Spring 4-11-2017

A Frequency Domain Based Approach to Evaluating Manual Tracking Behavior in Parkinson's Disease

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THESIS

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Science

in Electrical Engineering

The University of New Mexico

Albuquerque, New Mexico

May, 2017

Dedication

To my friends, family, and my wife Jessica who always believed in me

Acknowledgments

I would like to thank my professors in the ECE department for the time they spent teaching, and mentoring me. I would especially like to thank my advisor, Dr. Meeko Oishi for her help and guidance as I progressed throughout my education. She imparted knowledge on me that will be extremely valuable throughout the rest of my career. I would also like to thank Dr. Martin McKeown for collecting, and allowing the use of the data contained in this thesis. This data was collected from his lab at the Pacific Parkinson's Research Center. His medical insights were also very useful and very much appreciated.

Funding Statement

Funding for this thesis was provided by the National Science Foundation under Grand Number CMMI-1254990 (CAREER, Oishi). Any opinions, findings, conclusions, and recommendations expressed in this material are those of the author and do not necessarily reflect the views of the National Science Foundation.

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Abstract

Parkinson's disease (PD) is characterized in part by its neurodegenerative effects, which include bradykinesia, tremor, rigidity, and many other symptoms. While treatments such as Levodopa and deep brain stimulation are available, they both have associated complications. Galvanic vestibular stimulation (GVS) is a non-invasive method used to stimulate the vestibular nerves with electric current and it has shown promise as a possible treatment for patients with PD. In order to assess the efficacy of GVS, I examined data collected from a manual pursuit tracking experiment. The experiment involved ten patients with varying severities of PD who were asked to perform a series of eight 90 second tasks both before and after receiving a dose of fast acting Levodopa. The patients unknowingly received GVS below sensory threshold for four of the tasks. They were asked to track a vertically oscillating target on a screen by using a joystick to move a cursor next to the

target. I applied Welch's power spectral density method to determine the power of high frequency noise associated with sub-movement induced error in patient's tracking signal. I then paired trials where patients received GVS with trials where they did not. These pairs were normalized by adding the input signal to the output signal of the other trial in the pair. The results of a paired t-test determined there was a statistically significant ($p < 0.05$) improvement in performance when GVS was applied in the trails that occurred after Levodopa was administered. The results suggest there are some synergistic effects between Levodopa and GVS. More research is needed to determine if GVS can provide statistically significant increases in performance minus the apparent synergistic effects.

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Chapter 1

Introduction

1.1 Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder that affects motor control and cognitive abilities. Motor control symptoms include tremor, rigidity, and bradykinesia. Late stage patients exhibit postural instability, which may lead to frequent falls. The cognitive impairments can include difficulties with memory, decision-making, and attention. Dementia is prevalent in the later stages of the disease, with PD patients having a two to six times increased chance of developing the condition relative to the general population [1].

The pathology of the disease is manifested in the loss of neurons in the substantia nigra. This results in severely reduced dopaminergic activity, which in turn affects the basal ganglia. The basal ganglia is specifically innervated by the dopaminergic system and the reduced levels of dopamine inhibit the primary functions of the basal ganglia. Because the primary functions of the basal ganglia are associated with motor control, cognition, and emotion, the lack of dopamine to stimulate this area causes the primary symptoms seen in PD [2].

Although there is no known treatment that reverses the effects of PD, there are several treatments, which can reduce the severity of symptoms. The effectiveness of these treatments depends on the progression of the disease and how long the treatments have

been used. The primary pharmacological treatment is Levodopa, which is more commonly known as L-Dopa. It is converted into dopamine in the substantia nigra, which temporarily reduces motor symptoms of PD [3]. However, there are complications associated with long term use [4][5]. Surgical treatment in the form of deep brain stimulation is also available. It is effective at treating symptoms associated with motor control but it is highly invasive [5][6]. Recent research has shown success in non-invasive brain stimulation treatment. Procedures such as transcranial brain stimulation and galvanic vestibular stimulation (GVS) have shown promise in improving motor control for PD patients [7][8][9].

1.2 Galvanic Vestibular Stimulation

GVS is applied through electrodes attached to the mastoids behind the ears. When an electric current is applied through the electrodes, the vestibular nerves are stimulated which has a number of effects on motor control in both healthy individuals and patients with neurodegenerative disorders. The vestibular nerves are polarized which in turn activates a number of regions in the brain through stimulation of the Parieto-Insulo-Vestibular-Cortex (PIVC). Figure 1 highlights the neuropathway used in GVS to stimulate the PIVC. According to functional imaging of the brain, this stimulation activates other areas including the basal ganglia [10]. In addition to stimulating brain activity, GVS has also been shown to modulate the amplitude of EEG synchrony patterns, particularly in the beta (13-30 Hz) and gamma (31-50Hz) bands. GVS is thought to be effective in treatment of PD symptoms due to the Parkinsonian condition of the brain being characterized by

synchronous activity in the beta band. This is thought to be one cause of the many of the movement disorders associated with PD [11].

