Tremor in Parkinson's Disease: Loading and Trends in Tremor Characteristics

by

Fariborz Rahimi

A thesis
presented to the University of Waterloo
in fulfillment of the
thesis requirement for the degree of
Doctor of Philosophy
in
Electrical and Computer Engineering

Waterloo, Ontario, Canada, 2010

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Parkinson's disease (PD) is a neuro-degenerative chronic disorder with cardinal signs of bradykinesia, resting tremor, rigidity, and postural abnormality/instability. Tremor, which is a manifestation of both normal and abnormal activities in the nervous system, can be described as an involuntary and periodic oscillation of any limb. Such an oscillation with a small amplitude, which is barely visible to the naked eye, is present in healthy people. This is called a physiological tremor and is asymptomatic. This tremor is believed to be the result of at least two distinct oscillations. A passive mechanical oscillation that is produced by the irregularities of motor unit firing, and by blood ejection during cardiac systole. The frequency and amplitude of these oscillations are dependent on the mechanical properties of the limb including joint stiffness and limb inertia. There is another component of oscillation that does not respond to elastic or inertial loading, which is called the central component, and is believed to arise from an unknown oscillating neuronal network within the central nervous system.

Unlike physiological tremor, pathological tremors are symptomatic and can impair motor performance. Parkinson's disease (PD) tremor is generally manifested at rest, but also occurs during posture or motion. Classical PD rest tremor is known to be a central tremor of 4-6 Hz and peripheral origins have only a minimal role. However, whether or not the same central mechanism remains active during action tremor (including posture and movement) should yet be answered. Contrary to PD rest tremor, reported results on action tremor in the literature are diverse; and the reason for the changes in tremor characteristics in situations other than rest, or generally during muscle activation, is not fully understood.

The lack of generality in the results of studies on action tremor, makes the efforts of treatment difficult, and is a barrier for mechanical/engineering approaches of suppressing this tremor. To investigate the role of mechanisms other than *classic rest tremor*, and possible sub-categories of tremulous PD in yielding diverse results, this study was conducted on twenty PD patients and fourteen healthy age-matched (on average) controls. To evaluate the possible contribution of (enhanced) physiological tremor, the study considered the effect of loading on postural hand tremor in a complete range of 0-100% MVC (Maximum Voluntary Contraction). The study looked at two measures of tremor amplitude and one measure of tremor frequency, and focused on two frequency bands of classic-rest (3.5-6.5 Hz) and physiological (7.5-16.5 Hz) tremors.

The study revealed that PD tremor was not uniformly distributed in the three dimensional space, and then focused on the investigation of tremor in the dominant axis, which

was the same as direction of loading. It also revealed that dopaminergic medication could significantly affect tremor components only in the PD band, compared to the components in the physiological band. The study was an extension of previous studies and yielded similar results for the previously reported range of loading. However, with the extended range of loading, it revealed novel results particularly after separating PD patients into sub-groups.

It was hypothesized that the coexistence of physiological mechanism, and considerable difference between sub-types of tremulous PD patients, are responsible for most of the diversity in the previously reported studies. This study showed that for clearer results the sub-groups are inevitable, and that automatic classification (clustering) provided the most separable sub-groups. These sub-groups had distinct trends of load effect on tremor amplitude and frequency. No matter which categorization method was used, at least one sub-group exhibited significantly higher tremor energy compared to the healthy participants not only in the PD band, but also in the physiological band. This meant that, for some sub-groups of PD, the physiological tremor is a very important mechanism and not the same as that of healthy people. The coexistence hypothesis was also affirmed by examining tremor spectrums' peak frequency and magnitude in the two separate bands.

The necessity of the separation of tremulous PD patients into sub-groups, and the coexistence of physiological and classic PD tremor mechanisms for some of them are the factor that should be considered in the design of a suppressing device and also in the proposed treatment of action tremor in this population.

Acknowledgements

First, I would like to express my appreciation and gratitude to my advisors Professor David Wang and Professor Farrokh Janabi-Sharifi for their precious assistance, thoughtful guidance, support and encouragement during my graduate studies at the University of Waterloo. I am also thankful to them for reading and editing this dissertation. I thank professors Kathleen Norman, Jack Callaghan, Dwight Aplevich, and Daniel Davison for serving on my thesis dissertation committee.

It is my pleasure to convey my sincere gratitude to Prof. Quincy Almeida for constructive advice, helpful discussions, and for for providing the research atmosphere at the Movement Disorders Research and Rehabilitation Centre (MDRC), Wilfrid Laurier University.

I express my gratitude toward Professor Jack Callaghan for his kind advice, whenever I asked for it.

This project would not have been possible without the contributions of many individuals. I appreciate the valuable advice of Prof. Oleg Michailovich on the signal processing aspects, and Prof. Shoja'eddin Chenouri on the muscle modelling issues. I Thank Mr. Matthew Brown for useful discussions and for reading some parts of the thesis. I am grateful to Mr. Seyed Mahdi Hosseini for wonderful discussions and his contribution in wavelet and cluster analyses.

I thank past and present fellow students in the Systems and Control Research Group at the University of Waterloo. Their valuable inputs are highly appreciated. Particularly Roop Samra, Julie Vale, Darrell Gaudette. I would like to thank Masoud, Ibrahim, Dave, Mehri, Babak, Mehrdad, Yusof, and all those individuals that I could not list their names.

I am especially grateful to all participants in my experiments, both at MDRC, Wilfrid Laurier University, and at the ECE department in University of Waterloo. I thank the administrative and technical supporting staff at the ECE department, Wendy Boles, Annette Dietrich, Karen Schooley, Lisa Hendel, Katja Czarnecki, Fernando Rivero Hernandez, Philip Regier, and Paul Ludwig.

I thank my parents Azizeh and Azim and also my brothers and sisters for their life time support.

Finally, I would like to express my special thanks to my wife, Rashin, and our daughter, Deniz, for their support, love, patience and understanding during the hard work of graduate study.

Dedication

This thesis is dedicated

To my wife Rashin
for her inspiring love and patience

To our daughter Deniz
for being the joy in our lives

To my parents Azizeh and Azim
for their unconditional love and support

Contents

List of Tables

List of Figures

List of Abbreviations

ANOVA	Analysis of Variance
B1	Frequency range for general physiological tremor (7.5-16.5 Hz)
B2	Frequency range for classic PD tremor (3.5-6.5 Hz)
B3	Frequency range for central component in physiological tremor (8-12 Hz)
CWT	Continuous Wavelet Transform
db	Daubechies family wavelets
dB	decibel
DC	Direct Current (mean value of a signal)
DWT	Discrete Wavelet Transform
EMG	Electromyography
EPT	Enhanced Physiological Tremor
ET	Essential Tremor
FFT	Fast Fourier Transform
g	gram
g	gravitational acceleration (9.8 m/s2)
MVC	Maximum Voluntary Contraction
MVT	Maximum Voluntary Torque
N	Newton (force unit)
N.m	Newton meter (torque unit)
PD	Parkinson's Disease
PRT	classic Parkinsonian Rest Tremor
PSD	Power Spectral Density Power spectrum
RMS	Root Mean Square
s	scaling parameter in wavelet
sec	seconds
TD	Tremor Dominant

Chapter 1

Introduction

1.1 Motivation and Objectives

Parkinson's disease (PD) is a neurodegenerative chronic disorder. In other words, it is a disease of nervous system that does not go away and its severity increases over time. It affects almost 100,000 Canadians and 6.3 million people around the world [1]. This figure, which is believed to be underestimated, is expected to double by 2016. With the proportion of seniors increasing faster than all other age groups, Canada confronts significant aging of its population. It is estimated that by 2026, one in five Canadians will be over age 65 [2]. With eighty-five percent of diagnosed PD patients being in this age group, the socio-economic impact on the nation is aggravating. The total burden of PD, including direct and indirect costs, was $558.1 million in 1998 [3].

Cardinal signs or symptoms of PD include *bradykinesia* (slowness of movement), resting *tremor*, *rigidity*, and *postural abnormality/instability* [4]. Along with medical (pharmacological and surgical) methods of treatment, engineering techniques have been proposed to help with diagnosis [5] [6], assessment [7] [8] [9] and alleviation [10] [11] of these symptoms. For example, a method of analysis of alternating movement was proposed to detect PD [12]; another device has been introduced to quantify rigidity at the elbow and the wrist [13]; walking stabilizers and laser beam projectors have been proposed to help with stabilization and gait freeze [14].

Tremor, which is possibly the most common movement disorder, is a rhythmical involuntary continuous oscillation of any body part [15]. It can happen to otherwise normal people in the form of physiological tremor, or affect people with specific pathologies such as PD. While physiological tremor interferes merely with precise manipulations such as microsurgery or cell manipulation, pathological tremors are more disabling in everyday life. Visible pathological tremor can cause embarrassment and have psychological impacts [16][17]. With nearly 75% of PD patients exhibiting tremor, PD tremor is the second most prevalent pathological tremor after Essential tremor (ET)[18]. Behavioral classification divides tremors to *rest* and *action* tremors. Action tremor is defined as a tremor caused by any voluntary contraction of muscle, which includes *postural* (while holding a limb motionless against gravity), *isometric* (contracting limb muscles against a stationary object; includes loading in posture), *kinetic* (during movement), and *task specific* (goal oriented) tremors [19]. In case of PD, classic tremor occurs mainly in rest, but action tremor is also considerable (for example, 50% occurrence reported in [20]). Generally, PD tremor is the least responsive symptom to medication [21][22]. PD action tremor, which is more disabling, is even less responsive than rest tremor [23][24]. Severe PD tremor is treated with alternative methods such as *deep brain stimulation (DBS-* sending electrical impulses to particular parts of the brain) [25], or *functional electrical stimulation (FES-* activation of opposite muscle in anti-phase with electric pulses) [26], which are often less effective on action tremor [27] compared to rest tremor.

PD action tremor is interesting to both neuroscientists and engineers. Neuroscientists are concerned with the driving mechanisms behind this tremor to better alleviate it with pharmacological, and surgical methods. Engineers have attempted to suppress or cancel (in interfaces) this tremor with designing new devices or adopting the few current ones, which are mainly aimed at physiological tremor [28] or at ET [29]. PD rest tremor has one accepted central (transmitted from the central nervous system) mechanism. However, PD action tremor is suspected to have more or different mechanisms [30][31][32]. Contrary to PD rest tremor with one peak in frequency spectrum (limited to 4-6 Hz), PD action tremor exhibits one or two [32][30][33] major peaks of frequency (in a wide range of 4.8-12 Hz [34][32][30][20]).

The possibility of having a different or second mechanism in PD action tremor, and the fact that the tremor frequency is related to pathology/mechanism necessitates this study of tremor energy using frequency bands. Because of nonlinear interaction between possible mechanisms involved in the tremor [35][36], peaks' position and amplitude in the spectrum do not seem to be the most reliable measures of tremor evaluation. Alternatively, tremor energy in the classic PD band (3.5-6.5 Hz), and energy in the band above it (up to

acceptable range of tremor for wrist, 17 Hz) is going to be used in this study as the main evaluation measure.

1.2   Scope of this dissertation

This study is limited to the tremors in idiopathic PD and examines it at rest and during some conditions that involves muscle activation. The pilot study examines rest and isometric elbow tremors while elbow flexors are activated. The main study, on wrist, includes rest, posture, and loading in posture. Loading targets wrist flexor muscles while upper arm is supported, wrist is free to move in flexion/extension, and forearm constraints limit wrist pronation/supination. Therefore, action tremor in this study indicates either tremor during isometric elbow contractions, or tremors of wrist in posture and while loaded in this condition, but does not include tremor in movement. All the hypotheses on action tremor in Chapter 5 are limited to the wrist tremor in such situation (and not a completely free to move arm). In examining the loading effect, the goal is to investigate the steady state effect of loading, contrasted to spontaneous or transient effects. During the trials participants are free to look at their hands, and no visual feedback effect is tested.

1.3   Major Contributions

The major contributions of this dissertation on PD action tremors are listed as follows:

- Proposed and implemented haptic devices for an objective clinical assessment of tremor.

- Proposed and investigated the loading effect on tremors' amplitude in the two separate bands (of classic PD, 3.5-6.5 Hz, and physiological band, 7.5-16.5 Hz), and answered the question of whether physiological tremor in PD patients differ from that of healthy individuals. Using RMS energy as tremor amplitude measure, the study revealed that one sub-group of the patients have stronger physiological tremors than healthy controls (this could not be confirmed using tremor spectrum's peak magnitude as tremor amplitude).

- Provided possible explanation for some controversial results in PD action tremor's literature. The study suggested that co-existence of physiological tremor, and sub-groups of PD patients with different characteristics (such as strength of physiological

tremor), are responsible for most of the contradictory results on the following items: medication effect on PD action tremor, the frequency range, and the loading effect on this tremor.

- Implemented automatic classification (clustering) as a new method of finding sub-categories of PD patients with distinct trends in reaction of tremor amplitude to loading. The found separable trends for sub-groups of PD patients, and the fact that one sub-group has stronger physiological tremor compared to the healthy controls, can be potentially helpful for neuroscientists and engineers. While the former might use this information in suggestion of treatment methos, the latter can use it in the design and customization of their tremor suppression devices.

- Proposed and implemented wavelet decomposition and reconstruction instead of band-pass filtering in hand tremor extraction. This method is particularly favorable when tremor's background artifacts are considerable, such as in moving hand's tremor.

- Recommended 3-dimensional tremor assessment based on our finding that PD tremor is not uniformly distributed in the three dimensional space.

1.4 Organization of this dissertation

The thesis is organized as follows:

Chapter 2 begins with the current understanding of tremor and its classification. It reviews the most common tremor assessment methods in one and three spatial dimensions. This chapter describes the frequently used characteristics of tremor in both time- and frequency-domains. A detailed review of the literature about the mechanisms (origins), for both physiological and PD tremors, is provided. The most contradicting results about PD action tremor are listed. Then a summary is presented that also describes the proposed methods to justify the contradicting results in the literature.

Chapter 3 describes the details about tremor signal quantification that is used in this study. The means and the specification of the devices that are used in tremor acquisition are provided. The methods of extraction of tremor data from the acquired signal are explained. The merits of tremor extraction based on wavelet theory, which is used throughout the

study, is compared to those of standard band-pass filtering. Frequency domain, and time-frequency representations of the tremor signal, that are utilized in separation of tremor from motion artifacts, are presented. A spectral estimation technique that provides unbiased and consistent results is described. Finally, a summary of the adopted signal processing steps is presented.

Chapter 4 is pilot study about action tremor in human elbow. It examines action tremor superimposed on generated isometric elbow torque. It involves six healthy people, two PD patients that are assumed to be the representation of typical tremor presentation, and one severely affected PD patient. The implemented hardware and the developed software for the experiment are described. It hypothesizes the coexistence of physiological and PD tremors in generated elbow torque of the patients. The results reveals that for the typically affected patients, in rest and during tracking, the two tremors are comparable. At higher levels of muscle activation, the tremor is predominantly (enhanced) physiological. It suggests that, for these patients, the physiological tremor is different from healthy people and might coexist with PD tremor at elbow. For the severely affected patient, tremors at any condition are predominantly in PD band. This chapter suggest a separation between the patients based on the severity of their tremors.

Chapter 5 presents the results of the main study on twenty PD patients and fourteen healthy controls. It investigates the effects of loading (up to MVC) on the hand tremor of PD patients (compared to the controls) that are separated into subgroups. It evaluates the proposed hypotheses that are mainly related to coexistence of the two types of tremor in PD patients. The results of comparisons, for two amplitude- and one frequency-measures, are presented and discussed. Using the categorization techniques and separate assessment of tremors in the two bands, the study confirms that the two tremors co-exist for some of the sub-groups of PD.

Chapter 6 summarized the findings and discusses how these findings might help explain some of the contradicting results in PD action tremor. It also suggests how the findings might be beneficial for neuroscientists or designers of tremor suppression devices.

The current study is considered to be the first part of a more comprehensive and joint project on improved clinical assessment, and design of a tremor suppression device, for PD population. Chapter 7 provides direction for such future investigations on tremor in PD population and concludes the thesis.

Chapter 2

Background and Related Works

2.1 Tremor

Tremor, which is a manifestation of both normal and abnormal activities in the nervous system, can be described as an involuntary and periodic oscillation of any limb. Tremor's continuous and rhythmical characteristic makes it different from other involuntary movements such as tics, chorea, and myoclonus [15]. Among various movement disorders encountered in clinical practice, tremors are the most prevalent [37].

Any voluntary activation of muscle is accompanied by a tiny tremor. It happens mainly in response to the irregularities of subtetanic firing in motor units [36]. Although this tremor is considerably larger than the passive vibration in body parts caused by contractionsin the heart, it is still barely visible to the naked eye [38]. This tremor, which is called physiological tremor and is asymptomatic, exists in healthy subjects just as it does in patients with different disease of the motor system. While physiological tremor interferes merely with precise manipulations such as microsurgery or cell manipulation, pathological tremors are more disabling in everyday life.

2.2 Tremor Classification

Other than the broad categorization of tremors to Physiologic and pathologic tremors, they have been classified in numerous ways. The most common method of classification is based on the behavior or the state of activity [37, 39]. *Rest, postural, kinetic, task specific,* and

isometric tremors are the results of such classification. *Action* tremor that happens during any voluntary contraction of muscles, is accepted to include postural, kinetic, isometric, and task specific tremors [19].

From the origin point of view, they can be broadly classified into central and peripheral tremors. The former is produced by vibratory properties of central neural networks, and the latter by oscillations in sensorimotor loops, which is also known as mechanical-reflex tremors [36]. Tremors can be further classified according to aetiology or underlying disease, response to medication, accompanying conditions, the frequency, body segments affected, and so on [15].

2.3 Tremor Assessment

Tremor can be subjectively measured by clinical rating scales through observations of the limb in different situations or through its effect on different functions such as finger-to-nose movement, writing, drawing lines, or Archimedes spirals. The Unified Parkinson's Disease Rating Scale (UPDRS, Appendix F) is the most accepted scale among clinicians and researchers, and its part *III* (motor section) includes items for tremor evaluation. However, because of variability between raters or within different evaluations of one rater [40], researchers have also tried to replace/improve these scales with systematic methods. For example, a device has been proposed to continuously and accurately quantify hand tremor [7]. Hand gloves [6], or digitizing tablets [8] have been suggested to evaluate tremor during writing, drawing Archimedes spirals, or pentagons [41].

Objective assessment of tremor is usually carried out through kinematic measurements or evaluation of muscle activities with electromyography (EMG). Introduction of various miniaturized sensors, including accelerometers and gyroscopes, has facilitated tremor assessment with minimum loading effect (which is a low-pass filtering effect [42]).

2.3.1 Accelerometry

Accelerometry is by far the most popular method of tremor amplitude and frequency quantification [43]. It is usually used in conjunction with surface EMG. The measured amplitude, by accelerometry, would be in units of gravitational acceleration g (or milli-g, g = 981 cm/s^2). Tremors can be compared with such a unit for their amplitude unless there is an explicit need for presenting them in displacement units. In that case, acceleration can

be approximately transformed into displacement with an assumption that tremor waveform is a single harmonic (sinusoidal) wave. By integrating such a harmonic acceleration waves twice, an estimate of the displacement amplitude would result. For example, the root-mean-square (RMS) amplitudes of acceleration and displacement can be related with the following approximation:

$$displacement \text{ (RMS)} \approx acceleration \times 981/(2\pi f)^2 \text{ (RMS)} \qquad (2.1)$$

where f is the frequency of the harmonic in Hz, and displacement in cm [44]. Needless to say, the farther the tremor spectrum from a single sharp peak, the less accurate would be the equation.

2.3.2   1D-3D Assessment

Before the introduction of miniaturized and cheap 3-dimensional sensors, most of the tremor related kinematic and dynamic measurements were performed unidirectionally. However, tremor is almost never a 1-dimensional movement [45] and such measurements would introduce major limitations. A study with uni-axial accelerometers, presented poor correlation with tremor disability [46]. Another study, using a 3-dimensional mechanical linkage, proved that postural tremors can be validly and reliably quantified [47]. Their results suggested that the previous failures might have been due to 3-dimensional aspects of tremor that lost by measuring single spatial dimension. Therefore, since the earlier studies on quantification of tremor, theoretic aspects of multi-dimensional tremors were considered ([48, 20]) and are increasingly utilized in recent studies [30, 49, 50].

2.3.3   Displacement Measurement

Although accelerometers (particularly piezoelectric ones) can be light-weight and small, they do not directly provide positional information, and this information is not easily and accurately obtainable [51]. In some clinical tests, tremor or performance measures need position of the limb (or joint) to be acquired during the task. In these cases, a variety of sensors from linear or angular goniometers [52], electromagnetic tracking devices [53], digitizing tablets [8], motion capture cameras [54], haptic devices (robotic devices that provide sense of touch while interacting with virtual environments) [55], and laser displacement measuring devices [56, 57] have been used. One study on healthy and PD participants' finger tremor, compared the results of electromyography, measurements from a uni-axial

accelerometer, and laser based displacement and velocity sensors [58]. The study revealed a high correlation among all kinematic measurements and favored velocity measurement over the others due to higher sensitivity to changes in tremor amplitude and spectral content.

2.3.4   Force Measurement

Accelerometers and gyroscopes operate based on the forces (usually very small) that a vibrating limb applies on the device. However, focus of some studies are on the tremor of body part while it (a group of related muscles) is inserting larger forces in an isometric contraction or against a load [59, 60]. In such studies, the force measuring element (usually one or a number of strain gauges [61, 62, 9]) measures the overall (the intended or voluntary, plus tremor components) force/torque from which the tremor should be extracted with filtering or other appropriate methods.

2.3.5   Electromyography

Electromyography, either as surface EMG or needle EMG is the most common method of assessment for muscle activity. It is the best method to identify the muscles or limb segments that are involved in the tremor. Surface EMG is often used solely or combined with kinematic measurements to diagnose tremors or quantify their response to medication [63]. Various parameters of EMG signals have been used in diagnosis of different types of tremor. For example, EMG burst duration in forearm muscles was proven to distinguish between various types of tremors [42]. EMG can provide reliable information about frequency of tremor. However, its amplitude is less reproduceable because of variable factors including contact resistance. According to the pattern of activation in antagonistic muscles, tremors can be separated to two subgroups. The EMG bursts are synchronous for one subgroup, and alternating for the other. One study on 525 patients with six different tremors, revealed that a combination of EMG pattern, frequency, amplitude, and burst duration can objectively separate the tremor types [64].

2.4   Characteristics of Tremor

The two most common measures or characteristics of tremor have been its amplitude and frequency. However, sometimes the mentioned measures are not capable of clearly separating tremors of different pathologies, or separating healthy people's physiological tremor

from other weak pathological tremors. Researchers have proposed other indices (characteristics) of tremor signal that could be more discriminative. Although they have been meant to differentiate between the groups, these characteristics can also be used in comparisons within a group or among tremors in different conditions. These measures, that are usually evaluated on kinematic or force signals, can be divided into two categories of time- and frequency-domain characteristics. The details about calculating such characteristics can be found in references including [35, 65, 66, 30].

2.4.1 Time domain Characteristics

Amplitude: Usually the RMS value of the acquired tremor signal after being high pass filtered (at ~2 Hz) to provide the total amplitude of tremor, or after being band passed to provide the amplitude in the specified band. In either case, since the signal does not have a DC (mean) value, the standard deviation of the signal is used to provide the RMS value.

Amplitude fluctuations: Because the RMS amplitude provides an average over the whole time span of tremor signal, amplitude fluctuations are lost. Therefore, instantaneous amplitude envelope is proposed for visualizing these fluctuations. It is obtained by removing the drift in the signal (high pass filtering at ~2 Hz), then removing the oscillations in squared results (low pass filtering at ~2 Hz). The final envelope can be the square root of such signal (that is usually multiplied by $\sqrt{2}$).

Shape of the tremor signal: Similar to the RMS value of a signal (standard deviation of a signal with zero mean, or the second moment of data distribution), higher statistical moments are suggested in discriminating between the tremor signals. These moments demonstrate the deviation from a Gaussian random process. The third moment (**skewness**) is a measure of asymmetry. Similarly, the fourth moment is an indicator of **peakedness**. **Entropy** in the tremor signal is also proposed as a discriminative characteristic that quantifies the amount of disorder (details in [35, 65]).

2.4.2 Frequency domain Characteristics

After the power spectrum is estimated for a tremor signal, which uses Fourier analysis and assumes stationarity in the signal, various measures could be used in discriminating between tremors.

Amplitude: The magnitude of the highest peak in the spectrum can be a measure of tremor amplitude ([67, 68]), though it is not as reliable as RMS amplitude, because it highly depends on the distribution of the power. Therefore, the following measures of amplitude are proposed in spectral domain. The **average peak power**, is the power in a small portion (usually 1 Hz) of the spectrum around the peak frequency [30]. The **total power**, is the contribution of all spectral components, in the frequency range of tremor ($\sim$3-17 Hz), to power spectrum [35, 30]. It should be noted that, if ideal filters are used in extracting tremors (in the same frequency band), this measure would be very similar to RMS amplitude of the signal (Parseval's theorem [69]):

$$\sum_{-\infty}^{\infty} |x[n]|^2 = \frac{1}{2\pi} \int_{-\infty}^{\infty} |X(e^{j\omega})|^2 d\omega \qquad (2.2)$$

where $x[n]$ is the discrete signal, X is its discrete-time Fourier transform, and ω is the angular frequency (in radians per sample).

Spectral power distribution: The relative power contained in a sub-range of tremor spectrum presents the contribution of that frequency range to the tremor. This is important because the frequency of oscillation appears to be related to tremor mechanism or pathology. In study of PD tremor, the two ranges of interest are $\sim$4-6 Hz, and $\sim$7-12 Hz [66].

Peak power ratio: This measure is proposed to quantify how peaked a tremor spectrum is. It is defined as the ratio between the previously defined average peak power, and the total power [30].

Harmonicity: This measure quantifies the peakedness of tremor spectrum as well. **Dispersion** is the width of a frequency band around the *median frequency* that includes 68% of the total power [70, 71]. **Harmonic index** is a measure of similarity of tremor spectrum to a single sharp peak [66].

Frequency: The most common measure of tremor frequency is the frequency of **highest peak** in the range of interest. However, because this measure is not very robust particularly for weaker tremors, other measures of central tendency are proposed. **Median frequency** divides the power spectrum to two equal halves. It could be more robust than the highest peak frequency, but is not very useful in case of multiple peaks. The center of a small interval (usually with a width of 1 Hz) that contains highest power among all intervals of the same length is also proposed as a measure of tremor frequency [35].

Frequency Range of Tremor

Oscillatory limb movements that are considered to be tremor, have a frequency of at least 2-3 Hz [35]. The upper limit in the study of hand tremor is considered to be 17, 18, and 20 Hz [72, 30, 19, 73]. In this study, movements in the frequency range of 3-17 Hz are considered as total hand tremor.

2.5 Physiological Tremor versus PD Tremor

2.5.1 Physiological Tremor

Skeletal muscles are made up of separate components called muscle fibers. Each alpha motor neuron is responsible for activating a number of muscle fibers; together they are called a motor unit. One discharge of such a motor neuron creates a twitch in the fibers of related motor unit. Usually, combinations of motor units work together to accommodate for the contractions of a skeletal muscle. Activation of motor units are asynchronous and the contractions of a muscle is not very smooth. Small oscillations called *physiological tremor* are superimposed on the produced force [74].

Physiological tremor is believed to consist of two ([36]), or three ([74][75]) distinct origins. **Central** oscillators (through firing of motor units) contribute directly and indirectly (through *stretch reflex*) to this tremor. Like any physical object, limb segment's **mechanical** properties affect the resonance frequency. One source of oscillation in physiological tremor, that is considered as mechanical, is cardioballistic thrust of the heart. This is considered the main source of oscillation when the limb is at rest [36]. It perturbs all body parts and causes them to oscillate at their own resonant frequencies. It also contributes indirectly to the tremor through blood ejection in the vessels. Some researchers combine the mechanical and stretch reflex components as muscle-mechanical [74], mechanical-reflex [36], or mechanical resonant [76] component and demonstrate that this (peripheral mechanism) is the predominant component in physiological tremor. Each of the three mentioned origins (oscillators) of this tremor are defined separately as the following:

central oscillators: A central origin has been proved for physiological tremor by studies on normal subjects exhibiting no loading effect on tremor components (of 8-12 Hz), or by continuation of this tremor in posture while the sensory feedback loop is cut [77]. This 8-12 Hz tremor component has been observed in various muscles of different size.

12

stretch reflex oscillation: These reflexes, that are produced by muscle spindles and Golgi tendons (both are muscle afferents) and spinal alpha motor neurons, have been confirmed to contribute to physiological tremor. This feedback loop's effect can be tested when a contraction in a flexor muscle triggers a contraction in the extensor muscle. Depending on the reflex gain and transmission delays, oscillations might result [75, 74].

mechanical resonance: This oscillation (produced by the heart and spinal reflex) is governed by the inertial, viscous, and elastic properties of the body limb. Therefore, depending on the joint, its resonant frequency has reported to be ∼3-5 Hz for the elbow, ∼8-12 Hz for the wrist, and ∼12-30 Hz (∼17-30 Hz [36]) for the finger (Metacarpophalangeal joint) [78, 75]). The following equation presents the relation between the mechanical resonant frequency and the limb's (joint) stiffness (K) and moment of inertia (J) [79, 75]:

$$f_0 = \frac{1}{2\pi} \sqrt{K/J} \tag{2.3}$$

To summarize, physiological tremor is a mainly peripheral tremor at *rest*, but a multifactorial tremor when muscles are activated. Depending on activation, specific origins could dominate under different conditions[78].

Loading Effect on Physiological Tremor

Inertial loading would affect physiological tremor's (its load dependent, or peripheral components) frequency and amplitude. Various studies have examined the effect of (different) loads on the healthy population. For example, effect of 100-1500 g [72], 300 g [80], 500 and 1000 g [81, 76], on hand tremor, 70 g [56] on finger tremor, or 50 and 100 g [82] on finger, hand, forearm, and arm have been studied with electromyography, accelerometry, or laser displacement. One recent study on 100 young and 100 elderly healthy participants [80], examining loading effect on hand tremor's displacement, accelerometry, and EMG, revealed that loading increases tremor displacement amplitude; it reduces frequency of tremor (in recorded acceleration) significantly, and does not affect tremor acceleration amplitude. Similar results, of no significant change, on tremor's acceleration amplitude have been reported [81]. Depending on both EMG and tremor kinematics, the reaction of physiological tremor to loading is separated to 4 categories:

1. Rhythmic oscillation of the limb is present, but no entrainment in EMG (no spectrum

peaks). Tremor's acceleration frequency decreases with loading. This is a sign of major mechanical-resonant tremor, with negligible contribution from stretch reflex or central oscillators.

2. Spectrum peak is present in EMG. The frequencies of hand tremor and EMG are equal and both decrease (more than 1 Hz) with loading. This indicates that mechanical-resonant frequency of the hand oscillation controls the EMG pattern. This pattern is often observed in people with enhanced physiological tremor.

3. Spectrum peak is present in EMG, and its frequency is equal to tremor's frequency for unloaded hand. After loading, two peaks are present in tremor's acceleration spectrum. The lower peak resembles the mechanical-resonant frequency. The higher peak, which is the same for EMG spectrum and is not affected with load amount, represents a central oscillator.

4. Regardless of loading, the frequencies of hand tremor and EMG are equal and both decrease (less than 1 Hz) with loading. This is a sign of a major central oscillator.

Enhanced Physiological Tremor

Unlike physiological tremor that is not noticeable, enhanced physiological tremor presents a relatively large amplitude and a peaked spectrum whose peak is in the range of 8-12 Hz. This quite symptomatic tremor appears when a normal subject is anxious, fatigued, frightened, contracts a muscle forcefully, receives adrenergic medication, or has an increase in release of adrenaline [38]. It is accepted that an increase in the synchronization of the stretch reflex is the fundamental neuronal mechanism of this tremor [75].

2.5.2   PD tremor

After bradykinesia (slowness of movement), tremor is one of the most noticeable signs of Parkinson's disease (PD) [4]. Although rest tremor is the classic one, tremors in posture (when the limb takes an outstretched position), and in other situations in which the muscles are voluntarily contracted (generally referred to as action), are frequently reported during posture and pre-defined tasks [83], flexion and extension of joints [20], or in posture, isometric contraction, and movement [84]. As mentioned earlier, postural, isometric, kinetic, and task specific are all termed action tremor [19]. Compared to rest tremor, results of studies on PD action tremor are less consistent and hence open to more questions.

Action Tremor - Medication Effect

The well known ($\sim$4-6) Hz classical PD tremor, that occurs mainly in rest, is known to respond to different Parkinsonian medications [85], although this response is weaker than those to bradykinesia and rigidity [21][22]. For the postural and action tremors, the reported medication results are diverse and generally weaker. For example, patients in one study on postural tremor ([68]) reported similar reduction of tremor in rest and posture, while other studies present weaker response to medication [21][23]. Some studies reveal postural tremor activity in two frequency bands with negligible response in the higher band [30, 86] to different treatments. For action tremor, response to dopaminergic medication is reported to be 62% (compared to 98% for rest tremor)[23]; and different antiparkinsonian medications are reported to reduce action tremor in torque by 37% [61]. While a dopamine agonist is claimed to significantly reduce the rest tremor in PD, it is not better than placebo for action tremor [24].

Action Tremor - Tremor Activity Outside Classic Band

As mentioned before, any involuntary hand movement in the frequency range of 3-17 Hz is considered to be tremor. Classic PD rest tremor has been verified in a small portion of this range (3.5-6.5 [33], 3.5-7 [73], 4-6 [58], and 4-7 Hz [87]). The reported frequency range for postural tremor in most of the studies is the same [88] (classified as Type I in [19]), although other studies have reported higher ranges in postural tremor (6-12 Hz[30], 4-12 Hz [86]), and in non-resting conditions [31] as well. In this study, the 3.5-6.5 Hz frequency range is considered to be the classic PD band. For comparing tremors in this range with every other tremor (for example, from a suppression device designer's point of view), the remaining range (7.5-16.5 Hz) is considered to be broadly the physiological band. The filters are tried to be non-overlapping to avoid some tremor components being considered in the other ranges. A 0.5 Hz transition from stop-band to pass-band is considered for each filter.

Although various tremors result from neuronal activities that exist in the absence of sensory feedback and are independent of reflex arc length, no source of oscillation can be completely isolated and limb mechanics and segmental loops affect all forms of tremor [36]. Furthermore, if the natural frequencies are close, a central mechanism can resonate with the mechanical-reflex oscillator. Therefore, PD patients can also exhibit (enhanced) physiological tremors. However, it is not currently clear whether the physiological tremor is any different in PD patients and in otherwise healthy human beings.

Recent studies revealed that although the underlying mechanisms of PD tremor are not clear yet, it is produced by multiple oscillators rather than a single one. The results state that, especially in action (kinetic) tremor, many patients exhibit lower amplitude oscillations in 8-12 Hz range as well [87]. The idea of multiple oscillators have motivated some researchers to investigate separate bands of frequency in examining tremors in PD [73, 33] or healthy [56] populations.

Action Tremor - Sub-groups in PD

To deal with somehow contradictory results in PD action tremor, tremulous patients have been separated to subgroups that exhibit more consistent characteristics. The categorizations in the literature have been based on various factors including tremor *amplitude* [70], the *delay* in the onset of tremor [4], single/double-peaked *spectrums* [32], non/re-*emergent* tremors [68], with/without accompanying *EMG* oscillations [84]. The most comprehensive categorization is proposed by the ad-hoc scientific committee of the Movement Disorder society to subdivide the tremulous PD patients according to their clinical signs to three types: **type I**, classic Parkinsonian tremor, presents rest tremor or rest and postural/kinetic tremor with the same frequency. **type II**, exhibits rest and postural/kinetic tremors with different frequencies. **type III**, exhibits only postural/kinetic tremor [19].

Action Tremor - Loading Effect

Evidence of (enhanced) physiological components (which is mainly peripheral in non-rest conditions) in PD action tremor, requires the related studies to consider load effects. Various levels of loading, combined with observation of tremor frequency components inside and above the classic PD frequency band, provides detailed information about load-dependent (peripheral) and load-independent (central) components of tremor. For this reason, some researchers favor loading over postural conditions in identifying tremor subtypes [67].

Studies that have considered loading effects on PD tremor have provided inconsistent results. A study involving PD action tremor, in isometric wrist contactions, revealed that loading affects tremor amplitude and its peak frequency in half of PD subjects [67]. Another study on finger tremors, dividing components to two ranges of frequency, observed significant change in amplitude and frequency in the higher frequency range [30, 33]. While peripheral mechanisms (load dependent) are involved in PD rest tremor [89] and during movement [90], it has been reported that loading has a minimal effect on the amplitude

and frequency of rest [91] and postural [49] tremors. Similarly, it has been stated that the periodicity of central oscillators in PD dominates the loading effects [72].

One factor that might add to the inconsistency in the results is the amount of loading in the mentioned studies. Different values have been used in assessing load's effect and loads have been barely chosen with respect to subject's strength (one such example is [57] in which wrist tremor has been investigated under 0-25% maximum possible load for physiological and essential tremor). The following are examples of the load values, limb, and population under tremor study. Loads of 0.2-0.3-0.5-0.8-1.2 N.m in wrist tremor study used for PD and essential tremor populations [67]. Loads of 300 g and 900 g, in finger (wrist) tremor study, was examined for PD and healthy populations [30]. In a study of PD and healthy subjects, 500 g was used for finger tremor investigation [33]. Loads of approximately 100g, 250 g, and 580 g were used in study of hand tremor in PD patients [49]. A study of healthy finger tremor used 70 g as load value [56]; and another study on healthy hand tremors utilized loads of 500 g and 1000 g [81].

2.6   Summary

One open question in Parkinson's disease studies is why the results on PD action tremor are not as consistent as those of rest tremor. The dopaminergic medication gets less effective in decreasing tremor as the muscle activation increases (from rest to posture, and to other action conditions). More tremor components are observed above the classic PD frequency band as the muscles are activated. Some researchers have concluded that action tremor is different from classic rest PD tremor, and is enhanced physiological tremor. However, tremor components in classic band are not completely disappeared, and not every tremulous PD patient exhibits tremors similar to enhanced physiological tremor in action.

One study compared tremor characteristics in PD patients *without* visible tremor to those in healthy controls, to investigate pathological or physiological origin of tremor in the patients [70]. Their results indicated that the rest tremor in this sub-group of PD patients was significantly different from physiological tremor, but postural tremor was not. They suggested that, for this sub-group, parkinsonian and physiological tremors *coexist*. They further assumed that if PD patients with larger tremors had been examined, this (coexistence) would not have happened. In this study, the contrary assumption is going to be investigated. In other words, we are interested to know if (enhanced) physiological tremor is any stronger in PD patients than the healthy people; meaning that the both mechanisms coexist for all PD patients.

The coexistence hypothesis (if proven) cannot explain most of the present diverse results by itself. However, if the two mechanisms (of physiological and classic PD tremors) coexist, but with a different relative strength in different sub-groups of PD, it could provide better explanation. To find out about the relative strength of the two mechanisms in sub-groups of PD, we will indirectly examine the trend of change in tremor characteristics with increased muscle activation (loading). If loading is applied in a complete range of 0-100% MVC (Maximum Voluntary Contraction), it can provide the full picture of (enhanced) physiological tremor components for this population. Comparisons with the healthy population, in similar conditions, will reveal if the reflex-mediated oscillations are any different between PD patients and the healthy people. Furthermore, loading with respect to MVC makes the results more comparable between the individuals.

To investigate the two mechanisms, tremor characteristics will be evaluated separately in each of the two frequency bands. These two bands are 3.5-6.5 Hz as classic PD band, and 7.5-16.5 Hz as broad physiological band. Since neurological systems (including tremor mechanisms in PD) exhibit nonlinear behavior [36, 35], it is expected that interactions would be complex (not predictable by sum of the components). In other words, two tremor mechanisms might amplify each other and resonate or suppress each other. Therefore, to evaluate tremor amplitude, energy in the bands is favored over peak magnitude or other measures relying on the shape of tremor spectrum.

