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Towards the Development of Wearable Tremor Suppression Systems Combining Functional Electrical Stimulation and Mechanical Actuation

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Abstract

Parkinson's disease (PD), the second most prevalent neurological disorder, is characterized by motor and non-motor symptoms including tremor. Wearable tremor suppression devices (WTSDs), have shown promising results for tremor reduction, using functional electrical stimulation (FES) or active actuators. However, results and study procedures are not consistent in the literature. Although stimulations below and above motor threshold can suppress tremor, the mechanisms of the first is still not clear, and the second might lead to muscle fatigue and discomfort over time. While active actuators have shown better results for tremor suppression, they are often heavy and bulky for daily use. Lastly, while many studies have analyzed characteristics of essential tremor (ET) under different circumstances, the difference between the pathophysiology of ET and PD suggests a need for better understanding of parkinsonian tremor characteristics.

To this end, a hybrid approach using electrical stimulation and mechanical suppression has been proposed. This system reduces the required motor torque and stimulation intensity for tremor suppression by using the other mechanism simultaneously, decreasing motor size, muscle fatigue, and discomfort. The hybrid approach improved tremor suppression by 12% and reduced voluntary motion tracking error by 57% compared to the FES-only approach in simulation. A case study showed that this approach could reduce the weight of a device with electric motors to about one-third of its initial weight.

Secondly, a systemic approach was proposed and tested to evaluate the effectiveness of various FES settings in parkinsonian tremor. Initially, individuals' tremor, sensory, and motor thresholds were evaluated. These measurements were used to generate stimulation combinations for tremor suppression at the wrist. Results showed that tremor suppression using FES highly depends on the tremor intensity, with a tremor power suppression ratio (TPSR) of $80.1 \pm 2.9\%$ and 59.55 ± 2.9 % for low to medium and higher tremor power intensities, respectively. Stimulations around the motor threshold showed an overall TPSR increase of 10% and 4% compared to below and above motor threshold stimulations, respectively.

Finally, approximate entropy (ApEn), frequency, power spectrum density, and magnitude of parkinsonian tremor were evaluated under different circumstances. An increase in ApEn from 0.74 $\pm$ 0.13 at baseline compared to 0.81 $\pm$ 0.22 with FES suppression aligns with previous studies, using surgery or medication for tremor suppression.

Understanding the effectiveness of different FES combinations on parkinsonian tremor can be used in further development of the hybrid approach, while findings of the last study are beneficial for the design of an adaptive controller.

Lay Summary

Many individuals across the world suffer from tremor. Tremor is one of the symptoms of many diseases including Parkinson's disease. Tremor has negative effects on people's lives and cannot be easily cured by medicine. As a potential solution, a worn robotic glove that can reduce tremor has become popular. These gloves reduce tremor by either twitching muscles or applying forces to the joints. However, currently they are heavy, bulky, or might result in muscle pain.

To improve these gloves, a new method was tested that reduces tremor by both twitching the muscles and applying force to the joints in a way that none of them become overwhelming and uncomfortable. Tests showed that using force and muscle twitch methods at the same time is better, since the same amount of tremor suppression can be achieved with less muscle twitch, and therefore, it causes less pain. Also, the tremor suppression requires less force on the joints, thus, less equipment on the glove, resulting in a lighter robotic glove.

Second, a test with individuals with Parkinson's disease was performed to find out how much muscle twitch can reduce tremor. Results showed that too little and too much muscle twitch have downsides, and an average value is better.

Lastly, parkinsonian tremor was studied for a better understanding of how tremor changes. These changes were compared at different times and situations. The results indicated that tremor not only changes in time but also is different while the individual is at rest or moving.

Overall, more tests are needed to build a good robotic glove. However, the results of this work showed that using both muscle twitch and force on the joints, while the level of muscle twitch is not very high or low, can be a good starting point for building a good robotic glove, as far as changes in the vibratory motion of tremor are being considered. Thus, the amount of twitch and force should be tuned based on the changes in tremor.

Statement of Co-Authorship

The presented work has been written by Zahra Habibollahi under the supervision of Dr. Ana Luisa Trejos. Three articles form the main body of this thesis. One article has been published in a peer reviewed journal, one has been accepted in a peer reviewed journal, and the last one is under review for publication. The extent of the collaboration of the co-authors is listed below.

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Dr. Yue Zhou: Co-author, collected patient data, and assisted in editing and correcting the manuscript.

Dr. Mary E. Jenkins: Co-author, recruited 18 participants with PD, supervised the experimental trial, and assisted in editing and correcting the manuscript.

Dr. S. Jayne. Garland: Co-author, assisted in development of the study protocol, and assisted in editing and correcting the manuscript.

Dr. Michael D. Naish: Co-author, supervised the development of the study and data analysis, and edited and corrected the manuscript.

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Dr. S. Jayne. Garland: Co-author, assisted in development of the study protocol, and assisted in editing and correcting the manuscript.

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Dr. Michael D. Naish: Co-author, supervised the development of the study and data analysis, and edited and corrected the manuscript.

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Dedicated to:

My dearest parents

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Nomenclature

Acronyms

ADL	Activities of Daily Living
AMT	Above Motor Threshold
ANOVA	Analysis of Variance
ApEn	Approximate Entropy
AR	Amplitude Reduction
BMT	Below Motor Threshold
DBS	Deep Brain Surgery
DC	Direct Circuit
DOF	Degrees of Freedom
EAP	Electroactive Polymers
ECRB	Extensor Carpi Radialis Brevis
ECRL	Extensor Carpi Radialis Longus
ECRU	Extensor Carpi Ulnaris
EFE	Elbow Flexion–Extionsion
eHWFLC-KF	Enhanced High-order Weighted-Frequency Fourier Linear Combiner in cascade with a Kalman Filter

EMG	Electromyography
ET	Essential Tremor
ETVM	Error when Tracking the Voluntary Motion
FCR	Flexor Carpi Radialis
FCU	Flexor Carpi Ulnaris
FDA	Food and Drug Administration
FES	Functional Electrical Stimulation
FPS	Forearm Pronation–Supination
GD	Goal-Directed
HT	Healthy Individual Tremor
IF	Index Finger
IFFE	Index Finger Flexion–Extionsion
IMU	Inertial Measurement Unit
MAA	Maximum Amplitude Attenuation
MDS-UPDRS	Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale
MFFE	Middle Finger Flexion–Extension
MPTP	1-Methyl-4-Phenyl-1,2,3,6-TetrahydroPyridine
MRF	Magnetorheological Fluid
MS	Multiple Sclerosis
MT	Motor Threshold
NA	Not Applicable
NMPC	Nonlinear Model Predictive Control

PD	Parkinson's Disease
PID	Proportional-Integral-Derivative
PSD	Power Spectral Density
PwP	People with Parkinson's Disease
RMA	Repeated Measures Analysis
RMS	Root-Mean-Squared
SD	Standard Deviation
SMA	Shape Memory Alloy
sMAD	Scaled Median Absolute Deviation
ST	Sensory Threshold
STN DBS	SubThalamic Nucleus Deep Brain Stimulation
TCA	Twisted and Coiled Actuators
TFE	Thumb Flexion–Extionsion
TPSP	Tremor Power Suppression Percentage
TPSR	Tremor Power Suppression Ratio
WFE	Wrist Flexion–Extension
WTSD	Wearable Tremor Suppression Device
WUD	Wrist Ulnar Deviation

Greek Variables

$\ddot{\theta}$	Joint angular acceleration
$\dot{\theta}$	Joint angular velocity
θ	Joint angle

τ_i	Torque generated by the flexor/extensor muscles due to stimulation
τ_m	Torque generated by the electrical motor
τ_p	Passive torque due to the passive dynamics in the muscle model
τ_{ac}	Muscle activation time constants
τ_{da}	Muscle deactivation time constants
τ_{fat}	Muscle fatigue time constant
τ_{rec}	Muscle recovery time constant

Latin Variables

a_1	Normalized FES amplitude for the wrist flexor
a_2	Normalized FES amplitude for the wrist extensor
F_i	Muscle force due to the electrical stimulation
f_l	Muscle force–length factor
f_v	Muscle force–velocity factor
F_{max}	Maximum muscle force
g	Gravitational constant
I	Moment of inertia
L	Hand length
m	Mass of the hand
p_{min}	Minimum level of muscle fatigue
$u_{1,2}$	Controller output to the FES system
u_3	Controller output to the motor
z	Actual current intensity from the FES unit

Units

$^\circ$	Degrees
$^\circ$/s	Degrees per second
dB	Decibel
Hz	Hertz
m	meters
mA	milli amperes
ms	milli seconds
Nm/rad	Newton meters per radians
rad/s	Radians per second

Chapter 1

Introduction

Parkinson's disease (PD) is the second most prevalent neurological disorder, and the incidence of PD has risen over the past two decades [1]. PD can have a large impact on society by affecting the quality of life for people with Parkinson's disease (PwP) and having consequences for caregivers.

Major motor-related symptoms in PD include resting tremor, slowness of movement referred to as bradykinesia, rigidity, shuffling gait, and postural instability. In addition, people with PD can experience secondary motor symptoms, including soft voice, slow, slurred speech, difficulty swallowing, difficulty handwriting, masked facial expression, decreased blink rate, and pain. Furthermore, gait freezing, inability to initiate movements, or unexpected stop of a movement, which is a major cause of falls, are other symptoms of PD [2].

While PD is mostly associated with rest tremor, postural and action tremor can also be seen in the later stages of PD. On the other hand, action and postural tremor can be seen more often in essential tremor (ET) [3]. Figure 1.1 and Table 1.1 show the differences between ET and PD tremors.

As shown in Table 1.1, ET and PD tremor frequency ranges have overlaps but are different. Studies comparing ET, PD tremor, and voluntarily mimicked tremor in healthy individuals (Healthy tremor, HT) have shown two similar sources in cortical networks of the brain for ET, PD, and HT, responsible for the first harmonic of the tremor. However, the third source responsible for generating the first harmonic of the tremor is different in the PD group vs. ET and HT groups. Furthermore, sources of the second tremor harmonic are different from the first harmonic

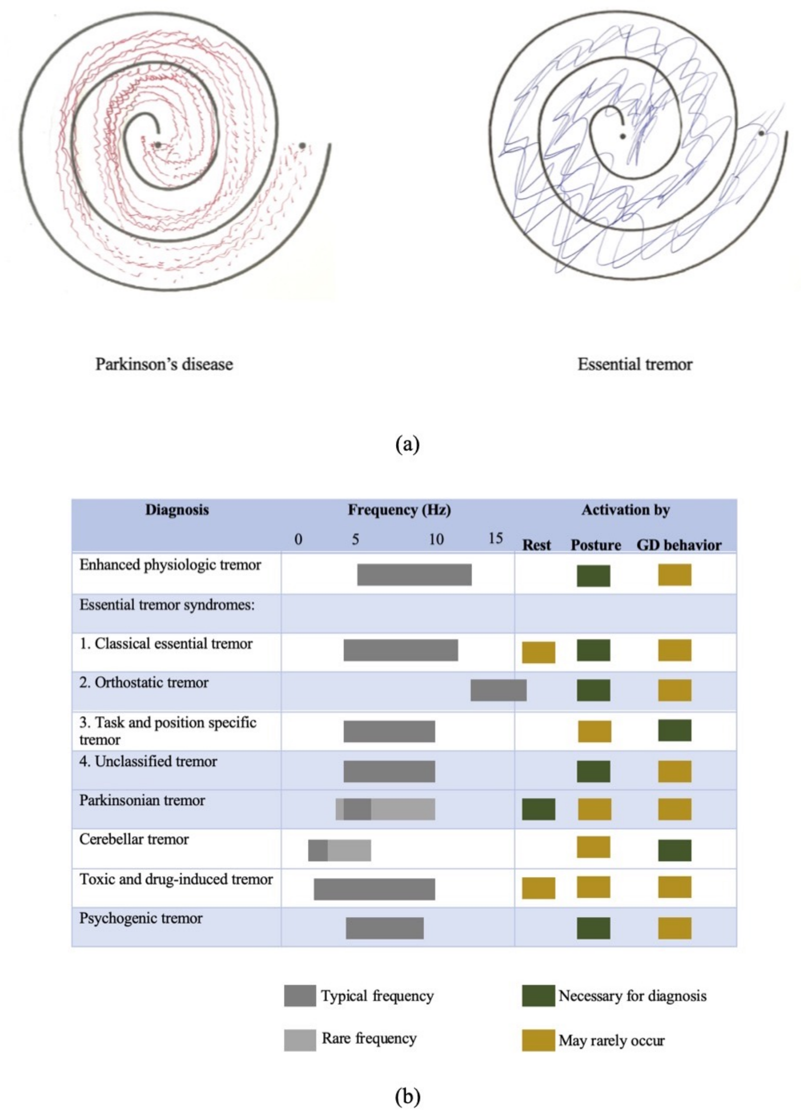

Figure 1.1: (a). Examples of Archimedes spirals traced by patients with PD and ET. (b). (Adapted from [4]) Differential diagnosis of tremor based on tremor frequency and provocation pattern. GD stands for goal-directed.

Table 1.1: Comparison of tremor features in PD and ET, from [4].

Features	PD tremor	Essential tremor
Tremor	At rest, increases with walking. Decreases with posture, holding or action	Posture, holding, or action
Frequency (Hz) [5]	Resting: 4.52 ± 0.43 Posture: 4.94 ± 0.66 Loaded, 500 g: 5.17 ± 0.62 Loaded, 1000 g: 4.71 ± 0.96	Resting: 5.38 ± 1.23 Posture: 7.32 ± 2.63 Loaded, 500 g: 6.46 ± 2.04 Loaded, 1000 g: 6.31 ± 1.36
Distribution	Asymmetrical	Symmetrical (mostly)
Body parts	Hands and legs, head (chin)	Hands, head, voice
Writing	Micrographia	Tremulous
Course	Progressive	Stable or slowley progressive
Family history	Less common (1%)	Often (30–50%)
Other neurological signs	Bradykinesia, rigidity, loss of postural reflexes, non-motor symptoms	Gait disturbances
Improvement with	Levodopa, anticholinergics	Alcohol, propranolol, primidone
Latency from rest to postural [5]	80%	0%
After mental concentration [5]	100%	0%
Synchronous EMG of the forearm muscles [5]	20%	80%

sources in patients with PD yet are similar in participants with ET and HT. Further investigations revealed that the second harmonic of the tremor in ET is exactly twice the first harmonic, while it is slightly different in PD [6].

In another study, comparing the HT tremor of 12 participants with tremor in 8 PD participants revealed that while tremor is similar in amplitude and peak frequencies, it is different in the variability factors, including standard deviation (SD) of peak frequency and proportional power, as well as in approximate entropy, which is the measure of regularity [7]. Differences and similarities in the cortical sources of tremor in these three groups result in different tremor characteristics and variabilities.

1.1 Motivation

Variations in causes, presentation of symptoms, and personal preferences result in complications in clinical practices, and therefore, treatments are mostly symptomatic [1]. Current pharmacological treatments to manage motor symptoms of PD are medications that either raise the dopamine levels in the brain or activate dopamine receptors [2]. However, PD is a progressive disorder, and therefore, patients response to medications declines over time [2, 8]. On the other hand, these medications, such as Levodopa and Carbidopa, cannot reduce the damage caused by PD, and high doses of Levodopa, the first line treatment of PD [1], can result in uncontrolled movements [8]. Furthermore, medications can have several side effects, including memory problems, dry mouth, disorientation, constipation, hallucinations, and urinary problems [8].

Alternatively, surgical interventions can be used to treat PD by implanting electrodes in targeted parts of the brain [8]. Deep brain surgery (DBS) is an invasive neurosurgical procedure [2] that is approved by the FDA for severe PD cases that are not responding to medications or have fluctuations in response to medications [1,2,8]. While DBS positively affects PD motor symptoms, it has adverse side effects such as tonic muscle cramps, gaze deviation, speech disturbances, and gait and postural instability [2]. Furthermore, it still has critical problems, such as finding the right brain regions for the surgery, placing the electrodes, and finding the right patients for the surgery due to the complications of the intervention.

Recent advancements in assistive technologies and wearable devices resulted in the development of wearable mechatronic devices for tremor suppression and management [9]. Wearable tremor suppression devices (WTSD) have been developed and studied to suppress pathological tremor, including parkinsonian tremor and essential tremor. A key component in all WTSDs is actuation. Actuators can be either mechanical actuation to the target joint, or electrical stimulation of the target muscle and sensory nerves in order to generate motion in opposition to tremor. Sensors and control systems can be incorporated into the system, depending on the design [10].

Although studies have shown tremor suppression up to 99% using WTSDs, further assessments and analysis are required to improve the adaptability of WTSDs in terms of suppression and user comfort. Adaptability assessments in terms of suppression can be divided into the evaluation of suppression based on tremor presence and its levels, and the presence of voluntary motion; while comfort analysis can be defined in terms of reduction of the weight and size of the device, pain, and discomfort.

An Ideal WTSD is required to adapt to the tremor intensity of the users in real time and in target joints. In other words, WTSDs must not resist the user's voluntary motion while suppressing tremor, and are required to suppress tremor to the desired level by the user. Furthermore, the device is required to be lightweight and compact, so that the user can benefit from it in daily life activities. Damping systems, also known as passive mechanical actuators have been used to reduce and manage tremor by damping the vibration on the target joint [11]. Despite the effectiveness of the approach, there is not a high level of control over the damping effect of the system for various tremor levels and when voluntary motion is involved. Therefore, this technology might resist voluntary motion. Active mechanical actuators have been incorporated into WTSDs along with real-time sensing and control to improve damping systems. However, the overall device has become heavy, bulky, and not comfortable to incorporate into daily life activities. Functional electrical stimulation (FES), as another approach that is used in WTSDs, also requires further development. FES stimulates the muscles of the target joint to suppress and reduce the tremor. Despite the effectiveness of this method in tremor suppression in the literature, it requires further improvements in terms of adaptability for tremor suppression while the user is performing different activities, comfort, pain and muscle fatigue reduction, and acceptability among users. Lastly, there have not been major clinical experiments with these devices and technologies on participants with pathological tremor, and therefore, their adaptability regarding tremor intensity and the presence of voluntary motion has not been well-studied.

1.2 General Problem Statement

As has been mentioned in Section 1.1, an ideal WTSD is adaptable to the tremor intensity and voluntary motion, while it is lightweight and comfortable for users. While FES devices can be lightweight, they might cause muscle fatigue and discomfort, and active mechanical devices, despite their effectiveness in tremor suppression, can be heavy and bulky. Thus, a hybrid approach can be investigated in which FES and mechanical actuators are combined to reduce the drawbacks of each technology—including excessive muscle fatigue and bulkiness caused by the former and latter, respectively—while taking advantage of their tremor suppression abilities, such as compactness and higher suppression rate. In order to design a hybrid adaptive system, a better understanding of FES, in terms of FES parameter tuning, duration of application and potential impacts on tremor levels, is required. Although, there have been many studies with a focus on tremor suppression with FES, a lack of a systemic approach to test multiple sets of FES parameters and report outcomes in participants with PD is evident. Lastly, a better understanding of tremor changes over time and the response to an external mechanical or electrical stimulus is needed for the future design and development of an adaptive system for tremor suppression.

1.3 Research Objectives and Scope

In order to address these gaps, this thesis specifically focuses on the electrical stimulation approach for tremor suppression and evaluates potential approaches for improving this technology for future use in WTSDs for tremor suppression. To achieve this goal, the following objectives have been established:

1. To evaluate and assess the feasibility of combining FES and electrical motors in a simulation study and testing different potential real-life scenarios in the simulation.
2. To analyze and evaluate changes in different FES parameters and their potential effect on tremor suppression in a study performed with participants with PD.
3. To evaluate changes in tremor and tremor characteristics under different circumstances to further investigate the need for an adaptive controller in a WTSD.

1.4 Overview of the Thesis

The structure of this thesis is summarized in the outline below:

Chapter 2 Literature Review: Presents the background information about Parkinson's disease and tremor, potential causes and solutions other that WTSDs, and available research of WTSDs up to date.

Chapter 3 Multimodal Tremor Suppression of the Wrist using FES and Electric Motors—A Simulation Study: Multimodal Tremor Suppression of the Wrist using FES and Electric Motors—A simulation study: Presents a simulation study performed on combining FES and electrical motors for tremor suppression and asseses the feasibilty of the hybrid approach using an adaptive control system.

Chapter 4 Tremor Suppression Using Functional Electrical Stimulation: Presents a study performed on participants with PD to assess the effectiveness of FES on tremor suppression, while changing FES parameters and settings.

Chapter 5 Variability of Parkinsonian Tremor in Time, During Different Tasks, and Under External Interference: Presents the study that was done to further evaluate the fluctuation of tremor characteristics such as tremor power intensity, approximate entropy, and frequency under different circumstances, including the application of electrical or mechanical suppression.

Chapter 6 Conclusion and Future Work: Presents the contributions of this work and potential studies for future work.

Appendix A Permissions and Approvals: Includes the permissions and approvals for the studies and copyrighted material used throughout this document.

Chapter 2

Literature Review

2.1 Introduction

This chapter provides a review of the literature on wearable tremor suppression devices and technologies. Several comprehensive literature reviews were performed during different time frames between September 2019 and October 2023, using the Google Scholar search engine and with the following keywords: Parkinson's disease, parkinsonian tremor, Essential tremor, pathological tremor characteristics, parkinsonian tremor variability, essential tremor variability, tremor suppression, electrical stimulation for tremor suppression, assistive devices, Parkinson rehabilitation. A total of 91 papers were used in this review, which were selected based on published year (2000-current) or older publications if required for a better understanding of the concepts and methods. The remainder of this chapter is organized as follows: Section 2.2 provides information about Parkinson's disease, Section 2.3.1 provides information on WTSDs based on mechanical actuators, Section 2.3.2 describes methods and studies on tremor suppression using functional electrical stimulation, and lastly, mechanical vibration as a method to suppress tremor has been reviewed in Section 2.3.3.

2.2 Parkinson's Disease

Parkinson's disease is heterogeneous in causes and presentation [1]. Damage to dopaminergic neurons in basal ganglia is known to be a cause of PD. Dopaminergic modulation of the direct and indirect pathways in basal ganglia is required for movement initiation. Therefore, losing dopaminergic neurons results in excessive movement suppression symptoms such as slowness of movement, referred to as bradykinesia [12].

Genetics, environment, and potential interaction between them are relevant factors that might cause PD. While genetic causes of Parkinson's have been relatively well studied, environmental effects, their accumulation over time, and potential interactions on genetic causes are even more difficult than deciphering an individual's entire genome. Therefore, environmental causes are not well evaluated to this date. Among all of the studies in the literature about environmental and lifestyle causes and factors of PD, head injury and exposure to toxins and pesticides such as MPTP—1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a potent toxin that can cross the blood–brain barrier [13] —have been shown to correlate with PD [1, 8]. Accumulation of several complications in the central nervous system results in dopamine deficiency in the substantia nigra compacta nigra pars, which results in several symptoms such as motor-related symptoms [8].

While the general thought is that PD is mostly defined by movement abnormalities, dysregulation of the autonomic nervous system results in a large number of non-motor features among PD symptoms. These symptoms include depression and anxiety, constipation, temperature control dysregulation, and sleep disorders [1] and [2].

While tremor is one of the most common motor symptoms of PD, up to 20% of PwP do not have tremor, yet bradykinesia is always present [1]. On the other hand, several other conditions, such as ET, multiple system atrophy vascular parkinsonism, and cortico-basal degeneration, can have similar symptoms to PD. Therefore, clinical diagnosis of PD is a multi-step process as shown in Figure 2.1, often through elimination, clinical assessment, expert opinion, and evaluation of disease progression over time [2].

As shown in Figure 2.1, the presence of bradykinesia, combined with either rest tremor, rigidity, or both, is required to confirm the presence of Parkinsonism in the first step of evaluation. In the

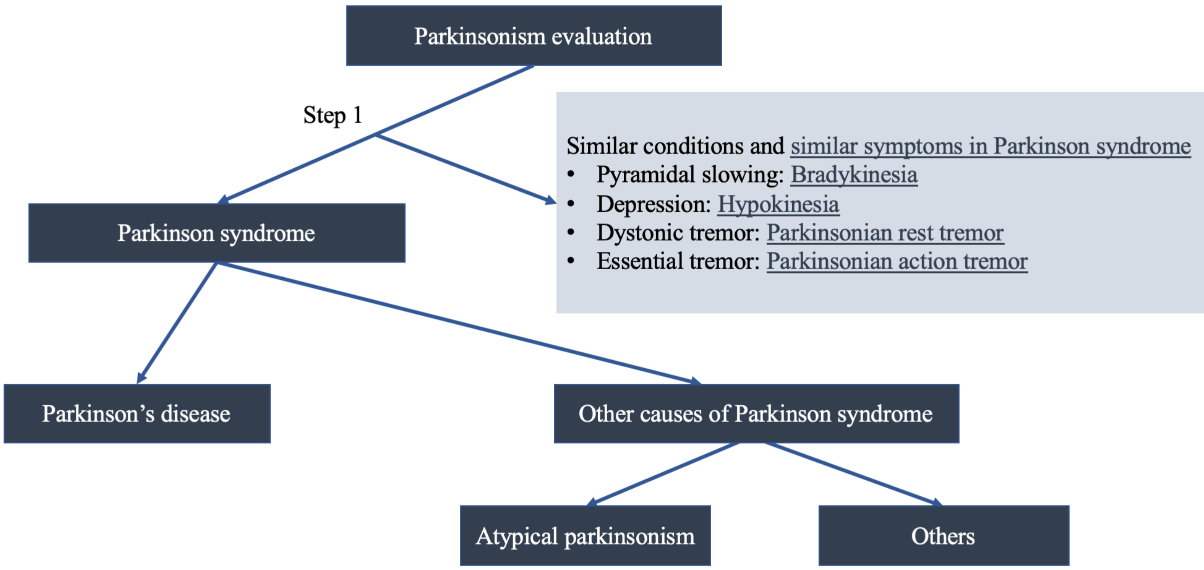

Figure 2.1: Procedure followed to diagnose PD and similar disease, from [1].

next step, evaluations are performed to distinguish PD from other causes of Parkinson syndrome. One of the sub-categories of Parkinson syndrome, also referred to as atypical parkinsonism, generally has faster disease progression, a less or no response to dopaminergic medication, a faster appearance of debilitating complications such as falls or dementia, and a remarkably reduced survival.

2.3 Wearable Mechatronic Tremor Suppression Devices

As mentioned in Chapter 1, in the past few decades, researchers have focused on the design and development of wearable tremor suppression devices to manage and suppress pathological hand tremor and to improve the quality of daily living activities. External exoskeletons based on mechanical loading, vibration, or damping of the target joint or electrical stimulation of the target muscles or nerves have been designed and tested.

The main components of these mechatronic devices are the actuators, sensors, control, and computation units. Sensors are used to measure the motion and are needed by the control system in order to generate appropriate commands to the actuators and suppress tremor. The computational unit is used for data acquisition, conversion, filtering, and processing.

Based on the actuators used in a WTSDs, they can be categorized as mechanical-loading suppression, electrical stimulation suppression, and mechanical vibration devices. Mechanical-loading suppression can be further divided into three sub-categories: active, semi-active, and passive actuators, as described in Section 2.3.1. Tremor suppression based on muscle or nerve stimulation is explained in Section 2.3.2. Lastly, devices using mechanical vibration are explained in Section 2.3.3.

2.3.1 Mechanical Loading

Passive actuators work by applying a constant damping factor to absorb disturbances. WTSDs based on passive actuators only have mechanical dampers, and no sensing, control, computer, or electrical system is designed for them. The major drawback of these devices is that the same amount of damping is also applied to the voluntary motion of the target joint, resulting in reduced comfort, acceptance, and effectiveness of the device. Table 2.1 shows a summary of devices designed and tested in this category.

Semi-active actuators are dampers with controllable damping magnitude, which can be adjusted actively as opposed to the constant damping factor of passive actuators. Unlike active actuators that input additional forces to the system, semi-active actuators absorb unwanted disturbances in the system. Semi-active actuators are tunable to different frequencies or can be switched on and off relative to the tremor occurrence. Magnetorheological fluids (MRF), piezoelectric actuators, shape memory alloys (SMA), and twisted coiled actuators (TCA) are examples of semi-active actuators. The rigid form and shape of conventional piezoelectric actuators limit the ability to use these actuators in WTSDs. While thermally activated actuators such as shape memory alloys [14] and twisted coiled actuators [15] are lightweight and can provide high power, they have limited efficiency in terms of operating bandwidth and mechanical power, due to the inefficient process of electrical heating and thermomechanical activation. Table 2.2 shows a summary of devices designed and tested in this category.

Active devices use actuators to produce controlled levels of force. These devices also include sensing and control systems, electrical circuitry to support actuation and sensing systems, and a computer component for data acquisition, filtering, processing, and managing the communication between actuators, sensors, and the controller. Electric motors, as one of the most widely used actuators in WTSDs have a number of positive features for the application of tremor suppression. Electric motors have high positioning accuracy, low noise, and fast reaction times, and can be operated at frequencies above the voluntary motion and even maximum tremor frequency. Despite their positive characteristics, electric motors are often heavy, and bulky, and due to their form, it is not easy to incorporate them into a wearable device that adapts to the geometry of the human body. Alternative to electric motors, pneumatic actuators have been used in the literature for tremor suppression. Pneumatic actuators create motion using pressurized air, which results in less weight compared to electric motors. Pre-pressurized air can be used in high-pressure tanks to mitigate the bulkiness and noise of air compressors. Lastly, electroactive polymers (EAP) are still under development for the feasibility of use in WTSDs [16]. While EAPs are lightweight and can conform to the human body, they have high excitation voltages, viscoelasticity, low mechanical output strains, and low manufacturability [17]. Table 2.3 shows a summary of devices designed and tested using active suppression. As shown in this table, active actuators have been able to suppress tremor at a high rate. However, benchtop experiments are not enough for the evaluation of these methods, and further systemic clinical trials—with separated groups of individuals, affected by different conditions that have tremor as a symptom—are required to confirm the effectiveness of these actuators. Furthermore, a high rate of tremor suppression might not be practical for daily living activities, since a high level of suppression might negatively affect voluntary motion or comfort. Further studies are required to assess the clinically relevant and practical levels of tremor suppression in individuals while performing different activities of daily living.

Table 2.1: Summary of features for existing WTSDs using passive mechanical suppression.

Reference	Device details				Testing	
	Actuator	Weight (g) total/ one attenuator	DOF[1]	Level of suppression (Metrics)	Clinical	Benchtop Validation
Kotovsky et al. [18]	Constrained-layer-damping	265/NR[2]	1 (WFE[3])	NR	Five tremor subjects	-
Takanokura et al. [19]	Air dashpots	NR/37	3 (EFE[4], WFE, WUD[5])	20-62%	1 HT[*]	-
Katz et al. [11]	Rotary damper	200/NR	1 (WFE)	NR	1 PD	
Buki et al. [20]	Tuned mass damper (mass+spring)	280/NR	1 (FPS[6])	85% (MAA[7])	12 PD	Yes
Fromme et al. [21]	Air-filled	33	2 (WFE, WUD)	78%	1 PD	-

[*] It was tested on a healthy individual with FES-induced tremor. [1]Degrees of Freedom, [2]Not reported [3]Wrist flexion–extension, [4]Elbow flexion–extension, [5]Wrist ulnar deviation, [6]Forearm pronation–supination, [7]Maximum amplitude attenuation.

