ASSESSMENT OF WRIST RIGIDITY IN PATIENTS WITH PARKINSON'S DISEASE: A NEW APPROACH BASED ON FREQUENCY ANALYSIS

by

Günay Züngör

B.S., Mechanical Engineering, Doğuş University, 2015

Submitted to the Institute for Graduate Studies in
Science and Engineering in partial fulfillment of
the requirements for the degree of
Master of Science

Graduate Program in Mechanical Engineering

Boğaziçi University

2020

ACKNOWLEDGEMENTS

First, I want to especially thank my advisor Assoc. Prof. Evren Samur and my co-advisor Prof. Çetin Yımaz for their support and guidance during my master study. It would not be possible to complete this study without the help of them. I would also like to thank Prof. Muhittin Cenk Akbostancı, Assist. Prof. Sinan Öncü and Assist. Prof. İsmail Faik Başkaya. who accepted to be jury members of my thesis.

I would also like to thank the neurologists: Rezzak Yılmaz, Sabiha Tezcan Aydemir, Turgut Şahin, Yasemin Ünal, Nazlı Durmaz Çelik for their cooperation, sincerity, and kindness. They helped us a lot in working with the patients, and their experience has a great influence on the progress of this thesis.

I sincerely thank my friends at Boğaziçi University: Burcu Seyidoğlu, Serhat Demirtaş, Taylan Atakuru, Kübra Karacan, Bora Baydere, Şeref Kemal Talaş and Haluk Kundakçıoğlu for their support, and my study partner Uğur Dinçer for his contributions and patience.

Finally, I would like to thank my family for their love and support.

ABSTRACT

ASSESSMENT OF WRIST RIGIDITY IN PATIENTS WITH PARKINSON'S DISEASE: A NEW APPROACH BASED ON FREQUENCY ANALYSIS

Wrist rigidity is accepted as a major indicator of the Parkinson's Disease (PD). In the current medical practice, wrist rigidity is qualitatively measured by movement disorder specialists as a part of the Unified Parkinson's Disease Rating Scale (UPDRS) method. This study aims to develop a novel method for quantitative assessment of wrist rigidity. In this thesis, a frequency analysis-based approach is proposed. Frequency response of the wrist is obtained by analyzing data measured with the built-in sensors of a mobile phone attached to the hand. For this purpose, a mobile app and an experimental protocol are developed. An experimental study with 10 PD patients and 11 able-bodied participants is performed to correlate frequency response of the wrist with the UPDRS rigidity score. Along with the UPDRS rigidity score, differences between on and off states of PD patients, the effect of the Froment maneuver, differences between PD patients and healthy subjects are observed. Two analyses are performed with the collected data: (1) Model-based analysis, and (2) Deep learning-based analysis. A second-order mass-spring-damper model is fit to the data to identify stiffness of the wrist in the model-based analysis. On the other hand, a convolutional neural network is used to extract features related to wrist rigidity in the deep learning-based analysis. Statistical analysis of the results shows that it is possible to correctly identify UPDRS rigidity scores of the participants using the model-based analysis. Similarly, accurate rigidity extraction is possible using the machine learning-based analysis. These promising results indicate that the proposed method along with the developed mobile app may be used for quantitative measurement of the muscle rigidity of PD patients.

ÖZET

PARKİNSON HASTALARINDA BİLEK SERTLİĞİNİN DEĞERLENDİRİLMESİ: FREKANS ANALİZİ ÜZERİNE YENİ BİR YAKLAŞIM

Bilek sertliği, Parkinson Hastalığının (PH) önemli bir göstergesi olarak kabul edilir. Mevcut uygulamada, bilek direngenliği, Birleşik Parkinson Hastalığı Derecelendirme Ölçeğinin (BPHDÖ) bir parçası olarak hareket bozukluğu uzmanları tarafından niteliksel olarak ölçülür. Bu çalışma, bilek direngenliğinin nicel olarak değerlendirilmesi için yeni bir yöntem geliştirmeyi amaçlamaktadır. Bu tezde, frekans analizine dayalı bir yaklaşım önerilmektedir. Bileğin frekans cevabı, ele takılan bir cep telefonunun tümleşik sensörleri ile ölçülen verilerin analiz edilmesiyle elde edilir. Bu amaçla, bir mobil uygulama ve bir deneysel protokol geliştirilmiştir. Bileğin frekans cevabını BPHDÖ sertlik skoru ile ilişkilendirmek için 10 Parkinson hastası ile deneysel çalışma yapılmıştır. BPHDÖ sertlik skoru ile birlikte, Parkinson hastalarının açık ve kapalı durumları arasındaki farklılıklar, Froment manevrasının etkisi, Parkinson hastaları ve sağlıklı denekler arasındaki farklılıklar gözlemlenmiştir. Toplanan verilerle iki analiz yapılmıştır: (1) Model bazlı analiz ve (2) Derin öğrenme bazlı analiz. Model bazlı analizde bileğin direngenliğini belirlemek için ikinci dereceden bir kütle yay sönümleme modeli kullanılmıştır. Öte yandan, derin öğrenme temelli analizde bilek direngenliği ile ilgili özellikleri çıkarmak için evrişimli sinir ağı kullanılmıştır. Sonuçların istatistiksel analizi, model tabanlı analiz kullanılarak katılımcıların BPHDÖ katılık puanlarını doğru bir şekilde tanımlanabilir olduğunu göstermektedir. Benzer şekilde, makine öğrenimine dayalı analiz kullanılarak doğru sertlik çıkarımının mümkün olduğu görülmüştür. Bu sonuçlar, geliştirilen mobil uygulama ile birlikte önerilen yöntemin Parkinson hastalarında görülen kas direngenliğinin niceliksel ölçümü için kullanılabileceğini göstermektedir.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SYMBOLS

c	Damping coefficient
I	Moment of inertia
k	Stiffness coefficient of the wrist
k_t	Torsional stiffness
l	The distance between the mass center of the hand and the center of rotation of the wrist
m	Mass
m_1	Mass of the hand
m_2	Total mass of hand and added mass
m_a	Added mass to the system
r	Normalized frequency
ζ	Damping ratio
θ	Rotational displacement of the wrist
ω	Excitation frequency
ω_{mass}	Natural frequency when mass added
$\omega_{massless}$	Natural frequency of the hand without any additional mas
ω_n	Natural frequency of oscillation

LIST OF ACRONYMS/ABBREVIATIONS

Anova	Analysis of variance
BiRD	The Bionics Institute Rigidity Device
BPHDÖ	Birleşik Parkinson Hastalığı Derecelendirme Ölçeği
CNN	Convolutional neural network
CWT	Continuous wavelet transform
DBS	Deep brain stimulation
EEG	Electroencephalography
EMG	Electromyography
HY	Hoen and Yahr Scale
Hz	Hertz
MDS	Movement Disorder Society
MDS-UPDRS	The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale
PD	Parkinson's Disease
PH	Parkinson Hastalığı
UPDRS	Unified Parkinson's Disease Rating Scale

1. INTRODUCTION

1.1. Background

1.1.1. Parkinson's Disease

Parkinson's Disease (PD) is the second most common neurological disease after Alzheimer's Disease. The number of PD patients is estimated at 680,000 for individuals over 45 in 2010, and expected to be 1,230,000 in 2030 in the USA [1]. The prevalence of PD in Turkey is estimated by Durmuş *et al.* [2]. According to their study, the prevalence in Turkey was 202 patients per 100,000 people in 2011.

PD was firstly described by James Parkinson in his famous work "Essay on the Shaking Palsy" [3] in 1817. After this description of PD, French neurologist Jean-Martin Charcot who work at the Salpêtrière made a great contribution to the diagnosis of PD from other diseases which show tremor symptom in 1872 [4]. He divided PD into two sub-branches like tremor-based and rigidity-bradykinesia based. Moreover, Parkinson's Disease term was used for the first time by Charcot [4] in 1872. Today the symptoms of PD, and assessment of the symptoms are clearly described by the International Parkinson and Movement Disorder Society (MDS) through their well-known rating system Unified Parkinson's Disease Rating Scale (UPDRS).

PD is a progressive central nervous system disorder. PD is caused by losing brain cells in a specific area which is responsible for producing dopamine. Due to losing brain cells, PD has numerous symptoms that can be collected under two main categories, namely motor and non-motor symptoms. These symptoms are the main criteria used for diagnosing and monitoring PD patients. Some of the motor symptoms of PD are tremor, rigidity, bradykinesia, and postural instability [5].

Assessment of the PD motor symptoms is crucial because of their potential for precise evaluation of PD. Thus, a brief description of these symptoms is mentioned below followed by rigidity which is the main focus of this study that will be explained broadly.

1.1.2. Symptoms of PD

Tremor is described by involuntary rhythmic oscillating motion which affects part of the body [6]. Tremor is one of the major symptoms that affect PD patients, and can be observed at their wrist visibly. Tremor is classified into two main categories by its activation conditions, namely rest and action tremor. Rest tremor is observed when muscles are relaxed, and disappears during movement. Postural tremor is the exact opposite of the rest tremor. It occurs when the limb is tried to move against gravity. The type of tremor seen in PD patients is rest tremor. Detailed information about tremor types and diseases that induce tremors are given by Bhatia *et al.* [6].

In PD, a repetitive movement like opening and closing of the palm gets slower, and the stroke of the movement becomes smaller. This type of resistance to movement is called bradykinesia [7]. This phenomenon is generally accompanied by rigidity and tremor. Bradykinesia is described by James Parkinson as decreased muscle power [3]. However, Charcot and his colleagues (1880s) state that bradykinesia is not caused by weakened muscle but it appears even if tremor and rigidity are not present [4]. Thus, they accepted bradykinesia as a new indicator of the PD.

Some of the PD patients struggle to maintain their balance during some movements like rising from a chair. This symptom is called the postural instability [5]. It is one of the most immobilizing consequences of PD, and can cause life-threatening accidents for elderly PD patients. For instance, falling is one of the most common results of the postural instability. Willemsen *et al.* [8] state that 78% of the falling is caused by postural instability rather than environmental factors. Roller and his colleagues examined one hundred PD patients about their experience of falling. 38% of these

patients fall, and 13% of them broke their bones. Moreover, these patients struggle with the fear of falling and its consequences [9].

1.1.3. Rigidity Symptom of PD

Rigidity can be described as the resistance to motion. The wrist joint is the most used joint for the assessment of this symptom. There are numerous reasons for that choice such as easy to move structure of the wrist, relatively high range of motion, multilateral motion ability. Parkinsonian rigidity refers to the decreased ability of the motion of PD patients [10]. At the same time, it may cause pain in the muscles that can be relieved by dopaminergic treatments [11]. The rigidity can be classified into two groups as lead pipe and cogwheel rigidity [12]. Lead pipe is the most common rigidity type for PD patients. In lead pipe, rigidity does not change through the range of motion. However, in cogwheel, rigidity is not continuous throughout the range of motion, and interrupted at frequencies 4 to 6 Hz or 8 to 9 Hz corresponding to the resting and postural tremor frequencies [13]. Another feature of the PD rigidity is the dependency on the posture. French neurologist Jules Froment show this dependency in his studies [13] during the 1920s. During his studies, he found that voluntary motion at one side of the body increases rigidity on the opposite side of the body. Today, this movement is called Froment manoeuvre [14].

1.1.4. Clinical Ratings of the Symptoms

Due to the complexity of the disease, the ranking of the severity of PD is a very challenging task. To assess the severity of the PD, several signs are used: diaries and self-reports of PD patients, level of disabilities, motor, and non-motor symptoms, the effects of symptoms on daily life etc. Commonly accepted and used scales are the Unified Parkinson's Disorder Rating Scale (UPDRS) and the Hoen and Yahr Scale (HY).

1.1.4.1. Unified Parkinson's Disease Rating Scale. UPDRS was firstly established by Fahn *et al.* [15] in 1987, and has become the most popular rating scale for PD [16]. UPDRS includes some of the previous studies, and has detailed rating scores of the symptoms. The Movement Disorder Society sponsored the modernization of UPDRS in 2001, and a new form of the scales published as MDS-UPDRS in 2008 [16]. UPDRS consists of four sections (parts). This test is in the form of questions and answers, except for part 3, which is the manual examination stage. Questions asked by the examiner are answered by the patient and/or the caregiver. The second part of the test is the assessment of the motor symptoms of the PD conducted by the examiner. The first and second part of the test is about the effect of the non-motor and motor symptoms to daily life, respectively. The last part is about motor fluctuations. All these sections include 65 subsections and these subsections are scored 0 to 4. subsection 3.3 is related to the evaluation of joint stiffness and this section can be seen in Table 1.1. At the end of the test, these scores are summed up, and this sum gives us the UPDRS score of the patient which is accepted as an indicator of the severity of the disorder [16].

Table 1.1. Rigidity section of UPDRS [15].

UPDRS Score	**Rigidity**
0	Absent
1	Slight or detectable
2	Mild
3	Marked, however range of motion easily achieved
4	Severe, range of motion achieved with difficulty

1.1.4.2. Hoehn and Yahr Scale. HY is first published by Margeret Hoen and Melvin Yahr in 1967 [17]. HY classifies patients by syndromes, unilaterality, and general condition of the patient. Modified HY can take 7 different scores between 1 to 5 with respect to the severity of PD. It is used broadly because the duration of the test is significantly lower than UPDRS due to its simplicity. However, it is not accepted as an exhaustive test because of its overgeneralization and less emphasis on the symptoms. Moreover, MDS-UPDRS includes HY. HY scale is shown in Table 1.2.