Chapter 3

Tremor Quantification

Clinical scales such as Unified Parkinson Disease Rating Scale (UPDRS), Tremor Rating Scale (TRS), or The Essential Tremor Rating Assessment Scale (TETRAS), provide clinical measures for overall tremor severity. However, to obtain detailed characteristics of tremor for a limb under study, tremor signals are collected through one or more of the following methods: accelerometry, electromyography (often in conjunction with accelerometry or electro/magnetoencephalograms), ultrasound/infrared/laser displacement sensing, electromagnetic tracking, force/torque measurements, goniometers, digitizing tablets, etc ([92, 42]). The acquired signals usually contain non-tremor components such as intended motions, drift, jerks, contamination from breathing, heartbeat, and other motion artifacts that should be removed before the tremor can be characterized.

3.1   Tremor Signal Acquisition

Throughout the different stages of the experiments, some or all of the following signals were collected that contain information about the tremor on the target limb: Acceleration, position, Surface Electromyogram (SEMG), and Force (see Fig. 3.1). Primarily, two PHANTOM$^{\textcircled{R}}$ Omni^{TM} (The SensAble Technologies Inc.) have been chosen for recording the position signal (including the tremor) during different situations (of rest, posture, and movement with and without exerted forces). However, the nominal resolution ($\sim$0.055mm) was not achievable in recording the last joint's position. Therefore, the devices were just used to apply the required forces in posture and moving situations (Chapter 5) and the recorded positions were used in gross motion amplitude calculations, finding quasi-

19

stationary periods (for investigation of tremor in movement, Chapter 7), and for checking the artifacts during rest and posture.

(a) Accelerometer

(b) Haptic (Phantom-Omni) device

(c) Surface EMG electrodes

(d) Force measurement (MVC) and accelerometer axes
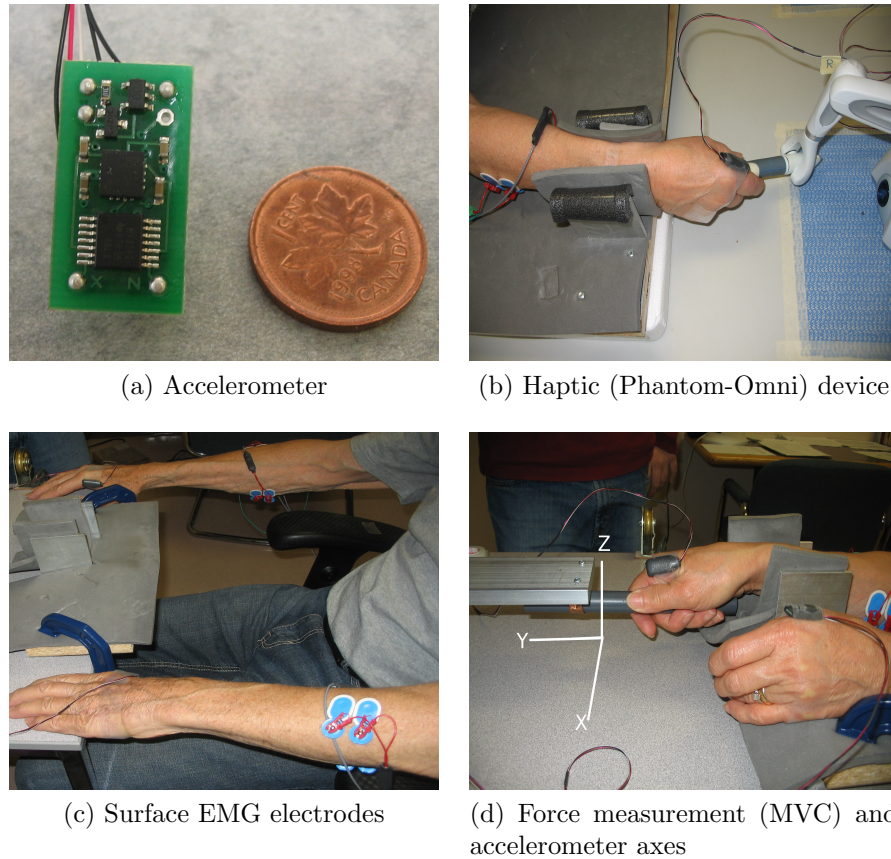
Figure 3.1: Collected signals during the experiments

The surface Electromyograms of the muscles involved in the motion (voluntary/tremor) is also a reliable source of tremor assessment (especially its frequency, and in pathological tremors). In this study, which involved healthy and Parkinsonian populations, SEMG's power spectrum was used as secondary sources of tremor frequency assessment.

Force measurement using a reaction torque sensor (TQ301-400, OMEGA$^{\text{TM}}$Technologies) helped finding maximum voluntary contraction (MVC) level for each hand, each medical condition (On-, Off-medication), and for each individual. Later in the experiment, limb loading was performed with respect to this MVC level. In some experiments (Chapter 4), the force signal was utilized to extract the tremor.

The main sources of tremor information were the tri-axial accelerometers (DE-ACCM3d Buffered ±3g Tri-axis accelerometer) that were attached to both hands for the whole experiment session. The accelerometer is a complete 3-axis acceleration measurement system (ADXL330) based on a micro electro-mechanical sensor on a single monolithic IC, capable of measuring static (gravitational) and dynamic accelerations. Placement of this accelerometer and the axes of measurement are shown in Fig. 3.1-d.

3.2   Tremor extraction

Standard band-pass filtering is still the most common method of extracting tremor component from related signals. Any involuntary, and approximately rhythmical, motion in body parts is considered to be tremor[19] and it is assumed to have a frequency of at least 3 Hz [35]. The upper limit for the tremor frequency depends on the body part and researchers have used a wide range for the highest frequency in their spectral analysis of tremor (17, 18, 20, 25, 30 Hz [30, 19, 73, 92, 35]). This study focuses on wrist tremor and we have considered 3-17 Hz for the range of tremor evaluation. Fig. 3.2 shows a band-pass filter that is used for the whole tremor range (Appendix B provides details about all the filters and the chosen FIRLS method: Least Square linear-phase Finite Impulse Response filtering).

However, Fourier-based spectral analyses (including spectrum-reshaping with filtering), assume that the signal is stationary with no time-dependent spectral content. Not only tremor signal (especially intermittent Parkinsonian tremor) can be non-stationary, but also many background components in the measured signal are time-varying. In our measured signals, these components include drift, jerk/stepwise changes during postural tremor, and non-stationary intended movements during kinetic tremor. Some time-frequency analysis techniques can overcome these shortcomings.

3.3   Time-Frequency Analysis Techniques

Fourier-based spectral analysis cannot determine when in time specific frequencies of a signal appear. Time-frequency representation of the signals is achievable with non-parametric (linear, and quadratic) and parametric methods, which assume that the signal evolves from a statistical model whose parameters are time-varying [93]. Linear, non-parametric methods are based on linear filtering operation and we have used two most popular techniques
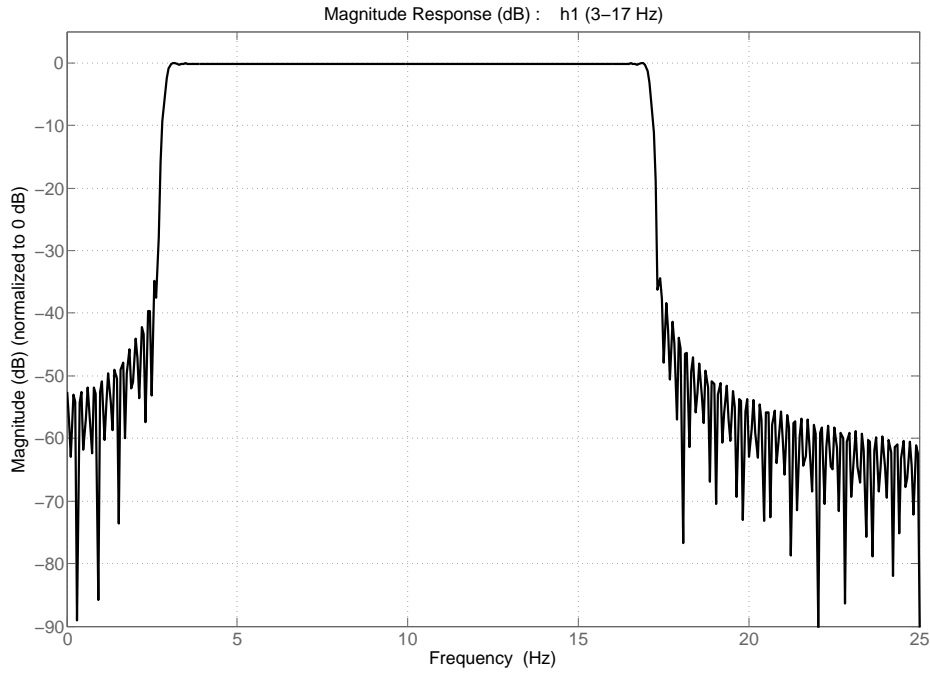
Figure 3.2: Magnitude response for the filter that extracts all tremor components from the collected signal

from this category that are the short-time Fourier transform, and the wavelet transform.

3.3.1 Short-Time Fourier Transform

Windowed or short-time Fourier transform (STFT) is possibly the simplest method of implementing time-frequency analysis. In this method, the signal $x(t)$ is divided into a sequence of shorter (and perhaps overlapping) sections. The division takes place using a window function $w(t)$ which reduces large-amplitude sidelobes in the spectrum by avoiding discontinuities. Hamming, Hanning, Kaiser, and Blackman are some of the most popular window functions. When the segments are ready, the Fourier-based spectrum is evaluated for each of them. Thus STFT would be the following two-dimensional function as described in [93] :

$$X(t,\Omega) = \int_{-\infty}^{\infty} x(\tau)w(\tau - t)e^{-j\Omega\tau}d\tau, \tag{3.1}$$

in which Ω represents analog frequency. Usually, the squared magnitude of the STFT, which is called spectrogram, is plotted as time-frequency spectral visualization:

$$S_x(t, \Omega) = |X(t, \Omega)|^2. \tag{3.2}$$

One interpretation for STFT is local spectrum of the signal $x(t)$ around t (the analysis time). The outcome of such Fourier transform is mainly dependent on the choice of the window length and its type. For a good time resolution of the STFT, a narrow window in time is required, which yields a poor frequency resolution. The opposite is true for a long analysis window in time. We have used this time-frequency visualization mainly for finding consistent time-frame over which tremor spectrum was not changing.

Rest/Postural/Isometric Tremor

In the studies not involving large movements, after removing all the artifacts, STFT results visualized with a MATLAB contour plot (*imagesc* in Fig. 3.3), helps examining the concentration of energy in the tremor as participant switches from rest to posture, or as she/he remains in posture, or as different forces are applied on the hand in posture.

STFT can be used in the same way for the tremor signals collected from isometric contractions (Chapter 4). It also helps to examine the consistency of a peaked/wide-spectrum tremor over time, or to check possible contribution of transient effects in some part of the spectrum (thus helping correct the period over which the tremor/spectrum should be taken into consideration). While Fig. 3.3 displays consistent peaks in tremor spectrum for a PD patient during different stages of rest and posture, Fig. 3.4 reveals that transient portions of the filtered tremor signal, caused by rest-posture transition (around 15-sec) or application of forces on the hand (around 46, 61, 66-sec), have the most contribution to the overall spectrum and the only consistent peak might be the one around 12 Hz.

A three-dimensional representation of tremor spectrogram, on the other hand, helps keeping the track of overall spectrum and non-dominant tremors for the whole period. Fig. 3.5 displays such a visualization for the same trials of a PD patient and a control participants in Fig. 3.3- 3.4.

Kinetic Tremor

It is not only the tremor that can be non-stationary, but also the intended movements during a kinetic trial are usually non-stationary specially for the patients. During free-
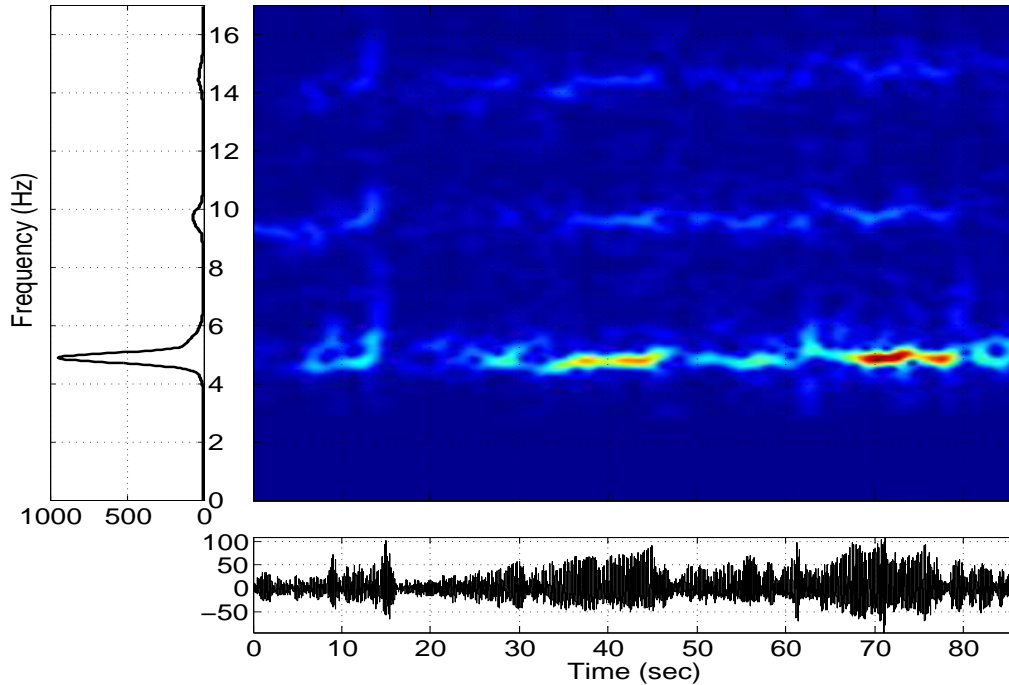
Figure 3.3: STFT helps visualizing the change in energy concentration of the right hand tremor (accelerometer in x-direction) over one whole postural trial for a Parkinsonian patient with severe tremor (main panel). The left panel presents the power spectrum of the tremor signal for this period. The bottom panel presents the tremor signal (filtered 3-17 Hz).

motion trials (Chapter 5), participants are asked to perform wrist flexion-extensions (of full range) according to a metronome whose frequency increases every 6-sec. In order to examine the consistency of the movements in each segment, and the trend of increasing the speed, STFT proves to be very useful. Furthermore, using these plots, the quasi-stationary segments, over which the gross motions are almost stationary, are identifiable. Using these segments for spectral estimation will provide more accurate results. However, for some patients in off-medication state, finding such segments is very difficult. Fig. 3.6 presents such free-motion trials for two PD patients and one of them has identifiable quasi-stationary segments, while the other can barely keep a consistent movement in any direction.

24
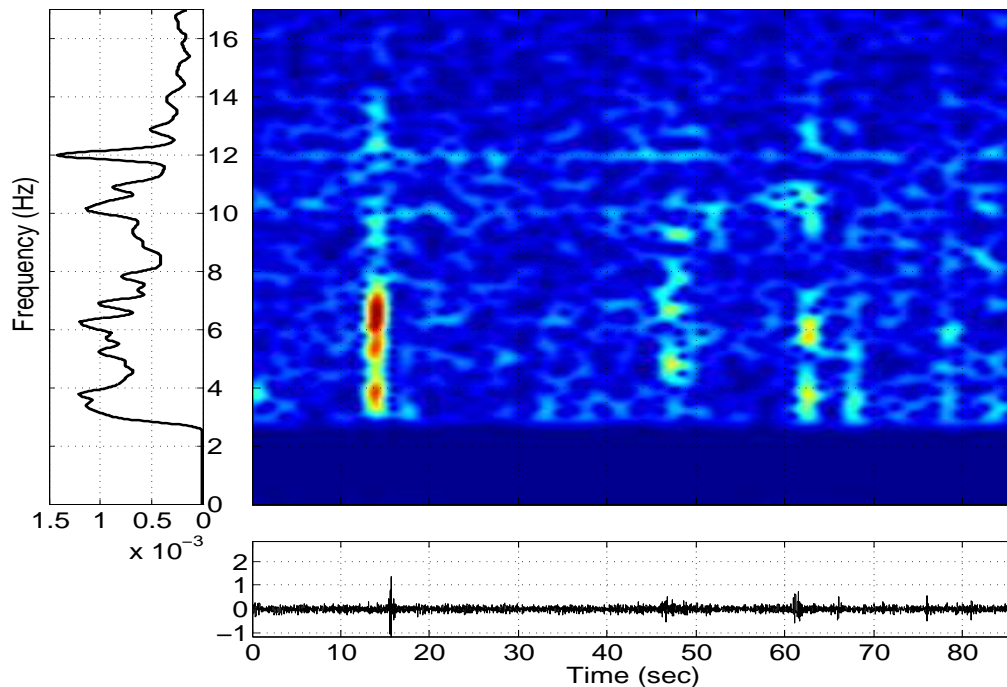
Figure 3.4: STFT of the left hand tremor in x-direction over the whole postural trial for a healthy control with no noticeable tremor (main panel). The left panel presents the power spectrum of the tremor signal for the whole period. The bottom panel presents the tremor signal (filtered 3-17 Hz).

3.3.2 Wavelet Analysis and Tremor in Posture

the STFT is inadequate when studying signals containing features of different size, whereas wavelet analysis is able to provide more accurate time-frequency representation of a signal containing both low and high-frequency components [94]. Although this is not a critical issue in the study of low-frequency body limb tremor, but background components, especially in examining the postural tremor in displacement signals, contain both high frequency components (sharp changes) and low-frequency components (movements slower than tremors), and wavelet seems more powerful in removing all these unwanted background signals.

In wavelet analysis the goal is to express the signal as a linear combination of specified sets of functions (oscillating function whose energy is concentrated in a period of time to better express non-stationary, and transient signals [93]). This is achieved by translation

(a) PD patient
(b) Healthy participant
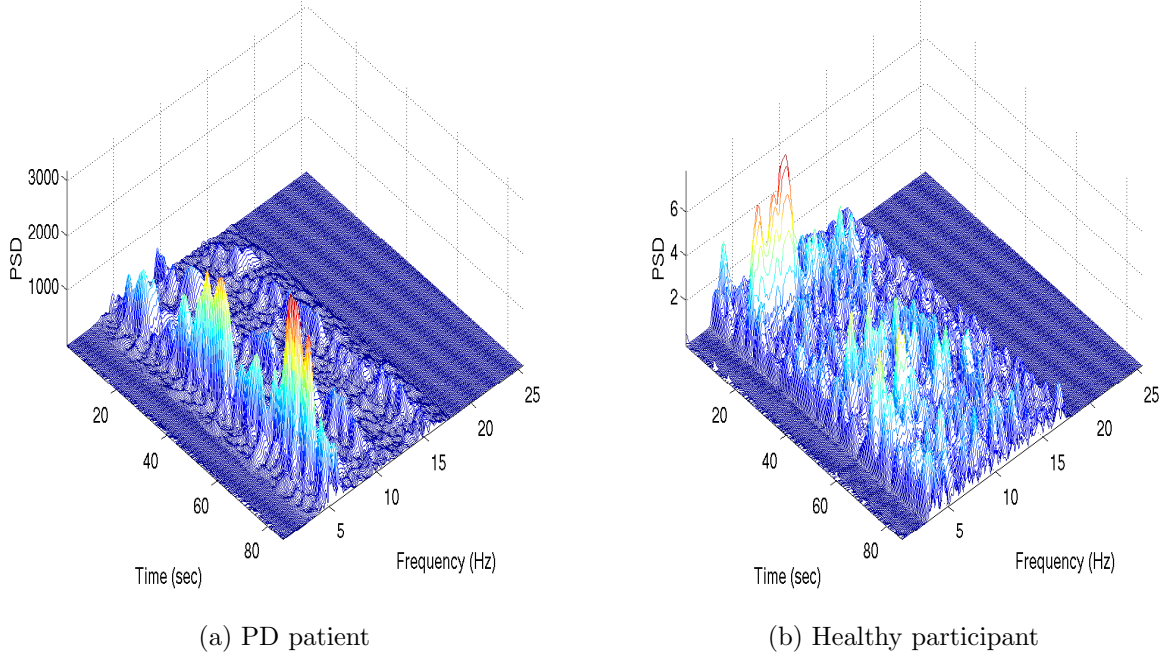
Figure 3.5: Three-dimensional representation of STFT amplitude for filtered (3-17 Hz) tremor signals from accelerometer data in X-direction

and scaling of a function $\psi(t)$ (called mother wavelet) in time. For a continuous-time signal $x(t)$, the continuous wavelet transform (CWT) is defined by the correlation of that signal and scaled and translated mother wavelet:

$$\psi_{s,\tau}(t) = \frac{1}{\sqrt{s}}\psi(\frac{t-\tau}{s})$$ (3.3)

and the result $(w(s,\tau))$ would be a two-dimensional mapping onto the time-scale domain from which the original signal is completely recoverable. The CWT can be regarded as a bandpass analysis in which the scaling parameter s modifies the bandwidth and the center frequency [93]. Since this two-dimensional function is highly redundant, scaling and translation parameters can be discretized and one popular method is using dyadic sampling as follows:

$$s = 2^{-j}, \quad \tau = k2^{-j}, \quad j,k \in \mathbb{Z}$$ (3.4)

from which the discretized wavelet function, and discrete wavelet transform (DWT) can

(a) PD patient #1 (b) PD patient #2
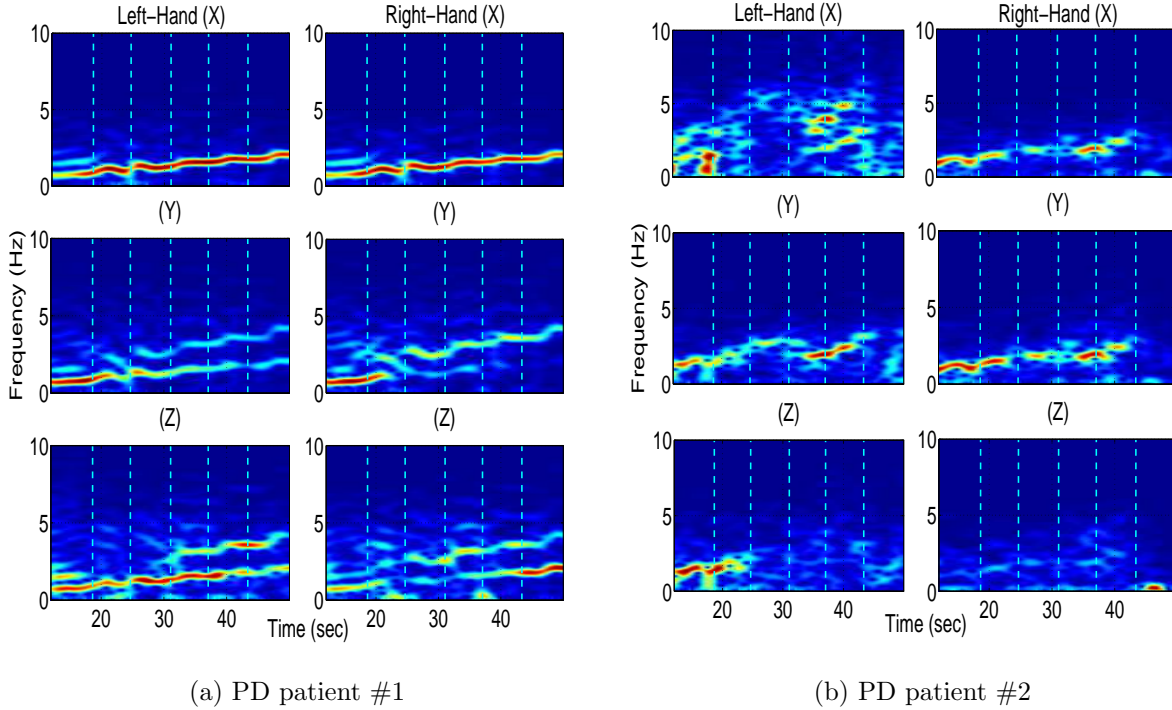
Figure 3.6: Time-frequency representation of both hand displacements in all three dimension (position data recorded by two Phantom Omni devices). The vertical dash-lines divide the whole trials into segments over which the metronome speed is constant.

be derived:

$$\psi_{j,k}(t) = 2^{j/2}\psi(2^j t - k) \tag{3.5}$$

$$w_{j,k} = \int_{-\infty}^{\infty} x(t)\psi_{j,k}(t)dt \tag{3.6}$$

The following inverse DWT helps retrieving the original signal:

$$x(t) = \sum_{j=-\infty}^{\infty} \sum_{k=-\infty}^{\infty} w_{j,k}\psi_{j,k}(t) \tag{3.7}$$

Any signal can be considered as the combination of *coarse* components (approximation) representing the main features of the signal, and *fine* components (detail) corresponding to faster changes. Researchers have used DWT decomposition of tremor signals for analyzing the frequency composition and energy distribution, to further classify them, or to diagnose

27

tremor types [5]. Being able to decompose a noisy signal, along with prior knowledge about both the signal and the noise or artifacts, can also help *denoising* it or extracting the expected information. Therefore, wavelet-base denoising is a simple and powerful algorithm containing three main steps: decomposition or calculating DWT coefficients, selecting or thresholding certain coefficients, and reconstructing the signal from them [95, 93]. DWT denoising has improved signal processing in many fields including human eye tremor [96] and seismic tremor [97] studies. Usually, this denoising manipulates the detail coefficients according to determined thresholds, or sets the coefficients of fast enough details to zero (thus removing those high frequency components). In a similar method, the tremor component can be extracted from the signal which is contaminated with both high frequency noise (and sharp changes/jerk) and low frequency drift and voluntary movements. In the following section, based on a typical postural tremor signal (see Fig. 3.7), a systematic method helps choosing the type of the wavelet and the detail levels that should be used in reconstruction of the tremor signal.

Typical Features of Postural Tremor

Unlike in rest tremor, signals collected during posture (especially displacement signals) include motion artifacts and drift that are larger than (or at least comparable to) the tremor signal and make the simple filtering and Fourier analysis inaccurate. This problem aggravates if forces are applied to the limb in posture (see Chapter 5), which introduces step-like and impulse-like components to the displacement signal.

The possible tremor components that should be extracted from displacement (or torque, or acceleration) signal are physiological and classical Parkinsonian rest tremors. From the literature, the frequency of these two tremors are known to be around 8-12 Hz and 4-6 Hz respectively. The amplitude of the physiological tremor is dependent on the load of the limb in posture. The amplitude of PD tremor can fluctuate slowly, but not necessarily with the amount of limb load. Fig. 3.7 presents components of such a typical recording in posture.

To extract the tremors, DWT-based signal decomposition is utilized. Fig. 3.8 displays one such decomposition for the whole artificial signal (see Fig. 3.7-e) with MATLAB wavelet toolbox (*Wavelet 1-D*) with ten levels of detail.

To find the optimal combination of detail levels that can reproduce the tremor components, the RMS error between the original tremors (see Fig. 3.7-f) and the reconstructed DWT version is compared for many types of wavelets (Daubechies, Coiflets, Symlets, Discrete Meyer, Biorthogonal, Reverse Biorthogonal) and for all possible combinations. The
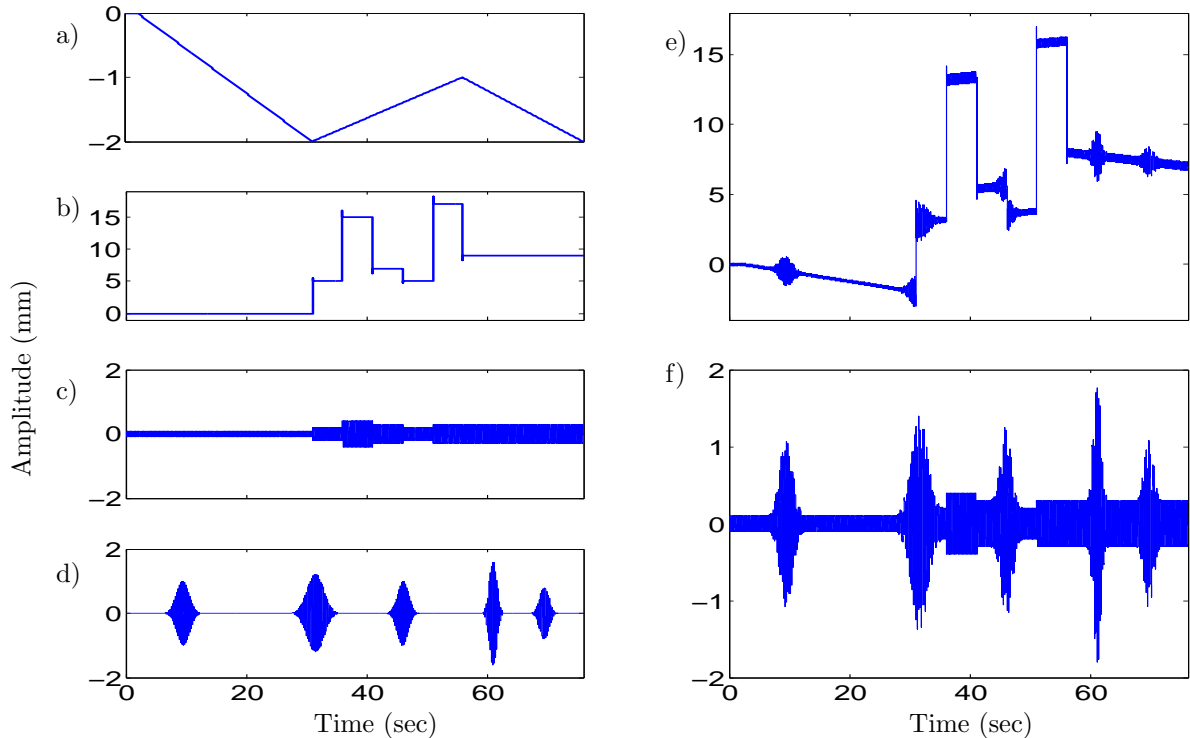
Figure 3.7: A synthetic signal containing main features of a typical recording during posture. a) drift component which is bigger in absence of visual feedback and can include breathing artifact. b) stepwise and jerky artifacts introduced by forces applied on the hand in posture. c) physiological tremor component that is assumed to aggravate with the applied load (10 Hz sinusoid). d) PD tremor component that is assumed to be intermittent (sinusoids of 4.5, 5.8, and 5.9 Hz with a Gaussian envelope). e) the overall collected signal. f) sum of the tremor components that should be extracted.

comparison also included 5-15 levels of detail for decomposition. The minimum RMS error was obtained with *db6* and for the tremor reconstructed with detail *levels 5-6*. Fig. 3.9 shows that the reconstructed tremors using DWT gives a better estimate of the original tremors when compared to simple band-pass filtering in Fig. 3.2. The improvement in percentage of mean-absolute, RMS, and maximum errors are respectively 2.2, 23.1, and 5%.
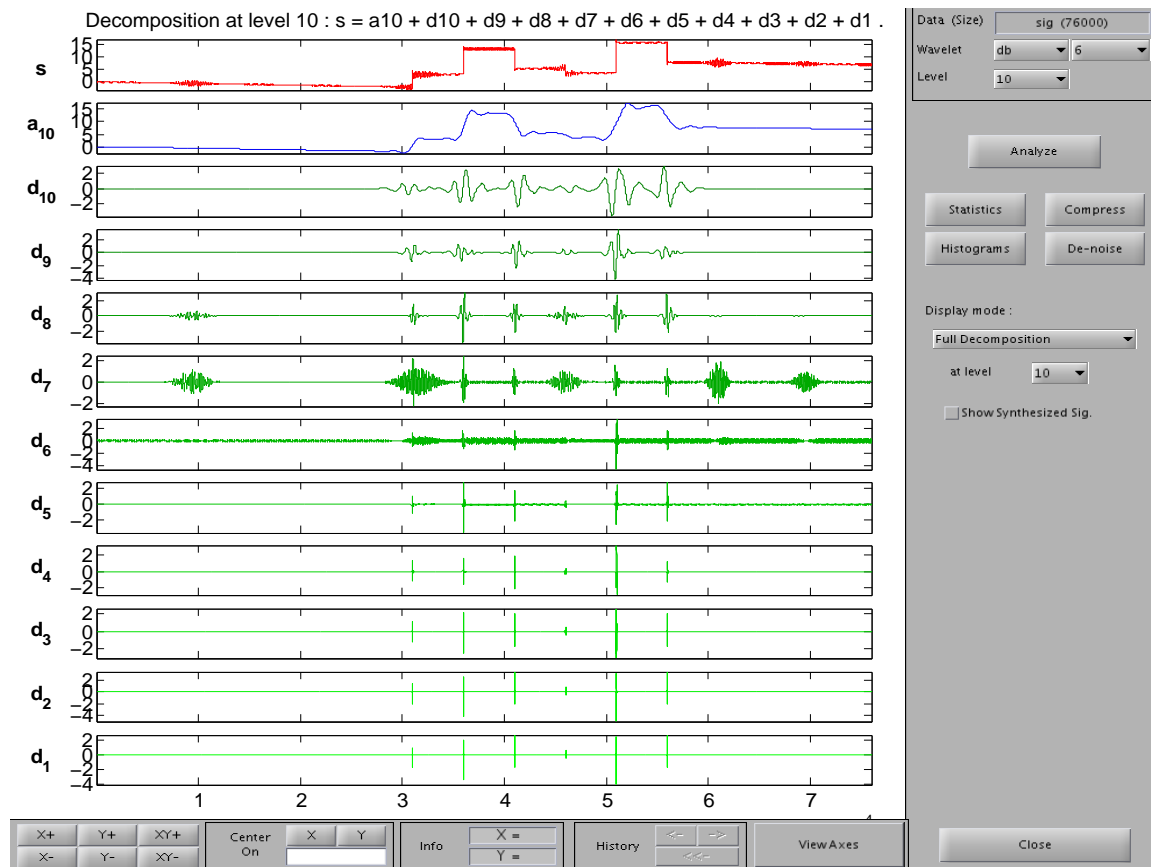
Figure 3.8: Decomposition of a typical tremor in posture (artificial) using MATLAB one-dimensional wavelet toolbox for ten levels of detail and db6 as the chosen wavelet type.

3.4 Spectral Estimation

STFT and spectrograms (or scalograms using DWT) provide information about the change of frequency components over time. After extracting tremor, we assume that the tremor over each segment (condition) is quasi stationary and Fast Fourier Transform (FFT)-based spectrum can give us a good estimation of tremor's energy distribution.

Spectrum or power spectral density (PSD) estimation is usually based on FFT which generates reasonable results, but has two main drawbacks ([98]): 1- The frequency *resolution* (in Hz) is limited to approximately the reciprocal of the data length (in seconds). 2- Windowing (tapering) which is inevitable in this process, brings about *leakage* of energy from main lobe to the sidelobes. There are two main categories for spectral estimation; in *parametric* methods the main assumption is that the signal under study is generated by a

30
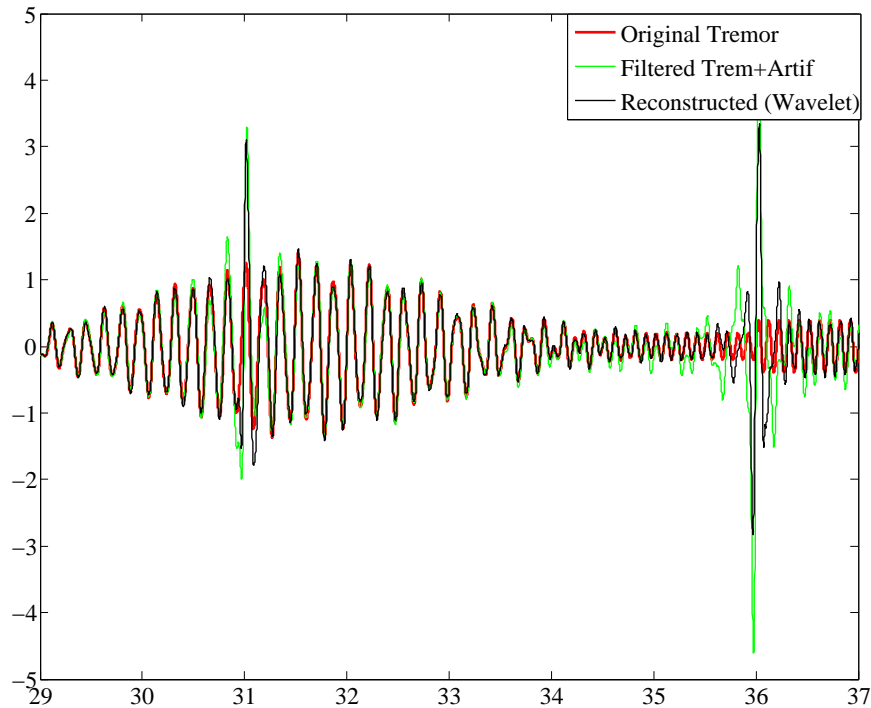
Figure 3.9: Tremor, reconstructed Tremor, and filtered data. Absolute error= 29.4%, 38.2% respectively

particular parametric model. On the contrary, *non-parametric* methods allow the model or form to be decided entirely by the data segment. Successful operation of parametric methods need adequate a priori information about the signal and inappropriate choice of model will produce erroneous results [69]. Since the physical process which generates tremor is not well-known, non-parametric estimation was chosen for this study. The classical non-parametric PSD estimator is the Fourier transform of an autocorrelation of the signal and is called *periodogram*. Periodogram is unfortunately a biased and inconsistent estimator which means increasing the length of data segment does not decrease its variability [69]. Modifying the type of window improves some of the problems, but to decrease the variance two main solutions have been proposed. Welch-Bartlett method, which is a periodogram *averaging* method with overlapping windowed segments, and produces asymptotically unbiased and consistent results, has been adopted as the PSD estimation method. Fig. 3.10 presents the results of such power spectral estimation (using MATLAB-*pwelch*)

on the typical postural tremor signal. It compares PSDs for original tremor components, reconstructed tremor using DWT, and also for the whole signal without removing the DC component.
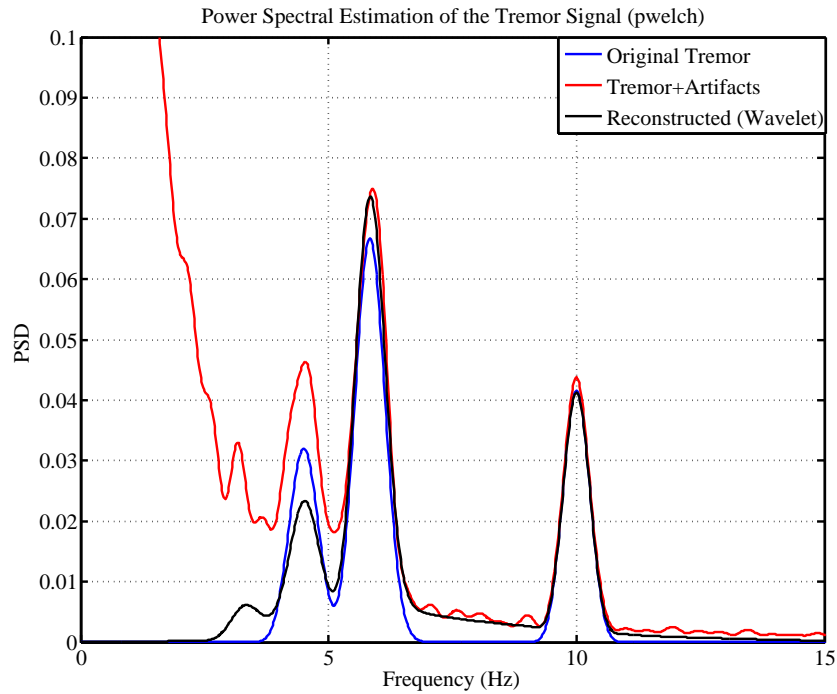
Figure 3.10: Comparison of estimated power spectral densities for the typical postural tremor recording using Welch's method.

If the mean (DC) value of the signal is relatively large, because of the leakage, it will obscure the low-frequency and weak components. Therefore, before PSD estimation this component is removed for any tremor signal. Interpreting the resulted spectrum should be made carefully especially in the presence of multiple peaks. As stated in [99], asymmetry of the tremor waveform produces harmonic distortion and also if tremor amplitude and frequency have dependent fluctuations, the spectrum will contain a pattern of asymmetrical sidebands resembling combined signals from different independent oscillators.