Table 2.2: Summary of features for existing WTSDs using semi-active mechanical suppression.

Reference	Device details				Testing	
	Actuator	Weight (g) total/ one attenuator	DOF[1]	Level of suppression (Metrics)	Clinical	Benchtop Validation
Loureiro et al. [22]	MRF	NR[2]/200	1 (WFE[3])	43 dB (PSD[4])	1 ET	-
Herrnstadt et al. [23]	Electro magnetic brake	942/150	1 (EFE[5])	88% (PSD)	3 HT (3–4 Hz)[*1]	-
Case et al. [24–29]	MRF	NR	4 (EFE, FPS[6], WFE, WUD[7])	32 ± 2.5 dB (PSD1[8]) 13.7 ± 5.7 dB (PSD2[8])	-	Yes: 10 (PD, ET)
Yi et al. [30]	MRF	262	1 (WFE)	60.39 %	5 HT (2–4 Hz)[*1]	-
Zahedi et al. [31,32]	RSAA MR damper[9]	MRF 350	2 (WFE, WUD)	61.55 %	5 HT (2–8 Hz)[*1]	-
Fromme et al. [33]	Mechanical brake	152/NR	1 (WFE)	Simulation: 78.8% test bench: 66.5% Case study: 40.8%	1 ET	Yes

[1]Degrees of Freedom, [2]Not reported,[3]Wrist flexion–extension, [4]Power spectral density, [5]Elbow flexion–extension, [6]Forearm pronation–supination, [7]Wrist ulnar deviation, [8]Spectral power at the 1st and 2nd harmonic, [9]Rotational semi-active actuator magnetorheological damper, [*1]Healthy individuals were asked to mimic tremor by shaking the target limb/joint. [*2]Benchtop validation using data collected from specified patients.

Table 2.3: Summary of features for existing WTSDs using active mechanical suppression.

Reference	Device details				Testing	
	Actuator	Weight (g) total/ one attenuator	DOF[1]	Level of suppression (Metrics)	Clinical	Benchtop Validation
Rocon and Pons et al. [34–44]	DC motor	850/165	3 (WFE[2], FPS[3], EFE[4])	40% (PSD[5])	10 tremor subjects (ET, PD, MS[6])	-
Ando et al. [45–48]	DC motor	330/NR[7]	1 (EFE)	-	1 ET	-
Matsumoto et al. [49, 50]	DC motor	410/NR	1 (EFE)	50-80% (AR[8])	1 ET, 1 HT[*2]	-
Huen et al. [51]	Servo motor	350/72	2 (FPS, WFE)	77% (AR)	6 HT (3Hz)[*3]	-
Zhou et al. (V1) - 2017 [52]	DC motor	NR/229	1 (WFE)	-	-	Yes: 7 PD [*4]
Zhou et al. (V2) - 2018 [53]	DC motor	320-340	3 (WFE, Index, Thumb)	$85 \pm 8\%$ (AR) $88 \pm 14\%$ (PSD1[9]) $92 \pm 7\%$ (PSD2[9])	-	Yes: 7 PD
Zhou et al. (V3) - 2021 [54]	DC motor	580/NR	3 (WFE, Index, Thumb)	For IFFE[10], TFE[11], WFE: Rest tremor: 73.1, 80.7, 85.5 %, Postural tremor: 70.2, 79.5, 81%, Kinetic tremor: 60, 58.7, 65%.	1 PD	-
Herrnstadt et al. [55–58]	DC motor	1700 /NR	1 (EFE)	94.4% (PSD)	9 (PD, ET)	Yes
Zamanian et al. [59, 60]	Linear motor	NR/315	2 (WFE, WUD[12])	97.6 % (PSD)	-	Yes: 10 (PD, ET)
Taheri et al. [61–65]	Pneumatic piston-coil	NR/378	4 (WFE, EPS, EFE, WUD)	98.8% (PSD)	-	Yes: 10 (PD, ET)
Wang et al. [66]	Servo motor	485/NR	2 (WFE, WUD)	-	-	-
Wanasinghe et al. [67]	Layer-jamming	30/NR	2 (IFFE, MFFE[13])	Bench test (AR) : 78.32% IFFE (MFP[14]): $41.74 \pm 12.11\%$ MFFE(MFP): $41.99 \pm 14.82\%$ Grasping(MFP): $24.71 \pm 12.18\%$	11 Tremor patients[*4]	Test rig
Skaramagkas et al. [68, 69]	Pneumatic artificial muscles	280-430/NR	2 (IF[15], Metacarpal area MFFE)	42 - 75%	1 ET	-

[1]Degrees of Freedom, [2]Wrist flexion–extension, [3]Forearm pronation–supination, [4]Elbow flexion–extension, [5]Power spectral density, [6]Multiple sclerosis, [7]Not reported, [8]Amplitude reduction reported, [9]Spectral power at the 1st and 2nd harmonic, [10]Index finger flexion–extension, [11]Thumb flexion–extension,[12]Wrist ulnar deviation, [13]Middle finger flexion–extension, [14]Mean frequency power reduction, [15]Index finger, [*1] Healthy participants with FES–induced tremor, [*2]Simulated tremor motion with vibration at 3 Hz, [*3] Participants with tremor in right hand, and with Parkinson's disease, essential tremor, stroke, or visible hand tremor, [*4]Benchtop validation using data collected from specified patients.

2.3.2 Stimulation of Muscles and Sensory Nerves

Despite the effectiveness of mechanical actuators for managing tremor, they tend to make the devices uncomfortable and have not gained acceptance among users. As an alternative, research has explored the development of tremor reduction techniques using electrical stimulation. Functional Electrical Stimulation (FES) uses modulated electrical signals to activate muscle fibers and produce a motion to suppress tremor. Co-contraction and out-of-phase stimulation are the two main strategies used to apply FES for tremor suppression. In both approaches, the stimulation intensity is above the motor threshold.

The co-contraction strategy is based on manipulating the target joint impedance by applying stimulation to a pair of antagonistic muscles, and therefore increasing the joint stiffness to counteract tremor. As the dynamic response of the muscle to tremor is comparable to a low-pass filter, the increased joint stiffness and viscosity decreases the cutoff frequency and consequently filters out the tremorous movement.

Grimaldi et al. [70] and Gallego et al. [71] showed the usefulness of the co-contraction method for tremor suppression by achieving $35 \pm 9\%$ and $52.3 \pm 25.5\%$ tremor suppression levels, respectively. The second study concludes that FES can be useful for both ET and PD groups despite their different etiology and symptomatology [71].

From a straightforward on/off open-loop configuration strategy, Bó et al. [72] concluded that tremor attenuation is not always immediate and clear, despite the simplicity of the method compared to other FES-based devices. Therefore, a prior adaptation and training phase may be necessary to improve suppression. Lastly, Jitkritsadakul et al. [73], [74], showed a reduction in the UPDRS score, peak amplitude and RMS value of the angular velocity in PD participants using the co-contraction strategy. These studies are summarized in Table 2.4.

Compared to the co-contraction approach, in the out-of-phase method, electrical stimulation is applied to the antagonist of the muscle that generates tremor. To be effective, the applied stimulation must have sufficient intensity to generate forces that oppose the tremor.

Several studies including [75–77], and [78] showed the effectiveness of the out-of-phase stimulation on participants with tremor using different control approaches. Further explorations conducted by Widjaja et al. [79] and Dosen et al. [80] aimed to compensate for electromechanical delays and improve the prediction of tremor. These studies used EMG signals for detection of tremor onset in advance, giving the system enough time to calculate and generate an appropriate stimulation for out-of-phase tremor suppression. Table 2.5 summarizes studies that use the out-of-phase method for tremor suppression.

While electrical stimulation with an intensity above the motor threshold has shown effectiveness in tremor reduction, several limitations are associated with this approach, such as muscle selectivity, non-adaptive control systems, and muscle fatigue due to the artificially induced contractions. Results from [80] showed that stimulation below the motor threshold can manipulate and reduce tremor. An average tremor reduction of 42 ± 5% was achieved for five participants in this study when using sensory stimulations. While these results are promising for reducing muscle fatigue, inconsistency in tremor suppression suggested that further studies were required. Therefore, other studies focused on the effect of low-level stimulations and the relationship between the activation of afferent pathways and tremor generation and reduction. The underlying neurophysiological mechanism of tremor suppression using sensory stimulation is still unclear; however, the hypothesis is that activating sensory afferent pathways may generate a response in the central nervous system (CNS) that modulates the tremor motion.

Following the study from Dosen et al., other researchers studied the effectiveness of sensory stimulation in wrist tremor suppression using surface and intramuscular electrodes [81–83], and the stimulation of cutaneous afferents in participants with PD [84,85]. Heo et al. achieved tremor reduction for postural and action tremor in ET participants during and within five minutes after the sensory stimulation, while inconsistent results were achieved with resting tremor in PD participants and patients with scans without evidence of dopaminergic deficits (SWEDDs) [86–89]. Further work in four studies led by Delp, [90–93], studied the effect of stimulation of the wrist median and radial nerves in ET participants. In another study by Kim et al. [94], variable tremor suppression results with different stimulation parameters suggests the need for an optimization algorithm to obtain stimulation parameters. Lastly, Metzner et al. [95] studied the effect of various frequencies of synchronous stimulation with amplitudes below the motor threshold on 20 participants with ET. The group applied stimulation to the wrist flexor and extensor muscles for 45 seconds and showed that synchronous sub-motor-threshold stimulation, regardless of the stimulation frequency does not affect ET tremor power or frequency to a significant level, and hypothesizes that submotor-threshold stimulation requires longer and asynchronous stimulation for effectiveness. Table 2.6 summarizes the above-mentioned studies, which use sensory stimulation methods for tremor suppression.

Table 2.4: Summary of features for existing WTSDs using co-contraction electrical stimulation.

Reference	Device/Method details				Testing
	Level of suppression	Target joint(s)/ muscle(s)	Comment(s)	Strategy	
Grimaldi et al. [70]	35 ± 9% (Suppression ratio)	Flexor radialis carpi, extensor radialis carpi, biceps and triceps	Constant frequency and pulse width, pulse intensity based on the subject's comfort.	Co-contraction	1 ET, 1 PD, 1 cerebellar syndrome
Gallego et al. [71]	52.3 ± 25.5% (AR[1])	Wrist	Stimulation intensity adapted to the tremor frequency and amplitude in real-time.	Co-contraction	9 ET, 3 PD
Bó et al. [72]	60 ± 27% (Average suppression ratio using the RMS of the tremor amplitude)	Wrist or fingers	Joint with higher tremor amplitude selected for stimulation. Stimulation frequency: 40 Hz, Pulse width:150 µs, pulse amplitude based on the patient's comfort and muscle contraction levels. Results showed tremor amplitude reduction in eight subjects and no positive response in two subjects.	Co-contraction	10 ET
Jitkritsadakul et al. (V1) [73]	49.6 ± 38.89% (Angular velocity peak amplitude), 43.8 ± 33.2% (RMS value for resting tremor)	Abductor pollicis brevis and interosseurs muscles	Constant stimulation frequency and pulse width, Pulse intensity below 20 mA.	Co-contraction	34 PD
Jitkritsadakul et al. (V2) [74]	Reduction in UPDRS score	Abductor pollicis brevis and interosseurs muscles	Similar stimulation approach using a designed glove. Dividing participants into the glove and sham group (n = 15).	Co-contraction	30 PD

[1]Amplitude reduction reported.

Table 2.5: Summary of features for existing WTSDs using out-of-phase electrical stimulation.

Reference	Device/Method details				Testing
	Level of suppression	Target joint(s)/ muscle(s)	Comment(s)	Strategy	
Javidan et al. [75,76]	ET: 73%, PD: 62%, CS: 3 (AR[1])	Tricepts and biceps branchii	Using a closed-loop system to filter out the tremor motion with greater frequencies.	Out-of-Phase	3 ET, 4 PD, 6 cerebellar syndrome
Gillard et al. [77]	84% digital, 65% analog (mean attenuation ratio)	Wrist or finger flexor and extensor muscles	Compared the performance of the proposed approach in (Javidan et al. 1992a, b) using analog and digital filters.	Out-of-Phase	3 PD
PopovicManeski et al. [78]	67 ± 13% (AR)	Wrist	Pulse width: 250 µs, pulse frequency: 40 Hz, pulse intensity was set to the minimal value that can produce full extension and flexion mot Variable number of pulses, controlled according to the tremor amplitude. Used a multichannel system with adaptive sensor-driven control. Initial experiments on healthy individuals. Tremor reduction in six out of seven tremor participants, with no improvements in one ET subject. Approach: 3 seconds stimulation window, 1 second recording window.	Out-of-Phase	5 HT, 4 PD, 3 ET
Widjaja et al. [79]	57% (power reduction ratio)	Wrist flexors and extensors	Pulse width: 200 µs, pulse frequency: 25 Hz, pulse intensity: 23 mA. Approach: real-time closed-loop on/off control, based on an algorithm, that is, if the first sEMG signal is large enough to be considered as tremor, then combines accelerometer and sEMG phase estimation to determine when to start the signal to ensure it is out of phase.	Out-of-Phase	1 ET
Dosen et al. [80]	60 ± 14% (suppression ratio)	Wrist and finger flexors a extensors	Stimulation above motor threshold.	Out-of-Phase	2 ET, 4 PD

[1] Amplitude reduction reported.

Table 2.6: Summary of features for existing WTSDs using sensory stimulation.

Reference	Device/Method details				Testing
	Level of suppression	Target joint(s)/ muscle(s)	Comment(s)	Strategy	
Dosen et al. [80]	42 ± 5% (suppression ratio)	Wrist and finger flexors and extensors	Stimulation below motor threshold	Sensory	2 ET, 4 PD
Dideriksen et al. [81]	52% (average suppression level based on the joint angle)	Wrist flexors/ extensors	Used intra-muscular and surface electrodes. Variable stimulation intensity, Pulse frequency: 100 Hz, pulse : 400 µs. Effective tremor suppression in six participants.	Sensory	4 ET, 5 PD
Muceli et al. [82]	58% (average suppression level based on the joint angle)	Wrist flexors/ extensors	Same strategy as (Dosen et al. 2015) for sensory stimulation and data recording. Used a newly-designed multichannel intramuscular electrode. Results for tremor suppression are only for one PD subject.	Sensory	3 HT, 2 ET, 4 PD
Pascual-Valdunciel et al. [83]	32% with selective and adaptive timely stimulation, no improvement with continuous stimulation	Wrist flexors/ extensors	Using intramuscular electrodes from (Muceli et al. 2019). Two stimulation strategies used and compared. Tremor power used to calculate tremor score for reporting the suppression level. Prolonged tremor reduction resulting from the sensory stimulation was observed in four patients.	Sensory	9 ET
Heo et al. [86–89]	ET: (RMS average) During stimulation: MP: 60%, Wrist: 40% After 5 minutes: MP: 67%, Wrist: 45% PD (Hand tremor reduction rati During stimulation: 62.1 ± 20% After stimulation: 58.6 ± 29.9%	Flexor Carpi Radialis, extensor carpi radialis, Biceps brachii, and triceps brach	Pulse frequency:100 Hz, pulse width: 300 µs. 50–71% of PD participants showed a decrease in tremor amplitude. No significant tremor reduction among SWEDD participants	Sensory	18 ET, 14 PD 9 SWEDD

Reference	Device/Method details				Testing
	Level of suppression	Target joint(s)/ muscle(s)	Comment(s)	Strategy	
Xu et al. [84]	verification only	Superficial radial nerves	Stimulation to the dorsal side of the hand, near the MP joint of the index finger, using a stimulation amplitude of 1.5 to 1.75 times the radiating threshold, Tremorous motion monitored for five seconds before, during, and after the stimulations.	Sensory	2 PD
Hao et al. [85]	61.56% (peak spectral amplitude) 47.97% (EMG)	Superficial radial nerves	Tremorous motion monitored for five seconds before, during, and after stimulations.	Sensory	8 PD
Lin et al. [90]	60 ± 8.4% Tremor amplitude	Median and radial nerves at the wrist	calibrated stimulation frequency based on the participant's tremor frequency, Treatment group (n = 10), stimulation duration: 40 minutes	Sensory	23 ET
Pahwa et al. [91]	49% BF-ADL score (subject-rated Bain and Findley Activities of the Daily Life)	Median and radial nerves at the wrist	Treatment group (n = 40)	Sensory	77 ET
Isaacson et al. [92]	62% TETRAS 68% BF-ADL scores	Median and radial nerves at the wrist	Evaluated the effect of this neuromodulation therapy over the long term, using a repeated therapy protocol at home for three months. Tremor reduction for 92% of patients, with 54% of patients experiencing improvements in tremor power of more than 50	Sensory	205 ET
Yu et al. [93]	Tremor reduction effect lasts for at least 60 minutes after the therapy for 80% of participants.	Median and radial nerves at the wrist	Studied the duration of tremor reduction after the treatment session.	Sensory	15 ET
Kim et al. [94]	42.17 ± 3.09% (tremor power reduction rate)	Wrist radial nerve	Design and development of a wireless wearable device, using an open and closed loop stimulation system, with multiple sets of parameters.	Sensory	9 ET
Metzner et al. [95]	12.2 ± 1.0 %	Wrist flexor and extensor	Collected data 30 s prior to stimulation, followed by 45 s of stimulation, and 60 s of rest. Tested 15 different frequencies, 10-150 Hz, Compared tremor power and frequency from acceleration and sEMG signals from pre, per, and post stimulation.	Synchronous-Sensory	20 ET

2.3.3 Vibration

Another method for tremor reduction found in the literature is the use of mechanical vibration. Kazi et al. [96] developed a vibration glove using piezoelectric actuators to suppress PD postural tremor. Even though the experimental results showed tremor reduction, the small sample size is insufficient to validate the method.

In another study, Lora-Millán et al. [97] achieved inconsistent results by activating afferent pathways using mechanical vibration and therefore, concluded that the method could not systematically suppress tremor in subjects with ET. Lastly, Liu et al. [98], used the phenomenon of tonic vibration reflex (TVR)— defined as the involuntary sustained contraction of the stimulated muscle using vibration stimulation and reciprocal relaxation of its antagonist muscle—to generate a counter-phase motion of the ET for tremor reduction. In three experiments on healthy individuals, the group showed that the method can generate the counter-phase motion of the periodic pronation–supination motion; however, the study did not provide any support for tremor suppression in real subjects with ET. Table 2.7 summarizes studies that have investigated vibration methods for tremor suppression.

Table 2.7: Summary of features for existing WTSDs using mechanical vibration.

Reference	Device/Method details			Testing
	Level of suppression	Target joint(s)/ muscle(s)	Comment(s)	
Kazi et al. [96]	7 Hz :34.50% 8 Hz: 63.39%, 9 Hz: 76.16%. (From displacement signal results)	Wrist	Used three different vibration frequencies.	1 PD
Lora-Millán et al. [97]	Increase in tremor amplitude for 50–72% of cases, and reduction in 5–22% of the patients, depending on the strategy.	Fingers, the back of the hand, below the wrist, and below the elbow.	Stimulation frequencies ranging from 50 Hz to 450 Hz. Seven piezoelectric actuators were used.	18 ET
Liu et al. [98]	No support for tremor suppression in subjects with ET.	Forearm pronation–supination	Three experiments conducted to investigate the idea, and to compare ET tremor with generated vibrations.	5 HT*

* The goal of this study was to induce tremor in healthy individuals and compare the generated vibration with essential tremor, to verify that tonic vibration reflex can generate counterphase motion of the ET.

2.4 Discussion

Considering the device weight ranges from Table 2.1–2.3, passive devices are lighter than semi-active and active devices. This is mainly due to the use of actuators and several electrical/computer components in semi-active and active WTSDs, respectively. However, based on a survey of 101 PwP and 24 movement disorder specialists across Canada [99], the weight and size of the device are among the top three most important aspects of the design. The two other essential aspects of the design to be acceptable among PwP are lifestyle adaptability and motion accuracy. These aspects can be translated into an unobtrusive effect on the voluntary motion of the user. In order to improve currently available WTSDs to be closer to the desired device for users, this thesis focuses on the following projects:

- Combining FES and mechanical suppression: While mechanical-based devices have shown higher efficacy in tremor reduction, using multiple actuators for multiple joints and DOFs will make the device even heavier and bulkier. Smaller actuators can be replaced to improve the design, but that could result in declined efficacy in tremor suppression, as the more miniature actuators might not be able to fulfill the torque requirements for tremor suppression. It was hypothesized that combining muscular electrical stimulation with mechanical-based actuation in a single device would improve this downside. This project was designed to simulate and evaluate the potential of combining FES and DC motors in a single device. The second goal of the project was to design a control system that optimally allocates the control effort between FES and DC motors by considering an estimation of muscle fatigue and maximum allowed motor torque.

- Open loop functional electrical stimulation: It was hypothesized that varying FES parameters might have different effects on tremor suppression and comfort levels of PwP. To this end, this project was designed to perform clinical trials on participants with Parkinson's disease by applying electrical stimulation to the wrist flexor and extensor muscles. Stimulation amplitude and number of pulses in each stimulation burst were variable, while frequency and pulse width were kept constant. This project was designed to investigate the out-of-phase stimulation method further, to find a pattern between stimulation parameters and suppression rates, and to further understand the various suppression rates in different experiments presented in the literature.

- Tremor variability: To further understand the requirements for designing a WTSD and specifications for an appropriate control system, this study was designed to assess PD tremor changes in different time frames and under different circumstances. Therefore, this project improves the insights into tremor variability and regularity and further improves the understanding of the need to design an adaptive control system for WTSDs.

Chapter 3

Multimodal Tremor Suppression of the Wrist using FES and Electric Motors—A Simulation Study

3.1 Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disease characterized by a number of motor and non-motor symptoms that affect the quality of life of people with PD (PwP) [100]. Tremor, defined as an involuntary, rhythmic, and oscillatory movement, is one of the most common motor symptoms of PD. It can affect the hands and arms, reducing the ability of PwP to perform daily living activities, and often causes embarrassment and self-isolation [101].

Wearable tremor suppression devices (WTSDs) have been developed over the past few decades to reduce and manage tremor using mechanical loading [38, 53] or external electrical stimulation of the target limb [75, 76, 102].

Functional electrical stimulation (FES) elicits a muscle contraction using electrical pulses that can be applied in an alternating fashion to antagonist muscles to counteract the tremor in the target limb. Even though FES has been shown to reduce tremor, and can be incorporated into a lightweight and portable wearable device [103], it may increase the risk of muscle fatigue and discomfort over time [78]. Furthermore, increased muscle fatigue may result in decreased efficiency of the method for tremor suppression, as the fatigued muscles cannot generate sufficient torque at the same stimulation level [104, 105]. In order to suppress tremor with electrical stimulation effectively, it is necessary to control the stimulation level in real time. Filter-based controllers [75, 76], proportional–integral–derivative (PID) controllers [106], neural oscillator based controllers [107], and repetitive controllers [108, 109] have been used previously, either in simulation studies or clinical trials to suppress tremor. These studies have shown promising results by using closed-loop control approaches for tremor suppression; however, they might not be efficient in muscle fatigue reduction, or have not been tested in the presence of voluntary motion.

On the other hand, mechanical suppression devices often achieve higher suppression rates by applying mechanical loads to the target limb, counteracting the tremor motion, or increasing joint stiffness. The main drawback of using mechanical suppression is the weight, size, and power consumption of the device, due to the use of electric motors. The idea of a hybrid system has been evaluated by Kirsch et al. [110] in a leg neuroprosthesis, but there has not been a study that evaluates the combination of both methods for tremor suppression.

Therefore, the contribution of this work is the design and validation of a multimodal tremor suppression controller to reduce the drawbacks of FES and mechanical suppression simultaneously by incorporating both methods into a single device. The assumption is that incorporating FES into a mechanical device will lead to a reduction in the power consumption, weight, and size of the device.

This study evaluates the performance of a multimodal tremor suppression system with minimal impact on voluntary motion. This system incorporates a nonlinear model predictive control (NMPC) approach and a simulated model for the human wrist joint and muscle activity. The main contributions of designing this control system are to reduce tremor, track the voluntary motion, and reduce the muscle fatigue and motor power consumption, as explained in the following sections.

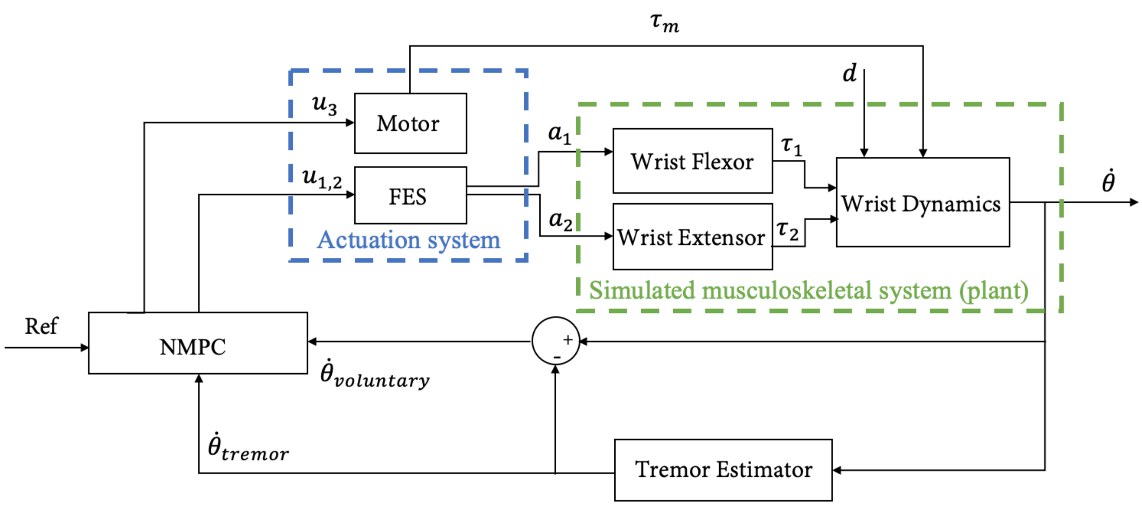

Figure 3.1: Simplified block diagram of the simulation study with NMPC controller and the simulated musculoskeletal model.

3.2 Model Design

The block diagram of the system proposed for tremor suppression is shown in Fig. 1. It contains the following main parts: the controller, the actuation block displayed inside the dashed blue box, the musculoskeletal model shown inside the dashed green box, and the tremor estimator. The goal of the control system is to reduce the error by tracking the voluntary motion as the reference signal (ref) and suppressing the tremor as a disturbance (d) to the system. The voluntary motion from simulated plant output motion is estimated by subtracting the estimated tremor from the feedback of the plant. From the input signals to the controller at each step, the NMPC has to allocate control effort between FES and the motor to achieve the desired motion. The musculoskeletal model consists of wrist flexor and extensor muscles, as well as the wrist skeletal dynamics model. Further details about each component of the proposed tremor suppression system are given in the sections below.

3.2.1 Muscle Model

The first step to design the suppression system is to define and recognize the plant, which is the musculoskeletal model for the wrist. The simplest way to model the wrist is as a one-degree-of-freedom (DOF) single joint in the 2D plane, where the target motion is the wrist flexion–extension. Wrist extension is controlled primarily by Extensor Carpi Radialis Longus (ECRL), Extensor Carpi Radialis Brevis (ECRB), and Extensor Carpi Ulnaris (ECRU); while wrist flexion is controlled by Flexor Carpi Radialis (FCR) and Flexor Carpi Ulnaris (FCU). In this work, only the model of flexor carpi ulnaris and the extensor carpi radialis longus muscles were considered. They will be referred to as wrist flexor (f) and extensor (e) in the rest of this article. The dynamics of a one-DOF wrist joint can be modeled as Eq. 3.1 [107].

$$\tau_{\mathrm{p}} + \tau_{\mathrm{m}} + \tau_i = (\frac{1}{4}mL^2 + I)\ddot{\theta} + \frac{1}{2}mgL\sin\theta \tag{3.1}$$

Here, $\tau_{\mathrm{p}}(\theta, \dot{\theta})$ is the passive torque due to the passive dynamics in the muscle model (from muscles, tendons, and ligaments); τ_{m} and $\tau_i(\theta, \dot{\theta}, a_{\mathrm{r}})$ are the torques generated by the electrical motor and the flexor/extensor muscles due to stimulation, represented by $i = [\mathrm{f}, \mathrm{e}]$, respectively; m is the mass of the hand; I is the moment of inertia; L is the hand length; and g is the gravitational constant. Also, $\theta, \dot{\theta}, \ddot{\theta}$ are the joint angle, angular velocity, and angular acceleration, respectively. Finally, $a_{\mathrm{r}} \in [0, 1]$ is the normalized stimulation amplitude, which can be defined as a piecewise function

$$a_r = \begin{cases} 0 & z < I_{\min} \\ \frac{z - I_{\min}}{I_{\max} - I_{\min}} & I_{\min} < z < I_{\max}, \\ 1 & z > I_{\max} \end{cases} \tag{3.2}$$

where $I_{\min}, I_{\max} \in \mathbb{R}^+$, are the sensory threshold and maximum current that the participant can tolerate, and z is the actual current intensity from the FES unit. An average value for sensory threshold and maximum current intensities can be found in the literature [111]. However, these values do not affect the final result of the simulation, since the algorithm is based on the normalized stimulation amplitude. On the other hand, these values should be measured and tuned for each participant in a real time experiment, since the normalized output of the control system will then be converted to the real values to be applied to the participant's muscles using the reverse function in Eq. 3.2.

It should be noted that the force generated by the muscle with FES decreases over time, as a result of muscle fatigue, and can be influenced by the muscle activation level. Muscle activation, a, is described as a first-order differential equation that considers the time delay in transition between muscle activation and relaxation, as shown in Eq. 3.3, where τ_{ac} and τ_{da} are the activation and deactivation time constants [112].

$$\dot{a} = \frac{a_{\mathrm{r}}^2 - a_{\mathrm{r}}a}{\tau_{\mathrm{ac}}} + \frac{a_{\mathrm{r}} - a}{\tau_{\mathrm{da}}} \tag{3.3}$$

The rate of change in muscle fatigue, $p \in [p_{\min}, 1]$, can be expressed as a simple, first-order differential equation based on the muscle activation and thus, can be modulated with the stimulation amplitude, as shown in Eq. 3.4 [113].

$$\dot{p} = \frac{(p_{\min} - p)a}{\tau_{\mathrm{fat}}} + \frac{(1-p)(1-a)}{\tau_{\mathrm{rec}}} \tag{3.4}$$

Here, $\tau_{\mathrm{fat}}, \tau_{\mathrm{rec}}, p_{\min}$ are the fatigue time constant, recovery time constant, and minimum level of muscle fatigue, as described in [113, 114]. Note that the muscle fatigue model is based on reduced muscle force when applying electrical stimulation, and therefore the parameters can be calculated for each participant during a model identification phase. Furthermore, it should be highlighted that muscle fatigue depends on several factors including the stimulation parameters, such as frequency, intensity, and pulse width, as well as the actual muscle properties of the participant and the duration of the stimulation compared to the rest periods in between stimulation sessions. Therefore, muscle fatigue might not affect every individual in similar conditions. This work considered Eq. 3.4 as a fatigue rate component to improve the model accuracy compared to the real life situations.