Table 1.2. Rating scale to describe the progression of PD by Hoehn and Yahr [17]

	Corresponding Clinical Severity
Stage I	Unilateral involvement only, minimal or no functional impairment
Stage II	Bilateral or midline involvement, without impairment of balance
Stage III	First sign of impaired righting reflexes
Stage IV	Fully developed, severely disabling disease
Stage V	Confinement to bed or wheelchair unless aided

1.2. Motivation

A valid cure for PD has not been developed yet except for syndrome treatment. Therefore, assessment of the severity of the syndromes is the key for the treatment strategies. However, it is a very challenging problem because PD has various syndromes along with side effects. For example, one of the most advantageous treatment methods for PD is deep brain stimulation (DBS). DBS is simply the placement of a neurostimulator at a specific part of the brain, which is responsible for producing dopamine. The appropriate area of the brain can be chosen by the medical imaging method. However, optimal parameters of this neurostimulator for an affective stimulation is decided by monitoring motor symptoms of the patient [18]. Rigidity (increased muscle tone) is one of the most used indicators for that purpose because it reacts to the change of states between on and off states of DBS in less than one minute [19].

Monitoring patients' condition is part of the treatment because treatment strategies depend on the symptoms. Result of the treatments can be tracked by motor symptoms and their resultants. The dosage and frequency of use have a direct effect on the results of dopaminergic treatments. Thus, this kind of monitoring needs to be done quantitatively. However, rigidity, the major motor symptoms of PD, cannot be assessed quantitatively in the current clinical practice due to the lack of a broadly accepted, easy to employ and objective method. Thus, the motivation of this study is to develop a feasible, and reliable method for the assessment of Parkinson's rigidity.

1.3. Objectives

The aim of this study is to develop a new method to evaluate viscoelastic properties of the wrist, and find a correlation between these viscoelastic properties and rigidity scores of UPDRS. Currently, smartphones come with built-in sensors used for numerous purposes such as gaming, navigation, mobile health. Quality of the built-in sensors is increasing every day. Consequently, the idea to use mobile phones as health tracking devices is one of the popular areas in biomedical engineering because, they are easily accessible, and affordable [20, 21]. In this thesis, a mobile-phone based measurement method is proposed to assess the rigidity of PD patients. The following objectives are followed to achieve the aim of the study:

Objective 1: To develop a mechanical model of the wrist rigidity. A second-order mass, spring, and damper model will be utilized as a simplified mathematical model of the hand and wrist.

Objective 2: To develop an experimental setup and experimental procedure to conduct experiments with PD patients and a control group consisting of healthy individuals to measure the frequency response of the wrist. For this purpose, a mobile application will be developed, as well.

Objective 3: To develop an algorithm to find a correlation between mechanical parameters of the wrist and UPDRS rigidity score.

2. LITERATURE REVIEW

Assessment of PD rigidity is a very challenging task, due to the time-dependent and non-linear mechanics of the wrist. Despite these handicaps, the mechanical model of the wrist can be simplified under specific conditions. A second-order mass, damper, and spring system is a convenient choice for modelling human wrist. Among these parameters, stiffness is the major component affecting wrist dynamics at low speeds [22]. Thus, the experimental setup and the test procedure must be designed accordingly.

One tool that is used to determine joint rigidities of the human body is the isometric dynamometer. That device moves the limb at constant velocity and measures used force to maintain that motion. Obtained force results are accepted as equal to the muscular force that is needed for this activity. This muscular force is directly related to the stiffness of the joint thus, this result is considered as a measure of rigidity [23].

There are also medical imaging methods for the assessment of Parkinson rigidity such as electromyography (EMG), myotonometry, and elastography. EMG is used for tracking the electric activity of the muscles, and this activity can be correlated with muscle rigidity [24]. It is shown that EMG activities for PD patients are higher than healthy control groups [25]. Myotometry is an instrument used for objective measurement of the mechanical properties of the muscles. This method estimates the natural frequency of the soft tissues. Repeatable tests can be conducted with this instrument for rigidity at rest [26]. Elastography is a method that uses small shear waves or low frequency impulses to map the mechanical properties of soft tissues. This method is mostly used for soft tissues like breast, liver, prostate [27]. Du *et al.* [28] use shear wave elastography and an ultrasound device for calculating Young's modulus of a biceps muscle. They found higher Young's modulus at PD patients than the healthy control groups and moderate positive correlation with UPDRS rigidity subscale.

Teravainen *et al.* [29] built an experimental setup using a torque motor with position feedback for assessment of the wrist rigidity. They fixed the arm with cushions and hand moved +30 degrees to -30 degrees at 11 different frequencies. Figure 2.1 demonstrate this experimental setup. They summarize that optimal velocity for assessment of wrist rigidity is between 140 or 190 degrees per second and they enounced optimal range of motion between +/- 25 or +/- 30 degrees.

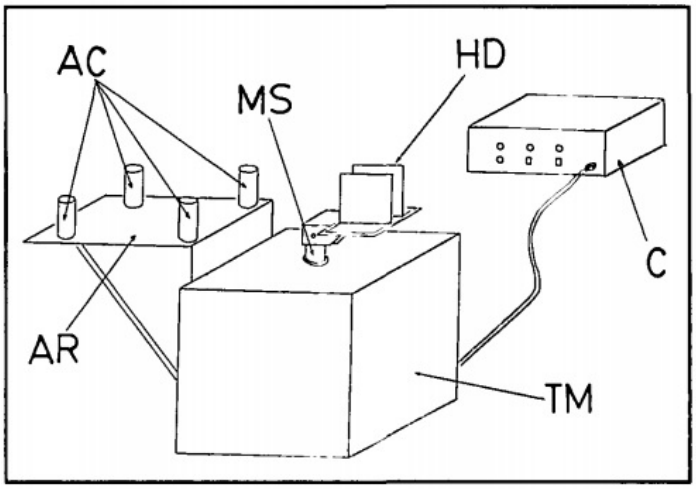


Figure 2.1. Experimental setup of the Teravaninaen et. al. research; AC: adjustable rubber cushions, AR: arm rest. MS: motor shaft, HD handle, C: controller, TM: torque motor inside aluminium case [29].

Caligiuri [30] has developed a portable device to assess rigidity in 1994. A resistive strain gauge was used to measure applied forces by an examiner to move the hand. Movement of the hand is measured by a potentiometer. His experimental setup can be seen in Figure 2.2. This method could detect, PD patients from the healthy control groups and the effect of the single-dose dopamine therapy.

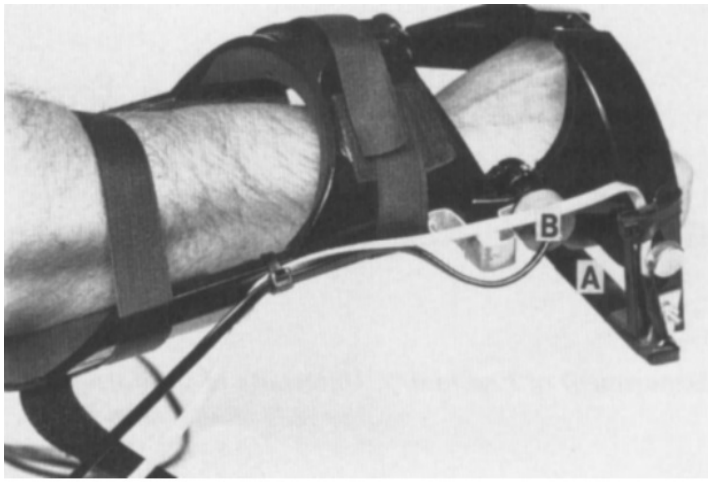


Figure 2.2. Experimental setup of the Caliguri's research [30]; A: Force gauge, B: Rotational encoder.

Viscoelastic properties of the wrist were investigated by Park *et al.* [31]. Figure 2.3 demonstrate their experimental setup. They utilize three different models for this purpose. The first one is composed of one spring and one damping constants, the second one is composed of one spring and two damping constants and finally, two damping and two spring constants are utilized for modelling the wrist. In their experiment, the best consistency with UPDRS rigidity score was achieved by the model which contains one spring and one damping constant [31].

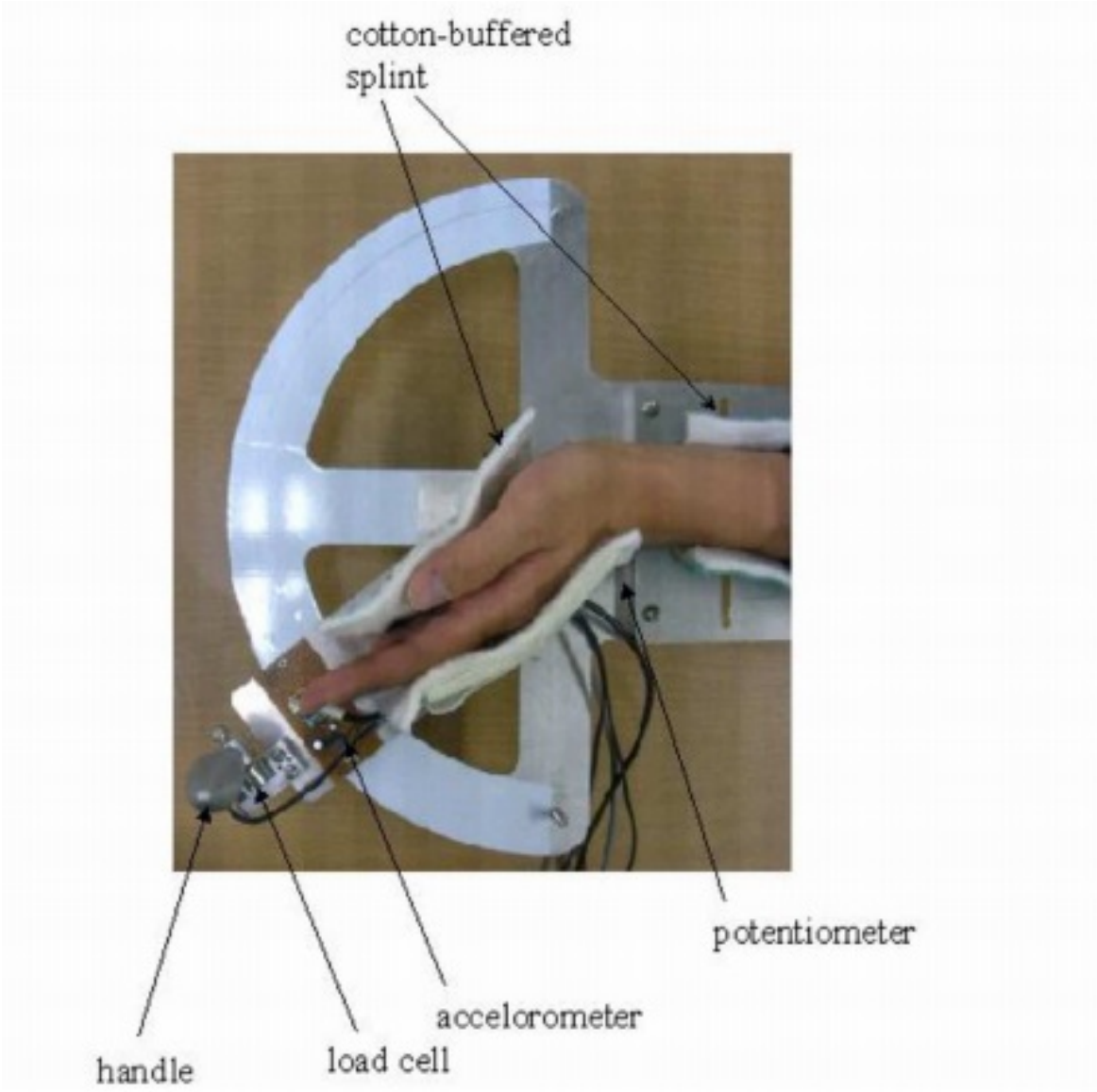


Figure 2.3. Experimental setup used by Park *et al.* [31].

Costa *et al.* [32] developed a system for evaluating PD rigidity during the DBS. Their apparatus contains a microcontroller, a gyroscope, a magnetometer and an accelerometer. The apparatus and brief illustration of their experiments are demonstrated in Figure 2.4. They established a signal descriptor for the assessment of rigidity. The apparatus was attached to the palm, and collected data while the examiner moves the hand. The descriptor consists of average angular velocity and average peak values. It had a positive correlation with UPDRS rigidity score, and could detect the cogwheel effect.

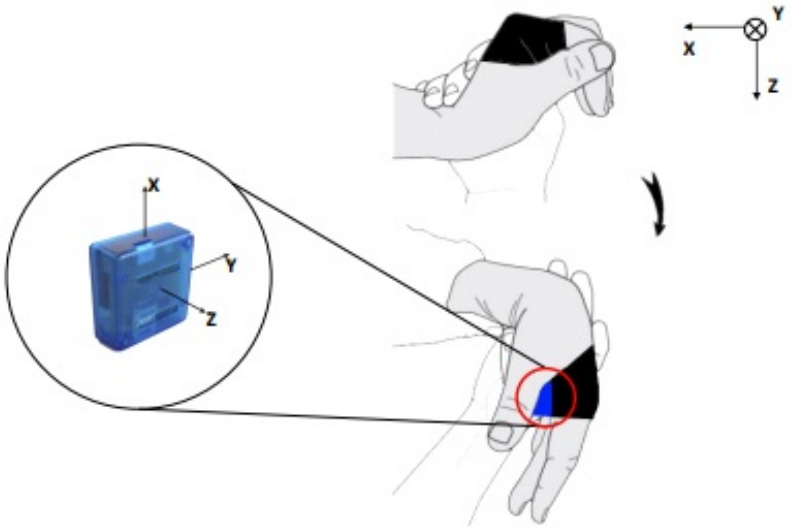


Figure 2.4. Experimental setup and brief illustration experiment of the Costa's research [32].