3.5   Selected Tremor Characteristics

To compare tremor behavior in different situations (rest, posture, loading the limb, and movement), or to compare it between different groups of people or medication states, some characteristics of tremor should be extracted from the collected data. As mentioned in Chapter 2, they can be categorized into frequency and time domain characteristics. In frequency domain, after the spectrum is estimated, its peaks and the power distribution in the two bands (physiological, and Parkinsonian) are calculated as the selected characteristics. In time domain, root-mean-square (RMS) amplitude of the extracted tremor is the selected characteristic. RMS amplitude which is a measure of tremor energy is calculated for the overall extracted tremor as well as for the filtered tremor in each band.

3.6   The Adopted Signal Processing Procedure

The following are the principal steps of processing for data collected in the main experiment on wrist tremor (see Chapter 5). The processing steps in pilot study on elbow tremor (see Chapter 4) are meant to extract tremor from the torque signal, but are essentially very similar:

- The collected signal is processed separately for each hand, each medical condition, each trial, and each degree of freedom (X, Y, and Z). RMS amplitudes of tremor for all degrees of freedom can be combined later to provide an overall amplitude.

- Screening:

  - Plotting position data helps choosing the most appropriate trials for analysis (rest, posture, timely transition, acceptable disturbance level, etc.) and the most appropriate time-span for each situation.

  - STFT plots helps checking quasi-stationarity for the segments chosen for movement analysis, checking the transients' effect on the overall PSD especially for weak tremors, and also checking the consistency and the harmonic distortion Fig. 3.3-3.4.

- Tremor is extracted for the whole trial using DWT decomposition-reconstruction. For comparison, the same collected data is band-pass filtered (3-17 Hz) and both are displayed.

- Before any filtering operation, the signal is symmetrically padded on both sides (with enough length) to eliminate filter transient effect (or boundary conditions) [100]. Then the mean value is removed from signal to minimize leakage in spectral estimation. After filtering, the original length in the middle was kept as the filtered signal.

- PSD is estimated for the extracted tremor (and plotted for both DWT and filtering methods for the whole trial).

- The whole extracted tremor is filtered to provide components in each of the three different bands. The main two bands are 3.5-6.5 Hz (B2) for classical PD, and 7.5-16.5 Hz (B1) for physiological tremors. The central component of physiological tremor (8-12 Hz (B3), which is also the same as mechanical-resonant component for wrist), is also calculated for comparison.

- For each segment (corresponding to rest, posture with no force, etc.), the RMS amplitudes are calculated for the extracted tremor and its filtered components in each band. Additionally, estimated PSD for each segment was used to find peak tremor frequency and magnitude in the spectrum. This is repeated for the second and third largest peaks in the spectrum, to investigate multiple peaks.

- Each participant's data is processed in a similar way and added to a multidimensional matrix which is finally used for statistical analysis.

3.7 Conclusion

In this chapter, after introducing the acquired signals during the experiments, the techniques that improve tremor extraction were studied. The improvements were compared with the standard band-pass filtering which assumes stationarity for the tremor and background signals. This band-pass filtering is performed in parallel to the adopted procedure during the analysis and its frequency range is decided based on the literature and the limb under study. STFT proved to be helpful in tremor analysis in choosing the segments to be included in the analysis (Quasi-stationary segments) and the segments to be excluded (segments containing transient artifacts). This was accomplished by visualizing STFT along the tremor signal and transient factors such as displacement or applied force.

Wavelet transform (CWT and DWT) was briefly introduced and a technique similar to wavelet denoising was used to extract tremor components. In this technique, after

the collected signal is decomposed into finite *approximate* and *detail* levels, tremor is reconstructed by adding the chosen detail levels. The decomposition-reconstruction levels and also the type of wavelet were optimized for a typical (simulated) position recording during posture. The extracted tremor had improved accuracy compared to band-pass filtering. The chosen method was used for tremor extraction from acceleration and force signals as well.

After the tremor is separated from background signal, its characteristics need to be evaluated. Frequency domain features are based on spectral estimation and it was shown that the chosen Welch-Bartlett method has significant advantages over the standard periodogram method. Finally, the main steps in processing the collected signals, which is kept consistent for all the analyses were presented.

Chapter 4

PD and Physiological Tremors in Isometric Elbow Torque: A Pilot Study

4.1 Introduction

[1]

Parkinson's disease (PD) is associated with bradykinesia, rigidity, tremor, and postural instability. Tremor represents a particularly interesting symptom because its responsiveness to dopamine therapy is quite variable [104]. Generally, tremors can be classified into rest and action, which includes postural, kinetic, task specific, and isometric tremors (Chapter 2). Although 4-6 Hz rest tremor with pill rolling is typical, many researchers have reported additional action (including postural) tremors, occurring in a varying range of 40% to 93.4% of participants depending on the study ([20, 105, 106, 83]). Unlike rest tremor, with a standard frequency range of 4-6 Hz, the range of frequency for this action tremor is diverse in the literature. Reports of the same or higher than rest tremor frequency covers a broad range of 4-12 Hz [92, 87, 35]. Because PD action tremor interferes with daily activities, it is more disabling than rest tremor. Yet, its underlying pathophysiology remains unclear [83]. A group of researchers have proposed that action tremor (just during movement) might represent an enhancement of physiological tremor in PD patients [31]. Both physiological tremor and enhanced physiological tremor (EPT) are of higher

---

[1]Parts of this chapter have been published in [101, 102, 103]

frequency (8-12 Hz) than classical parkinsonian rest tremor (PRT), and, while the former is barely noticeable unaided, the latter can produce clinical symptoms [75]. Physiological tremor is a weak tremor which is minimal or absent at rest; it appears or intensifies in posture and remains present during movement with no increase in amplitude [75]. Among other factors like fright and fatigue, limb loading enhances the physiological tremor [38]. Although PRT is reported to subside with any deliberate muscle activation [92], it has been also reported to remain visible even during posture or movement [71, 30, 31] or re-emerge in posture after a delay [68]. Similarities that are often observed between PD action tremor and EPT have led to the assumption that Parkinson's action tremor is, in fact enhanced (or alternatively known as exaggerated) physiological tremor [30, 107, 20, 32, 64]. One study, on fingertip movements, demonstrated the coexistence of physiological and PD action tremors in patients without visible rest tremors [70].

Many of the current wearable tremor suppression devices, such as the Double Viscous Beam (DVB) [108] and the Wearable Orthosis for Tremor Assessment and Suppression (WOTAS) [109], are intended to suppress essential tremor. Examining the coexistence of the two aforementioned tremors and their dominance during action in PD patients with different levels of tremor presentation would be a necessary step to use these types of devices to suppress the tremor in these patients.

The aim of this pilot study was to test the coexistence hypothesis for elbow tremors on a small group of PD patients. PD and (enhanced) physiological tremor characteristics were compared between these patients and a group of young healthy controls at rest and while generating torque at the elbow in flexion. Pilot subjects were chosen in an attempt to represent different levels of tremor severity. Unified Parkinson's Disease Rating Scale (UPDRS, Appendix F) was used to assess tremor severity in different limbs and situations. Item 20 (motor section III) evaluates rest tremor in face, lips, chin and each of feet and hands. Item 21 is for action tremor in each hand. Two sub-items of hand-rest and hand-action, each evaluated on a 0-4 basis by a movement disorder specialist, are used in assessment of tremor severity.

The main analysis was on tremor amplitude in torque signal. However, frequency analysis will be performed on the torque signal as well as on electromyographic (EMG) signals acquired from related flexor and extensor muscles. The root mean square (RMS) values are calculated as the most common measure of tremor amplitude [35, 30]. RMS value of a signal, filtered in a specific frequency band, has been referred to as both RMS *amplitude* and RMS *energy* in the literature. For consistency, the term *amplitude* will be used throughout the study. The spectrum's peak frequency is used as tremor frequency measure.

4.2 Hypotheses

In this section, the main hypotheses of this study are presented:

H_1: PD patients, regardless of tremor severity and muscle activation levels, have larger tremors at the elbow as compared to healthy controls. It implies that, with disease progression, the possibility of the need for suppression increases.

H_2: For PD patients, elbow tremor in the physiological band is comparable to that of PD band, at least at higher levels of muscle activation. It implies the co-existence of tremors in the two bands.

4.3 Methods

4.3.1 Participants

Six healthy male students, (age 31.7 ± 5.8 years), participated in this study. With scores of 3.5/8 (at rest and in action in the tremor-dominant hand) for patient #1 and 3/8 for patient #2, they were proposed to represent a *typical* tremor severity. Patient #3 had a tremor score of 7/8 that was proposed to represent a more *severe* tremor. The two PD male patients with typical tremor presentation had mean age of 76.5 ($\pm$ 2.1 years). The PD patient with high degree of tremor presentation was 53 years old and right-handed female. This subject had strong rest, and action tremors on the dominant (right) side which was highly disabling even at elbow level and responded positively to L-dopa medication (according to UPDRS).

4.3.2 Experimental Apparatus to Measure Elbow Torque

The apparatus in this experiment was designed to measure the isometric elbow flexion-extension torque at different elbow angles, and for each hand (Fig. A.3). In the apparatus, that was attached to the experiment table, a reaction torque sensor (OMEGA$^{®}$ TQ301, 45$\pm$0.09 N.m, Fig. 4.1-e) measured the applied torque. The accuracy of this sensor was $\pm$0.2% of full scale output ($\pm$0.09 N.m). The participants were seated upright in a chair facing the device with the shoulder fully adducted, lower arm fully supinated, and palm facing up. All the trials were performed at an elbow angle of $\theta = 135°$, which is similar to the arm position in clinical tremor assessments.
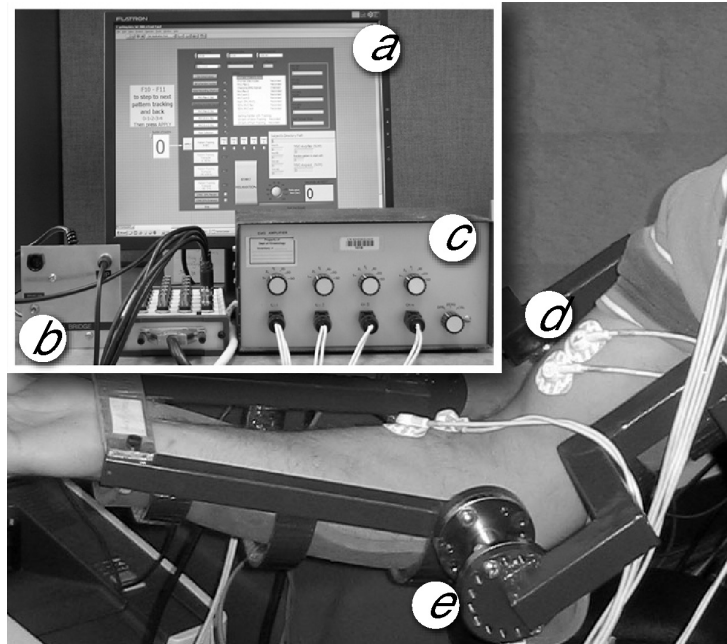
Figure 4.1: A subject at experimental apparatus. a) Software interface. b) Torque amplifier. c) EMG amplifier. d) Surface EMG electrodes. e) Torque sensor. Trials of isometric elbow torque were either constant at rest and maximum, or changing stepwise according to random patterns. All trials were performed at an elbow angle of 135°.

The subjects' applied torque was collected along with the 4 channels of bipolar EMG signals. These were fed to a 16-bit data acquisition card (National Instruments, PCI-6221) at a sampling frequency of 1 kHz. EMG signals were used in another study (of modeling torque generation), but were examined here to avoid muscle fatigue. The torque signal was amplified using a full bridge amplifier (Entran$^{\textregistered}$ PS-A, calibration was performed once with amplifier included, Fig. 4.1-b). Software user-interface was written in LabVIEW$^{\textregistered}$8.0 (Laboratory Virtual Instrumentation Engineering Workbench) . The software interface (see Fig. A.2) provided the experimenter with online information about the acquired signal facilitating different stages of the experiment and provided the subject with real time visual feedback of the applied torque along with the target torque pattern which the participant should follow.

4.3.3 Procedure

Subjects gave informed consent to experiment procedure which was approved by Office of Research Ethics at the University of Waterloo. For the PD patients, anti-Parkinsonian medication was withheld for a minimum of 12 hours (Off condition) and UPDRS was administered by a movement disorder specialist before the experiment session. For the severely affected patient, the experiment was repeated after two hours post administration of medication. In each session the subject sat at the experimental apparatus and performed the experiment with both hands, one at a time, and with a short break in between. For the rest of the participants, the experiment was done in one session and only on the dominant hands. Before each data collection session, noise signal was recorded (2-sec) for session-to-session comparisons. Two Maximum Voluntary Torques (MVTs) were collected, from the limb under study, in flexion, each of 5-sec duration and with a 2-minute rest in between to avoid fatigue. One 5-sec rest segment was also recorded to analyze rest tremor. Then main data collection was carried out in 3 trials of 40-sec each. In each trial, the subject attempted to exert torques according to a pattern that was randomly chosen from a group of patterns displayed on the computer monitor (Fig. 4.2). It should be mentioned that the healthy participants' data was adopted from an experiment on biofeedback effects on torque generation. Therefore, the procedures had minor differences. For PD patients, two MVTs were also collected in the extension direction. Each pattern, for PD patients, included ± 50%, ± 20% and 0% MVT (or rest) intervals of 8-sec each. For the healthy subjects, the patterns included 10-20-30-40-50-60-70% MVT in the flexion direction. Only 20% and 50% flexion MVTs were used for the presented comparisons in tremor during tracking.

4.4 Data Processing and Analysis

For tremor analyses, segments of 2-sec long were chosen from the most steady parts of the rest and MVT trials, by visual inspection. This was done to have a true rest and to avoid motion artifacts. Similarly, for tracking trials, steady segments of 4-sec long were chosen. All the analyses were done off-line using MATLAB$^{\circledR}$2007b (MathWorks). The power spectrum of EMG signals of all muscles were checked for possible fatigue. Noticeable sign of fatigue (a considerable downward shift in the frequency components of EMG [110]) was not observed in any of the trials. Before working with the torque signals, rest torque averages (weight of the upper arm at rest) were subtracted to account for gravitational components. The details about signal processing steps are described in Section 3.6. Briefly,
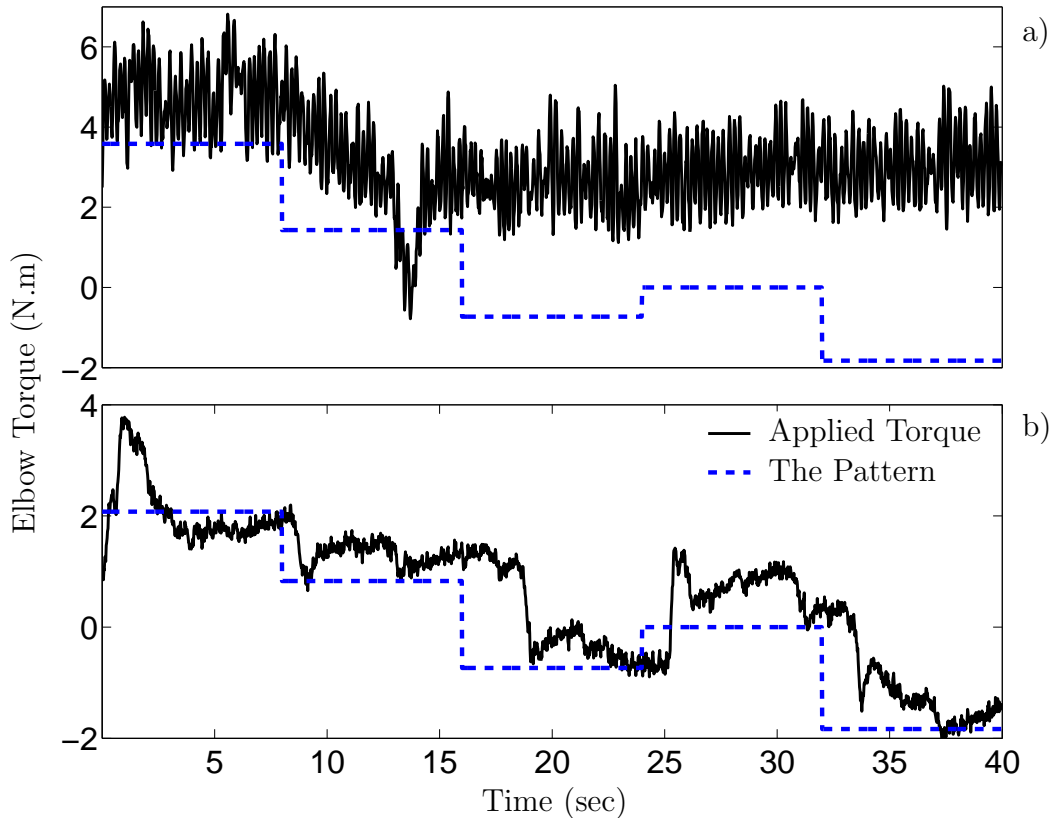
Figure 4.2: Tremor in isometric elbow torque while the severely affected patient is tracking torque patterns. a) Off medication, b) On medication.

to find the tremor, the DC value was removed from the signal. The signal was padded symmetrically with an appropriate length at the ends to eliminate the transient effects of filtering. A band-pass filter (discrete-time FIR filter using a least-squares minimization error) in 3-17 Hz range was used to obtain all tremor related fluctuations in the torque signal. For each trial (whether rest, target tracking, or MVT), the power spectral densities (PSDs) for the tremor signals were estimated after they passed through the aforementioned filter. The resulting signals were then digitally differentiated to provide the torque-rate signals and their PSD were estimated. The main advantage of such a differentiation (using torque-rate dT/dt instead of T) was suppressing non-tremor low-frequency oscillations in torque (or force) signals and is discussed more in [58, 30].

To compare tremor amplitudes, three bands were considered and the corresponding band-pass filterings were applied on all the signals (the choice of the bands are described in Section 2.5.2). RMS values in 3-17 Hz band represented the amplitude for the total

41

tremor. RMS values in 3.5-6.5 Hz band (B2) represented the tremor amplitude in PRT range and RMS values in 7.5-16.5 Hz band (B1) represented the tremor amplitude in EPT range. It should be noted that 6.5-7.5 Hz gap was intentionally considered for the two band-pass filters not to overlap in transition bands. The relative amplitude, for each band, was also defined as the ratio of RMS amplitude in that band to the total RMS amplitude. Boxplots were used as graphical means of summarizing the data through five numbers (of smallest and largest observations, lower and upper quartiles, and median) and possible outliers. Independent-samples t-test was used in reporting the difference between the groups and conditions.

4.5 Results

Total tremor amplitudes were compared in boxplots of Fig. 4.3 for all the participants and all the conditions (rest, target tracking, and MVT). For PD patients with typical tremor presentation, the rest tremor was significantly higher than those of healthy people (t=3.0, p=0.018); while tremors during target tracking and MVT were comparable to those of the healthy participants (t=1.1, p>0.05; t=0.2, p>0.05). For the severely affected PD patient, total tremors were much higher than the other two groups in all conditions.

To investigate the contribution of tremors in each frequency band (B1 and B2) to the mentioned total tremor, relative RMS amplitudes were calculated. These ratios were found for each tremor signal and the results were shown in Fig. 4.4. The healthy participants demonstrated a tremor which was predominantly in EPT band (B1) at rest (t=5.1, p<0.001); the contributions of B1 and B2 were comparable for target tracking and MVT conditions. For PD patients with typical tremor presentation, contributions of the two bands to total tremor were comparable at rest and in target tracking. However, in MVT they demonstrated tremors that were predominantly in EPT band (B1) (t=5.8, p<0.001). The severely affected PD patient, exhibited a tremor which was primarily in PRT band (B2) and the band dominance did not change over the conditions.

Because the severely affected patient had an excellent response to dopaminergic medication, more details were investigated for this participant on both hands and before and after medication. The total score on the UPDRS (motor section III, which was mainly in tremor items) was 32 off and 21 on medication. Dopaminergic medication effect was evident on the tremor-dominant (TD) hand. Before medication, the subject was almost incapable of following the pattern presented on the monitor, because of a high amplitude tremor of oscillation at 4.5 Hz whereas on medication, tracking was improved in following the same
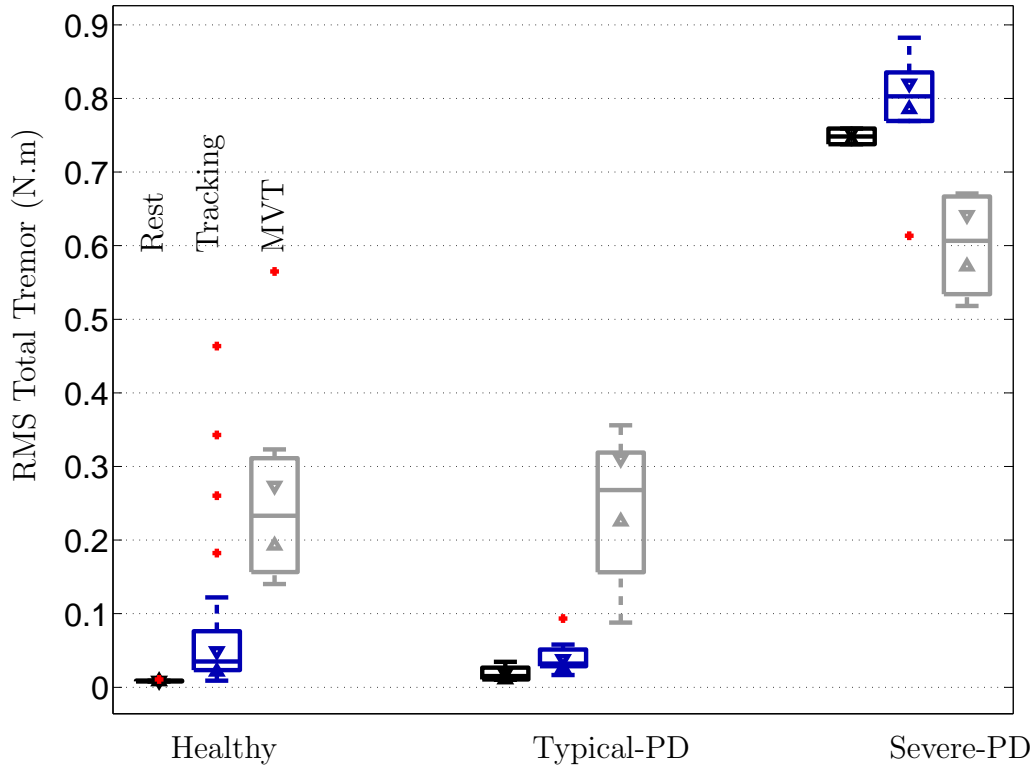
Figure 4.3: Comparison of total tremor amplitudes for all groups of participants and all three conditions.

pattern with smaller amplitude of oscillation at a higher ($\approx$ 9 Hz) frequency. In the TD hand, off medication case, EMG from antagonist muscles exhibited alternating pattern of bursts and had peak frequencies that often closely followed the peak frequency in tremor PSD. Tremor peak frequency at rest was 3.9 Hz and during action ($\pm 20\%, \pm 50\%$, and $\pm 100\%$ isometric MVT) was between 4.1-5.1 Hz. RMS amplitude had a range of 0.5-0.9 N.m, and was only significantly different between tracking and MVT (t=3.2, p=0.012).

For the same (TD) hand on medication, the rest tremor frequency increased (compared to off medication) to 8.2 Hz and action (tracking and MVT) tremor frequency, which was between 7.2-10.5 Hz, also exhibited a significant increase (t=11.7, p<0.001). Tremor amplitude was significantly (t=18.7, p<0.001) reduced over all conditions to 0.02-0.06 N.m and was not significantly different among the conditions. Fig. 4.5 presented sample PSDs for both hands (TD a-b, NTD c-d) and both medication states. Peak frequencies and RMS amplitudes were also compared in boxplots in Fig. 4.6 among hands, conditions, and
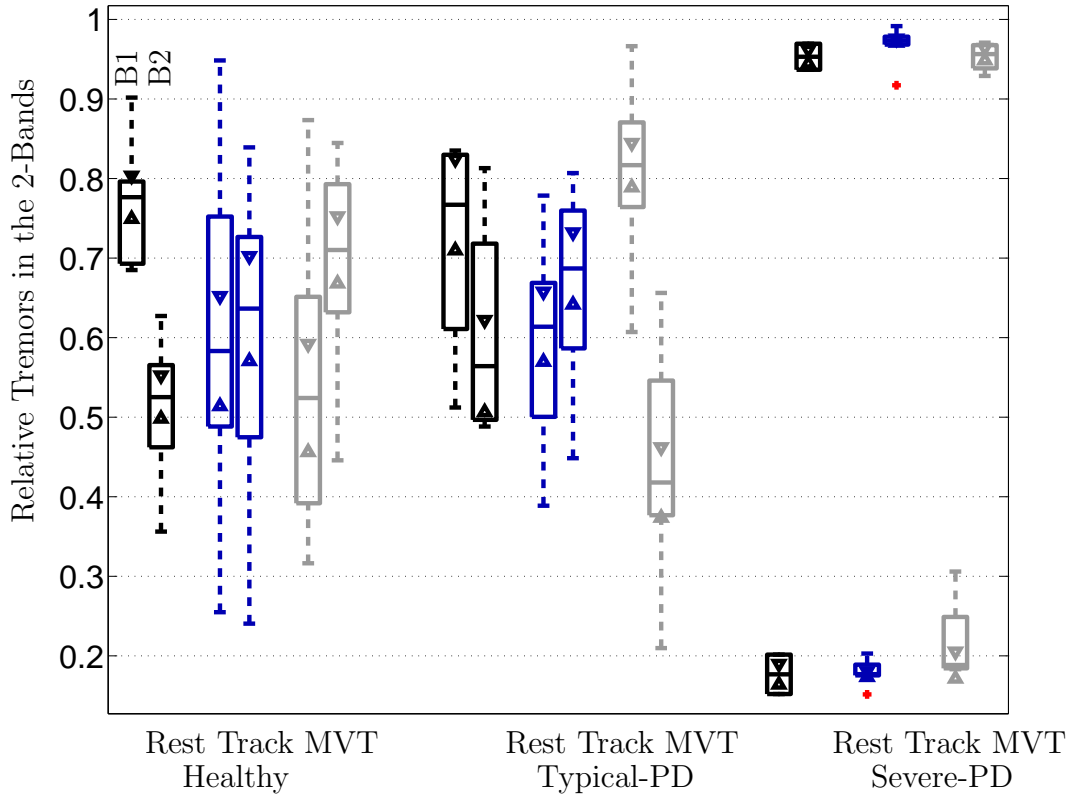
Figure 4.4: Comparison of relative tremor amplitudes in two bands of PRT (B2) and EPT (B1) for all groups of participants and all three conditions.

medication states.

For non-tremor-dominant (NTD) hand, while off medication, rest tremor PSD exhibited two almost equal peak frequencies (Fig. 4.5-c, one in B1 and the other in B2 band) with RMS amplitude of 0.03 N.m. In action, tremor frequencies were between 7.7-11.8 Hz and their amplitudes were between 0.03-0.12 N.m. The amplitude at MVT was significantly higher compared to rest and tracking tremor (t=7.7, p=0.005; t=4.6, p=0.002). After medication the rest tremor's peak frequency was 10 Hz and those of action tremor were between 8.7-12.7 Hz. The tremor amplitude for rest was 0.02 N.m and those in action were between 0.02-0.13 N.m (only significantly higher in MVT, t=5.0, p<0.001).
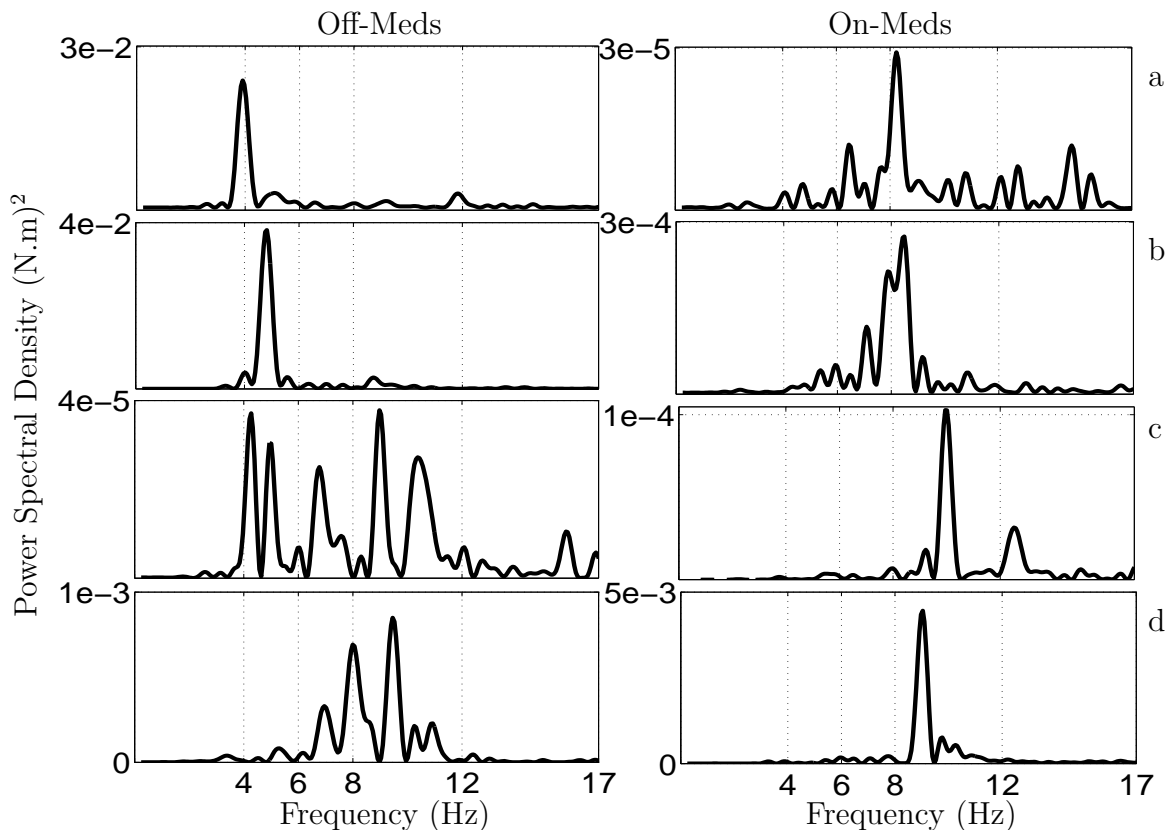
Figure 4.5: Comparison of tremor signals' PSDs (from TD hand's torque rate signals, rows a-b) and NTD hand (rows c-d). Left column shows the results off medication and right column is the results of similar trials after medication. Rows a) and c) correspond to rest trials and rows b) and d) correspond to one of the MVT trials (flexion #2) of severely affected patient.

4.6 Discussion

4.6.1 Elbow Tremor Amplitude

The highly affected patient had very strong action (during tracking and MVT) and rest tremors in tremor-dominant elbow while off medication. These tremors were larger than those of all other participants in all conditions. The two typically affected patients, off medication, exhibited elbow tremors that were comparable to the healthy participants in action, but had significantly higher amplitude at rest. Therefore, at rest, both groups of PD patients had significantly larger elbow tremors compared to the healthy participants. In other words, the results were capable of affirming hypothesis H_1 only at rest. For the

45
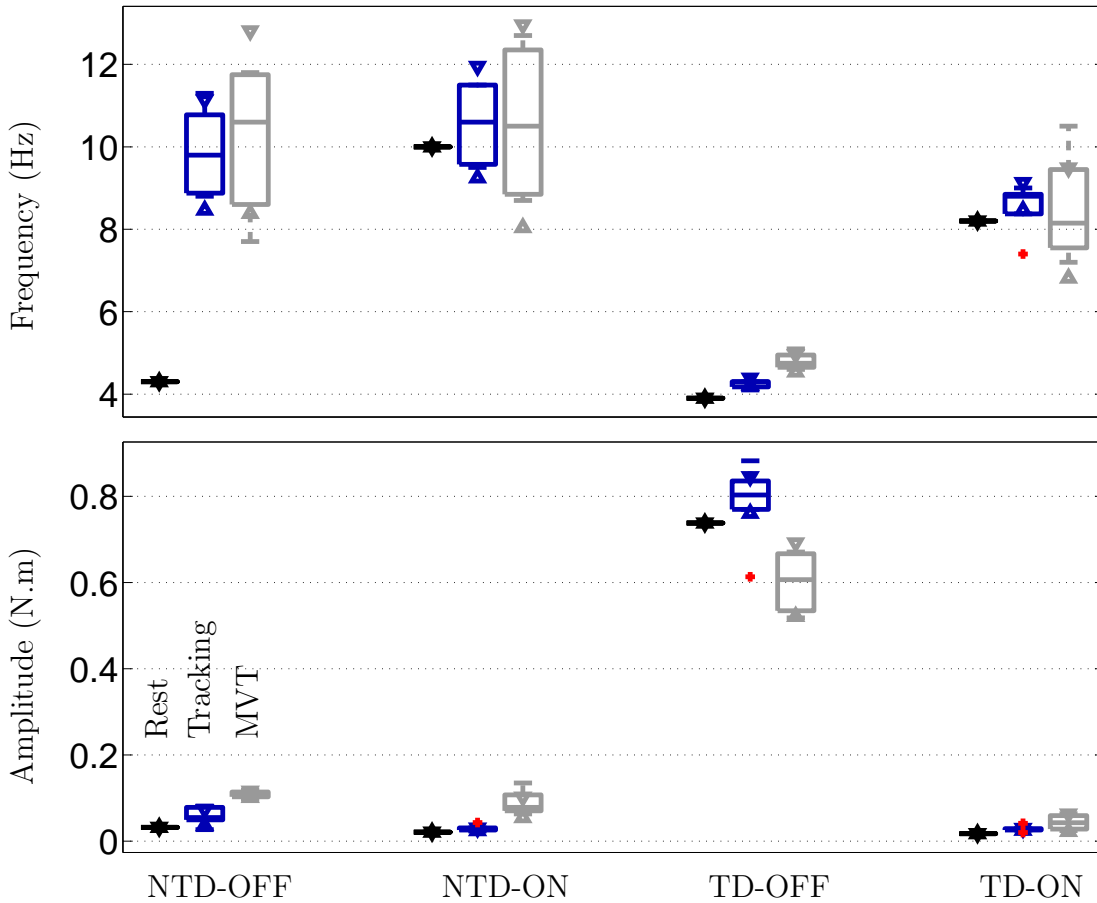
Figure 4.6: Frequency and amplitude of tremors in all 4-cases of patient #3: TD and NTD hands, off and on medication. a) represents peak (or dominant) frequencies for each trial's PSD. b) represents RMS amplitude of all tremors in 3-17 Hz range.

other conditions, the typically affected patients did not exhibit significantly larger tremors.

4.6.2 Coexistence of PRT and EPT

To examine the contribution of tremors in EPT and PRT frequency bands (B1 and B2 respectively) to the total tremor, relative RMS amplitudes were calculated. For the healthy participants, at rest, tremor components were mainly in EPT. In action (during tracking and MVT) components in both bands were comparable. This was an indication of a wide-band physiological tremor (contrasted to enhanced physiological tremor with a con-

centration of energy or a sharp spectrum peak in B1). In patients with typical tremor presentation, at rest and in tracking, components in both bands were comparable. This was contrary to expected PRT band tremor, particularly at rest. At higher levels of muscle activation (MVT), this group exhibited tremors that were predominantly in EPT band. Therefore, for this group of participants tremors in both bands coexisted over conditions.

For the severely aflicted patient, for TD hand off medication, tremors in PRT band had the dominance over all conditions. However, sample tremor PSDs usually presented sharp peaks in EPT unless when stronger PRT peaks obscure them. Even in those cases when the strong PRT components were disappeared with expected excellent response to medication, the remaining components were concentrated in PRT band. Consequently, for this patient as well, EPT tremors played a significant role.

Therefore, the results of this study supported the coexistence of PRT and EPT for PD patients. However, the two tremors' relative amplitude depended on the severity of the disease, medication state, and muscle activation level. For example, EPT tremors were not comparable to PRT tremors for the severely affected patient in off medication. In other words, the results affirmed hypothesis H_2 only for the PD participants with typical presentation.

4.7   Conclusion

While the majority of tremor-affected Parkinsonian (PD) patients present rest tremors, which is not considered highly disabling, a portion of these PD patients also demonstrate action tremors that interfere with their daily lives. Two main considerations in designing an orthosis that aims at suppressing the tremor, are the frequency bands of the tremor and the joints tremor affects.

The purpose of this pilot study was to investigate the elbow tremor at rest and in action (isometric). Another objective was to examine the hypothesis of coexisting PRT and EPT at typical and high levels of PD tremor presentation. The motivation for the study was the diverse previously reported results on PD action tremor and the outcome would be beneficial in designing tremor suppression orthosis for PD patients.

Nine subjects,which included six healthy people, two PD patients with typical tremor presentations, and a PD patient with severe tremor of not only in the fingers and wrist, but also in the elbow, participated in this study. The severely affected patient displayed the need for tremor suppression in action as well as when at rest. The study focused on

uncommon elbow tremors and demonstrated that, for typically affected patients, tremor amplitudes were comparable to those of healthy subjects, but the frequency distribution of the tremors were different at high levels of elbow torque. For the severely affected patient, both tremor amplitude and its frequency distribution were different at all levels of elbow torque.

The study further investigated the tremors in two bands of frequency on both hands of the highly affected patient before and after medication. Power spectrum and tremor amplitude comparisons revealed that, for typically affected PD patients, both tremors coexisted (similar to a study on subclinical finger tremors [70]). However, unless they were at the maximum level of muscle activation (MVT), the action tremors were not merely enhanced physiological tremors (as suggested by [30, 107, 20, 32, 64]). Furthermore, for the severely affected patient, action tremor on the affected elbow was mainly in classic PD rest tremor band, and not in physiological band. It meant that, depending on the level of tremor severity (or maybe on the relative strength of tremor mechanisms in each band), the elbow action tremor could be in either band. However, in this study, only the severely affected patient needed tremor suppression; and it was in classic PD band.

Chapter 5

PD and Physiological Hand Tremors: Effect of Loading During Posture

5.1 Introduction

Parkinson's disease (PD) tremor has been commonly identified as a resting tremor in one hand and then, with the progression of the disease, becomes bilateral and spreads to the arm/leg/jaw. It usually appears as a pill rolling movement of fingers, extension-flexion in wrist and pronation-supination of forearm [92].

The consequence of maintaining a body limb in a steady position is a rhythmical oscillation called physiological tremor [111]. It happens to healthy population and can be seen in any limb and any situation. Physiological tremor comprises of both central and peripheral origins ([36],[74]) from which the latter is the main component and is load dependent (both in frequency and amplitude). In healthy subjects, small to moderate loading is proven to lower the frequency of the main component in tremor [76]. Larger loads (among other factors like fright and fatigue) enhance the reflex mediated oscillation and produce considerably larger tremors.

Hand movements in the frequency range of 3-17 Hz (Chapter 2) has been considered as total tremor in this study. Classic PD rest tremor has been reported in a small portion of this range (3.5-6.5, 3.5-7, 4-6, and 4-7 Hz Chapter 2), and the 3.5-6.5 Hz frequency range is considered to be the PD band, B2. To have non overlapping ranges, the remaining range of 7.5-16.5 Hz is considered to be the physiological band, B1. The central component of physiological tremor (8-12 Hz, which is also the same as the mechanical-resonant compo-

nent for the wrist), is also filtered as B3 to compare its role with the broader physiological band. Therefore, the extracted tremors are further filtered into the three bands. Fig. 5.1 represents the three bands.
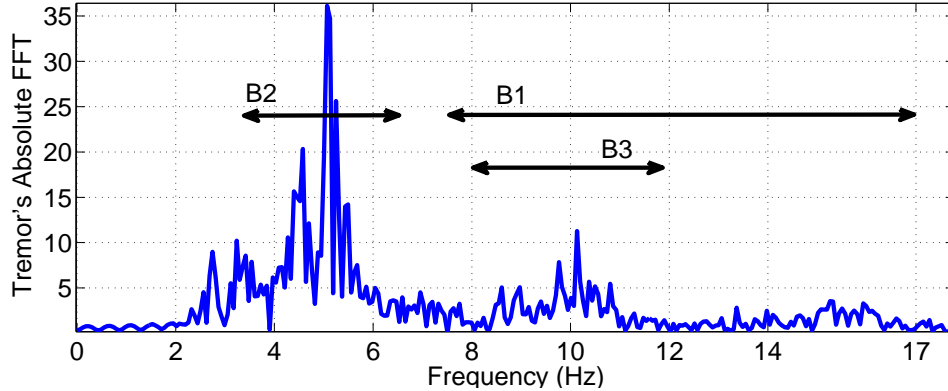
Figure 5.1: Fast Fourier Transform (FFT) presents frequency components and the three bands of interest for a sample tremor signal.