The muscle torque, τ_i, generated from the electrical stimulation applied to the flexor and extensor muscles to suppress the wrist tremor can be written as Eq. 3.5, where F_i is the muscle force due to the electrical stimulation for the extensor and flexor muscles, and r is the muscle moment arm. The muscle force, F_i, due to the electrical stimulation can be written as Eq. 3.6, where $F_{\max}$ is the maximum muscle force, f_{l} and f_{v} are the force–length factor and the force–velocity factor, and were obtained from [107].

$$\tau_i = \sum_i F_i r_i, \qquad i = [\mathrm{f}, \mathrm{e}] \tag{3.5}$$

$$F_i = F_{\mathrm{max},i} \times f_{\mathrm{l},i} \times f_{\mathrm{v},i} \times a_i \times p_i \tag{3.6}$$

The passive torque can be represented by Eq. 3.7 [115]:

$$\tau_{\mathrm{p}} = k_0\theta + b_0\dot{\theta} + k_2(e^{k_1\theta} - 1), \tag{3.7}$$

where k_0, k_1, k_2, and b_0 are subject specific constants. It should be noted that all of the subject specific parameters of the model used in this study were acquired from the literature. Please see Section 3.6 for further details.

Lastly, to define the state space of the system, the state vector is defined as $\vec{x} = [x_1, x_2, x_3, x_4, x_5, x_6] = [\theta, \dot{\theta}, \dot{p}_{\mathrm{f}}, \dot{a}_{\mathrm{f}}, \dot{p}_{\mathrm{e}}, \dot{a}_{\mathrm{e}}]$, in which $\dot{a}_f, \dot{a}_e, \dot{p}_f, and\ \dot{p}_e$ were obtained from Eqs. 3–4. Each equation was used twice: once for the flexor muscle ($\dot{a}_f$, $\dot{p}_f$), and once for the extensor muscle ($\dot{a}_e$, $\dot{p}_e$).

The input vector is specified as $\vec{u} = [u_1, u_2, u_3] = [a_{\mathrm{r,f}}, a_{\mathrm{r,e}}, \tau_{\mathrm{m}}]$, and f is the system dynamics function. The state space of the system, using Eqs. 3.1–3.7 is shown in Eq. 3.8.

$$\dot{x} = f(x,u) = \begin{bmatrix} x_2 \\ \\ \frac{\tau_{\mathrm{p}}+u_3+\tau_{\mathrm{i}}-\frac{1}{2}mgL\sin(x_1)}{\frac{1}{4}mL^2+I} \\ \\ \frac{(p_{\min}-x_3)x_4}{\tau_{\mathrm{fat}}} + \frac{(1-x_3)(1-x_4)}{\tau_{\mathrm{rec}}} \\ \\ \frac{u_1^2-u_1x_4}{\tau_{\mathrm{ac}}} + \frac{u_1-x_4}{\tau_{\mathrm{da}}} \\ \\ \frac{(p_{\min}-x_5)x_6}{\tau_{\mathrm{fat}}} + \frac{(1-x_5)(1-x_6)}{\tau_{\mathrm{rec}}} \\ \\ \frac{u_2^2-u_2x_6}{\tau_{\mathrm{ac}}} + \frac{u_2-x_6}{\tau_{\mathrm{da}}} \end{bmatrix} \tag{3.8}$$

3.2.2 Control System

Once the target plant has been defined, the next step is to design a control system to achieve the desired outcomes. The WTSD is required to suppress tremor with reduced muscle fatigue and resistive effects on voluntary motion. Further, the goal is to reduce the control efforts and therefore reduce the required power and actuation resources in the designed prototype. It must also suppress tremor in real time, and therefore it is necessary to compute FES and motor inputs online and without delay. Thus, considering the nonlinear nature of the system and the plant model presented in the previous section, a nonlinear model predictive controller [116] was used to allocate control effort between the FES and the electric motors dynamically. The foundation of the NMPC is that, at each sampling time, the future behavior of the system is optimized over a finite time horizon. Thus, the algorithm uses the first element of the optimal control law as the feedback control value for the next sampling step [116].

From the architecture provided in Fig. 3.1, the controller takes the current state of the plant and the output of the tremor estimator module as inputs. The outputs of the control system are the control actions of the motor (u_3) and FES (u_1 for the wrist flexor, and u_2 for the wrist extensor). The FES controller output is then normalized using Eq. 3.2, and the motor controller output is translated to the desired torque.

The tremor estimator shown in Fig. 3.1 is an enhanced High-order Weighted-Frequency Fourier Linear Combiner in cascade with a Kalman Filter (eHWFLC-KF) [117] to extract the tremor motion and calculate the voluntary motion by subtracting the tremor from the original signal.

The NMPC can be formulated as an optimization problem over the state and control trajectories, x and u, as shown in Eq. 3.9. $V(\cdot)$ and $l(\cdot)$ are the terminal and integral cost functions, defined in Eq. 3.10 and Eq. 3.11, respectively.

$$\min_{u} J(x_k, \bar{u}_k) = V(\Delta x(T)) + \int_{t0}^{T} l(\Delta x(\tau) + \Delta u(\tau))\, d\tau \tag{3.9}$$

subject to:

$$\begin{aligned}
&\dot{\bar{x}}(\tau) = f(\bar{x}, \bar{u}),\\
&\bar{x}(t_0) = x_k,\\
&\bar{u}_k \in \mathcal{U}.
\end{aligned}$$

$$V(\Delta x(T)) \triangleq \Delta x(T)^T P \Delta x(T) \tag{3.10}$$

$$\begin{aligned}
l(\Delta x(\tau), \Delta u(\tau)) \triangleq \Delta x(\tau)^T Q \Delta x(\tau) + \\
\Delta u(\tau)^T R \Delta u(\tau)
\end{aligned} \tag{3.11}$$

In Eq. 3.9, $\Delta x = \bar{x} - x_d$, where x and x_d are the current and desired states of the system, respectively. $\Delta u = u - u_d$, where u and u_d are the current input and the desired control law. Also, x_k represents the actual state of the system at time $t_k \in [t_0, T_N]$, where $[t_0, T_N]$ is the entire control process time. $\bar{x}(t_0)$ is the initial state of the system for the prediction horizon $[t_0, T]$ and is set to be x_k. $\bar{u}_k$ is the input trajectory at t_k and $\mathcal{U} = [u^-, u^+]$ represents the input constraints. It should be noted that variables with a bar, including $\bar{x}$ and $\bar{u}$, represent the internal model variables of the control system, while variables without a bar are the actual plant variables.

To define the desired states, x_d, muscle fatigue and muscle activation were set to the minimum value since there is no optimal trajectory planned for different participants. In the case of no voluntary motion, the desired trajectory for x_1 and x_2 are considered zero, while in the case of voluntary motion, the predicted motion was fed into the control system as the reference to track. Lastly, the desired control trajectory, u_d, was set to zero without a loss of generality [118], and therefore the controller task is to minimize the control effort over time.

The terminal cost function in Eq. 3.10 is defined as a quadratic function where P is a positive-definite and symmetric weight matrix. This terminal cost function represents a control Lyapunov function to ensure stability [119]. Also, Q and R in Eq. 3.11 are positive-definite and symmetric weight matrices that can be tuned to achieve the desired control performance.

The optimal control problem defined in Eq. 3.9 is designed to achieve multiple control objectives at the same time:

First, the goal of the cost function is to reduce the steady-state error by keeping the states as stable and close as possible to the desired trajectory. The error between the current state and the reference state is penalized using the integral cost function in Eq. 3.11, while stability is achieved by the terminal cost function in Eq. 3.10.

Second, the integral cost function decreases the total control effort defined by Eq. 3.11. The discrete time step for the controller was set to be 0.01 s, and the NMPC time horizon was chosen to be 0.5 s for all participants. These values were selected by trial and error. A larger horizon toward infinity requires high computational resources, while a short horizon leads to potential suboptimality. The weight matrix on the control output trajectory was selected to share the control effort equally, 1:1, resulting in R = 1. On the other hand, the controller was designed to track the voluntary motion and suppress tremor (in the case of no voluntary motion, the tracking reference was set to zero). Also, there is no optimal trajectory for other states, including the muscle fatigue and muscle activation. Therefore, the weight matrix was designed with gains for x_1 and x_2 5 times higher than the rest of states. Lastly, the optimal trajectory follows the nonlinear dynamics of the musculoskeletal system from the initial state using the first two equality constraints in Eq. 3.9. The inequality constraint on the control outputs limits the maximum actuation output to optimize a feasible control signal.

Another approach to ensure the stability of the closed-loop system is to use terminal constraints. While this approach also ensures the stability of the system, it may require an infinite number of iterations in the nonlinear optimization problem to satisfy the terminal constraint, which may not be feasible for real time implementation [116].

3.3 Evaluation

To assess the performance of the proposed system, a simulation study was designed in MATLAB (R2022a, The Mathworks, Inc.), using a dataset from 18 participants (11 males, 7 females) with parkinsonian tremor [120]. Approval for this study was obtained from the Human Research Ethics Board at Western University (Protocol #106172) prior to the start of the trials. The most affected side was selected for data collection, and inertial measurement units (IMU, five 9-axis IMUs, STEVAL-MKI108V2, STMicroelectronics®) were placed on each side of the wrist joint. IMU sensors were interfaced with an STC89C52RC microcontroller through the I2C protocol at 100 Hz. Participants were seated on a chair in front of a table, and the subject's forearm was strapped to a table, allowing only the hand to move freely. Participants were asked to perform different tasks to collect angular velocity data from resting, postural, and kinetic tremor, as follows:

- Resting tremor (Task 1a, 1b): The participant's arm was rested on the table with the palm facing down in Task 1a and the palm facing up in Task 1b. Data collection for Tasks 1a and 1b took about 60 seconds.

- Postural tremor (Task 2): Participants were asked to keep their hand outstretched at approximately 45 degrees above the table level while their forarm was strapped securely to the table. Data collection for Task 2 took about 60 seconds.

- Kinetic tremor and voluntary motion: Data collection for the following tasks was performed in one repetition by each participant. The recording length was less than 60 seconds and equal to the time it took each participant to perform each task.

  - Task 3: Participants were asked to move their hand from the flexion position to the extension position, pinch a pencil and move back to the flexion position.

– Task 4: Participants were asked to pinch a pencil with the thumb and the index finger while extending their wrist joint.

– Task 5: Participants were asked to trace a spiral on paper with a lightweight pen.

Participants were asked simple math questions to distract their attention from suppressing their tremor.

3.3.1 Data Preprocessing and Analysis

Before starting the simulation, it was necessary to separate the tremor signals from the voluntary motion signal to evaluate the control system performance. Therefore, two second-order zero-phase bandpass Butterworth filters with frequency ranges of 0.1 to 2 Hz, and 3 to 18 Hz were used to separate the voluntary and tremor signals and use as ref and d, respectively. The tremor power suppression percentage (TPSP) described by Eq. 3.12 and the error when tracking the voluntary motion (ETVM) described by Eq. 3.13 were used to evaluate the performance of the control system on tremor suppression and voluntary motion tracking. In Eq. 3.12, $\text{PSD}_{\text{suppressed}}$ is the power spectrum density of the residual tremor after suppression, and $\text{PSD}_{\text{original}}$ is the power spectrum density of the original tremor signal separated using the bandpass filter, as explained above. In Eq. 3.13, y is the voluntary motion output of the plant (angular velocity), and y_d is the desired voluntary motion from the dataset.

$$\begin{aligned}\text{Tremor Power Suppression Percentage (TPSP)} = \\ (1 - \frac{\text{PSD}_{\text{suppressed}}}{\text{PSD}_{\text{original}}}) \times 100\%\end{aligned} \tag{3.12}$$

$$\text{ETVM} = \text{RMS}(y - y_d) \tag{3.13}$$

Control effort, defined as the instantaneous value of the controller output, was also used to evaluate and compare the FES and motor usage in each scenario, see Section 3.3.2. The normalization of the FES output was done using the piecewise linear function in Eq. 3.2. The controller output for the motor was normalized using the min–max normalization method. Therefore, all

Table 3.1: Tremor power suppression percentage (TPSP) of Tasks 1a, 1b, and 2 in each scenario (mean ± std).

Scenario	Task 1a	Task 1b	Task2
Motor only	99.86 ± 0.02	99.83 ± 0.03	99.90 ± 0.01
FES only	99.24 ± 0.58	99.48 ± 0.16	98.94 ± 0.77
Motor + FES	99.84 ± 0.00	99.60 ± 0.01	99.90 ± 0.00

values are in the range between zero and one.

Statistical analyses, including repeated measures ANOVA (RMA) with Bonferroni correction or the univariate ANOVA, were used to study the significance of the difference in the obtained results. The normality of the data was tested using the Mauchly's test of sphericity for each analysis separately. The IBM Statistical Package for Social Sciences (SPSS Statistics v28) software was used to perform all of the statistical analyses with an α value of 0.05.

3.3.2 Simulation Scenarios and Procedure

To compare the performance of the multimodal system with motor-only and FES-only variations, the following scenarios were considered in this study:

1. Motor only: as shown in [38, 53], motors were used to reduce and suppress tremor in joints, including the wrist.

2. FES only: as shown in [75, 76, 102], out-of-phase FES is used to control and reduce the wrist tremor by alternatively activating the wrist flexor and extensor muscles.

3. Motor + FES: motors and out-of-phase FES are responsible for controlling the tremor, by applying external torque and by activating the flexor–extensor muscles, respectively.

3.4 Results and Discussion

3.4.1 Tremor Suppression and Voluntary Motion Tracking

Table 3.1 shows the performance of each control scenario on tremor suppression in Tasks 1a, 1b, and 2, where there is no voluntary motion to track. As shown in Table 3.1, there is no significant difference in the performance of each method while suppressing rest or postural tremor. In other

Table 3.2: Power suppression percentage and voluntary motion tracking error of Tasks 3–5 in each scenario (mean ± std).

Scenario	Metric	Task3	Task 4	Task 5
Motor only	TPSP	99.74 ± 0.06	99.77 ± 0.03	99.65 ± 0.20
	ETVM (°/s)	0.30 ± 0.18	0.12 ± 0.01	0.04 ± 0.00
FES only	TPSP	95.45 ± 1.22	96.28 ± 0.87	87.16 ± 4.63
	ETVM (°/s)	0.47 ± 0.19	0.28 ± 0.02	0.15 ± 0.01
Motor + FES	TPSP	98.67 ± 0.33	99.01 ± 0.23	99.28 ± 0.57
	ETVM (°/s)	0.36 ± 0.17	0.12 ± 0.00	0.05± 0.01

words, all methods can suppress tremor (TPSP) to a high degree in the absence of voluntary motion.

However, in the presence of voluntary movement, there is a difference in both tremor suppression and voluntary motion tracking error when using each method, as shown in Table 3.2. Statistical analysis shows a statistically significant difference between TPSP in motor only and FES only ($p = 0.001$), motor only and motor + FES ($p = 0.027$), and a statistically highly significant difference between FES only and motor + FES ($p < 0.001$) considering all tasks.

To evaluate the performance of each scenario on different tasks, RMA shows a statistically significant difference in TPSP for Task 3, between motor only and FES only ($p = 0.007$), motor only and motor + FES ($p = 0.018$), and FES only and motor + FES ($p = 0.015$). In TPSP for Task 4, a statistically significant difference between motor only and FES only ($p = 0.002$), motor only and motor + FES ($p = 0.006$), and FES only and motor + FES ($p = 0.004$) was observed. Lastly, results for TPSP in Task 5 showed a statistically significant difference between motor only and FES only ($p = 0.037$) and between FES only and motor + FES ($p = 0.027$). A univariate ANOVA test also shows a statistically high significance in tremor power suppression rate in all tasks and all different scenarios ($p < 0.001$). However, it should be noted that the differences obtained in suppression rates are not necessarily clinically important, as all methods, individually, can suppress tremor to a high level when using a real time control system.

Statistical analysis on voluntary motion tracking error using RMA shows a statistically significant difference between ETVM in motor only and FES only ($p < 0.001$), FES only and motor + FES ($p < 0.001$), and no significant difference between motor only and motor + FES ($p > 0.05$) for Task 3. Similarly, a statistically significant difference was observed for Task 4, in motor only and FES only ($p < 0.001$), FES only and motor + FES ($p < 0.001$), but not between motor only and motor + FES ($p > 0.05$). Lastly, RMA shows a statistically significant difference between ETVM in motor only and FES only ($p < 0.001$), FES only and motor + FES ($p < 0.001$), but not between motor only and motor + FES ($p > 0.05$) for Task 5. (See Table 3.2 for ETVM in each task and each scenario.)

Figure 3.2 shows a sample of the dataset in both time and frequency domains. Figure 3.2(a) shows the resting tremor signal in blue, and the suppressed tremor using motor only, FES only, and motor + FES in orange, yellow, and purple, respectively. Figure 3.2(b) shows the resting tremor and suppressed signal in the frequency domain. To compare the suppression in the frequency domain, a zoomed-in version of Figure 3.2(b) is shown in Figure 3.2(e). Figure 3.2(c) shows a tremorous signal, including tremor and voluntary motion. The orange signal is the pure voluntary motion, filtered using a bandpass filter with a cutoff frequency between 0.1 and 2 Hz. The yellow, purple, and green signals are the simulated motion, where the tremor suppression and motion tracking were based on motor only, FES only, and motor + FES, respectively. Figure 3.2(d) shows the signals in Figure 3.2(c) in the frequency domain, and Figure 3.2(f) is a zoomed-in version of Figure 3.2(d).

From the results, in the absence of voluntary motion in Tasks 1a, 1b, and 2, all methods can suppress tremor to a high percentage using the NMPC controller. On the other hand, the tremor suppression ratio with FES only decreases in Tasks 3–5 in the presence of voluntary motion. Comparing the TPSP of each scenario in Tasks 3–5, it is clear that motor only and FES only have the highest and lowest TPSP, respectively, while TPSP for motor + FES is in between. Voluntary motion tracking error is greater in FES only, while the difference in error in motor only and motor + FES is negligible. Therefore, in the presence of voluntary motion, it is more difficult to suppress tremor just using FES to a higher percentage (TPSP) without affecting voluntary motion (ETVM). This could be due to insufficient muscle torque generated from the out-of-phase strategy to suppress tremor and track voluntary motion accurately and simultaneously. On the other hand, the improved results in motor + FES could be due to several reasons. First, muscle fatigue caused by FES may reduce the generated muscle torque over time. Since the muscle fatigue dynamics were considered in this simulation, the reduction in FES input levels as a result of incorporating the motor in motor + FES may compensate for the reduced muscle torque and therefore improve

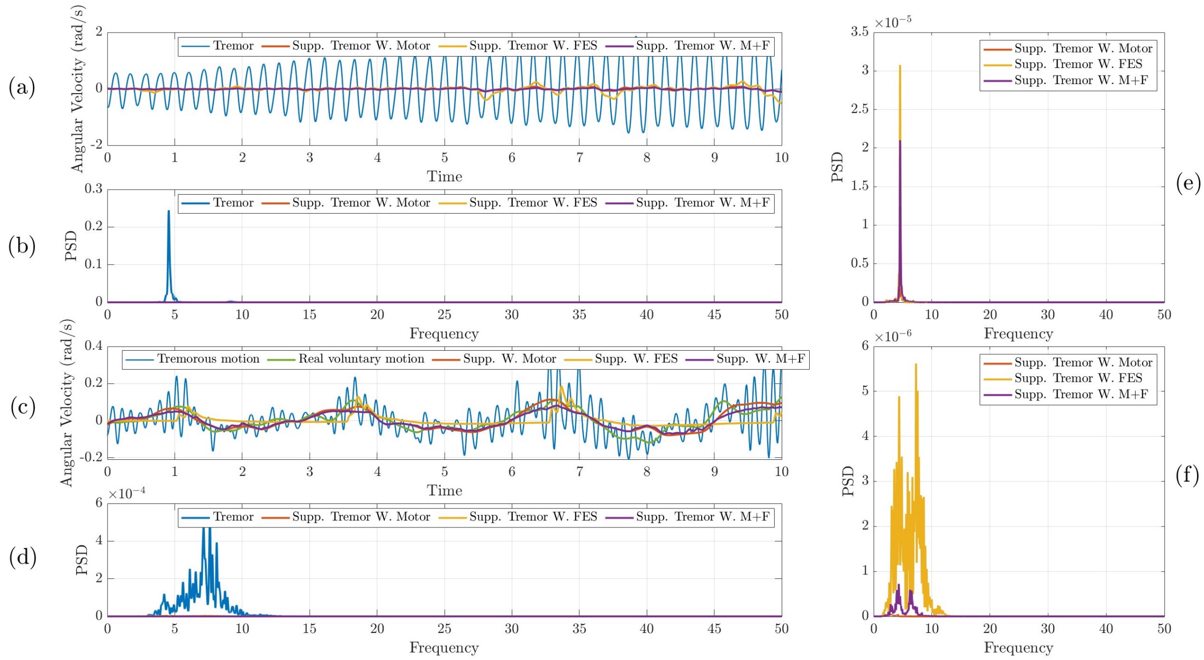

Figure 3.2: Sample of tremor signal and suppression results. (a) The blue signal is the original resting tremor; the suppressed tremor using the motor, FES, and combination scenario are shown orange, yellow, and purple, respectively. (b) Resting tremor and suppressed tremor in the frequency domain. (c) Tremorous motion from Task 5 in blue; the original voluntary motion in orange; the suppressed tremor using the motor, FES, and the combination scenario in yellow, purple, and green, respectively. (d) Filtered tremor and suppressed tremor from Task 5, in the frequency domain. (e) Zoomed-in suppressed tremors from (b). (f) Zoomed-in suppressed tremors from (d).

the overall performance. Second, the motor contributes to both tremor suppression and voluntary motion tracking with reduced power in motor + FES, resulting in overall improved performance. Therefore, the multimodal approach has the advantage of improved performance over FES-only systems when suppressing tremor. The voluntary motion tracking performance difference between motor only and motor + FES is negligible; however, the tremor suppression performance is higher in the first scenario.

Lastly, the effect of different model parameters to account for differences among participants will be considered in a future real-life implementation. In other words, the parameters selected from the literature represent one theoretical participant with highly variable tremor. This also implies that the algorithm optimizes the controller response for only one theoretical participant, and produces sub-optimal solutions for the rest of participants in the dataset. The model identification and parameter estimation can be performed using methods proposed in the literature [121, 122], by applying FES to the target muscles in a controlled condition.

3.4.2 Impact on Control Effort

Even when the performance of the motor-only scenario was higher in TPSP and ETVM, the assumption is that there is a higher level of energy required to achieve this performance. Therefore, an additional evaluation was performed to evaluate the control effort. Figure 3.3(a), (b) shows the mean of the motor and FES control effort for all participants for each task and each scenario. From this figure, it is clear that FES and motor control effort have been reduced in the combination scenario (motor + FES).

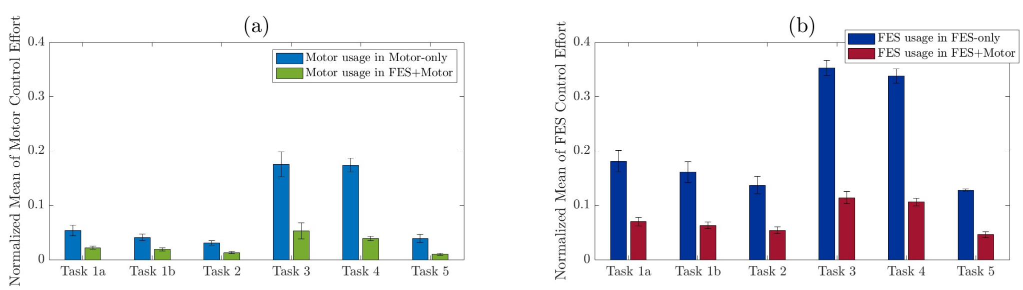

Figure 3.3: (a) Mean of motor control effort for all participants, separated based on task and control scenario. (b) Mean of FES control effort for all participants, separated based on task and control scenario.

Also, RMA was used to compare the motor usage in motor only and FES + motor and FES usage in FES only and motor + FES. From this analysis, there is a statistically significant reduction in motor usage in motor only and FES + motor ($p < 0.001$), and in FES usage in FES only and motor + FES ($p < 0.001$).

3.4.3 Comparison of the Multimodal and Current Approaches

Current tremor suppression devices based on electric motors and FES have shown up to 99% and 90% tremor suppression rates in simulation, respectively. Even though no study suggests the optimal rate of tremor suppression for PwP, almost all methods can reduce tremor to a high level using an accurate control system. Therefore, the results obtained in this paper for TPSP might not be clinically important or remarkably different to previous studies. On the other hand, survey results from [99] showed that the most critical aspects of an acceptable WTSD among PwP are the adaptability to lifestyle, the weight and size of the device, and accurate motion. From the design perspective, a WTSD requires distributed and lightweight actuators with an adaptive control system and a compact design that does not block upper-limb motion. The benefit of using motor + FES instead of motor only is the reduced amount of motor torque that is required for tremor suppression and voluntary motion tracking. A reduction in the required torque from the motor results in reduced power draw, and therefore reduced weight and size of a wearable device, leading to a more acceptable WTSD among users. For example, the tremor torque is estimated to be 0.2 to 0.4 Nm for postural and kinetic tremor, respectively [123]. Therefore, by comparing the motor torque reduction ratio, when using the motor only scenario, compared to the motor + FES scenario in Fig. 3.3(a), it is estimated that an ECX SPEED 16 L Ø16 mm, brushless motor, (Maxon Motors®) with a gear ratio of 29:1 can fulfill the minimum torque requirements in the first scenario. On the other hand, an ECX SPEED 13M Ø13 mm, brushless motor, (Maxon Motors®) with a gear ratio of 29:1 seems to be sufficient in the combination scenario. The weights of the first and second motor are 73 and 24 g, respectively. Furthermore, the electrical stimulation drawbacks, including muscle fatigue and pain, can be controlled by limiting the maximum current intensity selected by the controller and limiting the allocation of FES to compensate for muscle fatigue.

3.5 Conclusion

Even though the use of motors is beneficial in both tremor suppression and voluntary motion tracking, it requires a higher output torque than the multimodal approach, which leads to a heavier wearable device. The results further demonstrate that there is a trade-off between efficiency in tremor suppression, voluntary motion tracking, and the use of actuators. While the combination scenario might not have a clinically significant improvement in tremor suppression, it would reduce the device weight by about three times for tremor suppression in a single degree of freedom.

Therefore, a WTSD with additional degrees of freedom in multiple joints could be made more comfortable using lightweight motors in a combined technology device.

The first limitation of this work is that it is only based on simulations and has not yet been verified in a real life setup. Thus, the muscle model parameters have been selected from the literature instead of tuning the model for each participant during the tremor data collection phase. As a result, the physiological differences between participants were neglected in this study using a single set of model parameters. Another limitation is the lack of accuracy in selecting and stimulating the exact target muscles mentioned in the model of this work, due to the nature of commercially available surface electrodes. Therefore, in real clinical applications, the tremor suppression rate may drop when using surface electrodes. Electrode arrays could be used in future work for more accurate muscle stimulation. Lastly, to determine the elapsed time while running the program in MATLAB (R2022a, Mathworks, Inc.), the functions “tic,” ”toc,” and “cputime” were used to measure the run time for participants in all tasks and all scenarios. Considering the non optimal coding style, and the parameters of the control system including sampling rate and prediction horizon, results showed that the processing time for the motor-only scenario and the FES-only scenario are roughly equal to the actual time of data recordings. This means that the FES and motor-only scenarios are easier to implement in a real-world application. However, the combination scenario has a processing time of 1.06 times of the actual time of data recording. This could be reduced by further optimizing the code, and by tuning the control parameters to obtain both acceptable results and lower processing time.

It should also be noted that expanding the plant with multiple joints not only might require higher processing time, but will also require larger memory. It is expected that implementing the program on a microcontroller, which is the only suitable processing unit to be used in a wearable tremor suppression device, might add further complications that can be solved by optimizing the program.

As future work, participants will need to be recruited for model identification so that the simulation is as close as possible to a real clinical application. Also, to further improve the simulation model, a friction model [124] will be incorporated into the current model, and further improvements suggested by other studies will be considered [125]. Furthermore, to test the control system with a real device, it is first necessary to develop a compact FES device that allows the stimulation amplitude to be controlled with a microcontroller. It is then necessary to embed this system into a sleeve design and integrate it with a glove containing the electrical motors. It is further required to measure tremor torque in different tasks and from different participants, in order to further verify the benefits of using a hybrid system by comparing torque requirements for tremor suppression and output torques of electric motors. Since this study has demonstrated the feasibility of the approach, it would be worth developing such a system. The accuracy, comfort, and performance of the final design can then be compared with existing designs that utilize only FES or only electric motors. Lastly, the optimal clinically relevant amount of tremor suppression (TPSP) and the error while tracking the voluntary motion (ETVM) are currently under study and will be incorporated in future work.

3.6 Appendix

The parameters used in the equations of Section 3.2-A are summarized below. Furthermore, from Eq. 3.6, $f_\mathrm{l} = \exp[-(\frac{\frac{r\theta}{l_\mathrm{opt}}-1}{0.4})^2]$ and $f_\mathrm{v} = 0.54\,\mathrm{atan}\Big(5.69\frac{r\dot{\theta}}{v_\mathrm{max}} + 0.51\Big) + 0.745$, where l_opt is the muscle length at which the peak force F_max occurs, v_max is the maximum contraction velocity of the muscle, and r is the muscle moment arm.

The parameters used in Eqs. 3.3–3.4 are l_opt (m), v_max (m/s), F_max (N), and r (m), and are 0.051, 0.255, 128.9, and 0.019 for the Flexor muscle, and 0.081, 0.405, 304.9, and 0.018 for the extensor muscle, respectively. Further, τ_ac (ms), τ_da (ms), τ_fat (ms), and τ_rec (ms) are 40, 70, 0.2, 18, and 30, respectively.

Parameters in Eqs. 3.1 and 3.7 are m (kg), I (kg/m^2), L (m), k_0 (Nm/rad), k_1 (1/rad), k_2 (Nm), and b_0 (Nm/rad) and are equal to 0.43, 0.0039, 0.18, -0.4, -1.3, 0.5, -0.2, respectively.

Chapter 4

Tremor Suppression Using Functional Electrical Stimulation

4.1 Introduction

Tremor is one the most common motor symptoms of Parkinson's Disease (PD) and Essential Tremor (ET), and it can significantly affect the quality of life of people with PD or ET [126, 127]. Tremor is characterized by high amplitude oscillations at frequencies ranging from 3 Hz and above. It can affect different body parts such as the hands, arms, legs, and face. Most participants experience arm tremor, which can affect their activities of daily living (ADLs) [128, 129]. Surgical interventions [130, 131] or pharmaceutical treatments [132] are often used for tremor management. However, medications often lose effectiveness over time and some patients may experience side effects [132]. Brain surgery, as the second alternative, is costly and may not be suitable for all patients.