Biase *et al.* [33] design an experimental setup which consisted of five magneto inertial sensors placed on the arm as shown in Figure 2.5. They could extract four features from their experiment: fatigability, total time, total power, and smoothness. They claim that smoothness could be correlated with PD rigidity of the finger. In their experiments, they can differentiate on state rigidity from off state rigidity. For the off state, patients stopped taking the medication 12 hours before tests.

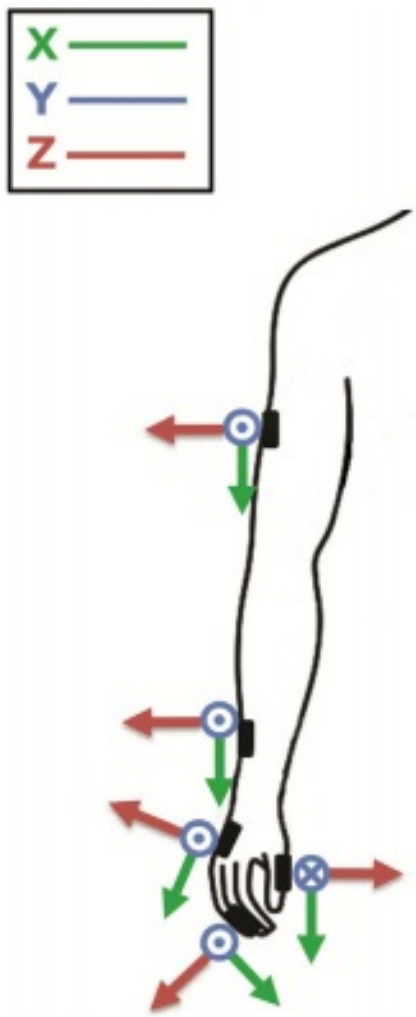


Figure 2.5. Orientation of sensors in Biase *et al.* [33].

A wearable device for the palm was designed by Perera *et al.* [34]. Brief description of the device can be seen in Figure 2.6. Their devices can be seen in Figure 2.6. In their method, a motor flexed and extended the middle finger. They assumed that increasing rigidity could cause more power needed to maintain this motion. They used four features for the assessment of rigidity, which are force rate, peak force, work estimate, and charge. Their method has a moderate agreement with UPDRS rigidity score and can distinguish on-off dopaminergic states and healthy subjects from PD patients.

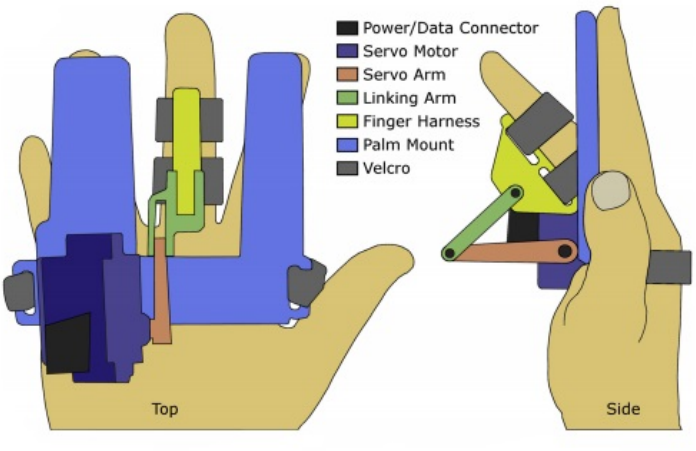


Figure 2.6. The Bionics Institute Rigidity Device (BiRD) [34].

3. MATERIALS AND METHODS

Quantitative assessment of PD rigidity is more complicated than assessing other motor symptoms of PD. While other symptoms can be recorded by a video camera, and investigated afterwards by movement disorder specialist, for rigidity this is not possible. Thus, many researchers are addressing this topic in the literature. In this section, experimental setup, methodology and subsequently two analysis method will be explained.

3.1. Experimental Setup

A mobile phone, Samsung s10e, was used for measurement purposes. It has a built-in accelerometer that can be used up to 512 Hz. As frequency range of interest is between 2 and 20 Hz, the accelerometer is suitable for the measurement of the frequency response of the wrist [35]. Accelerometer data were obtained using the Android sensor framework [36]. Raw accelerometer data was acquired by registering a sensor event listener. The sampling size can be configured with a handler class that allowed us to perform a process at fixed time intervals, for this experiments sample size is set at 3072. The coordinate system used by built-in sensors that was used in this study is shown in Figure 3.1

An Android application has been developed for collecting sensor data. The user interface of the developed application can be seen in Figure 3.2. The sensor listening event starts when the buttonis shown in Figure 3.2(a) is pressed and continues until the specified sample size is reached. Settings of the app as shown in Figure 3.2(b) are sample size, name of the test, and the number of the trials. When the listening event ends, two buttons appear on the screen, the first one sends the data to the server, and the other allows the test to be renewed. Renew option is used when the test fails because of external factors. These two buttons and the screenshot of the application while it is running, can be seen in Figure 3.3.

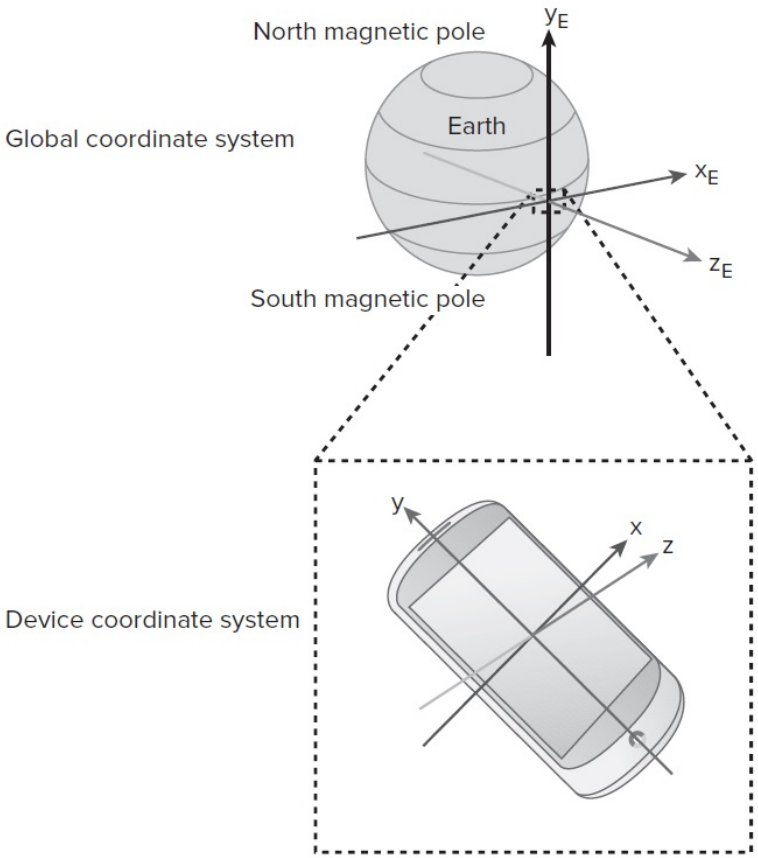
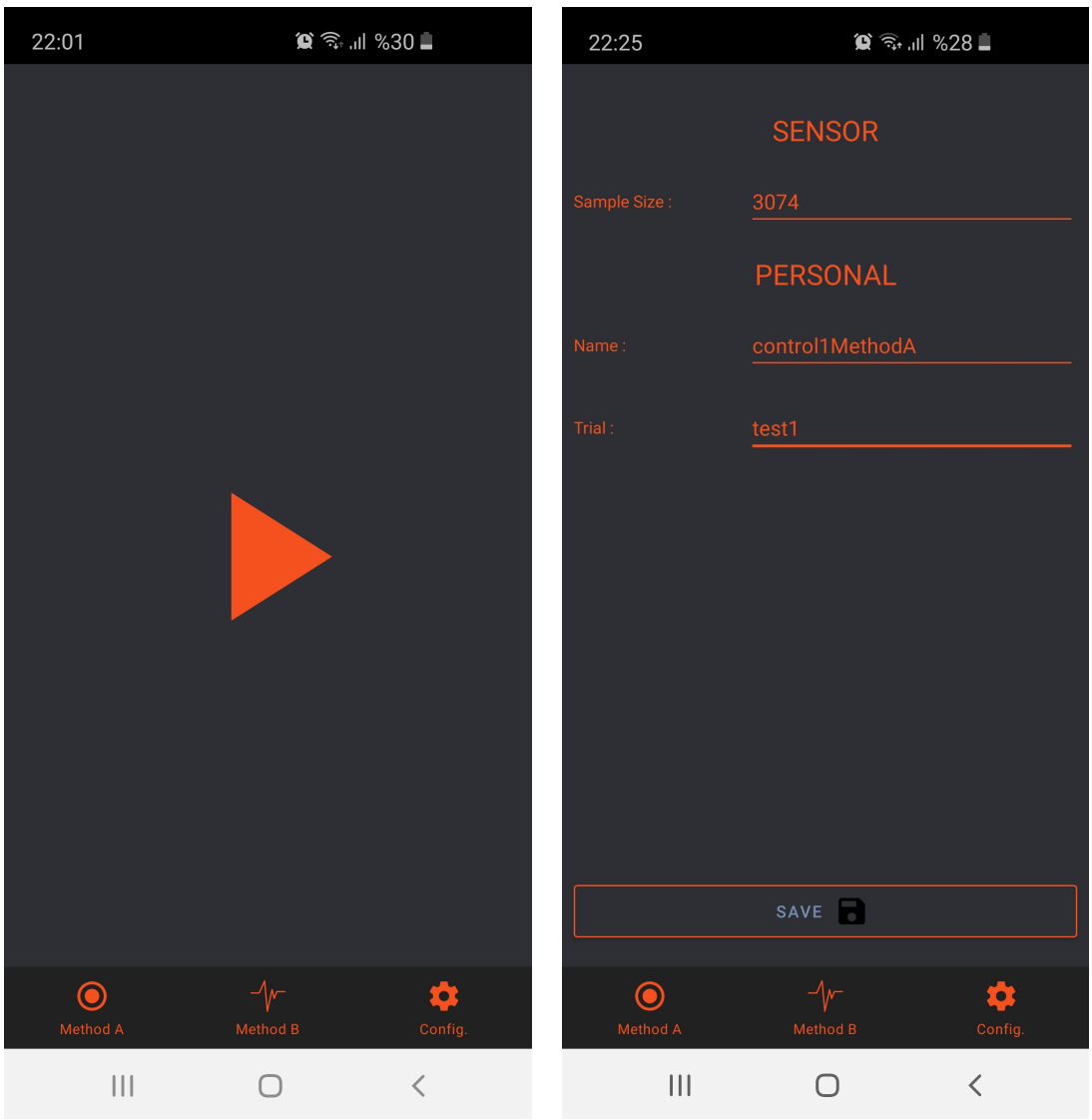


Figure 3.1. Coordinate system of mobile phone and global coordinates [37].

Two method names that appear at the bottom of the application screen as shown in Figures 3.2 and 3.3, which are Method A and Method B, refer to two parallel studies. Method B is the frequency response-based approach followed in this study, and Method A refers to the method that is used for Dinçer's thesis [38]. He uses a silicone-based semi-conductive gadget for measuring force, that is applied by an examiner to the phone screen attached to the palm of a PD patient.



(a) (b)

Figure 3.2. User interface of the developed mobile application; (a) main screen (b) configuration screen.

(a) (b)

Figure 3.3. The screens after the play button is pressed; (a) the application starts to collect data from the sensor , (b) after data size reaches the desired sample size.

3.2. Methodology

We decided to let the hand make a free fall from the neutral position to flexion position while the mobile phone is attached to the hand to measure the frequency response of the wrist. Acceleration of the hand is collected in three dimensions via the built-in accelerometer of the hand.

In order to validate this novel assessment methodology, an experimental study has been conducted in the Department of Neurology of Ankara University School of Medicine. 10 PD patients and 11 healthy subjects have voluntarily participated in the study. The whole experimental procedure has been approved by the Institutional Review Board of Ankara University. In the following section, the experimental procedure is given in detail.

3.2.1. Experimental Procedure

First, an informed consent form is read to the subject, and permission is requested. If the subject agrees to participate in the experiment, then he/she is asked to sign the informed consent form. After that, a neurologist from the Department of Neurology of Ankara University School of Medicine conducts the UPDRS test, and results of the test are entered into a UPDRS form.

After a brief description of the experiment is told to the subject, and he/she was asked to sit on a chair next to a desk as shown in Figure 3.4 . Then, his/her right forearm is bandaged to the desk with a loop strap , which is utilized for this purpose. A glove that has a pocket on the top of it is worn to the right hand of the subject. This equipment used is shown in Figure 3.5.

Figure 3.4. The subject sits on a chair next to a table on which his right forearm is fixed.

The subject number is written on the UPDRS form and on the settings menu of the mobile phone. Then, the mobile phone is attached to the palm of the hand with a specially designed case. Subsequently, the developed app is started by pressing the button on the screen.

