremor
I.2	***Short Title (required):*** Tremor Detection
I.3	***Project is primarily:*** Biomedical
I.4	***Do you want the IRB to give this project*** Regular (expedited or full board) review
I.7	***Enter the estimated date you will be ready to begin recruiting participants or collecting data for this project.*** 04/2014

I.8 ***Provide a short summary of the purpose and procedures of the study proposed in this IRB application.***

- ***DO NOT include information on studies not proposed in this application. (If your source of support proposal describes multiple aims, refer to the information button for an example on how to complete this question.)***
- ***Use LAY terminology only. This must be easily understandable by IRB community members and nonscientists.***
- ***DO NOT cut and paste technical abstracts from source of support applications that may not be understood by a general audience.***

The main purpose of this study is to determine whether it is possible to predict, with reasonable accuracy, if a patient has Parkinson Disease based on their rest tremor. The rest tremor will be measured by recording the three-dimensional position and acceleration of their index finger while at rest over a set period of time. This will be done using two devices. The first device, the Tremorometer, uses a three-dimensional accelerometer(a device that measures changes in acceleration) and has 510k clearance by the FDA to measure and quantify tremor by measuring acceleration and calculating tremor statistics in human patients. The second device, the Leap Motion Controller, is a three-dimensional camera that uses two CCD (Charged Coupled Device) cameras and three infrared LEDs to obtain position data. Tremor statistics obtained and calculated from both devices will be compared to determine if data obtained from the Leap Motion Controller are substantially equivalent to that obtained from the Tremorometer. The data obtained from the Leap Motion Controller will then be used to determine the characteristic features of rest tremor in Parkinson Disease and then be used to create an algorithm that can predict whether a patient has Parkinson disease.

I.9 ***Specify your research question(s), study aims or hypotheses (do not indicate "see protocol")***

Hypothesis 1: The Leap Motion Controller can be used in place of a triaxial accelerometer to record rest tremor in Parkinson Disease.
Aim 1: Determine whether the Leap Motion Controller can be used to obtain similar tremor statistics as those obtained from a triaxial accelerometer (Tremorometer).

Hypothesis 2: The data obtained from the Leap Motion Controller can be used to identify characteristic features of rest tremor in Parkinson Disease that will distinguish PD patients from patients with Essential Tremor.
Aim 2: Determine whether patients with rest tremor in Parkinson disease can be identified when compared to patients with Essential Tremor, using the positional data collected by the Leap Motion Controller.

I.10 ***Background and significance and/or Preliminary studies related to this project.***
(do not indicate "see protocol")

Parkinson Disease (PD) is a debilitating and progressive movement disorder that affects over one million people in the United States alone. One of the most characteristic symptoms of PD is resting tremor, as it has been shown that the proportion of patients with resting tremor ranged from 69-100% in 3 series of patients with autopsy-proven PD[1,2,3]. Several methods currently exist to quantitatively measure tremor including accelerometry, electromyography, the spirogram, and most recently three-dimensional cameras [4]. Advances in three-dimensional cameras have allowed for more accurate recordings and can now be used to provide much more accurate measurements in microdisplacements of upper extremities that are involved in movements such as resting tremor. One such three-dimensional camera is the Leap Motion Controller, produced by Leap Motion, Inc. The device is a small USB three-dimensional camera that utilizes two CCD (Charged Coupled Device) cameras and three infrared LEDs to obtain depth information, and is capable of measuring changes in position to within 0.01 mm, and requires no external sensors or markers unlike accelerometry, electromyography, and the spriogram. The advantage of having no sensors attached to the body is that the mass of the sensors decrease the peak frequency of finger tremor by approximately 0.85 Hz for every gram of additional mass with

no solid data for its effects on the amplitude of acceleration [5]. Therefore the attached sensors may change the characteristics of the tremor, thus altering interpretation of tremor. Unlike accelerometers, the Leap Motion Controller does not require calibration eliminating possible errors caused by recalibrating. Unlike electromyography, the Leap Motion Controller is not affected by interference from electrical sources, mechanical artifacts, stimulus artifacts, and the electrical activity of muscles that are not of interest. This is why the Leap Motion Controller is of interest and may be superior in measuring tremor.

I.11 ***Literature cited / references (if attaching a grant or protocol enter N/A).***

1. Hughes AJDaniel SELees AJ The clinical features of Parkinson's disease in 100 histologically proven cases. Adv Neurol. 1993;60595- 599

2. Louis EDKlatka LALiu YFahn S Comparison of extrapyramidal features in 31 pathologically confirmed cases of diffuse Lewy body disease and 34 pathologically confirmed cases of Parkinson's disease. Neurology. 1997;48376- 380

3.Rajput AHRozdilsky BAng L Occurrence of resting tremor in Parkinson's disease. Neurology.1991;411298- 1299

4. Wenzelburger, R., Raethjen, J., Löffler, K., Stolze, H., Illert, M. and Deuschl, G. (2000), Kinetic tremor in a reach-to-grasp movement in Parkinson's disease. Mov. Disord., 15: 1084–1094.

5. Stiles RN, Randall JE; Mechanical factors in human tremor frequency; J Appl Physiol 1967;23(3):324-30

I.12 ***Select up to three key words below that best describe this research study:***

- Engineering
  - Electrical
- Investigational Devices

II. Research Team

II.1 ***The Principal Investigator of this study is:***
Graduate student/Medical Student

II.3 ***Do you want to add a team member who is a WUSTL faculty, student or staff member?***
Yes

II.4 ***Do you want to add a team member who is <u>not</u> a WUSTL faculty, student or staff member?***
No

II.*Team Members*
5

WUSTL Team Members

Role	Name	E-mail	College	Department	Contact	WUSTL COI	Consent Process Involvement
PI	Matthew Johnson, Biomedical Engineering, BS	johnson.m@wustl.edu	School Of Engineering And Applied Science	General Engineering	Yes		Yes
FS	Arye Nehorai, PHD	nehorai@ese.wustl.edu	School Of Engineering	Electrical & Systems Engineering	Yes		No
	Scott Norris, MD, BA	norriss@npg.wustl.edu	School Of Medicine	Neurology	Yes		Yes
	Mwiza Ushe, MD, MA-	ushem@neuro.wustl.edu	School Of Medicine	Neurology	Yes		Yes

Name	Financial Interests
Matthew Johnson, Biomedical Engineering, BS	none
Arye Nehorai, PHD	none
Scott Norris, MD, BA	none
Mwiza Ushe, MD, MA-	none

Non-WUSTL Team Members

Name	Institution	Location	FWA	Role	DHHS	Contact	WUSTL COI	Consent Process Involvement
Nothing found to display								

Name	Financial Interests
Nothing found to display	

III. Source(s) of Support

III.1 *Source(s) of Support*

	Type	Source	Grant Title	Name of PI on Grant	Status	Status Description
	No Support					

* new source name

IV. Waiver of Consent

IV.1 ***Are you requesting a waiver of informed consent (participants will not be given <u>any</u> oral or written information about the study <u>prior</u> to their participation)?***
No

V. Other Institutional Reviews/Requirements

V.1 ***Do you or a family member have within the past twelve months or anticipate having within the next twelve months any financial interests in the company/organization providing support for this research or from a company/organization that owns or licenses the drug, device, or intellectual property being utilized in this research?***

Name	Financial Interests
Matthew Johnson, Biomedical Engineering, BS	none
Arye Nehorai, PHD	none
Scott Norris, MD, BA	none
Mwiza Ushe, MD, MA-	none

V.4 ***Do any of the objectives of this study involve the diagnosis, prevention, screening, evaluation, treatment or support of cancer patients?***
No

V.5 ***Are more than 30% of the patients involved in this study likely to have an active cancer diagnosis?***
No

V.7 ***Will any subject be asked to undergo a radiation therapy procedure (including external beam therapy, brachytherapy, or radiopharmaceutical therapy)?***

No

V.10 ***Does your study involve the administration of radiopharmaceuticals (radioactive drugs) for research purposes?***

No

V.12 ***Will any participant be asked to undergo any of the following:***

- ***a standard radiology procedure involving ionizing radiation (includes X-rays, fluoroscopy, DEXA, CT)***

OR

- ***a standard nuclear medicine examination with FDA-approved radioactive drugs (including bone scans, radionuclide ventriculogram (RVG or MUGA), myocardial perfusion imaging, FDG-PET)***

- ***DO NOT include MRI or ultrasound***

No

V.17 ***Will the study involve <u>any</u> of the following activity at WUSM or any BJC hospitals, even if subjects or their insurance will not be billed for the item or service, and regardless of the study funding source (including studies with departmental or no funding)?***

- ***Procedures, tests, examinations, hospitalizations, use of Pathology services, use of clinic facilities or clinical equipment, or any patient care services, including services conducted in the Clinical Research Unit; or***
- ***Physician services or services provided by non-physicians who are credentialed to bill (ARNPs, Physician Assistants, etc.)***

Yes

V.18 ***Does this project involve administration of recombinant DNA (gene therapy) or microorganisms?***

No

V.19 ***Does this study involve the use of human embryonic stem cells or human induced pluripotent stem cells?***

No

V.20 ***Does this study involve research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero?***
No

V.21 ***Will you be utilizing participants, data or tissue from the Memory & Aging Project (MAP) or Alzheimer's Disease Research Center (ADRC)?***
No

V.22 ***Is the PI of this study a BJH Registered nurse or a staff member of Patient Care Services (Pharmacy, PT/OT/, Respiratory, Rehabilitation, and Social work)?***
No

V.23 ***Will any portion of this project be conducted in any Center for Applied Research Sciences Units, Clinical Research Unit (CRU), Clinical Trials Unit (CTU) and/or the Pediatric Research Unit (PCRU)?***
No

V.24 ***Will this research be performed in the Neonatal Intensive Care Unit (NICU)?***
No

V.25 ***Is this research being conducted in the Emergency Department?***
No

V.26 ***Are you recruiting or screening patients in the Emergency Department?***
No

VI. Participants

VI.1 ***How many adult participants do you expect to consent for this project?***
30

VI.2 ***What is the age of the youngest adult participant?***
18.0

VI.3 ***What is the age of the oldest adult participant?***
No age limit

VI.4 ***How many minor participants do you expect to consent for this project?***
0

VI.7 ***Describe EACH of your participant populations***

- ***Include description of any control group(s)***
- ***Specify the Inclusion/Exclusion criteria for EACH group***

Study patient groups:
1) 10 patients diagnosed with Parkinsonism with tremor

Inclusion criteria:
a. age greater than or equal to 18
b. male or female
c. any race or ethnicity
d. physician confirmed Parkinsonism, with tremor as a symptom, based on diagnostic criteria (Calne DB, Snow BJ, Lee C. Criteria for Diagnosing Parkinson's Disease. Annals of Neurology 1992; 32:S125-S127.)
e. ability to give informed consent

Exclusion criteria:
a. History of stroke, seizure, cerebral palsy, or additional neurological diagnosis
b. Severe upper limb tremor
c. Any serious medical or psychiatric condition
d. Age less than 18
e. Cognitive impairment (Mini-Mental State Score <19)

2)10 patients diagnosed with Essential Tremor

Inclusion criteria:
a. age greater than or equal to 18
b. male or female
c. any race or ethnicity
d. physician confirmed essential tremor based on diagnostic criteria (Bain P, Brin M, Deuschl G, Elble R, Jankovic J, Findley L, Koller B, Pahwa R. Criteria for the diagnosis of essential tremor. Neurology 2000;54(Suppl. 4):57.)
e. ability to give informed consent

Exclusion criteria:
a. History of stroke, seizure, cerebral palsy, or other major psychiatric illness
b. Severe upper limb tremor
c. Any serious medical or psychiatric condition
d. Age less than 18
e. Cognitive impairment (Mini-Mental State Score <19)

3) 10 normal control subjects

Inclusion criteria:
a. age greater than or equal to 18
b. male or female
c. any race or ethnicity
d. ability to give informed consent

Exclusion criteria:
a. History of stroke, seizure, cerebral palsy, or other major psychiatric illness
b. Severe upper limb tremor
c. Any serious medical or psychiatric condition
d. Age less than 18
e. Cognitive impairment (Mini-Mental State Score <19)

VI.8 ***Describe why you believe there is a sufficient number of potential participants available to meet your recruitment goals.***

Over one million people in the United States suffer from Parkinson disease alone. The clinical database in the Washington University Movement Disorders Clinic follows a large number of patients with Parkinsonism with tremor as a symptom as well as patients with Essential Tremor. Therefore, the 10 subjects with Parkinsonism with tremor and the 10 subjects with Essential Tremor required for this study represents a very small proportion of the potential participants within this database. 10 healthy control subjects will be recruited among the spouses or from the Volunteer for Health initiative of Barnes-Jewish Hospital and Washington University School of Medicine's Research Participant Registry with a pool of over 8000 volunteers.