Alternatively, external tremor suppression using electrical stimulation [72, 75–78, 102, 133] has been proposed and studied. Functional electrical stimulation (FES) stimulates the muscles of the target joint to suppress tremor. FES contracts the flexor and extensor muscles simultaneously (co-contraction method) [72, 133], or in an alternating way to counteract tremor (out-of-phase) [75–78, 102]. FES parameters that can be varied include pulse width, current intensity, frequency, and the number of pulses. Even though the results of existing studies have shown FES to be a promising solution for tremor suppression, most studies have only experimented with a limited number of stimulation parameters.

Although longer stimulation durations below motor threshold have been studied in the past [81, 83, 95], stimulation above motor threshold has only been applied for 10 seconds or less in the literature. Applying electrical stimulation during extended periods might show highly variable results because of changes in the tremor patterns and the participant's reaction to the stimulation. In other words, it might not be feasible to specify a single set of parameters for an individual to suppress their tremor, as they might result in a decrease or increase in tremor, depending on the situation.

Lastly, as has been mentioned in [134], further studies are needed in this field, since it has been challenging to draw conclusions about the effectiveness of using FES for tremor suppression. Results to date have been limited by the combination of ET and PD groups in many studies in the literature, the use of various stimulation parameters in different studies, the lack of a standard method for changing these parameters, and by some studies only reporting the highest reduction in tremor. The objective of this study is to focus on these gaps by designing and implementing a protocol to address the lack of a consistent and standard method for systematically applying different stimulation parameters only to individuals with Parkinson's disease. Since different participants have different tolerance levels for stimulation, as well as different levels of tremor, the protocol initially establishes a baseline for motor threshold and sensory threshold for each participant, and follows a general rule for assigning parameter settings afterward. Using different levels of stimulation for each individual permits analysis to understand the effectiveness of different stimulation levels on different tremor intensity levels in various individuals. Each combination has been repeated three times to increase the accuracy. In other words, an approach that considered the effect of cognitive co-activation and muscle fatigue, repeated each combination three times, compared the results with the baseline, and averaged the results was implemented to allow more explicit conclusions to be made about the effectiveness of the method. This approach was designed to address the lack of consistency in previously published results, such as studies that only have reported the maximum tremor suppression.

4.2 Methods

To evaluate the effect of FES on tremor suppression as described above, an experiment was conducted on participants with PD, using a custom-developed experimental setup. Details of the experiment are explained in the subsections below.

4.2.1 Participants

The research protocol (114632) for this study was approved by the University of Western Ontario's Human Research Ethics Board before starting the trials. A total of 14 participants (three females, eleven males) with PD volunteered for this study; all were diagnosed and recruited by a movement disorders neurologist. Since the focus of this study is tremor suppression of the wrist, all of the participants were chosen by the neurologist to have relatively high tremor in their hands and arms. The study was completed with a small percentage of female participants despite efforts to include more women in the study. Part of the difference comes from PD being more prevalent in a male population; however, this only explains a portion of the imbalance. Unfortunately, recruitment was limited to the patient population at the clinic at the time of the study. On average, participants have been diagnosed with PD for 5 years, with a maximum duration of 10 years and a minimum of 6 months at the time of the experiment. The Unified Parkinson's Disease Rating Scale (MDS-UPDRS) of the resting tremor for the most affected side was evaluated on a scale of 1 to 4, with 1 indicating slight tremor and 4 severe tremor. In three of the 14 participants, tremor was at Level 1. It was Level 2 for three other participants, Level 4 for one participant, and Level 3 for the remaining seven participants. The most affected hand was the right hand for all but four participants. An explanation of the experiment, including the procedure, risks, and objectives, was given to each participant, and all participants signed a written informed consent before starting the trials.

4.2.2 Experimental Setup

Figure 4.1 shows the interactions between the participant and the hardware and software used in the experimental setup. The computer software block in Fig. 4.1 is custom software for online

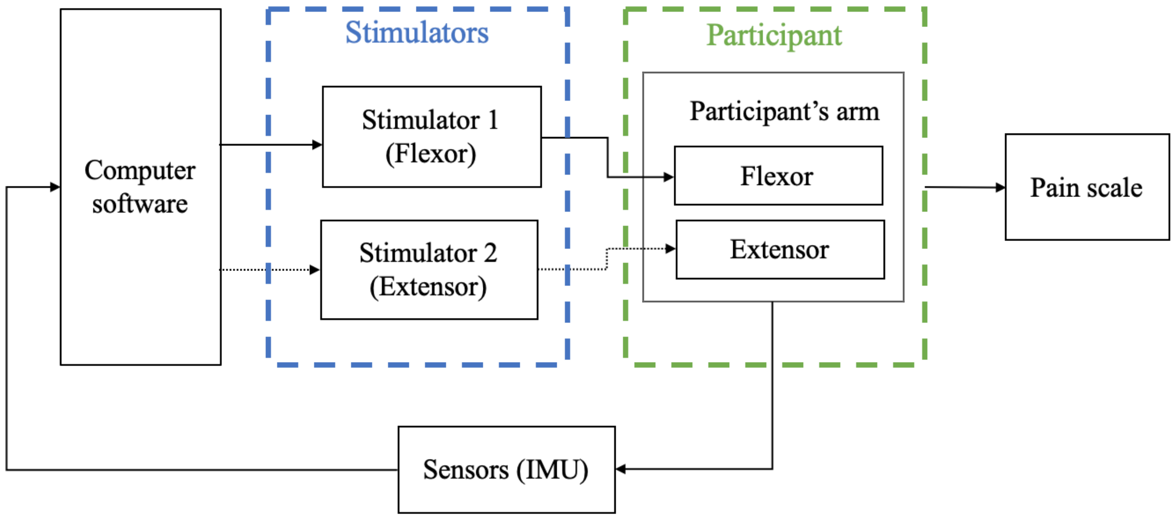

Figure 4.1: A summary of interactions between the software, hardware, and the participant.

configuration of the system and to control tremor suppression. The software was developed in Visual C# (Visual Studio, Update 5, Microsoft®, 2013), as shown in Figure 4.2. The software presents a user-friendly interface for the different steps of the study, as well as the recording of the tremor data, generating stimulation combinations (as will be explained in Section 4.2.3), and generating commands to activate the stimulators in an opposite direction to the tremor motion. The software uses a central controller that orchestrates all of the components and associated controllers required during all of the experiment steps. These components are the IMU sensors, the stimulators, and the pain scale keyboard, and they are connected to the PC using microcontrollers and a serial to USB adapter.

The stimulators block in Fig. 4.1 consists of two constant current electrical stimulators (DS7A, DS7AH, Digitimer) that were used to apply electrical stimulation to the flexor and extensor muscles. The stimulators were controlled by an external trigger connected to the software to stimulate the antagonistic muscle to the tremor motion. The frequency of the monophasic pulses was set to 120 Hz, and an external trigger controlled the number of pulses at the desired stimulation current intensity. Two pairs of self-adhesive electrodes (square, 2" $\times$ 2") placed over the flexor and extensor muscle bellies to deliver the stimulation pulses. Tremor motion was collected using a motion-sensing system, including five IMUs (LSM9DS1, $\pm 2000^{\circ}$/s angular rate scale, 16-bit reso-

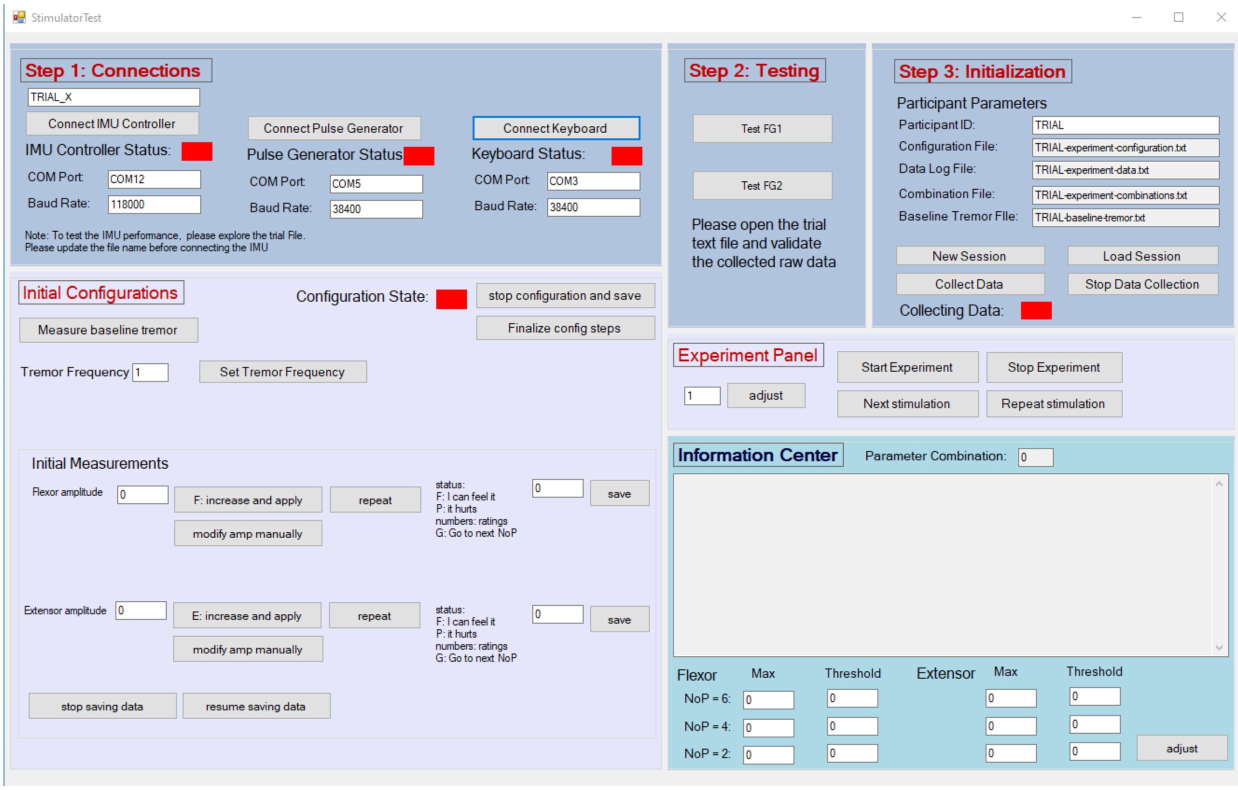

Figure 4.2: The user interface of the developed data collection software. In the first step, all of the peripherals, including the sensors, the stimulator pulse generator, and the comfort rating keyboard are connected through serial ports to the computer. After each connection, the red light turns green, indicating a successful connection. In the second step, the stimulators are tested to ensure that they are connected and the collected data are verified. The third step includes initializing the file names based on numbers. The next step is to collect the baseline tremor and calculate the tremor frequency using the software, as shown in the Initial Configurations Panel. Sensory and motor threshold and maximum tolerable current intensity are measured following the steps in the Initial Configurations Panel. The Experiment Panel runs the experiment combinations in the last step. Each combination can be repeated, or the experiment can be stopped if necessary. The Information Center is a communication panel from the software to the proctor that provides information regarding failures or required actions by the proctor. If required, the proctor can adjust thresholds using the panel below the Information Center.

lution, STMicroelectronics ®, Geneva, Switzerland) in the format of angular velocity. Gyroscope data, collected at a sampling rate of 50 Hz, using a microcontroller through the I^2C protocol, were sent to the PC using a serial to USB adapter. Figure 4.3 shows the experimental setup that was used in this study. IMU sensors were placed proximal to the wrist joint (IMU 1, Fig. 4.3), on the metacarpals of the hand (IMU 2, Fig. 4.3), on the proximal phalanx of the index finger (IMU 3,

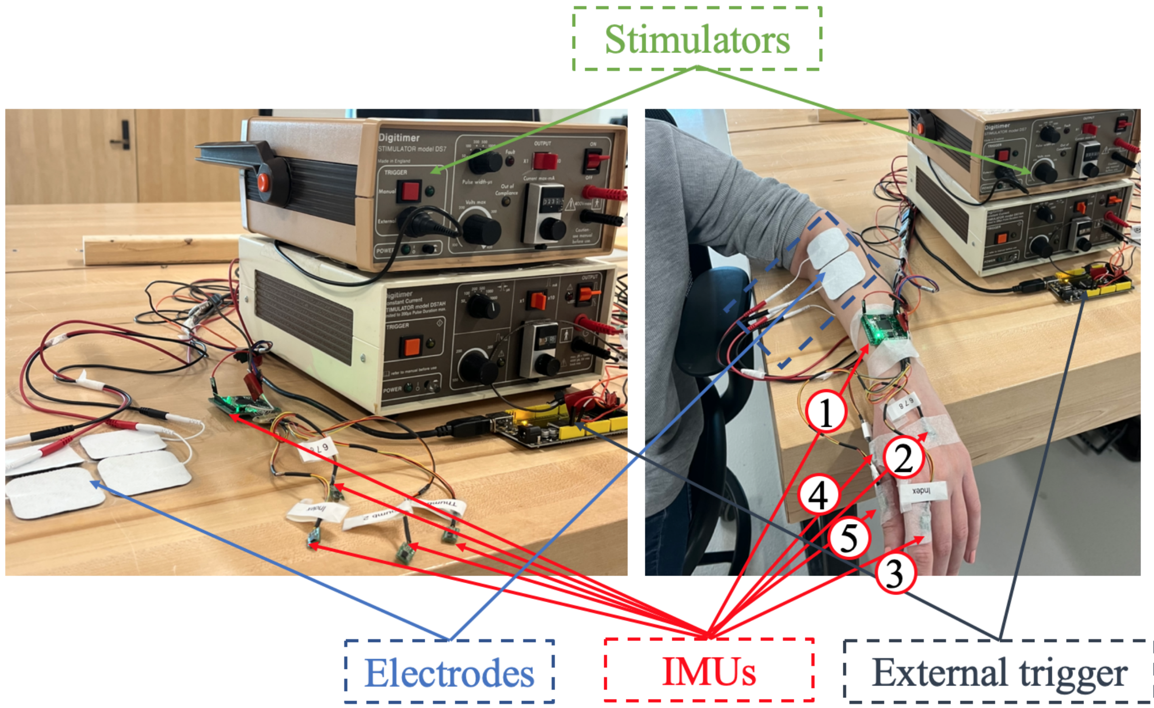

Figure 4.3: The experimental setup including two stimulators, five IMU sensors, two pairs of electrodes, and an external trigger that activates the stimulators when determined by the software.

Fig. 4.3), on the thumb metacarpals (IMU 4, Fig. 4.3), and on the thumb proximal phalanx (IMU 5, Fig. 4.3). All sensors were placed on the dorsal side of the hand and on the majorly affected arm of the participant. IMUs 1 and 2 were used to measure the wrist tremor by subtracting the values in real time. The absolute values were used to measure the tremor amplitude, and the signs after subtraction were used to measure the direction of the wrist tremor. Pitch was used in these real-time measurements. The participant's arm was placed in a neutral orientation and was monitored during the experiment to make sure that the orientation was not changing. This information was used in real time using a multi-threaded software calculation to perform out-of-phase stimulations. IMUs 2 and 3 were used to measure the tremor on the MCP joint of the index finger, and IMUs 4 and 5 were used to measure thumb MCP joint tremor. The collected data and the calculated tremor frequency were used to estimate tremor direction and apply stimulation to the target muscles at the time of directional changes.

4.2.3 Experimental Protocol

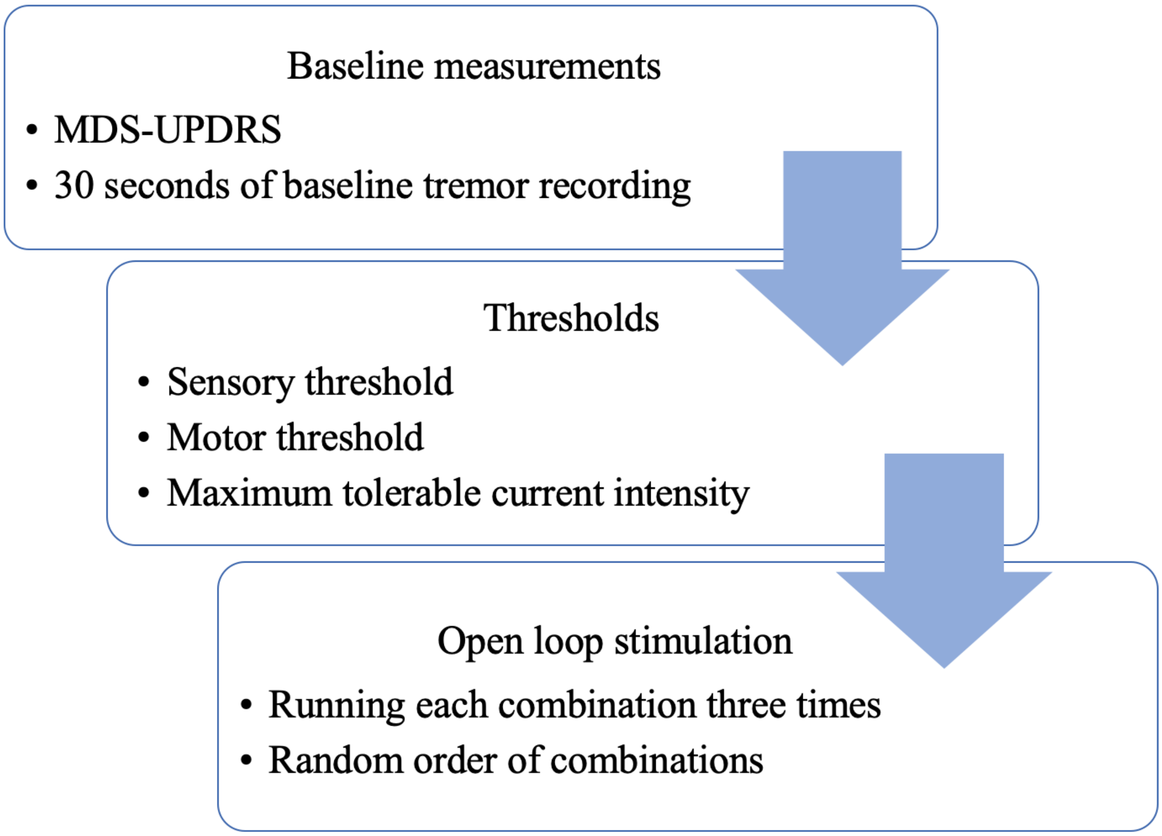

Figure 4.4: A summary of the experimental steps. The first step requires baseline measurements, including the MDS-UPDRS score, recorded rest tremor, and a calculation of the dominant frequency. In the second step, the stimulation amplitude is changed step by step to measure the sensory and motor threshold for each participant and the maximum current intensity that each participant can tolerate. Lastly, the open loop stimulations are performed in the third step.

After obtaining consent, the severity of PD was assessed by a movement disorders neurologist using the MDS-UPDRS score. The participants were seated comfortably in a chair next to a desk. The most affected arm was selected for the experiment, and was placed on the desk. The skin overlying the wrist flexor and extensor muscles was cleaned using an alcohol swab, and stimulating electrodes were placed on the belly of the flexor and extensor muscles of the wrist. A set of IMUs was placed on the skin on either side of the thumb, index finger, and wrist joints using medical tape to collect the motion data.

As has been mentioned in [135], cognitive co-activation can affect tremor intensity and variability in different ways. To avoid this effect on participants during data collection and later on when they receive the stimulation, and in order to bring out the tremor in a consistent fashion during the experiment, participants were asked a variety of simple questions (such as travel memories or counting downward) to invoke the tremor. As not all participants respond the same to mental arithmetic, engaging them in other conversations was more effective.

As shown in Figure 4.4, the experiment started by recording the tremor motion for 30 seconds. This recording represents the baseline tremor, and it was used to calculate the dominant frequency of the tremor during the trial and for further offline analysis.

In the next step, the sensory (ST) and motor threshold (MT) [136], as well as the maximum tolerable current (MAX), were determined for each muscle group. At first, the sensory threshold was determined by starting from a low-level stimulation intensity (e.g., 8 mA), a level at which all the participants could feel the stimulation without pain or side effects. The current intensity was then decreased in fixed steps (1 mA) until the participants could not feel the stimulation anymore. The step right before the stimulation could no longer be felt was denoted as the sensory threshold.

After determining the sensory threshold, the motor threshold for each muscle was determined by stimulating the muscle at increasing levels of current intensity, in steps of 1 mA. The current intensity when the proctor could observe the muscle twitch was denoted as the motor threshold.

Table 4.1: Parameter sets for each of the four stimulator parameters

Stimulator Parameters	Parameter Values
Current Intensity (mA)	max (50% MT, ST) min (MT +50% MT, MAX) MT
Pulse Width (µs)	200
Frequency (Hz)	120
Number of Pulses	2, 4, 6

From this point, the current was increased in fixed steps (1 mA), and the participant was asked to rate their comfort level. This process was repeated until the participant reached a comfort rating of three out of 10 using a graphical pain scale [137]. On this pain scale, three is considered tolerable, minor pain that does not interfere with most daily activities, and patients can adapt to the pain psychologically, while ten is unimaginable, unspeakable, severe pain that disables the patients from performing normal activities. This current value was recorded as the maximum current intensity (MAX). The process of measuring the sensory threshold, the motor threshold, and the maximum current intensity was repeated three times for each muscle using trains of two, four, and six pulses. After these measurements, a set of combinations that varied the amplitude and number of pulses was generated with a fixed frequency and pulse width to test the experimental procedure, as explained below. The study started with a pilot trial with four participants. In this pilot trial, stimulations were applied to the target muscles with high variability in the parameters for one repetition per combination and for only five seconds. It was observed that regardless of the ongoing conversations with the participants aimed at distracting them, they reacted differently to the new sensation of stimulation. Since this reaction could affect the results, to reduce the transient effect on the final results and considering the total time of the stimulation and individual exhaustion, the final protocol was adjusted to apply only nine stimulation combinations for an extended period of time (30 seconds). Table 4.1 shows the parameter sets for each stimulator parameter. It should be noted that bursts of pulses were applied in this study. Each burst or train of pulses that was delivered to the target muscle contained 2, 4, or 6 pulses, with a frequency of 120 Hz, and each burst had a pulse width of 200 µs. Time off between each burst was equal to the full burst time. From Table 4.1, the value of max (50% MT, ST) for current intensity is the larger of the sensory threshold and half of the motor threshold. Since both of these values are below the motor threshold, this value is referred to as the current intensity below motor threshold (BMT) in this article. On the other hand, the min (MT +50% MT, MAX) value is determined as the smaller of two values—the current intensity that participants labeled as level three out of 10, and a current that is 50% above the motor threshold. This ensures that the stimulation level does not exceed the participant's tolerance level (MAX). As both of these values are above the motor threshold, this value is referred to as the current intensity above motor threshold (AMT) in this article.

After determining the combinations of FES parameters for each participant, the out-of-phase tremor suppression strategy was tested at all parameter combinations. Each combination was repeated three times in random order, with blinded onset, and the stimulation duration was

30 seconds for each combination. Compared to previous studies and observations in our pilot trials, longer stimulation durations were used in this study to account for cognitive co-activation, tolerance, and mental effects during the study. Similarly, the reason for repeating each stimulation 3 times was to consider the effect of muscle fatigue, and cognitive co-activation as highlighted in [135]. It was hypothesized that averaging the overall signal acquired in 30 s and comparing the results of the 3 rounds would balance out the effects mentioned above.

After each stimulation, the participant was given a rest of at least 60 seconds. The tremor frequency was recalculated and compared to the baseline frequency during this period. Participants could stop the experiment anytime during the session if they felt discomfort or had concerns.

4.2.4 Data Analysis

As shown in Eq. 4.1, the power spectrum density (PSD, W/Hz) of the baseline tremor and the PSD of the tremor during the stimulation was used to calculate the tremor power suppression ratio (TPSR) in each experiment. From Eq. 4.1, when the tremor power during stimulation is lower than the baseline tremor power, the TPSR shows a higher percentage and therefore, greater tremor suppression. On the other hand, if the PSD during stimulation exceeds the baseline PSD, TPSR shows a negative value. A more negative TPSR signifies a larger increase in the tremor and worse results.

$$\mathrm{TPSR} = 1 - \frac{\mathrm{PSD}_{\mathrm{stimulation}}}{\mathrm{PSD}_{\mathrm{baseline}}} \times 100\% \tag{4.1}$$

It was decided that it was best to compare each stimulation with the baseline recording and not with the recordings during the pre-stimulation window because some studies have suggested that FES might reduce the tremor intensity for a while even after the stimulation is turned off [86]. Also, tremor is highly variable over time, and using the baseline to compare all of the stimulation results is expected to be a more consistent way of comparing different FES parameter combinations.

Due to the variability of pathological tremor over time in a single participant and due to environmental or psychological effects of stimulation, participants showed different reactions to each repetition of any single combination. It was observed that the first round of each combination generally showed a different trend in its effect on the tremor compared to other rounds. For example, the first round had a high tremor suppression in some cases; which could be because the stimulation drew the participant's attention, and they might have intentionally suppressed their tremor regardless of the purposeful distractions during the experiment. On the other hand, sometimes the stimulation caused no tremor suppression, or even an increase in tremor, in the first round, which could be due to the stress and unfamiliarity of the participant with long stimulation periods and its sensation. This appeared to be a psychological reaction to the stimulation when it was a new sensation for the participants. It was hypothesized that participants might get used to the stimulation over time, since it was observed that the results of the second and third rounds were in more similar ranges. Nevertheless, a highly different TPSRs for a single participant using a single combination could be considered an outlier. Therefore, to statistically evaluate the outliers in the dataset, the scaled median absolute deviation method (sMAD) was used to detect and remove outlier data points. The scaled median absolute deviation (sMAD) is defined as

$$\text{sMAD} = c \times \text{median}(|A_i - \text{median}(A)|), \qquad i = 1, 2, ..., N \tag{4.2}$$

$$c = \frac{1}{Q(0.75)} \tag{4.3}$$

where A is a vector of length N, in Eq. 4.2, and $Q(0.75)$ in Eq. 4.3 is the 75th percentile of the z-score, which is estimated as $c = 1.4826$ [138]. Using sMAD, a value that was more than three sMAD from the median was labeled as an outlier.

Statistical analyses, including the repeated measures ANOVA (RMA) with a Bonferroni correction and alpha value of 0.05, or the univariate ANOVA, were performed to evaluate the effectiveness of different combinations and stimulation levels in tremor suppression. Since MT and ST differ among participants, stimulation amplitudes were labeled as 0, 1, and 2 for BMT, MT, and AMT levels, respectively. It should be noted that the difference between individuals and repeated stimulations were not considered as factors, but as covariates. However, since covariates did not affect the outcome, they were removed in the final results to improve the power. The IBM Statistical Package for Social Sciences (SPSS Statistics v28) software was used to perform all of the statistical analyses. Further details are explained in Section 4.3.

4.3 Results and Discussion

4.3.1 Baseline Tremor and General Effect of Stimulation

Figure 4.5 shows a sample of the collected data. In Fig. 4.5, the first and second rows represent the baseline tremor in blue and the tremor during stimulation in red in both the time and frequency domains, respectively. The third row shows five seconds of tremor before stimulation in blue, followed by the tremor during stimulation in red. Each column of this figure represents one round of stimulation with an identical parameter combination (pulse = 2, the amplitude at motor threshold) in a single participant. As shown in Fig. 4.5 (a), (b), and (c), the first round of stimulation with this particular combination has no positive effect on tremor suppression. Indeed, the stimulation has increased the tremor power, as shown in Fig. 4.5(b), and has slightly increased the tremor amplitude, compared to both baseline and pre-window tremor, as shown in Fig. 4.5(a), (c), respectively. On the other hand, the second and third rounds of stimulation have reduced tremor, as shown in Fig 4.5(d)–(f), and (g)–(i), respectively, with more tremor suppression in the last round.

The TPSR for each participant calculated using Eq. 4.1 is shown in the second column of Table 4.2. In the third column of Table 4.2, results are shown after applying the sMAD algorithm discussed in Section 4.2. In the analysis, 9.4% of the data points were identified as outliers by the algorithm. These outliers were present in different repetitions of the combinations of P 02, P 08, and P 12–P 14. When an outlier was detected in a repetition, the algorithm removed the entire repetition for all combinations. Consequently, further analyses did not consider P 12–P 14, and the TPSR values for these participants were recorded as “Not Applicable” (NA) in Table 4.2.

From Table 4.2, the overall effect of tremor suppression varied among different participants and had no mean positive effect in the last three participants. The difference in results of tremor suppression among participants could be due to several reasons, which will be discussed in Section

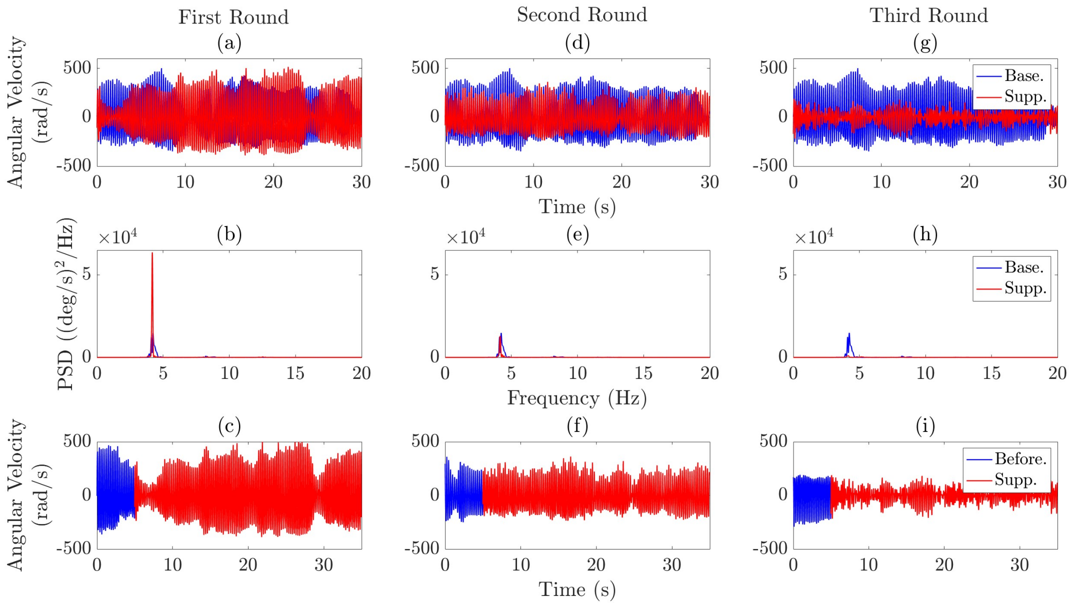

Figure 4.5: A sample of collected data from a single participant with identical stimulation combinations in three different repetitions during the experiment. (a), (d), (g) Angular velocity (AV) of the baseline tremor in blue, AV of the tremor during stimulation in red, in the time domain. (b), (e), (h) PSD of the baseline tremor in blue, PSD of the tremor during stimulation in red, in the frequency domain. (c), (f), (i) AV of the tremor during the five seconds before stimulation in blue, and AV of the tremor during stimulation in red, in the time domain. All signals are showing the wrist tremor, collected by subtracting the signals from IMU 1 and 2.

4.3.5.