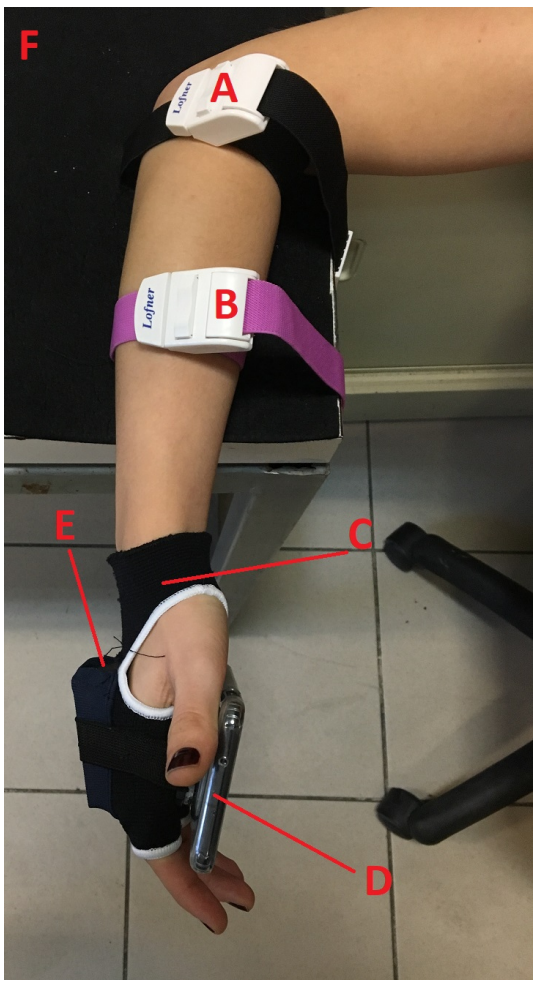
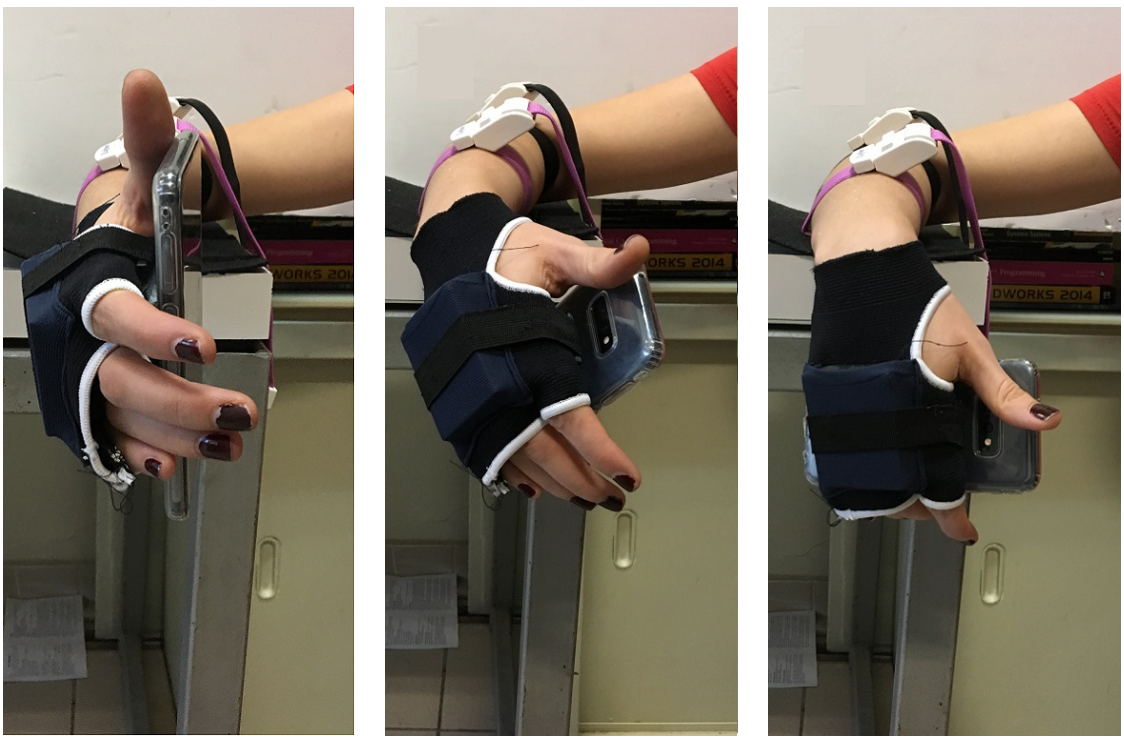


Figure 3.5. The forearm posture during the clinical trials; A and B are medical loop straps to forearm to the table, C is the glove, D is the case for smartphone, E is the rectangular metal piece, and F is the cushion to make forearm comfortable.

The subject is asked to naturally let his/her right hand fall as shown in Figure 3.6. The falling motion of the hand should be inward. The subject releases his/her hand at the position as shown in Figure 3.6(a), then hand follows a natural trajectory as shown in Figure 3.6 (b) and (c). In order to let the participant make this motion properly, the motion is repeated several times without collecting data until the desired motion is achieved successfully. The motion is repeated 10 times for each trial. Total of 4 trials are conducted for each subject. The whole experiment is repeated after removing the mass from the glove's pocket with the same steps. Experiments with an additional weight were necessary for the model-based analysis as explained in Section 3.3.1. As a next step, the whole experiment is repeated with a contralateral voluntary activity to mimic the Froment manoeuvre, after the subject rested for 5 minutes.



(a) (b) (c)

Figure 3.6. Rotation of the wrist during free fall; (a) the initial position of the hand, (b) position of the hand while falling freely, (c) the final position of the hand.

The procedure described in this section is explained without taking into account the sorting of the trials. The order of the trials was fully randomized. Some patients first participated in the experiments in the on state, and some in the off state. Likewise, some participants performed the test first with the Froment maneuver while others started without the Froment maneuver.

Four different types of data are obtained from the experiments for PD patients with respect to their, medical condition (i.e., on or off) and activation of the opposite side of the body. For PD patients these groups are on and off states with respect to the medical condition of the PD patient, and two subgroups of these groups. These two subgroups for the control group are, activated and rest states, which refers to the activation of the opposite side of the body with a Froment maneuver. For control group subjects, just two types of data are rest and activated states. "On" state means that the DBS device and medical treatment is effective on patients, off state is the vice versa. UPDRS rigidity score is not determined at the activated state, thus the relation between rigidity and UPDRS rigidity score is investigated at the rest state. In this study, two different Froment maneuvers are used. The first one is palm opening-closing motion and the second one is finger to nose motion. The subject is asked to open and close the palm at a constant speed for palm opening-closing motion. The subject is asked to fully extend his/her arm

3.3. Postprocessing and Analysis

Analysis methods that are suggested for the assessment of PD rigidity will be described in this section. The first method depends on the stiffness coefficient, the second one depends on the Wavelet transform-based analysis.

3.3.1. Method 1: Model-based Analysis

Operational and experimental model analysis which are based on frequency analysis, are used for identifying joint dynamics. These methods in the literature require more than one sensor package or complex simulations of the joints. Nowadays, broadly used mobile health tracking systems cannot fulfil these requirements. Thus, new methods for identifying joint dynamics are needed. An acceleration sensor is generally sufficient for the measurement of the natural frequency of system. However, for identifying mass stiffness and damping properties of a system, a second entity is needed. For this reason, the model-based analysis method is proposed. This method is based on identifying the change in the natural frequency by adding mass to the system to predict stiffness.

Dependence of the natural frequency of the human joint on the applied force and change of the gravitational force is investigated by Lakie *et al.* [39]. They show that adding mass on the joint decreases the natural frequency of the system. This result is normally expected for a second-order mass, spring, and damper system, Figure 3.7 shows the proposed second-order mass (m), spring (k), and damper (c) model, and transmissibility equation of the system is given in Equation 3.6 where Y and X represent the magnitude of change of position of the base and mass respectively, ζ is the damping ratio, r is the normalized frequency which is defined as excitation frequency ω divided by the natural frequency of oscillation ω_n. Figure 3.8 shows the effect of the added mass to the system on the frequency response. Thus, the proposed method assumes that adding mass to the system does not change the system stiffness and damping coefficient but it decreases only the natural frequency as shown by Lakie *et al.* [39].

Therefore, the change of mass is the only affecting factor for the change in natural frequency and can be calculated as shown in Equations 3.4 and 3.5 where m_1 is the mass of the hand, m_a is added mass to the system, m_2 is the total mass of the hand, ω_{mass} is the natural frequency when mass added, $\omega_{massless}$ is the natural frequency of the hand without any additional mass, and k is the stiffness coefficient of the wrist. The result of this model in time domain is shown in Figure 3.9.

$$\frac{X}{Y} = \sqrt{\frac{1 + (2 \times \zeta \times r)^2}{(1 - r^2)^2 + (2 \times \zeta \times r)^2}} \tag{3.1}$$

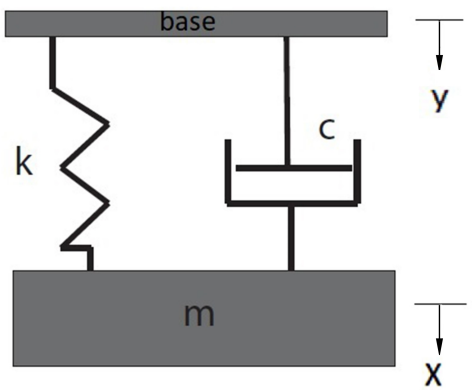


Figure 3.7. A second-order mass-spring-damper model with a base excitation.

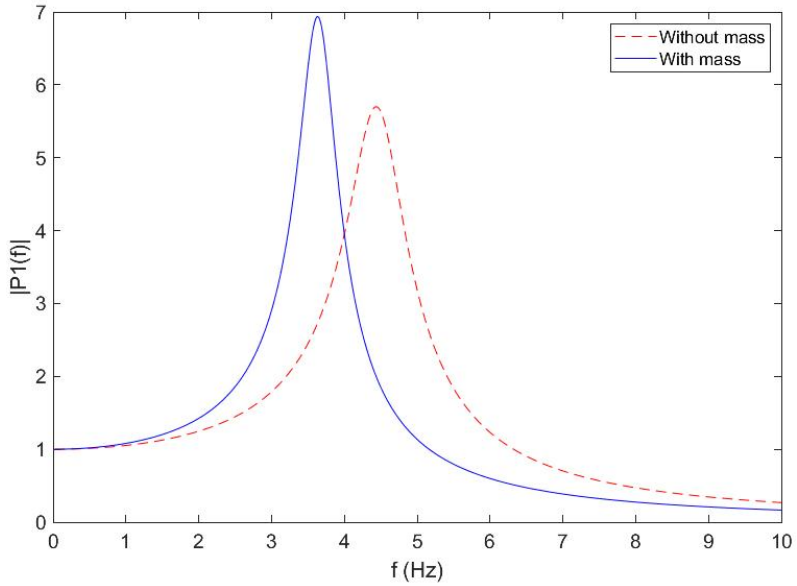


Figure 3.8. Effect of the adding mass on the natural frequency of an example system with k= 200 N/m, c= 8 Ns/m, m_1 = 1 kg, m_2= 1.5 kg.

$$m_2 = m_1 + m_a \tag{3.2}$$

$$m_1 = \frac{m_a \times \omega_{mass}^2}{\omega_{massless}^2 - \omega_{mass}^2} \tag{3.3}$$

$$k = \omega_{massless}^2 \times m_1 \tag{3.4}$$

$$k = \omega_{mass}^2 \times m_2 \tag{3.5}$$

Acceleration data obtained from the measurements are converted to the frequency domain by Fast Fourier Transform (FFT) after the corresponding signal to the first fall that causes low frequency noise is extracted. To eliminate noise in the data, a moving average filter with window size 8 is applied. Then, FFT is applied to signals, and the results of the FFT that belongs to trials of each subjects' are averaged to obtain a representative signal. This process aims to eliminate external factors that affect trials. To dispose of the factors of the external effects, a bandpass filter between 3 Hz and

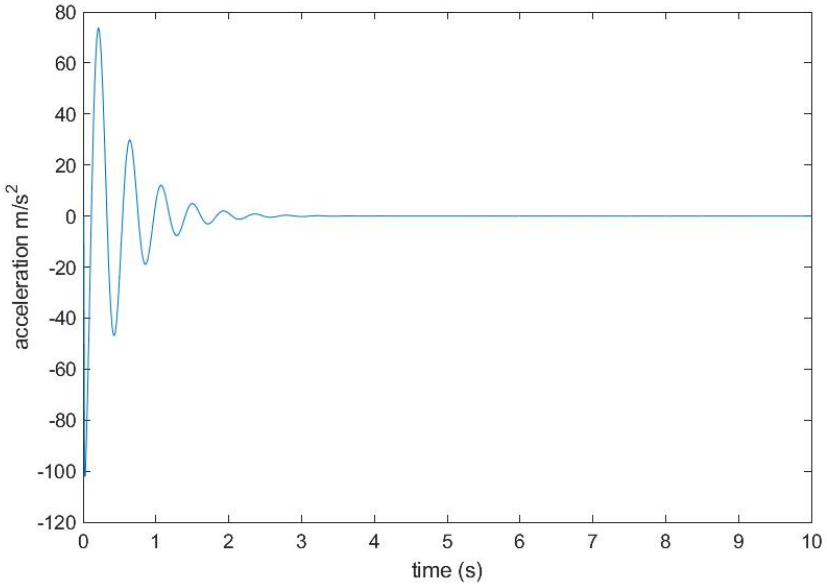


Figure 3.9. Time domain response of the second order model with base excitation by initial displacement (x_1), k= 200 N/m, c= 8 Ns/m, m = 1 kg, x_1 = 0.1 m.