Studies have shown positive results when GVS is applied at the sub sensory threshold on patients with PD. One study demonstrated reduced postural sway in PD patients when they were in certain stance conditions [12]. Another study demonstrated improved autonomic and motor responsiveness when GVS was applied during a prolonged period of twenty-four hours [9]. There have also been several studies that measure performance of manual pursuit tracking tasks designed to measure responsiveness to visual stimuli. These manual tracking tasks are vital to understanding the impact and effectiveness of GVS on PD patient's cognitive response and motor control [7][8].

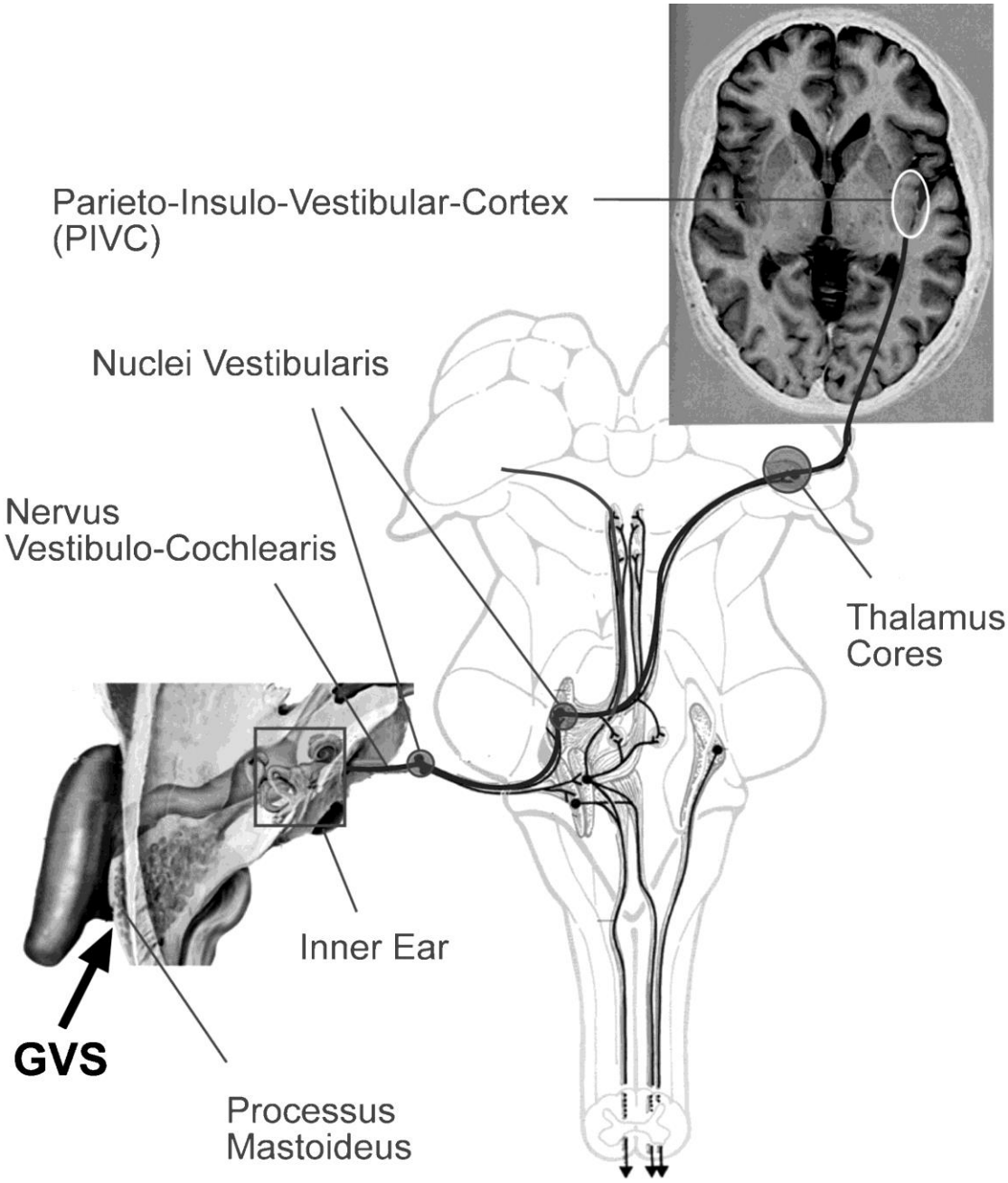

Fig. 1. The functional pathway for GVS. Electrodes are attached to the mastoid process behind the ear. Stimulation of the vestibular nerve excites a neural pathway that leads to the PIVC. Image obtained from [10].