VI.9 ***Describe how you will have access to each of your study populations in sufficient number to meet your recruitment goals.***

Participants with Parkinsonism and Essential Tremor will be recruited from the Movement Disorders Center at Washington

University School of Medicine. Healthy control subjects will be recruited among their spouses or from the Volunteer for Health initiative of Barnes-Jewish Hospital, an affiliate of the Washington University School of Medicine with a pool of over 8000 volunteers.

VI.10 ***Choose the appropriate description of the disease/condition under study (for example consider race, ethnicity, gender, socioeconomic status etc.)***

The disease/condition under study is represented equally throughout the population

VI.13 ***Will participants provide any information about their relatives or another person (third party)?***

No

VI.16 ***Will any individual(s), other than the participant, provide you with information about the participant (e.g. proxy interviews)?***

No

VI.21 ***Do you <u>plan</u> to recruit/enroll non-English speaking people?***

No

VI.24 ***Do you propose to enroll any of the following in this study as participants?***

- ***Employee of the PI or employee of a research team member***
- ***Individual supervised by PI or supervised by member of research team***
- ***Individual subordinate to the PI or subordinate to any member of the research team***
- ***Student or trainee under the direction of the PI or under the direction of a member of the research team***

No

VI.26 ***Is this project <u>about</u> pregnant women?***

No

VI.27 ***Will this project involve fetuses?***

No

VI.28 ***Does this project involve adult participants who may be incompetent or have limited decision-making capacity on initial enrollment into the study?***

No

VI.34 ***Does this project involve participants whose capacity to consent may change over the course of the study?***

No

VI.38 ***Does this project involve prisoners as participants?***
No

VII.A. Basic Project Information

VII.A.1 ***Is there a separate, written protocol that will be submitted in addition to this IRB New Project form? (Note: a grant application is not considered to be a protocol)***
Yes

VII.A.2 ***Who initiated/provided the protocol?***
WUSTL Investigator

VII.A.4 ***Protocol#:***

VII.A.5 ***Protocol Version#:***

VII.A.6 ***Protocol Date:***

VII.A.7 ***Provide a list of the amendments for this study (this may be left blank if none). Any amendments previously listed should not be removed.***

Amend. #	Amend. Date
Nothing found to display	

VII.A.8 ***Where will project procedures take place (check all that apply)?***

- Barnes Jewish Hospital (BJH)
- Washington University School of Medicine (WUSM)

VII.A.9 ***Is this project also being conducted by other researchers at their own sites (e.g. a multi-site collaborative project)?***
No

VII.B. Drugs/Devices

VII.B.1 ***Does this project involve any of the following:***

- ***clinical intervention***
- ***pharmacologic intervention***
- ***therapeutic intervention***
- ***physiology studies (e.g. studying the functions of organs, tissues, or cells)***

Yes

VII.B.2 ***Does this project involve any substance ingested, injected, or applied to the body?***
No

VII.B.9 ***Are any contrast agents used for any purpose in this study?***
No

VII.B.11 ***Does this project involve a drug washout (asking participant to stop taking any drugs s/he is currently taking)?***
No

VII.B.15 ***Will any participants receive a placebo in this study when, if they were not participating, they could be receiving an FDA-approved treatment for their condition?***
No

VII.B.20 ***Does this project involve testing the safety and/or efficacy of a medical device?***
Yes

VII.B.21 ***Describe in detail procedures in place for maintaining device shipment and receipt records:***
N/A since the devices are currently marketed and currently on hand.

VII.B.22 ***Who will be responsible for maintaining these shipment and receipt records?***
N/A

VII.B.23 ***Describe in detail procedures in place for tracking use and disposition of devices described in this study:***
N/A

VII.B.24 ***Who will be responsible for maintaining these use and disposition tracking records?***
N/A

VII.B.25 ***Describe in detail procedures in place to limit access to authorized study personnel for the storage, control, and dispensing of the investigational devices.***
N/A

VII.B.26 ***Is the device FDA-approved for the way it will be used in this study?***
No

VII.B.27 ***Is there an IDE (Investigational Device Exemption) for this device in this research project?***
No

VII.B.31 ***Indicate the appropriate FDA status you and/or the sponsor are requesting for the use of this device in this study.***
Non-Significant Risk (NSR) device/software

VII.B.33 ***Provide a detailed rationale for why this device meets the FDA definition of a Non-Significant Risk Device (NSR)***
The Leap Motion Controller meets the FDA definition of a Non-Significant Risk Device (NSR) because:
1. It is not an implant
2. It will not be used in supporting or sustaining human life
3. Is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health
4. It does not present a potential for serious risk to the health, safety, or welfare of a subject

The Leap Motion Controller is a consumer three-dimensional camera and will be used in accordance with its purpose: to measure and record hand and finger motions.

The Tremorometer meets the FDA definition of a Non-Significant Risk Device (NSR) because:
1. It is not an implant
2. It will not be used in supporting or sustaining human life
3. Is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health
4. It does not present a potential for serious risk to the health, safety, or welfare of a subject

The Tremorometer has 510k clearance for measuring and quantifying tremor in human participants, which will be its only use in this study.

VII.B.34 ***Provide a summary of prior investigations with this device.***

Prior investigations with the Leap Motion Controller

Mauser, Stanis & Burgert, Oliver. (2014, Feb. 12) Touch-Free GestureBased Control of Medical Devices and Software Based on the Leap Motion Controller. In J.D Westwood, S. W. Westwood, and L. Felländer-Tsai, eds. Medicine Meets Virtual Reality 21: NextMed/MMVR21. Paper presented at 21st NextMed/MMVR conference, Manhattan Beach, California. (pp. 265-270) Vol. 196. IOS Press, 2014.

F. Weichert, D. Bachmann, B. Rudak, D. Fisseler
Analysis of the accuracy and robustness of the leap motion controller
Sensors, 13 (5) (2013), pp. 6380–6393
http://dx.doi.org/10.3390/s130506380

I. Tarnanas, W. Schlee, M. Tsolaki, R. Müri, U. Mosimann, T. Nef
Ecological validity of virtual reality daily living activities screening for early dementia: longitudinal study
JMIR Serious Games, 1 (1) (2013)
http://dx.doi.org/10.2196/games.2778 e1, 1–13

Guna J, Jakus G, Pogačnik M, Tomažič S, Sodnik J. An Analysis of the Precision and Reliability of the Leap Motion Sensor and Its Suitability for Static and Dynamic Tracking. Sensors. 2014; 14(2):3702-3720.

Taha Khan, Dag Nyholm, Jerker Westin, Mark Dougherty, A computer vision framework for finger-tapping evaluation in Parkinson's disease, Artificial Intelligence in Medicine, Volume 60, Issue 1, January 2014, Pages 27-40, ISSN 0933-3657, http://dx.doi.org/10.1016/j.artmed.2013.11.004. (http://www.sciencedirect.com/science/article/pii/S0933365713001565)

Prior investigations with the Tremorometer

Aasef G. Shaikh, Kenichiro Miura, Lance M. Optican, Stefano Ramat, Robert M. Tripp and David S. Zee, “Hypothetical membrane mechanisms in essential tremor”, Journal of Translational Medicine, 2008, 6:68

Aasef G. Shaikh, H. A. Jinnah, Robert M. Tripp, Lance M. Optican, Stefano Ramat, Frederick A. Lenz, David S. Zee, "Irregularity distinguishes limb tremor in cervical dystonia from essential tremor", Journal Neurology, Neurosurgery, Psychiatry, (2008), 79, 187-189; originally published online 14 Sep 2007, doi: 10.1136/JNNP.2007.131110

Aasef G. Shaikh, Kenichiro Miura, Lance M. Optican, Stefano Ramat, R. John Leigh, David S. Zee, "A new familial disease of saccadic oscillations and limb tremor provides clues to mechanisms of common tremor disorders", Brain (2007), 130, 3020-3011

S. M. Bowyer, K. Mason, B. Weiland, J. E. Moran, G. L. Barkley, N. Tepley, "Localization of Motor Cortex by MEG Using a Tremorometer", International Congress Series, Elsevier (2007) doi: 10.1016/j.ics.2007.02.001

Khalafalla O. Bushara, Taimur Malik, Rupert E. Exconde, "The Effect of Levetiracetam on Essential Tremor", Neurology 2005; 64;1078-1080; doi: 10.1212/01.WNL.0000154596.21335.2E

Michael P. Caligiuri, Robert M. Tripp, "A portable hand-held device for quantifying and standardizing tremor assessment", Journal of Medical Engineering and Technology (2004), 28(6):254-262

Michael P. Caligiuri, Robert M. Tripp, "The TremorometerTM: A Portable Instrument for Quantifying Hand Tremor", Biol Psychiatry Abstr (2000), 47:142S

VII.B.35 ***Have there been any prior IRB reviews (at WUSTL or elsewhere) and/or determinations made with regard to this device?***

No

VII.B.37 ***Has the FDA made an assessment of risk with regard to this device?***

Yes

VII.B.38 ***Has this device/software been approved by the FDA for another indication or in another form from its use in this project?***

No

VII.C. Genetic Research

VII.C.1 ***Does this project involve any research on genes or genetic testing/research?***

No

VII.D. Recruitment & Consent

VII.D.1 ***Check all materials/methods that will be used in recruiting participants (you will need to attach copies of all materials at the end of the application):***

- **Existing Registry/database , Describe**

  Washington University Movement Disorders electronic medical record (MARS) clinical database. This is the clinical database for which clinical information is entered for all patients seen in the movement disorders division of neurology. We may utilize the Washington University School of Medicine Research Participant Registry powered by the Volunteer for Health to recruit normal control subjects.

- **PHI**
  - **Use of any information available to the researchers or their colleagues because this person is a patient OR use of any information considered to be Protected Health Information (PHI) OR review of patient/clinic records , Describe source of records**

    We will review patient records in the Washington University Movement Disorders electronic medical record clinical database (MARS) to identify potential participants.

- **Referral from colleague , Describe**

  Physician colleagues within the division of Movement Disorders at Washington University School of Medicine will be verbally notified of the ongoing study. If they evaluate a patient in clinic that fits inclusion criteria, they may provide potential participants with contact information for the research team or direct them directly to the testing room on the day of study.

VII.D.2 ***List the individual data elements you will need to access/use from the patient or clinic records to identify potential participants for recruitment***

1. Definite diagnosis of Parkinsonism or Essential Tremor
2. Mini-mental Status Exam
3. Information regarding examination findings with regard to tremor (i.e. whether present, degree of severity, etc).

VII.D.3 ***Describe why you could not practicably recruit participants without access to and use of the information described above***

The above information is critical inclusion/exclusion criteria which must be confirmed from the medical record.

VII.D.4 ***Describe why you could not practicably obtain authorization from potential participants to review their patient or clinic records for recruitment purposes.***

Without knowing the definite diagnosis and medical history of a patient, it is not possible to identify appropriate subjects to recruit based on specific inclusion criteria.

VII.D.5 ***Describe plans to protect the identifiers from improper use or disclosure***

Only study team members will have access to the medical record of any potential and/or enrolled subjects. These records are password protected in the clinical movement disorders database (MARS) which is HIPAA compliant. Any data collected will not contain any identifiers, except for what is mentioned in the inclusion and exclusion criteria for each group and will only be stored on a LOK-IT Secure Flash Drive, which is automatically encrypted with military-grade 256-bit AES hardware encryption, which is HIPAA compliant.

VII.D.6 ***Describe plans to destroy identifiers at the earliest opportunity consistent with conduct of the research***

There will be no need to utilize any identifiers in this study.

VII.D.7 ***Does the research team agree that the requested information***

will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the study, or for other research for which the use or disclosure of the requested information would be permitted by the HIPAA Privacy Rule

Yes

VII.D.8 ***Will a member of the research team discuss the study with the participant in person prior to the participant agreeing to participate?***

Yes

VII.D.9 ***Describe the physical location where the consent process will take place:***

Meetings with participants will occur in the following location within the Washington University School of Medicine:

1) The movement disorder clinic in the lower level of McMillan Building. The study will be performed behind closed doors in an examination room.

VII.D.10 ***Will a member of the research team discuss the study with the participant by phone prior to the participant agreeing to participate?***

No

VII.D.12 ***Who will be involved in the consent process (including review of consent document, answering participants' questions)?***

Name	Consent Process Involvement
Matthew Johnson, Biomedical Engineering, BS	Yes
Arye Nehorai, PHD	No
Scott Norris, MD, BA	Yes
Mwiza Ushe, MD, MA-	Yes

VII.D.13 ***Check all materials that will be used to obtain/document informed consent:***

- Consent Document

VII.D.14 ***Does the study include any form of deception (e.g., providing participants with false information, misleading information, or withholding information about certain study procedures)?***

Examples:

- ***Procedure includes a cover story that provides a***

plausible but inaccurate account of the purposes of the research.