8 Hz is applied. For calculating natural frequency, a curve is fitted to this data with the least square method. Hence, the required parameters for model-based analysis method are estimated. An example of the FFT plot and fitted curve is demonstrated in Figure 3.10

In this study, the rotational motion of the wrist is considered. Thus, the calculated system parameters (stiffness, damping and mass) values need to be converted to rotational parameters as torsional stiffness, torsional damping constant and mass moment of inertia. Figure 3.11 shows the rotational motion of the wrist where l is the distance between the mass center of the hand and the center of rotation of the wrist, k_t is the torsional stiffness, I is the moment of inertia and θ is the rotational displacement of the wrist. Moment of inertia is calculated as shown in Equation 3.6, and torsional stiffness values are calculated using Equation 3.7.

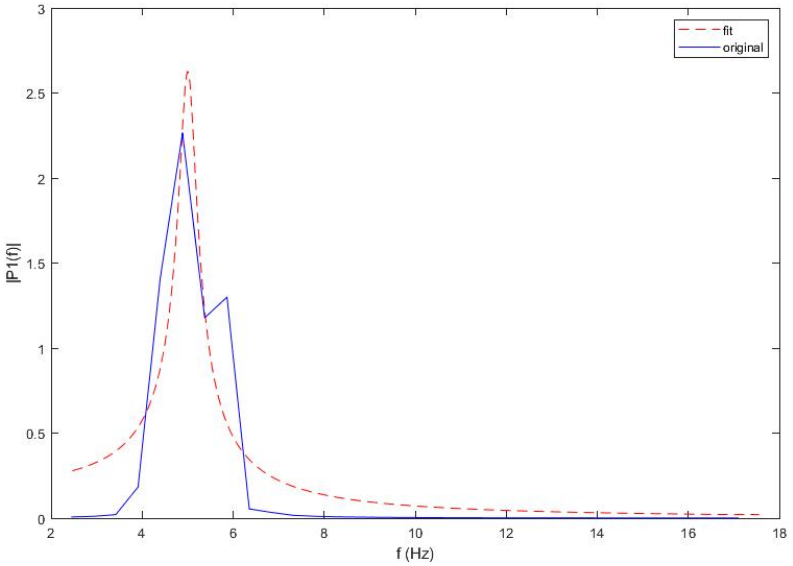


Figure 3.10. An example of fitted curve to the FFT domain data from experiments.

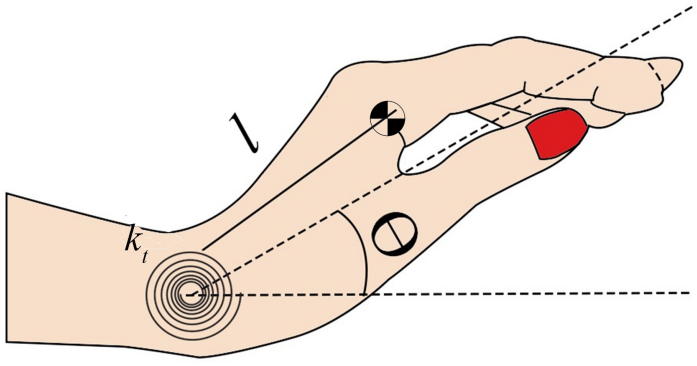


Figure 3.11. An ilustration of the hand.

$$I = \frac{4}{3} \times m_1 \times l^2 \tag{3.6}$$

$$k_t = k \times l^2 \tag{3.7}$$

3.3.2. Method 2: Deep Learning-based Analysis

Besides the determination of the stiffness of the wrist system, data acquired from the experiment, possesses a substantial amount of information. Therefore, the entire process of the clinical assessment of the wrist rigidity can be handled as a classification problem. The main phase of a classifications problem is feature extraction. A deep learning algorithm can automatically extract such features. Convolutional neural network (CNN) is one of the sub-classes of deep learning algorithms. GoogleNet got first place at ImageNet Large-Scale Visual Recognition Challenge 2014 for the classification area [40]. Thus, Googlenet is used as the neural network algorithm in this thesis.

Continuous wavelet transform (CWT) is one of the signal representation methods which contains both time and frequency information. Wavelet is used as a mapping stationary and nonstationary signals on time and frequency domains. Hence, a three-dimensional graph of a signal can be represented as an RGB picture. Some researchers are using wavelet transform and deep learning techniques for assessments of the Electroencephalography (EEG) signals [41, 42]. The proposed method in this section is based on CWT and GoogleNet algorithms.

The acceleration signal measured during the wrist rigidity measurements has 3072 samples. An example of the time domain signal is demonstrated in Figure 3.12. The portion of the signal which is used for analysis, is exhibited in the red box in the picture. The drop in the first part of the acceleration signal is due to free-fall motion. Then,

the hand oscillates about the equilibrium position. One of the most important factors that affect the performance of the CNN is the data size. However, due to the small size of the experiment group, the data size is very limited. To handle this problem, data augmentation is needed to apply to time-domain data. Before increasing the number of data, a moving average filter with window size 8 is applied to the signals for smoothing the data. Sliding windows are used for data augmentation, and window size is selected as 512 samples. Each window slides 16 samples to the right of the previous window as can be seen in Figure 3.13. In other words, each window overlaps with 496 samples. Totally, there are 33 sliding windows for a signal, that means 33 images are obtained from each signal. Subsequently, continuous wavelet transform is applied to each window, the results of the transformations are converted to RGB images. Each image is an array of size 224x224x3. Figure 3.14 is a short demonstration of this process.

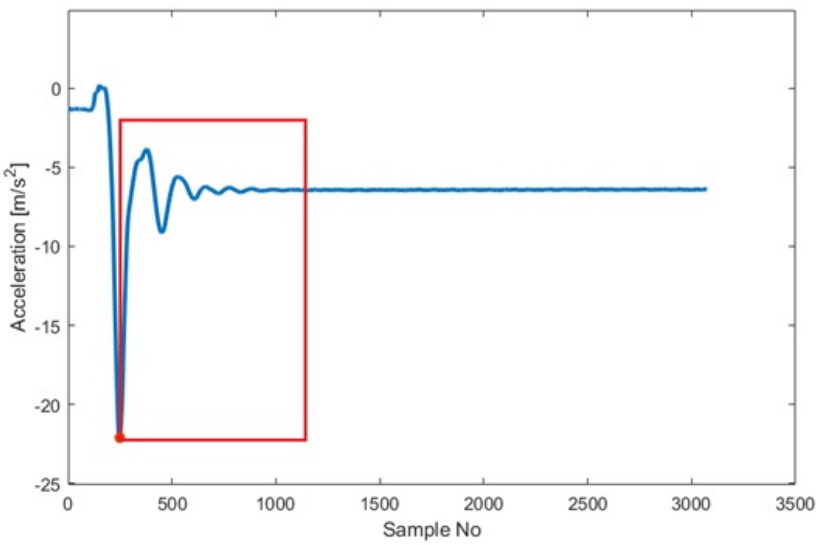


Figure 3.12. Line plot of the acceleration along the z-axis.

GoogLeNet is a pretrained network to classify images into 1000 object categories. It must be retrained for the rigidity classification problem. To prevent overfitting, a dropout layer is used. A dropout layer randomly sets input elements to zero with a given probability. The final dropout layer in the network is replaced with a dropout layer of probability 0.5.

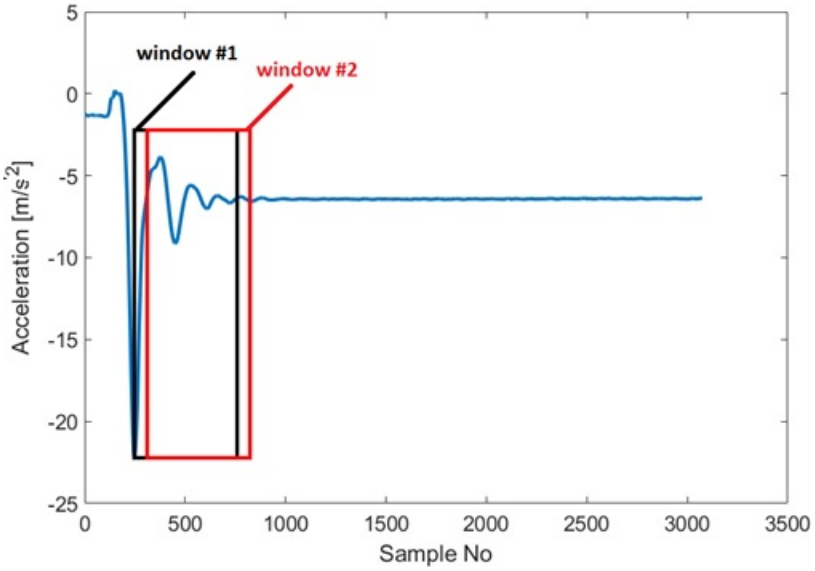


Figure 3.13. Reproducing process with sliding windows.

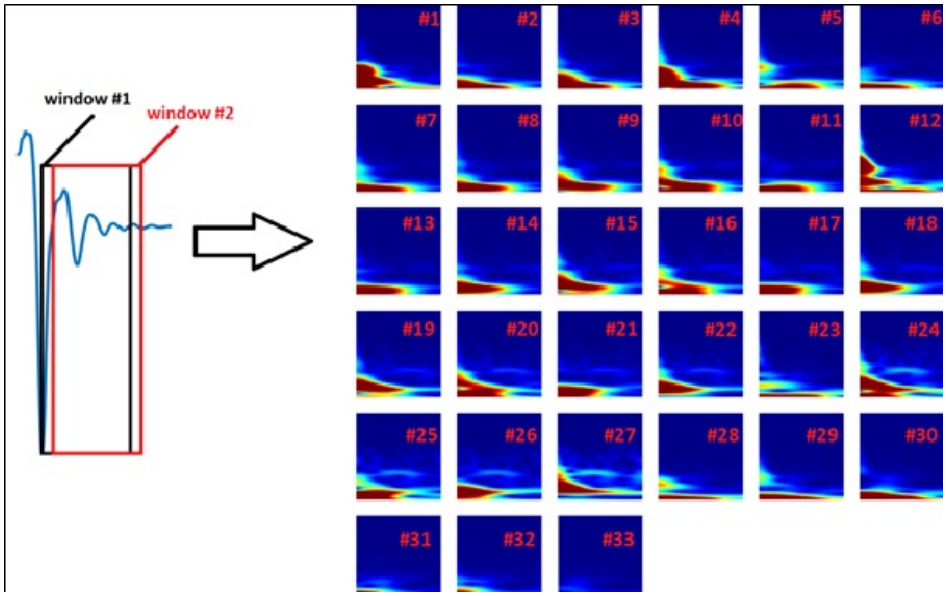


Figure 3.14. Converting each window to an RGB image having an array of size 224x224x3.

4. RESULTS AND DISCUSSON

In this section, results of the two analysis methods which were described in Section 3.3 will be presented. Analysis conducted with 10 PD patients and 11 healthy subjects. Their UPDRS rigidity scores are shown in Table 4.1 and Table 4.2.

Table 4.1. The UPDRS rigidity scores of PD patients.

ON		OFF	
	UPDRS rigidity score		UPDRS rigidity score
subject 1	1	subject 1	2
subject 2	4	subject 2	3
subject 3	0	subject 3	1
subject 4	1	subject 4	3
subject 5	1	subject 5	2
subject 6	1	subject 6	2
subject 7	1	subject 7	2
subject 8	3	subject 8	4
subject 9	1	subject 9	2
subject 10	0	subject 10	0

Table 4.2. The UPDRS rigidity scores of healthy subjects.

	UPDRS rigidity score
control 1	1
control 2	1
control 3	0
control 4	0
control 5	0
control 6	1
control 7	0
control 8	1
control 9	1
control 10	1
control 11	0

4.1. Results of the Model-based Analysis

Stiffness values obtained by the model-based analysis are given in Table 4.3. Some stiffness values are turned out to be negative, which means that the natural frequency, when mass is added to the wrist is higher than the normal mass case, which contradicts Lakie's study [39] that investigated the effect of adding mass to the wrist. This shows that the results are affected by some external factors other than the mechanical effect of the free fall test. To eliminate this problem, false-negative stiffness values are eliminated and the remaining data can be seen in Table 4.4.

Table 4.3. Results of the Method 1.

	ON		OFF	
	Rest k_t(N.m/rad)	Activated k_t(N.m/rad)	Rest k_t(N.m/rad)	Activated k_t(N.m/rad)
subject 1	0.88	0.94	-1.07	0.62
subject 2	-1.12	1.62	-1.90	6.78
subject 3	2.59	3.70	1.50	-0.97
subject 4	1.04	-1.03	1.30	2.99
subject 5	-1.46	1.94	-3.73	-1.91
subject 6	1.03	0.83	-2.94	1.07
subject 7	-10.97	-11.49	-2.59	3.29
subject 8	1.97	-5.49	3.37	-4.10
subject 9	2.81	-8.01	1.67	1.33
subject 10	0.88	1.02	1.61	-0.68

For investigating the relation between the UPDRS rigidity scores and calculated stiffness coefficients, the result of the rest state data are used. Rest state stiffness values and their corresponding UPDRS rigidity scores are shown in Table 4.5. To increase intelligibility, the same data is displayed in Figure 4.1 as UPDRS rigidity score versus calculated rigidity. Except for some data points, a positive correlation can be seen between the UPDRS rigidity scores and the calculated stiffness values. This kind of outlier data points occurs when massless and with mass natural frequencies are either too close or too far from each other. These two cases can be explained by the low resolution in the frequency domain or the other external factors which cause higher peaks than the mechanical free-fall effects. For these reasons, these values which are caused by the uncertainties need to be eliminated. The final results are shown in Table 4.6.