Unlike PD rest tremor, reported results on action [1] tremor are diverse in response to dopaminergic medication ([23],[61],[24]), in the reported frequency of tremor ([32],[30],[20], [34]), in the medication effect on different frequency components of the tremor spectrum ([33],[30]), and in being similar or different from classic resting tremor ([36],[33],[20]). Finding frequency components in a range higher than classic PD band (B2), some studies ([31], [30],[83],[87],[112]) suggest that PD action tremor is in fact enhanced/exaggerated physiological tremor. The lack of generality in the results of studies on action tremor makes the efforts of treatment difficult, and is a barrier for mechanical methods of suppression.

Loading combined with observation of tremor frequency components inside and above the classic PD frequency band at various loading levels (0-100% MVC), have been considered in the study. For PD patients, relative dominance between the bands in various loading conditions, would be of interest. Comparison between PD participants and healthy controls in the PD band is expected to provide significantly larger tremors for the PD patients. Similar results in the physiological band, would suggest (enhanced) physiological tremor mechanism as another substantial mechanism for PD population. Finally, comparing dopaminergic medication's effect on each band, can reveal if the tremors in the two bands are originally related (react similarly to medication). In this chapter, an experiment is designed to investigate these comparisons on the hand tremors of both healthy and

---

[1]including postural, isometric and kinetic

50

PD populations. In the experiment, enough rest between the trials is considered to avoid fatigue.

To generalize the diverse results of PD tremor, researchers have frequently resorted to sub-groups or categorizations based on various factors (Chapter 2). Furthermore, contradicting results of minimal ([72, 92, 49]) or significant ([67, 30]) effect of loading have been reported. In this study, to generalize the loading effect, two methods of categorization are used to find distinct trends in these sub-groups of PD. Patients are first categorized into subgroups according to their severity of tremor at rest and/or in posture. Subsequently, automatic classification or cluster analysis are utilized and the results are compared.

Tremor, especially in the hand with various degrees of freedom in movement, is not one dimensional. Furthermore, there is not a proven dominant direction in PD tremor. For example, a study by Meshack and Norman [49] on the tremors of PD hand in horizontal posture, revealed that about 60% had larger tremors in vertical direction than horizontal. To avoid loss of information, tremor signals are collected in three dimensions. This would also help investigating tremor's possible directional dominance in the both PD and healthy populations.

The effects of loading are studied with respect to tremor amplitude and frequency measures in each frequency band of interest. The two commonly used amplitude measures have been tremor's Root Mean Square (RMS) energy and the spectrum's peak magnitude ([32, 68, 58]). The spectrum's peak frequency is the only examined frequency measure. The following section proposes the main hypotheses on PD hand tremors and the specified frequency bands. These hypotheses are subsequently evaluated.

5.2   Hypotheses

In this section, the main hypotheses of this study are presented:

H_3: PD Tremor is not uniformly distributed along three dimensions.

H_4: Loading (up to MVC), should result in more than one clear trend in tremor amplitude changes. It means that in examining the loading effect categorization is necessary and generalization should be avoided.

For PD patients, the co-existence of classic PD tremor and (enhanced) physiological tremor mechanisms can be evaluated in the form of three sub-hypotheses:

H_{5_1}: Physiological tremor is not the same for all PD patients and healthy adults. Some PD patients will have higher tremor energy in the physiological band (B1) as well as in the PD band (B2), compared to healthy people.

H_{5_2}: Tremor spectrum will have comparable peaks, in B1 and B2, for some of the patients; and for these patients, comparable peaks will remain present for most of the conditions.

H_{5_3}: Increasing the amount of load up to Maximum Voluntary Contraction (MVC), significantly changes the amplitude of hand tremor in B2, for those patients who have higher than normal (than those of healthy controls) energy in B1.

H_7: If a tremor responds to medication, reduction should be seen only in the PD band (B2).

5.3 Methods

5.3.1 Participants

Twenty subjects (n=20) with idiopathic Parkinson's disease (PD) (Table C.1, age 67.8 ±9.6 years, nineteen right-handed, eight women and twelve men) were compared with fourteen (n=14) age-matched (t(32)=0.50, p=0.6) healthy control subjects (Table C.2, age 66.3 ±6.9 years, all right-handed, eight women and six men). Participants were excluded from the study if they had corrected vision or hearing, history of stroke, or upper limb injury. However, they were not excluded based on any PD specific symptoms. Each subject provided informed consent to participate in the experiment. Ethical approval was granted by the Research Ethics Boards (REB) at UW, Wilfrid Laurier, and Ryerson Universities (ORE # 13614, # 1687, and #2008-221, respectively). All PD patients had a clinically confirmed diagnosis from at least one licensed neurologist and were recruited from a database at the Sun Life Financial Movement Disorders Research and Rehabilitation Centre (MDRC) at Wilfrid Laurier University, Canada. Healthy volunteers were recruited from family and friends of PD patients. Participants in both groups were also screened for dementia (loss of cognitive abilities) using the Modified Mini-Mental State Examination (3MS). None of the participants exhibited signs of memory or cognitive impairments. In addition, the two groups were not significantly different in this evaluation (Healthy: 96.4 ±3.8, PD: 94.4 ±4.7, t(32)=1.16, p=0.25).

Healthy participants were asked to report on their medication; three were taking none or just vitamins; one was taking a beta-blocker for hypertension (atenolol); none of them were taking well-known tremorgenic drugs (lithium, neuroleptics, sympathomimetics, tricyclic antidepressants, or methylxanthines according to [80]). Furthermore, no neurological impairments or disorders, or drug-induced tremors were reported. For the healthy control group, limb was matched based on tremor dominant hands of PD group. In the PD group, Table C.1, 60% of tremor dominant hands (hereafter called TD hands), were the same as dominant hands. Similarly, 60% of the dominant hands were randomly chosen for the healthy control group for comparisons. These hands were considered as the matched hands (MH).

5.3.2 Experimental Setup

The experiment was performed using two different experimental setups in order to cover a full range of loading: Tables A (High loading) and B (Low loading, Fig. 5.2 a-b), each equipped with similar forearm constraints and height adjustable chairs. The constraints (see also Fig. 3.1-b) had four primary purposes: They provided a comfortable arm rest without hands touching the tables.

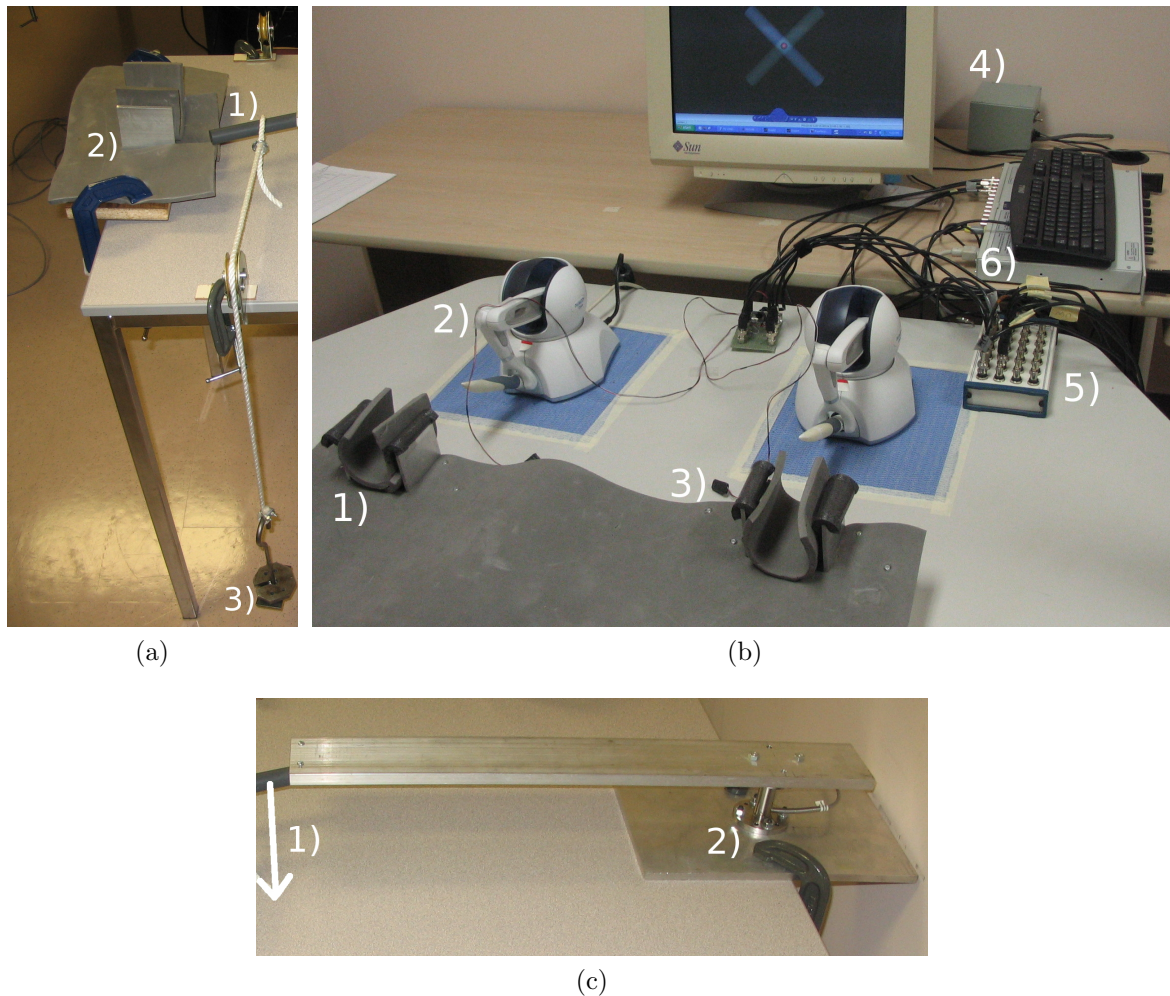(a)   (b)

(c)

Figure 5.2: Experimental setup: a-1) Stylus, 2) Forearm constraint 3) Weights. b-1) Forearm constraint 2) Omni device 3) Accelerometer 4) Torque amplifier 5) BNC connector block 6) EMG amplifier. c-1) Applied force, 2) Torque sensor.

They limited wrist pronation/supination, while allowing ulnar/radial deviation for consistent rest or elevation to posture, plus full wrist flexion/extension (see Chapter 7). They prevented transmission of tremors in one hand to the other and directed the loading effect to the wrist flexor muscles. Wrist flexion forces were measured by a reaction torque sensor (TQ301-400, OMEGA ^{TM}Technologies, 45 N-m, Accuracy Class: $\pm 0.2\%$ full scale, Fig. 5.2-c). The torque signal was amplified by a strain gage amplifier before being recorded (DMD-465WB OMEGA ^{TM}Technologies, Fig. 5.2-b). Two PHANToM ^{TM}Omni devices (SensAble Technologies Inc.) were used to apply low forces according to a pattern on the hands and to measure hand position during low-force trials. At Table B, the Omni devices were connected to a personal computer through a Firewire adapter card and programmed in Simulink® R2008b (The MathWorks^{TM}, Natick, MA, USA) using QUARC® Blocksets (QUANCER Inc., ON, Canada). PHANToM haptic devices were used to apply different (constant, damping, and inertial) loading in various simulated situations (of posture and movement), but in the current study, only constant forces in posture were investigated.

For higher levels of loading, comparable to each subject's Maximum Voluntary Contraction (MVC), a system of pulleys and weights was used at Table A, with a stylus. For consistency the stylus was made similar to that of the haptic device in size and weight (Fig. 5.2-a). To measure the tremor, an accelerometer was attached, with a medical tape, to the lateral part of each index finger, between the Metacarpophalangeal joints of the thumb and index finger on each limb (Fig. 3.1 also shows the axes of measurement). Accelerometer attachment and the hand situation in which they were taped were kept consistent among all participants. Accelerometers (1.3 g, not including the heat-shrink casing and wires' effect) remained fastened for the whole duration of the experiment to provide consistent recording during trials. The tri-axial accelerometers used for the experiment were DE-ACCM3d, Dimension Engineering^{TM}, pre-amplified for improved signal-to-noise, with a sensitivity of 333 mV/g, a minimum range of $\pm 3g$ (g=acceleration of gravity), and a bandwidth of 500 Hz. Accelerometers were used due to the haptic devices' lack of resolution for measuring milder tremors by last joint encoder, as verified in our pilot work. The pilot study also revealed that some of the tremor might be lost because of imperfect hand-stylus coupling (a very tight grip would affect tremor, and was not demanded from the participants). For each trial, the signals of position, force, acceleration, and EMG were collected at a sampling rate of 1000 Hz. Force, acceleration, and EMG signals were acquired with a 16-Bit data acquisition card (NI PCI-6221, NATIONAL INSTRUMENTS^{TM}) through a shielded BNC connector block (Fig. 5.2-b).

5.3.3 Procedures

Each participant performed two tasks at Tables A and B respectively, Fig. 5.2. These will be referred to as Task A and Task B. PD patients were tested in two consecutive sessions on the same day. Dopaminergic withdrawal occurred at least 12 hours before the first session (17 ±7.7 hours). At the completion of first session, normal dosage of medication was self-administered and after approximately one hour (78 ±11 min), the second session was performed. Evaluation on the motor sub-section of Unified Parkinson's Disease Rating Scale (UPDRS) was performed before each experiment session began, by a movement disorder specialist.

For each participant, before the first session began, skin was prepared, and EMG electrodes were placed over the flexor and extensor muscle groups on both forearms. Accelerometers were attached to both hands using medical tape. Prior to each task, the goal of the task was carefully demonstrated to the subject and practice trials were performed when necessary. To perform each task, the subjects put their forearms in the constraint in a neutral position (sagittal plane). The height of the chair was adjusted such that the subject was able to sit straight with an elbow angle of approximately 120° flexion. For Task A, one hand was tested at a time while for Task B, both hands were tested together. The weights needed for 20, 40, and 60% MVC loading in Task A were rounded to 0.5 *lb*. The loading (either by haptic devices or by weights) was applied to the hand through the stylus.

Task A

In the first four trials at Table A, the participant's MVC was measured in wrist flexion for each hand (two trials per hand that were separated by 90-sec of rest). In each trial the participant was encouraged to apply and keep maximum force, for 5-sec. The average maximum force in the two trials was considered as that hand's MVC. One example of an MVC trial is presented in Fig. 5.3.

The participant grabbed the stylus and applied the maximum wrist flexion force with supported forearm on the apparatus (shown in Fig. 5.2-c). The two MVCs were used to calculate the weights (20, 40, and 60% MVC) for the next six trials per hand. For each hand, the six trials comprised of two repetitions of each three loading levels in a semi-randomized order. Loading through weights, pulley, and stylus is presented in Fig. 5.2-a. Each trial started when the loaded hand was already in posture. Only the first stationary
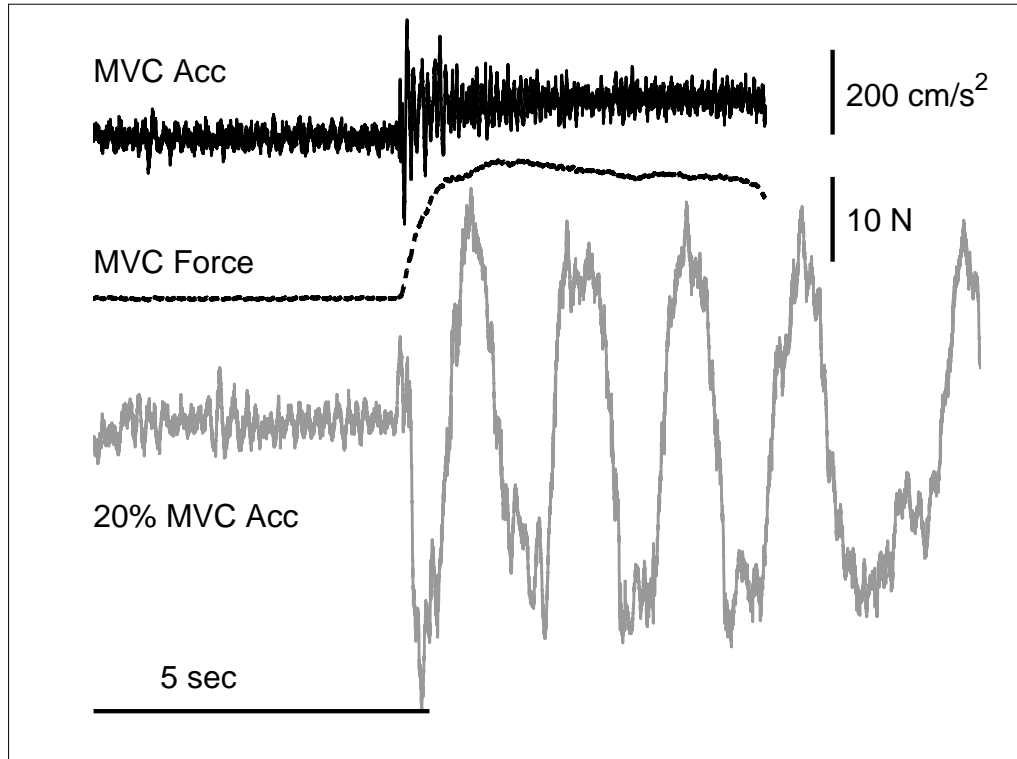
Figure 5.3: Sample MVC and 20 %MVC trials (bottom) for PD patient #9.

part of the trials (4.2 sec, Fig. 5.3) was used in the current study. The rest of the trial, involving wrist movements, was stored for future analysis (see Chapter 7).

Task B

At the completion of Task A, participant moved to Table B (Fig. 5.2-b) while keeping the accelerometers attached. Task B involved about 30 minutes of coordinated movements with Omni devices followed by the two trials of loading the hands in posture. Each trial lasted 86-sec following a rest interval of 60-sec. The participant was instructed to start the trial with the hands relaxed, and then elevate the hand to *no-load-posture* (wrist moving to neutral radial/ulnar position; the tip of the stylus would be elevated 5-10 cm) on hearing an auditory cue. After the hands were elevated to posture, there was a long delay before forces were applied on the hands (25-sec for the right-hand, 40-sec for the left hand) which was intended to capture re-emergent tremors in posture ([68]). The applied forces on each hand (Fig. 5.4) had a semi-random order and were chosen to contain symmetric and non-
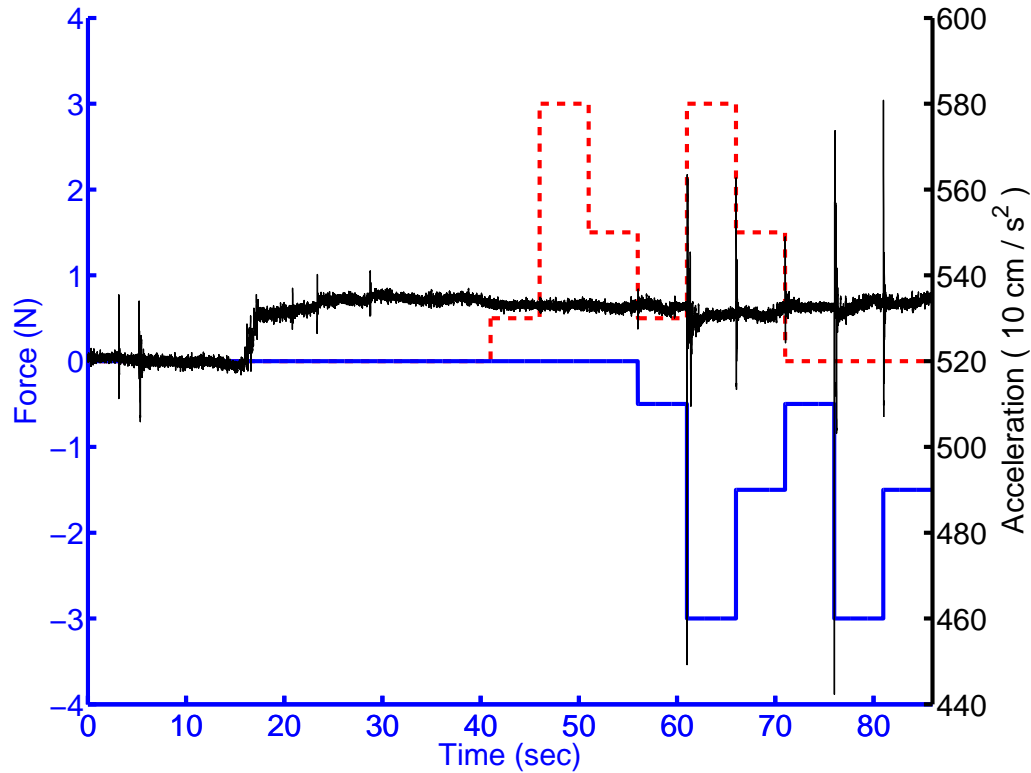
Figure 5.4: Applied force and recorded X-acceleration on the left-hand (solid lines), and applied force on the right-hand (dashed) for PD patient #8, Off-medication.

symmetric parts (to study the effect of contralateral loading on tremors as well). In these two trials, Segments of rest, *no-load-posture*, and loading at 0.5 N, 1.5 N, and 3 N were collected. The haptic devices provided the loading against flexion in each wrist. These three levels were constant forces of 0.5, 1.5, and 3 N, and each lasted for 5-sec. During the trials, participants were free to look at their hands, but no other source of visual feedback was provided.

5.3.4 Data Analysis

Force, position, and acceleration signals were all sampled at 1000 Hz and stored for off-line processing and analysis. In the analysis of recorded data, sections of data were chosen in a way to avoid any transient effect caused by force application or displacement. Such segments along with the involved signals are shown in Fig. 5.5 for a trial with low forces

for the TD hand of a PD patient.
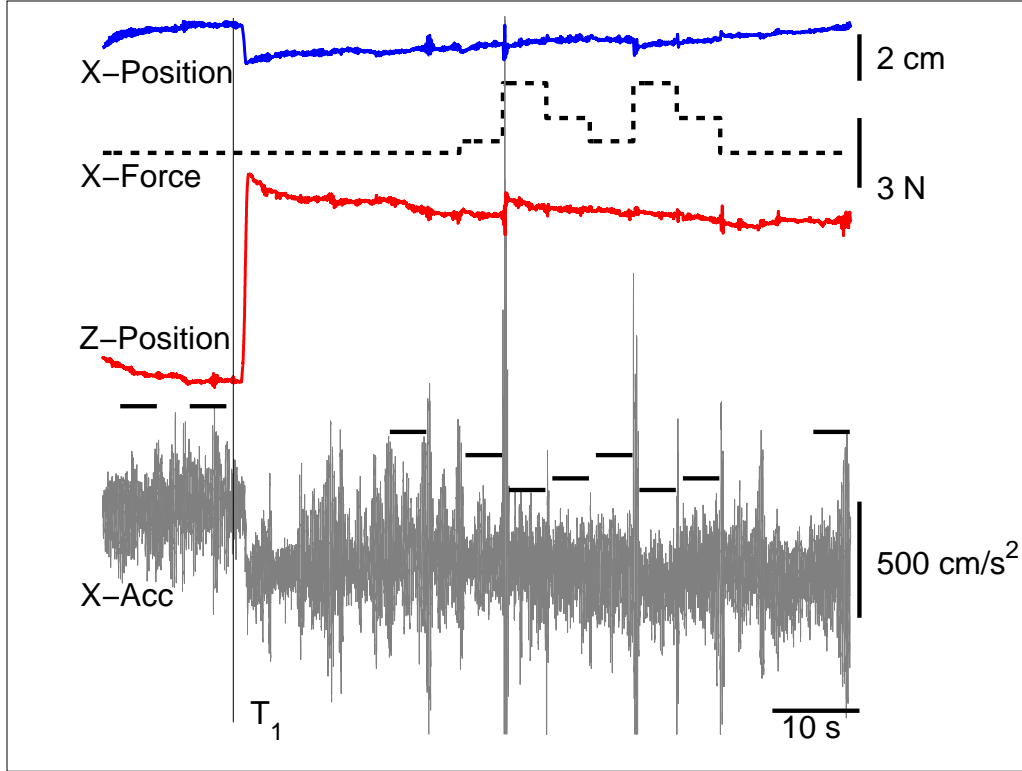
Figure 5.5: Loading with low forces on the TD hand of PD patient #17, Off-medication. T_1 represented the auditory cue at 15-sec. Horizontal lines, transient-free sections.

Tremor was analyzed in 9-conditions of rest, *no-load-posture*, loading with 0.5-1.5-3 N, and 20-40-60-100% MVC. After visual examination of recorded data, 4.2-sec was chosen as transient-free data segment to maintain a consistent time frame to analyze all data. All comparisons between conditions were performed on data with such a length and were the same for every participant. To increase accuracy, two segments of data were analyzed for each of the 5-conditions (rest, posture, 0.5, 1.5, 3 N loading, Fig. 5.5) in the two trials involving the haptic devices. However, due to the length of trials, only one segment could be analyzed for the 4-conditions of loading with 20, 40, 60, and 100% MVC (Fig. 5.3). Root Mean Square (RMS) value and the peak magnitude in power spectrum of the acceleration signal, were used to measure tremor amplitude. It should be mentioned that because the RMS value of a signal filtered in different frequency bands can represent signal's energy in each of the bands, term RMS *amplitude* implies RMS *energy* in this study. The peak frequency in power spectrum of the acceleration signal was used as the frequency measure.

The steps for processing the data is described in Chapter 3. Briefly, every collected signal underwent the same process of tremor extraction, padding, and filtering. The measures were then calculated for each segment. All processing was done through custom written codes in MATLAB® R2008b (The MathWorks™, Natick, MA, USA).

For the measures in the spectral domain, after finding the spectrum (see Chapter 3), an algorithm searched for the peaks. The number of local peaks in a non-smooth function could be large, and they could be very close to each other. The following algorithm was optimized, using different healthy and PD participants' spectrum, to provide peaks that are separate enough and comparable to the largest peak (without losing the major ones). For each segment, the peaks (maximum of 50) that were above 25% of the largest peak, and were at least separated by 1.5 Hz were sorted according to their magnitude. The three largest peaks were chosen for frequency and amplitude analysis. Out of the three peaks, the frequency and magnitude of the largest in each frequency band of B1 and B2 (if any), was saved for the related analysis. In case all of the three peaks were located in one band (no peaks above 25% of the largest, or such a peak had overall rank of four and below), the peak magnitude of the other band was considered to be zero.

To examine the effect of loading on the frequency of spectrum peak, the change with respect to the rest condition was evaluated for the remaining 8-conditions. For each person, in each of the two frequency bands, spectrum's largest peak frequency for tremor at rest in the same band was chosen as reference. For every condition, over two trials, each participant had 2 or 4 collected data segments (Section 5.3.4). Therefore, depending on the spectrums, for each band and condition, the participant would have zero to four peaks. If one data segment had a peak in one band, was considered in the comparisons of that band (peak data was not necessarily balanced between the two bands). For the reference frequency at rest, in each trial, the average peak from the two segments was calculated for each band (Fig. 5.6). If one data segment did not have a peak in one band, the reference frequency at rest was based on the peak from the other segment. If neither segments had a peak in one band, the reference frequency at rest was chosen as the other trial's reference. If one participant did not have a reference in either trials, in one band, that band's data were not considered in the comparisons.

To deal with the contradictory observations on loading and PD action tremor, separating patients to sub-groups have been tried in the literature (Section 2.5.2). In analyzing the results of loading on tremor, different categorization schemes were utilized, in this study. First, patients were classified according to their tremor severity, which had been used in similar studies [70]. One possible criteria, to assess tremor severity, was UPDRS scores. Three tremor-related sections of the UPDRS on patient's most affected side (items 20-21,
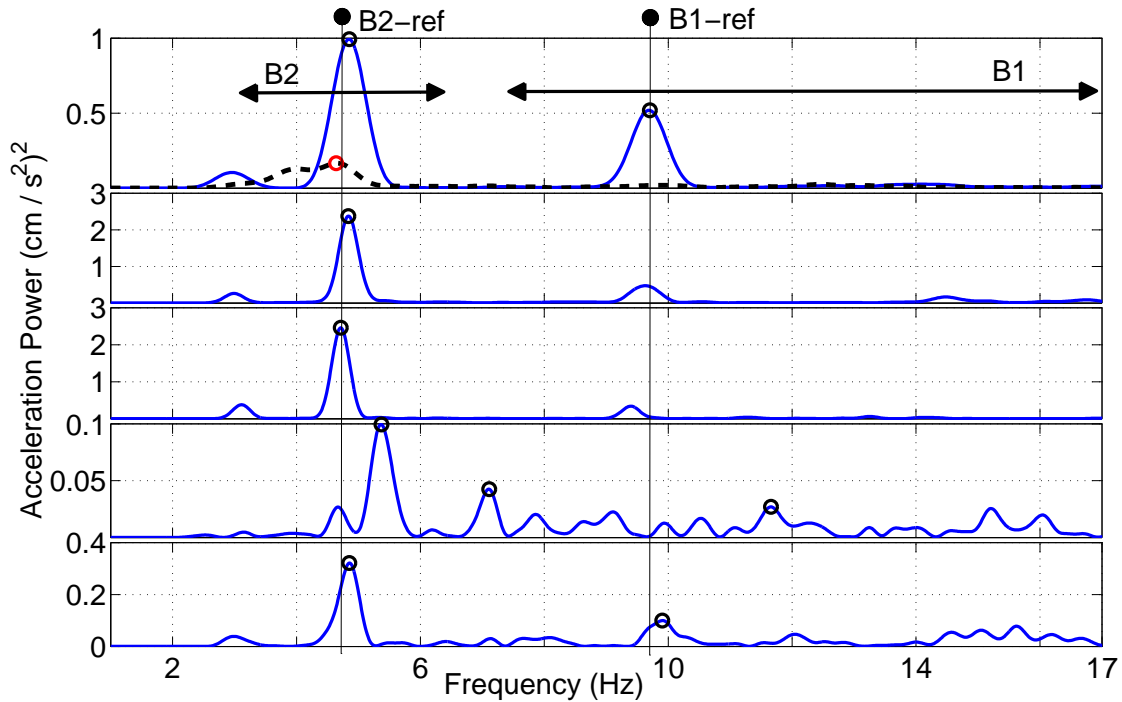
Figure 5.6: The reference frequencies for TD hand of PD patient #6. Top row, two rest segments of one trial, dashed line was from segment-2. The average of the two peaks in B2 and the only peak in B1 were the references for this trial. Spectrums from 4 other conditions (out of 8) were presented in the following rows.

hand-leg's rest tremor, and hand's action tremor), were available from clinical assessments. Likewise, measured tremor during rest and posture were also objective measures of tremor severity without involving loading effect. Therefore, these measures were used to divide PD patients into sub-groups with larger and smaller tremors. The patients whose tremor score were above or equal to the median score was considered to be the group with larger tremor (or visible tremor; scores $\geqslant 2$ in items 20-21 UPDRS considered mild to moderate [113][114]). The remaining PD patients who had less than median scores, considered to be the group with smaller tremors.

Clustering was also proposed as a second method of classification. Cluster analysis or automatic classification is a method of assigning a set of observations into natural groupings or clusters. The objective is that the items in a cluster be similar to each other, but different from the items in other clusters [115]. There are different measures for evaluating dissimilarity (distance) between the items (objects). The correlation between the sequence of data points was the appropriate measure in separating the trends. Consecutive data

points for each patient were tremor's total energy (in 3-17 Hz range), averaged over the two trials, in each condition. The details about the utilized methods on clustering is presented in Appendix **??**.

Statistical analyses were all performed using STATISTICA^{TM}8.0 (StatSoft, Inc.) software. Separate repeated-measures analysis of variance (ANOVA) was used to investigate the effects of direction of analysis (X, Y, and Z), medication, group (healthy vs. PD, and sub-groups in PD as well), and loading on the measures of tremor. Most of the comparisons were between the TD hand in PD, and the matched hand in Healthy groups. The results of comparisons were presented in plots of mean values plus standard errers (standard deviation of mean). Statistical significance level was set at 5% (α-level, $p < 0.05$). Post-hoc comparisons were performed by Tukey's range test (Honestly Significant Difference, HSD).

To quantitatively describe the major features in a dataset, boxplots are frequently used. They demonstrate dispersion (25th and 75th percentiles, and the extent), central tendency (mean or median), and possible outliers in the data sets that are being compared. To examine how two sets of data are different, *notches* are often added to boxplots to display the uncertainty about the means (or medians) of datasets. For two boxes, if the notches do not overlap, the means (medians) are significantly different. Boxplots have been used here to compare the relevant measures between the groups, frequency bands, and conditions. They were particularly useful when comparisons involved data sets with considerable missing cells, such as in analysis of peaks in the two bands.

5.4   Results

5.4.1   Tremor in 3-D Space: X, Y, Z Components

Total tremor energy (in the range of 3-17 Hz) was compared in 3-dimensions (see Fig. 3.1-d for accelerometer axes), and for all 9-conditions (described in Section 5.3.4). The comparison was between the TD hand in PD, and the matched hand in healthy groups. To study the effects of direction and condition on the tremor total energy, a two-way (3 direction $\times$ 2 group) ANOVA was conducted.

A main effect of direction (F(2,132)=75.0, p<0.001) and an interaction between direction and group (F(2,32)=11.7, p<0.001) was found. Fig. 5.7 presented the comparison of relative RMS values for X, Y, and Z with respect to combined X-Y-Z tremor energy ($\sqrt{X^2 + Y^2 + Z^2}$). Post-hoc analysis (Fig. E.1) revealed that X component was significantly larger than Y or Z, for both groups of participants. Post-hoc also revealed that the
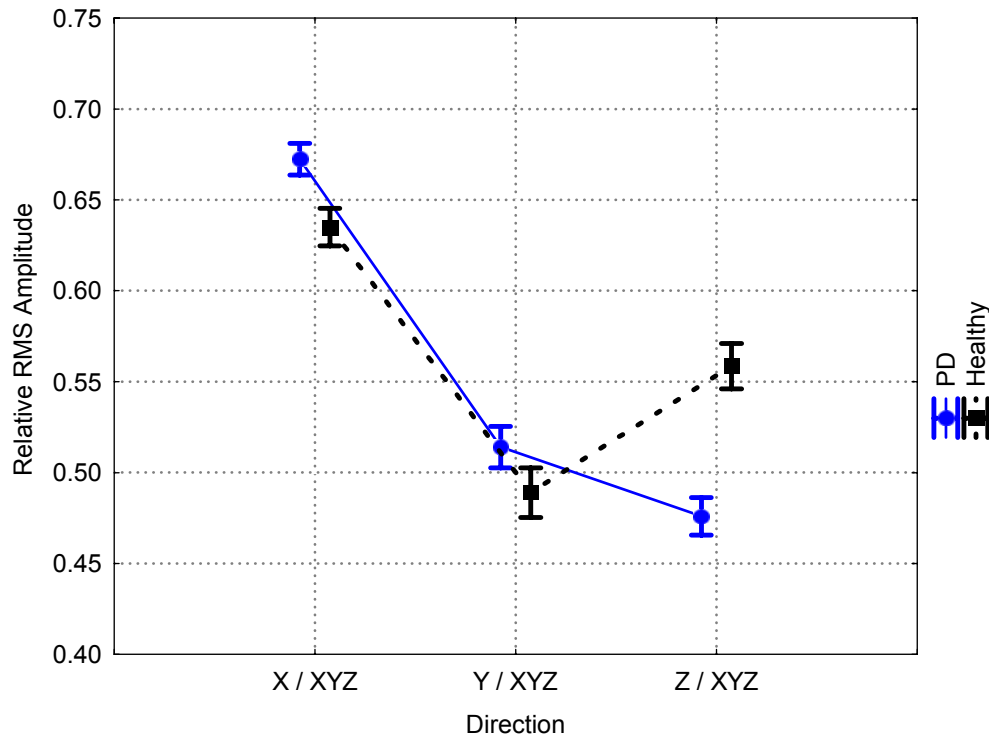
Figure 5.7: Mean relative RMS amplitude in X, Y, and Z with respect to combined X-Y-Z tremor energy over all conditions. TD hand in PD versus the matched hand in healthy groups.

Z-component of tremors was significantly larger in healthy compared to PD regardless of loading. Therefore, in the subsequent analyses, only tremors in X direction (as dominant dimension for both groups) were considered.

5.4.2 Loading and Tremor Amplitude: Trends in RMS Energy

In the following sections, tremor's RMS value was used as a measure of amplitude. All the comparisons were in X-direction and compared the TD hand in PD patients and the MH for the healthy participants. Total tremor (3-17 Hz) was compared once between the healthy and PD participants (a 2-way, 2 group $\times$ 9 condition ANOVA). A main effect of conditions $(F(8,528)=2.4, p=0.016)$ and an interaction between group and condition $(F(8,528)=3.0, p=0.002)$ were observed. Post-hoc revealed significant effect of loading at higher loads for PD participants (Fig. E.2). Then the remainder of the study involved comparisons of

separate frequency bands. To evaluate how far a dataset was from a Gaussian distribution, raw or standardized residuals were plotted to check the deviation from a bell-shaped normal distribution. Fig. E.3 presents an example for all PD patients in Off-medication and in postural condition.

Medication Effect on Tremor Energy in Different Frequency Bands

Tremor RMS amplitude was calculated for each of the three bands (as described in Section 3.6) for TD hand of all PD patients. The calculation was performed for each of the 9-conditions (Section 5.3.4) and for both before and after medication. Fig. 5.8 presented the results for the 2-way (2 meds × 3 bands) ANOVA. An interaction between medica-
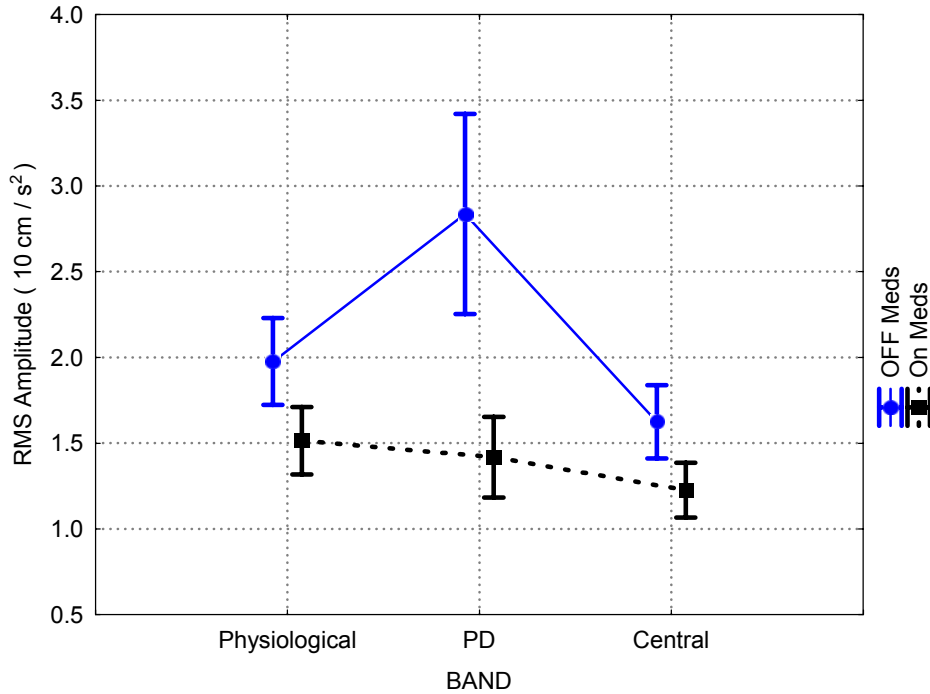
Figure 5.8: Mean tremor RMS amplitude in the three bands (Section 3.6), and meds effect.

tion state and frequency band was observed (F(2,76)=8.9, p<0.001). Post-hoc analysis (Fig. E.4) revealed a decrease in RMS amplitude from Off- to On-medication only in the PD band. Moreover, there was no significant difference between the RMS amplitude in the whole physiological band (7.5-16.5 Hz), and its central component (8-12 Hz) and both did not decrease significantly on medication. Therefore, in the subsequent analyses, only the whole physiological band was considered to avoid redundancy.