Figure 4.6 shows the mean and standard error of the TPSR for each combination, using the filtered dataset with the sMAD algorithm. From this figure, stimulation amplitude levels at the motor threshold, shown in blue, have a generally better trend in tremor suppression for almost all pulse numbers compared to stimulation amplitude levels below the motor threshold, shown in green, and stimulation amplitude levels above the motor threshold shown in red. However, there is a slight improvement in the results for stimulation amplitudes above the motor threshold for six pulses. It should be noted that the results of an RMA test showed no statistically significant difference among different stimulation combinations (pulse $\times$ amplitude).

Further analysis was performed using an RMA on the filtered dataset with the first 11 participants, in order to evaluate the effectiveness of the different stimulation parameters, including

Table 4.2: Average of TPSR for each participant over all stimulation trials, before and after the outlier detection algorithm. The symbol * means that the highlighted participant's data had significant changes after applying the outlier detection algorithm.

Participant ID	Average of TPSR (before outlier detection)	Average of TPSR (after outlier detection)
P 01	76.5	76.5
P 02*	52.1	51.1
P 03	88.3	88.3
P 04	86.1	86.1
P 05	56.9	56.9
P 06	59.3	59.3
P 07	76.3	76.2
P 08*	47.2	61.7
P 09	74.6	74.6
P 10	80.9	80.9
P 11	52.3	52.3
P 12	-37.0	NA
P 13	-11.7	NA
P 14	-25.8	NA

three different numbers of pulses and three amplitude intensity levels (Table 4.1), on the TPSR. The results of these analyses are discussed in Sections 4.3.2 and 4.3.3.

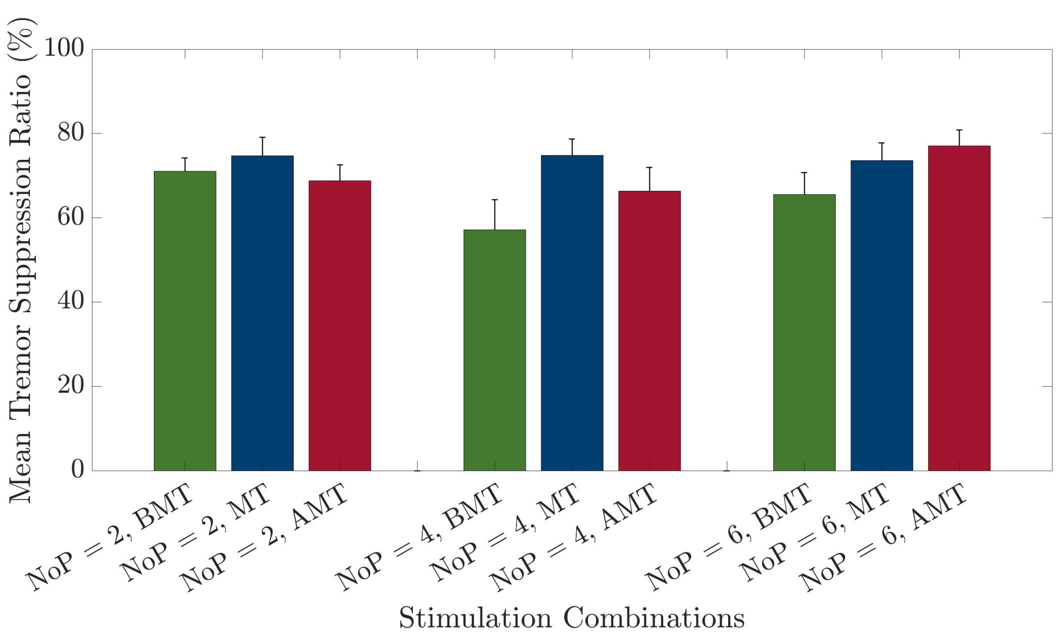

Figure 4.6: Mean of TPSR in different stimulation combinations. RMA showed no statistically significant difference among these combinations (pulse $\times$ amplitude, $p = 0.254$). NoP represents the number of pulses.

4.3.2 Effect of Stimulation Pulses

As shown in Fig. 4.7(a), it was not possible to find a significant difference in the TPSR based on the number of pulses using the filtered dataset ($p = 0.087$). When comparing two, four, and six pulses with the three stimulation intensities combined, the mean ± std are 71.4 ± 2.3, 66.1 ± 3.6, and 72 ± 3.2, respectively. Therefore, changing the number of pulses might not be a valuable control parameter for future stimulation and tremor suppression studies.

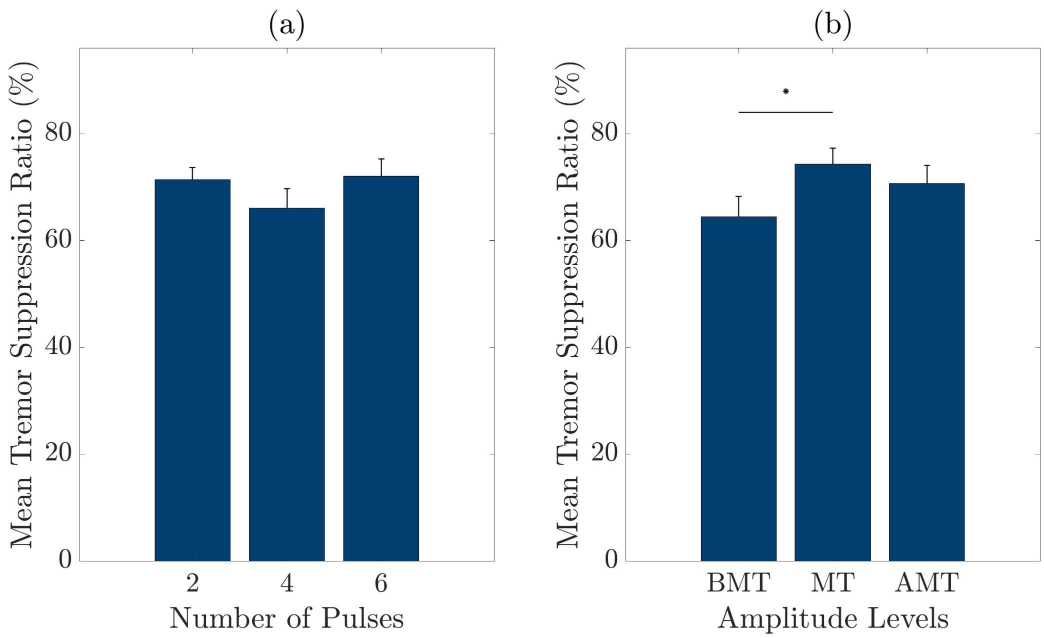

Figure 4.7: Effect of different stimulation variables on TPSR. (a) Mean of TPSR for the different number of pulses. (b) Mean of TPSR for different amplitude levels. Whiskers represent the standard error in each data group, and * represents a statistically significant difference between groups.

4.3.3 Effect of Stimulation Intensity

The results show that the amplitude level has a significant effect on the tremor suppression ratio ($p = 0.042$). As shown in Fig. 4.7(b), there is a significant difference between amplitude levels below and at motor threshold (64.5 ± 3.8 for BMT vs. 74.3 ± 3.0 for MT, $p = 0.032$). However, no significant difference was observed between amplitudes below and above the motor threshold (64.5 ± 3.8 for BMT vs. 70.7 ± 3.4 for AMT, $p = 0.472$), or amplitudes at and above motor threshold

(74.3 ± 3.0 for MT vs. 70.7 ± 3.4 for AMT, $p = 0.781$). Therefore, as a general trend, amplitudes at the motor threshold tend to be more effective among most participants in most trials.

Several reasons could explain the above observations. First, amplitude levels below the motor threshold might not be enough to suppress tremors with higher power intensity. On the other hand, amplitude levels above the motor threshold might generate extra torque for tremors with lower power intensity. Furthermore, it was observed that higher amplitudes might cause an effect similar to co-contraction of the muscles, preventing participants from moving their hand comfortably. Second, as will be discussed in Section 4.3.5, unstable experimental situations, such as tremor changes and variable muscle and forearm properties—for example the thickness of the adipose tissue layer under the skin or muscle mass [139, 140]—among participants can highly affect the results.

Although the underlying mechanisms of tremor generation in Parkinson's disease and the suppression of tremor using out-of-phase submotor threshold stimulation is still unclear, studies have shown that this type of stimulation can suppress tremor by up to 88% [86, 102] (4 PD and 1 ET participant in the first study, and all ET participants in the second study). This could be explained by the hypothesis that sensory stimulation can produce reciprocal inhabitation [83, 95] by mimicking the effect of stretch receptors in the muscle. Stretch response happens when an external force is applied to a muscle and stretch receptors within that muscle are activated. Afferent fibers from stretch receptors then project to interneurons in the spinal cord and inhibit the activity of the motor pool of the opposing muscle [141]. Similarly, applying an out-phase stimulation right before the arrival of the tremor burst on the opposing muscle can activate the Ialpha afferents of the target muscle, inhibit the activity of the motor pool, and reduce tremor.

The final set of data to analyze corresponds to the comfort ratings given by the participants. As shown in Fig. 4.8(a), the comfort rating at amplitudes below the motor threshold is mostly zero, indicating no pain and normal feeling. As the amplitude increases in Fig. 4.8(b) and Fig. 4.8(c) to the motor threshold and above the motor threshold, the majority of the pain level ratings increase to two and three, respectively. The variability observed in the ratings of different stimulation intensity levels could be attributed to variations among participants, their perceptual sensitivity, and their ability to tolerate the stimulation. It is worth mentioning that one participant's (P 05)

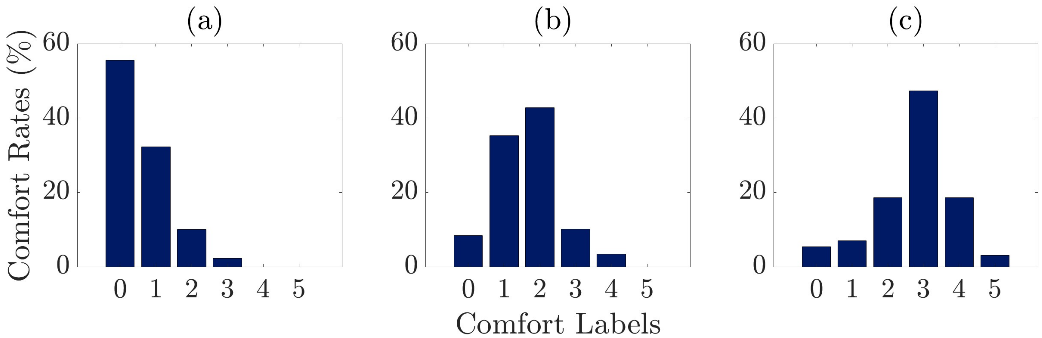

Figure 4.8: Effect of different stimulation amplitudes on the sensation of pain and discomfort. (a) Percentage of comfort levels for stimulation intensities below the motor threshold. (b) Percentage of comfort levels for stimulation intensities at the motor threshold. (c) Percentage of comfort levels for stimulation intensities above the motor threshold.

ratings were excluded from the analysis because of their overall misunderstanding of the rating scale.

4.3.4 Effect of Tremor Power Intensity

The effect of different stimulation combinations on tremor suppression has been discussed. However, observations suggest that different amplitude levels, even in a single participant, show different results in different situations and times. This observation suggests that tremor is highly variable over time, and higher tremor power intensities might require higher stimulation intensities for a higher suppression ratio.

To analyze this effect, tremor power intensities ((degrees/s)^2/Hz) in the five-second window prior (pre-window) to each stimulation were first extracted from the filtered dataset. Next, the common logarithm of the extracted data was calculated, which lies in the range of 1.84 to 5.89, with a mean value of 4.1, a first quartile of 3.289, a median of 4.38, and a third quartile of 5.01. The dataset, including the common logarithm of pre-window tremor power and TPSR, was then divided into four groups using the quartiles. The data below 3.29 (the first quartile) were categorized into "Group 1," the data within the range of 3.3 and 4.38 (between the first quartile and the median) were categorized into "Group 2," the data between 4.391 and 5.01 (between the median and the third quartile) were categorized into "Group 3," and the data above 5.02 (the third quartile) were categorized as "Group 4." This means that data included in Group 1 corresponded to the lowest intensity tremors, and the data included in Group 4 corresponded to the highest intensity tremors.

Using this categorization, Fig. 4.9 shows the mean of the TPSR in each tremor level group. It can be seen that Group 1 and Group 2 have a better suppression ratio than Group 3 and Group 4. A univariate ANOVA test was used to study the relationship between the amount of suppressed tremor (TPSR) and the tremor power intensity before stimulation (the pre-window). The test showed a highly statistically significant difference among tremor power groups and TPSR ($p < 0.001$). There is a highly significant difference between the Group 1 and Group 3 ($p < 0.001$), a significant difference between Group 1 and Group 4 ($p < 0.001$), but no significant difference between Group 1 and Group 2 ($p = 1$). Also, a highly statistically significant difference was observed between Group 2 and Group 3 ($p < 0.001$), and a highly statistically significant difference between Group 2 and Group 4 ($p < 0.001$) was observed. No statistically significant difference was observed between Group 3 and Group 4 ($p = 1$). Table 4.3 summarizes these results.

Table 4.3: TPSR according to pre-window tremor power intensity and ANOVA comparison results.

Group	TPSR	p value			
		G1	G2	G3	G4
G1	81.2 ± 2.9	-	NS	$p < 0.001$	$p < 0.001$
G2	79.0 ± 2.9	NS	-	$p < 0.001$	$p < 0.001$
G3	59.2 ± 2.9	$p < 0.001$	$p < 0.001$	-	NS
G4	59.9 ± 2.9	$p < 0.001$	$p < 0.001$	NS	-

To explore these results further, Fig. 4.10 shows the relationship between TPSR and the common logarithm of the power of the tremor in the pre-window. In this figure, the y axis shows the TPSR, and the x axis represents the common logarithm of the tremor power in the pre-window.

Fig. 4.10(a) categorizes the data based on the stimulation intensity level. Three first-order polynomial fits in this figure demonstrate that regardless of the stimulation intensity, the TPSR decreases with an increase in tremor power. It is noteworthy that the stimulation intensities at the motor threshold (blue line) exhibit a higher trend in TPSR in the overall range of pre-window tremor power. On the other hand, Fig. 4.10(b) divides the data points based on different pre-window tremor power intensities, as described earlier. The TPSR in this figure is the outcome of all stimulation combinations. It can also be observed from this figure that the TPSR declines as the tremor power increases.

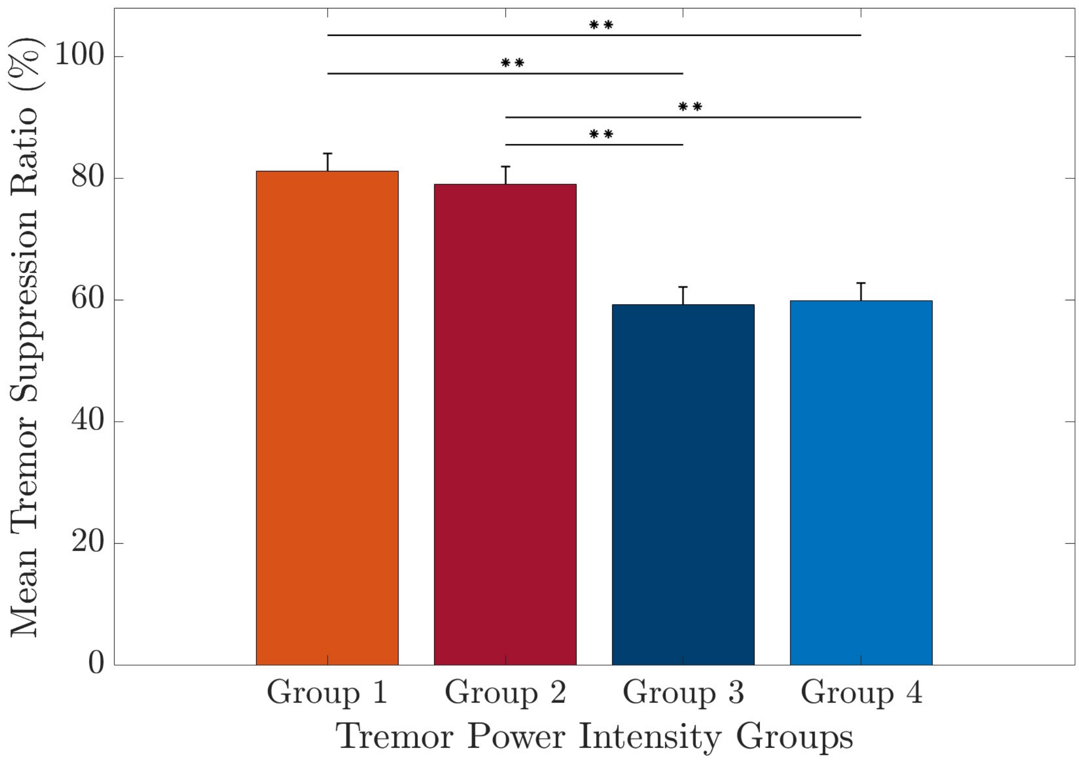

Figure 4.9: Mean of the tremor power suppression ratio for different tremor power groups, with statistical analysis. Whiskers represent the standard error in each group, ** shows a highly statistically significant difference between groups.

A univariate ANOVA test was performed on the filtered dataset, containing the TPSR as the dependent variable, and the pre-window power groups and the stimulation amplitude levels as fixed factors (V_1 and V_2). The results showed a statistically significant difference using various amplitude levels in different tremor power groups ($V_1 \times V_2$, $p = 0.016$). As shown in Fig. 4.11, there is a statistically significant difference in TPSR using BMT (green) for Groups 1, 3 ($p < 0.001$), Groups 1, 4 ($p < 0.001$), Groups 2, 3 ($p = 0.003$) and Groups 2, 4 ($p = 0.001$). Also, using MT (blue), the results showed a statistically significant difference between Groups 1, 4 ($p = 0.004$). Using AMT (red), there is a statistically significant difference among Groups 1, 3 ($p = 0.043$), and Groups 2, 3 ($p = 0.006$). Lastly, there is a statistically significant difference using BMT and AMT in Group 4 ($p = 0.035$). This figure further emphasizes the results obtained earlier in Fig. 4.10, which show that tremor suppression is lower at higher tremor intensities. Furthermore, by comparing the effect of stimulation intensity in each group, it can be seen that although there is no

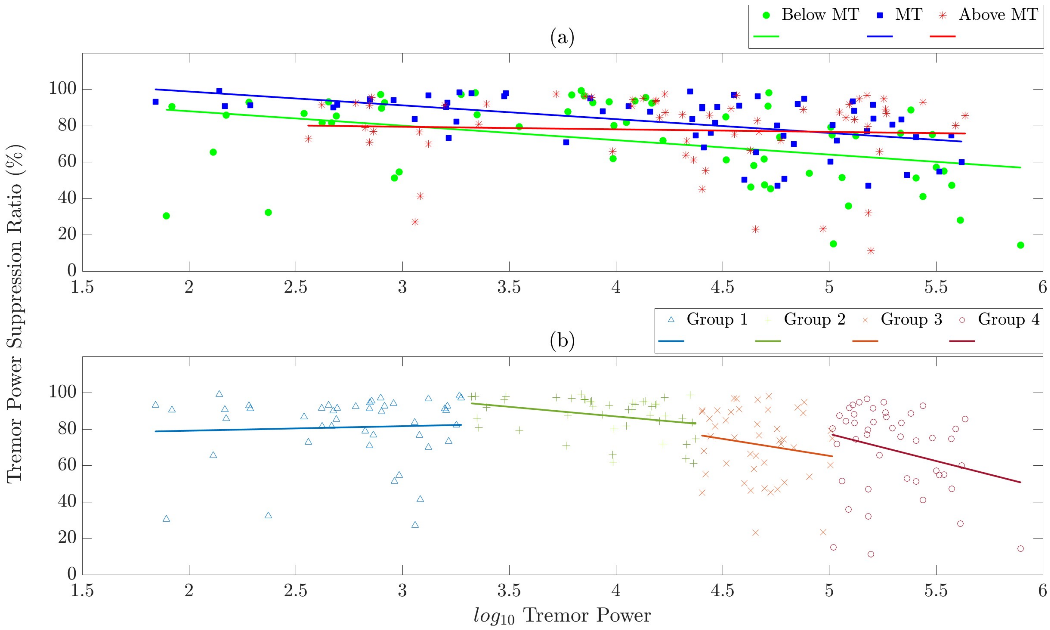

Figure 4.10: Relationship between TPSR and the tremor power in the pre-window before stimulation. (a) Data points in green show the TPSR using amplitudes below MT, data points in blue show the TPSR using amplitudes at MT, and data points in red show the TPSR using amplitudes above MT. Green, blue, and red lines show the first-order polynomial fit to the associated data points for below, at, and above motor threshold amplitudes, respectively. (b) Data points in blue, green, orange, and red show the TPSR in Group 1–Group 4 of pre-window tremor power groups. Each line corresponds to a first-order polynomial fit of the data points of the same color.

statistically significant difference between TPSR in the first three groups when changing amplitude levels, amplitudes above the motor threshold show better performance in the last group compared to amplitudes below the motor threshold.

4.3.5 Limitations

The response to Functional Electrical Stimulation (FES) can vary greatly among individuals, and even within the same individual using different combinations of FES, or the same combination at different times. This variability has been observed in relation to tremors, especially parkinsonian tremors, which can vary greatly depending on the time of day and mental state of the individual, including during times of stress and anxiety. A single participant can respond differently to an identical stimulation combination in different time frames. This problem could be addressed by de-

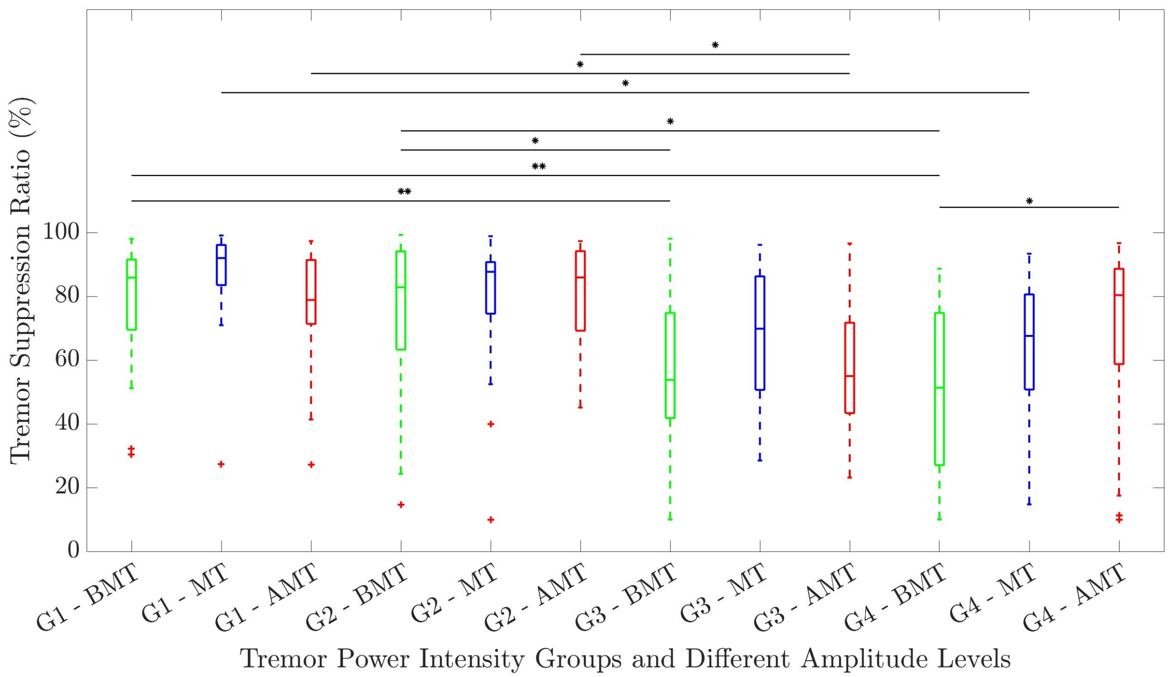

Figure 4.11: Effect of different amplitude levels on TPSR, compared in different pre-window tremor power ranges. Red, green, and blue boxes represent the range of TPSR using amplitude levels below (BMT), at (MT), and above motor threshold (AMT), respectively. On each box, the bottom and top edges of the box show the 25th and 75th percentiles, respectively. The central mark shows the median, and whiskers extend to the most extreme points that are not considered as outliers. Outliers are plotted as +. * and ** show a statistically significant difference and a highly statistically significant difference between groups, respectively.

signing and developing a closed loop control system that adapts to the changes in tremor intensity. As shown in [142, 143], repetitive control and model predictive control can be beneficial in this application. However, experiments and tunings involving participants with pathological tremor are required to evaluate and compare methods effectiveness. Tremor variability is not the only reason for different results among participants. Experimental conditions, such as skin conditions, or changes in the hand or arm orientation can slightly shift the targeted muscle belly, thereby reducing the effectiveness of stimulation from fixed electrodes [144]. Therefore, an electrode array with a control system might also help to improve the stimulation outcomes. Other limitations of this study that can be highlighted are the limited number of participants, the lack of balance between male and female participants, and the absence of a method to measure or estimate muscle fatigue. Simulations at and above the motor threshold might have caused muscle fatigue during the experiment and altered the results in later stimulations compared to the initial rounds. The rest time could have been extended in the study protocol to reduce this effect on the results; however, the total length of the study was kept as short as possible in order to limit the participant's inconvenience. For the same reason, the number of repetitions per stimulation combination was limited to three; however, further experiments can be performed in future work to extend the results. Generated muscle fatigue might have reduced the effectiveness of FES in tremor suppression since the torque generated by the fatigued muscles using the same level of stimulation decreases. Therefore, the potential negative effect on the suppression might have caused less tremor suppression in the later rounds of the stimulation. Lastly, further analysis can be conducted on the collected data to study changes in tremor power for different harmonics during suppression, and the effect of suppressed wrist tremor on tremor characteristics at the wrist and distal joints.

4.4 Conclusion

The effect of different stimulation parameters in 30 seconds of tremor modulation was studied in this work. Motion data were recorded from 14 participants with PD tremor to investigate the effect of different stimulation parameters, and comparisons were performed over tremor data with and without stimulation. Parameter combinations include a fixed frequency of 120 Hz, a fixed pulse width of 200 µs, a variable number of pulses at 2, 4, or 6, and variable current intensities derived from participant-specific sensory and motor thresholds. Observations and data analysis showed that tremor generally decreased during stimulation intensities close to or slightly above the motor threshold in most cases. Furthermore, different suppression ratios were obtained from different repetitions of each combination for a participant, and generally among different participants. Although stimulation duration was extended in this study to reduce transient response effects on the final results, it was observed that the effect of specific stimulation parameters is highly dependent on the ongoing intensity of the tremor. Therefore, the new method of testing electrical stimulation that was presented in this paper not only shows the highly variable suppression results within one individual, but also highlights the dependency of suppression rate on the existing tremor intensity. This implies that a real-time control approach is required to update the stimulation intensity online according to the tremor intensity for each individual. Lastly, it should be noted that although the focus of this study was the suppression of tremor in Parkinson's disease, and treatments and pathophysiology are different for Parkinson's disease, essential tremor, and other neurological disorders that cause tremor, the results of this study could support the understanding of other types of tremor, and lead to developing suppression technologies using FES.

Chapter 5

Variability of Parkinsonian Tremor in Time, During Different Tasks, and Under External Interference

5.1 Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, and it causes several motor and nonmotor symptoms. Symptoms are caused by the loss of dopamine producing cells in the substantia nigra pars compacta [8]. Medications used to treat tremor are often ineffective, and may produce unwanted adverse effects such as memory problems, disorientation, dry mouth, and hallucinations [8]. Other treatments include deep brain surgery [130, 131], which is not recommended for all individuals with PD because of the high risks associated with the surgery. Alternatively, wearable tremor suppression devices (WTSDs) are another solution to assist participants with PD tremor.

These devices are based on mechanical or electrical suppression actuation systems [38, 52, 53, 55, 65, 72, 78, 102, 133] and are designed to reduce tremor, and allow participants to perform their activities of daily living more comfortably. However, due to changes in tremor over time and in different daily conditions, an acurate tremor prediction and estimation is needed to enable tremor control using these devices.

Several studies have investigated tremor changes and variability in people who suffer from Essential Tremor (ET) using several factors to assess the tremor amplitude, frequency, and regularity [145–147].

Morrison et al. suggest that PD tremor presents differently in sitting and standing positions [148]. Zach et al. conducted a study demonstrating the impact of cognitive stress on the medication Levodopa's effectiveness in PD tremors and the reduction of medication effects in the presence of cognitive stress [135]. In a pilot study, Rahimi et al., compared rest and postural tremor data from the wrist and index finger and showed significant tremor amplitude variability in the measured tasks [149].

Changes in tremor regularity and frequency in response to mechanical loading, medication, and surgical interventions have been reported in several studies in the literature [150–152]. Furthermore, the dependency of tremor regularity on both neural factors and mechanical factors has been reported throughout the literature [153, 154]. Morrison et al. compared the linear and nonlinear characteristics of postural pathological tremor of participants with PD and ET and physiological tremor of elderly healthy individuals. By analyzing the accelerometer data, the group showed that pathological tremor in participants with ET is significantly more regular than in participants with PD, and tremor in the PD group is significantly more regular compared to the physiological tremor in healthy individuals. Furthermore, they have found that the postural tremor in participants with PD or ET has a single prominent frequency peak in the range of 4–6 Hz. In contrast, postural physiological tremor in healthy individuals has the frequency content spread in the range of 8–12 Hz. [155]. Sturman et al. [152] have compared the effect of medication and SubThalamic Nucleus Deep Brain Stimulation (STN DBS) on rest and postural tremor in PwP, before the surgery, after the surgery, with and without medications and in comparison to a control group. Results showed that tremor regularity decreases and frequency increases in case of a reduction in tremor magnitude. However, none of the treatments alone or in combination could decrease the tremor regularity to the level of the control group. They have also shown that medication and STN DBS reduce the coherence of tremor EMG in PwP, suggesting that treatments might also reduce motor unit synchronization.

Kovacs et al. [151] conducted a study in which tremor data were collected at three time points: two days before surgery (baseline), two days after surgery (short-term), and three months after surgery (long-term). They defined successful surgical interventions as those in which the tremor amplitude decreased after the operation and compared the frequency and regularity of the collected data at all time points. The results showed a decrease in tremor regularity and an increase in frequency only in successful surgical interventions for both short-term and long-term measurements, in comparison to the baseline. The group compared the differences between effective and ineffective neurosurgical interventions as well. An ineffective operation was defined as the condition in which the tremor reappeared six to 12 months post-surgery. Data collected from the patients with ineffective surgery revealed that despite a significant reduction in tremor amplitude shortly after the operation, similar to the effective surgeries, there is a lack of change in tremor frequency and ApEn even in the data collected two days after the surgery. Both studies suggested that DBS might reset or suppress the central oscillator(s) frequency and therefore, increase the effect of mechanical-reflex factors in the presentation of tremor.