Table 4.4. Results of Method 1 after false-negative stiffness values are eliminated.

	ON		OFF	
	Rest k_t(N.m/rad)	Activated k_t(N.m/rad)	Rest k_t(N.m/rad)	Activated k_t(N.m/rad)
subject 1	0.879857	0.9404259	x	0.6232307
subject 2	x	1.6212494	x	6.7821343
subject 3	2.586094	3.7030017	1.4951254	x
subject 4	1.035048	x	1.2982912	2.9913744
subject 5	x	1.9439485	x	x
subject 6	1.033359	0.825828	x	1.0687557
subject 7	x	x	x	3.2855128
subject 8	1.968283	x	3.3725614	x
subject 9	2.812342	x	1.6710315	1.3286984
subject 10	0.875118	1.0190507	1.610988	x

Table 4.5. Stiffness values after false-negative data is eliminated for the rest state, in Method 1 and the corresponding UPDRS rigidity scores.

ON		OFF	
Rest k_t(N.m/rad)	UPDRS	Rest k_t(N.m/rad)	UPDRS
0.88	1	1.50	1
2.59	0	1.30	3
1.04	1	3.37	4
1.03	1	1.67	2
1.97	3	1.61	0
2.81	1		
0.88	0		

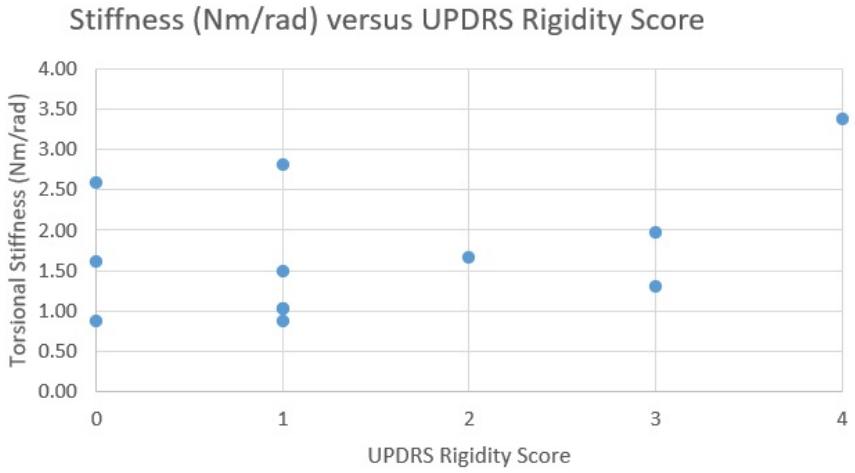


Figure 4.1. Scatter plot of the calculated stiffness values versus the UPDRS rigidity scores for subjects' rest state data.

One-Way Anova analysis is used to make the relation between calculated rigidity and the UPDRS rigidity score statistically meaningful. The result of the final version of the results can be seen in Table 4.7 as the Anova result table. The final version of the results has a strong relation with UPDRS rigidity score with a p-value of less than 0.05 specifically 0.0221.

Table 4.6. Final results of the calculated stiffness values and the corresponding UPDRS scores for the rest condition.

ON		OFF	
Rest k_t(N.m/rad)	UPDRS	Rest k_t(N.m/rad)	UPDRS
0.88	1	1.50	1
1.04	1	1.30	3
1.03	1	3.37	4
1.97	3	1.67	2
0.88	0		

Table 4.7. Anova result table of final version of the rest state data of subjects in Method 1.

Source	SS	df	MS	F	Prob>F
Groups	4.5441	4	1.13627	10.31	0.0221
Error	0.44072	4	0.11010		
Total	4.98582	8			

Table 4.8. Stiffness results of the control group in Method 1.

	Rest k_t(N.m/rad)	Activated k_t(N.m/rad)
control 1	17.61	1.23
control 2	0.44	0.27
control 3	-4.94	-30.95
control 4	1.53	0.71
control 5	-868.84	10.97
control 6	1.51	2.39
control 7	5.39	1.07
control 8	0.84	1.89
control 9	4.88	-2.72
control 10	-2.00	-2.81
control 11	-2.21	0.78

The results of the control group can be seen in Table 4.8. The results of the control group are coherent with wrist stiffness values reported in the literature [43,44].The same procedure which is used for eliminating some points for subject results is applied to the result of the control group and results are shown in Table 4.9. The P-value of the Anova results between the control group and the PD patients at rest state are less than 0.2 and which is acceptable because some of the control group participants' UPDRS rigidity score is not zero. As expected, the mean value and distribution range is greater for the PD patients. These one-way Anova results can be seen in Table 4.10 for the rest state and. Table 4.10 is Anova results for the activated state.

Table 4.9. Final version of control group data for Method 1.

	Rest k_t(N.m/rad)	Activated k_t(N.m/rad)
control 1	x	1.23
control 2	0.44	0.27
control 3	x	x
control 4	1.53	0.71
control 5	x	x
control 6	1.51	2.39
control 7	x	1.07
control 8	0.84	1.89
control 9	x	x
control 10	x	x
control 11	x	0.78

Table 4.10. One-way Anova results of the calculated stiffness values between the PD patients and the control group in the rest state data.

Source	SS	df	MS	F	Prob>F
Groups	0.52784	1	0.52784	0.99	0.3404
Error	5.84677	11	0.53152		
Total	6.37461	12			

Table 4.11. One-way Anova results of the calculated stiffness values between the PD patients and the control group in the activated state data.

Source	SS	df	MS	F	Prob>F
Groups	4.2933	1	4.29333	1.92	0.1839
Error	38.0333	17	2.23725		
Total	42.3266	18			

Along with the UPDRS rigidity score, the effect of the Froment manoeuvre can be investigated with this data set. Box plots of the rest versus activated for the PD patients and the control groups can be viewed in Figure 4.2 and Figure 4.3, respectively. Mean stiffness values are higher at the activated state for both groups, which are expected, and the distribution range is higher at the activated state than the rest state.

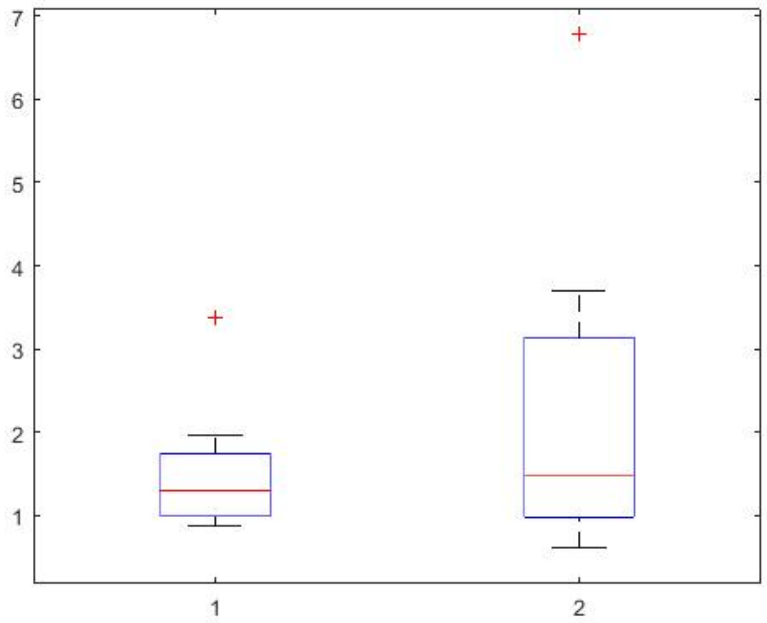


Figure 4.2. Box plot representation of the activated versus rest state results for the PD patients. 1 is the average of stiffness in the rest state, values and 2 is average of stiffness values in the activated state.

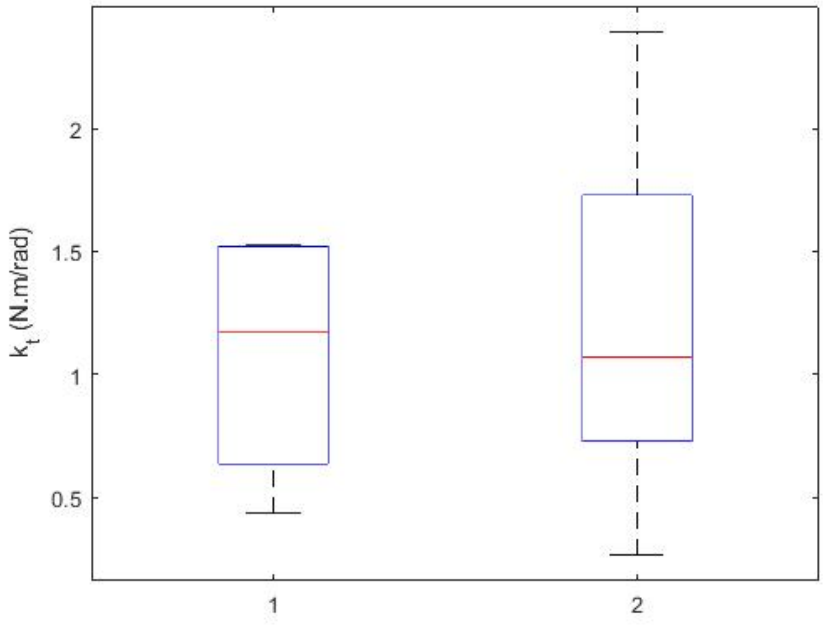


Figure 4.3. Box plot representation of the activated versus rest state results for control group. 1 is the average of stiffness in the rest state, values and 2 is average of stiffness values in the activated state.

The model-based analysis method gives promising results for stiffness measurement of the human wrist; however, false-negative data should be removed, which is a major impediment for clinical usage of this method. To overcome this problem, its cause needs to be determined. Vial *et al.* [45] investigate the mechanism of the natural frequency of the human joint, and they categorized the mechanism affecting the natural frequency into 3 subgroups. These are mechanical components, mechanical reflex component, and central components. The proposed method in this thesis tries to measure the effect of the mechanical component; nonetheless, the effect of the other components comes forward in some of our measurements. When the mechanical component is considered, the natural frequency decreases when a mass is added on the hand. However, the other components do not have this trend. This was the main rationale in eliminating false measurement results.

4.2. Results of the Deep Learning-based Analysis

A wavelet transform-based image processing method is used to convert the signal to the RGB images to use in CNN method. Data augmentation methods and GoogleNet algorithm are described before. Summary of the data set is provided in Table 4.12 for the subjects PD and in Table 4.13 for the control group. The subjects are randomly divided into two groups: training and validation. 60% of the subjects were used for the training process, 40% of them are used for validation.

Table 4.12. Summary of data set for the subjects with PD.

	State	Rigidity Score	Total Image Size	State	Rigidity Score	Total Image Size
subject 1	ON	1	297	OFF	2	330
subject 2	ON	4	330	OFF	3	396
subject 3	ON	0	330	OFF	1	330
subject 4	ON	1	330	OFF	3	330
subject 5	ON	1	330	OFF	2	330
subject 6	ON	1	264	OFF	2	330
subject 7	ON	1	297	OFF	2	330
subject 8	ON	3	297	OFF	4	297
subject 9	ON	1	264	OFF	2	264
subject 10	ON	0	264	OFF	0	231
Total						6171

The training process is given in Figure 4.4. Accuracy of validation and testing process changes during the iterations, the black and blue lines are indicated the change of the accuracy of testing and validation, respectively. The validation accuracy that evaluate the performance of training of the classification problem found as 46%. We then tested the GoogLeNet with the validation images again, and GoogLeNet accuracy is found as 45.9% when randomizing was conducted before the data augmentation

Table 4.13. Summary of data set for the control group.

	Rigidity Score	Total image size
Control 1	1	330
Control 2	1	330
Control 3	0	330
Control 4	0	330
Control 5	0	330
Control 6	1	330
Control 7	0	264
Control 8	1	264
Control 9	1	264
Control 10	1	264
Control 11	0	264
Total		3300

process. When the randomizing process was conducted after data augmentation process, the classification accuracy increases to 85.7% and GoogleNet accuracy increases to 84.9%. Because of the unbalanced distribution of the data, the first case, which data augmentation is conducted before randomization does not work well. However, the second case, which randomization process is conducted after data augmentation has higher accuracy with risk with overfitting because data augmentation does not ensure completely different images.