1.3 Manual Tracking Tasks

Manual tracking tasks are present in almost every facet of everyday life. For example, simple tasks such manipulating a mouse on a computer or driving a car involve motor control response to visual stimuli. In fact, some of the earliest research in manual tracking was conducted as aircraft pilot research. Mathematically these tasks can be modeled as feedback control systems. If the reference trajectory is known beforehand, then the model becomes a feedforward system as subjects use precognition to anticipate the output [13]. In certain experiments, disturbance rejection can also be assessed by adding a disturbance signal the subject is required to reject.

In a manual tracking experiment model, the input is usually a reference the subject is supposed to track using an input device such as a wheel or joystick. The objective is to match the position of the reference object with another object whose position changes from manipulation of the input device. Hence, the input of the feedback control system is the position of the reference object and the output is the position of the controlled object. Feedback occurs when the subject corrects the position of the output to match the trajectory of the reference. Different variants of the task will provide different reference trajectories or additive noise components. Some experiments have utilized reference signals composed of a summation of sine functions at various frequencies while others have used chirps or a 3-D reference target that required subjects to track a single fixed point.

The reference trajectory is often programed using a function generator. Recently, software programs such as MATLAB are used to create the reference. Data collection is also often performed in the same software program used to generate the reference signal.

Programs such as MATLAB are versatile enough to perform the experiment, collect data, and perform analysis of the data. Analysis of the data often requires system identification techniques to analyze performance of the manual tracking task [7][8].

1.4 System Identification

Determining parameters of the feedback control system in a manual tracking task is critical to assessing performance of the subject. Depending on the form of the reference input, several varieties of system identification may be used. When the reference input is sinusoidal in nature, frequency domain techniques can illicit performance differences between subjects and conditions. Some research has focused on modeling the feedback control system as a second order LTI system [13]. This research identified statistically significant differences in damping ratios and natural frequencies between control and PD populations in task that switched controller sensitivity in 30-second intervals. This study also used multiple model adaptive estimation to determine when subjects determined the switch in controller sensitivity.

Various methods of linear regression are also used to assess performance through system identification. Two techniques used in a study which I co-authored, were linear discriminant analysis and multivariate linear regression. In this study, GVS was applied to a set of manual tracking tasks performed by both a control group and set of PD patients. The PD patients performed the task both before and after a fast acting does of L-Dopa was administered. The coefficients identified in the resulting linear regression were statistically significant across the different subject populations [7]. Identifying and comparing both

LTI parameters and regression coefficients from different trials can be useful in determining differences between subject groups in a manual tracking task experiment. However there are other frequency based techniques that can be used to discriminate performance if the objective is not necessarily to determine parameters of the model but rather distinguish differences in the output of each trail by using time series analysis.

1.5 Contribution

As stated previously, assessing performance across multiple groups in manual tracking tasks performed by PD patients has focused on determining the parameters of the black box of visuomotor dynamics that performs a the task. These parameters are then compared across subject populations in order to determine if any statistical differences are present. This type of analysis can be helpful for research that focuses on creating models designed to predict future performance under different conditions. It has also shown to be helpful in experiments where parameters of the task are varied to produce a hybrid control environment. In this case, the subject may utilize different black boxes of control dynamics depending on a set of varying parameters, or modes, used in a particular duration of time in the experiment [14].

An in depth review of the research in the use of GVS in manual tracking tasks performed by PD patients has shown a lack of time series analysis performed on the output of the task in reference to the input. In tasks where a sum of sines input is used, the visuomotor dynamics of the subject performing the task transforms the input to an output that contains the same frequency content as the input from the tracking as well as additive

noise. The output also lags the input because of processing delay that occurs in visuomotor feedback loop. The additive noise is the direct result of what could be called sub movements. These sub movements occur when a subject deviating from the smooth tracking of the target either through an involuntary movement or a voluntary movement designed to reacquire tracking of the input through a corrective action. Often these involuntary movements are the result of an unintended overshoot of the tracking objective. The input and output of a manual tracking experiment, as well as identified sub movements can be seen in figure 2.