- ***Participants will be provided with false information regarding the particular behaviors of interest in the research.***
- ***Procedures include a confederate pretending to be another participant in the study.***
- ***Participants will be told that the research includes completion of a particular task, when in fact, that task will not be administered.***
- ***Study is designed to introduce a new procedure (or task) that participants are not initially told about.***

No

VII.D.25 ***Are you requesting a waiver of documentation of consent (either no participant signature or no written document)?***
No

VII.D.28 ***<u>Before</u> the participant gives consent to participate are there any screening questions that you need to directly ask the potential participant to determine eligibility for the study?***
Yes

VII.D.29 ***List any screening questions you will directly ask the potential participant to determine eligibility.***
1. What is your current age?
2. Have you every been diagnosed with any serious medical or psychiatric conditions?

VII.D.30 ***Will you keep a screening log or other record that would include information on people who do not consent to participate in the study?***
No

VII.D.34 ***<u>After</u> the participant agrees to participate (signs consent), are there any screening procedures, tests, or studies that need to be done to determine if the participant is eligible to continue participating?***
No

VII.D.36 ***Discuss how much time a potential participant will have to agree to consider participation and whether or not they will be able to discuss the study with family/friends before deciding on participation.***
The potential participant will have as much time as necessary (or until completion of the project, whichever comes first) to consider participation in the study. They will be allowed to discuss the study with family/friends before deciding on

participation.

VII.D.37 ***How long after the participant agrees to participate do study procedures begin?***

The study procedure can begin as soon as the participant signs the consent form.

VII.D.38 ***Provide a description of the enrollment and consent process for adult participants***

- ***Describe each study population separately including control population***
- ***Include when recruitment and consent materials are used***
- ***Use THIRD person active voice. For example, "the principal investigator will identify potential participants, the study coordinator will discuss the study with participants over the telephone and schedule the first study visit, etc..."***
- ***Describe the steps that will be taken by the research team to minimize the possibility of coercion or undue influence during the consent process***

Ten subjects with clinical diagnostic criteria for Parkinsonism, 10 subjects with clinical diagnostic criteria for Essential Tremor, and 10 normal control subjects will be enrolled in this study. The study team will identify potential participants from the clinical database in the movement disorder clinic at WUSM. Patients will be recruited in person in the movement disorder clinic at WUSM during clinic visits with their physician or nurse. The study team member will determine the capacity of the potential participant to consent for her/himself during initial contact and ask screening questions to determine if the potential participant fits the inclusion/exclusion criteria for the study. If the subject expresses interest in the study and is deemed to fit all inclusion/exclusion criteria, informed consent materials will be provided to the patient. A study team member will review the document with the potential participant to answer any questions or explain any unclear points. Potential participants will be given time to read the document in its entirety, ask questions, and speak with friends/family members if they so desire. Study participants will sign the informed consent, and will be offered a signed copy of the consent after both parties sign the document.

VII.E. Methods

VII.E.1 ***Will participants be randomized?***

No

VII.E.3 ***Will any questionnaires, surveys, or written assessments be used to obtain data directly from participants in this study?***

No

VII.E.5 ***Does this project involve creating any audiotapes, videotapes, or photographs?***

No

VII.E.6 ***Provide a detailed description in sequential order of the study procedures following the consent process - DO NOT cut and paste from the Consent Document.***

Describe study populations separately if they will be participating in different procedures - include CONTROL population if applicable.

DESCRIBE:

- ***What participants will be asked to do/what happens in the study (in sequential order)***
- ***The time period over which procedures will occur***
- ***The time commitment for the participant for individual visits/procedures***
- ***Long-term followup and how it occurs***

All participants, including the control participants, will follow the same procedure. Each participant will be measured twice and be measured individually. First, the participant will be asked to allow a study member to affix with tape the accelerometer (from the Tremorometer system) to the index finger on the hand that they believe to exhibit the most symptomatic tremor. The participant will then be asked to place said hand on a small slanted box and asked to spread their fingers so that no fingers are touching another finger. The participant will again be asked to allow their fingers to relax and drape over the edge of the box, still ensuring that their fingers are not touching each other. Once the participant has their hand in a comfortable position, they will be verbally alerted that the measurement will start and be asked to silently countdown from 100. After 30 seconds, the participant will be verbally alerted that the measurement is over and the accelerometer will be removed. The participant will then be

asked to again place the same hand on the small slanted box, this time in front of the Leap Motion Controller. The participant will again be asked to attempt to spread their fingers so that no fingers are touching another finger and then allow their fingers to relax and drape over the edge of the box, ensuring that their fingers are still not touching one another. Once the participant has their hand in a comfortable position, they will be verbally alerted that the measurement will start and be asked to silently countdown from 100. After 30 seconds, the participant will be alerted that the measurement is over. Once complete, the participant will be finished and thanked for their time. It is estimated that the time commitment for the individual visit will be approximately 10 minutes, which includes a short explanation of the study along with recordings of the individual participant. There will be no attempt at a long-term followup. Each participant will be given an option to be contacted with the results of the study, once the study is complete.

VII.E.7 ***Will you attempt to recontact participants who are lost to follow-up?***

No - followup is not required in this study

VII.E.9 ***Will participants be provided any compensation for participating in this study?***

No

VIII. Risks

VIII.1 ***What are the risks to participants including***
- emotional or psychological
- financial
- legal or social
- physical?

1. Attempting to hold one hand still in one position may be uncomfortable.
2. Participants may become uncomfortable, frustrated, or bored during the recording.
3. Participants may become stressed if they exhibit too severe of upper limb tremor to record the data.

VIII.2 ***What have you done to minimize the risks?***

- ***If applicable to this study ALSO include:***
  - ***How you (members of your research team at WUSTL) will monitor the safety of individual participants.***
  - ***Include a description of the availability of medical or psychological resources that participants might require as a consequence of participating in this research and how referral will occur if necessary (e.g. availability of emergency medical care, psychological counseling, etc.)***

To reduce the risks to the subjects, a physician will be present throughout all studies. Confidentiality will be maintained in accordance with applicable state and federal laws and all study data will be identified only by a code number. Personally identifying data will not be recorded or collected.

VIII.3 ***Does this study have a plan to have an individual or committee review combined data from all participants on a periodic basis (such as summary or aggregate safety and/or efficacy data)?***
No

IX. Benefits

IX.1 ***What are the direct benefits to the participant (do not include compensation)?***
There is no direct benefit to participants.

IX.2 ***What are the potential benefits to society in terms of knowledge to be gained as a result of this project?***
This study may help provide a better understanding of the characteristic features of rest tremor in Parkinsonism. It may also provide a better alternative method to record and measure rest tremor that may aid in the differentiation of Parkinsonism from Essential Tremor.

X. Privacy & Confidentiality

X.1 ***Describe your plans to protect the privacy interests of the participants during the conduct of the study including:***

- ***How will you provide a private setting during the recruitment process***
- ***How will you provide a private setting for the consent process including an opportunity for the participant to ask questions privately***
- ***Describe how interventions occur in a private setting and/or how information will be collected using methods that protect the participant's privacy.***
- ***Discuss why the information collected during the study is necessary to the conduct of the study and does not unnecessarily invade the rights of participants to privacy of their personal information.***

The potential subjects will be escorted into a separate examination room with closed doors in the clinic, after seeing their physician. The potential subjects will be given the opportunity to ask questions privately within the examination room.

The acceleration information collected using the Tremorometer and the position information collected using the Leap Motion Controller is necessary because it serves as a quantitative representation of tremor, which is needed for this study. This quantitative data is needed in order to compare the Leap Motion Controller and the Tremorometer for measuring tremor. It is also needed in order to identify, calculate, and use features of rest tremor that are characteristic of subjects with Parkinson Disease. The collection of this data does not invade the rights of participants to privacy of their personal information because the data being collected is not identifiable and cannot be used to identify the patient. The data will be used to extract underlying characteristics that are unique to their group (Parkinson Disease participants, Essential Tremor participants, healthy participants) and are not unique to the participants themselves.

X.2 ***Are you collecting or using the Social Security Number of any participants for any purpose?***
No

X.4 ***How will information/data be collected and stored for this study (check all that apply):***

- Electronic records (computer files, electronic databases, etc.) - The data that will be recorded will be fully de-identified and will not include names, dates of birth, or clinic numbers. The only data that will be recorded will be the positional and acceleration data of the fingers for each subject and whether or not they have Parkinsons Disease. This data will only be saved on a LOK-IT Secure Flash Drive, which is automatically encrypted with military-grade 256-bit AES hardware encryption. This level of encryption is HIPAA compliant and ensures that the data is unreadable if the flash memory were to be physically accessed.

X.5 ***Do the confidentiality protections indicated above allow only members of the research team to access identified data/specimens?***

Yes

XI. Data Analysis

XI.1 ***Provide a summary of the analysis methods you will use, including, if applicable, the data points or outcomes you will analyze.***

Tremorometer:
All participants will use the Tremorometer system, which will record the three-dimensional acceleration of one finger of the patient over a set period of time. This acceleration data will then be analyzed by the software included in the system to provide the frequency and intensity of the tremor.

Leap Motion Controller:
All participants will use the Leap Motion Controller, which will record the three-dimensional position of the one finger of the patient over a set period of time. This raw position data will then be analyzed using MATLAB in order to calculate the tremor frequency as well as the intensity of the tremor. These calculations will then be compared to those obtained from the Tremorometer system. The position data will further

be used to calculate other characteristics of tremor that will be used as features in creating an algorithm to predict whether a patient has Parkinson's disease.

XI.2 ***Provide the rationale or power analysis to support the number of participants proposed to complete this study.***

In a previous study entitled the Effect of deep brain stimulation on amplitude and frequency characteristics of rest tremor in Parkinson's disease by Beuter et al (2001), 8 Parkinsons subjects were used to determine some of the same characteristics that will also be calculated in this study. Likewise, in The dynamics of resting and postural tremor in Parkinson's disease by Vaillancourt et al (2000), 8 Parkinsons subjects and 8 healthy subjects were used to again obtain the time and frequency structure of tremor. Similarly, in a study that used a 3D motion analysis system to measure tremor, 6 Parkinson subjects were used (A novel quantitative method for 3D measurement of Parkinsonian tremor by Rajaraman et al. 1999). Based on these previous studies, we will recruit 10 healthy subjects, 10 Parkinsons subjects, and 10 Essential Tremor subjects. We expect that the number of participants will provide enough data to adequately examine tremor and to provide enough characteristic features involved in the rest tremor of Parkinsonism to create a predictive algorithm.

XII. Future Research

XII.1 ***Do you wish to keep any information about participants involved with this research project so that other researchers outside the current study team may contact them for future research?***

No

XII.3 ***Does this project involve storing any data for future research?***

Yes – contribution for future use is mandatory for participation in the study

XII.4 ***Does this project involve storing any tissues or specimens for future research?***

No

Appendix C

Informed Consent

Washington University in St. Louis

FOR IRB USE ONLY
IRB ID #: 201404034
APPROVAL DATE: 05/27/14
RELEASED DATE: 05/28/14
EXPIRATION DATE: 05/26/15

INFORMED CONSENT DOCUMENT

Project Title: Detection of Parkinson Disease Rest Tremor

Principal Investigator: Matthew Johnson

Research Team Contact: Matthew Johnson: (561) 906-1671

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research participant. By signing this form you are agreeing to participate in this study.

- If you have any questions about anything in this form, you should ask the research team for more information.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you: have been diagnosed with Parkinson Disease and have tremor as a symptom, have been diagnosed with Essential Tremor, or are healthy with no symptoms of tremor.

The purpose of this research study is to create an algorithm that will predict, with reasonable accuracy, if a patient has Parkinson Disease based on their rest tremor. To create this algorithm, rest tremor data will be collected by recording the three-dimensional position and acceleration of the index finger using two different devices. The first device, the Tremorometer, uses a three-dimensional accelerometer (a device that measures changes in acceleration) and is cleared by the FDA to measure and quantify tremor by measuring acceleration and calculating tremor statistics in human patients. The second device, the Leap Motion Controller, is a three-dimensional camera that can obtain position data and is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration. The data collected and analyzed by the Tremorometer will be compared to that of the Leap Motion Controller to determine whether the Leap Motion Controller can be used to obtain similar results as the Tremorometer. The data from the Leap Motion Controller will be analyzed and used to create an algorithm that can predict whether a patient has Parkinson Disease. It is hypothesized that the Leap Motion Controller will provide similar results as the Tremorometer and that the data from the Leap Motion Controller can be used to create a reasonably accurate algorithm that can identify a patient with Parkinson Disease from a patient with Essential Tremor or a healthy patient.

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WHAT WILL HAPPEN DURING THIS STUDY?

The study will occur in an examination room behind closed doors in the movement disorders clinic within the Washington University School of Medicine. The data that will be recorded will consist of the position and acceleration of your fingers over time and whether you have Parkinson Disease, Essential Tremor, or are healthy with no symptoms of tremor.