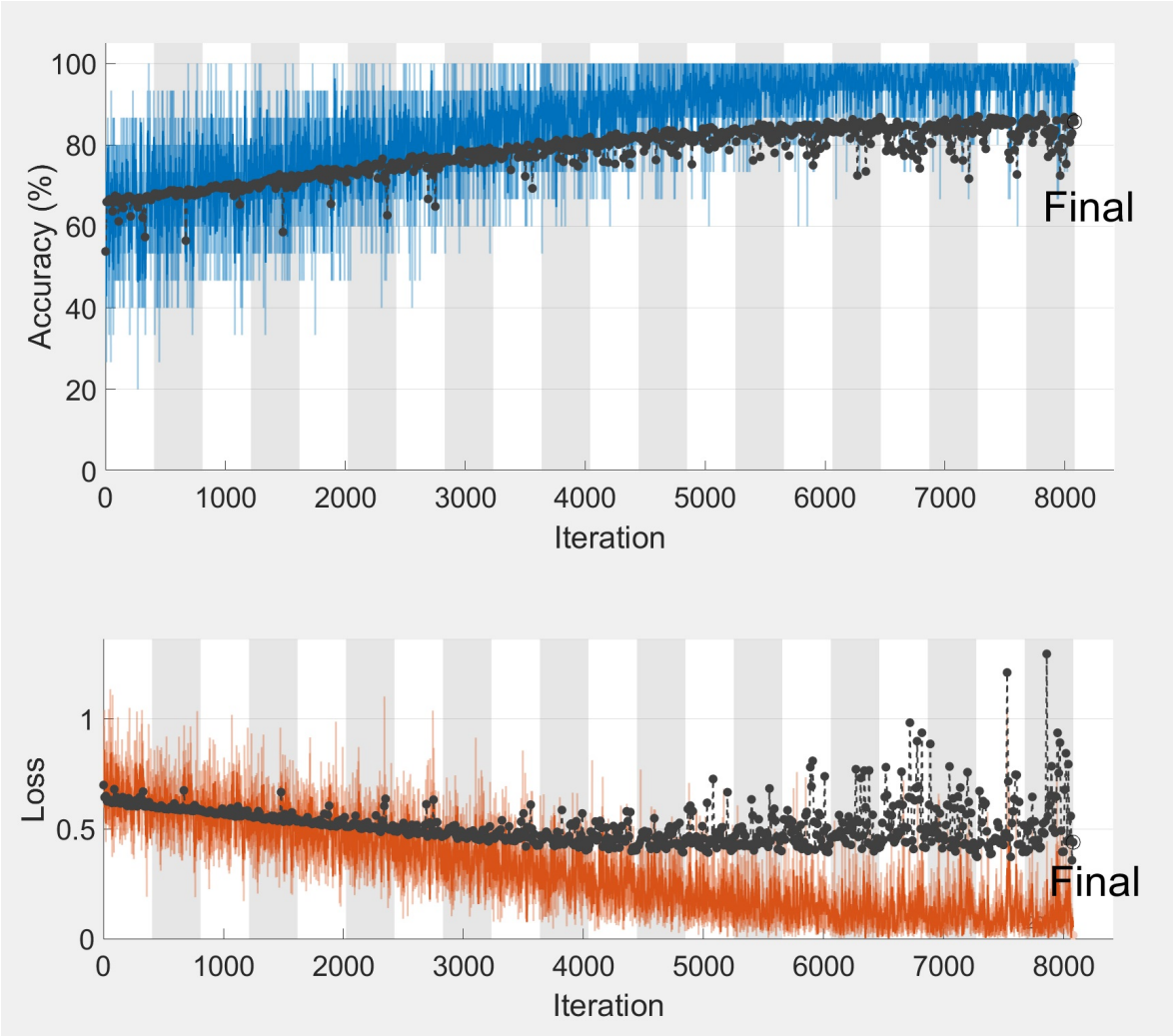


Figure 4.4. The training process of the interclass analysis.

To verify the proposed method between the PD patients and the control group subjects that have zero UPDRS rigidity score, a second model is trained.The training process of these cases is given in Figure 4.5. The validation accuracy of this case is 74.97%. This time, data is not divided into two parts for validation and testing because of the small data size. Test data is not used for this analysis because the number of control group subjects that have zero the UPDRS rigidity score is not enough.

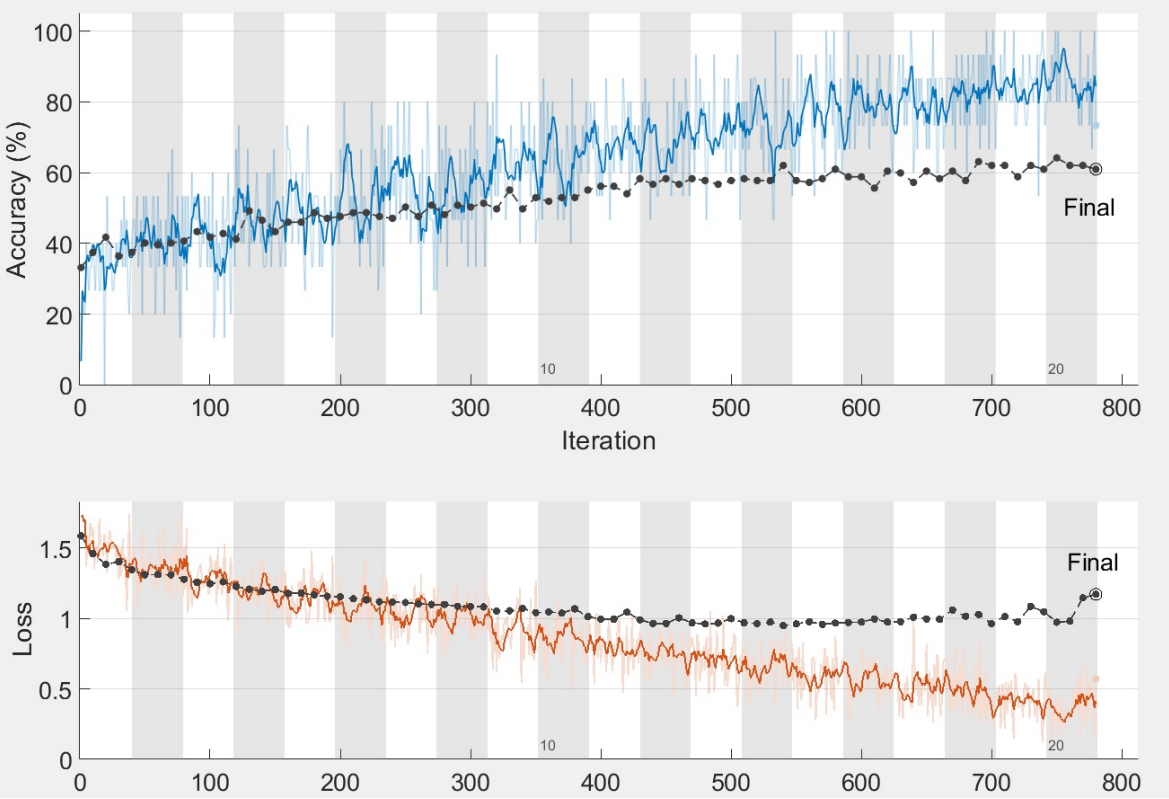


Figure 4.5. The training process of control group versus subjects.

5. CONCLUSION

In this study, a novel method has been proposed to measure wrist rigidity. An experimental study was performed with PD patients at different stages and healthy subjects to evaluate the proposed method. Two different analysis methods were described to find a relation between the experimental results and the UPDRS rigidity score. Furthermore, the effect of the Froment manoeuvre was also observed in the experiments.

A model based analysis method depending on the change of the natural frequency by applying mass on the hand has been proposed. When a mass is added on the hand, its mechanical natural frequency should decrease. However, in some measurements, other factors such as noise, low measurement resolution affect the results adversely and negative stiffness values are calculated. As this is not possible, these types of results should be eliminated. Interclass analysis of PD patients for UPDRS rigidity groups gives better results then intergroup analysis. This is because of the control group subjects that have a UPDRS rigidity score greater than zero. Results of these subjects are not extracted because of the small data size. For interclass analysis p-value is less than 0.05 meaning that the results are statistically significant.

The second analysis method is based on a convolutional neural network. Thus, acceleration data that are obtained from experiments are used for creating images by wavelet transformation. The interclass accuracy of this method was 45.9% when the data augmentation process was executed before choosing validation and test data randomly. Interclass accuracy is increased to 85.7% when validation and test data were chosen after data augmentation. All data were used for validation for intergroup analysis because the number of healthy subjects who do not have rigidity was small. The validation accuracy of the intergroup test was 74.97%. This method gave promising results, however, it is not possible to assess the performance of this method precisely because of the unbalanced and small data set. To make definitive judgments a larger

data set is needed.

To sum up and compare the two methods, the advantages and the disadvantages of the methods are reviewed. Pros and cons of the methods are listed in Table 5.1.

Table 5.1. Pros and cons of the analysis methods.

	Method 1	**Method 2**
Pros	-Does not need large data size. -Exact value of the stiffness coefficient can be calculated. - Relatively a lesser degree. of computational cost.	-Easy to implement. -More open to developments. -Does not need additional mass.
Cons	-Vulnerable to internal and external factors affecting natural frequency. - Relatively more complex experimental procedure. -Needs an additional mass.	- Relatively less dependent to external and internal factors. -Exact stiffness value cannot be calculated. -Needs large data size.

5.1. Contributions and Originality

Unlike the methods in the literature, the proposed method does not require force sensors or EMG based systems. For the first time in literature, the natural frequency shifting method is used to analyse human joints, and this analysis method enabled assessment of human joint rigidity using only one acceleration sensor. Similarly, a mobile phone is used for assessment of the wrist rigidity for the first time in literature. Moreover, the Wavelet transform-based image processing method is used to find a relation between the UPDRS rigidity scale and the acceleration data.

5.2. Outlook and Future Work

The proposed method allows us to evaluate the UPDRS rigidity scale by just using a mobile phone. As this evaluation is based on a quantitative method, this will make a significant contribution to the objective assessment of the severity of PD. As the result of the Dopamine based treatment is mostly tested by joint rigidity due to the fast reflection of the rigidity, this method can be used to assist DBS.

Mobile tracking systems for PD patients are becoming popular. Gait analysis, tremor tracking speech analysis, bradykinesia, and some other symptoms of the PD can be tracked with mobile applications. The proposed method enables the use of mobile phones for assessment of the joint rigidity which may be the only major symptom that can not be tracked remotely. Thus, usage of the mobile health tracking application for PD patients may be increased by adding this method to the existing applications.

The proposed method gives us promising results but that is not enough for clinical usage yet.The inaccuracy of the methods is mostly caused by; low-frequency resolution and other factors such as noise. These reasons can be eliminated by improving the experimental setup and procedure. The contributor mechanisms of human oscillation are described by Vial *et al.* [45]. Their study shows that the other affecting factors can be selected by EMG applications. By detecting these factors by EMG, a new

experimental procedure can be developed to eliminate the external factors affecting the hand dynamics.

In addition to the wrist, some of the other joints (elbow, knee etc.) are used for evaluating rigidity by clinicians. We proposed to use free falling motion to trigger an oscillation in the wrist because the duration of this falling motion is not enough for analysis. To improve this, the other joints can be used for analysis, and system identification methods can be used for estimating mechanical parameters of the joints. Besides, built-in sensors of mobile phones are improving every day, and this will enable us to obtain data with higher sampling rates such that both the noise problem of data and the duration problem of the procedure can be eliminated.

REFERENCES

1. Marras, C., J. C. Beck, J. H. Bower, E. Roberts, B. Ritz, G. W. Ross, R. D. Abbott, R. Savica, S. K. Van Den Eeden, A. W. Willis and C. Tanner, "Prevalence of Parkinson's disease across North America", *NPJ Parkinson's Disease*, Vol. 4, No. 21, pp. 1–7, 2018.

2. Durmus, H., M. A. Gokalp and H. A. Hanagasi, "Prevalence of Parkinson's disease in Baskale, Turkey: a population based study", *Neurological Sciences*, Vol. 36, No. 3, pp. 411–413, 2015.

3. Parkinson, J., *An Essay on the Shaking Palsy*, Sherwood, Neely, and Jones, London,UK, 1817.

4. Goetz, C. G., "The History of Parkinson's Disease: Early Clinical Descriptions and Neurological Therapies", *Cold Spring Harbor Perspectives in Medicine*, Vol. 1, No. 1, pp. a008862–a008862, 2011.

5. Erro, R. and M. Stamelou, "The Motor Syndrome of Parkinson's Disease", *International Review of Neurobiology*, Vol. 132, p. 25—32, 2017.

6. Bhatia, K. P., P. Bain, N. Bajaj, R. J. Elble, M. Hallett, E. D. Louis, J. Raethjen, M. Stamelou, C. M. Testa and G. Deuschl, "Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society", *Movement Disorders*, Vol. 33, No. 1, pp. 75–87, 2018.

7. Berardelli, A., "Pathophysiology of bradykinesia in Parkinson's disease", *Brain*, Vol. 124, No. 11, pp. 2131–2146, 2001.

8. Willemsen, M. D., Y. A. Grimbergen, M. Slabbekoorn and B. R. Bloem, "Falling in Parkinson disease: more often due to postural instability than to environmental

factors.", *Nederlands Tijdschrift voor Geneeskunde*, Vol. 144, No. 48, pp. 2309–2314, 2000.

9. Roller, W. C., Glatt, B. Vetere-Overfield and R. Hassanein, "Falls and Parkinson's Disease", *Clinical Neuropharmacology*, Vol. 12, No. 2, pp. 98–105, 1989.

10. Winogrodzka, A., R. C. Wagenaar, J. Booij and E. C. Wolters, "Rigidity and bradykinesia reduce interlimb coordination in Parkinsonian gait", *Archives of Physical Medicine and Rehabilitation*, Vol. 86, No. 2, pp. 183–189, 2005.

11. Ford, B., "Pain in Parkinson's disease", *Movement Disorders*, Vol. 25, No. 1, pp. 98–103, 2010.

12. Xia, R., "Physiological and Biomechanical Analyses of Rigidity in Parkinson's Disease", Abdul Qayyum Rana (Editor), *Parkinson's Disease: Pathogenesis and Clinical Aspects*, InTech, Rijeka, Croatia, 2011.