TD Hand, Off-Medication Compared to Matched Hand of Controls
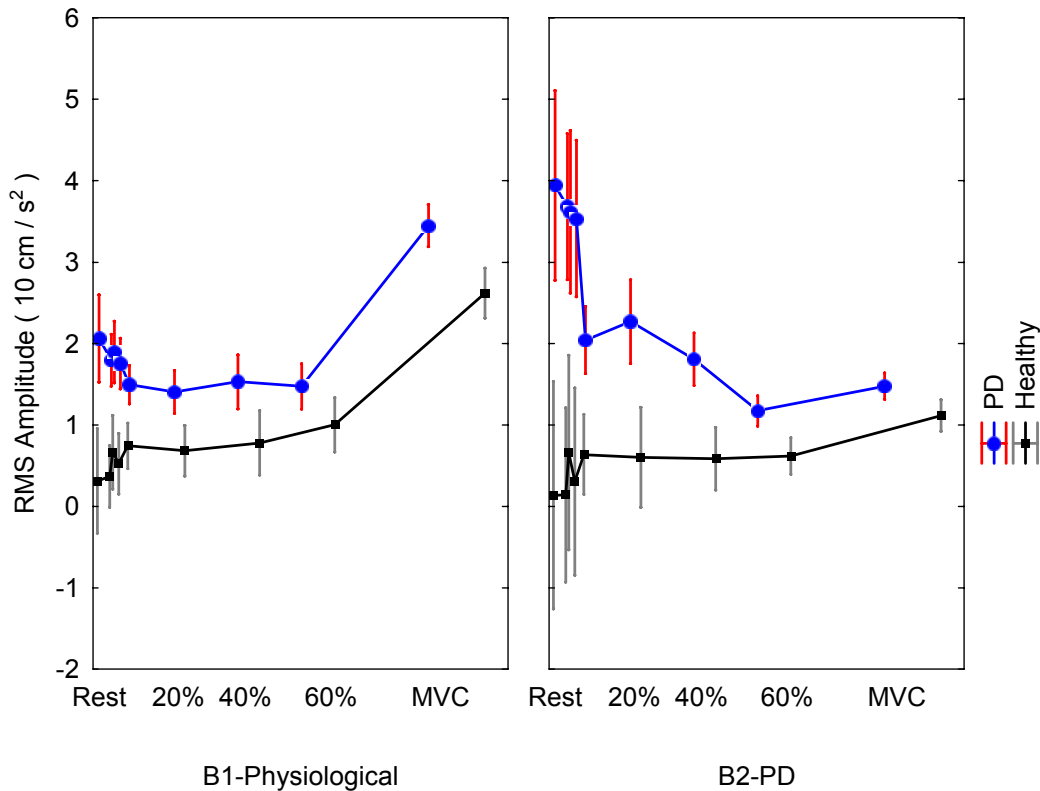
Figure 5.9: Loading effect on hand tremor in posture. Tremor energy in the frequency bands of interest is compared for healthy and PD. Horizontal axis presents loading in 9-conditions, described in Section 5.3.4, and average MVCs are used for the last 4-conditions. Since average MVC is different for each group, the last 4-conditions are presented at different absolute loads.

In this section, the loading effect on tremor amplitude (RMS energy) was compared between TD hands in off-medication state and healthy matched hands. A 3-way (2 band $\times$ 2 group $\times$ 9 condition) ANOVA was carried out to analyze tremor in the two frequency bands of interest (Physiological, and PD bands), for the two groups and for the 9-conditions described in Section 5.3.4. Fig. 5.9 presented the comparison in actual range. The average MVC for each group (52 N for PD, and 61.5 N for healthy) was used to demonstrate the amount of loading in the last 4-conditions. Although presenting loading effects in actual range was more informative, the first 5-conditions were squeezed in a small portion of the figures and were barely distinguishable. For this reason, graphs that presented loading

effect in the subsequent sections were not presented in actual range. Fig. 5.10 presented the same results in the new configuration. An interaction between band, group, and condition was observed ($F(8,528)=2.2$, $p=0.024$); post-hoc revealed significant decrease of tremor in B2 for PD at higher loads. A marginal interaction between band and group was also found ($F(1,66)=3.9$, $p=0.052$).
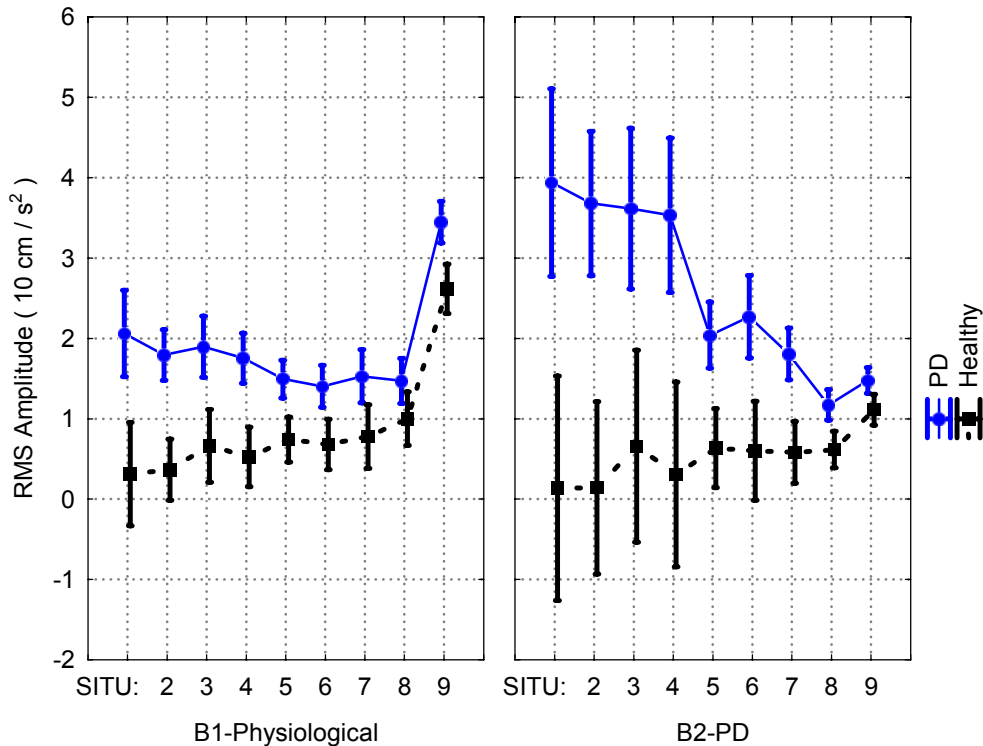
Figure 5.10: Loading effect on hand tremor in posture for 9-conditions. Comparisons are between Healthy and PD, and for the two frequency bands of interest.

Sub-Groups in PD

Fig.s 5.9 and 5.10 suggested an overall decrease in PD tremor with loading, particularly in B2, although the large variability (larger error bars) in this band made the generalization difficult. Examining the trend of tremor energy with loading for each individual, the most highly tremulous patients exhibited a trend of dominantly decreasing. However, the remaining majority had different trends that were certainly not decreasing. Fig. 5.11 demonstrated an example of two PD participants with opposite trends. Patient #16 presented a dominantly decreasing trend while for patient #2, the noticeable trend was an
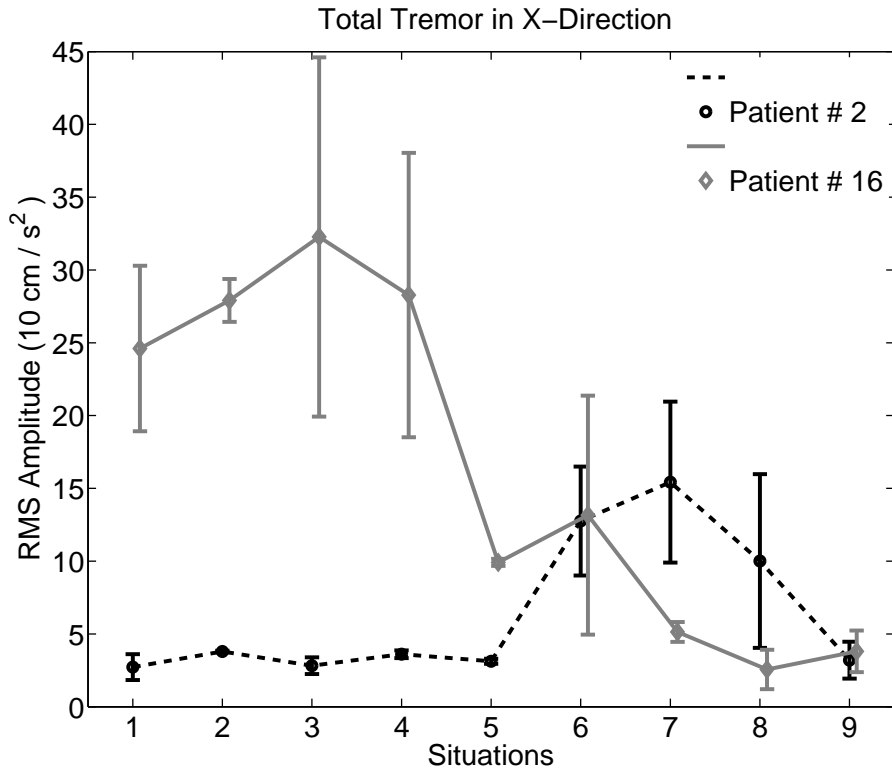
Figure 5.11: Mean RMS amplitude (total energy) for TD hand of two PD patients with clearly different trends in loading effect.

increase of tremor with larger loads. The overall difference in the observed trends would suggest that PD patients be sub-divided into two groups, with larger and smaller tremors, in order to find clearer trends in loading effect.

In this section, the first set of categorization schemes were investigated. They are methods of dividing PD patients into two groups, of larger and smaller tremors. The first five columns in Table 5.1, presented the five single measures of tremor severity. Three of them, that are based on UPDRS scores (columns 1,2, and 4), plus four combinations with the measured tremors (the middle 4-columns, described in Table 5.1) were considered as categorization methods: Cat1-7. The groups with smaller tremors were marked gray. The last row in the table exhibited the total number of patients in the group with larger tremors according to each categorizations. Subsequently, the two sub-groups from each categorization scheme were compared to the healthy controls. Fig. 5.12 presented how one of the schemes separated PD patients to groups with larger and smaller tremors.

The two PD sub-groups, resulted from each of the seven categorizations, were compared

67

Table 5.1: Comparison of different methods of making sub-groups in PD patients

Subj. code	Cat1[1] Tot.	Cat2 Rest	Meas.[2] Rest	Cat3 Act.	Maes. Post	Cat4	Cat5	Cat6	Cat7	Cat8	Cat9
17	9	A[2]	A	E	A	E	A	E	A	G1	G1
09	8	A		E		E					
02	7.5	A	A	A	A	A	A	A	A	G2	G2
03	7.5	A	A	A	A	A	A	A	A	G2	G2
16	7.5	A	A	E	A	E	A	E	A	G1	G1
13	7	A	A	A	A	A	A	A	A	G1	G1
15	6.5	A		A	A	A		A		G2	G2
18	6	A		E	A	E		E		G2	G2
06	5		A	E						G1	
07	4.5	A	A				A				
04	4		A	E							
12	4		A	E						G2	
08	4			E						G2	G2
01	3.5	A	A		A		A		A	G1	
19	3										
14	2		A		A				A	G1	G1
05	1.5										
20	1										
11	1				A					G2	G2
10	1										G2
Tot.	10 >	10 >	10 >	11 ≥	10 >	8 ≥	7 >	7 ≥	7 >		

[1] Cat1, categorization according to total tremor-related UPDRS scores on TD side (items 20-21, hands-legs). Cat2-3, according to UPDRS rest and action scores respectively. Cat4, joint rest and action in UPDRS. Cat5, rest UPDRS and measured rest tremor. Cat6, Action UPDRS and measured postural tremor. Cat7, both measured in rest and posture. Gray, below median (smaller tremor). Cat8, clustering according to Spearman's rank. PD is separated to 3-groups; G3, light gray. Cat9, Clustering according to Correlation.

[2] Meas., measured. A, above median. E, equal to median.
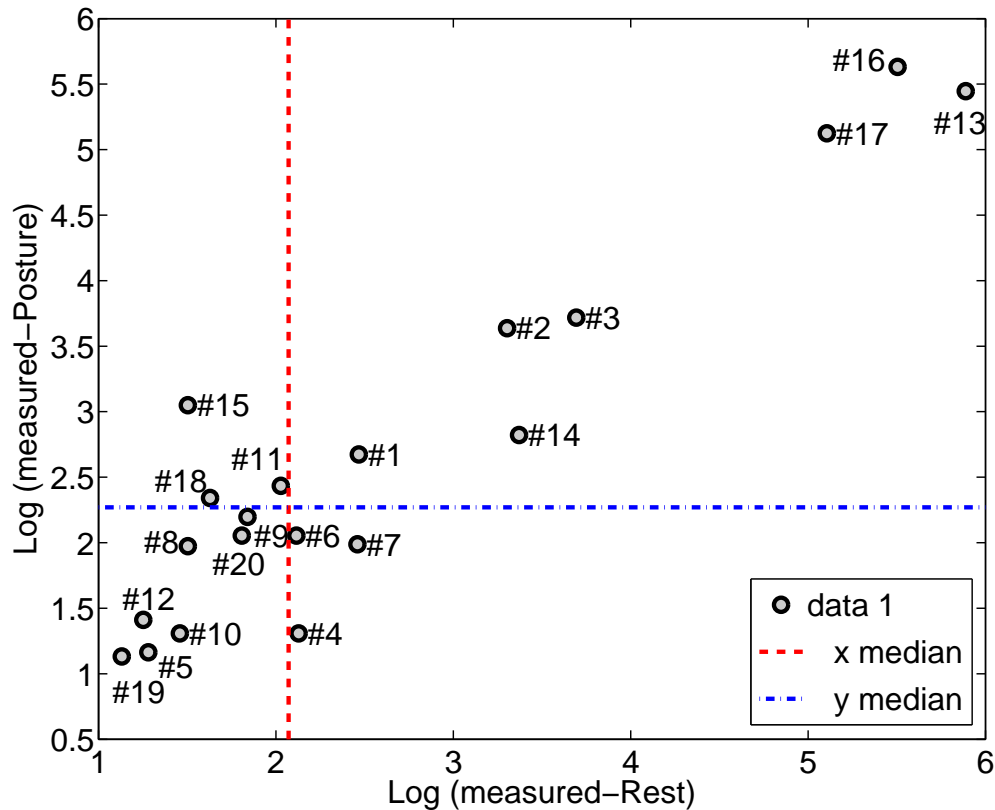
Figure 5.12: Categorization scheme-7 separates patients according to their measured rest and posture tremors. Group with larger tremors have above median scores in both axes. Natural logarithm of RMS amplitude (total, 3-17 Hz range) is used for uniform distribution.

separately with the healthy group, in a similar analysis (a 3-way, 2 band × 3 group × 9 condition ANOVA) to that of Section 5.4.2. The analysis was repeated for all seven categorization schemes. The results of analysis for each categorization schemes were fairly consistent. Fig. 5.13 presented the results of statistical analysis corresponding to Cat1, as an example of compared RMS amplitude in the two bands for each of the three groups. The group with larger (visible) tremors presented a clearer trend in both bands compared to the whole PD group in Fig. 5.10.

In order to examine energy in the bands, the three groups (patients categorized according to Cat1, plus the healthy) were compared in Fig. 5.14 over all conditions. An interaction between band and group was observed ($F_{(2,65)}=9.3$, $p<0.001$). The post-hoc revealed that for the group with larger tremors, energy was significantly higher not only in the PD band, but also in the physiological band compared to the other two groups. How-
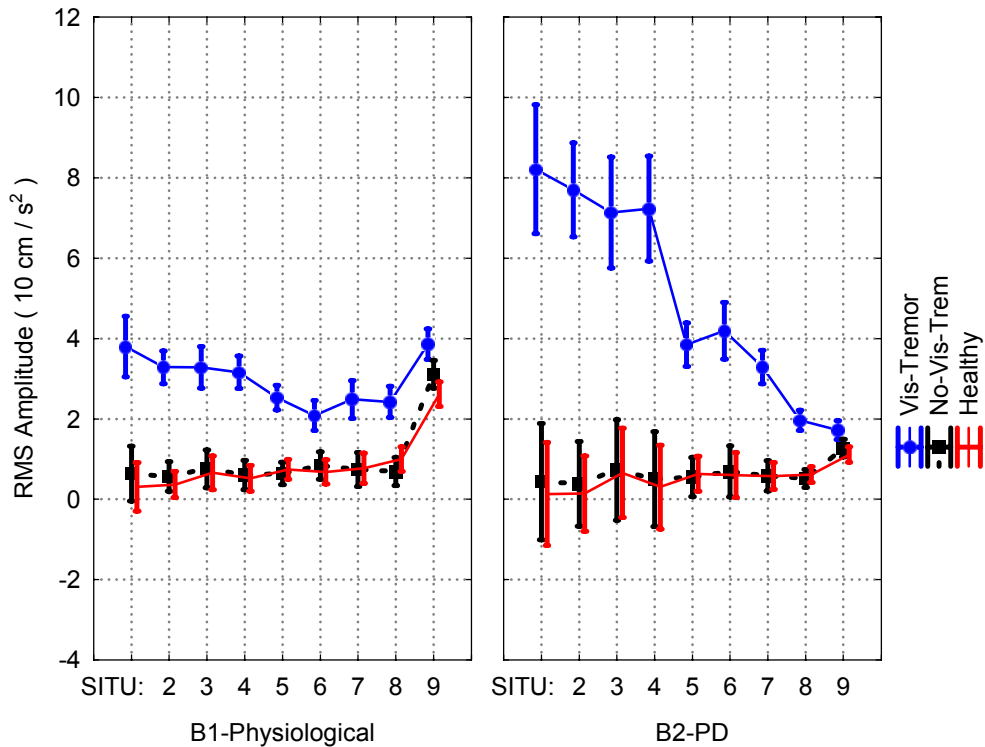
Figure 5.13: Loading effect on hand tremor in posture for 9-conditions. Comparisons are between Healthy and two sub-groups in PD, and for the two frequency bands of interest. The sub-group with larger (visible) tremor is clearly separable from the other two.

ever, the group with smaller tremor (in this case, those with total tremor-related UPDRS score of $\leqslant 4$) and the healthy did not show a significant difference.

Cluster Analysis and Trends in Tremor Energy

It was shown that the observed individual trends were generally different between the patients with smaller and larger tremors, and that such categorization provided clearer trends (compared to the whole PD group). However, categorization based on the similarity of trends between the patients should remove more variability. Therefore, to examine how the trends in loading were comparable between the PD patients, clustering was utilized. Two measures of distance (dissimilarity) between the trends were based on the shape of their curvatures, Appendix ??. The resulted cluster trees, were exhibited in Fig. 5.15. The vertical axis presented inter-cluster distance; the participants were separated to three distinct clusters. The utilized two methods of clusterings were fairly consistent and were
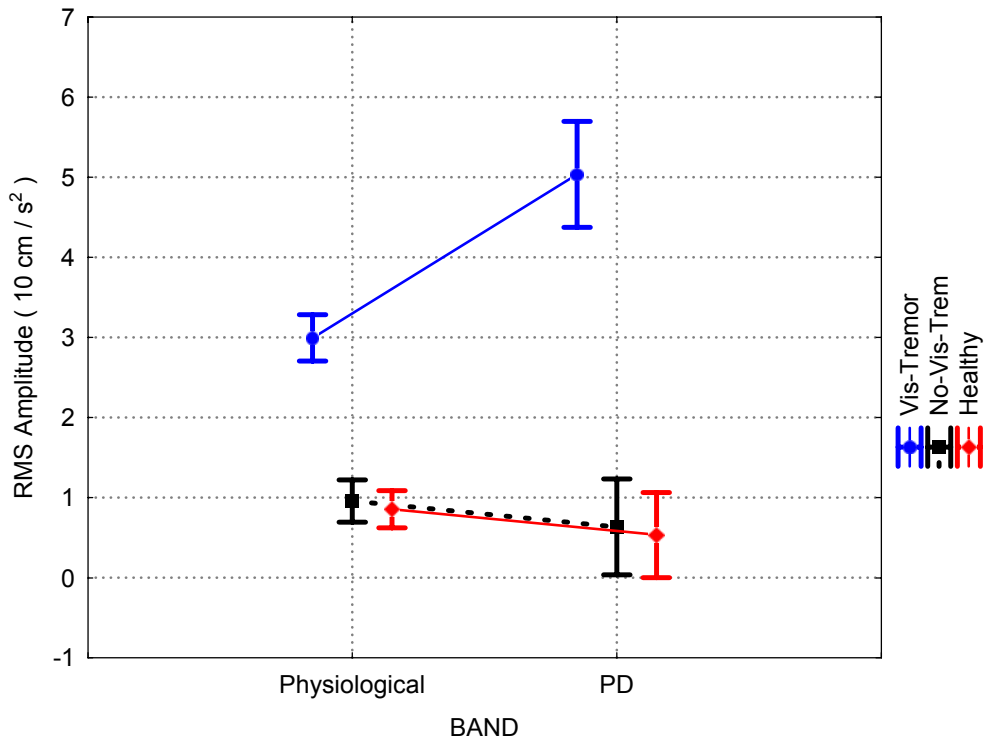
Figure 5.14: Mean tremor energy in the two bands compared for the 3-groups over all 9-conditions.

added to Table 5.1 as categorization methods Cat8-9.

Fig. 5.16-a presented the results of a 3-way (2 band × 4 group × 9 condition) ANOVA while the patients are categorized according to Cat9, with four patients in G-1, seven in G-2, and nine in G-3. A 3-way interaction was observed ($F(24,512)=10.1$, $p<0.001$). Subgroups G-1 and G-2 exhibited distinct trends (in both bands) that were clearly separable from G-3 and healthy. Fig. 5.16-b exhibited the results of comparison over all 9-conditions. A 2-way interaction was noticed between band and group ($F(3,64)=29.1$, $p<0.001$). Poshoc revealed that only for G-1 tremors in the both bands were significantly larger compared to the other groups. For a visual comparison of Cat9 (categorization based on clustering) and Cat7 (categorization based on severity of tremors in rest and posture), were presented in Fig. E.8.
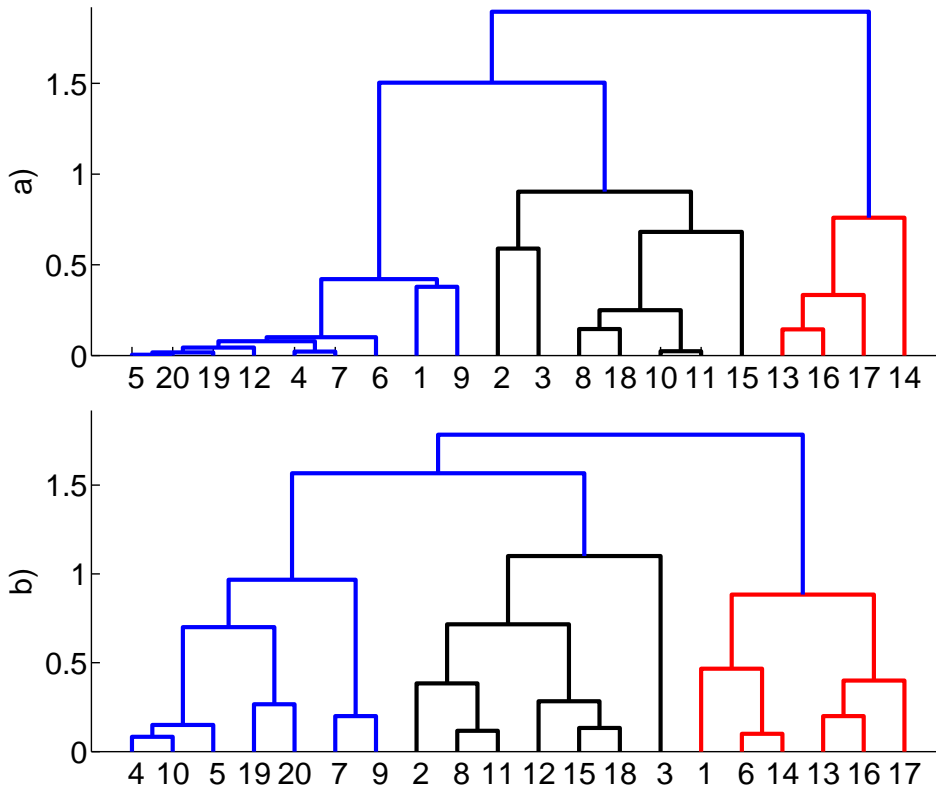
Figure 5.15: Dendrograms corresponding to hierarchical complete link cluster analysis for 20 PD patients. Clustering was based on the similarity between the sequence of data points for each participant. Data points were total tremor energy (in 3-17 Hz range) in 9-conditions. Dissimilarity between patients were based on: a) sample correlation between points,Cat9, b) sample Spearman's rank correlation between observations, Cat8.

5.4.3 Loading and Tremor Amplitude: Trends in Spectrum Peak-Magnitude

In this section, the effect of loading on tremor was examined with the peak magnitude in tremor's power specrum as the amplitude measure. TD hand in PD patients was compared to the matched hand in the healthy controls. Briefly, three largest peaks that were far enough from each others and are above 25% of the magnitude of the largest peak, were detected. Fig. 5.17 presented two example spectrums and the detected peaks for TD hands of two PD patients in Off-medication state. Each of the 9-rows depicted the tremor spectrum of the collected signal in one of the 9-conditions in loading (Section 5.3.4). The right
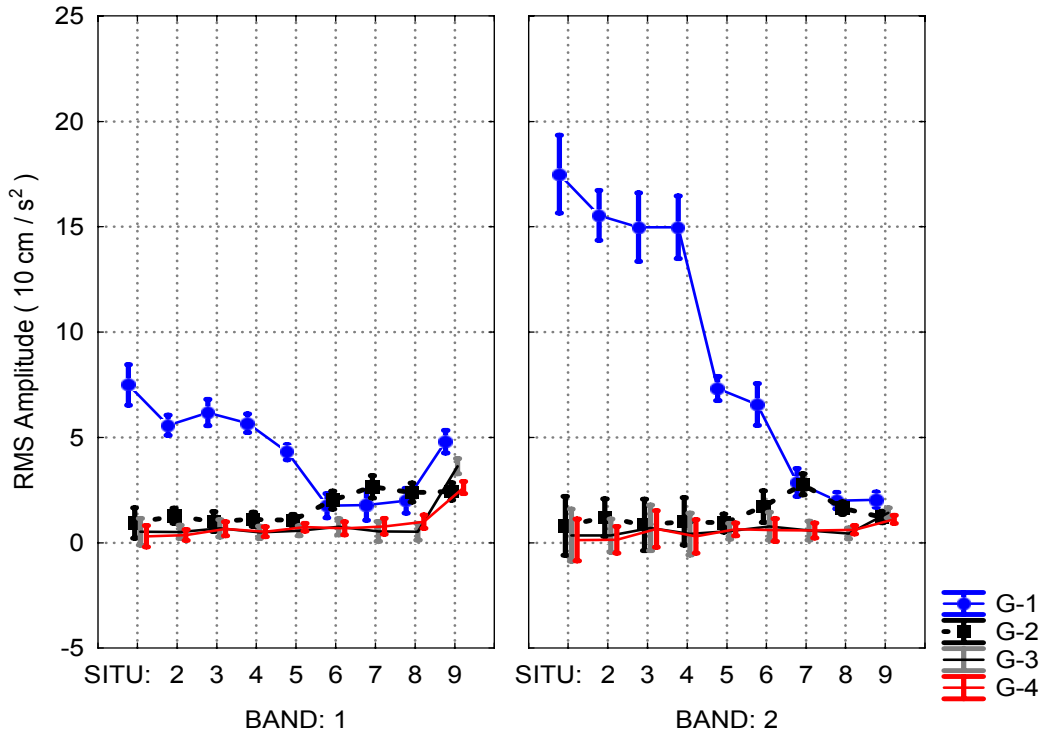
(a) Hand tremor in posture for 9-conditions and for the two frequency bands of interest.
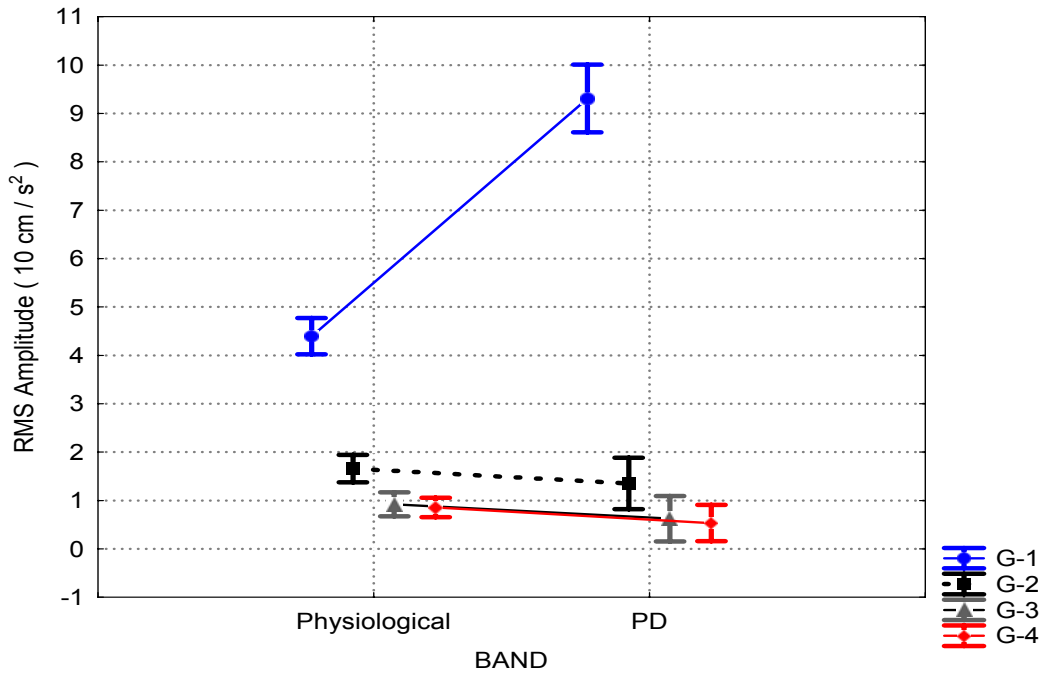
(b) Tremor over all 9-conditions.

Figure 5.16: Loading effect on tremor's energy for Healthy (G-4) and three sub-groups in PD (using cluster analysis, Cat9).

graph, patient#16, represented spectrums that were dominantly single-peaked. The left graph, patient#2, was an example of patients whose spectrums were mainly double/multi-peaked. On average 54% of analyzed data segments contained separable and comparable peaks in the both bands. Table C.3 provided such percentage for each PD patient in two trials, each containing all 9-conditions.

The square root of peak magnitudes was of the same unit as tremor energy (cm/s^2), and were considered in statistical analysis. To have an overview of loading effect on the spectrums, boxplots were provided in Fig. 5.18. The comparison were among the healthy controls and PD patients in the two sub-groups with smaller and larger tremors (Cat1). The key features were provided for the peak frequencies in the two bands of interest (B1-2), as well as the ratio of the largest peak in B2 to the largest peak in B1. To keep this ratio bounded, in case the peak magnitude in one of the bands was zero, the ratio was limited to $[\frac{1}{5}, 5]$.

A 3-way (2 band $\times$ 3 group $\times$ 9 condition) ANOVA compared the peak magnitudes among the two bands, three groups, and 9-conditions. Fig. 5.19-a presented the results of this comparison among the healthy control subjects and the two sub-groups in PD patients, categorized according to their tremor severity in rest and posture (Cat1). A 3-way interaction was observed ($F(16,520)=4.3$, $p<0.001$). The group with larger tremors exhibited distinct patterns in the both bands compared to the other two groups that were not clearly separable. Over all 9-conditions (Fig. 5.19-b), an interaction between band and group was noticed ($F(2,65)=12.3$, $p<0.001$) and post-hoc revealed that the group with larger tremors had significantly higher peaks in B2, but not in B1. These results could be compared to the results of the similar analysis on tremor energy in Fig. 5.13-5.14.

To compare the effect of the previously used categorization method, which was based on trends of loading in individual patient's total tremor energy, Cat9 was used in a similar analysis (A 3-way, 2 band $\times$ 4 group $\times$ 9 condition). The results were exhibited in Fig. 5.20. The comparisons were between the healthy controls (G-4) and the PD patients categorized into G1-2-3, using cluster analysis. A 3-way interaction was observed ($F(24,512)=11.5$, $p<0.001$). G-1 and G-2 exhibited distinct trends with loading that were clearly separable from the other two groups in both bands. Over all 9-conditions, an interaction between band and group was observed ($F(3,64)=34.5$, $p<0.001$). Only G-1 in PD band had significantly larger peaks (post-hoc analysis) compared to other three groups. For a better visualization of groups G-2, G-3, and healthy controls, loading effect on mean tremor amplitude in PD band was compared in Fig. 5.21. The results were provided for both measures of tremor amplitude (RMS amplitude, and peak magnitude in spectrum).
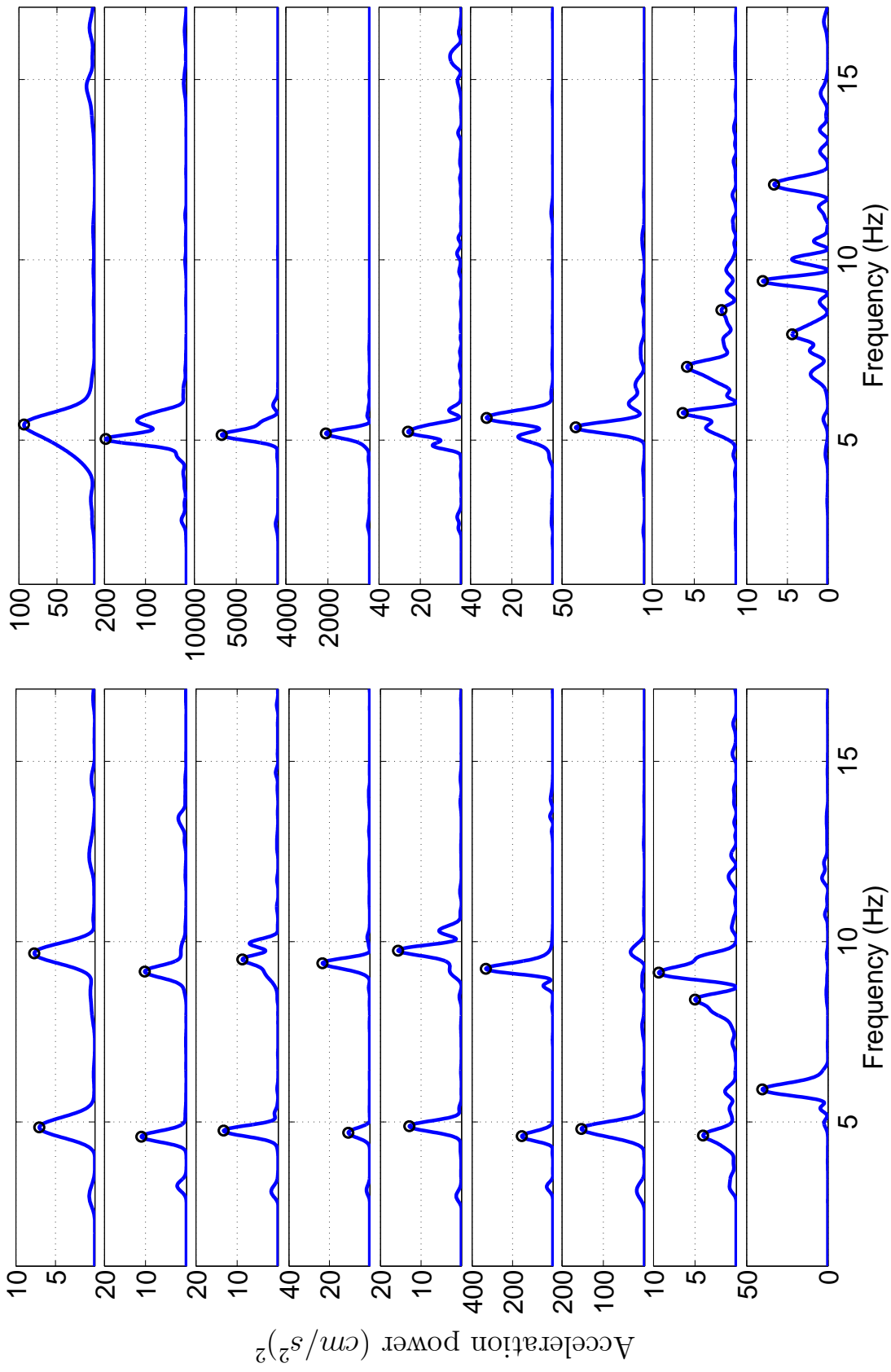
Figure 5.17: Power spectral densities for 9-conditions. From top: Rest, Posture, 0.5 N and up to 100% MVC loading. Left graph, patient #2, double-peaked spectrum. Right graph, patient #16, single-peaked spectrum.
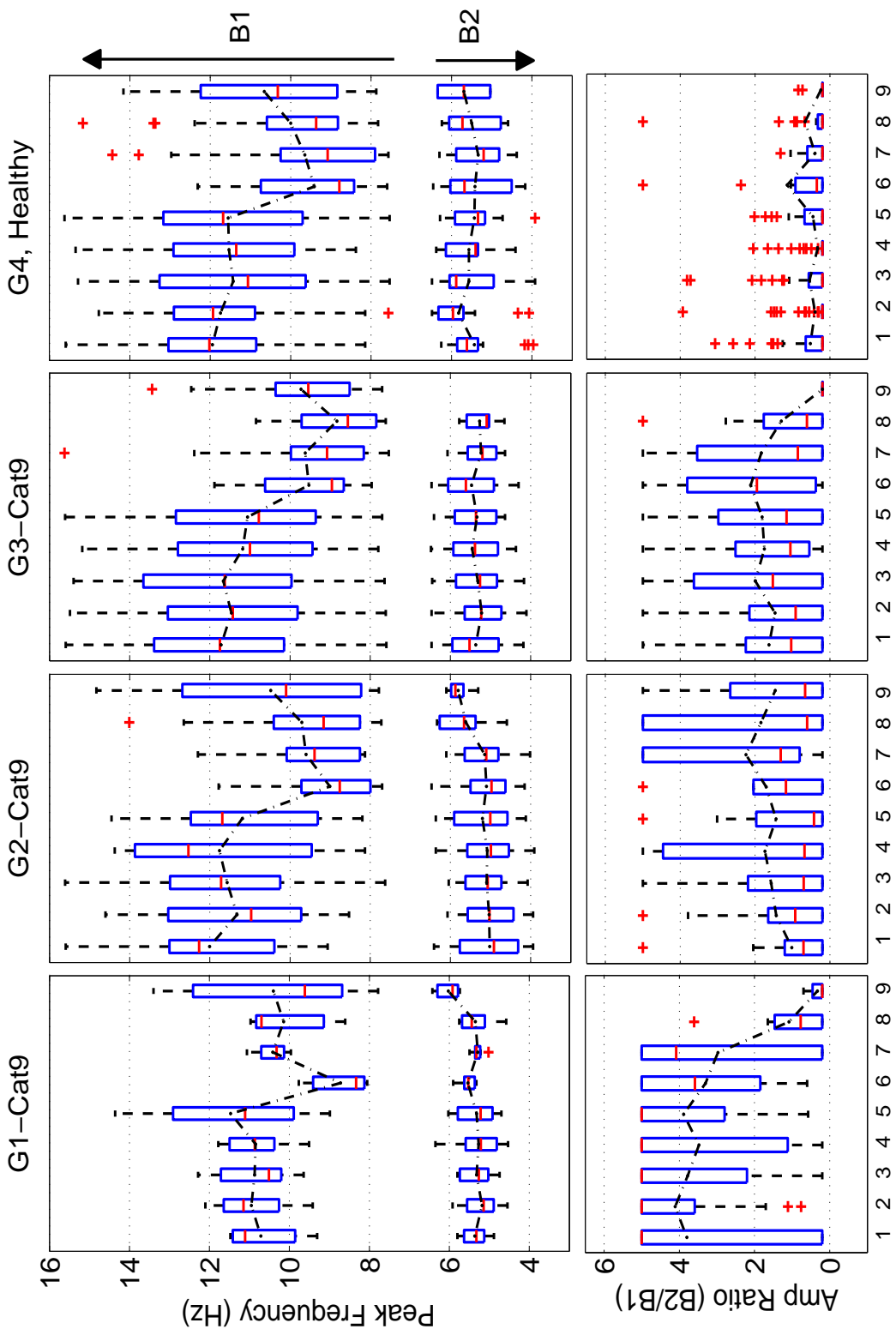
Figure 5.18: Comparison of loading effect among 4-groups, Cat9. Upper row boxplots, median frequency, quartiles, and trend in mean frequency (dash-dot line) for each band. Lower row, the ratio between the peak spectrum magnitude in the 2-bands. No peaks were found for G3 in B2. (Comparable results with 2 sub-groups, Cat1, in Fig. E.9)
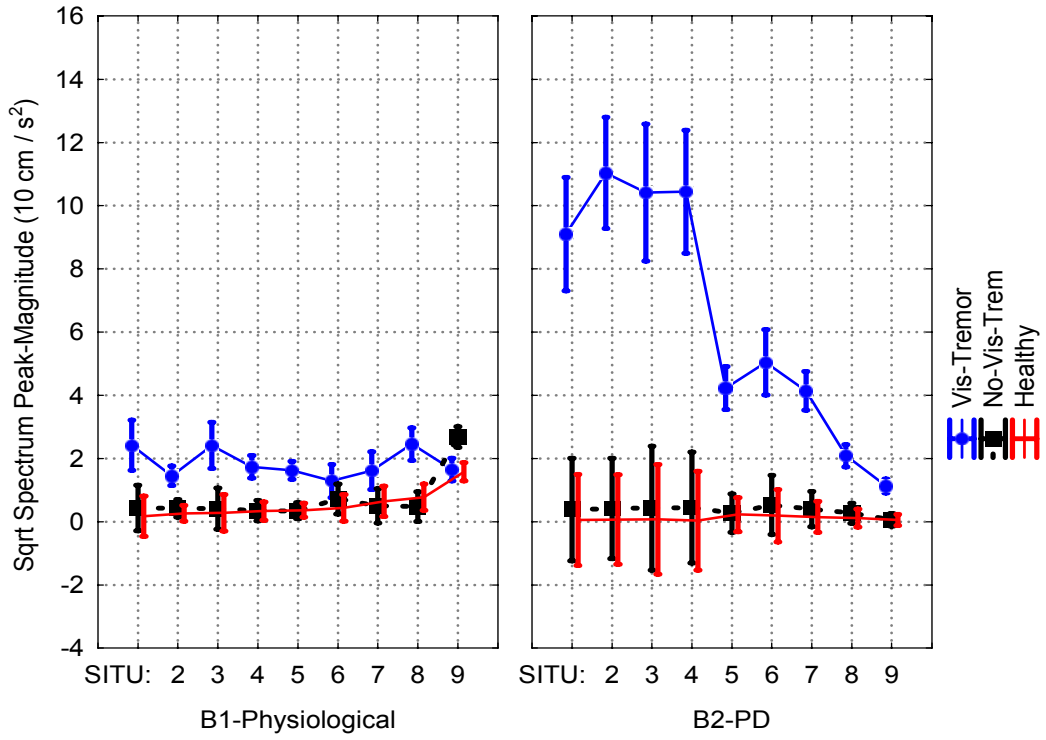
(a) Hand tremor in posture for 9-conditions and for the two frequency bands of interest.
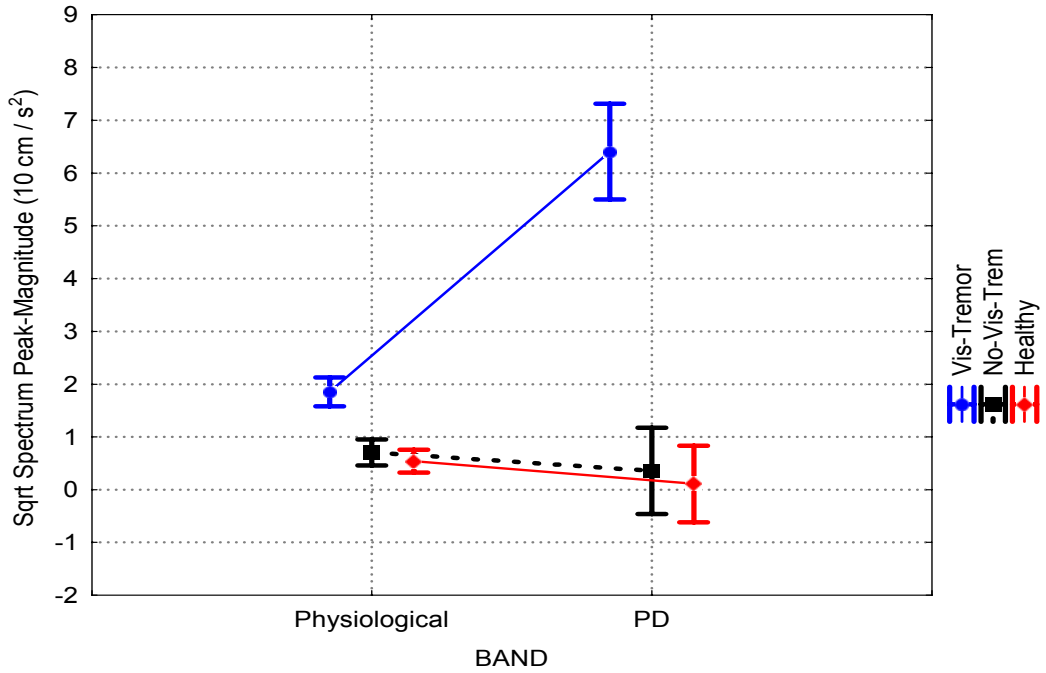
(b) Tremor over all 9-conditions.