You will first be asked to allow a study member to tape a small sensor (the accelerometer from the Tremorometer system) to your index finger on the hand that you exhibit the most symptomatic tremor. You will then be asked to place said hand on a small slanted box and be asked to spread your fingers so that no fingers are touching another finger. You will then be asked to allow your fingers to relax and drape over the edge of the box, still ensuring that your fingers are not touching. Once your hand is in a comfortable position, you will be warned that the recording will start and be asked to silently countdown from 100. After 30 seconds, you will be told that the recording is over and the sensor will be removed. You will then be asked to place the same hand on the small slanted box in front of the Leap Motion Controller (a small three-dimensional camera that tracks hand and finger movements and has not yet been used to measure hand or finger tremors.) You will again be asked to allow your fingers to relax and drape over the edge of the box, still ensuring that no fingers are touching another finger. Once your hand is in a comfortable position, you will be told that the recording will begin and be asked to silently countdown from 100. After 30 seconds, you will be told that the recording is over and the you will be finished with your participation in the study.

Will you save my samples or research data to use in future research studies?

As part of this study, we are obtaining tremor data (in the form of position and acceleration over time) from you. By agreeing to be part of this study you give up any property rights you may have in the tremor data. We would like to use your tremor data for other research projects in the future. These future studies may provide additional information that will be helpful in understanding Parkinson's Disease, but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your tremor data might be used to develop tests, treatments or cures. There are no plans to provide financial compensation to you should this occur. If you agree, this means we will store your tremor data and may use it for studies going on right now as well as studies that are conducted in the future.

I would also like your permission to share your tremor data with other investigators doing research in similar fields such as other diseases where tremor is a common symptom**.** These investigators may be at Washington University or at other research centers. We may also share you research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

Your tremor data will be stored without your name or any other kind of link that would enable us to identify which data are yours. Therefore, if you give permission to store and use your tremor data, it will be available for use in future research studies indefinitely and cannot be removed.

HOW MANY PEOPLE WILL PARTICIPATE?
Approximately 30 people will take part in this study conducted by investigators at Washington University.

HOW LONG WILL I BE IN THIS STUDY?
If you agree to take part in this study, your involvement will last for approximately 10 minutes.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Less Likely / Less Common

Mild

- Risk 1: Attempting to hold one hand still in one position may be physically uncomfortable.
- Risk 2: Become fatigued, frustrated, or bored during the recording.
- Risk 3: Become stressed if you exhibit too severe of upper limb tremor to record the data.

One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure, and we think the risk of accidental disclosure is very small. Please see the section in this consent form titled *"How will you keep my information confidential?"* for more information.

WHAT ARE THE BENEFITS OF THIS STUDY?

You will not benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because the study may help provide a better understanding of the characteristic features of rest tremor in Parkinsonism as well as provide a better alternative to record and measure rest tremor that may aid in the differentiation of Parkinsonism from Essential Tremor.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?
You will not have any additional costs for being in this research study. You and/or your medical/hospital insurance provider will remain responsible for your regular medical care expenses.

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WILL I BE PAID FOR PARTICIPATING?
You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?
This study is not being funded.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?
Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator at (561) 906-1671 and/or the Human Research Protection Office at (314) 633-7400 or 1-(800)-438-0445.

Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?
We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- People who use the Washington University School of Medicine's Research Participant Registry or the clinical movement disorders database (MARS)
- Hospital or University representatives, to complete Hospital or University responsibilities
- Information about your participation in this study may be documented in your health care records and be available to your health care providers who are not part of the research team.
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants.) The Institutional Review Board has reviewed and approved this study.

To help protect your confidentiality, we will have you escorted into a separate examination room with closed doors in the clinic, after seeing your physician. The data that will be recorded will be fully de-identified and will not include your name, date of birth, clinic number, or any other identifiable information. The only data that will be recorded will be the positional and acceleration data of your finger and whether or not you have Parkinson Disease. This data will only be saved on a LOK-IT Secure Flash Drive, which is automatically encrypted with military-grade 256-bit AES hardware encryption. This level of encryption is HIPAA compliant and ensures that the data is unreadable if the flash memory were to be physically accessed. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

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Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?".
Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- Your signature and this form will not expire as long as you wish to participate.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
  - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at http://hrpo.wustl.edu (or use the direct link: http://hrpohome.wustl.edu/participants/WithdrawalTemplate.rtf) or you may request that the Investigator send you a copy of the letter.
    - **If you revoke your authorization:**
      - The research team may only use and share information already collected for the study.
      - Your information may still be used and shared if necessary for safety reasons.
      - You will not be allowed to continue to participate in the study.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If

you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?
You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at http://hrpo.wustl.edu under Information for Research Participants.

Will I receive new information about the study while participating?
If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can someone else end my participation in this study?
Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. This might happen because in our judgement you are exhibiting upper limb tremor too severe to be recorded or if you have too much trouble keeping your fingers separated during the recording.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Matthew Johnson, (561) 906-1671**.** If you experience a research-related injury, please contact: Dr. Arye Nehorai, (314) 935-5565.

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office, 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO 63110, (314) 633-7400, or 1-(800)-438-0445 or email hrpo@wusm.wustl.edu. General information about being a research participant can be found by clicking "Participants" on the Human Research Protection Office web site, http://hrpohome.wustl.edu. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study.

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Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 05/26/15**.**

_____ _____
(Signature of Participant) (Date)

_____
(Participant's name – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that he or she understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

_____
(Name of Person who Obtained Consent - printed)

Appendix D

Assurance Document

Matthew Johnson, Biomedical Engineering, BS
Detection of Parkinson Disease Rest Tremor

Assurances

Principal Investigator (PI) - *As PI, I assure that:*

- I am ultimately responsible for the conduct of the study.
- I agree to comply with all applicable Washington University policies and procedures, and applicable federal, state and local laws.
- The application is consistent with proposal(s) submitted to external funding agencies.
- The research will only be performed by qualified personnel.
- All persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.
- I will not implement any changes in the approved IRB application, study protocol, or informed consent process without prior IRB approval (except in an emergency, if necessary to safeguard the well-being of a human participant).
- If unavailable to conduct this research personally, as when on sabbatical leave, I will arrange for another investigator to assume direct responsibility for the study. Either this person is named as another investigator in this application, or I will notify the IRB of such arrangements.
- I will obtain Continuing Review approval prior to 12:01 am on the date the approval for the study expires. I understand if I fail to apply for continuing review, approval for the study will automatically expire, and all study activity must cease until IRB approval is granted.
- The research team will only collect information essential to the study. To the greatest extent possible, access to the information will be limited within the research team. If protected health information is used or created, it will not be re-used or disclosed to any other person or entity, except as required by law, research oversight, or those uses outlined in the application.
- If members of the research team access protected health information in order to seek consent/authorization for research, such access is necessary for the research, is solely for that purpose, and the information will not be removed from the covered component.
- Neither I nor any member of the research team has a financial interest, as defined by the Washington University's conflict of interest policies, whereby the value of the interest to me or any member of the research team could be influenced by the outcome of the study. Any real or potential conflicts of interest that exist for the PI or any member of the research team that might affect the relationship with the research participant or the outcome of the research will be disclosed in accordance with institutional policies and appropriately managed, reduced, or eliminated, in cooperation with Washington University's Disclosure Review Committee.
- I further assure that the proposed research is not currently being conducted and will not begin until IRB approval has been obtained.

Matthew Johnson — Signature of Principal Investigator

04/09/14 — Date

Matthew Johnson — Printed Name of the Principal Investigator

Dean/Department Chair - *My signature assures that:*

- The investigator is qualified to conduct the research as described in this application.
- The investigator has adequate resources, budget, facilities, and numbers of qualified staff to conduct the research as described in this application.
- A scientific review of the research was conducted and any required changes resulting from the review are included in the submitted application.
- The research uses procedures consistent with sound research design.
- The research design is sound enough to yield the expected knowledge.
- The investigator has available time to oversee and conduct this project.
- If the investigator leaves Washington University without notifying the IRB, I will complete the necessary forms to either close the study or continue the study under the direction of a different investigator.

Ralph S. Quatrano
Dean/Department Chair

4/10/14
Date

RALPH S. QUATRANO
Printed Name of the Dean/Department Chair

Matthew Johnson, Biomedical Engineering, BS
Detection of Parkinson Disease Rest Tremor

Faculty Sponsor (If PI is a student) The faculty sponsor must be a member of the Washington University faculty and is considered the responsible party for the scientific, legal and ethical performance of the project.

As the faculty sponsor on this research application, I assure that:

- I will meet with the student investigator on a regular basis and monitor study progress.
- The student is knowledgeable about the regulations and policies governing research with human subjects and has sufficient training and experience to conduct this particular study in accord with the approved protocol.
- If I will be unavailable to supervise this research personally, as when on sabbatical leave, I will arrange for an alternate Faculty Sponsor to assume direct responsibility in my absence and I will advise the IRB in advance of such arrangements.
- If the student leaves Washington University without notifying the IRB, I will complete any requires forms necessary to either close the study or continue the study solely under my direction or name another student investigator.

Arye Nehorai
Signature of Faculty Sponsor

4/9/14
Date

ARYE NEHORAI
Printed Name of the Faculty Sponsor

Appendix E

Protocol

TABLE OF CONTENTS

A Introduction

A1 Study Abstract

This study is exploratory in nature and its purpose is to attempt to classify, with reasonable accuracy, if a subject can be classified as a Parkinson or non-Pakinson subject based on their rest tremor. The rest tremor will be measured by recording the three-dimensional position and acceleration of their index finger while at rest over a set period of time. This will be done using two devices. The first device, the Tremorometer, uses a three-dimensional accelerometer (a device that measures changes in acceleration) and has 510k clearance by the FDA to measure and quantify tremor by measuring acceleration and calculating tremor statistics in human patients. The second device, the Leap Motion Controller, is a three-dimensional camera that uses two CCD (Charged Coupled Device) cameras and three infrared LEDs to obtain position data. Tremor statistics obtained and calculated from both devices will be compared to determine if data obtained from the Leap Motion Controller are statistically similar to the data obtained from the Tremorometer. The data obtained from the Leap Motion Controller will then be used to determine the characteristic features of rest tremor in Parkinson Disease and be used to classify subjects used in the study as Parkinson or non-Parkinson subjects.

A2 Primary Hypothesis

The primary hypothesis is that the positional data from the Leap Motion Controller will be statistically similar to that of the Tremorometer, showing that the Leap Motion Controller has the potential to accurately quantify and record tremor. It is also hypothesized that the position data from the Leap Motion Controller can be used to identify characteristic features of rest tremor in Parkinson Disease that can be used to classify subjects as either Parkinson Disease or non-Parkinson Disease subjects.

A3 Purpose of the Study Protocol

The purpose of the protocol is to be used by all study team members as the approved procedures for conduct of the study.

B Background

B1 Prior Literature and Studies

Parkinson Disease (PD) is a debilitating and progressive movement disorder that affects over one million people in the United States alone. One of the most characteristic symptoms of PD is resting tremor, as it has been shown that the proportion of patients with resting tremor ranged from 69-100% in 3 series of patients with autopsy-proven PD.[1,2,3] Several methods currently exist to quantitatively measure tremor including accelerometry, electromyography, the spirogram, and most recently three-dimensional

cameras[4]. This study involves the use of accelerometry as well as a three-dimensional camera.

B2 Rationale for this Study

Advances in three-dimensional cameras have allowed for more accurate recordings and can now be used to provide much more accurate measurements in microdisplacements of upper extremities that are involved in movements such as resting tremor. One such three-dimensional camera is the Leap Motion Controller, produced by Leap Motion, Inc. The device is a small USB three-dimensional camera that utilizes two CCD (Charged Coupled Device) cameras and three infrared LEDs to obtain depth information, and is capable of measuring changes in position to within 0.01 mm, and requires no external sensors or markers unlike accelerometry, electromyography, and the spriogram. One advantage of having no sensors attached to the body is that the mass of the sensors decrease the peak frequency of finger tremor by approximately 0.85 Hz for every gram of additional mass, and also effect the amplitude of acceleration.[5] Therefore the attached sensors may change the characteristics of the tremor, thus altering interpretation of tremor. Attaching sensors to the body can also be inconvenient, uncomfortable, and provide a margin of error if not done correctly. Another advantage of the Leap Motion Controller over accelerometry is that it does not require calibration eliminating possible errors caused by consistent recalibration. Unlike electromyography, the Leap Motion Controller is not affected by interference from electrical sources, mechanical artifacts, stimulus artifacts, and the electrical activity of muscles that are not of interest. It is for these reasons that the Leap Motion Controller is of interest and may be superior in measuring tremor.

C Study Objectives

C1 Primary Aim

The primary aim of the study is to determine whether the Leap Motion Controller can be used to obtain similar tremor statistics as those obtained from a triaxial accelerometer (Tremorometer).