In another study, Meigal et al. [150] compared pathological rest tremor in PwP with physiological tremor in young, healthy individuals and older healthy individuals as control groups. They have obtained similar results to other studies in the literature by analyzing the accelerometer data, in which pathological tremor is significantly more regular than physiological tremor, with a higher range of tremor amplitude and lower frequency range. On the other hand, Meigal et al. compared the tremor in three groups with one and two kilograms of quasi-isometric holding. Results showed that tremor amplitude decreases with loading in PwP, while ApEn and frequency increase and merge with healthy control group values. Furthermore, analyzing EMG data and accelerometer data revealed that the coherence between accelerometer and EMG signals in PD decreases while the load is increasing [150]. This observation suggests that the asynchronous firings of the motor units that cause the postural muscle tonus might erase the difference between the PD and healthy control group values of ApEn [150]. Also, comparing the frequency range of pathological tremor in PD and ET with physiological tremor, both PD and ET have shown a narrow range of frequency in which the neural drive has been increased. Thus, the resultant motor output is less complex and more regular compared to healthy individuals [155].

To understand the changes and characteristics of parkinsonian tremor, especially when suppressed using nonmedical or surgical approaches, this type of tremor was evaluated under various conditions. The goal of the study was not to evaluate medications and regular treatments and their effect on tremor, since there are already studies in that area that have evaluated the effects of medication or brain surgery on tremor. Instead, novel treatments for tremor have been considering the use of FES and mechanical loading for tremor suppression. FES and mechanical loading are two of the most used technologies in the design and development of wearable tremor suppression devices (WTSD). Therefore, understanding how they might affect tremor and whether the effects are comparable to regular PD tremor is important for further developing WTSDs. In the first step, evaluations have been performed to understand how tremor changes among participants in five different tasks. Next, the study investigates the effect of FES on the characteristics of suppressed and unsuppressed tremor. Lastly, data from a related case study is provided to show the changes in tremor while applying mechanical loading, and a comparison of tremor characteristics when applying mechanical loading and FES in the same participant.

5.2 Method

Three different datasets from three experiments were used in this study. The details of each experiment are described in the following subsections. Figure 5.1 shows the summary of each dataset.

5.2.1 Experiment I

The first experiment aimed to collect tremor data during different tasks and compare tremor features [120]. Therefore, 18 participants (11 males, seven females) diagnosed with Parkinson's disease that have tremor in at least one hand were recruited by a movement disorder neurologist. The participants' age ranged from 60 to 84 at the time of the experiment (with a mean $\pm$ standard deviation of 69 ± 7). Approval for this study was obtained from the Human Research Ethics Board at Western University (Protocol #106172) prior to the start of the trials. Data were collected from the wrist of the participant's most affected side using inertial measurement units (IMU) at a

Experiment 1:	Experiment 2:	Experiment 3:
Type: Only tremor	Type: Tremor Suppression (FES)	Type: Tremor Suppression (Mechanical)
Task(s): Rest tremor, Postural tremor, Action tremor	Task(s): Rest tremor	Task(s): Rest tremor, Postural tremor, Action tremor
Number of Participants: 18	Number of Participants: 14	Number of Participants: 1
Target joint: Wrist	Target joint: Wrist	Target joint: Wrist

Figure 5.1: Summary of three datasets that were used in this study.

sampling frequency of 100 Hz. After obtaining written consent, IMU sensors were placed on each side of the wrist joint, and the participants were asked to sit on a chair in front of a desk. To restrict movement to only the hand, the participant's forearm was securely fastened to the table. Each participant performed the following tasks to collect rest, postural, and action tremor.

- Task 1a (Rest tremor): With the palm facing down, the participant's arm rested on the table for 60 seconds.
- Task 1b (Rest tremor): With the palm facing up, the participant's arm rested on the table for 60 seconds.
- Task 2 (Postural tremor): While the participant's arm was strapped securely to the table, they were asked to hold their hand outstretched at approximately 45° above the table level for 60 seconds.
- Task 3 (Action tremor): Participants were asked to pinch a pencil while moving their hand from flexion to extension and moving back to flexion.
- Task 4 (Action tremor): Participants were asked to extend their wrist and pinch a pencil with the thumb and index finger.
- Task 5 (Action tremor): Participants were asked to trace a spiral with a pen on paper.

Data collection for Tasks 3–5 took less than 60 seconds and was stopped when the participant managed to finish the task. Rest tremor is the most common type of tremor in PD. While postural and kinetic (action) tremor are more common in essential tremor, but can also appear in PD [156]. The first two tasks (1a, 1b, and 2) were implemented to assess rest tremor and postural tremor. Reach and grasp is also being used in the literature to assess parkinsonian tremor and was used in Tasks 3 and 4 of this study [157]. Pen and paper tasks can also be used for diagnosis of PD tremor, and can help in differentiation between different types of tremor [158]. From this category, the spiral drawing task was selected in this study. During data collection, participants were asked simple math questions to distract them from paying attention to their tremor and potentially suppressing it.

5.2.2 Experiment II

The second experiment aimed to evaluate the effect of different electrical stimulation parameters, including the number of pulses and stimulation intensity, on tremor suppression [159]. Fourteen participants (three females, eleven males) with PD that have tremor in at least one hand were recruited by a movement disorder neurologist for this study. The participants' age ranged from 58 to 80 at the time of the experiment (with a mean $\pm$ standard deviation of 72 ± 6). Before starting the trials, the research protocol (#114632) was approved by the Human Research Ethics Board of Western University. This study used two constant current electrical stimulators (DS7A, DS7AH, Digitimer) to apply electrical stimulation to the wrist flexor and extensor muscles. Stimulation was triggered using an external trigger controlled by custom-designed software. The stimulation frequency and pulse width were fixed at 120 Hz and 200 µs, respectively. Stimulation was delivered to the muscles using self-adhesive electrodes (2" $\times$ 2"), and tremor data were collected using IMU sensors, placed on both sides of the wrist joint, at a frequency of 50 Hz. During the experiment, participants were seated on a chair in front of a desk, with their most affected arm at rest on the desk and their wrist on the edge of the desk. Stimulation was delivered in three different numbers of pulses, including 2, 4, and 6 pulses. The stimulation amplitude was delivered at the motor threshold, below the motor threshold, and slightly above the motor threshold for each participant, based on their personal motor threshold that was measured at the start of the trial. A graphical pain scale [137] was used to find the maximum stimulation amplitude for each participant. After finding the motor threshold, the stimulation amplitude was increased by fixed steps (1 mA) until the participant rated the comfort level as three out of 10 on the pain scale. The maximum generated amplitude by the software was then calculated by comparing the maximum stimulation amplitude and 50% above the motor threshold, and the smaller value was selected as the value above the motor threshold for that participant.

The software generated nine combination sets with varying amplitudes and number of pulses and was repeated three times. The 27 stimulation combinations were tested in a random order for each participant. Each stimulation was delivered for 30 seconds, followed by a 60 second rest period. Before applying any stimulation, data were recorded as a base measure for future analysis. This is called baseline tremor in the rest of this article.

5.2.3 Experiment III

The goal of the third study was to evaluate the tremor suppression performance of a wearable tremor suppression device (WTSD) using electric motors [54]. This experiment was conducted with a single participant diagnosed with PD as a case study. The availability of these data was possible because the same participant volunteered for all of the studies over six years, and a customized WTSD was built for them. Because this is such a rare occurrence, it was decided to highlight and compare these results. After obtaining the protocol approval (#110453) from the Research Ethics Board of Western University, the participant was recruited by a movement disorder neurologist. The glove design is based on a pulley-cable transmission system. It consists of one 60 W Maxon Motor EC-max 16 BLDC motor with a planetary gearhead (29:1) and two 8 W Maxon Motor EC-max 16 BLDC motors with planetary gearheads (29:1) for wrist, index finger, and thumb tremor suppression, respectively. Data were collected using IMU sensors at a frequency of 70 Hz. In the first phase, data were collected with the glove on while the actuation was off. This is called the baseline tremor in the rest of this article. After baseline tremor, data were collected by activating the actuation to suppress tremor. Both the baseline tremor and tremor data during the mechanical actuation were recorded three times, once under each of the following conditions:

- Rest tremor: Participant's arm was at rest on the table.

- Postural tremor: Participant's hand was outstretched at 45° above the table level.

- Action tremor: The participant was asked to pinch a pen with the index finger and thumb with the hand outstretched and move it to the rest position.

Data collection for each phase and task took 60 seconds.

5.2.4 Data Analysis

After the data were collected, it was required to separate tremor and voluntary motion in Experiments I and III. Therefore, a second-order zero-phase bandpass Butterworth filter with a frequency range of 3 to 18 Hz was used to extract tremor signals in tasks involving voluntary motion. Next, tremor power spectrum density (PSD, degree^2/s^3), root-mean-squared (RMS) of tremor magnitude (degree/s), dominant tremor frequency (Hz), and approximate entropy (ApEn) as a measure of tremor regularity were calculated for all datasets.

Analysis of tremor signal in time and frequency domain are the most common methods used in the literature for characterizing different types of tremor including parkinsonian tremor [153, 155, 160]. Among different analysis in frequency domain, tremor frequency is an important measure to distinguish different types of tremor such as essential and parkinsonian tremor. Furthermore, tremor power intensity can be calculated as a measure to calculate the tremor severity [155]. Tremor regularity calculated with approximate entropy has been used multiple times in the literature for biological signals analysis [161], including tremor. Lastly, tremor amplitude or magnitude is also another measure for assessment of tremor severity.

Tremor power spectrum density was calculated using the "pspectrum" function in MATLAB (R2022b, Mathworks Inc.). The RMS of the tremor magnitude was calculated using Eq. 5.1, where $\vec{x}$, $\vec{y}$, and $\vec{z}$ are the tremor amplitudes in all three directions. The tremor dominant frequency was considered as the frequency at which the peak power was observed [155].

$$\mathrm{RMS}_{\text{tremor magnitude}} = \mathrm{RMS}(\sqrt{\vec{x}^2 + \vec{y}^2 + \vec{z}^2}) \tag{5.1}$$

Approximate entropy is a statistical tool, developed to quantify the complexity and regularity of short noisy datasets, which has shown potential in a wide variety of applications in physiological and clinical time-series analysis [162, 163]. The output of ApEn is a value in the range of 0–2, showing the unpredictability of fluctuations in a time-series dataset, where lower values represent higher regularity in the signal [161].

ApEn uses three parameters to compute the regularity of the signal. As shown in Eqs. 5.2–5.4, ApEn is dependent on the length of the signal (N), the embedding dimension (m), and the vector comparison length (r). Both m and r were selected based on the literature as 2 and $0.2 \times SD$, where SD is the standard deviation of the signal [162]. In Eq. 5.2, $x(i) = \{u(i), u(i+1), ..., u(i+m-1)\}$ and $x(j) = \{u(j), u(j+1), ..., u(j+m-1)\}$, given the sequence of $u = \{u(1), u(2), ..., u(N)\}$, which is the tremor signal from the IMU sensor. The distance between $x(i)$ and $x(j)$ is calculated as $d[x(i), x(j)] = \max_{k=1,2,...m}(|u(i+k-1) - u(j+k-1)|)$. The numerator (${C_i}^m$) in Eq. 5.2 counts the number of similar blocks of consecutive values of length m to a given block, within the resolution of r [163]. It should be highlighted that ApEn normalizes the vector comparison to the SD of each time series, which results in decorrelation of the ApEn output from the amplitude of the signal [161].

$$
\begin{aligned}
{C_i}^m(r) = \frac{1}{(N-m+1)}(&\text{number of } j \leq N-m+1, \\
&\text{such that } \; d[x(i), x(j)] \leq r)
\end{aligned}
\tag{5.2}
$$

$$\Phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \log {C_i}^m(r) \tag{5.3}$$

$$\text{ApEn}(N, m, r)(u) = \Phi^m(r) - \Phi^{m+1}(r), \tag{5.4}$$

Data from the first experiment were used to calculate the above factors using the full length of data in each task and each participant to compare tremor changes between tasks (Section 5.3.1).

Tremor data from Experiment II was separated into the following groups as shown in Figure

5.2:

- Suppressed tremor: When the ratio of tremor PSD during stimulation to the tremor PSD at baseline was lower than one (see Eq. 5.5), the stimulation window was labeled as "Suppressed tremor." In Figure 5.2, the first stimulation window, labeled as Win 1, is assumed to have reduced tremor power compared to the baseline PSD and is labeled as Suppressed tremor. To be able to analyze the tremor characteristics when the stimulation was turned off, 60 seconds of rest after a successful suppression was labeled as rest tremor data that followed suppressed tremor. Such a window is highlighted in green following Win 1 in Figure 5.2.

- Unsuppressed tremor: When the ratio of tremor PSD during stimulation to the tremor PSD at baseline was equal to or above one (see Eq. 5.5), the stimulation window was labeled as "Unsuppressed tremor." In Figure 5.2, the second stimulation window, labeled as Win 2, is assumed to have greater tremor power compared to the baseline PSD and is labeled as Unsuppressed tremor. To be able to analyze the tremor characteristics when the stimulation was turned off, 60 seconds of rest after an unsuccessful suppression was labeled as rest tremor data that followed unsuppressed tremor. Such a window is highlighted in green following Win 2 in Figure 5.2.

- Stimulation on: When the stimulation was on, regardless of the PSD ratios, the time series was assigned a second label as On.

- Stimulation off (Window 1): The first 30 seconds of the rest period between each stimulation was labeled as Off 1.

- Stimulation off (Window 2): The second 30 seconds of the rest period between each stimulation was labeled as Off 2.

- Baseline tremor: Data collected before any stimulation was delivered was labeled as baseline data.

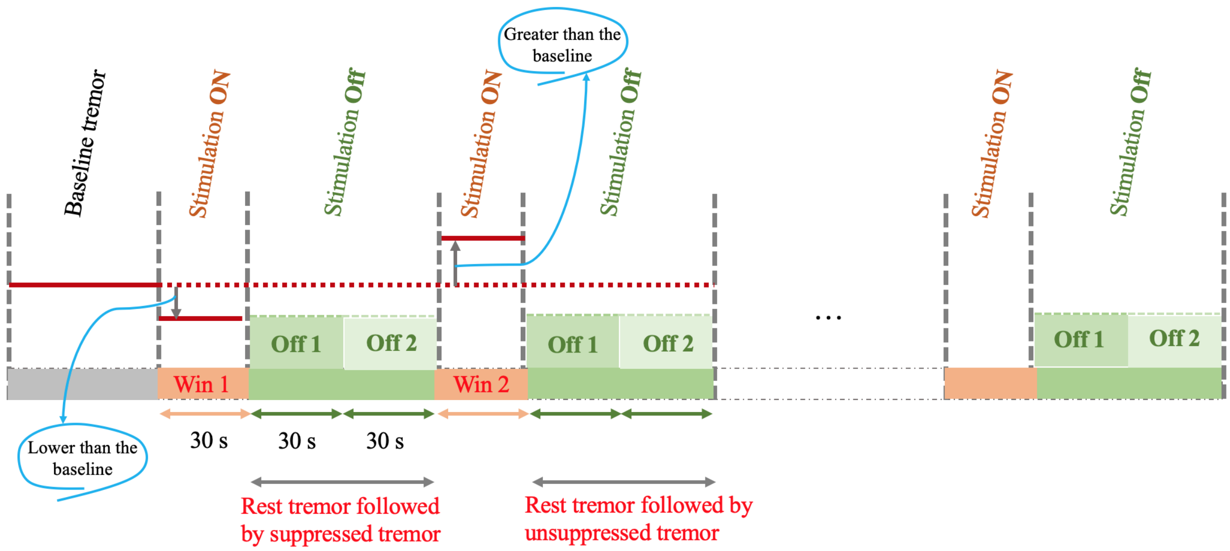

Figure 5.2: An example of tremor data windows from Experiment II. The gray area shows the baseline data collected before applying any stimulation. Orange windows show Stimulation on periods and green windows represent Stimulation off periods. Each rest period is 60 seconds and is equally divided into Off 1 and Off 2. The red line represents baseline tremor PSD in the baseline window and continues as a dotted line for comparison. It is assumed that tremor was suppressed in Win 1 and not suppressed in Win 2. The solid red lines in Win 1 and Win 2 are provided for visualization of tremor PSD in each window. Win 1 and the subsequent rest period are categorized as "suppressed tremor" and "rest period following suppressed tremor", respectively. Win 2 and the following rest period are categorized as "unsuppressed tremor" and "rest period following unsuppressed tremor", respectively.

$$\text{PSD Ratio} = \frac{\text{PSD}_{\text{stimulation}}}{\text{PSD}_{\text{baseline}}} = \begin{cases} < 1 & \text{Suppressed,} \\ \geq 1 & \text{Unsuppressed.} \end{cases} \tag{5.5}$$

After separating the dataset of Experiment II as above, PSD, RMS of the magnitude, ApEn, and frequency were measured for each tremor signal in each group.

Lastly, the data collected from Experiment III were separated into six equal windows. PSD of tremor, RMS of the tremor magnitude, ApEn and the dominant frequency of tremor were calculated for each window separately.

Statistical analyses were performed using repeated measures ANOVA (RMA), with a Bonferroni correction and an alpha value of 0.05. Different individuals in Experiment I, and different individuals and stimulation repetitions in Experiment II were initially used as covariates. However, no impact was observed by using the covariates, and therefore, they were removed in the final analyses to improve the observed power. The IBM Statistical Package for Social Sciences (SPSS Statistics v28) software was used to perform all of the statistical analyses. In addition, other analyses, including separating data into different groups and windows, and measuring the factors mentioned above, were performed using MATLAB (R2022b, The Mathworks, Inc.)

5.3 Results

5.3.1 Tremor Variability Amongst Different Tasks

Data from Experiment I were used to study the tremor changes across variable tasks. Figure 5.3 shows samples of the data collected in Experiment I from several participants performing different tasks. As shown in this figure, tremor angular velocity varies greatly between different participants and even within a single participant over time or in the presence of voluntary motion. This observation suggests that there is significant variability of tremor over time and during different daily living activities.

To confirm this variability, RMAs were used to compare tremor power in different tasks. Figure 5.4 shows the distribution of the common logarithm of the tremor PSD in Tasks 1a–5 for all 18 participants, and Table 5.1 summarizes the mean and standard deviation of tremor PSD in Tasks 1a–5. As shown in both Table 5.1 and Figure 5.4, there is a statistically significant difference in tremor power between rest tremor (Task 1b) and postural tremor (Task 2) and action tremors in Tasks 4–5, with a decreasing trend as the voluntary motion gets involved. The comparison of the mean and standard deviation of the tremor power in Table 5.1 also highlights the tremor variability in different tasks. As shown in Table 5.1, the standard deviation is as high as or even greater (in Tasks 2–5) than the mean value, which indicates that data points are widely spread out.

Table 5.2 summarizes the mean and standard deviation of the RMS of the tremor magnitude in all tasks, as well as the results of the RMA test. From this table, analyzing the RMS of the magnitude of tremor in each task using the RMA shows that there is a significant difference among tremor magnitude in rest tremor and action tremors, as well as a statistically significant difference

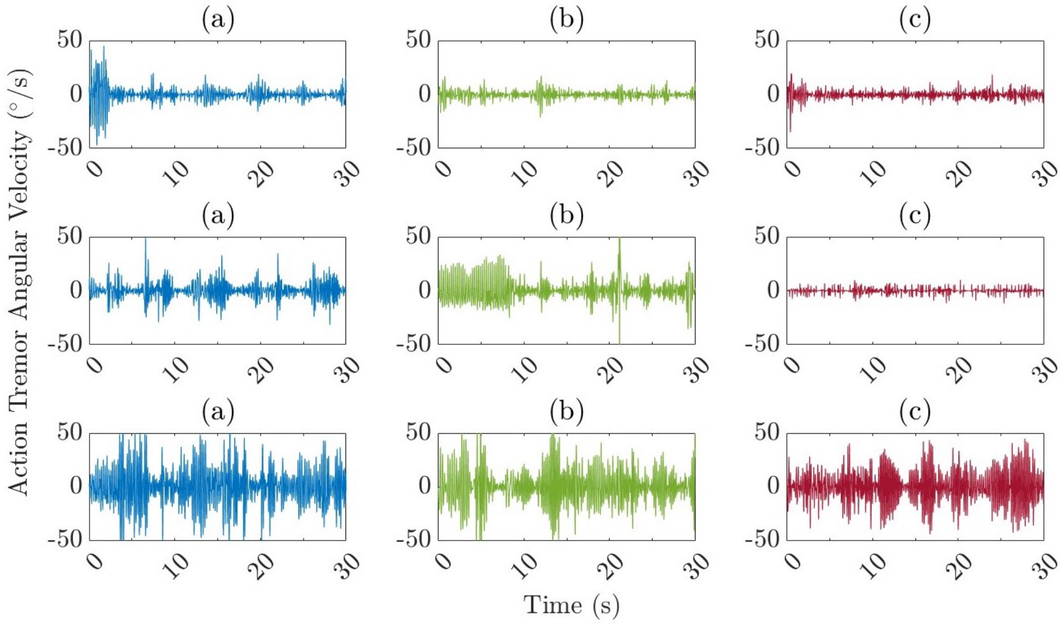

Figure 5.3: Sample of 30 seconds of angular velocity data corresponding to action tremor for three different participants. Each row represents the tremor data of one participant. In each row, (a) shows the action tremor in Task 2, (b) shows the action tremor in Task 4, and (c) shows the action tremor in Task 5.

Table 5.1: Mean, standard deviation, and p value of tremor PSD ($^{\circ 2}\backslash s^3$) in different tasks.

Task	Mean	Std. Deviation	p value (if significant)
Task 1a	5.5×10^4	6.8×10^4	NS
Task 1b	8.6×10^4	8.4×10^4	NS
Task 2	2.3×10^4	2.6×10^4	0.017 (with Task 1b)
Task 3	4.2×10^5	1.7×10^6	NS
Task 4	7448.9	14891.3	0.022 (with Task 1b)
Task 5	6055.9	11623.1	0.012 (with Task 1b)

between postural tremor and action tremor in Task 5. On the other hand, the comparison of the mean and standard deviation of the tremor magnitude in Table 5.2 shows that the standard deviation is as high as or even greater (in Task 3) than the mean value, which highlights the variation in tremor and that the data points are highly spread out. Furthermore, Figure 5.5 shows the distribution of the common logarithm of the tremor magnitude in Tasks 1a–5 for all participants. From both Table 5.2 and Figure 5.5, it can be concluded that tremor magnitude also decreases when voluntary motion is involved.

Figure 5.6 and Table 5.3 show the results of the RMA on tremor frequency among different

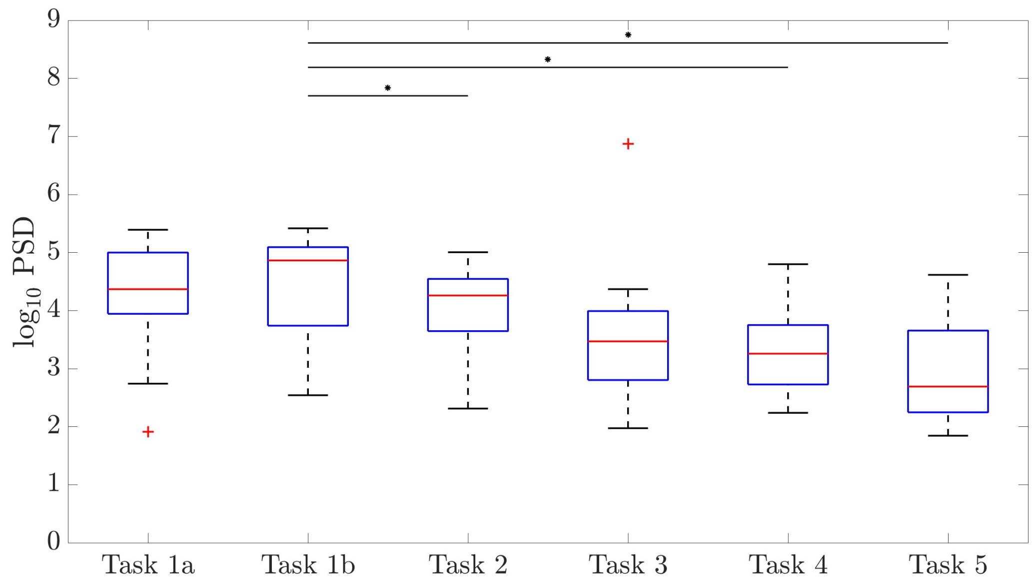

Figure 5.4: Distribution of the common logarithm of the tremor power spectrum density in each task from all 18 participants. The RMA shows a statistically significant difference between the PSD of Task 1b and Task 2, Task 4, and Task 5.

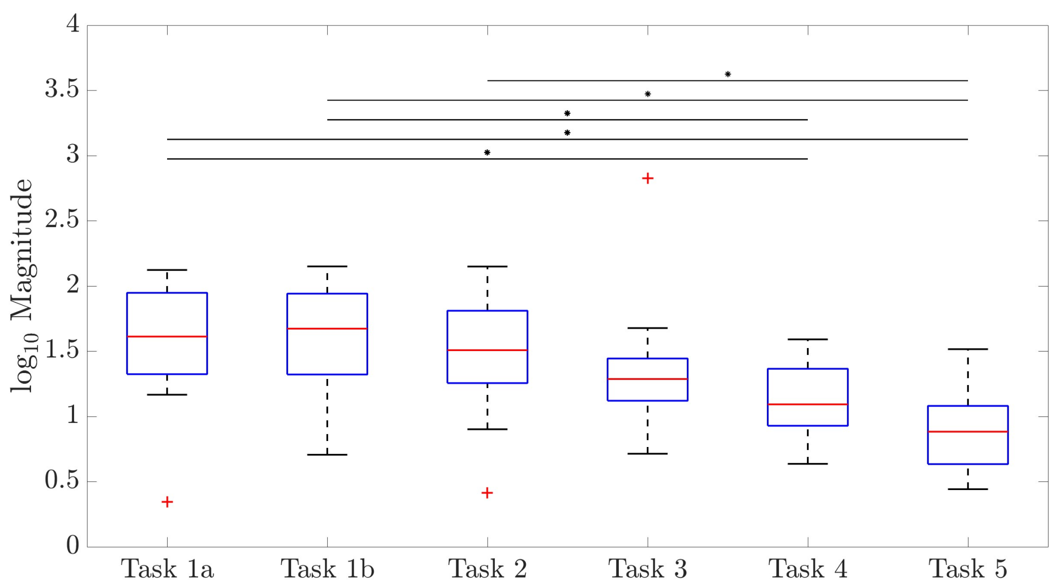

Figure 5.5: Distribution of the common logarithm of the tremor magnitude in each task from all 18 participants. The RMA shows a statistically significant difference between the magnitude of Task 1a, Task 4, and Task 5; between Task 1b, Task 4, and Task 5; and between Task 2 and Task 5.

Table 5.2: Mean, standard deviation, and p value of tremor magnitude (°\s) in different tasks.

Task	Mean	Std. Deviation	p value (if significant)
Task 1a	57.3	41.6	NS
Task 1b	56.7	39.6	NS
Task 2	45.5	39.2	NS
Task 3	56.5	153.6	NS
Task 4	16.5	10.7	0.011 (with Task 1a) 0.013 (With Task 1b)
Task 5	11.2	9.8	0.007 (with Task 1a) 0.005 (With Task 1b) 0.040 (With Task 2)

Table 5.3: Mean, standard deviation, and p value of tremor frequency in different tasks.

Task	Mean	Std. Deviation	p value (if significant)
Task 1a	4.8	1.1	NS
Task 1b	4.9	1.3	NS
Task 2	5.5	1.3	NS
Task 3	5.8	1.1	NS
Task 4	6.3	1.1	0.023 (with Task 1a) 0.010 (with Task 1b)
Task 5	6.4	1.2	0.034 (with Task 1a)

tasks. It can be seen that tremor frequency increases when voluntary motion is involved. Furthermore, there is a statistically significant difference in the frequency of rest tremor (Task 1a) and action tremor (Tasks 4–5) and between rest tremor in Task 1b and action tremor in Task 4.

Lastly, analyses of the approximate entropy of tremor among different tasks show that tremor is fairly stable in entropy in different conditions with or without voluntary motion. As shown in Figure 5.7, there is only a significant difference between ApEn of Task 1a and Task 3 (mean ± std. 0.61 ± 0.11 vs. 0.51 ± 0.15, $p = 0.027$). To summarize, tremor PSD, magnitude, and frequency show higher variations when voluntary motion is involved, with potentially variable trends among multiple participants and under different conditions.

5.3.2 Tremor Variability in the Presence of External Forces and Stimulations

Tremor characteristics might change under conditions aimed at reducing tremor power. To evaluate these changes, this section studies four different scenarios. The first two scenarios assess changes in tremor ApEn and frequency in the presence of out-of-phase FES as a method of tremor suppression, while the last two scenarios examine tremor ApEn and frequency in the presence of mechanical

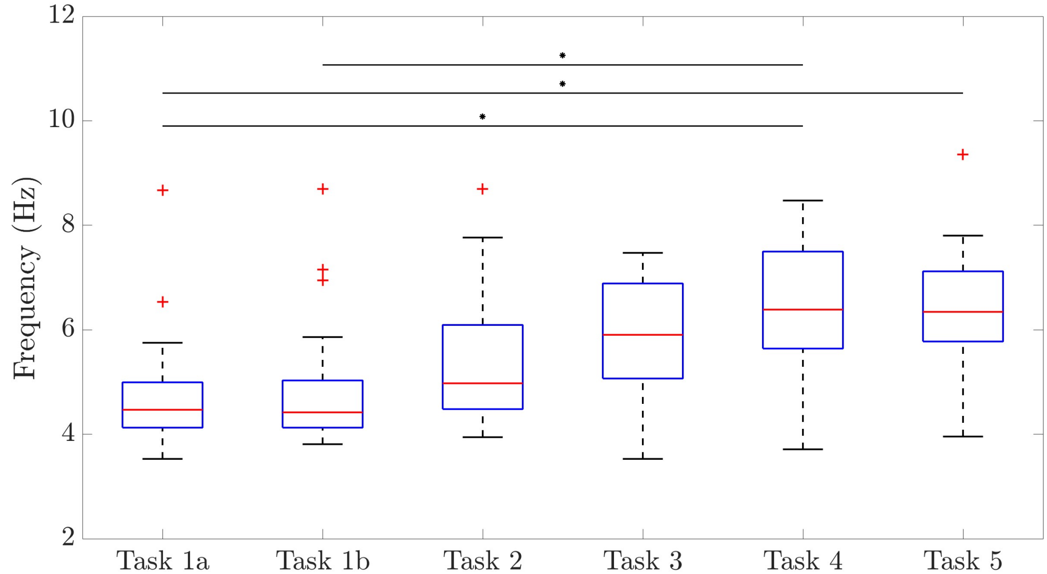

Figure 5.6: Distribution of the tremor frequency in each task from all 18 participants. The RMA shows a statistically significant difference between the frequency of tremor in Task 1a, Task 4, and Task 5; and between Task 1b and Task 4.