Figure 5.19: Loading effect on the square root of tremor's peak spectrum magnitude. Comparison among the healthy and PD sub-groups with smaller, nd larger tremors (Cat1).
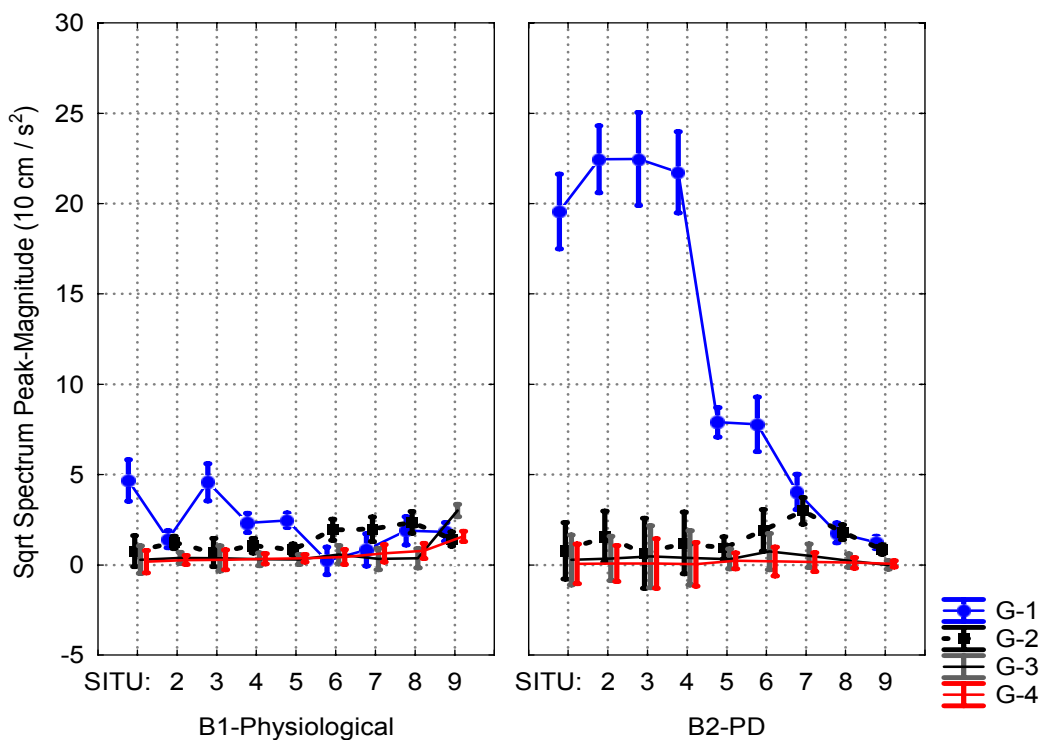
(a) Hand tremor in posture for 9-conditions and for the two frequency bands of interest.
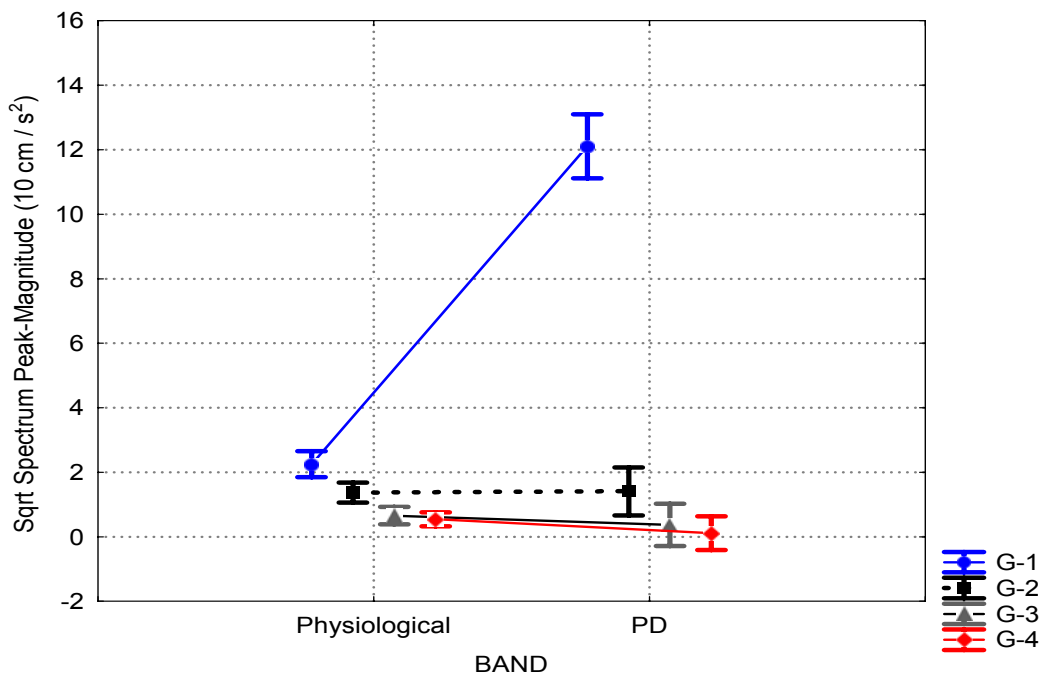
(b) Tremor over all 9-conditions.

Figure 5.20: Loading effect on the square root of tremor's peak spectrum magnitude. Comparison among the healthy and PD sub-groups according to cluster analysis (Cat9).
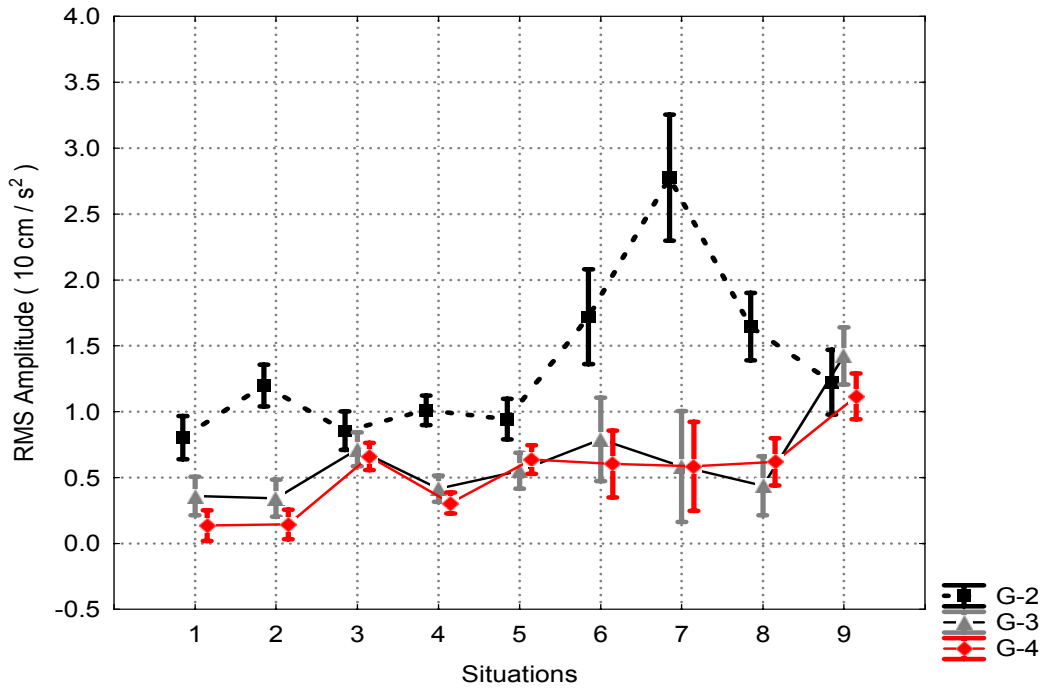
(a) RMS Energy as tremor amplitude.
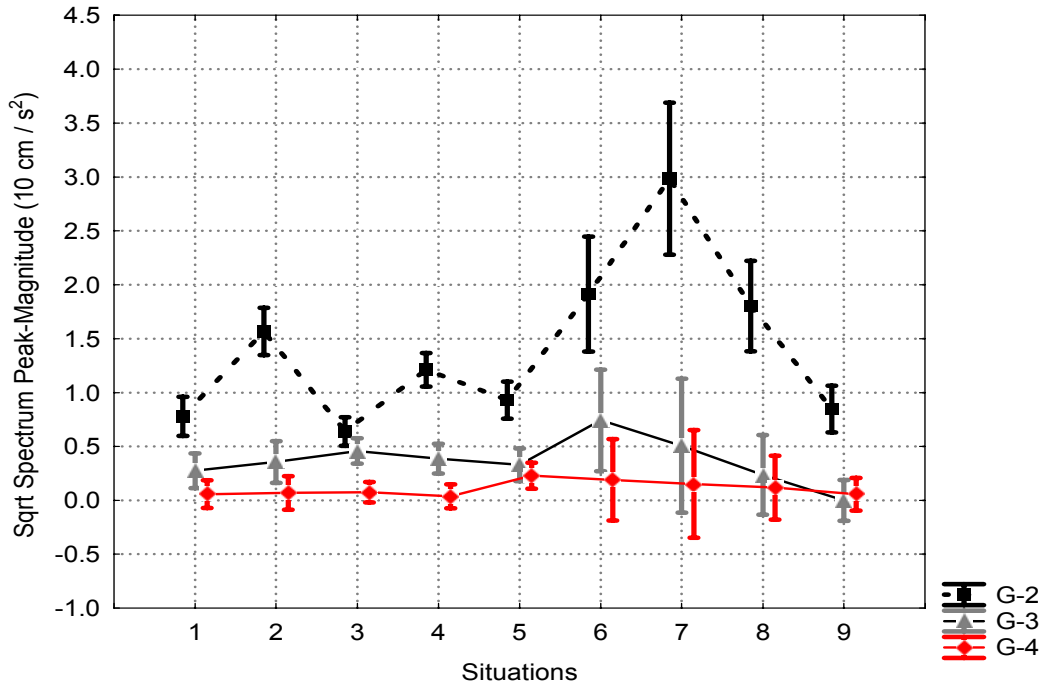
(b) Square root of peak-magnitude in spectrum as tremor amplitude.

Figure 5.21: Comparison of loading effect on mean tremor amplitude in B2, among 3 out of 4 groups: Healthy (G-4) and sub-groups G2-3 categorized with clustering method, Cat9.

5.4.4 Loading Effect: Trends in Tremor Frequency

In this section, the peaks in tremor spectrum were examined for the effect of loading on tremors peak frequency. TD hand in PD patients, categorized using clustering, were compared to the matched hand in the healthy controls. Similar comparisons, with categorization based on the severity of tremors, were presented in Appendix E. Each frequency band of interest (B1-2) were examined separately for occurrence and frequency of the peaks in the tremor spectrum. The examined spectrums were from the 2 data segments (see Section 5.3.4) for each of the 9-conditions. Fig. 5.22 exhibited percentage of peak occurrence for each of the four sub-groups, and for each frequency band. The PD sub-group G1 usually
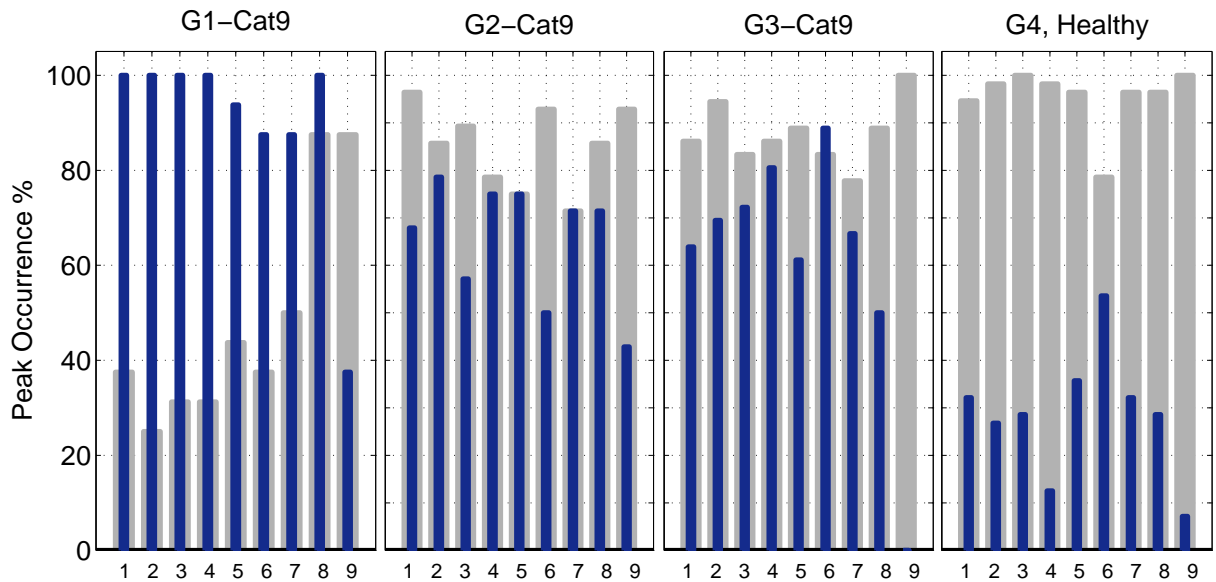
Figure 5.22: Percentage of peak occurrence in the two bands of interest among analyzed segments of data. Gray wider bars correspond to peaks in the physiological band, B1. Narrow darker bars correspond to peaks in the PD band, B2. PD patients (categorized with Cat9 into 3 sub-groups G1-G3) compared to healthy controls, G4. No peaks were found for G3 in B2. (Comparable results with 2 sub-groups, Cat1, in Fig. E.10).

exhibited peaks in B2 while at least 25% of their tremor spectrums contained comparable peaks in B1 as well. For this sub-group, occurrence of peaks in B1 increased at larger loads and, in B2, decreased at MVC (condition-9). For PD sub-group G2, spectrums often contained peaks in B1; and at least 43% of them had comparable peaks in B2 as well. G3 exhibited similar results to G2, with no peaks in B2 at MVC. For the healthy controls

(G4), spectrums usually presented peaks in B1 while at least 7% of them also contained a comparable peak in B2.

To investigate the effect of loading on the frequency of spectrum peaks, shift in frequency with respect to rest condition was calculated for conditions 2-9. Fig. 5.23 presented the comparisons of the change in frequency with loading among the healthy controls and the sub-groups in PD (using clustering, Cat9). The boxplots compared the peak frequen-
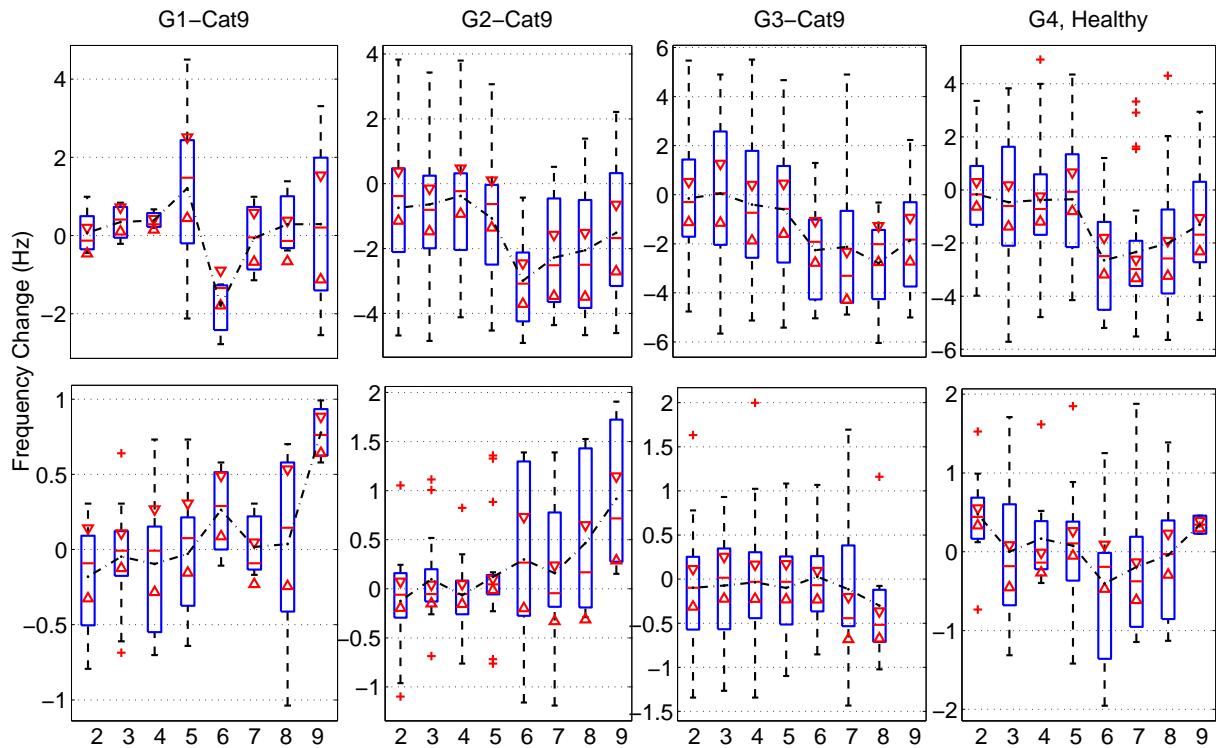
Figure 5.23: Change in frequency of spectrum's peak in each band, with loading (conditions 2-9 compared to rest or condition 1). PD patients (categorized with Cat9 into sub-groups G1-G3) compared to healthy controls, G4. Upper row, change in peaks' frequency in the physiological band, B1. Lower row, change in peaks' frequency in the PD band, B2. Dash-dot line, mean values. No peaks were found for G3 in B2. (Comparable results with 2 sub-groups, Cat1, in Fig. E.11).

cies for every condition and each band. Furthermore, the notches plotted in each box in the form of pair of tiny triangles helped comparing the means between boxes.

On average, peaks in physiological band (B1) exhibited more noticeable change in frequency with loading. All groups exhibited a decrease of frequency at medium to high

loads, which was significant at least in one condition for G1,G2, and G4. Peaks in PD band (B2) did not present a clear trend of change for the healthy and G3. For G1 and G2, however, an overall trend of increase in peaks with loading in this band appeared. Although, this increase was only significant for G1 at the maximum loading at MVC.

5.5 Discussions and Conclusion

5.5.1 Directional Analysis of Tremor : H_3

For the current study, the results of comparing tremor energy along 3-axes revealed that X components were significantly larger than Y or Z for both the healthy and PD participants. However, Y and Z components were not consistent between the two groups. The Y components were the smallest for the healthy, but it was not true for the PD participants. The results also revealed that Z-components were significantly larger in the healthy compared to PD. Similar results were observed regardless of loading and could not be related to difference in MVC, because it was not significantly different between the two groups (unpaired t-test failed to reject that MVC for the matched healthy hand, 61.5 $\pm$21N, and TD hand, 52 $\pm$22.5N, were different, p=0.22). The healthy and PD participants had received the same instruction. However, because we did not record the hand orientation, we were not able to objectively evaluate if this difference was caused by different (overall) orientation. If similar studies in the future, could not associate this directional difference between healthy and PD tremors to significantly different orientation in their hands, it might indicate that PD does not affect all muscles in the same way. It might otherwise indicate that tremor in B2 is predominantly in certain muscles (or fiber types), or alternatively it might be related to the different resonant frequency of wrist in different directions.

Although the combined 3-dimensional amplitude analysis would contain all tremor energy, the single dominant axis was chosen in this study for two reasons: The main loading was in X-direction; and the muscle group that was involved in X-movement experienced the change in load. Therefore, it was more appropriate to check the response of X-tremor to loading. Furthermore, X-direction tremor was the largest component for both the healthy controls and the PD participants; the second largest component was not the same for the two groups.

The results affirmed the hypothesis H_3 that PD Tremor was not uniformly distributed along three dimensions. This was also in-line with previous study, revealing that the postural tremor in PD patients were dominant in either vertical or horizontal direction [49].

Tri-axial tremor assessment would be necessary at least to detect the dominant dimension. In other words, arbitrary chosen single-axis tremor assessment might considerably affect the accuracy and validity of the results.

5.5.2   Sub-Groups in PD : H_4

Comparing all PD patients to the healthy controls, the overall decrease in tremor amplitude in B2 (with loading) was in-line with the classic understanding of PD tremor: "Voluntary muscle contraction typically suppresses the tremor, at least temporarily" [92]. However, the big variability (larger error bars) in this band, diverse previously reported results, and clearly opposing individual trends in tremor energy with loading, challenged the idea of decrease in tremor amplitude for every patient. For this reason, sub-groups in PD with more consistent trends of loading effect were sought.

The seven methods of categorization, that were based on the severity of tremor at rest and posture (Table 5.1), were fairly consistent in separating PD patients to sub-groups with smaller and larger tremors. The results of analysis for each categorization scheme were fairly consistent and helped reducing the variability compared to when all PD were contrasted to healthy controls. The sub-group with larger (visible) tremors presented a clearer trend in both bands compared to when the whole PD patients were considered. Furthermore, the sub-group with smaller tremors (Fig. 5.13), although was not completely separable from the healthy controls, did not follow the decreasing pattern of tremor with loading. The two separable trends for each PD sub-group supported hypothesis H_4.

The results of statistical analysis using clustering methods (Cat8-9) revealed considerable improvement in separability. The two mentioned schemes were fairly consistent and it was expected that any automatic classification based on the shape of the trends would yield similar sub-categories. Sub-groups G-1 and G-2 in Fig. 5.16 (using Cat9), exhibited two distinct trends in loading. For sub-group G-1, the trend in loading effect in B2 was decreasing and very similar to overall PD trend in Fig. 5.10. This may indicate that the overall PD trend is driven by strong tremors of G1. For sub-group G-2, loading effect in B2 was observed as an increase and peak at higher loads. No matter what caused this increase in PD band energy, without clustering this sub-group's different trend would be lost in statistical analysis. Sub-group G-3, that was not separable from the healthy controls, did not follow either of the mentioned trends. In other words, not every PD patient followed the same pattern of loading. Therefore, the hypothesis H_4, that loading up to MVC would result in more than one clear trend, was affirmed.

In general, statistical analysis of square root of peak magnitudes produced similar results to those of tremors' RMS amplitude. The results provided similar trends, while separating the PD patients to two or three subgroups, and confirmed H_4. In other words, based on peak magnitudes, loading resulted in more than one clear trend in tremor amplitude. Fig. 5.21 demonstrated an example of how both measures of amplitude would result in similar trends for the same sub-groups.

Analyzing trends in spectrum peak frequency supported the idea of different sub-groups in PD, as well. In band B1 (Fig. 5.23), G1 presented a fluctuation at medium loads, which separated its trend from those of other subgroups. In band B2, G1 and G2 exhibited trends that were mainly increasing, while for G3 it was not.

Overall, results of this study rejected the null hypothesis in favor of H_4 hypothesis. It means that, trying to generalize a result on action tremor to all PD, causes loss of non-similar information that belongs to subgroups.

5.5.3 Coexistence of PD and Physiological tremors

Comparison of tremors' energy in B1-B2 for all PD participants, in posture and at various levels of loading (which are instances of action tremor), did not show a dominantly physiological tremor in conditions 2-8, or a clear fading in B2 energy unless at MVC (Fig. 5.10). Therefore, the results did not confirm that PD action tremor and physiological tremors were necessarily of the same origin (as suggested in [31],[30],[83],[87],[112]). Instead, It might be safer to state that physiological tremor was playing a significant role in PD action tremor.

Sub-Groups and Strong Tremor in B2 : H_{5_1}

Classifying PD patients according to severity of their tremor, over all the conditions, the following was observed. For the sub-group with larger tremors, energy was significantly higher not only in the PD band, but also in the physiological band compared to the healthy controls. This was not true for the sub-group with smaller tremors. This was in support of H_{5_1} hypothesis for *some* PD patients. This hypothesis could not be evaluated for the whole PD patients, because the interaction between group and band was marginal. Generally, separating PD patients to sub-groups according to tremor severity at rest and posture was capable of providing a clearer picture about loading effect on tremor amplitude

(energy). However, the question was whether other categorization methods could improve the separability between the trends in response to loading.

Using clustering, over all the conditions, sub-group G-1 exhibited significantly larger tremor energy not only in B2, but also in B1. This was not true for the other two sub-groups in PD. Therefore, the results of this study was capable of affirming the hypothesis H_{5_1} for at least one sub-group, no matter what categorization technique is used. In other words, physiological tremor was not the same for all PD patients and healthy adults. Some PD patients would have higher tremor energy in the physiological band (B1) as well as in the PD band (B2), compared to healthy people.

Sub-Groups and Comparable Peaks in B1-B2 : H_{5_2}

Spectrum peaks that were separate enough and comparable in magnitude were found for each data segment. Three largest ones were chosen as the major peaks and were separated into two frequency bands of interest. On average 54% of the PD participants (Table C.3) exhibited comparable spectrum peaks in the both bands. This multi-peak feature of PD tremor was in-line with the literature ([32],[87],[30]). In other words, above half of the PD participants had both mechanisms of classic PD and physiological tremors of comparable strength. This supported the necessity of tremor study in the two bands.

Over all the conditions, both mechanisms maintained their presence; for the participants in sub-group G1, occurrence of comparable peaks in B1 and B2 was between 25-87% (Fig. 5.22). For the participants in sub-groups G2 and G3, similar presence was observed over conditions other than MVC (50-79%, and 50-83% respectively). At MVC, G3 did not exhibit any peak in B2.

The relative strength of the mechanisms (the ratio between the peak magnitudes in the two bands, Fig. 5.18) was considerably different between G1 and the other sub-groups. However, for all sub-groups, strength of mechanisms were comparable in the two bands over conditions 1-8. Over these conditions, G1 had peaks that were 3-4 times larger in B2 (compared to those in B1). For G2 and G3, this ratio was about 1-2. At MVC (condition-9), G1 and G3 lost their important peaks in B2, but G2 still had those peaks.

Overall, mechanisms that produced peaks in the two frequency bands (physiological and PD) were both important, but with different relative magnitudes for each sub-group of PD. This affirmed the hypothesis H_{5_2}: tremor spectrum will have comparable peaks for some of the patients; and for these patients, comparable peaks will remain present for

most of the conditions. It implies that multi-peak spectrum is characteristic of some PD patients, regardless of loading (ignoring MVC).

Sub-Groups and Significant Load Effect in B2 : H_{5_3}

When all the PD patients were compared to the healthy participants, the results on total energy (3-17 Hz), revealed a significant decrease in higher loads for the patients. Examining the both bands separately, the study indicated that tremor had more variability in B2 band regardless of participating group. Dominance of the energy in the bands changed over the conditions for PD, but not for the healthy controls. For the patients, energy in the PD band was dominant at rest, posture, and lower loads (post-hoc). At medium to high loads, the energy was not significantly different between the bands; and at MVC the energy in physiological band was dominant. Examinations of both the total and B2 energies, suggested that some of the diversity, in the reported results in the literature, might be related to the level of loading. This study confirmed that loading, below 20% MVC, had minimal effect on tremor amplitude of PD patients (consistent with the results mentioned in [72, 92, 49]). The results also confirmed that loading, of 20% MVC and above, significantly changed the amplitude (energy) of tremor in this population (supporting the results in [67, 30]). In other words, null hypothesis was rejected in favor of H_{5_3} hypothesis; and loading up to MVC significantly changes hand tremor's amplitude in B2 (and also changes the total energy).

Classifying PD patients according to severity of their tremor, the results complied with hypothesis H_{5_3}, as well. In other words, using any categorization scheme (Cat1-7), tremor energy in B2 for sub-group with larger tremors exhibited significant decrease at higher levels of loading.

Using clustering, the results affirmed hypothesis H_{5_3} as well. For the whole PD group, however, this significant change of tremor amplitude , when loading is increased up to MVC, might be driven by one or two sub-groups in this population. Similar results were obtained when the square root of peak magnitude was used instead of tremor RMS amplitude. After separating PD participants to sub-groups, at least one group exhibited significant change of tremor peak with increased loading. In the mentioned analyses, if there was a sub-group that exhibited higher than normal (than those of healthy controls) energy in B1, that sub-group was among the PD patients that loading significantly changed their tremors. The aforementioned results suggested affirming hypothesis H_{5_3}. This might indicate a significant interaction between the two mechanisms at higher levels of loading.

The different trends in tremor's peak frequency (Fig. 5.23), for G1 with stronger than normal tremors in B1, might be another sign for this interaction.

Finally, the results of tremor analysis, with both measures for tremor amplitude, affirmed sub-hypotheses H_{5_2} and H_{5_3} (related to the co-existence of classic PD tremor and physiological tremor mechanisms). The results based on tremor's peak magnitude were not able to reject null hypothesis in H_{5_1}, although on average PD participants had larger peaks in physiological band as well. Therefore, physiological tremor's importance for some of the PD patients (sub-groups) could be better proven using the RMS energy as amplitude measure.

5.5.4 Medication Effect : H_7

Dopaminergic medication effect on PD patients' tremor amplitude (RMS amplitude) was compared between the bands, but not among the conditions. The results revealed that the only significant (and meaningful) effect of medication was to lower tremor RMS amplitude in the PD band. This finding was in agreement with studies (e.g. [33]) that reported no significant decrease of tremor peaks of higher frequency, rather than studies (e.g. [30]) reporting significant decrease of the peaks of both lower and higher frequencies. One possible question could be whether this is also true for the PD patients with visible tremors, who had larger tremor outside the PD band, as well. Fig.E.5 presented the comparison when PD patients were classified according to their total-tremor UPDRS scores (items 20-21, hands-legs). Post-hoc analysis (Fig. E.6) revealed that even for PD group with significantly higher energy in physiological band, this energy did not decrease significantly with medication.

In other words, null hypothesis was rejected in favor of H_7 hypothesis and dopaminergic medication could only affect tremor components in PD band significantly. This might imply that the second important component in tremors of this population was not originally related to classic PD tremor.

Chapter 6

Summary and Discussions

Parkinson's disease (PD) is a neuro-degenerative disorder that affects approximately 1% of the population over the age of 65 [116]. With nearly 75% of PD patients exhibiting tremor, PD tremor is the second most prevalent after Essential tremor (ET)[18]. The present study addressed the action tremor in PD population. The term *action* tremor includes oscillations during maintaining a posture, movement (kinetic), task specific, and isometric contractions. This study examined tremors at rest, in postural condition, and while loads (or isometric forces) are applied on the limb.

Tremor was recorded tri-axially by accelerometers. It was observed that regardless of condition, PD tremor was not uniformly distributed along the three spatial axes; and tri-axial assessment of tremor is necessary at least to detect the dominant direction. With the current experimental setup, the tremors were dominant along the loading direction (assuming that the hand stayed in the sagittal plane, and no pronation/supination was involved); and study focused on examining the tremors in this direction.

Origins or mechanisms of tremor generation can be divided into two categories of *peripheral* and *central* and it is accepted that all tremors involve a combination of both [117]. In peripheral mechanism, the assumption is that every movable body limb can be considered as a pendulum that can oscillate at a resonant frequency in response to any mechanical perturbation. The perturbations are mainly the irregularities in subtetanic motor unit firing and the blood ejection at cardiac systole [36]. This low amplitude mechanical oscillation can lead to rhythmic activation of muscle receptors and initiate spinal (segmental) or long *reflex* loops. Because mechanics of the limb and reflex loops are the possible factors involved in these oscillations, they are also labeled as *mechanical-reflex* oscillations [118]. On the other hand, there are oscillatory activities within the central ner-

vous system that are transmitted to the peripheral muscles. Response of muscles to these oscillatory activities produce *central* tremors. Although both mechanisms are involved in every tremor, it is believe that in tremors such as PD and ET, rhythm of central oscillators dominate the peripheral effects [72].

The study summarized the diverse results on PD action tremor in the literature and hypothesized that the coexistence of physiological and classic PD mechanisms, and considerable difference between sub-types of tremulous PD patients, are responsible for most of the diversity in the previously reported studies. The study examined different methods of categorization, and showed that automatic classification (clustering) provided the most separable sub-groups. The sub-groups, showing different characteristics, were able to explain some of the diversity. For example, reported frequency of action tremor was usually higher than rest tremor in the ranges of 8-9 [32], 7-11 [30], and 7-12 Hz [20], but could also be as low as 4.8 Hz [34]. Our study, that examined both bands separately, confirmed all those results. While for some sub-groups the dominant component was in classic PD band, for others components in both bands were comparable (in terms of occurrence Figs. 5.22, E.10, and dominance Figs. 5.18, E.9).

Our results confirmed the previously reported results, by most of the researchers, that found mainly double peaked spectrum for PD action tremor [32][30][33]; The results also verified that, for some sub-groups, the tremor signals were mainly single-peaked over all conditions. The results were also in-line with the studies reporting a significant decrease only in the lower frequency components of action tremor on medication and no change in the high frequency components [33]; and contradicted reports of a similar tendency to decrease in the amplitude of components in both bands [30]. This might imply that, while the two mechanisms coexist, they are not originally related.

A main objective in the study was investigation of coexistence hypothesis for the two mentioned mechanisms. Neurological systems have nonlinear characteristics, and PD tremor has nonlinear dynamics [35]. Moreover, interactions between mechanisms were difficult to evaluate by only assigning shares to individual mechanisms. This was important because the physiological mechanism changes its main frequency with loading. In other words, two oscillators might have amplified each other and resonated or their interaction might have suppressed the oscillation [36]. Therefore, the RMS energy of tremors, which was less sensitive to mechanisms interaction, was favored over spectrum based amplitude measures.

Regardless of the categorization method, at least one sub-group exhibited significantly higher tremor energy compared to the healthy controls not only in the PD band, but

also in the physiological band. This was an indication that, for some sub-groups of PD, the physiological tremor is a very important mechanism, and is different between the healthy participants and PD patients. Our results, using tremor energy, did not reject the suggestion of coexistence for PD patients without visible tremors [70], but confirmed it for some sub-groups that generally had large tremors. The coexistence hypothesis was also affirmed by observing comparable peak magnitudes in the two bands. This was witnessed for majority of PD patients in all sub-groups. Furthermore, visual inspection of the peaks revealed that the number of peaks occurring in between the two bands is negligible, and the mentioned results are not sensitive to the choice of cut-off frequencies.

The need for the separation of tremulous PD patients into sub-groups, and the coexistence of physiological and classic PD tremor mechanisms for some of them would be of interest for both neuroscientists and engineers.

Neuroscience and Mechanisms of PD Action Tremor

Neuroscientists are interested in finding the driving mechanisms behind tremor to better alleviate tremor with pharmacological, surgical, and other methods. Since the results revealed that the physiological tremor mechanism is stronger than normal for some PD patients, the appropriate methods of treatment might be considered. For example, maybe exercise therapy [119],[120] should be recommended for those specific sub-groups as well as dopamine therapy. Furthermore, having considerable/dominant energy outside classic PD band in disabling action tremor, might be considered as a negative predicting factor for success of common pharmacological interventions or deep brain stimulation (DBS).