C2 Secondary Aim

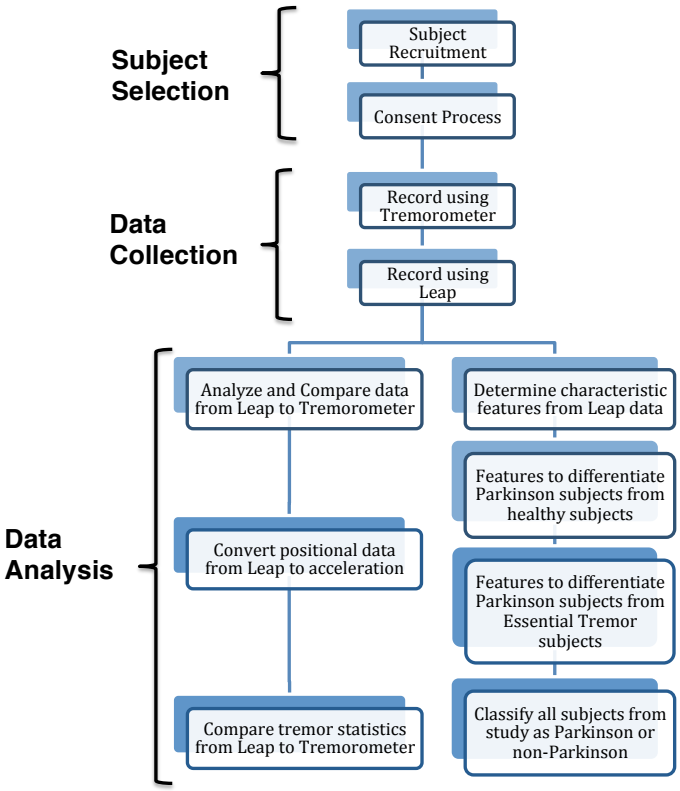
The secondary aim is to determine whether patients with rest tremor in Parkinson disease can be classified differently when compared to patients with Essential Tremor, using positional data collected by the Leap Motion Controller.

C3 Rationale for the Selection of Outcome Measures

The rationale for the selection of outcome measures is that the outcome measures are able to provide characteristic features of tremor such as peak frequency and amplitude, which are typically used when describing and quantifying tremor. The Tremorometer provides measurements of acceleration over time and the Leap Motion Controller provides measurements of position over time, both of which can provide the typical characteristics used in measuring and quantifying tremor.

D Study Design

D1 Overview or Design Summary



A total of thirty (30) subjects will be recruited for participation in this study and will consist of: 10 subjects diagnosed with Parkinsonsim with tremor, 10 subjects diagnosed with Essential Tremor, and 10 normal healthy control subjects. These subjects will be recruited in person through the Washington University Movement Disorders electronic medical record (MARS) clinical database, among the spouses of the subjects, and from the Volunteer for Health initiative of Barnes-Jewish Hospital. If the potential participant expresses interest in the study and is deemed to fit all inclusion/exclusion criteria, informed consent materials will be provided to the subject. A study team member will review the study and the informed consent materials with the potential participant, and provide the participant an opportunity to ask any questions or request further elaboration. If the potential participant agrees and signs the consent document, the data collection process can begin.

Each participant will be measured individually, twice with the Tremorometer and twice with the Leap Motion Controller. First, the participant will have the accelerometer from the Tremorometer taped to the index finger of the hand that they believe to exhibit the most symptomatic tremor. The participant will rest their hand on a small slanted box and be asked to relax their fingers and hands. The acceleration of their index finger will then be recorded for 30 seconds, while the participant counts down from 100. After the first Tremorometer recording, the subject will be asked to re-adjust their hand on the slanted box and again relax their fingers. The participant will again be asked to count down from 100 while the 30-second recording takes place for the second time. Once the second recording is complete, the accelerometer will be removed. The participant will then be asked to place the same hand on the small slanted box with their fingers relaxed, this time in front of the Leap Motion Controller. The position of each finger on the testing hand will then be recorded for 30 seconds, while the participant counts down from 100. After the first recording with the Leap Motion Controller, the subject will be asked to re-adjust their hand and again place it on the slanted box with their fingers relaxed. The second 30-second recording with the Leap Motion Controller will then take place, while the subject again counts down from 100. Once complete, the data collection for that participant will be over and the participant will be finished with the study and thanked for their time. It is estimated that the time commitment for each participant will be approximately 10 minutes.

Once the data for all subjects has been collected, the data analysis can begin. For the first part of the data analysis, the data from the Leap Motion and Tremorometer will be analyzed to compare several important characteristic features, such as peak frequency and amplitude of the tremor. To do this, the position data from the Leap Motion Controller will be converted to acceleration data to compare it to the acceleration data from the Tremorometer. Tremor statistics, such as peak frequency and amplitude, from the Leap Motion Controller and the Tremorometer will be calculated and compared. For the second portion of the data analysis, the position data from the Leap Motion Controller will be used to identify characteristic features that could be used to differentiate the Parkinson subjects from the other subjects. To do this, characteristic features will be selected that differentiate the Parkinson subjects from the normal healthy subjects. From there, the same features, and possibly more, will be used in an attempt to differentiate the Parkinson subjects from the Essential Tremor subjects since it is expected that it will be harder to differentiate Parkinson tremor from Essential tremor, based on past time-frequency analyses of tremor.[8] These features will then be used in an attempt to classify, as accurately as possible, all subjects from the study as either Parkinson or non-Parkinson.

D2 Subject Selection and Withdrawal

2.a Inclusion Criteria

1) 10 patients diagnosed with Parkinsonism with tremor
    a. age greater than or equal to 18
    b. male or female
    c. any race or ethnicity
    d. physician confirmed Parkinsonism, with tremor as a symptom, based on diagnostic criteria[6]
    e. ability to give informed consent
2) 10 patients diagnosed with Essential Tremor
    a. age greater than or equal to 18
    b. male or female
    c. any race or ethnicity
    d. physician confirmed essential tremor based on diagnostic criteria[7]
    e. ability to give informed consent
3) 10 normal control subjects
    a. age greater than or equal to 18
    b. male or female
    c. any race or ethnicity
    d. ability to give informed consent

2.a Exclusion Criteria

1) 10 patients diagnosed with Parkinsonism with tremor
    a. History of stroke, seizure, cerebral palsy, or additional neurological diagnosis
    b. Severe upper limb tremor
    c. Any serious medical or psychiatric condition
    d. Age less than 18
    e. Cognitive impairment (Mini-Mental State Score <19)
2) 10 patients diagnosed with Essential Tremor
    a. History of stroke, seizure, cerebral palsy, or other major psychiatric illness
    b. Severe upper limb tremor
    c. Any serious medical or psychiatric condition
    d. Age less than 18
    e. Cognitive impairment (Mini-Mental State Score <19)
3) 10 normal control subjects
    a. History of stroke, seizure, cerebral palsy, or other major psychiatric illness
    b. Severe upper limb tremor
    c. Any serious medical or psychiatric condition
    d. Age less than 18
    e. Cognitive impairment (Mini-Mental State Score <19)

2.b Ethical Considerations

Each participant will be an adult equal to or greater than 18 years of age and will have the ability to give informed consent. To ensure that the participant can give informed consent, they must not have a Mini-Mental State Score less than 19 or any serious medical or psychiatric condition. Only study team members will have access to the medical record of any potential and/or enrolled subjects. These records are password protected in the clinical movement disorders database (MARS), which is HIPAA compliant. Any data that will be collected will not contain any identifiers. The collected data will only be stored on a LOK-IT Secure Flash Drive, which is automatically encrypted with military-grade 256-bit AES hardware encryption and is HIPAA compliant.

2.c Subject Recruitment Plans and Consent Process

10 subjects with clinical diagnostic criteria for Parkinsonism, 10 subjects with clinical diagnostic criteria for Essential Tremor, and 10 normal control subjects will be enrolled in this study. The Washington University Movement Disorders electronic medical record (MARS) clinical database is the clinical database for which clinical information is entered for all patients seen in the movement disorders division of neurology. The database follows a large number of patients with Parkinsonism with tremor as a symptom as well as patients with Essential Tremor. Therefore, the 10 subjects with Parkinsonism with tremor and the 10 subjects with Essential Tremor will be recruited from this database. The 10 healthy control subjects will be recruited among their spouses or from the Volunteer for Health initiative of Barnes-Jewish Hospital, an affiliate of the Washington University School of Medicine with a pool of over 8000 volunteers. The study team will identify potential participants from this database and participants will be recruited in person in the movement disorder clinic at Washington University School of Medicine during clinic visits with their physician or nurse. The study team member will determine the capacity of the potential participant to consent for her/himself during initial contact and ask screening questions to determine if the potential participant fits the inclusion/exclusion criteria for the study. If the subject expresses interest in the study and is deemed to fit all inclusion/exclusion criteria, informed consent materials will be provided to the subject. A study team member will review the document and the study with the potential participant to answer any questions or explain any unclear points. Potential participants will be given time to read the document in its entirety, ask questions, and speak with friends/family members if they so desire. If the potential participant agrees, the participant will sign the informed consent and will be offered a signed copy of the consent after both parties sign the document.

2.d Randomization Method and Blinding

The participants will not be randomized and this study is not blinded.

2.e Risks and Benefits

The only potential risks for the participants are mild and considered unlikely. These risks include:

1. Attempting to hold one hand still in one position may be uncomfortable.
2. Participants may become uncomfortable, frustrated, or bored during the recording.
3. Participants may become stressed if they exhibit too severe of upper limb tremor to record the data.

To reduce any potential risk to the subjects, a physician will be present throughout all studies. Confidentiality will also be maintained in accordance with applicable state and federal laws and all study data will be identified only by a code number. Personally identifying data will not be recorded or collected.

The two devices being used, the Leap Motion Controller and the Tremorometer, meet the FDA definition of a Non-Significant Risk Device (NSR) because:

1. Neither is an implant
2. Neither will be used in supporting or sustaining human life
3. Neither will be of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health
4. Neither presents a potential for serious risk to the health, safety, or welfare of a subject

The Leap Motion Controller is a consumer three-dimensional camera and will be used in accordance with its purpose: to measure and record hand and finger motions. The Tremorometer has 510k clearance for measuring and quantifying tremor in human participants, which will be its only use in this study.

While there are no direct benefits to participants, this study may provide potential benefits to society by possibly providing a better understanding of the characteristic features of rest tremor in Parkinsonism. It may also provide a better alternative method to record and measure rest tremor that may aid in the differentiation of Parkinsonism from Essential Tremor.

2.f Early Withdrawal of Subjects

Potential participants will be informed that they may withdraw from the study at any point and that they will not be penalized or lose any benefits that they would otherwise qualify for.

2.g When and How to Withdraw Subjects

If a participant decides to withdraw, they may inform the study team member during the recording. In this case, the recordings will end and the data collected from the participant will be deleted and not used in the study. Participants may also be withdrawn from the study if they exhibit upper limb tremor too severe to be recorded or cannot spread their fingers enough to be detected by the Leap Controller. This withdrawal will be based on the judgment of the study team member at the time of recording. If the participant decides to withdraw from the study or if they are withdrawn due to severe upper limb tremor, the participant will be escorted out of the examination room and thanked for their time.

2.h Data Collection and Follow-up for Withdrawn Subjects

Any data collected by a subject who has decided to withdraw or is withdrawn during the recording will not be used and deleted. There will be no follow-up for withdrawn subjects.

E Study Procedures

E1 Screening for Eligibility

The Washington University Movement Disorders electronic medical record (MARS) clinical database will be used to recruit and screen potential participants for eligibility. This is the clinical database for which clinical information is entered for all patients seen in the movement disorders division of neurology. The Washington University School of Medicine Research Participant Registry powered by the Volunteer for Health may also be used to recruit normal control subjects. The study team members will review patient records in the Washington University Movement Disorders electronic medical record clinical database (MARS) will be reviewed to identify potential participants. The patient records will be used to screen for eligibility by reviewing the existence of a definite diagnosis of Parkinsonism or Essential Tremor, the Mini-Mental Status Exam, and information regarding examination findings with regards to tremor (i.e. whether present, the degree of severity, etc.) This information is critical inclusion/exclusion criteria that must be confirmed from the medical record. Without confirming the definite diagnosis and medical history of a patient, it is not possible to identify appropriate participants to recruit based on specific inclusion criteria.

E2 Schedule of Measurements

Once both parties sign the consent form, the study can begin that same day. All participants, including the control participants, will follow the same procedure. Each participant will be measured twice and be measured individually. First, the participant will be asked to allow a study member to affix with tape the accelerometer (from the Tremorometer system) to the index finger on the hand that they believe to exhibit the most symptomatic tremor. The participant will then be asked to place said hand on a small slanted box and asked to spread their fingers so that no fingers are touching another finger. The participant will again be asked to allow their fingers to relax and drape over the edge of the box, still ensuring that their fingers are not touching each other. Once the participant has their hand in a comfortable position, they will be verbally alerted that the measurement will start and be asked to silently countdown from 100. After 30 seconds, the participant will be verbally alerted that the measurement is over and the subject will be asked to readjust their hand and the recording will be repeated following the same procedure. Once the second recording using the Tremorometer is complete, the accelerometer will be removed. The participant will then be asked to again place the same hand on the small slanted box, this time in front of the Leap Motion Controller. The participant will again be asked to attempt to spread their fingers so that no fingers are touching another finger and then allow their fingers to relax and drape over the edge of the box, ensuring that their fingers are still not touching one another. Once the participant has their hand in a comfortable position, they will be verbally alerted that the measurement will start and be asked to silently countdown from 100. After 30 seconds, the participant will be alerted that the measurement is over. The participant will then be asked to readjust their hand and fingers and the second recording of the data using the Leap Motion Controller will then occur using the same procedure. Once complete, the participant will be finished and thanked for their time. It is estimated that the time commitment for each individual visit will be approximately 10 minutes, which includes a short explanation of the study along with recordings of the individual

participant. There will be no attempt at a long-term follow-up. Each participant will be given an option to be contacted with the results of the study, once the study is complete.