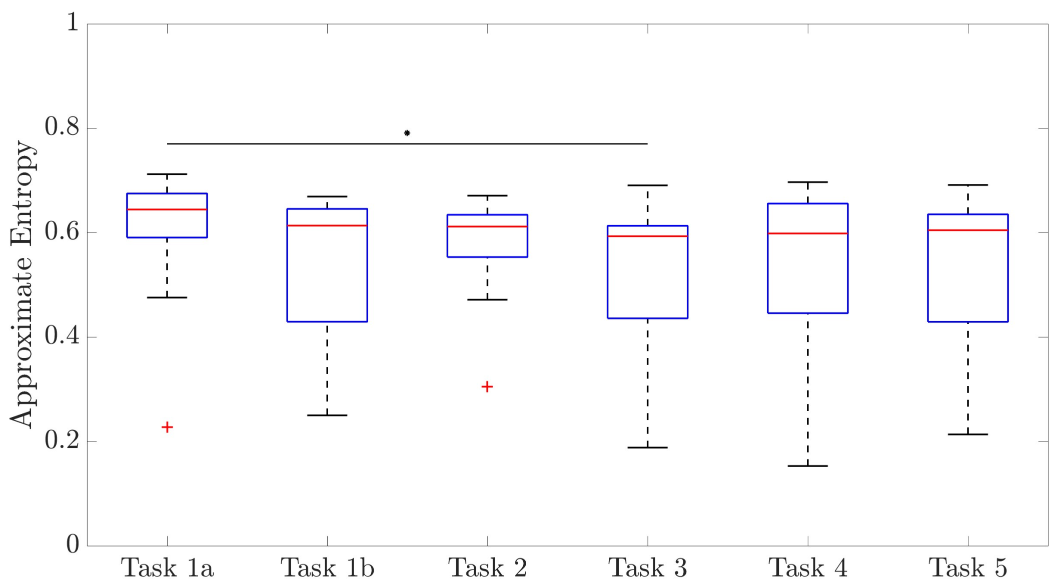

Figure 5.7: Distribution of the tremor ApEn in each task from all 18 participants. The RMA shows a statistically significant difference between the ApEn of tremor in Task 1a and Task 3.

loading.

Scenario 1. Approximate entropy of tremor in the presence of FES: Data from Experiment II were used to analyze the tremor characteristics when electrical stimulation was applied to muscles. Figure 5.8 compares the approximate entropy of tremor in different time frames with and without stimulation, as explained in Section 5.2.4. Figure 5.8 (a) compares tremor ApEn, when tremor is suppressed, the first 30 seconds after the stimulation, the last 30 seconds when the stimulation is off, and the baseline tremor associated with the suppressed tremors. As shown in Figure 5.8 (a), ApEn is slightly higher when the tremor is suppressed and starts to decrease right after the stimulation is turned off. To determine whether the differences in regularity are significant between the four windows of time, RMA was performed with ApEn as the measuring variable and the four states in which the tremor data were collected as the dependant variable: suppressed tremor, Off 1, Off 2, and the baseline.

From the results, there is a statistically significant difference between ApEn of suppressed tremor and baseline tremor, as well as the second window of the rest period (mean ± std., Supp.: 0.81 ± 0.22, Off 1: 0.78 ± 0.23, Off 2: 0.76 ± 0.22, Base: 0.74 ± 0.13, Supp. vs. Off 2: $p < 0.001$, Supp. vs. Base: $p < 0.001$). A statistically significant difference was also observed between the first window after the stimulation and the baseline tremor (Off 1 vs. Base: $p = 0.002$).

Figure 5.8(b) shows the ApEn changes of tremor, when tremor was not suppressed using FES. Similar to the RMA analysis for the suppressed tremor group, an RMA performed by considering ApEn as the measuring variable and the dependant variable as the state in which the tremor data were collected. Results showed that there is a statistically significantly difference in tremor entropy of unsuppressed tremor and tremor in the second window of the rest period (mean ± std., Unsupp.: 0.75 ± 0.17, Off 2: 0.64 ± 0.21, $p = 0.04$), a statistically significant difference between ApEn of tremor in the first and second window of the rest period (mean ± std., Off 1: 0.82 ± 0.20, Off 2: 0.64 ± 0.21, $p < 0.001$), and a significant difference between tremor ApEn in the second window of the rest period and baseline tremor (mean ± std., Off 2: 0.64 ± 0.21, Base: 0.76 ± 0.13, $p < 0.001$).

Lastly, Figure 5.8(c) shows that tremor ApEn is slightly higher when the stimulation is on. From the RMA results, there are statistically significant differences among tremor ApEn during

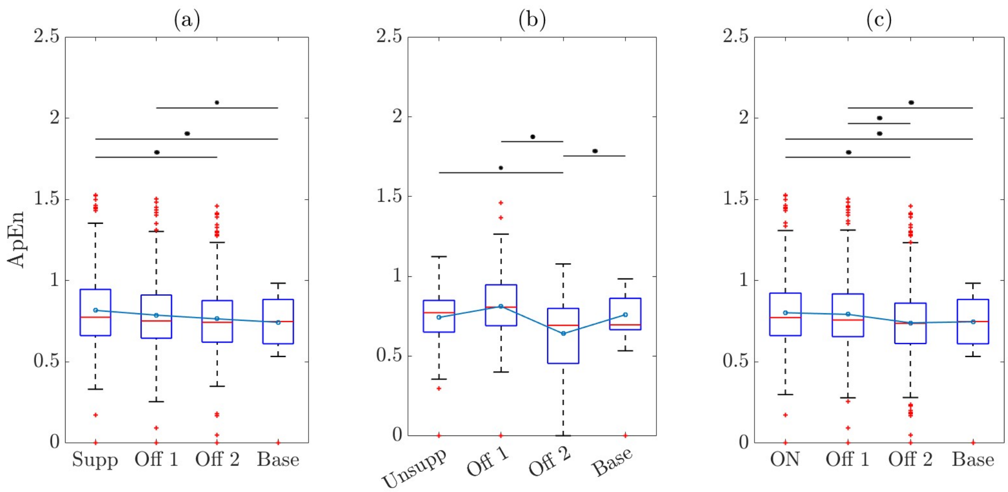

Figure 5.8: Distribution of the tremor approximate entropy in the presence of the FES. (a) Comparison of the ApEn in suppressed tremor to periods without stimulation; (b) comparison of the ApEn in unsupressed tremor to periods without stimulation; (c) comparison of the ApEn in active stimulation to periods without stimulation. Off 1, Off 2 and Base are defined in Section 5.2.4.

the stimulation period and the second window of the rest period (mean ± std., On: 0.80 ± 0.21, Off 2: 0.74 ± 0.22, $p < 0.001$), as well as the baseline tremor (mean ± std., On: 0.80 ± 0.21, Base: 0.75 ± 0.13, $p < 0.001$). Also, there is a statistically significant difference among tremor ApEn in the first window of the rest period and the second window (mean ± std., Off 1: 0.79 ± 0.23, Off 2: 0.74 ± 0.22, $p < 0.001$), as well as between the first window and the baseline tremor (mean ± std., Off 1: 0.79 ± 0.23, Base: 0.75 ± 0.13, $p < 0.001$). It should be noted that the number of data points in the suppressed group is four times higher than the unsuppressed group. Thus, Figure 5.8 is biased toward the suppressed tremor group.

Scenario 2. Frequency of tremor in the presence of FES: Figure 5.9 shows a summary of tremor frequency data from Experiment II. As shown in Figure 5.9(a), there is a statistically significant difference in tremor frequency when suppressed, compared to both windows of the rest period (mean ± std., Supp.: 4.3 ± 0.84, Off 1: 4.1 ± .66, Off 2: 4.1 ± .61, Supp. vs. Off 1 and Supp. vs. Off 2: $p < 0.001$), as well as a difference in tremor frequency between baseline tremor and both windows of the rest period (mean ± std., Base: 4.4 ± 0.58, Base vs. Off 1 and Base vs. Off 2: $p < 0.001$).

Figure 5.9(b) shows a statistically significant difference in tremor frequency when stimulation

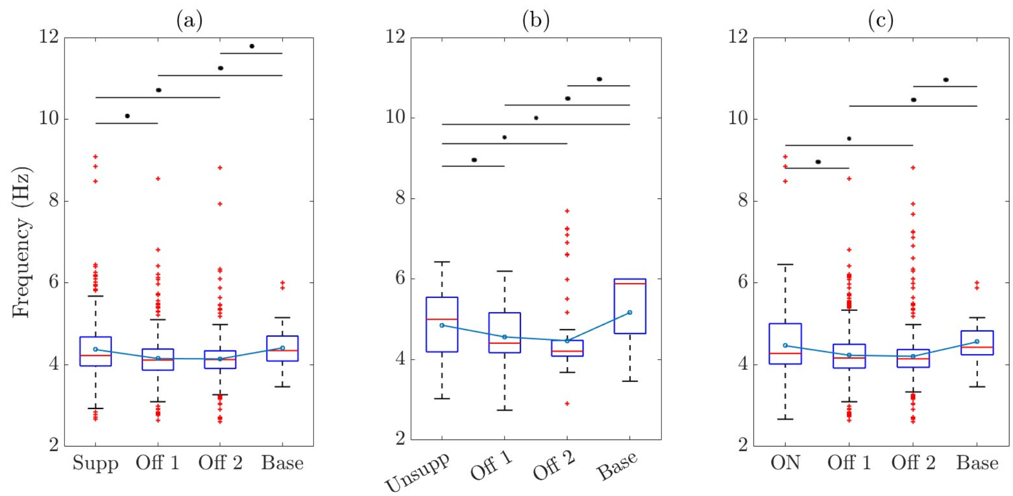

Figure 5.9: Distribution of the tremor frequency in the presence of the FES. (a) Comparison of the frequency in suppressed tremor to periods without stimulation; (b) comparison of the frequency in unsupressed tremor to periods without stimulation; (c) comparison of the frequency in active stimulation to periods without stimulation. Off 1, Off 2 and Base are defined in Section 5.2.4.

is On (even without suppression) and both windows of the rest period, as well as the baseline tremor (mean ± std. Unsupp., 4.9 ± 0.79, Off 1: 4.6 ± 0.71, Off 2: 4.5 ± 0.94, Base: 5.2 ± 0.80, Unsupp. vs. Off 1: $p < 0.001$, Unsupp. vs. Off 2 : $p = 0.006$, Unsupp. vs. Base: $p = 0.009$). Further, there is a significant difference in tremor frequency during the baseline compared to both rest period windows (Base vs. Off 1 and Base vs. Off 2: $p < 0.001$).

Lastly, from Figure 5.9(c), significant differences were observed between On and both rest windows (mean ± std., On: 4.4 ± 0.86, Off 1: 4.2 ± 0.69, Off 2: 4.2 ± 0.70, $p < 0.001$), as well as between the baseline and both windows of the rest period (mean ± std., base: 4.5 ± 0.71, $p < 0.001$).

The results show that tremor frequency and approximate entropy are susceptible to external stimulation, while both factors are constant in time during a single task and without external stimulation. Further experiments are required to evalute the cause of this change when an external stimulation is applied.

Scenario 3. Tremor characteristics in the presence of mechanical loading: Data from Experiment III were used to evaluate the findings of Scenarios 1 and 2 further. Figure 5.10 shows trends of tremor frequency and approximate entropy under three different conditions of rest tremor, postural tremor, and action tremor as explained in Section 5.2.3. Each dataset from these conditions was divided into six equal windows of 10 seconds during suppression and when the suppression system was off. Each column represents a task, including action, postural, and rest tremor from left to right. The first row represents the trends in tremor frequency, and the second row represents the trends in approximate entropy. A general trend can be seen that approximate entropy is increasing during suppression, and frequency is slightly decreasing, except for the postural tremor with a minor increase. While ApEn, as an indication of tremor regularity, remains relatively stable when voluntary motion is present, and both ApEn and frequency are not showing significant changes over time, they both tend to vary when external forces or stimulations are introduced in an attempt to suppress tremor.

As shown in Figs. 5.8 and 5.10, the mean of the ApEn in the suppressed tremor group is higher than the baseline. While ApEn has been increased during successful tremor suppressions in both Experiment II and III, changes in frequency are not necessarily similar in all cases. In other words, the mean tremor frequency during both suppressed and unsuppressed tremor is greater than the rest periods after the stimulation but less than the baseline. Furthermore, changes in tremor frequency in Experiment III are not highly consistent in rest, postural, and kinetic tremor.

Figure 5.11(a) shows the ratio of tremor ApEn during stimulation to the ApEn at baseline on the y axis, the common logarithm of the PSD ratio on the x axis, suppressed tremor data points in blue, unsuppressed tremor data points in orange, and the first-order polynomial fit in green. Figure 5.11(b) is very similar, except that it shows the ratio of tremor frequency during stimulation to the baseline frequency on the y axis. The slope of the line shows a decrease in both ApEn and frequency ratio as the PSD ratio increases. Although the R-squared value in both cases showed a low correlation, a more complex model can be used to estimate the relationship between PSD ratio, ApEn, and frequency better.

5.3.3 Case Study: Tremor Changes When Suppressed with FES and Mechanical Loading in One Individual

To compare the effect of the different suppression mechanisms used in Experiments II and III on tremor characteristics, a participant (4) agreed to participate in both studies. Experiments

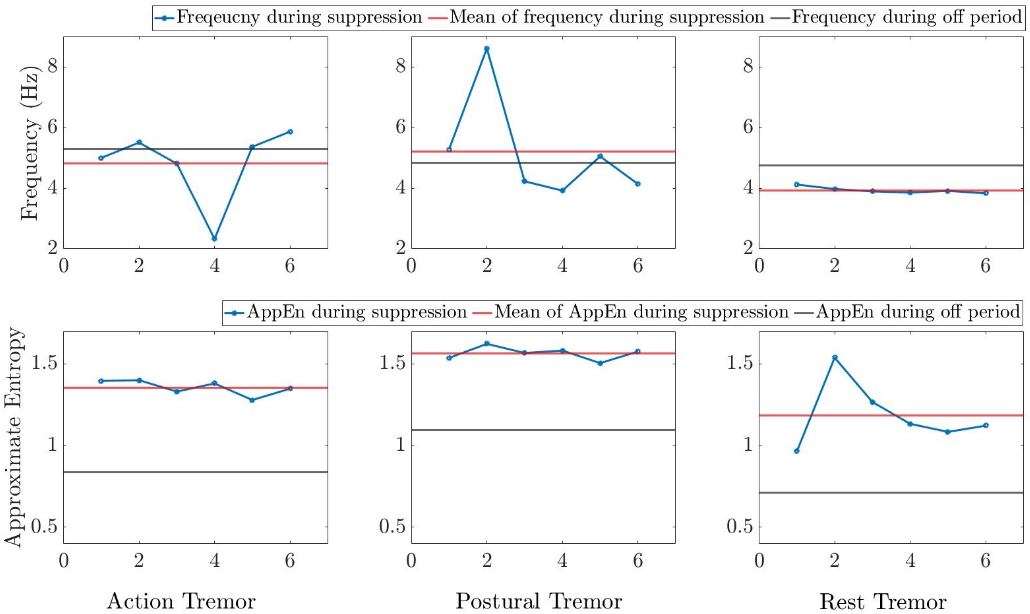

Figure 5.10: Tremor frequency (first row) and tremor ApEn (second row) during action tremor (first column from left), postural tremor (middle column), and rest tremor (third column from left). In each figure, the blue markers in the blue dotted line show the tremor characteristic in 10 seconds of the data while the mechanical actuation was active, the red line shows the mean values of the tremor characteristics during mechanical actuation activation, and the black line shows the tremor characteristics while the mechanical actuation was off.

were conducted on two different days by following the procedure explained in Sections 5.2.1–5.2.2. The first and second columns of Figure 5.12 show the results from Experiment II and Experiment III for Participant 4, respectively. As explained in Section 5.2.2, there are a total of 27 rounds of stimulation for each participant in Experiment II. Therefore, it should be noted that for consistency, the suppressed tremor with the closest percentage to the suppressed tremor using the mechanical approach was selected for inclusion in Figure 5.12.

By comparing the mean of changes in ApEn, and PSD for both methods in Figure 5.12, the mean of the PSD decreased using both methods, while the mean of the ApEn increased during both mechanical and FES suppression. Changes in frequency at each point do not follow a general trend; however, the average value of suppressed tremor frequency is higher than the average baseline when using mechanical suppression and slightly higher when using FES.

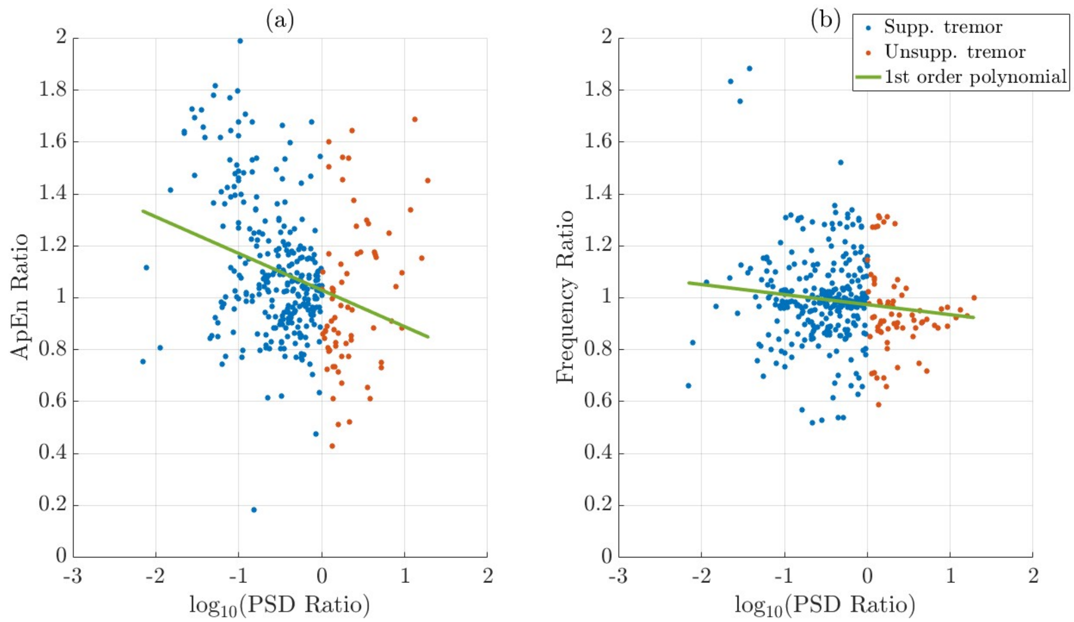

Figure 5.11: Changes in ApEn and frequency during FES. Common logarithm of PSD ratio on the x axis, suppressed and unsuppressed tremor datapoints in blue and orange, respectively. (a) Ratio of ApEn during stimulation to the ApEn at baseline tremor on the y axis. (b) Ratio of frequency during stimulation to the frequency at baseline tremor on the y axis, with the first order polynomial fit in green in both (a) and (b).

5.4 Discussion

From the results in Section 5.3.1, Tremor magnitude and power show greater values and higher variations compared to the kinetic tremor. Bartolic et al. [164], have hypothesized that the activity of central oscillators and synchronization among them are essential for tremor generation. They have tested their hypothesis by measuring rest tremor over time, and have shown that tremor frequency was reduced in the presence of clinically visible tremor. Furthermore, reductions in tremor amplitude were accompanied by an increase in tremor frequency variability [164]. Figures 5.4–5.6, also represent a similar concept, by showing that increasing the range of frequency for kinetic tremor results in reduced tremor magnitude and power, while reduction of frequency variability in rest and postural tremor leads to increased tremor magnitude and power. On the other hand, similar to essential tremor [146], it appears that parkinsonian tremor frequency is also task-dependent, and frequencies can vary across different tasks, with higher frequency in kinetic tremor compared to rest tremor. It was shown in [146] that essential tremor amplitude also drops when

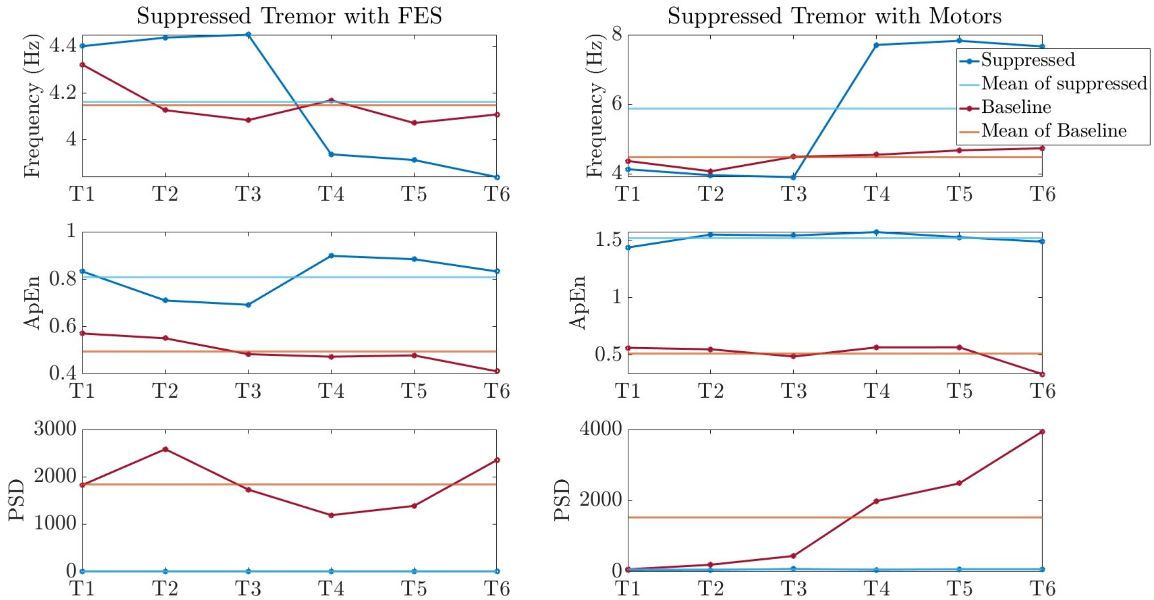

Figure 5.12: Comparison of suppressed tremor characteristics using FES (left column) and mechanical loading (right column). The dark blue dot line shows the values of suppressed tremor in six continuous time frames, the light blue line shows the average values of the suppressed tremor, the red dot line shows the baseline values in six continuous time frames, and the orange line shows the mean values of the baseline tremor. Note that the FES dataset from this individual was selected so that the tremor suppression ratio was closest to the mechanical suppression ratio.

a task is being repeated. Schuhmayer et al. [146] have explained the variation in essential tremor frequency by hypothesizing the existence of different neurological pathways for different types of tremor. Similarly, Wenzelburger et al. [157] have suggested to consider a different pathophysiology for tremor during voluntary motions. Furthermore, the reduction in essential tremor amplitude in repeated tasks was explained by potential adaptability and learning factors [146] . Although the tasks were not repeated in our study, this property can be further evaluated for parkinsonian tremor in a future study as well. It has been reported in [153] that tremor regularity increases (decrease in ApEn) when the target limb is not supported, the results in Section 5.3.1 do not show a significant difference among different experimented tasks. This might have been due to the limited size of the participants or the selection of tasks and can be examined further in a future study. Variations in tremor frequency and magnitude in different tasks can further highlight the neccessity of tremor prediction and estimation algorithms for WTSDs. On the other hand, it highlights that passive WTSDs cannot be beneficial in many cases, since tuning the suppression level in one situation such as rest, cannot be helpful for the individual in activities with voluntary motion. Changes in tremor regularity in response to FES and mechanical suppression are aligned with the studies in the literature [150–152, 155]. Reduction of coherence between EMG and accelerometer data in [150] suggests that FES in Scenario 2 or mechanical loading in Scenario 3 might have reduced tremor and increased irregularity by interrupting the motor unit synchronizations and neuron firing rates. A similar explanation could be used for the changes in the peak frequency. Various stimulation parameters in FES, transient time in both experiments and their effects on the firing rates of neurons and their synchronization could be the base of inconsistent changes in the tremor peak frequency. In addition to the changes in tremor frequency and magnitude in different tasks, changes in tremor regularity further highlights the importance of real time tremor analysis in WTSDs. It should be noted that data from Experiment III were collected only from one participant. A larger dataset could potentially be used in a future study to statistically analyze changes in frequency and tremor regularity during mechanical suppression.

5.5 Conclusion

Wrist tremor data were collected at rest, at hand 45° above the table level, during three activities involving voluntary motion, by applying FES, and mechanical loading. Data analysis was conducted on all three datasets, by analyzing four tremor characteristics, including tremor frequency, magnitude, power spectrum density, and approximate entropy in different time frames. Results revealed that linear and nonlinear tremor characteristics are not only different among different individuals, but also can change in a single participant when voluntary motion or external manipulation of the tremor using either FES or mechanical loading are involved. Therefore, not only medical or surgical treatments can affect the tremor regularity, but stimulations and mechanical loading can also affect the tremor regularity. On the other hand, the variations in tremor highlights that not only passive actuators for WTSDs cannot be fully beneficial, but also real time and accurate tremor estimation is needed when designing WTSDs. Changes in tremor regularity require further investigation and a larger dataset to understand the cause of this observation, the potential long-term effects of a WTSD on tremor characteristics and voluntary motion, and to evaluate the potential relationship between suppressed tremor, tremor regularity, and the method of suppression.

Chapter 6

Concluding Remarks

One of the symptoms of PD is tremor, which can be controlled to a certain level with medication or brain surgery. However, WTSDs can be an alternative solution for PwP to address existing limitations. While there have been several studies in the literature with a focus on the design and development of WTSDs with different technologies, the lack of adaptability and comfort of current devices are evident. Often devices are heavy and bulky, or they might cause discomfort, pain, and muscle fatigue over time. On the other hand, there is a lack of consistency in evaluating the effectiveness of FES as a method for reducing tremor. Studies have often reported the results in mixed groups of PD, ET, and other conditions that lead to tremor. This might be helpful in understanding the effects of FES on different types of tremor. However, since the pathophysiology is different among these groups, results should not be combined when reported. Furthermore, the use of a systemic approach in testing multiple FES settings and reporting results is missing in the literature, since studies have reported maximum suppression of tremor or best outcomes. Lastly, while many studies are highlighting the variability of tremor in ET by analyzing various features of the tremor, there are not a lot of studies with this focus on parkinsonian tremor. A better understanding of tremor changes in time and under different circumstances is beneficial for future efforts in designing a WTSD.

To this end, the focus of the first study was to design and evaluate a hybrid system using both FES and mechanical suppression in simulation. Electric motors were used in this study, since they are easy to incorporate and have shown promising results when suppressing tremor. While electric motors can be beneficial in WTSDs, they are heavy and bulky when added together to suppress tremor in multiple joints, and to provide sufficient torque for tremor suppression. Thus, FES was added to the structure to reduce the required torque for tremor suppression and thus, reduce the weight and size of the overall device. On the other hand, FES can cause muscle fatigue, and therefore the generated muscle torque decreases over time and cannot suppress tremor to the desired level. Electrical motors were used in this hybrid approach to provide torque support for tremor suppression, and to reduce the required stimulation levels to generate required muscle torque, and thus, reduce muscle fatigue and pain over time. Results of this study showed that the hybrid approach has better performance in terms of tremor suppression and error while tracking voluntary motion for an average of 12% and 57%, respectively, and in comparison with the FES only method. On the other hand, the overall weight of the hybrid WTSD can be reduced to one-third of a WTSD with DC motors only. Comparison of the control effort for DC motors between the motor only approach and hybrid approach, as well as the FES control effort in FES only and hybrid approach, showed a significant difference. The results therefore showed the potential improvement of a hybrid WTSDs.

The second study in this thesis focused on designing a systemic approach to evaluate and report the effects of FES on parkinsonian tremor. To this end, a protocol was designed and tested on 14 participants with PD. The protocol evaluated the participant's tremor in the first step, followed by their tolerance level in the following step. After the evaluation phase, the system automatically generated FES combinations with variable amplitude and number of pulses. Each combination was tested three times for each participant, and outcomes were averaged to cancel the potential biases. Furthermore, participants were distracted during the experiment to ensure the tremor was not being affected psychologically during the experiment. The results showed that tremor reduction is dependent on the tremor intensity. An analysis was made by categorizing the tremor before stimulation into four percentiles of tremor power intensity, which showed an average suppression of 81.2 ± 2.9 for the first percentile, and 79.0 ± 2.9, 59.2 ± 2.9, and 59.9 ± 2.9 for the second, third, and last percentiles, respectively. On the other hand, stimulations with amplitude around the motor threshold suppressed tremor for 74.3 ± 3.0 % on average, while stimulations with intensity below and above the motor threshold suppressed tremor for 64.5 ± 3.8 and 70.7

$\pm$ 3.4, respectively. An analysis of participants feedback on the level of comfort based on a pain scale from zero to 10 showed that as the stimulation intensity increases, the sensation becomes less comfortable. Therefore results from the first study can be used to improve the comfort levels of a WTSD, since the hybrid approach can provide sufficient torque for tremor suppression, without increasing the stimulation intensity and discomfort.

Lastly, and in the third study, parkinsonian tremor variability was studied. Tremor data were recorded while participants were asked to perform different tasks, were at rest, or were receiving electrical stimulation or mechanical suppression. Approximate entropy, frequency, magnitude, and PSD of tremor were analyzed in different time frames and under the abovementioned circumstances to provide a better understanding of changes in parkinsonian tremor. The outcome of this study revealed that parkinsonian tremor is not only variable in time, but is also dependent on the task, and if the individual is at rest or is performing activities. Changes in tremor frequency and magnitude have been discussed in the literature in the past, mostly for essential tremor, and it has been hypothesized that the change in synchronization of neural oscillators can change and potentially reduce the tremor amplitude. Tremor regularity indeed was reduced in tremor ApEn analysis during suppression. The reduction in tremor regularity has also been reported in previous studies that have evaluated tremor after an effective deep brain surgery or during the time frame that medications still have their effects on tremor.

6.1 Contributions

The work in this thesis has contributed in three major areas:

1. While current WTSDs have shown positive results in tremor suppression for individuals with PD, available technologies limit the use of these devices. The heavyweight and bulkiness of these devices on one hand, and the discomfort and muscle fatigue caused by FES-based devices, reduce the popularity of these devices for daily use. Thus, in the first project, the feasibility of combining FES with electric motors was demonstrated. In this project, an adaptive control system was designed and developed to manage the use of FES and electric motors in real time and based on the input tremor signal. The results showed that the

hybrid approach is beneficial in the reduction of required stimulation intensity, as well as the reduction in torque requirements of electric motors and therefore, reduction in the generated muscle faituge and the weight and size of the device.

2. Although there are many studies in the literature regarding the effects of electrical stimulation on tremor suppression, there is a lack of consistency within these studies. Although the results could be helpful for potential solutions for tremor suppression for each condition, but cannot be conclusive or exchangeable among these groups of individuals. Inconsistency in the reported results by reporting the maximum suppression rate, different reported factors, and mixed groups of individuals with different conditions such as PD and ET that might cause tremor, are examples of inconsistency in the literature. The last is especially important since the pathophysiology of different conditions resulting in tremor is different and although the results are helpful, but cannot be conclusive. To this end, the focus of this project was to assess the effect of FES on tremor suppression in a more systematic way. This was done by designing a study protocol in which differences in stimulation tolerance among different individuals were considered. Each stimulation combination was repeated three times and results were averaged to reduce the bias, and the onset of stimulations was blinded. This study was limited to only individuals with parkinsonian tremor, and individuals were engaged in conversations during the experiment to remove the psychological effects on the tremor intensity. Since different individuals might have different responses to various stimulation levels, there is a gap in the literature for using the same stimulation levels on all participants per study. Therefore, applying different stimulation levels to each participant closes this gap. In other words, each individual experienced all three levels of stimulation three times, and the results were averaged. The study also closes the gap in the literature caused by reporting mixed results from groups of individuals with PD and ET who participated in previous studies involving FES.