13. Broussolle, E., P. Krack, S. Thobois, J. Xie-Brustolin, P. Pollak and C. G. Goetz, "Contribution of Jules Froment to the study of Parkinsonian rigidity", *Movement Disorders*, Vol. 22, No. 7, pp. 909–914, 2007.

14. Mendona, D. A. and M. S. Jog, "Tasks of Attention Augment Rigidity in Mild Parkinson Disease", *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*, Vol. 35, No. 4, pp. 501–505, 2008.

15. Fahn S, Elton RL, UPDRS Program Members, "Unified Parkinson's disease rating scale", *Recent developments in Parkinson's disease*, Vol. 2, pp. 153–163, 1987.

16. Goetz, C. G., B. C. Tilley, S. R. Shaftman, G. T. Stebbins, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, M. B. Stern, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A. E. Lang, A. Lees, S. Leurgans, P. A. LeWitt, D. Nyenhuis, C. W. Olanow, O. Rascol, A. Schrag, J. A. Teresi, J. J. van Hilten and N. LaPelle, "Movement Disorder Society-sponsored revision of the Unified Parkin-

son's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results", *Movement Disorders*, Vol. 23, No. 15, pp. 2129–2170, 2008.

17. Hoehn, M. M. and M. D. Yahr, "Parkinsonism: onset, progression, and mortality", *Neurology*, Vol. 17, No. 5, pp. 427–427, 1967.

18. Costa, P., M. J. Rosas, R. Vaz and J. P. Cunha, "Wrist rigidity assessment during Deep Brain Stimulation surgery", *37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pp. 3423–3426, IEEE, 2015.

19. Levin, J., S. Krafczyk, P. Valkovič, T. Eggert, J. Claassen and K. Bötzel, "Objective measurement of muscle rigidity in parkinsonian patients treated with subthalamic stimulation", *Movement Disorders*, Vol. 24, No. 1, pp. 57–63, 2009.

20. Fino, E. and M. Mazzetti, "Monitoring healthy and disturbed sleep through smartphone applications: a review of experimental evidence", *Sleep and Breathing*, Vol. 23, No. 1, pp. 13–24, 2019.

21. Baig, M. M., H. GholamHosseini and M. J. Connolly, "Mobile healthcare applications: system design review, critical issues and challenges", *Australasian Physical & Engineering Sciences in Medicine*, Vol. 38, No. 1, pp. 23–38, 2015.

22. Charles, S. K. and N. Hogan, "Dynamics of wrist rotations", *Journal of Biomechanics*, Vol. 44, No. 4, pp. 614–621, 2011.

23. Mak, M. K., E. C. Wong and C. W. Hui-Chan, "Quantitative measurement of trunk rigidity in parkinsonian patients", *Journal of Neurology*, Vol. 254, No. 2, pp. 202–209, 2007.

24. Mortimer, J. A. and D. D. Webster, "Evidence for a quantitative association between EMG stretch responses and Parkinsonian rigidity", *Brain Research*, Vol. 162, No. 1, pp. 169–173, 1979.

25. Cantello, R., M. Gianelli, C. Civardi and R. Mutani, "Parkinson's disease rigidity: EMG in a small hand muscle at "rest"", *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control*, Vol. 97, No. 5, pp. 215–222, 1995.

26. Marusiak, J., E. Jarocka, A. Jaskólska and A. Jaskólski, "Influence of number of records on reliability of myotonometric measurements of muscle stiffness at rest and contraction.", *Acta of Bioengineering and Biomechanics*, Vol. 20, No. 4, pp. 123–131, 2018.

27. Sarvazyan, A., T. J. Hall, M. W. Urban, M. Fatemi, S. R. Aglyamov and B. S. Garra, "An Overview of Elastography - An Emerging Branch of Medical Imaging.", *Current Medical Imaging Reviews*, Vol. 7, No. 4, pp. 255–282, 2011.

28. Du, L.-j., W. He, L.-g. Cheng, S. Li, Y.-s. Pan and J. Gao, "Ultrasound shear wave elastography in assessment of muscle stiffness in patients with Parkinson's disease: a primary observation", *Clinical Imaging*, Vol. 40, No. 6, pp. 1075–1080, 2016.

29. Teräväinen, H., J. K. Tsui, E. Mak and D. B. Calne, "Optimal Indices for Testing Parkinsonian Rigidity", *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*, Vol. 16, No. 2, pp. 180–183, 1989.

30. Caligiuri, M. P., "Portable device for quantifying parkinsonian wrist rigidity", *Movement Disorders*, Vol. 9, No. 1, pp. 57–63, 1994.

31. Byung Kyu Park, Yuri Kwon, Ji-Won Kim, Jae-Ho Lee, Gwang-Moon Eom, Seong-Beom Koh, Jae-Hoon Jun and Junghwa Hong, "Analysis of Viscoelastic Properties of Wrist Joint for Quantification of Parkinsonian Rigidity", *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, Vol. 19, No. 2, pp. 167–176, 2011.

32. Costa, P., M. J. Rosas, R. Vaz and J. P. Cunha, "Wrist rigidity assessment during Deep Brain Stimulation surgery", *37th Annual International Conference of the*

IEEE Engineering in Medicine and Biology Society (EMBC), pp. 3423–3426, IEEE, 2015.

33. di Biase, L., S. Summa, J. Tosi, F. Taffoni, M. Marano, A. Cascio Rizzo, F. Vecchio, D. Formica, V. Di Lazzaro, G. Di Pino and M. Tombini, "Quantitative Analysis of Bradykinesia and Rigidity in Parkinson's Disease", *Frontiers in Neurology*, Vol. 9, No. 121, pp. 1–12, 2018.

34. Perera, T., W.-L. Lee, M. Jones, J. L. Tan, E. L. Proud, A. Begg, N. C. Sinclair, R. Peppard and H. J. McDermott, "A palm-worn device to quantify rigidity in Parkinson's disease", *Journal of Neuroscience Methods*, Vol. 317, pp. 113–120, 2019.

35. Stiles, R. N., "Mechanical and neural feedback factors in postural hand tremor of normal subjects.", *Journal of Neurophysiology*, Vol. 44, No. 1, pp. 40–59, 1980.

36. Yi, W.-J., W. Jia and J. Saniie, "Mobile sensor data collector using Android smartphone", *IEEE 55th International Midwest Symposium on Circuits and Systems (MWSCAS)*, pp. 956–959, IEEE, 2012.

37. Milette Greg, S. A., *Professional Android Sensor Programming*, John Wiley & Sons, New York, USA, 2012.

38. Dinçer, U., *Quantitative Assessment of Wrist Rigidity in Parkinson's Disease by Using Built-In Sensors of a Smartphone*, Master's Thesis, Boğaziçi University, 2020.

39. Lakie, M., C. A. Vernooij, C. J. Osler, A. T. Stevenson, J. P. R. Scott and R. F. Reynolds, "Increased gravitational force reveals the mechanical, resonant nature of physiological tremor", *The Journal of Physiology*, Vol. 593, No. 19, pp. 4411–4422, 2015.

40. Stanford Vision Lab, *ImageNet Large Scale Visual Recognition Challenge 2014*

(ILSVRC2014), 2014, `http://exoplanet.eu/catalog.php`, accessed in August 2020.

41. Yahya, N., H. Musa, Z. Y. Ong and I. Elamvazuthi, "Classification of Motor Functions from Electroencephalogram (EEG) Signals Based on an Integrated Method Comprised of Common Spatial Pattern and Wavelet Transform Framework", *Sensors*, Vol. 19, No. 22, 2019.

42. Xu, B., L. Zhang, A. Song, C. Wu, W. Li, D. Zhang, G. Xu, H. Li and H. Zeng, "Wavelet Transform Time-Frequency Image and Convolutional Network-Based Motor Imagery EEG Classification", *IEEE Access*, Vol. 7, pp. 6084–6093, 2019.

43. Charles, S. K. and N. Hogan, "Dynamics of wrist rotations", *Journal of Biomechanics*, Vol. 44, No. 4, pp. 614–621, 2011.

44. Byung Kyu Park, Yuri Kwon, Ji-Won Kim, Jae-Ho Lee, Gwang-Moon Eom, Seong-Beom Koh, Jae-Hoon Jun and Junghwa Hong, "Analysis of Viscoelastic Properties of Wrist Joint for Quantification of Parkinsonian Rigidity", *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, Vol. 19, No. 2, pp. 167–176, 2011.

45. Vial, F., P. Kassavetis, S. Merchant, D. Haubenberger and M. Hallett, "How to do an electrophysiological study of tremor", *Clinical Neurophysiology Practice*, Vol. 4, pp. 134–142, 2019.

APPENDIX A: APPLICATION

"Parkinson Hastalarında El Bileğindeki Rijiditenin Cihaz Aracılığı ile Objektif Olarak Ölçülmesi" Çalışması Bilgilendirilmiş Gönüllü Olur Formu

Dr …… tarafından …… Üniversitesi Tıp Fakültesi Nöroloji A.D.'da tıbbi bir araştırma yapılacağı belirtilerek bu araştırma ile ilgili bilgiler bana aktarıldı. Bu bilgilerden sonra böyle bir araştırmaya "katılımcı" (denek) olarak davet edildim. Eğer bu araştırmaya katılırsam hekim ile aramda kalması gereken şahsi bilgilerimin gizliliğine bu araştırma sırasında büyük özen gösterileceğini biliyorum. Araştırma sonuçlarının eğitim ve bilimsel amaçlarla kullanımı sırasında kişisel bilgilerimin ihtimamla korunacağı konusunda bana yeterli güven verildi.

Çalışmanın yürütülmesi sırasında herhangi bir sebep göstermeden araştırmadan ayrılabilirim. Ayrıca tıbbi durumuma herhangi bir zarar verilmemesi koşuluyla araştırmacı tarafından araştırma dışı tutulabilirim. Araştırma için yapılacak harcamalarla ilgili herhangi bir ödeme yapmayacağım. Bana da bir ödeme yapılmayacaktır. Araştırma sırasında bir sağlık sorunu ile karşılaştığımda; herhangi bir saatte, hangi araştırıcıya, hangi telefon ve adresten ulaşabileceğimi biliyorum.

Çalışma kapsamında; Parkinson hastalığı bulguları açısından hekim tarafından muayene edileceğim, akıllı cep telefonunu elimde tutarken, bilek hareketlerimin çeşitli ölçümlerinin alınacağı, uygulamanın yaklaşık 2 saat süreceği söylendi.

Bu çalışmaya katılmak zorunda değilim. Araştırmaya katılmam konusunda zorlayıcı bir davranışla karşılaşmadım. Eğer katılmayı reddedersem, bu durumun tıbbi bakımıma ve hekim ile olan ilişkime herhangi bir zarar getirmeyeceğini de biliyorum. Bana yapılan tüm açıklamaları ayrıntılarıyla anladım. Kendi başıma belli bir düşünme süresi sonunda adı geçen bu araştırmada "katılımcı" (denek) olarak yer alma kararını aldım. Bu konuda yapılan daveti büyük bir memnuniyet ve gönüllülük içerisinde kabul ediyorum. İmzalı bu form kağıdının bir kopyası bana verilecektir.

Ben ……., bu çalışma bana açıklandı. Çalışma ile ilgili tüm sorulara tatmin edici yanıtlar aldım. Çalışmaya kendi rızamla gönüllü olarak katılmayı kabul ediyorum.

Katılımcı Adı Soyadı: Tarih İmza

Dr. Adı Soyadı: Tarih İmza

Tanıklık Eden Kurum Yetkilisi Adı Soyadı: Tarih İmza

Figure A.1. The informed consent form.

“Parkinson Hastalarında El Bileğindeki Rijiditenin Objektif Olarak Ölçülmesi” Çalışması Hasta Takip Formu

Hastanın adı:
Yaş:
Cinsiyet:
Eğitim:
El tercihi:
Meslek:
Hastalık Başlangıç Tarihi:
Özgeçmiş:

Kullanılan ilaçlar:

Hoehn Yahr:

Hipomimi varlığı:

Hipofoni varlığı:

	SAĞ		SOL	
	ÜST	ALT	ÜST	ALT
Bradikinezi				
İstirahat tremoru				
Çekme testi:				
Rijidite				

SAĞ EL BİLEĞİ	SOL EL BİLEĞİ
0: Normal: Rijidite yok. 1: Silik: Sadece aktivasyon manevrasıyla rijidite var. 2: Hafif: Aktivasyon manevrası olmadan rijidite var; ancak hareketin tamamı kolayca yapılıyor. 3: Orta: Aktivasyon manevrası olmadan rijidite var, hareketin tamamı eforla yapılıyor. 4: Şiddetli: Aktivasyon manevrası olmadan rijidite var, hareketin tamamı yapılamıyor.	0: Normal: Rijidite yok. 1: Silik: Sadece aktivasyon manevrasıyla rijidite var. 2: Hafif: Aktivasyon manevrası olmadan rijidite var; ancak hareketin tamamı kolayca yapılıyor. 3: Orta: Aktivasyon manevrası olmadan rijidite var, hareketin tamamı eforla yapılıyor. 4: Şiddetli: Aktivasyon manevrası olmadan rijidite var, hareketin tamamı yapılamıyor.
Sağ el bileği cihaz rijidite ölçümü	Sol el bileği cihaz rijidite ölçümü

Figure A.2. The patient follow-up form.