E3 Study Outcome Measurements and Ascertainment

The study outcome measurements will consist of the position and acceleration measurements from the Leap Motion and from the Tremorometer. These measurements will be used to calculate tremor statistics to compare the measurements from the two devices. The positional measurements from the Leap Motion Controller will then be used to determine characteristic features that will classify subjects in the study as either Parkinson subjects or non-Parkinson subjects. The positional data from the Leap Motion Controller will be obtained using Java code and the Leap Motion SDK and saved as a tab-delimited .txt file. The data would be recorded at a rate of approximately 150 frames per second, with each frame consisting of a timestamp and the three dimensional position of each of the five fingers of the hand being recorded. The acceleration data from the Tremorometer would be obtained using the program TremTest, a part of the Tremorometer package, which would collect data at 100 frames per second and save the three-dimensional acceleration every 10 milliseconds. The data will be saved to a LOK-IT Secure Flash Drive, which is automatically encrypted with military-grade 256-bit AES hardware encryption, which is HIPAA compliant.

F Statistical Plan

F1 Sample Size Determination and Power

In a previous study entitled the *Effect of deep brain stimulation on amplitude and frequency characteristics of rest tremor in Parkinson's disease* by Beuter et al (2001), 8 Parkinsons subjects were used to determine some of the same characteristics that will also be calculated in this study.[9] In a similar study, 8 Parkinsons subjects and 8 healthy subjects were used to again obtain the time and frequency structure of tremor.[10] Also, in a study that used a 3D motion analysis system to measure tremor, 6 Parkinson subjects were used.[11] Based on these similar studies, we will recruit 10 healthy subjects, 10 Parkinson subjects, and 10 Essential Tremor subjects. We expect that the number of participants will provide enough data to adequately examine tremor and to provide enough characteristic features involved in the rest tremor of Parkinsonism to classify subjects with Parkinsons differently than healthy subjects and subjects with Essential Tremor.

Each subject will be recorded twice for 30 seconds using the Leap Motion Controller and twice for 30 seconds using the Tremorometer. The Leap Motion Controller records data at an approximate rate of 150 times per second, while the Tremorometer records data at a rate of 100 times per second. Therefore, each subject will provide approximately 9,000 position measurements and 6,000 acceleration measurements from the Leap Motion and Tremorometer, respectively. Given that there will be 10 subjects per group, this will result in approximately 90,000 position measurements and 60,000 acceleration measurements per group.

F2 Analysis Plan

The primary aim of the study is to determine whether the Leap Motion Controller can be used to obtain similar tremor statistics as those obtained from a triaxial accelerometer (Tremorometer). To do this, the three-dimensional positional data from the Leap Motion Controller will be used to derive three-dimensional acceleration data in order to compare it to the acceleration data obtained from the Tremorometer. To compare the data, certain tremor statistics will be calculated and compared in MATLAB. These tremor statistics consist of parameters obtained from a power distribution of the tremor within a certain frequency band, some of which include the peak tremor intensity and the peak tremor frequency along with other statistics used in previous studies.[9,10,11]

The secondary aim of this study is to determine whether subjects with Parkinson disease can be classified differently from healthy patients and patients with Essential Tremor by using positional data collected by the Leap Motion Controller. To do this, positional data collected by the Leap Motion Controller will be imported using Java and the LeapSDK and analyzed in MATLAB. A variety of tremor statistics will be calculated and used to determine characteristic features that identify each group of subjects. These characteristic features will again stem from a power distribution of the tremor and be chosen based on how well they differentiate the different groups of subjects.

F3 Statistical Methods

The position data from the Leap Motion Controller will be converted into acceleration data. The tremor parameters from the Tremorometer and the Leap Motion Controller will then be obtained from the power distribution of the tremor within a certain frequency band. The tremor parameters, such as peak frequency and amplitude, from the Tremorometer will be compared against the tremor parameters from the Leap Motion Controller using a Bland-Altman plot as well as a paired t-test. The position data from the Leap Motion Controller will also be used to identify different tremor statistics that can be used to classify subjects as Parkinson or non-Parkinson subject.

F4 Missing Outcome Data

Missing outcome data will be approached using listwise deletion, also known as complete case analysis. If one sample of a recording does not return an acceleration or position, that sample will be deleted from the recording. This will have virtually no effect on the data due to the high sampling rate of the devices.

G Data Handling and Record Keeping

G1 Confidentiality and Security

Only study team members will have access to the medical record of any potential and/or enrolled subjects. These records are password protected in the clinical movement disorders database (MARS), which is HIPAA compliant. Any data that will be collected will not contain any identifiers. This collected data will only be collected to and stored on a LOK-IT Secure Flash Drive, which is automatically encrypted with military-grade 256-bit AES hardware encryption, which is HIPAA compliant.

H Study Administration

H1 Organization and Participating Centers

The coordinating site will be the Movement Disorders Clinic at the Washington University School of Medicine with the lead PI being Matthew Johnson.

H2 Study Timetable

Portion of Study	Estimated Duration
Subject Recruitment/Data Collection	2 months
Data Analysis/Study Report	2 months

I Attachments

I1 Informed consent documents

Washington University in St. Louis

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INFORMED CONSENT DOCUMENT

Project Title: Detection of Parkinson Disease Rest Tremor

Principal Investigator: Matthew Johnson

Research Team Contact: Matthew Johnson: (561) 906-1671

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research participant. By signing this form you are agreeing to participate in this study.

- If you have any questions about anything in this form, you should ask the research team for more information.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you: have been diagnosed with Parkinson Disease and have tremor as a symptom, have been diagnosed with Essential Tremor, or are healthy with no symptoms of tremor.

The purpose of this research study is to create an algorithm that will predict, with reasonable accuracy, if a patient has Parkinson Disease based on their rest tremor. To create this algorithm, rest tremor data will be collected by recording the three-dimensional position and acceleration of the index finger using two different devices. The first device, the Tremorometer, uses a three-dimensional accelerometer (a device that measures changes in acceleration) and is cleared by the FDA to measure and quantify tremor by measuring acceleration and calculating tremor statistics in human patients. The second device, the Leap Motion Controller, is a three-dimensional camera that can obtain position data. The data collected and analyzed by the Tremorometer will be compared to that of the Leap Motion Controller to determine whether the Leap Motion Controller can be used to obtain similar results as the Tremorometer. The data from the Leap Motion Controller will be analyzed and used to create an algorithm that can predict whether a patient has Parkinson Disease. It is hypothesized that the Leap Motion Controller will provide similar results as the Tremorometer and that the data from the Leap Motion Controller can be used to create a reasonably accurate algorithm that can identify a patient with Parkinson Disease from a patient with Essential Tremor or a healthy patient.

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WHAT WILL HAPPEN DURING THIS STUDY?

The study will occur in an examination room behind closed doors in the movement disorders clinic within the Washington University School of Medicine. The data that will be recorded will consist of the position and acceleration of your fingers over time and whether you have Parkinson Disease, Essential Tremor, or are healthy with no symptoms of tremor.

You will first be asked to allow a study member to tape a small sensor (the accelerometer from the Tremorometer system) to your index finger on the hand that you exhibit the most symptomatic tremor. You will then be asked to place said hand on a small slanted box and be asked to spread your fingers so that no fingers are touching another finger. You will then be asked to allow your fingers to relax and drape over the edge of the box, still ensuring that your fingers are not touching. Once your hand is in a comfortable position, you will be warned that the recording will start and be asked to silently countdown from 100. After 30 seconds, you will be told that the recording is over and the sensor will be removed. You will then be asked to place the same hand on the small slanted box in front of the Leap Motion Controller (a small three-dimensional camera that tracks hand and finger movements and has not yet been used to measure hand or finger tremors.) You will again be asked to allow your fingers to relax and drape over the edge of the box, still ensuring that no fingers are touching another finger. Once your hand is in a comfortable position, you will be told that the recording will begin and be asked to silently countdown from 100. After 30 seconds, you will be told that the recording is over and the you will be finished with your participation in the study.

Will you save my samples or research data to use in future research studies?

As part of this study, we are obtaining tremor data (in the form of position and acceleration over time) from you. By agreeing to be part of this study you give up any property rights you may have in the tremor data. We would like to use your tremor data for other research projects in the future. These future studies may provide additional information that will be helpful in understanding Parkinson's Disease, but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your tremor data might be used to develop tests, treatments or cures. There are no plans to provide financial compensation to you should this occur. If you agree, this means we will store your tremor data and may use it for studies going on right now as well as studies that are conducted in the future.

I would also like your permission to share your tremor data with other investigators doing research in similar fields such as other diseases where tremor is a common symptom**.** These investigators may be at Washington University or at other research centers. We may also share you research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

Your tremor data will be stored without your name or any other kind of link that would enable us to identify which data are yours. Therefore, if you give permission to store and use your tremor data, it will be available for use in future research studies indefinitely and cannot be removed.

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Please place your initials in the blank next to Yes or No for each of the questions below:

My tremor data may be stored and used for future research as described above.

_____ Yes **_____ No**
Initials **Initials**

My tremor data may be shared with other investigators and used by these investigators for the future research as described above.

_____ Yes **_____ No**
Initials **Initials**

HOW MANY PEOPLE WILL PARTICIPATE?
Approximately 30 people will take part in this study conducted by investigators at Washington University.

HOW LONG WILL I BE IN THIS STUDY?
If you agree to take part in this study, your involvement will last for approximately 10 minutes.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Less Likely / Less Common

Mild
- Risk 1: Attempting to hold one hand still in one position may be physically uncomfortable.
- Risk 2: Become fatigued, frustrated, or bored during the recording.
- Risk 3: Become stressed if you exhibit too severe of upper limb tremor to record the data.

One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure, and we think the risk of accidental disclosure is very small. Please see the section in this consent form titled *"How will you keep my information confidential?"* for more information.

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WHAT ARE THE BENEFITS OF THIS STUDY?

You will not benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because the study may help provide a better understanding of the characteristic features of rest tremor in Parkinsonism as well as provide a better alternative to record and measure rest tremor that may aid in the differentiation of Parkinsonism from Essential Tremor.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?
You will not have any additional costs for being in this research study. You and/or your medical/hospital insurance provider will remain responsible for your regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?
You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?
This study is not being funded.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator at (561) 906-1671 and/or the Human Research Protection Office at (314) 633-7400 or 1-(800)-438-0445.

Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the Office for Human Research Protections) to complete federal or state responsibilities
- People who use the Washington University School of Medicine's Research Participant Registry or the clinical movement disorders database (MARS)
- Hospital or University representatives, to complete Hospital or University responsibilities
- Information about your participation in this study may be documented in your health care records

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$STAMP_EXP_DT

and be available to your health care providers who are not part of the research team.
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants.) The Institutional Review Board has reviewed and approved this study.

To help protect your confidentiality, we will have you escorted into a separate examination room with closed doors in the clinic, after seeing your physician. The data that will be recorded will be fully de-identified and will not include your name, date of birth, clinic number, or any other identifiable information. The only data that will be recorded will be the positional and acceleration data of your finger and whether or not you have Parkinson Disease. This data will only be saved on a LOK-IT Secure Flash Drive, which is automatically encrypted with military-grade 256-bit AES hardware encryption. This level of encryption is HIPAA compliant and ensures that the data is unreadable if the flash memory were to be physically accessed. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?".
Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect
- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:
- You authorize the use of your PHI for this research
- Your signature and this form will not expire as long as you wish to participate.

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- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
  - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at http://hrpo.wustl.edu (or use the direct link: http://hrpohome.wustl.edu/participants/WithdrawalTemplate.rtf) or you may request that the Investigator send you a copy of the letter.
    - **If you revoke your authorization:**
      - The research team may only use and share information already collected for the study.
      - Your information may still be used and shared if necessary for safety reasons.
      - You will not be allowed to continue to participate in the study.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?
You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at http://hrpo.wustl.edu under Information for Research Participants.

Will I receive new information about the study while participating?
If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can someone else end my participation in this study?
Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. This might happen because in our judgement you are exhibiting upper limb tremor too severe to be recorded or if you have too much trouble keeping your fingers separated during the recording.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Matthew Johnson, (561) 906-1671**.** If you experience a research-related injury, please contact: Dr. Arye Nehorai, (314) 935-5565.

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office, 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO 63110, (314) 633-7400, or 1-(800)-438-0445 or email hrpo@wusm.wustl.edu. General information about being a research participant can be found by clicking "Participants" on the Human Research

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Protection Office web site, http://hrpohome.wustl.edu. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after $STAMP_EXP_DT.