3. Tremor characteristics have been studied throughout the literature. However, the focus of most studies is on essential tremor. While understanding the characteristics of ET can provide insights into understanding PD tremor, the pathophysiology among these conditions

is different. Furthermore, the effect of FES or mechanical loading on nonlinear characteristics of tremor such as regularity has not been evaluated. Therefore, this study focused on evaluating the linear and nonlinear characteristics of tremor under different circumstances and evaluating their changes. This study resulted in new information about changes in tremor regularity when suppressed. These findings not only confirm that changes in tremor regularity occur when tremor is being suppressed regardless of the suppression method but also further confirm that tremor intensity is dependent on the synchronization of central oscillators. It can also be concluded that the activity of central oscillators not only can be influenced by medication and surgery but also by external interventions. Furthermore, the evaluation of tremor in time and during different tasks highlights the variability of tremor, and that passive actuators for WTSDs are not ideal due to their negative impact on the voluntary motion as well as constant suppression rate regardless of changes in tremor intensity. Thus, real time and accurate tremor estimation is needed when designing WTSDs.

6.2 Limitations

Although this work has been focused on deriving more conclusive results on the use of FES and changes in tremor characteristics in PwP, the limited number of individuals who volunteered for this study can be counted as one of the major limitations in both Chapters 4 and 5. Initially, participants in both experiments (see Sections 4.2, 5.2.1, and 5.2.2), and the repetition of rounds in the stimulation experiment (Sections 4.2, 5.2.2) were considered as covariates during the statistical analyses. However, since the added covariates did not have impacts on the outcome, they were removed to increase the power. There is clear overlap seen in the box and whisker plots in Figures 4.11, 5.4–5.9, even when statistical significance was found. The overlap might be explained by the small sample size that was used in this work. Nevertheless, it is clear that the statistical analyses are showing that the distributions are not equal. To resolve this discrepancy, a larger dataset acquired from a larger group of participants will be required to increase the power, and support the results presented.

Furthermore, the long-term effect of stimulation on PwP needs to be studied in a large group of participants to gain knowledge on the potential side effects of using FES for the suppression of tremor. Since it has been shown that tremor regularity changes during suppression episodes, further evaluations are needed to investigate the cause, and potential negative effect of increased entropy in tremor on individuals.

6.3 Future Work

While the focus of this work was to assess the changes in tremor characteristics, various FES parameters and their effects on tremor reduction, and the possibility of combining FES with electric motors for more acceptable WTSDs, further studies can be done to improve WTSDs and specially WTSDs with FES. These potential studies can be listed as follows:

1. The application of FES to the exact muscle fibers of interest plays an important role both in muscle fatigue reduction and torque generation and therefore, tremor suppression. An electrode array that can switch between FES electrodes and EMG measurement can be developed in a future study. EMG signals can be used as feedback to a control system that optimizes the FES activation map on the electrode array over time, and based on the user's muscle and forearm characteristics.

2. Electrical stimulation below the motor threshold has been used in studies for tremor suppression. However; there is still not enough information on its effectiveness on different conditions that cause tremor, and during tasks that involve voluntary motion. Another study can be designed with the focus of sensory stimulation on suppression of only parkinsonian tremor at rest, postural, and kinetic tremor, with a large group of individuals for more conclusive results.

3. Although different studies have evaluated different adaptive controllers for WTSDs, there are not enough conclusive results on the performance of these controllers in a WTSD. The lack of conclusive results is because studies have mostly tested the controller in a simulation setup, and not in a real clinical study with a sufficient number of participants. This can be used as a topic of another study to evaluate controllers in clinical trials in individuals with

tremor, and under different circumstances.

4. Although the first study in this work showed the improvement of results in a hybrid approach, both in terms of tremor suppression rate and the use of resources, there is no study available up to now to evaluate the meaningful suppression rate in clinical trials. In other words, there is no information on clinically meaningful suppression rate of tremor at rest or while performing tasks of daily living. This is important since a high rate of tremor reduction might lead to resistance in voluntary motion. On the other hand, and as mentioned earlier, bradykinesia, rigidness, and slowness of motion are other motor symptoms in people with PD. Thus, increasing the resistance against voluntary motion to achieve a high level of tremor suppression might not be beneficial in real-life applications.

5. Although the first study in this work has shown the feasibility of the hybrid approach, more exhaustive work is required to first, integrate the hardware for both FES and mechanical suppression together, evaluate the approach in a benchtop setup, and further, in a clinical experiment.

6. Lastly, changes in tremor characteristics such as frequency and regularity during suppression with external devices can be studied deeper with a larger dataset, with and without voluntary motion being involved.

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Appendix A

Permissions and Approvals

Western Research

Date: 27 January 2022

To: Mary Jenkins

Project ID: 106172

Study Title: Assessment of Hand Tremor

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

Date Approval Issued: 27/Jan/2022

REB Approval Expiry Date: 20/Feb/2023

Dear Mary Jenkins,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

The Office of Human Research Ethics

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western Research

Date: 13 July 2023

To: Dr. Mary Jenkins

Project ID: 114632

Review Reference: 2023-114632-80823

Study Title: The Suppression of Parkinson's Tremor using Electrical Stimulation

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

Date Approval Issued: 13/Jul/2023 12:55

REB Approval Expiry Date: 27/Jul/2024

Dear Dr. Mary Jenkins,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Electronically signed by:

Mr. Joshua Hatherley, Ethics Coordinator on behalf of Dr. N. Poonai, HSREB Chair 13/Jul/2023 12:55

Reason: I am approving this document

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix B

Tremor Variability as a Function of Time

Figures B.3–B.6 show the tremor data of Experiment I (Chapter 5) for the different tasks as boxplots, separated into three different time frames, where each frame is 10 seconds of data (total of 30 seconds of data). As previously mentioned in Section 5.2.1, Tasks 3–5 took less than 60

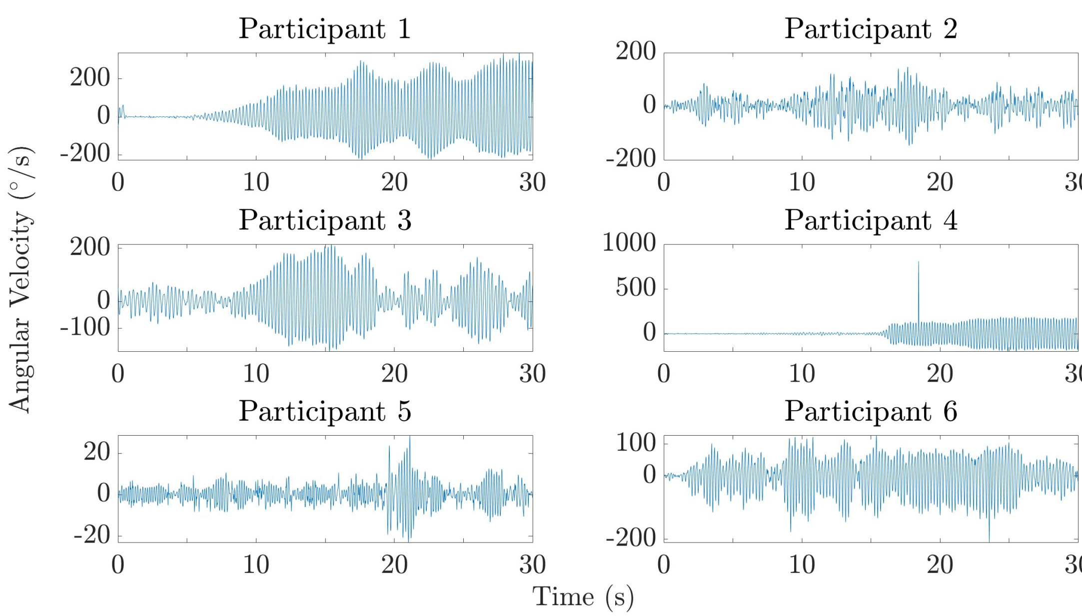

Figure B.1: Sample of 30 seconds of angular velocity data corresponding to rest tremor for six different participants (each image corresponds to a different participant).

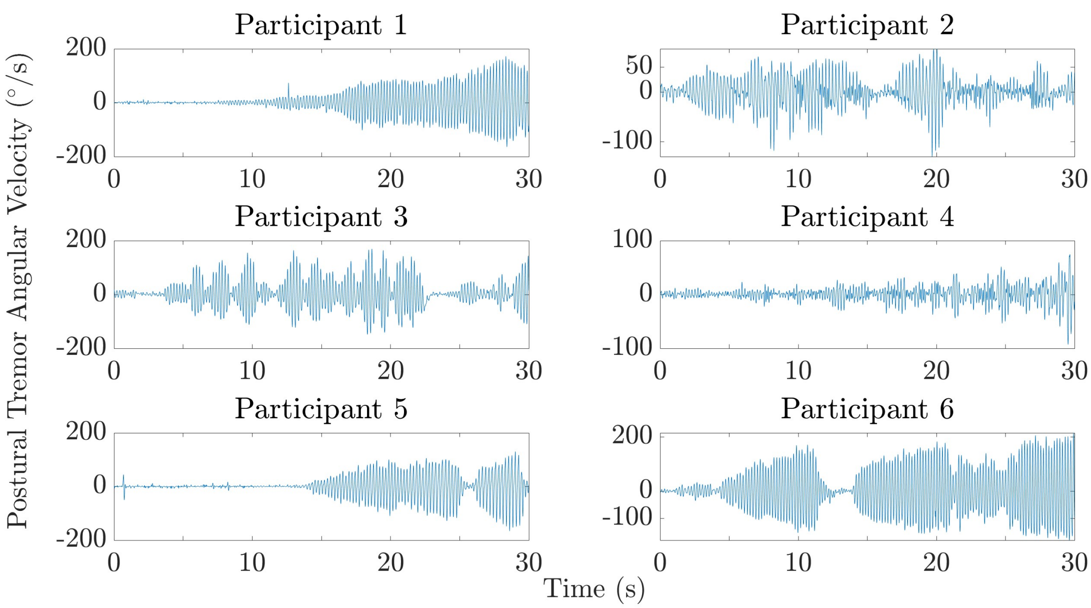

Figure B.2: Sample of 30 seconds of angular velocity data corresponding to postural tremor for six different participants (each image corresponds to a different participant).

seconds and the recording duration equaled the time that each participant needed to complete the task. Therefore, to be consistent in the length of data used in this section, the shortest data length was adopted as the limiting factor, and the first 30 seconds of other datasets were used in this analysis. From the results of the RMA, time is a significant factor in changes in tremor power spectrum density and tremor magnitude with $p = 0.009$ and $p = 0.008$ for PSD and magnitude, respectively. The means of the PSD and the magnitude tend to increase in time, considering the mean value of all tasks together in each time window (magnitude: 19.7, 20.8, 24.8 for T1, T2, and T3, respectively; PSD: 675.9, 829.8, 1483.9 for T1, T2, and T3, respectively). However, across variable tasks and different participants there is no certain increasing or decreasing trend in tremor PSD or magnitude over time. This can also be seen from Figures B.3 and B.4. A possible explanation for this could be the mental state of the participants or the environmental conditions during the time of data collection, which can affect the tremor by reducing or increasing stress levels. Lastly, the frequency and approximate entropy of tremor in each task is relatively consistent in time ($p = 0.187$ and $p = 0.057$ for frequency and ApEn, respectively).

Tremor intensity might show slight variations on different days due to various individual and

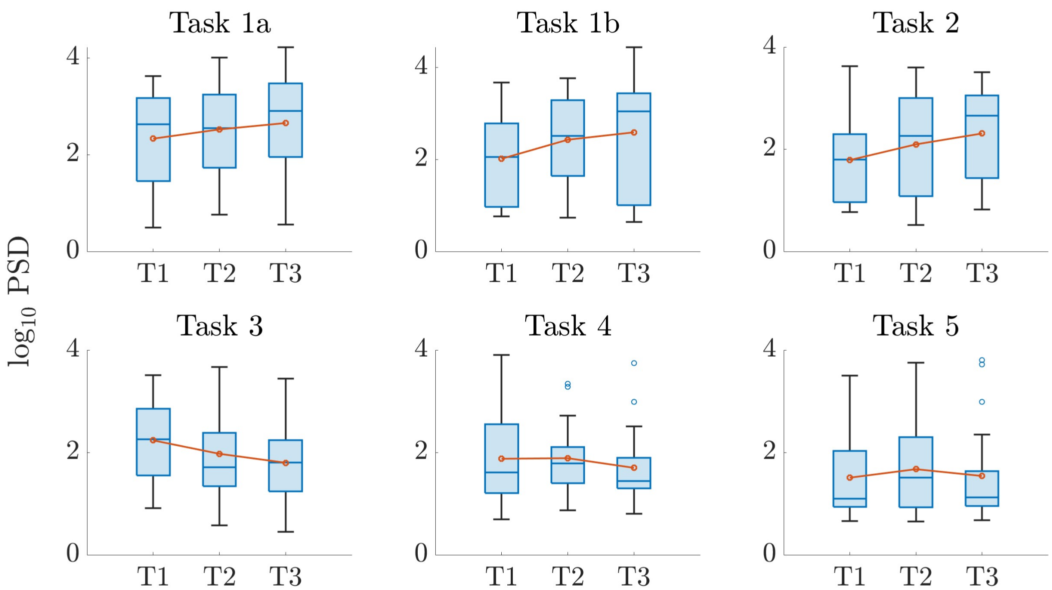

Figure B.3: Distribution of the common logarithm of the tremor power spectrum density in Tasks 1a–5 in three continuous time frames of 10 seconds as T1, T2, and T3.

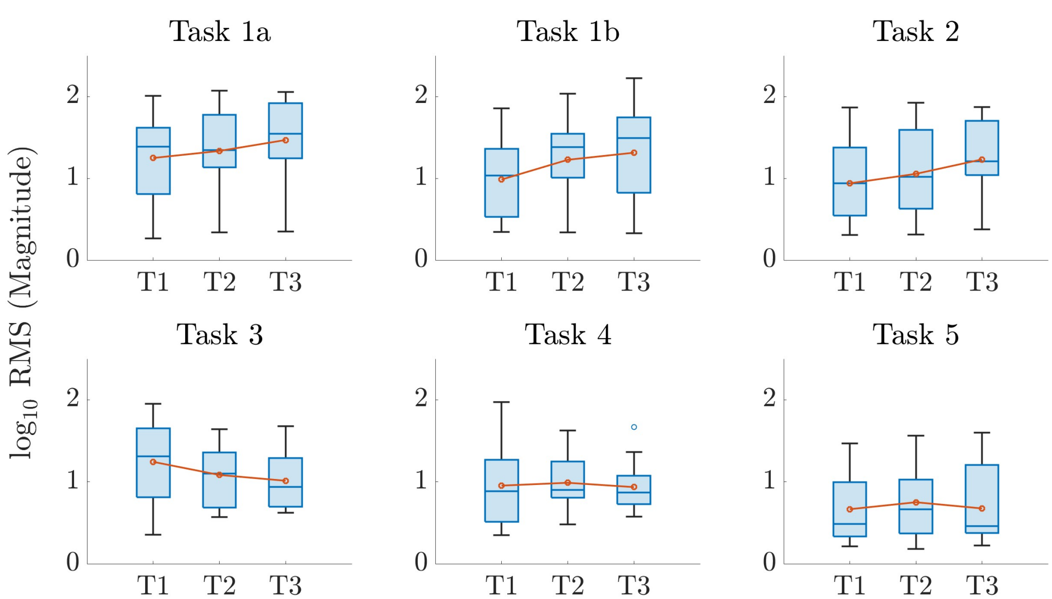

Figure B.4: Distribution of the common logarithm of the tremor magnitude in Tasks 1a–5 in three continuous time frames of 10 seconds as T1, T2, and T3.

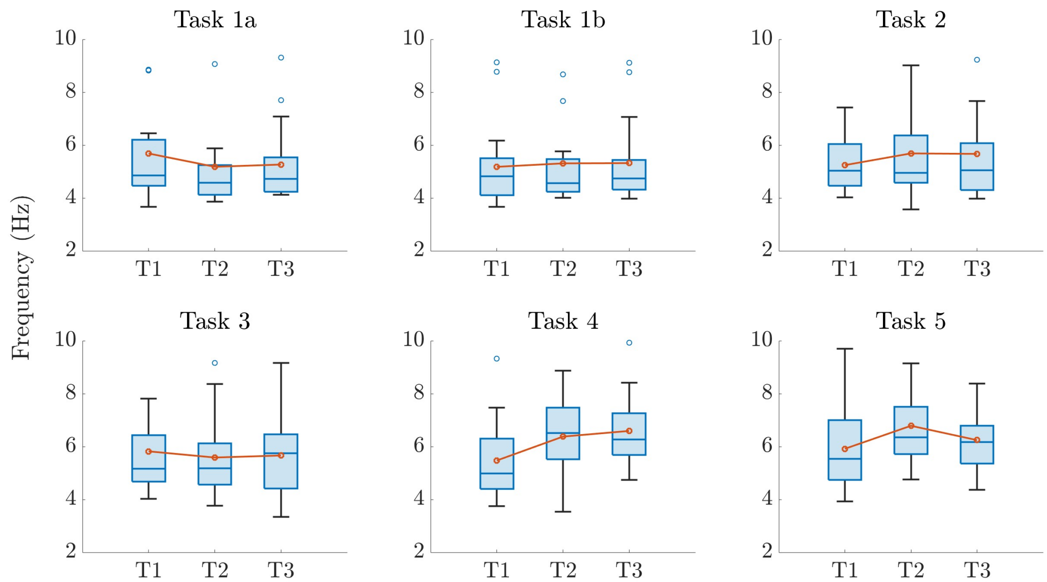

Figure B.5: Distribution of the tremor frequency in Tasks 1a–5 in three continuous time frames of 10 seconds as T1, T2, and T3.

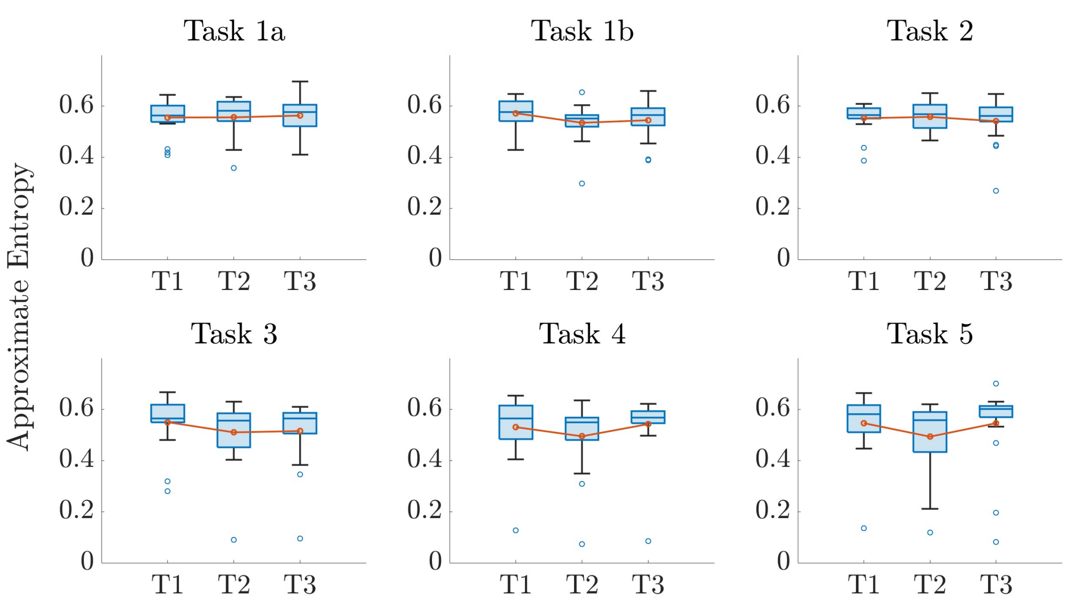

Figure B.6: Distribution of the tremor approximate entropy in Tasks 1a–5 in three continuous time frames of 10 seconds as T1, T2, and T3.

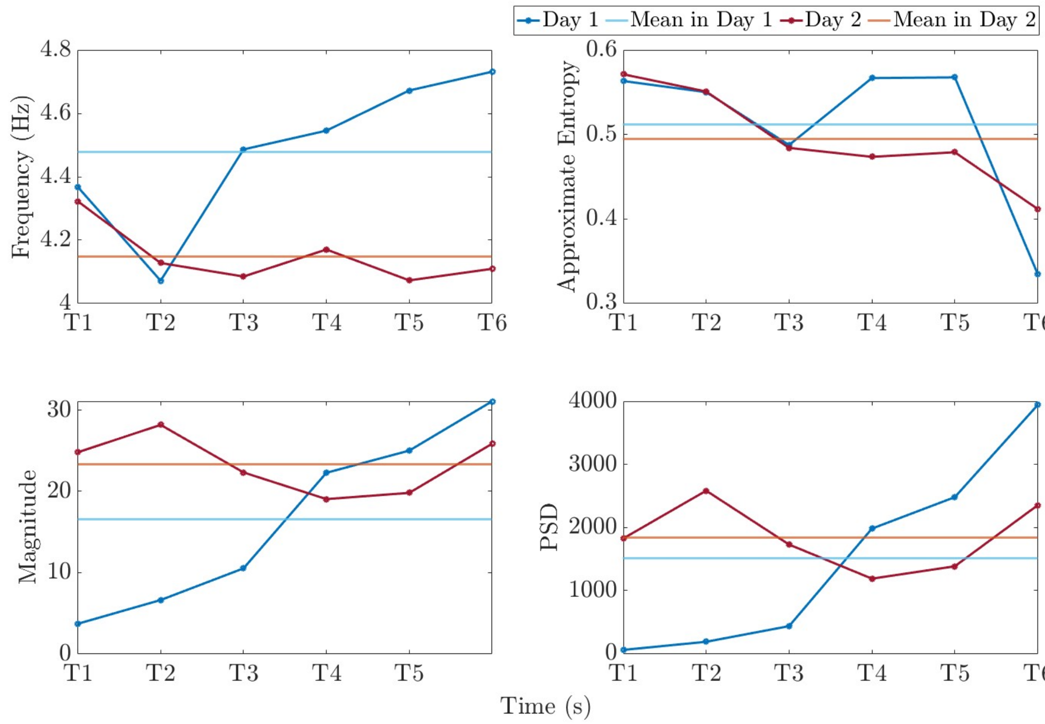

Figure B.7: Tremor characteristics, including frequency, approximate entropy, magnitude, and PSD for Participant 1, based on the rest tremor data collected over two days. The dark blue dot line shows the results in six continuous time frames of 10 seconds on Day 1, the light blue line shows the average values on Day 1, the red dot line shows the results in six continuous time frames of 10 seconds on Day 2, and the orange line shows the mean values on Day 2.

environmental factors. To explore these fluctuations further, rest tremor data were collected from three different participants on two different days and are compared in this section. Figures B.7–B.9 show tremor magnitude, PSD, ApEn, and frequency for Participants 1–3, respectively. The figures show that tremor is highly variable in different time frames for a single individual. Changes could be due to several reasons, such as disease progression, the effect of medications, and mental or environmental conditions.

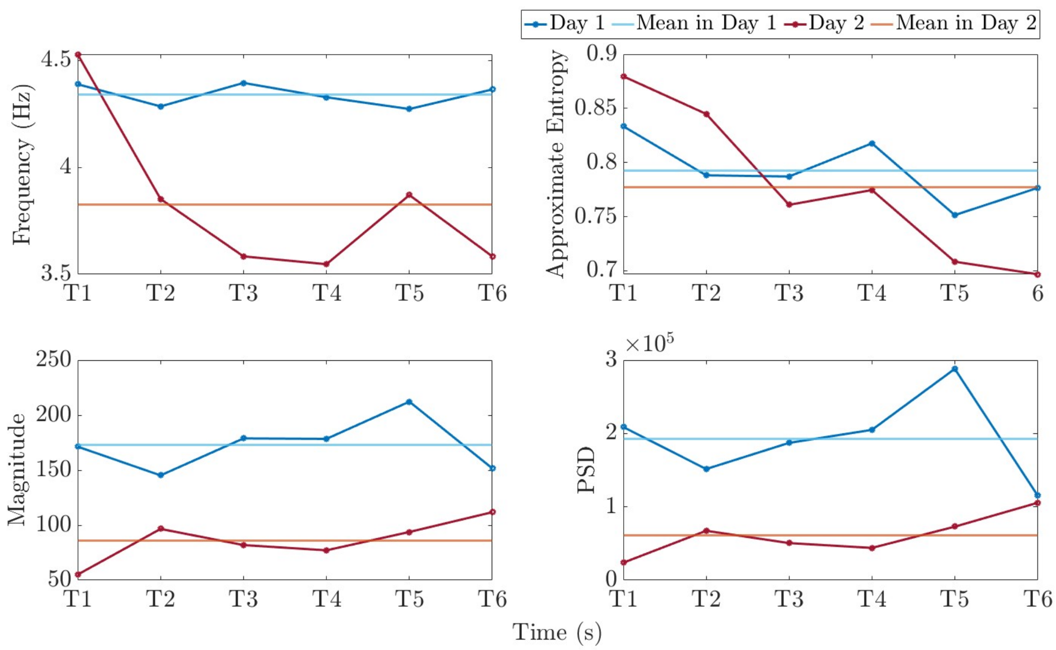

Figure B.8: Tremor characteristics, including frequency, approximate entropy, magnitude, and PSD for Participant 2, based on the rest tremor data collected over two days. The dark blue dot line shows the results in six continuous time frames of 10 seconds on Day 1, the light blue line shows the average values on Day 1, the red dot line shows the results in six continuous time frames of 10 seconds on Day 2, and the orange line shows the mean values on Day 2.

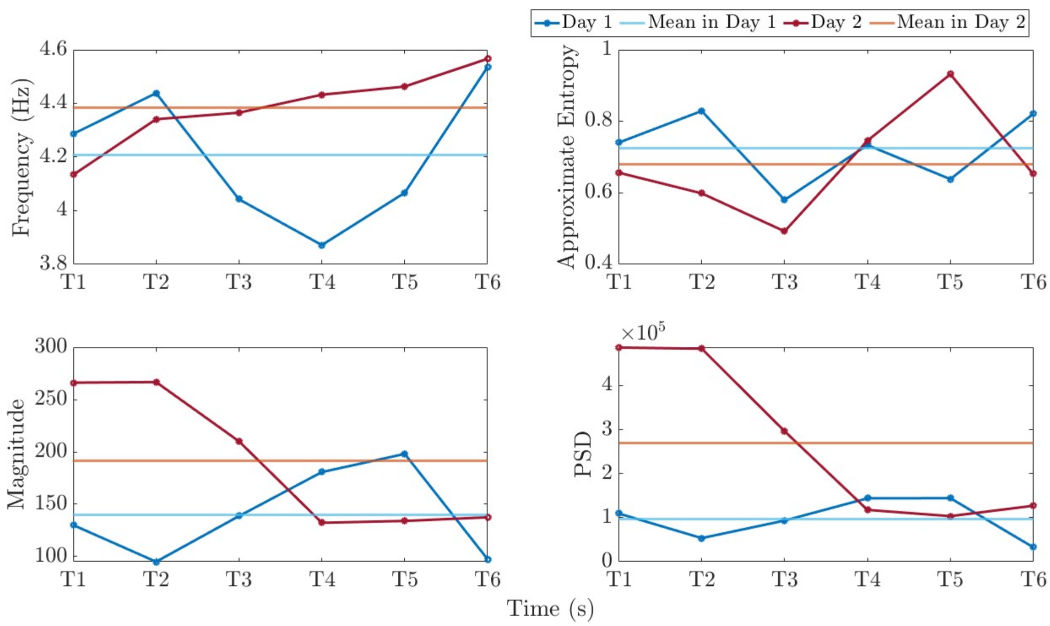

Figure B.9: Tremor characteristics, including frequency, approximate entropy, magnitude, and PSD for Participant 3, based on the rest tremor data collected over two days. The dark blue dot line shows the results in six continuous time frames of 10 seconds on Day 1, the light blue line shows the average values on Day 1, the red dot line shows the results in six continuous time frames of 10 seconds on Day 2, and the orange line shows the mean values on Day 2.

Curriculum Vitae

Zahra Habibollahi Najafabadi

Education

Sep. 2019 – Present	PhD, Electrical Engineering, Robotics, University of Western Ontario, London, Ontario, Canada Thesis: Toward Development of a Wearable Tremor Suppression Device Using Functional Electrical Stimulation Supervisor: Dr. Ana Luisa Trejos
Sept. 2014 – Feb. 2019	BSc, Electrical Engineering, University of Tehran, Tehran, Iran

Honours and Awards

2023	Recipient of Best Graduate Research Symposium Presentation, University of Western Ontario
2019	Recipient of Best Undergraduate Project Award, Unversity of Tehran

Research Experience

Sep. 2019 – Present	**Graduate Research Assistant**, University of Western Ontario, Wearable Biomechatronics Laboratory (WearMe Lab)
Apr. 2018 – May 2019	**Undergraduate Research Assistant**, University of Tehran, Iran Worked on developing an optimization toolbox for mixture models parameters optimization, based on MixEst toolbox in MATLAB
May 2018 – Sep. 2018	**Undergraduate Internship**, Royan Institute, Tehran, Iran Worked on an image processing project for Vitiligo lesions detection and analyzing the effectiveness of applied treatments over time.

Industry Experience

Jan. 2024 – Present	**Sr. Applications Specialist**, KUKA Robotics, Canada

Teaching Experience

Sep. 2019 – Dec. 2023	**Graduate Teaching Assistant**, University of Western Ontario, School of Biomedical Engineering *ECE4455 – Biomedical Systems Analysis* *ECE3399 – Principles and Practices of Design of Electronic Systems*

ECE 9013 – Programming for Engineers (Python)
ES 1036 – Programming Fundamentals for Engineers (JAVA)

Volunteer Experience

Aug. 2023 – Nov. 2023 — **KaggleX Project Mentor**

Sep. 2019 – Dec. 2023 — **Lab Outreach Tour Demonstrations**, Wearable Biomechatronics Laboratory (WearMe Lab), University of Western Ontario

Jan. 2021 — **FIRST Lego League Referee**, Western Engineering FIRST LEGO League London Qualifier, University of Western Ontario

Publications

Z. Habibollahi, Y. Zhou, M. E. Jenkins, S. J. Garland, M. D. Naish and A. L. Trejos, "Multimodal tremor suppression of the wrist using FES and electric motors–A simulation study," *IEEE Robotics and Automation Letters*, vol. 8, no.11, pp. 7543-7550, 2023.

Y. Zhou, P. Daemi, B. Edmonds, Z. Habibollahi, M. E. Jenkins, M. D. Naish and A. L Trejos, "Mechatronic Devices for Upper Limb Tremor," *Mechanisms and Emerging Therapies in Tremor Disorders*, Grimaldi, G., Manto, M. (eds), pp. 489–526, *Springer International Publishing*, 2023.

Y. Zhou, Z. Habibollahi, A. Ibrahim, M. E. Jenkins, M. D. Naish and A. L. Trejos, "Real-Time performance assessment of high-order tremor estimators used in a wearable tremor suppression device," *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 30, no.11, pp. 2856–2865, 2022.