Mechanical Suppression/Cancellation of PD Tremor

Most of the current tremor suppression/cancelling devices are aimed either at physiological tremor [28] or at essential tremor (ET) [29]. Two main reasons why PD has not been considered yet should be the higher incidence of ET, and that dominant form of PD tremor is assumed to be at rest. However, more recent studies, with reported high incidences of up to 65% [33] and 93% [83], suggest that kinetic tremor impairments in PD may have been underestimated [112]. From engineering point of view, it would be interesting to know if the same methods can be applied for PD tremor suppression or cancellation and if not, what are the limiting assumptions.

Usually, the devices apply forces either directly to the tremulous joints (suppression) or to the instrument/intermediate (cancelling). The necessary forces are generated according

to active or passive strategies. In passive systems, dissipative force of a mechanical damper selectively attenuates the tremor, which is assumed to be of higher frequency (compared to intended movements) [10]. Active systems need to estimate the tremor component of the movement in real time to generate the forces. Because of inherent considerable delay, simple filtering is not the preferred choice for tremor estimation. Most of the devices [121],[122], use an adaptive notch filter called Weighted frequency Fourier linear combiner (WFLC) introduced by Riviere [123].

One limitation of WFLC is its failure in tracking more than one dominant frequency. Many PD action tremor studies have reported double peaked spectrums, which means a need for suppression in a wide band or simultaneous suppression of two frequencies. Although this shortcoming has been recently improved [124],[51], a clearer understanding of PD tremor behavior at different levels of muscle activation, would be beneficial for any adaptive tremor estimation algorithm. Even if the peak frequencies in a band move significantly, information regarding this move would be beneficial.

Chapter 7

Future Directions

7.1 Future Work

Like any study, the results could be improved in many ways. Furthermore, the study of action tremor in PD patients provides many opportunities for future research, particularly if sub-groups with different characteristics and coexisting mechanisms are considered.

- More accurate and stronger haptic devices might eliminate the need for accelerometry and weights and pulleys, and become a standard clinical method of tremor assessment. Such devices, combined with a standard test procedure and automatic classification and access to electronic database, could quickly and objectively categorize PD patients. This categorization could help the clinician for a treatment suggestion, or the engineer for design/customization of the suppression device.

- Tremor is a multi degree of freedom movement. A more complete study could investigate similar hypotheses in other joints and degrees of freedom.

- In this study, a relatively complete set of data was collected that included tremor during free movement, and loaded movement. Movement related part has not been analyzed yet, many of the procedures for processing and analysis have been written; the related results could potentially strengthen the study.

- A similar study can compare different types of loading (viscous, spring, and inertial forces applied by a robotic device) to find out which type is better for tremor suppression.

- There are strong and promising mathematical techniques that are used in similar fields such as volcanic tremor extraction. For example, *Empirical mode decomposition*, could improve the accuracy of tremor extraction, particularly when tremor in movement is of interest. Similarly, in observing ENERGY in time-frequency space, Hilbert-Huang Transformation or Instantaneous frequency in spectral bands [94] worth trying.

- Adding Coherence analysis between EMG and tremor [57] may make the speculations on the mechanisms more reliable.

- As any experimental study, larger number of participants would increase the power in the analyses, particularly when the PD participants are divided into subgroups.

- Tremor is quite a variable phenomenon and varies considerably even for one patient. Increasing the length of tremor acquisition in related studies would be recommended. Visual feedback may also be effective and its influence could be studied.

- Including more information about the aspects of the disease and tremor itself can improve classification (Clustering). For example, including EMG signals and possible entrainment with loading, considering other subtypes in clinical assessment (like tremor-dominant, akinetic-rigid, etc.).

- If the study focuses on one dimension tremor, maybe finding the direction for maximum amplitude (from three-dimensional tremor in acceleration [47]) could improve the accuracy.

- Not all aspects of signal processing were optimized in our study. For example, finding 3 largest peaks in the whole spectrum and picking the largest peak in each band among them, or considering minimum ratio of 25% for the peak magnitudes to be considered comparable, could be optimized.

- Classification could be based on trends (or strength in rest and posture) in separate bands instead of total (3-17 Hz band).

- Although the same instruction (encouragement) were provided for acquiring MVC trials, this is not the most reliable method of finding maximum strength for individuals (for the targeted degree of freedom).

Appendix A

Experimental Elbow Setup

A.1 Labview Software Interface Capabilities
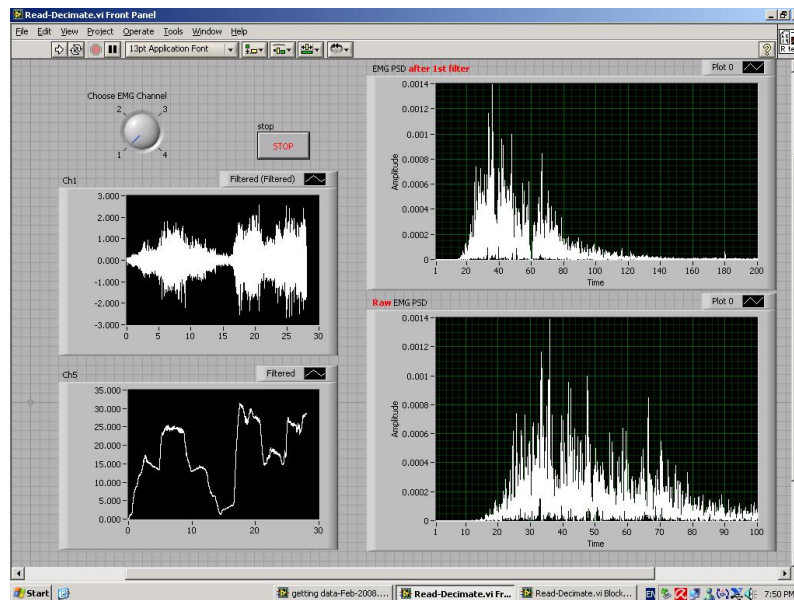
Figure A.1: The software had the capabilities of presenting components of each EMG or torque signals in time and spectrum domains.

A.2 Design of Experimental Apparatus
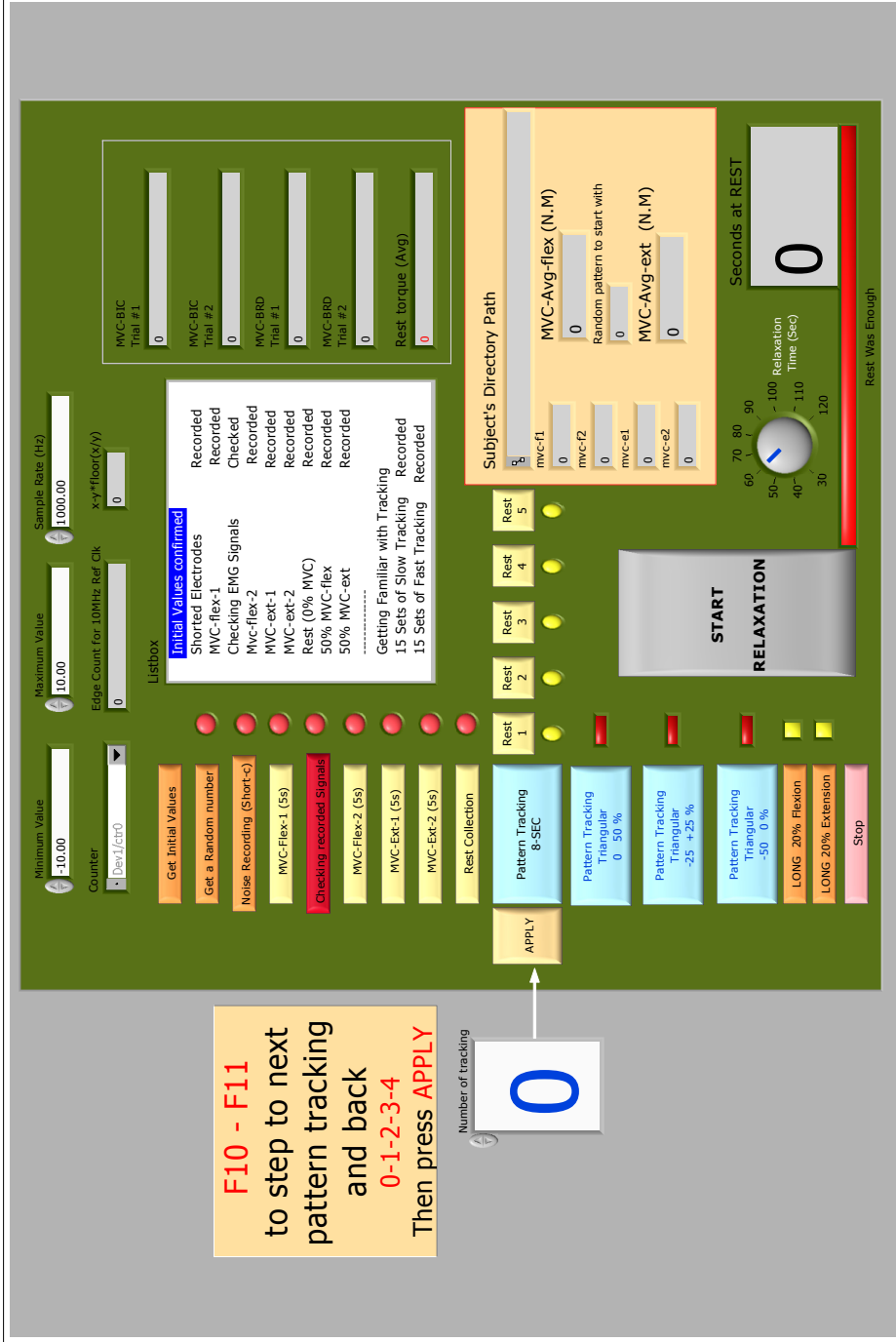
Figure A.2: User software interface, designed in LabVIEW^{TM}, to facilitate various steps of data collection. The interface provides automatic and flexible functioning for a faster and consistent data collection in conjunction with the elbow apparatus (Fig. A.3) and the related EMG signals.
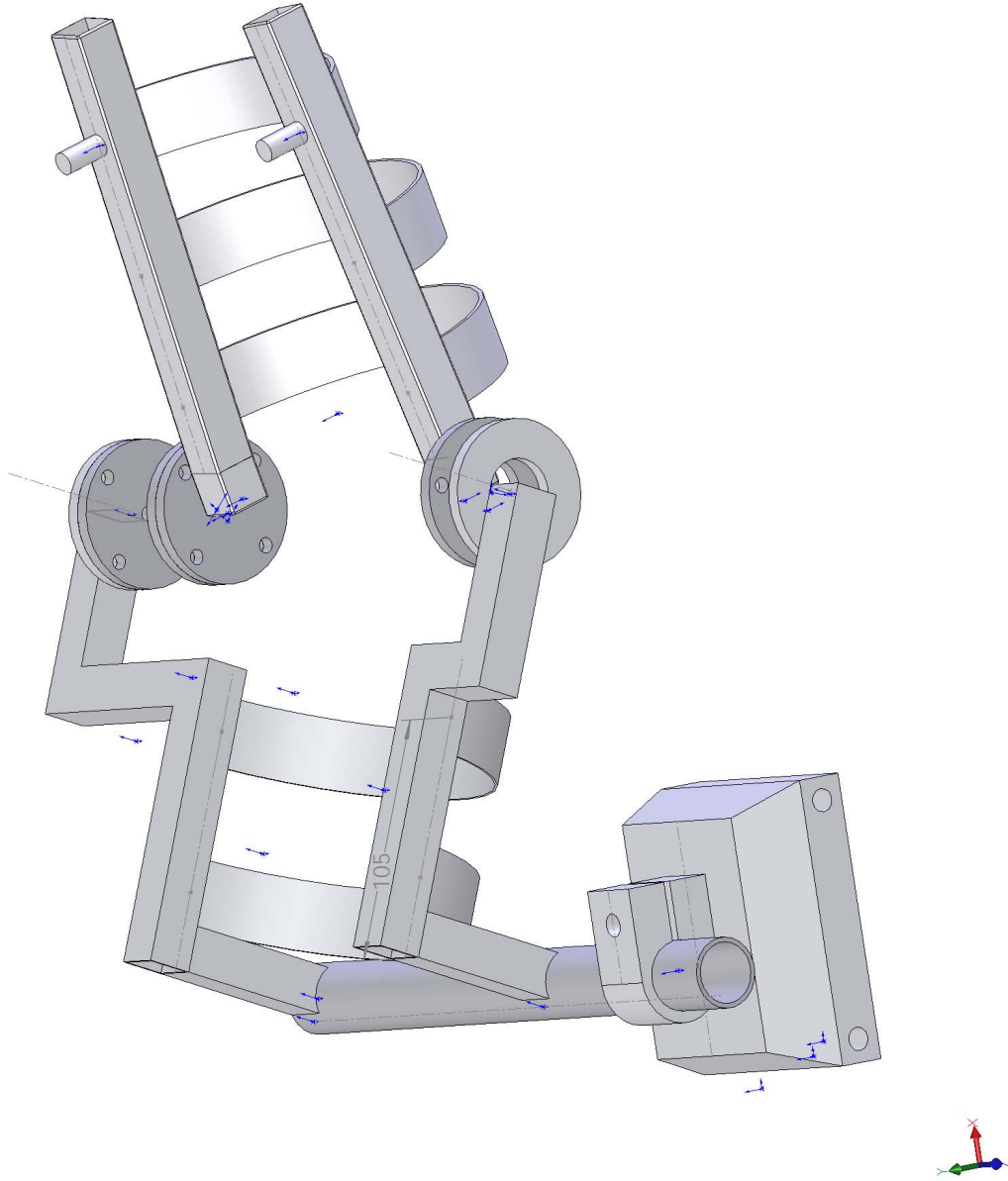
Figure A.3: Experimental apparatus, designed in SolidWorks™, to measure isometric torque. The apparatus is capable of measuring flexion/extension torque for both left/right hands, and at adjustable elbow and shoulder flexion angles. The actual piece, on which the wrist torque is applied, is not displayed

Appendix B

Adopted Digital Filters

All band-pass filters for accelerometer and EMG signals, and notch filters for removing power line interference in EMG signals were Finite Impulse Response (FIR) digital filters. These filters were used for their flatness of pass band and implementation via fast convolution [125].
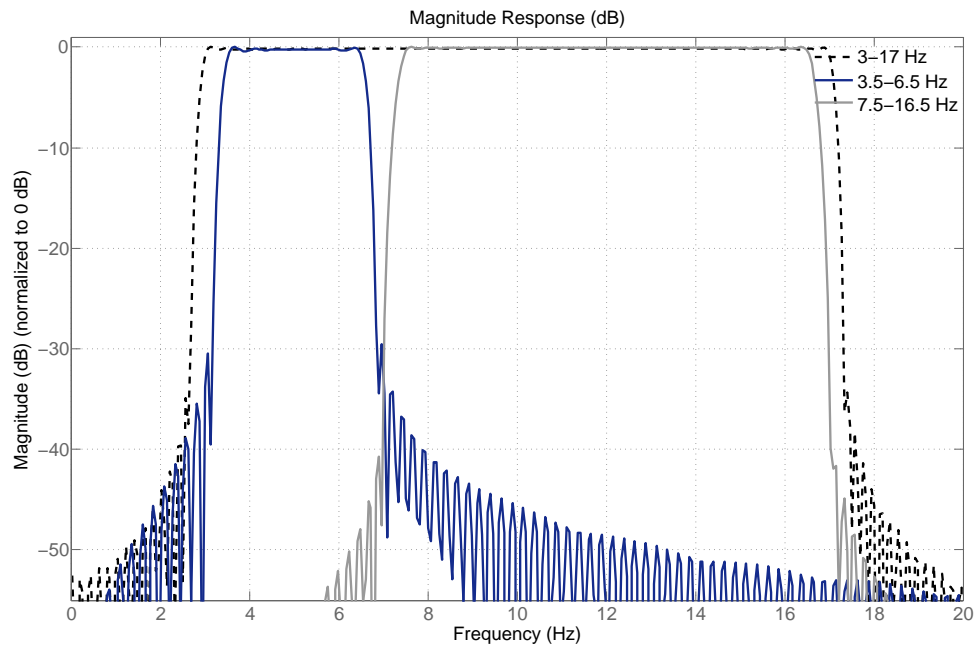
Figure B.1: The three adopted band-pass filters. Least square linear-phase FIR (firls) filters of order 4000 were designed and implemented in MATLAB.

Appendix C

Participants' Information: Tables Summarizing Demographic and Key Experimental Measurements

Table C.1: Demographic information of the PD participants including age, disease duration, sex, dominant and TD hands, medication and tremor related scores in Unified Parkinson's Disease Rating Scale (UPDRS).

Patient code	Age (yrs)	Disease duration[2] (yrs)	Sex	Dom[1] Hand	TD hand	Anti-Parkinsonian medication[3]	UPDRS on Tremor-Dom Side		
							Rest hand	Action hand	Total[2] hand-foot
01	67	4	F	R	L	LDCD	3.0	0.0	3.5
02	75	4	F	R	L	LDCD	2.5	3.0	7.5
03	65	4	F	R	R	LDCD,PR	3.0	2.5	7.5
04	72	0.5	M	R	R	LDCD	1.0	2.0	4.0
05	66	8	F	R	R	LDCD,EN,RA	0.5	0.0	1.5
06	63	2	F	R	L	LDCD	1.5	2.0	5.0
07	69	1	M	R	L	LDCD	2.0	1.5	4.5
08	76	9	M	R	R	LDCD,TR,PR	1.5	2.0	4.0
09	67	6	F	R	R	LDCD	3.0	2.0	8.0
10	67	11	M	R	R	LDCD,RA,DO,PR	0.5	0.0	1.0
11	77	4	M	R	R	LDCD	0.5	0.0	1.0
12	72	8	M	R	L	LDCD	1.5	1.5	4.0
13	52	9	F	R	R	LDCD	3.0	3.0	7.0
14	42	1	M	R	R	RO	1.0	1.0	2.0
15	76	2	M	R	R	LDCD	3.0	2.5	6.5
16	53	8	F	R	L	LDCD,EN	3.0	2.0	7.5
17	74	3	M	R	R	LDCD,RO	3.5	2.0	9.0
18	72	10	M	R	L	LDCD	3.0	2.0	6.0
19	68	3	M	L	L	LDCD	1.5	1.0	3.0
20	83	4	M	R	L	LDCD,PR	0.0	1.0	1.0
Sum[1]	67.8 (9.4)	5.1 (3.3)	12 M 8 F	19 R 1 L	11 R 9 L		1.9 (1.1)	1.6 (1.0)	4.7 (2.6)

[1] Dom, dominant; Sum, summary: Mean(SD), or Totals.
[2] duration, considered since diagnosis; Total, tremor-related UPDRS scores (items 20-21, hands-legs).
[3] LDCD, levodopa/carbidopa; PR, pramipexole dihydrochloride; EN, entacapone; RA, rasagiline; TR, trihexyphenidyl; DO, domperidone; RO, ropinirole.

Table C.2: Demographic information of the healthy control participants including age, sex, dominant and matched hands (MH), and measured experimental values on the MH.

Subject code	Age (yrs)	Sex	Dom[1] Hand	MVC(N) MH	%Multi-peak (MH)	Tremor[3]Total Energy (cm/s^2)			
						Rest	Posture	Loading	MVC
01	54	M	R-R	82	22.2	3.5	3.2	6.2	29.4
02	58	F	R-R	78	33.3	3.2	3.1	6.5	18.5
03	68	F	R-R	60	22.2	3.7	5.4	6.9	27.1
04	62	M	R-R	84	33.3	3.9	5.1	6.1	28.0
05	58	M	R-L	83	22.2	8.9	7.3	9.0	32.5
06	66	F	R-L	79	27.8	2.3	3.3	7.0	19.1
07	67	M	R-R	89	50.0	2.9	3.3	6.5	17.8
08	75	F	R-L	53	72.2	0.7	0.7	4.1	57.0
09	76	F	R-L	33	61.1	3.5	3.0	9.3	16.2
10	63	F	R-L	36	33.3	2.9	3.6	6.6	10.3
11	65	F	R-R	29	27.8	3.1	2.9	8.8	21.5
12	74	M	R-L	61	27.8	8.3	11.9	13.7	43.8
13	74	F	R-R	50	55.6	2.2	2.8	4.1	52.4
14	68	M	R-R	44	50.0	3.2	4.1	5.2	15.6
Sum[2]	66.3 (6.9)	6 M 8 F	14-8 R 0-6 L	61.5 (21)	38.5 (16.2)	3.7(2.2)	4.3(2.7)	7.1(2.5)	27.8(14.2)

[1] Dom, dominant hand -(vs. the matched hand).
[2] Sum, summary: Mean(SD), or Totals.
[3] Results in line with a study on healthy people, mean RMS acceleration: 1.1-11.7 (cm/s^2) [80].

Table C.3: Key measured experimental values for the PD subjects including MVC, percentage of double-peaked spectrums, average tremor energy in different conditions and its reduction on medication.

Patient code	TD	MVC (N) TD (Off)	% Multi-peak (Off)	Total tremor Energy / %Redu			UPDRS / Redu		
				Rest (cm/s^2) / %Redu	Posture	Loading[2]	Rest (4)	Posture (4)	Total (108)
01	L	8.5	83.3	11.8/-43	14.5/24	11.4/-25	3 / 2	0 / 0	26.5/16
02	L	29	66.7	27.2/-202	38 /-73	63.7/-23	2.5/0.5	3 / 0	41.5/ 9
03	R	74	61.1	40.2/71	41.2/54	9.8 /11	3 /0.5	2.5/1	34 /11
04	R	62	61.1	8.4 /51	3.7 / 8	9.4 / 3	1 /0.5	2 / 1	21.5/ 9
05	R	68	77.8	3.6 /14	3.2 /-9	3.6 / 6	0.5/0.5	0 / 0	18.5/8.5
06	L	62	55.6	8.3 /12	7.8 /-17	6.7 / 3	1.5/0.5	2 /0.5	32/ 8
07	L	41	55.6	11.7/8	7.3 /11	8.8 /51	2 / 0	1.5/0.5	21/6.5
08	R	36	61.1	4.5 /-4	7.2 /26	8.1 /23	1.5/0.5	2 / 0	41/9.5
09	R	17	33.3	6.3 /-5	9 /34	6.3 /-21	3 /1.5	2 / 2	43.5/21
10	R	47	66.7	4.3 / 5	3.7 / 5	3.9 /-182	0.5/ 0	0 / 0	31/ 9
11	R	81	16.7	7.6 /-43	11.4/-4	9.5 /-42	0.5/ 0	0 / 0	20/7.5
12	L	76	61.1	3.5 /-14	4.1 /-12	4.4 /-11	1.5/ 0	1.5/1.5	33.5/11
13	R	44	61.1	361/98	232/91	65 /85	3 / 2	3 / 2	27/13.5
14	R	68	55.6	29.1/66	16.8/26	7.7 /-16	1 / 1	1 / 1	10.5/8.5
15	R	60	50.0	4.5 /-56	21.1/-3	12.5/-25	3 /0.5	2.5/0.5	32.5/ 9
16	L	69	16.7	246/91	279/76	180/55	3 /0.5	2 / 0	42.5/10.5
17	R	87	27.8	165/61	168/53	57 /46	3.5/0.5	2 / 0	29.5/ 6
18	L	24	44.4	5.1 /-2	10.4/38	11.6/18	3 / 1	2 / 1	47.5/14.5
19	L	30	66.7	3.1 /-6	3.1 /-6	6.1 /16	1.5/ 1	1 /0.5	30/13
20	L	56	55.6	6.1 /25	7.8 /-69	10.5/-58	0 /-0.5	1 /0.5	38/9.5
Sum[1]		52.0(22.5)	53.9(18)	48(96)	44(81)	25(42)	1.9(1.1)	1.6(1.0)	31.1(9.6)
Redu				6(66)%	13(41)%	-4(55)%	0.6(0.6)	0.6(0.7)	10.5(3.6)

[1] % Redu, %reduction in total tremor energy (RMS in 3-17 Hz range) on medication. Reduction was also calculated for tremor-related and total UPDRS scores. Sum, summary: Mean(SD).

Appendix D

Details about Cluster Analysis

D]cluster-appen

The employed algorithm was *pdist* in MATLAB® R2008b (The MathWorks™, Natick, MA, USA) to find the pairwise distance between each item (participant). The resulted cluster trees, using *linkage* with hierarchical complete link clustering, were exhibited as dendrograms.

pdist (MATLAB): Calculates the Euclidean distance between each pair of objecs. The method for computing the distance can be accordingly chosen. Two measures of distance (dissimilarity) between the trends were chosen to be sample correlation, and sample Spearman's rank correlation between observations. Correlation between two sequence of pionts can be used as a measure for how their curvatures are similar.

linkage (MATLAB): When the distances between the items are calculated, creates a hierarchical cluster tree. It means first the whole items are divided to two most similar clusters, then to three, and so on.

dendrogram: Tree-like diagrams used to present the arrangement of the clusters, so that distances between the clusters are clear.

Appendix E

Tables and Figures for Statistical Analyses

Cell No.	Tukey HSD test; variable DV_1 (M4GDir1Cat1) Approximate Probabilities for Post Hoc Tests Error: Between; Within; Pooled MSE = .00419, df = 137.63							
	Var1	DIR	{1} .67249	{2} .51398	{3} .47593	{4} .63499	{5} .48908	{6} .55852
1	1	1		0.000020	0.000020	0.174017	0.000020	0.000020
2	1	2	0.000020		0.252426	0.000020	0.624463	0.058702
3	1	3	0.000020	0.252426		0.000020	0.963204	0.000023
4	2	1	0.174017	0.000020	0.000020		0.000020	0.003624
5	2	2	0.000020	0.624463	0.963204	0.000020		0.011934
6	2	3	0.000020	0.058702	0.000023	0.003624	0.011934	

Figure E.1: Post-hoc analysis for tremor's total energy, relative RMS values, as shown in Fig. 5.7. Dir:1,2, and 3 are X, Y, and Z respectively. Var1:1-2, correspond to PD and healthy groups respectively.
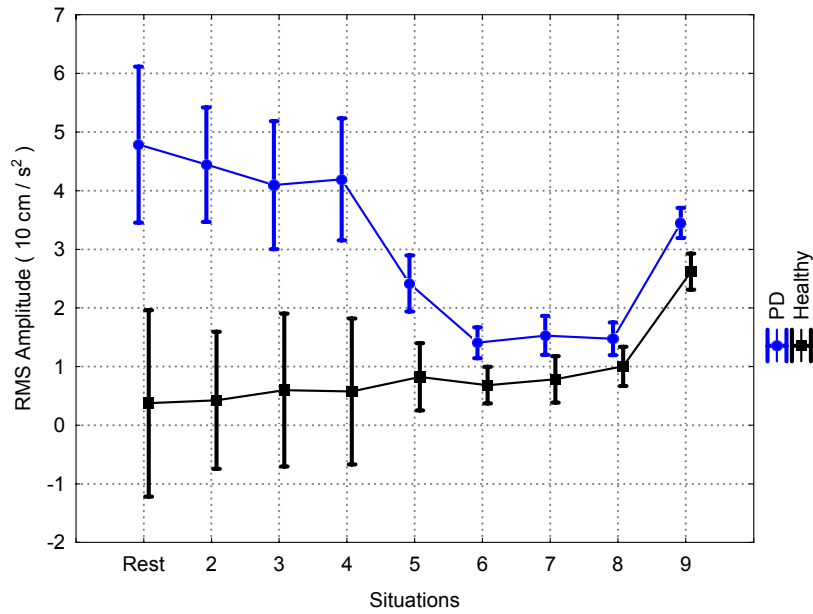
Figure E.2: Mean RMS amplitude of total tremor (3-17 Hz) over 9-conditions. A 2-way interaction between group and conditions ($F(8,528)=3.0$, $p=0.002$).
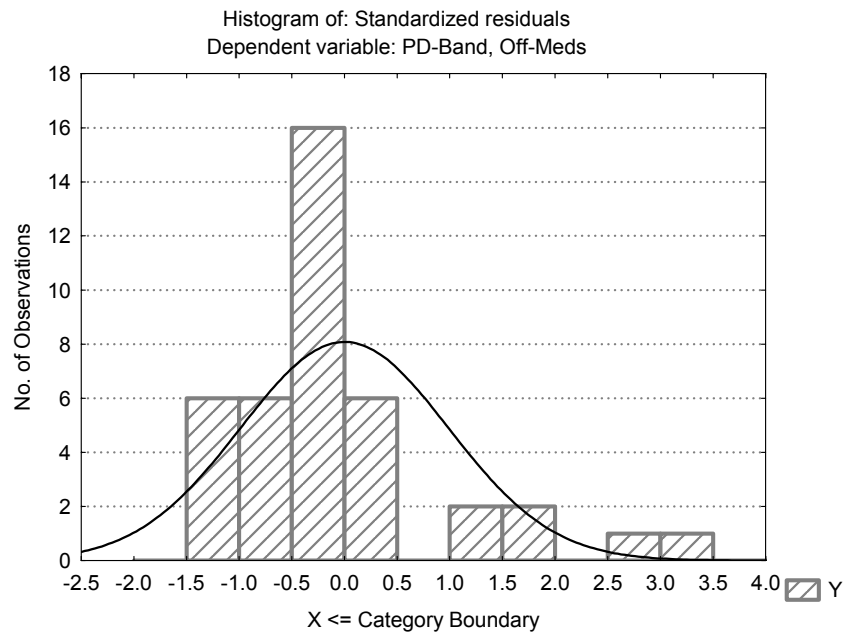
Figure E.3: Standardized residuals for observations of PD patients in TD hand and Off-medication. The histogram presents the results for tremor RMS amplitude in PD band and in posture situation.

Cell No.	MEDS	BAND	{1} 1.8743	{2} 2.6166	{3} 1.5395	{4} 1.4559	{5} 1.3418	{6} 1.1770
			Tukey HSD test; variable DV_1 (M_PD_Meds_3BandCat1) Approximate Probabilities for Post Hoc Tests Error: Within MSE = 6.5192, df = 76.000					
1	1	1		0.0028	0.4979	0.2507	0.0687	0.0060
2	1	2	0.0028		0.0001	0.0001	0.0001	0.0001
3	1	3	0.4979	0.0001		0.9979	0.9033	0.4073
4	2	1	0.2507	0.0001	0.9979		0.9908	0.6868
5	2	2	0.0687	0.0001	0.9033	0.9908		0.9534
6	2	3	0.0060	0.0001	0.4073	0.6868	0.9534	

Figure E.4: Post-hoc analysis of medication effects in the three bands. Meds 1-2, Off- and On-medication respectively. Band 1-3, physiological, PD, and central respectively.

Figure E.5: Tremor RMS amplitude in the three bands and medication effect. PD patients are categorized according to their total-tremor UPDRS scores (items 20-21, hands-legs) to Group-1 with larger tremors, and Group-2 without visible tremors.

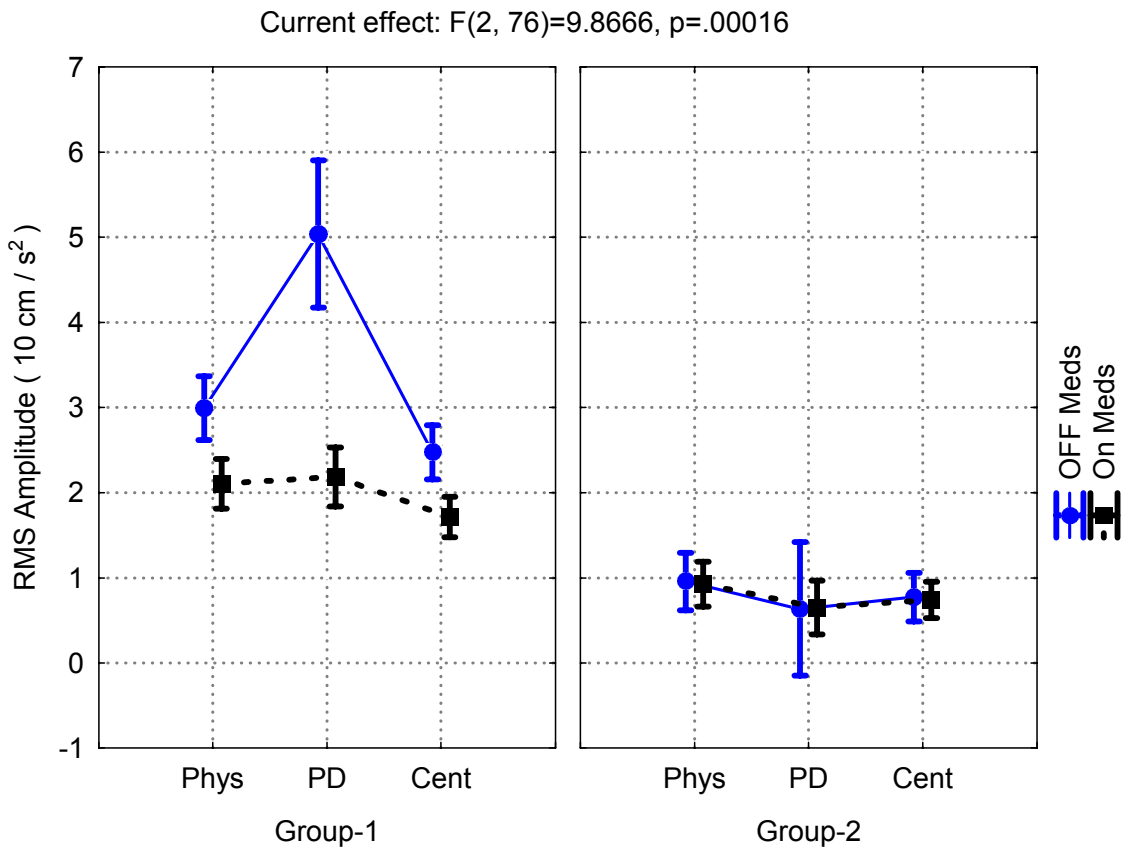| Cell No.	Var2	MEDS	BAND	{1} 2.9940	{2} 5.0381	{3} 2.4745	{4} 2.1038	{5} 2.1856	{6} 1.7140	{7} .95819	{8} .63532	{9} .77454	{10} .92587	{11} .65146	{12} .73761
1	1	1	1		0.000116	0.795670	0.092375	0.180918	0.001431	0.142007	0.045806	0.076340	0.127954	0.048680	0.066881
2	1	1	2	0.000116		0.000116	0.000116	0.000116	0.000116	0.000138	0.000129	0.000131	0.000136	0.000129	0.000130
3	1	1	3	0.795670	0.000116		0.975849	0.996845	0.256144	0.536382	0.254773	0.363742	0.504526	0.266191	0.332599
4	1	2	1	0.092375	0.000116	0.975849		1.000000	0.965066	0.865453	0.583879	0.718679	0.843438	0.599913	0.684061
5	1	2	2	0.180918	0.000116	0.996845	1.000000		0.879246	0.806353	0.502939	0.640714	0.780022	0.518791	0.604287
6	1	2	3	0.001431	0.000116	0.256144	0.965066	0.879246		0.992629	0.905047	0.961337	0.989649	0.913347	0.949664
7	2	1	1	0.142007	0.000138	0.536382	0.865453	0.806353	0.992629		0.981851	0.999886	1.000000	0.987865	0.999345
8	2	1	2	0.045806	0.000129	0.254773	0.583879	0.502939	0.905047	0.981851		0.999993	0.992194	1.000000	1.000000
9	2	1	3	0.076340	0.000131	0.363742	0.718679	0.640714	0.961337	0.999886	0.999993		0.999984	0.999998	1.000000
10	2	2	1	0.127954	0.000136	0.504526	0.843438	0.780022	0.989649	1.000000	0.992194	0.999984		0.995172	0.999855
11	2	2	2	0.048680	0.000129	0.266191	0.599913	0.518791	0.913347	0.987865	1.000000	0.999998	0.995172		1.000000
12	2	2	3	0.066881	0.000130	0.332599	0.684061	0.604287	0.949664	0.999345	1.000000	1.000000	0.999855	1.000000	

Tukey HSD test; variable DV_1 (M_PD_Meds_3BandCat1)
Approximate Probabilities for Post Hoc Tests
Error: Between; Within; Pooled MSE = 4.5698, df = 47.181

Figure E.6: Post-hoc analysis for tremor RMS amplitude in the three bands and medication effect, as shown in Fig. E.5. Var2:1-2, correspond to Groups 1 and 2 respectively. Meds:1-2, Off-, and On-medication respectively. Band:1-3, as described in section 3.6, Physiological, PD, and Central bands respectively.