_____ _____
(Signature of Participant) (Date)

_____
(Participant's name – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that he or she understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

_____
(Name of Person who Obtained Consent - printed)

I2 Device Documentation

2.a The Leap Motion Controller

i EU Declaration of Conformity

EU Declaration of Conformity

We, Leap Motion, Inc., of 333 Bryant Street, Ste LL 150 San Francisco CA 94107 declare under our own responsibility that the product:

Product Name: Leap Motion Controller

Model Number: LM-010

Is in conformity with Directive 2011/65/EU of the European Parliament and of the Council of 8 June 2011 on the restriction of the use of certain hazardous substances in electrical and electronic equipment, and of the following standards:

Safety - IEC 60950-1

Electromagnetic Compatibility – EMC Directive 2004/108/EC

EN 55022:2010
EN 61000-3-2:2006+A2:2009
EN 61000-3-3:2008
EN 55024:2010

Signed for and on behalf of Leap Motion, Inc.

Raul Corella
VP Operations
San Francisco, July 8, 2013

The product carries the CE mark, which was first affixed in 2013.

LEAP MOTION

Leap Motion Controller
Important Information Guide

This *Important Information Guide* contains safety, handling, disposal, recycling and regulatory information, as well as the limited hardware warranty for your Leap Motion Controller.

⚠ Read all safety information and operating instructions below before using your Leap Motion Controller to avoid injury. For user instructions for the Leap Motion Controller and the latest version of this Important Information Guide visit: leapmotion.com/support

Important Safety and Handling Information

High-risk activities
THE PRODUCT IS NOT INTENDED FOR CONTROL, WHETHER DIRECT OR INDIRECT, OF OR USE WITH INDUSTRIAL OR MEDICAL EQUIPMENT OF ANY TYPE, AND IS NOT INTENDED FOR ANY USE WHERE FAILURE OR FAULT OF THE PRODUCT COULD DIRECTLY OR INDIRECTLY CAUSE RISK OR DAMAGE TO LIFE OR PROPERTY.

Operating environment
Operating your Leap Motion Controller outside these ranges may affect performance:
Operating temperature: 32° to 113° F (0° to 45° C)
Storage temperature: 14 to 122° F (-10° to 50° C)
Relative humidity: 5% to 85% (non-condensing)
Operating altitude: 0 to 10,000 feet (0 to 3048 meters)

Operating your Leap Motion Controller in bright sunlight, or where bright light sources or reflective surfaces (including exposed metal vents) are above the device, will impact performance. In order to improve performance, move to a less bright or reflective environment.

For best performance, maintain a clear field of view between your Leap Motion Controller and your hands and fingers. Loose sleeves, large or loose jewelry, and non-transparent objects or materials that are near the device, or between the device and your hands, or right above your hands, may impact performance. In addition, avoid wearing dark gloves, or using dark or transparent instruments to use the controller.

Cleaning your Leap Motion Controller
Dust, dirt and fingerprints on the top of the device may degrade the performance of your Leap Motion Controller. When cleaning the outside of the device, first unplug the cable. Then use a dry cloth to wipe the surface. Do not use detergents, abrasive cleaners or other cleaners, which may scratch the surface, and harm performance. Do not allow the device to become wet.

Proper handling
The surface of your Leap Motion Controller may become warm during normal use. The Leap Motion Controller complies with the user-accessible surface temperature limits defined by the International Standard for Safety of Information Technology Equipment (IEC 60950-1).

Ergonomics
When using your Leap Motion Controller, locate it so that it is comfortable to use. Center your controller in front of your keyboard or laptop. Adjust your chair or work surface so that your elbows are near your side and your forearms are roughly parallel to the floor. Your chair may need to be slightly higher or your work surface slightly lower than usual.

You should sit at such a height so that your forearms extend at roughly a right angle from your body to a position slightly above your Leap Motion Controller, with your wrist and hands in roughly a straight line. Your hands should be just above the device, and your shoulders should be relaxed. You can rest your forearms on your work surface, but do not rest on a sharp edge.

If you have discomfort, take a break, and when using the controller again, change your arm posture. If you have persistent or recurrent discomfort after use, stop use and see a physician.

Disposal and Recycling Information
This symbol on the product (and on its packaging) is in accordance with the European Union's Waste Electrical and Electronic Equipment (WEEE) Directive. The symbol indicates that this product must be recycled/disposed of separately from other household waste. It is the end user's responsibility to dispose of this product by taking it to a designated WEEE collection facility for the proper collection and recycling of the waste equipment. The separate collection and recycling of waste equipment will help to conserve natural resources and protect human health and the environment. For more information about recycling, please contact your local environmental office, an electrical/electronic waste disposal company or the store where you purchased the product.

Device Information
To get information about your Leap Motion Controller, use the "About" box in your Leap Motion software. It shows you what software is installed, the serial number, and more.

Compliance

FCC Compliance Statement
Tested to comply with FCC standards. FOR HOME OR OFFICE USE.

This device complies with Part 15 of the FCC Rules. Operation is subject to the following two conditions: 1) this device may not cause harmful interference, and 2) this device must accept any interference received, including interference that may cause undesired operation.

This equipment has been tested and found to comply with the limits for a Class B digital device, pursuant to part 15 of the FCC Rules. These limits are designed to provide reasonable protection against harmful interference in a residential installation. This equipment generates, uses and can radiate radio frequency energy. And, if not installed and used in accordance with the instructions, may cause harmful interference to radio communications. However, there is no guarantee that interference will not occur in a particular installation. If this equipment does cause harmful interference to radio or television reception, which can be determined by turning the equipment off and on, the user is encouraged to try to correct the interference by one or more of the following measures:

-- Reorient or relocate the receiving antenna.
-- Increase the separation between the equipment and receiver.
-- Connect the equipment into an outlet on a circuit different from that to which the receiver is connected.
-- Consult the dealer or an experienced radio/TV technician for help.

Warning: Where shielded interface cables or accessories have been provided with the product or specified additional components or accessories elsewhere defined to be used with the installation of the product, they must be used in order to ensure compliance with FCC limits. Changes or modifications to the product not expressly approved by Leap Motion, Inc. could void your right to use or operate your product.

Canada Compliance Statement
CAN ICES-3 (B)/NMB-3(B)
IC Statement: This Class B digital apparatus complies with Canadian ICES – 003.
Déclaration IC: Cet appareil numérique de catégorie B est conforme à la norme canadienne NMB-003.

European Compliance Statement
A copy of the EU Declaration of Conformity is available at: www.leapmotion.com/legal

Software License Agreement

Use of the Leap Motion Controller constitutes acceptance of the Leap Motion and third-party software license terms found at: www.leapmotion.com/legal

Leap Motion Hardware Limited Warranty

Leap Motion, Inc. ("Leap Motion" or "we") warrants this Leap Motion hardware product against material defects in materials and workmanship for a period of one year from the date of purchase ("Warranty Period") by the original end user purchaser ("you"). Except where prohibited by applicable law, this warranty is nontransferable and is limited to the original purchaser. This warranty gives you specific legal rights, and you may also have other rights that vary under local laws.

Software distributed by Leap Motion with or without the Leap Motion brand name (including, but not limited to, the software that interacts with or that is pre-installed in the product) is not covered under this limited warranty. Refer to the licensing agreement accompanying the software for details of your rights with respect to its use. Leap Motion does not warrant that the operation of the product will be uninterrupted or error-free. Leap Motion is not responsible for damage arising from failure to follow instructions relating to the product's use.

Remedies
If the product is determined to be materially defective during the Warranty Period, Leap Motion will (at its option) (1) repair or replace the product, or (2) refund the price paid, provided that the product is returned to the point of purchase or such other place as Leap Motion may direct with a copy of the sales receipt or dated itemized receipt. Shipping and handling charges may apply except where prohibited by applicable law. Leap Motion may, at its option, use new or refurbished or used parts in good working condition to repair or replace any product. Any replacement product will be warranted for the remainder of the original warranty period or thirty (30) days, whichever is longer or for any additional period of time that may be applicable in your jurisdiction.

This warranty does not cover problems or damage resulting from (1) accident, abuse, misapplication, or any unauthorized repair, modification or disassembly; (2) improper operation or maintenance, usage not in accordance with product instructions or connection to improper voltage supply; (3) use of cables or other equipment not supplied by Leap Motion; or (4) other causes that are not defects in material and workmanship except where such restriction is prohibited by applicable law. This warranty additionally does not cover products marked as "sample" or sold "AS IS".

How to Obtain Warranty Support
Before submitting a warranty claim, we recommend you visit the support section at www.leapmotion.com for technical assistance. Valid warranty claims are generally processed through the point of purchase during the first 30 days after purchase; however, this period of time may vary depending on where you purchased your product – please check with Leap Motion or the retailer where you purchased your product for details. Warranty claims that cannot be processed through the point of purchase and any other product related questions should be addressed directly to Leap Motion. The addresses and customer service contact information for Leap Motion can be found in the documentation accompanying your product and on the web at: www.leapmotion.com/support

Limitation of Liability
LEAP MOTION WILL NOT BE LIABLE FOR ANY SPECIAL, DIRECT, INDIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES WHATSOEVER ARISING FROM THE USE OR SERVICE OF THE PRODUCT. IN ADDITION, LEAP MOTION WILL NOT BE LIABLE FOR ANY LOSS OF PROFITS, REVENUE OR DATA (WHETHER DIRECT OR INDIRECT) OR COMMERCIAL LOSS FOR BREACH OF ANY EXPRESS OR IMPLIED WARRANTY ON YOUR PRODUCT EVEN IF LEAP MOTION HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. EXCEPT WHERE PROHIBITED BY LAW, THE WARRANTY AND REMEDIES DESCRIBED ARE EXCLUSIVE AND IN LIEU OF ALL OTHER WARRANTIES, REMEDIES, AND CONDITIONS, WHETHER ORAL, WRITTEN, EXPRESS, STATUTORY OR IMPLIED. Any recovery is limited to repair, replacement, or refund as described above. Some jurisdictions do not allow the exclusion or limitation of special, indirect, incidental or consequential damages, so the above limitation or exclusion may not apply to you.
THE PRODUCT IS NOT INTENDED FOR CONTROL, WHETHER DIRECT OR INDIRECT, OF OR USE WITH INDUSTRIAL OR MEDICAL EQUIPMENT OF ANY TYPE, AND IS NOT INTENDED FOR ANY USE WHERE FAILURE OR FAULT OF THE PRODUCT COULD DIRECTLY OR INDIRECTLY CAUSE RISK OR DAMAGE TO LIFE OR PROPERTY. THIS WARRANTY WILL NOT APPLY IF THE PRODUCT IS USED IN SUCH A MANNER. ANY SUCH USE IS ENTIRELY AT THE USER'S DISCRETION AND RISK. ANY SUCH USER WILL BE SOLELY RESPONSIBLE FOR (AND LEAP MOTION DISCLAIMS) ANY AND ALL LOSS, LIABILITY, OR DAMAGES RESULTING FROM SUCH USE.

Duration of Implied Warranties
EXCEPT TO THE EXTENT PROHIBITED BY APPLICABLE LAW, LEAP MOTION DISCLAIMS ALL IMPLIED AND STATUTORY WARRANTIES, INCLUDING WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. ANY IMPLIED WARRANTY OR CONDITION OF MERCHANTABILITY OR FITNESS

FOR A PARTICULAR PURPOSE ON THE PRODUCT IS LIMITED IN DURATION TO THE DURATION OF THE WARRANTY PERIOD ABOVE. Some jurisdictions do not allow limitations on how long an implied warranty lasts, or do not allow exclusions or limitations on certain damages, including damages for death or personal injury caused by negligence, so the above limitation may not apply to you.

National Statutory Rights
Consumers in some jurisdictions may have legal rights under applicable national legislation governing the sale of consumer goods. These rights are not affected by the warranties in this limited warranty.

No Other Warranties
No Leap Motion dealer, agent, or employee is authorized to make any modification, extension, or addition to this warranty. Your seller is solely responsible for any other warranties.

Service and Support

Your Leap Motion Controller does not contain any user-serviceable parts. If you need service, contact Leap Motion at one of the numbers below. Helpful information is also available on our website at:
www.leapmotion.com/support

Within the United States: 1-866-745-4609 (toll-free).
Outside the United States: +1-415-692-3860 (carrier charges apply - please contact your telecom service provider for details).
The hours our customer support is available may be found at:
www.leapmotion.com/support

Leap Motion Address
Leap Motion, Inc.
333 Bryant Street, Ste LL 150
San Francisco CA 94107
USA

EU fiscal representative office:
CTPark BrnoTuřanka 110 627 00 Brno-Slatina
Czech Republic

46-0006

2.b Tremorometer 510(k) Summary

i 510k Summary

JUL 2 5 2001

K010270

510(k) SUMMARY

TREMOROMETER®

Common/Classification Name: System, Telemetry, Physiological Signal Conditioner

FlexAble Systems, Inc.
16410 East Tombstone Avenue
Fountain Hills, AZ 85268-6545.

Contact: Robert M. Tripp, Ph. D., President

Preparation Date: January 12, 2001

A. LEGALLY MARKETED PREDICATE DEVICES

The **Tremorometer®** is substantially equivalent to the legally marketed **Axiom or FlexiPlus™** and/or the **Actiwatch®** devices.

B. DEVICE DESCRIPTION

The Tremorometer is a system designed to improve the measurement and quantification of tremor in human patients regardless of the underlying etiology of the tremor. It consists of a Tremor Sensor, a microcomputer and programs to operate the microcomputer. The federally registered trademark "Tremorometer" is intended to cover the system comprised of these three parts.

The Tremor Sensor is a three axis accelerometer that attaches to a patient's finger and transmits the tri-axial tremor measurements to the Tremorometer. Other acceleration measuring devices could be used in place of the current Tremor Sensor provided they met the sensitivity, accuracy, resolution and range of the current device.

The microcomputer is the FlexLab™ manufactured by FlexAble Systems, Inc. that is used in a number of industrial applications. It is a battery powered, hand-held, self-contained, programmable device. Other microcomputers with the capability of reading the pulse width modulated signals generated by the Tremor Sensor could be used in place of the FlexLab.

The programs range from general system software to control the keypad and LCD displays to proprietary algorithms that process the tremor data. The code is written in 'C' and could be easily ported to another microcomputer.

The FlexLab has a keypad and LCD display for interaction with the user. General purpose software provides for setting and reading date and time from a clock/calendar IC; bi-directional serial communication using Xmodem CRC and CSum protocols at selectable Baud rates; display and control of system settings; and more. Custom software designed specifically for the tremor measuring and processing application include routines to take precisely timed measurements from the Tremor Sensor; perform calibration of the Tremor Sensor using Earth's gravity as a reference; run automated, timed series of tests; process and store data with check digits to insure data integrity; display the data graphically on the LCD; generate and maintain record headers; control the transmission of complete records to a PC; clear records; download user generated test lists; and more.

The three-axis reading may be combined into a single composite measure of total movement by proprietary algorithms that eliminate some of the non-tremor signals such as rotational components, orientation relative to Earth's gravity and other artifacts.

C. **INDICATIONS FOR USE**

The Tremorometer is designed to measure a patient's tri-axial tremor movements.

D. **SUBSTANTIAL EQUIVALENCE SUMMARY**

The Tremorometer has the same indications for use as the legally marketed **Axiom or FlexiPlus™** (referred to as the FlexiPlus) and/or the **Actiwatch®** devices. The Tremorometer has the same technological characteristics as the legally marketed **FlexiPlus™** and/or the **Actiwatch®** devices. However, the characteristics may not be sufficiently precise to assure equivalence. Therefore, FlexAble Systems, Inc. has carried out validation and performance testing. The results of this testing documents that the Tremorometer performs as well as the legally marketed **FlexiPlus™** and/or the **Actiwatch®** devices.

E. **TECHNOLOGICAL CHARACTERISTICS**

The technological characteristics of the Tremorometer are very similar to those of the legally marketed **FlexiPlus™** and/or the **Actiwatch®** devices. The similarities and differences include:

Characteristic	FlexiPlus™	Actiwatch	Tremorometer
Measures muscle testing	Yes	No	No
Measures occurrence and degree of motion	No	Yes	No
Measures tremor	No	No	Yes
Attaches to arm	Yes	No	Yes
Attaches to wrist	No	Yes	Yes
Attaches to finger	No	No	Yes
Battery operated	Yes	Yes	Yes
Stores measured data internally	Yes	Yes	Yes
Amplifies data	Yes	Yes	Yes
Proprietary software analyses data	Yes	Yes	Yes
Downloads collected data to PC	Yes	Yes	Yes

F. **TESTING**

The Tremorometer device has undergone extensive alpha and beta testing. Beta testing included testing at a variety of study centers conducted by qualified researchers operating under current and valid IRBs, informed consent and protocols coordinated by Robert M. Tripp, Ph.D., and Michael P. Caligiuri, Ph.D. a qualified Scientific Investigator.

The Tremorometer software was subjected to internal verification and validation testing, the results of which are documented in this submission.

The accessory software and third-party software used in combination with this device and the data created by this device has been subject to validation and comparison to other data management system.

G. **CONCLUSIONS**

The validation studies document that the Tremorometer is substantially equivalent to the legally marketed **FlexiPlus™** and/or the **Actiwatch®** devices.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room –WO66-G609
Silver Spring, MD 20993-0002

Robert M. Tripp, Ph.D.
President
Flexable Systems, Inc.
16410 E. Tombstone Avenue
Fountain Hills, Arizona 85268

APR - 9 2012

Re: K010270
Trade/Device Name: Tremorometer®
Regulation Number: 21 CFR 882.1950
Regulation Name: Tremor transducer
Regulatory Class: II
Product Code: GYD
Dated (Date on orig SE ltr): April 24, 2001
Received (Date on orig SE ltr): April 27, 2001

Dear Mr. Tripp:

This letter corrects our substantially equivalent letter of July 25, 2001.

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Kesia Alexander

for

Malvina B. Eydelman, M.D.
Director
Division of Ophthalmic, Neurological,
and Ear, Nose and Throat Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

STATEMENT OF INDICATIONS FOR USE

510(k) Number (if known): K010270

Device Name: **TREMOROMETER®**

Indications For Use:

The Tremorometer is designed to be used to measure and record tri-axial readings of a patient's tremor motions, to optionally combine the three axis tremor information into a single measurement of total tremor movement by a proprietary algorithm that eliminates some of the rotational, orientation and other artifacts, to display the information graphically, and to transfer the data to a PC for further analysis, display, printing or storage.

(PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

for Mark N. Milhauser

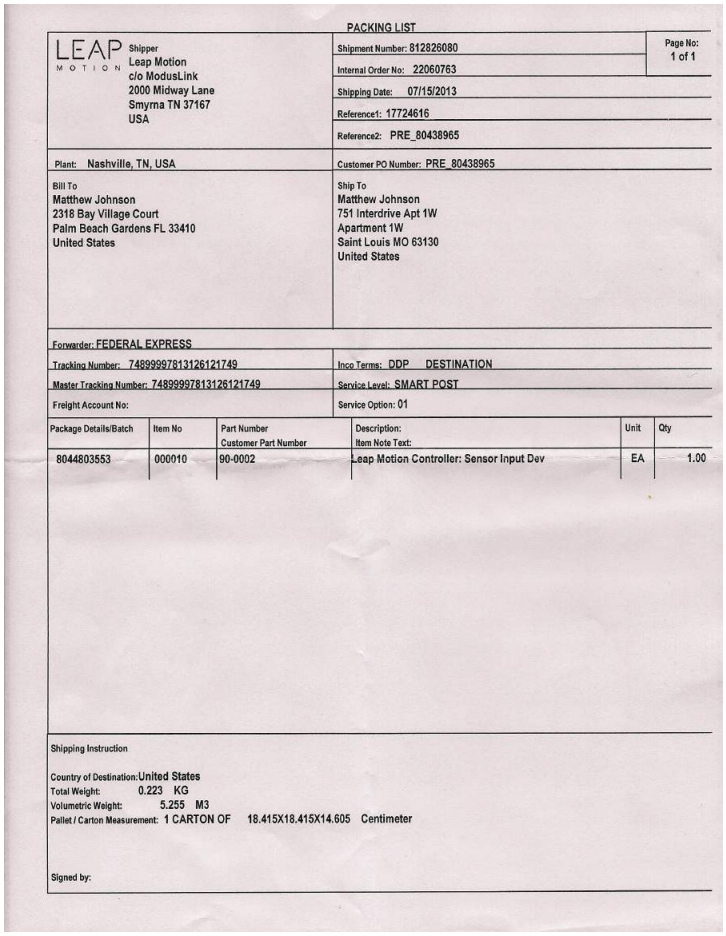
(Division Sign-Off)
Division of General, Restorative
and Neurological Devices

510(k) Number K010270

Prescription Use ✓ OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

I3 Device Tracking Forms

3.a Leap Motion



PACKING LIST

LEAP MOTION

Shipper
Leap Motion
c/o ModusLink
2000 Midway Lane
Smyrna TN 37167
USA

Shipment Number: 812826080
Page No: 1 of 1
Internal Order No: 22060763
Shipping Date: 07/15/2013
Reference1: 17724616
Reference2: PRE_80438965

Plant: Nashville, TN, USA
Customer PO Number: PRE_80438965

Bill To
Matthew Johnson
2318 Bay Village Court
Palm Beach Gardens FL 33410
United States

Ship To
Matthew Johnson
751 Interdrive Apt 1W
Apartment 1W
Saint Louis MO 63130
United States

Forwarder: FEDERAL EXPRESS
Tracking Number: 7489999781312612174 9
Inco Terms: DDP DESTINATION
Master Tracking Number: 7489999781312612174 9
Service Level: SMART POST
Freight Account No:
Service Option: 01

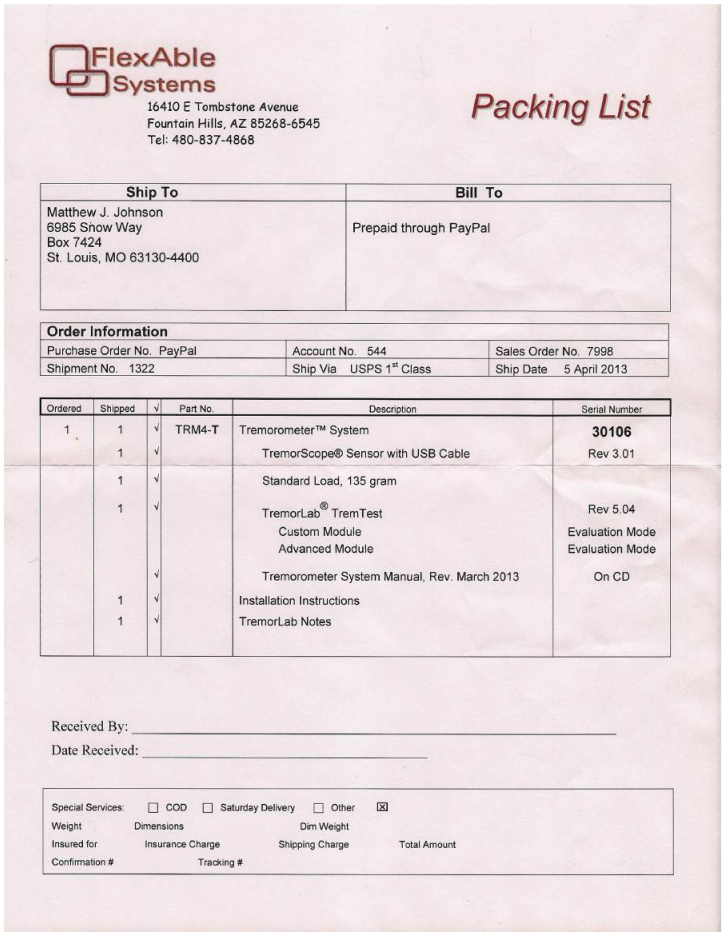
Package Details/Batch	Item No	Part Number / Customer Part Number	Description: / Item Note Text:	Unit	Qty
8044803553	000010	90-0002	Leap Motion Controller: Sensor Input Dev	EA	1.00

Shipping Instruction

Country of Destination: United States
Total Weight: 0.223 KG
Volumetric Weight: 5.255 M3
Pallet / Carton Measurement: 1 CARTON OF 18.415X18.415X14.605 Centimeter

Signed by:

3.b Tremorometer



FlexAble Systems

16410 E Tombstone Avenue
Fountain Hills, AZ 85268-6545
Tel: 480-837-4868

Packing List

Ship To	Bill To
Matthew J. Johnson 6985 Snow Way Box 7424 St. Louis, MO 63130-4400	Prepaid through PayPal

Order Information		
Purchase Order No. PayPal	Account No. 544	Sales Order No. 7998
Shipment No. 1322	Ship Via USPS 1st Class	Ship Date 5 April 2013

Ordered	Shipped	√	Part No.	Description	Serial Number
1	1	√	TRM4-T	Tremorometer™ System	**30106**
	1	√		TremorScope® Sensor with USB Cable	Rev 3.01
	1	√		Standard Load, 135 gram	
	1	√		TremorLab® TremTest	Rev 5.04
				Custom Module	Evaluation Mode
				Advanced Module	Evaluation Mode
		√		Tremorometer System Manual, Rev. March 2013	On CD
	1	√		Installation Instructions	
	1	√		TremorLab Notes	

Received By: _____

Date Received: _____

Special Services: ☐ COD ☐ Saturday Delivery ☐ Other ☒

Weight Dimensions Dim Weight

Insured for Insurance Charge Shipping Charge Total Amount

Confirmation # Tracking #

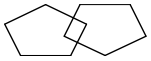
I4 Miscellaneous

4.a Mini-Mental Status Exam

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Interpretation of the MMSE:

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Interpretation of MMSE Scores:

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with ADL.

Source:

- Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." *J Psychiatr Res* 1975;12:189-198.

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