Cell No.	Var2	BAND	{1} 2.9940	{2} 5.0381	{3} .95819	{4} .63532	{5} .85580	{6} .53399
			Tukey HSD test; variable DV_1 (M_PD_Healthy_3BandCat1) Approximate Probabilities for Post Hoc Tests Error: Between; Within; Pooled MSE = 4.7067, df = 97.644					
1	1	1		0.0008	0.0444	0.0115	0.0186	0.0040
2	1	2	0.0008		0.0001	0.0001	0.0001	0.0001
3	2	1	0.0444	0.0001		0.9736	1.0000	0.9831
4	2	2	0.0115	0.0001	0.9736		0.9993	1.0000
5	3	1	0.0186	0.0001	1.0000	0.9993		0.9563
6	3	2	0.0040	0.0001	0.9831	1.0000	0.9563	

Figure E.7: Post-hoc analysis for tremor RMS amplitude in the two bands and for three groups, as shown in Fig. 5.14. Var2:1-3, correspond to PD with larger (visible) and smaller tremor, and healthy respectively. Band:1-2, Physiological, and PD respectively.
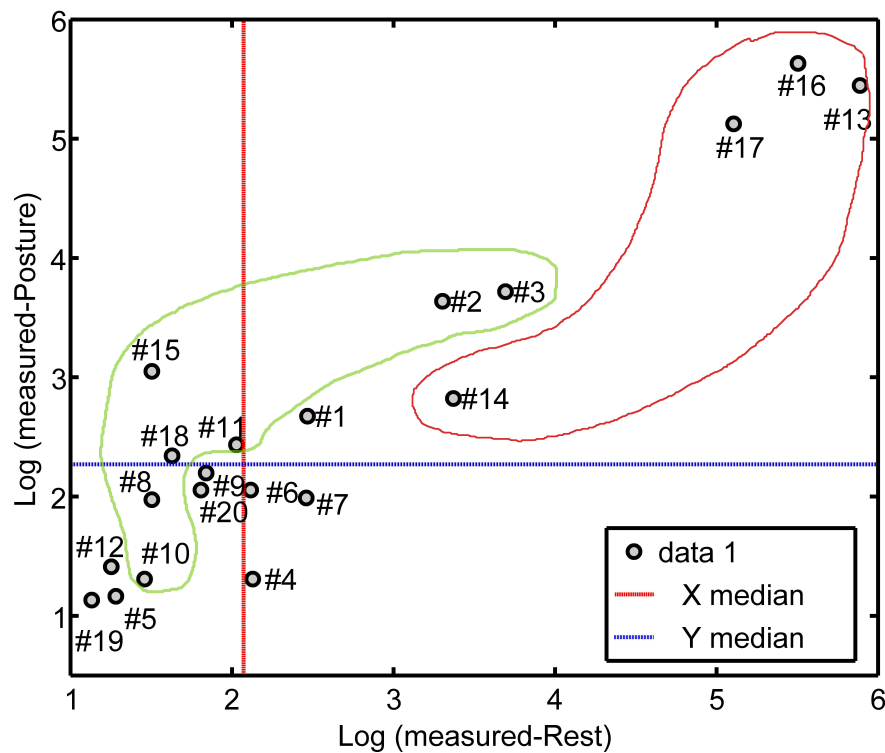
Figure E.8: PD patients are categorized first according to their severity of tremor (Cat7). The sub-group with larger tremors have above median tremors in both rest (horizontal) and posture (vertical). The results of automatic categorization (Cat9), based on the similarity of the trends in tremor amplitude (with loading) are also presented. Sub-group G-1 is seperated with a red line; sub-group G-2, with a green line; and the reminder are in sub-group G-3.
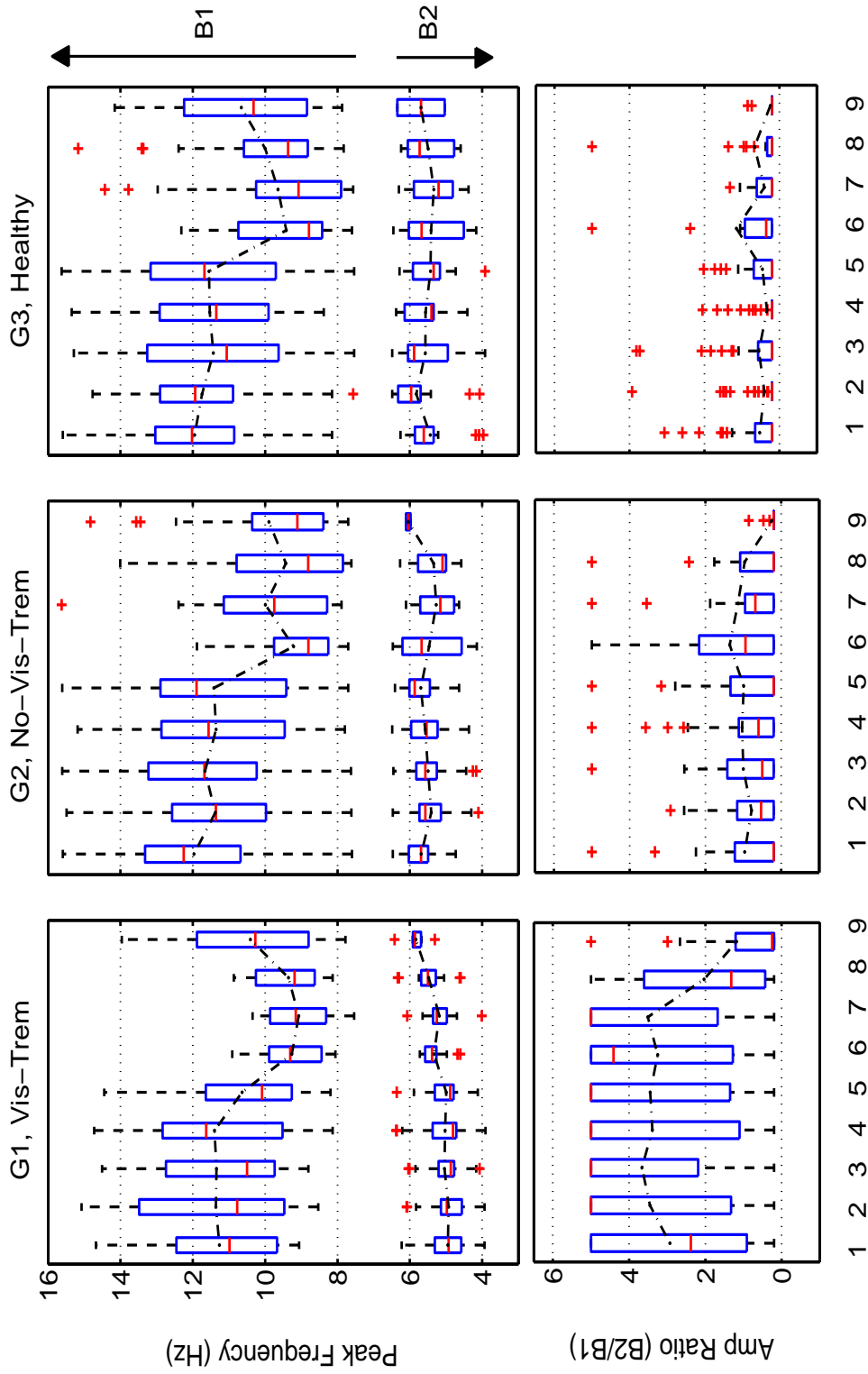
Figure E.9: Comparison of loading effect among 3 sub-groups, Cat1. Upper row boxplots, median frequency, quartiles, and trend in mean frequency (dash-dot line) for each band. Lower row, the ratio between the peak spectrum magnitude in the 2-bands.
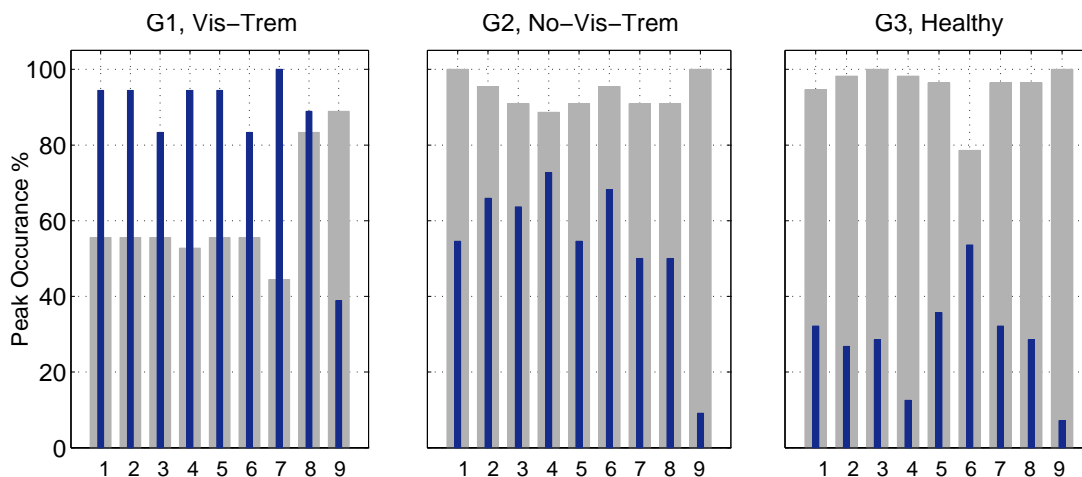
Figure E.10: Percentage of peak occurrence in the two bands of interest among analyzed segments of data. Gray wider bars correspond to peaks in the physiological band, B1. Narrow darker bars correspond to peaks in the PD band, B2. PD patients (categorized with Cat1 into sub-groups with visible tremor, G1; and non-visible tremor, G2) compared to healthy controls, G3.
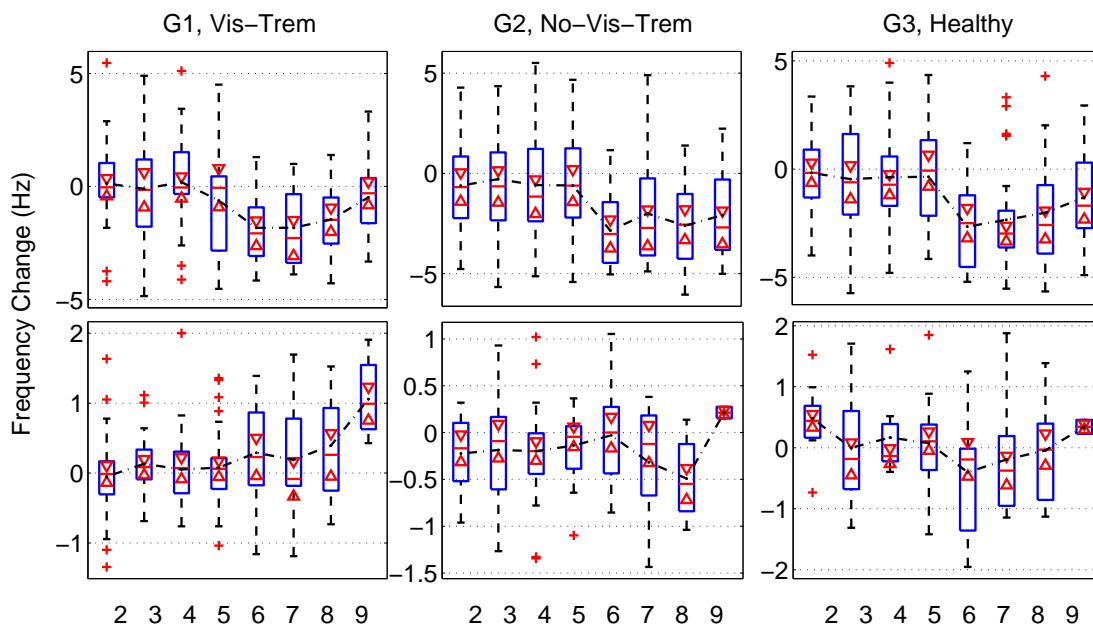
Figure E.11: Change in frequency of spectrum's peak in each band, with loading (conditions 2-9 compared to rest or condition 1). PD patients (categorized with Cat1 into groups with visible tremor, G1; and non-visible tremor, G2) compared to healthy controls, G3. Upper row, change in peaks' frequency in the physiological band, B1. Lower row, change in peaks' frequency in the PD band, B2. Dash-dot line, mean values.

Appendix F

UPDRS Assessment Scale

UNIFIED PARKINSON'S DISEASE RATING SCALE [113, 126]

UNIFIED PARKINSON'S DISEASE RATING SCALE

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)
0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.

3. Depression
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have starthesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?
0 = No
1 = Yes

37. Are "off" periods unpredictable?
0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

114

41. Any sleep disturbances, such as insomnia or hypersomnolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis?
(Record the patient's blood pressure, height and weight on the scoring form)
0 = No
1 = Yes

V. MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease.
STAGE 1 = Unilateral disease.
STAGE 1.5 = Unilateral plus axial involvement.
STAGE 2 = Bilateral disease, without impairment of balance.
STAGE 2.5 = Mild bilateral disease, with recovery on pull test.
STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.
STAGE 4 = Severe disability; still able to walk or stand unassisted.
STAGE 5 = Wheelchair bound or bedridden unless aided.

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50% = More dependent. Help with half, slower, etc. Difficulty with everything.
40% = Very dependent. Can assist with all chores, but few alone.
30% = With effort, now and then does a few chores alone or begins alone. Much help needed.
20% = Nothing alone. Can be a slight help with some chores. Severe invalid.
10% = Totally dependent, helpless. Complete invalid.
0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

Bibliography

[1] "Facts about parkinsons. parkinson society canada," http://www.parkinson.ca/atf/cf/7D/facts-en.pdf, March 2010. 1

[2] "Canadas aging population. health canada," Tech. Rep., 2002. [Online]. Available: http://www.phac-aspc.gc.ca/seniors-aines/publications/public/various-varies/papier-fed-paper/index-eng.php 1

[3] "Parkinson's disease: Social and economic impact. resources, parkinson society canada," http://www.parkinson.ca/site/c.kgLNIWODKpF/b.3536141/k.ED2E/Resources.htm, June 2003. 1

[4] J. Jankovic, *Handbook of Parkinson's disease (R. Pahwa and K. E. Lyons).* USA: informa, 2007, ch. 4: Pathophysiology and Clinical Assessment. 1, 14, 16

[5] L. Ai, J. Wang, and X. Wang, "Multi-features fusion diagnosis of tremor based on artificial neural network and d-s evidence theory," *Journal of Signal Processing*, vol. 88, pp. 2927–2935, 2008. 1, 28

[6] R. Vinjamuri, D. Crammond, D. Kondziolka, H.-N. Lee, and Z.-H. Mao, "Extraction of sources of tremor in hand movements of patients with movement disorders," *Information Technology in Biomedicine, IEEE Transactions on*, vol. 13, no. 1, pp. 49–56, Jan. 2009. 1, 7

[7] J. P. Giuffrida, D. E. Riley, B. N. Maddux, and D. A. Heldman, "Clinically deployable kinesia technology for automated tremor assessment," *Movement Disorders*, vol. 24, no. 5, pp. 723–730, 2009. 1, 7

[8] H. Wang, Q. Yu, M. M. Kurtis, A. G. Floyd, W. A. Smith, and S. L. Pullman, "Spiral analysis–improved clinical utility with center detection," *Journal of Neuroscience Methods*, vol. 171, no. 2, pp. 264 – 270, 2008. 1, 7, 8

[9] J. Rozman, A. Bartoli, and S. Ribari, "A new method for selective measurement of joint movement in hand tremor in parkinson's disease patients," *Journal of Medical Engineering & Technology*, vol. 31, no. 4, pp. 305–311, 2007. 1, 9

[10] J. Kotovsky and M. J. Rosen, "A wearable tremor-suppression orthosis," *Journal of Rehabilitation Research and Development*, vol. 35, no. 4, pp. 373–387, 1998. 1, 91

[11] C. A. Avizzano and M. Bergamasco, "Technological aids for the treatment of the tremor," in *Proceedings of the 6th International Conference on Rehabilitation Robotics (ICORR)*, Stanford University, Stanford, CA, USA, 1999. 1

[12] E. J. Fimbel, P. P. Domingo, D. Lamoureux, and A. Beuter, "Automatic detection of movement disorders using recordings of rapid alternating movements," *Journal of Neuroscience Methods*, vol. 146, no. 2, pp. 183 – 190, 2005. 1

[13] S. Patrick, A. Denington, M. Gauthier, D. Gillard, and A. Prochazka, "Quantification of the updrs rigidity scale," *Neural Systems and Rehabilitation Engineering, IEEE Transactions on*, vol. 9, no. 1, pp. 31 –41, march 2001. 1

[14] W. D. Weitzel and J. K. Carney, *Handbook of Stressful Transitions Across the Lifespan (T. W. Miller Ed.).* USA: Springer, 2010, ch. 17 : Life Stress and Managing Transitions. 1

[15] R. Capildeo and L. J. Findley, *Movement Disorders: Tremor.* Great Britain: MACMILLAN Press, 1984, ch. 1 : Classification of tremor. 2, 6, 7

[16] E. D. Louis and E. Rios, "Embarrassment in essential tremor: Prevalence, clinical correlates and therapeutic implications," *Parkinsonism & Related Disorders*, vol. 15, no. 7, pp. 535 – 538, 2009. 2

[17] S. L. Reese, "Psychosocial factors in parkinson's disease," *Disease-a-Month*, vol. 53, no. 5, pp. 291 – 295, 2007, non-Motor Aspects of Parkinson's Disease. 2

[18] J. I. Sirven and B. L. Malamut, *Clinical neurology of the older adult.* Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008, ch. 11 : Tremor. 2, 88

[19] G. Deuschl, P. Bain, and M. Brin, "Consensus statement of the movement disorder society on tremor. ad hoc scientific committee," *Movement Disorders*, vol. 13, no. Supl.3, pp. 2–23, 1998. 2, 7, 12, 14, 15, 16, 21

[20] J. Lance, R. Schwab, and E. Peterson, "Action tremor and the cogwheel phenomenon in parkinson's disease," *Brain*, vol. 86, pp. 95–110, 1963. 2, 8, 14, 36, 37, 48, 50, 89

[21] P. G. Wasielewski, J. M. Burns, and W. C. Koller, "Pharmacologic treatment of tremor," *Movement Disorders*, vol. 13, no. S3, pp. 90–100, 1998. 2, 15

[22] M. A. Hellmann, T. Sabach, E. Melamed, and R. Djaldetti, "Effect of subcutaneous apomorphine on tremor in idiopathic parkinson's disease," *Biomedicine & Pharmacotherapy*, vol. 62, no. 4, pp. 250 – 252, 2008. 2, 15

[23] A. Schrag, L. Schelosky, U. Scholz, and W. Poewe, "Reduction of parkinsonian signs in patients with parkinson's disease by dopaminergic versus anticholinergic single-dose challenges," *Movement Disorders*, vol. 14, no. 2, pp. 252–255, 1999. 2, 15, 50

[24] A. Schrag, J. Keens, and J. Warner, "Ropinirole for the treatment of tremor in early parkinson's disease," *European Journal of Neurology*, vol. 9, no. 3, pp. 253–257, 1999. 2, 15, 50

[25] C. Blahak, H. Bäzner, H.-H. Capelle, J. C. Wöhrle, R. Weigel, M. G. Hennerici, and J. K. Krauss, "Rapid response of parkinsonian tremor to stn-dbs changes: Direct modulation of oscillatory basal ganglia activity?" *Movement Disorders*, vol. 24, no. 4, pp. 1221–1225, 2009. 2

[26] F. Widjaja, C. Y. Shee, D. Zhang, W. T. Ang, P. Poignet, A. Bo, and D. Guiraud, "Current Progress on Pathological Tremor Modeling and Active Compensation using Functional Electrical Stimulation," in *Proceedings of the 6th Conference of the International Society for Gerontechnology, ISG'08*, 2008, pp. 001–006. 2

[27] A. L. Benabid, P. Pollak, D. Gao, D. Hoffmann, P. Limousin, E. Gay, I. Payen, and A. Benazzouz, "Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders," *Journal of Neurosurgery*, vol. 84, no. 2, pp. 203–214, 1996. 2

[28] C. N. Riviere, R. S. Rader, and N. V. Thakor, "Adaptive canceling of physiological tremor for improved precision in microsurgery," *Biomedical Engineering, IEEE Transactions on*, vol. 45, pp. 839–846, 1998. 2, 90

[29] M. Manto, E. Rocon, J. Pons, J. M. Belda, and S. Camut, "Evaluation of a wearable orthosis and an associated algorithm for tremor suppression," *Physiological Measurement*, vol. 28, pp. 415–425(11), April 2007. 2, 90

[30] H. Forssberg, P. Ingvarsson, N. Iwasaki, R. Johansson, and A. Gordon, "Action tremor during object manipulation in parkinson's disease," *Movement Disorders*, vol. 15, no. 2, pp. 244–254, 2000. 2, 8, 10, 11, 12, 15, 16, 17, 21, 37, 41, 48, 50, 51, 84, 85, 86, 87, 89

[31] R. Wenzelburger, J. Raethjen, K. Loffler, H. Stolze, M. Illert, and G. Deuschl, "Kinetic tremor in a reach-to-grasp movement in parkinson's disease," *Movement Disorders*, vol. 15, no. 6, pp. 1084–1094, 2000. 2, 15, 36, 37, 50, 84

[32] L. Findley, M. Gresty, and G. Halmaghy, "Tremor, the cogwheel phenomenon and clonus in parkinson's disease," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 44, pp. 534–546, 1981. 2, 16, 37, 48, 50, 51, 85, 89

[33] J. Raethjen, S. Pohle, R. Govindan, A. Morsnowski, R. Wenzelburger, and G. Deuschl, "Parkinsonian action tremor: Interference with object manipulation and lacking levodopa response," *Experimental Neurology*, vol. 194, no. 1, pp. 151 – 160, 2005. 2, 15, 16, 17, 50, 87, 89, 90

[34] U. Hadar and F. Rose, "Is parkinsonian arm tremor a resting tremor?" *European Neurology*, vol. 33, no. 3, pp. 221–228, 1993. 2, 50, 89

[35] A. Beuter, R. Edwards, and M. Titcombe, *Nonlinear Dynamics in Physiology and Medicine*. New York: Springer, 2003, ch. 10: Data Analysis and Mathematical Modeling of Human Tremor, pp. 303–355. 2, 10, 11, 12, 18, 21, 36, 37, 89

[36] R. J. Elble, "Central mechanisms of tremor," *Journal of Clinical Neurophysiology*, vol. 13, no. 2, pp. 133–144, 1996. 2, 6, 7, 12, 13, 15, 18, 49, 50, 88, 89

[37] L. J. Findley, "Classification of tremors," *Journal of Clinical Neurophysiology*, vol. 13, no. 2, pp. 122–132, 1996. 6

[38] R. Capildeo and L. J. Findley, *Movement Disorders: Tremor*. Great Britain: MACMILLAN Press, 1984, ch. 7 : Physiological and enhanced physiological tremor. 6, 14, 37

[39] P. Bain, "A combined clinical and neurophysiological approach to the study of patients with tremor," *Journal of Neurology Neurosurgery & Psychiatry*, vol. 69, pp. 839–844, 1993. 6

[40] M. Richards, K. Marder, L. Cote, and R. Mayeux, "Interrater reliability of the unified parkinson's disease rating scale motor examination," *Movement Disorders*, vol. 9, no. 1, pp. 89–91, 1994. 7

[41] N. M. Aly, J. R. Playfer, S. L. Smith, and D. M. Halliday, "A novel computer-based technique for the assessment of tremor in Parkinson's disease," *Age and Ageing*, vol. 36, no. 4, pp. 395–399, 2007. 7

[42] G. Grimaldi and M. Manto, *Tremor: From Pathogenesis to Treatment.* USA: Morgan & Claypool, 2008. 7, 9, 19

[43] P. G. Bain, *Handbook of Essential Tremor and Other Tremor Disorders (K. E. Lyons and R. Pahwa Ed.s).* Taylor and Francis Group, 2005, ch. 7: The Clinical Assessment of Essential Tremor. 7

[44] M. Smeja, F. Foerster, G. Fuchs, D. Emmans, A. Hornig, and J. Fahrenberg, "24-h assessment of tremor activity and posture in parkinsons disease by multi-channel accelerometry," *Psychophysiology*, vol. 13, p. 245256, 1999. 8

[45] R. J. Elble and W. C. Koller, Eds., *Tremor.* Baltimore, Maryland: The Johns Hopkins University Press, 1990. 8

[46] P. G. Bain, L. J. Findley, P. Atchison, M. Behari, M. Vidailhet, M. Gresty, J. C. Rothwell, P. D. Thompson, and C. D. Marsden, "Assessing tremor severity." vol. 56. 8

[47] J. Y. Matsumoto, D. W. Dodick, L. N. Stevens, R. C. Newman, P. E. Caskey, and W. Fjerstad, "Three-dimensional measurement of essential tremor," *Movement Disorders*, vol. 14, no. 2, pp. 288–94, 1999. 8, 93

[48] J. D. Frost, "Triaxial vector accelerometry: A method for quantifying tremor and ataxia," *Biomedical Engineering, IEEE Transactions on*, vol. BME-25, no. 1, pp. 17 –27, jan. 1978. 8

[49] R. Meshack and K. Norman, "A randomized controlled trial of the effects of weights on amplitude and frequency of postural hand tremor in people with parkinson's disease," *Clinical Rehabilitation*, vol. 16, pp. 481–492, 2002. 8, 17, 51, 82, 86

[50] Y. Su, C. Allen, D. Geng, D. Burn, U. Brechany, G. Bell, and R. Rowland, "3-d motion system ("data-gloves"): application for parkinson's disease," *Instrumentation and Measurement, IEEE Transactions on*, vol. 52, no. 3, pp. 662 – 674, jun. 2003. 8

[51] U.-X. Tan, K. Veluvolu, W. T. Latt, C. Y. Shee, C. Riviere, and W. T. Ang, "Estimating displacement of periodic motion with inertial sensors," *IEEE Sensors*, vol. 8, no. 8, pp. 1385–1388, 2008. 8, 91

[52] H. K. E. Young, R R, "Physiological tremor enhanced by manoeuvres affecting the segmental stretch reflex." *Journal of Neurology, Neurosurgery & Psychiatry.* 8

[53] P. E. O'Suilleabhain and R. B. Dewey, "Validation for tremor quantification of an electromagnetic tracking device," *Movement Disorders*, vol. 16, no. 2, pp. 265–271, 2001. 8

[54] F. Widjaja, C. Shee, W. Latt, W. Au, P. Poignet, and W. Ang, "Kalman filtering of accelerometer and electromyography (emg) data in pathological tremor sensing system," in *Proceedings of the IEEE International Conference on Robotics and Automation, ICRA 2008.*, may. 2008, pp. 3250–3255. 8

[55] G. Grimaldi, P. Lammertse, N. Van Den Braber, J. Meuleman, and M. Manto, "Effects of inertia and wrist oscillations on contralateral neurological postural tremor using the wristalyzer, a new myohaptic device," *Biomedical Circuits and Systems, IEEE Transactions on*, vol. 2, no. 4, pp. 269 –279, dec. 2008. 8

[56] C. Duval and J. Jones, "Assessment of the amplitude of oscillations associated with high-frequency components of physiological tremor: impact of loading and signal differentiation," *Experimental Brain Research*, vol. 163, no. 2, pp. 261–266, 2005. 8, 13, 16, 17

[57] M. Hroux, G. Pari, and K. Norman, "The effect of inertial loading on wrist postural tremor in essential tremor," *Clinical Neurophysiology*, vol. 120, no. 5, pp. 1020 – 1029, 2009. 8, 17, 93

[58] K. Norman, R. Edwards, and A. Beuter, "The measurement of tremor using a velocity transducer: comparison to simultaneous recordings using transducers of displacement, acceleration and muscle activity," *Journal of Neuroscience Methods*, vol. 92, pp. 41–54, 1999. 9, 15, 41, 51

[59] P. E. Ingvarsson, A. M. Gordon, and H. Forssberg, "Coordination of manipulative forces in parkinson's disease," *Experimental Neurology*, vol. 145, no. 2, pp. 489 – 501, 1997. 9

[60] T. Eakin, K. Francis, and W. Spirduso, "Decoupling tremor and volitional force control factors in analyses of motor task performance," *Computational Statistics & Data Analysis*, vol. 37, no. 3, pp. 363 – 372, 2001. 9

[61] P. Brown, D. Corcos, and J. Rothwell, "Does parkinsonian action tremor contribute to muscle weakness in Parkinson's disease?" *Brain*, vol. 120, no. 3, pp. 401–408, 1997. 9, 15, 50

[62] E. Kunesch, A. Schnitzler, C. Tyercha, S. Knecht, and G. Stelmach, "Altered force release control in parkinson's disease," *Behavioural Brain Research*, vol. 67, no. 1, pp. 43 – 49, 1995. 9

[63] E. P. Lukhanina, M. T. Kapoustina, and I. N. Karaban, "A quantitative surface electromyogram analysis for diagnosis and therapy control in parkinson's disease," *Parkinsonism & Related Disorders*, vol. 6, no. 2, pp. 77 – 86, 2000. 9

[64] I. Milanov, "Electromyographic differentiation of tremors," *Journal of Clinical Neurophysiology*, vol. 112, pp. 1626–1632, 2001. 9, 37, 48

[65] R. Edwards and A. Beuter, "Using Time Domain Characteristics to Discriminate Physiologic and Parkinsonian Tremors." *Journal of Clinical Neurophysiology*, vol. 17, no. 1, pp. 87–100, 2000. 10

[66] A. Beuter and R. Edwards, "Using Frequency Domain Characteristics to Discriminate Physiologic and Parkinsonian Tremors." *Journal of Clinical Neurophysiology*, vol. 16, no. 5, pp. 484–494, 1999. 10, 11

[67] J. A. Burne, T. Blanche, and J. J. Morris, "Muscle loading as a method to isolate the underlying tremor components in essential tremor and parkinson's disease," *Muscle & Nerve*, vol. 30, no. 3, pp. 347–355, 2004. 11, 16, 17, 51, 86

[68] J. Jankovic, K. Schwartz, and W. Ondo, "Re-emergent tremor of parkinson's disease," *Journal of Neurology Neurosurgery & Psychiatry*, vol. 67, pp. 646–650, 1999. 11, 15, 16, 37, 51, 57

[69] D. Manolakis, V. Ingle, and S. Kogon, *Statistical and adaptive signal processing: spectral estimation, signal modeling, adaptive filtering, and array processing.* ARTECH HOUSE, 2005. 11, 31

[70] A. Beuter, E. Barbo, R. Rigal, and P. Blanchet, "Characterization of subclinical tremor in parkinson's disease," *Movement Disorders*, vol. 20, no. 8, pp. 945–950, 2005. 11, 16, 17, 37, 48, 60, 90

[71] C. Duval, "Rest and postural tremors in patients with parkinson's disease," *Brain Research Bulletin*, vol. 70, pp. 44–48, 2006. 11, 37

[72] V. Hömberg, H. Hefter, K. Reiners, and H. J. Freund, "Differential effects of changes in mechanical limb properties on physiological and pathological tremor." *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 50, no. 5, pp. 568–579, 1987. 12, 13, 17, 51, 86, 89

[73] C. Duval, A. Sadikot, and M. Panisset, "The detection of tremor during slow alternating movements performed by patients with early parkinson's disease," *Experimental Brain Research*, vol. 154, pp. 395–398, 2004. 12, 15, 16, 21

[74] J. H. J. Allum, *Movement Disorders: Tremor (L. J. Findley, R. Capildeo Eds.)*. MACMILLAN Press, 1984, ch. 8 : Segmental reflex, muscle mechanical and central mechanisms underlying human physiological tremor. 12, 13, 49

[75] N. Huang and J. Tetrud, *Handbook of Essential Tremor and Other Tremor Disorders (Lyons KE and Pahwa R.)*. Taylor & Francis, 2005, ch. 24: Physiological Tremor, pp. 361–368. 12, 13, 14, 37

[76] J. Raethjen, F. Pawlas, M. Lindemann, R. Wenzelburger, and G. Deuschl, "Determinants of physiologic tremor in a large normal population," *Clinical Neurophysiology*, vol. 111, no. 10, pp. 1825 – 1837, 2000. 12, 13, 49

[77] C. D. Marsden, J. C. Meadows, G. W. Lange, and R. S. Watson, "Effect of deafferentation on human physiological tremor," *The Lancet*, vol. 290, no. 7518, pp. 700 – 702, 1967. 12

[78] J. H. McAuley and C. D. Marsden, "Physiological and pathological tremors and rhythmic central motor control," *Brain*, vol. 123, no. 8, pp. 1545–1567, 2000. 13

[79] E. G. Walsh, *Muscles, masses and motion : the physiology of normality, hypotonicity, spasticity and rigidity*, 1st ed. London: Mac Keith Press, 1992. 13

[80] R. J. Elble, "Characteristics of physiologic tremor in young and elderly adults," *Clinical neurophysiology*, vol. 114, no. 4, pp. 624–635, 2003. 13, 53, 100

[81] J. Raethjen, M. Lauk, B. Kster, U. Fietzek, L. Friege, J. Timmer, C. Lcking, and G. Deuschl, "Tremor analysis in two normal cohorts," *Clinical Neurophysiology*, vol. 115, no. 9, pp. 2151 – 2156, 2004. 13, 17

[82] I.-S. Hwang, Y.-C. Chen, and P.-S. Wu, "Differential load impact upon arm tremor dynamics and coordinative strategy between postural holding and position tracking," *European Journal of Applied Physiology*, vol. 105, no. 6, pp. 945–57, 2009. 13

[83] E. Louis, G. Levy, L. Cote, H. Mejia, S. Fahn, and K. Marder, "Clinical correlates of action tremor in parkinson disease," *Archives of Neurology*, vol. 58, no. 10, pp. 1630–1634, 2001. 14, 36, 50, 84, 90

[84] H. Teravainen and D. Calne, "Action tremor in parkinson's disease," *Journal of Neurology Neurosurgery & Psychiatry*, vol. 43, pp. 257–263, 1980. 14, 16

[85] P. G. Bain, "THE MANAGEMENT OF TREMOR," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 72, no. suppl 1, pp. i3–i9, 2002. 15

[86] M. M. Sturman, D. E. Vaillancourt, L. V. Metman, R. A. E. Bakay, and D. M. Corcos, "Effects of subthalamic nucleus stimulation and medication on resting and postural tremor in Parkinson's disease," *Brain*, vol. 127, no. 9, pp. 2131–2143, 2004. 15

[87] G. Deuschl, J. Raethjen, R. Baron, M. Lindemann, H. Wilms, and P. Krack, "The pathophysiology of parkinsonian tremor: a review," *Journal of Neurology*, vol. 247, no. 5, pp. V/33–V/48, 2000. 15, 16, 36, 50, 84, 85

[88] I.-S. Hwang, C.-C. K. Lin, and P.-S. Wu, "Tremor modulation in patients with parkinson's disease compared to healthy counterparts during loaded postural holding," *Journal of Electromyography and Kinesiology*, vol. 19, no. 6, pp. e520 – e528, 2009. 15

[89] S. Hua, S. G. Reich, A. T. Zirh, V. Perry, P. M. Dougherty, and F. A. Lenz, "The Role of the Thalamus and Basal Ganglia in Parkinsonian Tremor," *Movement Disorders*, vol. 13, no. S3, pp. 40–42, 1998. 16

[90] P. M. H. RACK and H. F. ROSS, "THE ROLE OF REFLEXES IN THE RESTING TREMOR OF PARKINSON'S DISEASE," *Brain*, vol. 109, no. 1, pp. 115–141, 1986. 16

[91] G. Deuschl, P. Krack, M. Lauk, and J. Timmer, "Clinical neurophysiology of tremor," *Journal of Clinical Neurophysiology*, vol. 13, no. 2, p. 110, 1996. 17

[92] A. Lang and C. Zadikoff, *Handbook of Essential Tremor and Other Tremor Disorders (Lyons KE and Pahwa R.).* New York: Taylor & Francis, 2005, ch. 13: Parkinsonian Tremor, pp. 195–220. 19, 21, 36, 37, 49, 51, 83, 86

[93] L. Sornmo and P. Laguna, *Bioelectrical Signal Processing in Cardiac and Neurological Applications.* Burlington: Elsevier, 2005. 21, 22, 25, 26, 28

[94] P. Lesage, F. Glangeaud, and J. Mars, "Applications of autoregressive models and time-frequency analysis to the study of volcanic tremor and long-period events," *Journal of volcanology and geothermal research*, vol. 114, pp. 391–417, 2002. 25, 93

[95] M. Misti, Y. Misti, G. Oppenheim, and J.-M. Poggi, *Wavelets and their Applications.* Great Britain: Antony Rowe Ltd, 2007. 28

[96] M. Al-Kalbani, N. Collins, G. Boyle, T. Foran, F. Hegarty, N. Sheahan, and D. Coakley, "Recovering the ocular microtremor signal using wavelet denoising technique," in *Proceedings of the IEEE International Conference on Signal Processing and Communications, ICSPC 2007.*, Nov. 2007, pp. 1571–1574. 28

[97] R. Wyzgolik, "Wavelet analysis in sensors signal processing," in *Proceedings of Optoelectronic and Electronic Sensors*, August 2001, pp. 315–322. 28

[98] S. Kay and J. Marple, S.L., "Spectrum analysis-a modern perspective," in *Proceedings of the IEEE*, vol. 69, no. 11, Nov. 1981, pp. 1380–1419. 30

[99] M. Gresty and D. Buckwell, "Spectral analysis of tremor: understanding the results." *Journal of Neurology, Neurosurgery, and Psychiatry*, vol. 53, pp. 976–981, 1990. 32

[100] P. Wallisch, M. Benayoun, M. Lusignan, A. Dickey, N. Hatsopoulos, and T. Baker, *Matlab for Neuroscientists: An Introduction to Scientific Computing in Matlab.* Academic Press, 2008. 34

[101] F. Rahimi, J. Callaghan, F. Janabi-Sharifi, and D. Wang, "Emg-biofeedback and load sharing problem in assistive and rehabilitation orthotic devices," in *Proceedings of the 10th Annual International Conference of the IEEE, Engineering in Medicine and Biology Society, EMBC 2009.*, Minnesota, MN, USA, sep. 2009, pp. 3000–3003. 36

[102] F. Rahimi, Q. Almeida, D. Wang, and F. Janabi-Sharifi, "Tremor suppression orthoses for parkinson's patients: A frequency range perspective," in *Proceedings of the 10th Annual International Conference of the IEEE, Engineering in Medicine and Biology Society, EMBC 2009.*, Minnesota, MN, USA, sep. 2009, pp. 1565–1568. 36

[103] F. Rahimi, D. Wang, Q. Almeida, and F. Janabi-Sharifi, "Isometric torque generation in a parkinsonian tremulous elbow and the effect of medication," in *Proceedings of the IEEE Toronto International Conference, Science and Technology for Humanity (TIC-STH), 2009*, Toronto, Canada, sep. 2009, pp. 285–289. 36

[104] R. J. Elble, "Tremor and dopamine agonists," *Journal of Neurology*, vol. 58, pp. S57–S62, 2002. 36

[105] G. Deuschl, J. Volkmann, and J. Raethjen, *Parkinson's Diseas & Movement Disorders (J. Jankovic and E. Tolosa)*. Philadelphia: Lippincott Williams & Wilkins, 2007, ch. 24-Tremors: Differential Diagnosis, Pathophysiology, and Therapy, pp. 298–320. 36

[106] W. Koller, B. Veter-Overfield, and R. Barter, "Tremors in early parkinson's disease," *Clinical Neuropharmacology*, vol. 12, no. 4, pp. 293–7, 1989. 36

[107] J. McLeod, "Pathophysiology of parkinson's disease," *Australian and New Zealand Journal of Medicine*, vol. 1, no. Supl. 1, pp. 19–23, 1971. 37, 48

[108] R. Loureiro, J. M. Belda-Lois, E. R. Lima, J. L. Pons, J. J. Sanchez-Lacuesta, and W. S. Harwin, "Upper limb tremor suppression in adl via an orthosis incorporating a controllable double viscous beam actuator," *Proceedings of the IEEE 9th International Conference on Rehabilitation Robotics*, pp. 119–122, 2005. 37

[109] J. Pons, E. Rocon, A. Ruiz, and J. Moreno, *Rehabilitation Robotics (Sashi S Kommu)*. Croatia: I-Tech Education and Publishing, 2007, ch. 25: Upper-Limb Robotic Rehabilitation Exoskeleton: Tremor Suppression. 37

[110] B. Giannesini, P. J. Cozzone, and D. Bendahan, "Non-invasive investigations of muscular fatigue: metabolic and electromyographic components," *Biochimie*, vol. 85, no. 9, pp. 873 – 883, 2003. 40

[111] D. E. Vaillancourt and K. M. Newell, "Amplitude changes in the 8-12, 20-25, and 40 hz oscillations in finger tremor," *Clinical Neurophysiology*, vol. 111, no. 10, pp. 1792 – 1801, 2000. 49

[112] P. Kraus, M. Lemke, and H. Reichmann, "Kinetic tremor in parkinson's disease - an underrated symptom," *Journal of Neural Transmission*, vol. 113, pp. 845–853, 2006. 50, 84, 90

[113] S. Fahn and R. Elton, *UPDRS program members. Unified Parkinsons Disease Rating Scale. In: S. Fahn , C. Marsden , M. Goldstein , D. Calne , editors. Recent Developments in Parkinsons Disease.* Florham Park, NJ: Macmillan Healthcare Information, 1987, vol. 2. 61, 110

[114] C. G. Goetz, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, G. T. Stebbins, M. B. Stern, B. C. Tilley, 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. V. Hilten, and N. LaPelle, "Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (mds-updrs): Process, format, and clinimetric testing plan," *Movement Disorders*, vol. 22, no. 1, pp. 41–47, 2007. 61

[115] P.-N. Tan, M. Steinbach, and V. Kumar, *Introduction to data mining.* Boston: Pearson Addison Wesley, 2006, ch. 8 : Cluster Analysis: Basic Concepts and Algorithms. 61

[116] C. M. Tanner and D. A. Aston, "Epidemiology of parkinson's disease and akinetic syndromes," *Current Opinion in Neurology*, vol. 13, pp. 427–430, 2000. 88

[117] L. J. Findley and R. Capildeo, *Movement Disorders: Tremor.* Great Britain: MACMILLAN Press, 1984. 88

[118] J. Raethjen and G. Deuschl, *Handbook of Essential Tremor and Other Tremor Disorders (Lyons KE and Pahwa R.).* New York: Taylor & Francis, 2005, ch. 3: Pathophysiology of Essential Tremor, pp. 27–49. 88

[119] M. Bilodeau, D. A. Keen, P. J. Sweeney, and R. M. Enoka, "Strength training can improve steadiness in persons with essential tremor," *Muscle & Nerve*, vol. 23, no. 5, pp. 771–778, 2000. 90

[120] J. W. L. Keogh, "Constraints on the control of physiological tremor," Ph.D. dissertation, Griffith University Gold Coast, 2005. 90

[121] C. Riviere, W.-T. Ang, and P. Khosla, "Toward active tremor canceling in handheld microsurgical instruments," *Robotics and Automation, IEEE Transactions on*, vol. 15, no. 5, pp. 793–800, October 2003. 91

[122] E. Rocon, J. Belda-Lois, A. Ruiz, M. Manto, J. Moreno, and J. Pons, "Design and validation of a rehabilitation robotic exoskeleton for tremor assessment and suppression," *Neural Systems and Rehabilitation Engineering, IEEE Transactions on*, vol. 15, no. 3, pp. 367–378, sept. 2007. 91

[123] C. N. Riviere, "Adaptive suppression of tremor for improved human-machine control," Ph.D. dissertation, The John Hopkins University, 1995. 91

[124] K. Veluvolu, U. Tan, W. Latt, C. Shee, and W. Ang, "Bandlimited multiple fourier linear combiner for real-time tremor compensation," in *Proceedings of the 29th Annual International Conference of the IEEE, Engineering in Medicine and Biology Society, EMBS 2007.*, Aug. 2007, pp. 2847–2850. 91

[125] C. Lessard, *Signal Processing of Random Physiological Signals*, 1st ed. USA: Morgan & Claypool, 2006. 97

[126] "Unified parkinson's disease rating scale," http://www.mdvu.org/library/ ratingscales/pd/, September 2010. 110