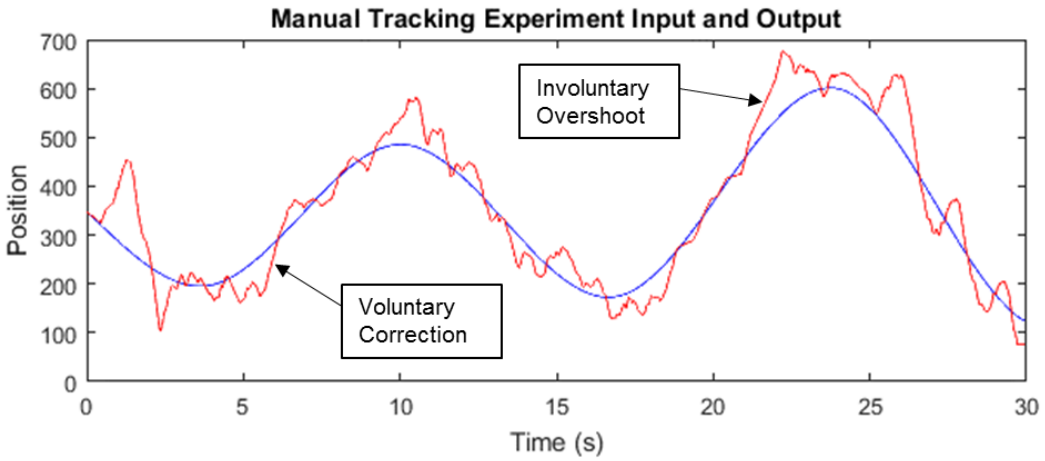

Fig. 2. An example of input and output data from a manual tracking task with a reference input signal consisting of a sum of two sine waves at different amplitudes and frequencies. The blue line is the reference trajectory and the red line is the output trajectory. The two classes of sub movements are indicated on the graph. This particular task is from the switching manual task described above. The parameters for this particular portion of the experiment result in the controller becoming less sensitive, requiring more effort on the part of the subject to perform the tracking.

The voluntary correction usually leads into an involuntary overshoot. The magnitude of the overshoot displays a degree of randomness, which in turn leads to randomness in the magnitude of the correction. This consistent oscillation between overshoot and correction leads to the presence of high frequency noise in the output signal.

The power associated with the high frequency noise is an indicator of how well a subject performed the task of tracking the reference input. If a subject has relatively low power in the range of frequencies that are higher than the input, then the subject will have performed the tracking well. The magnitude of the overshoots and corrections will be lower resulting in a better overall tracking of the signal. The analysis I performed on this data compared the total signal power of a trial under the influence of GVS versus a trial where GVS was turned off. This had the effect of eliciting performance differences between the two populations.

In PD patients, several of the motor symptoms, including tremor and bradykinesia, can exacerbate sub movements in manual tracking tasks. When studying the effects of potential treatments, such as GVS, my analysis of output signal power is useful as preliminary measure of performance that does not require significant additional preprocessing and can be applied across a variety of manual tracking tasks involving PD patients. The paper that included an analysis based on my method utilized the previously discussed switching manual tracking task [7]. It was performed on data obtained from the reduced controller sensitivity mode which is the result of increasing the tracking error between the input and output while the task is being performed. The increased tracking error amplifies sub movements and allows for better differentiation of output signal power relative to the other mode in which the tracking error is reduced. Reduction in error reduces the magnitude and number of sub movements in the experiment interval.

My analysis determined the use of GVS during manual tracking tasks lowers output signal power on PD patients performing the task. The output signal power for the population performing task while GVS is on was significantly lower ($p < 0.05$) than the

output signal power for the population performing the task while GVS was off. This analysis and the results were included in the following publication:

- S. Lee, D. Kim, D. Svenkeson, G. Parras, G., M Oishi, M. McKeown, "Multifaceted effects of noisy galvanic vestibular stimulation on manual tracking behavior in Parkinson's disease," *Frontiers in Systems Neuroscience*, vol. 9, pp. 5, 2015. http://journal.frontiersin.org/article/10.3389/fnsys.2015.00005/full

The signal power difference between the GVS off and GVS on condition is an additional strong indicator that GVS improved performance and may reduce the severity of motor symptoms in PD patients. This could lead to tremendous increases in quality of life through the non-invasive treatment that is GVS. This treatment is preferable to the complications that can arise with prolonged L-Dopa regimens or the invasiveness involved with deep brain stimulation.

Chapter 2

Frequency Based System Identification

2.1 Advantages and Disadvantages of Frequency Based System Identification

Frequency domain analysis is useful in determining the parameters that define an LTI system. If the input and output of a system are known and the input of the system contains uniform frequency content throughout the spectrum, then an accurate representation of the system can be determined. Frequency domain analysis has the advantage of being near absolute in terms of defining a system. However, the presence of Gibbs phenomena associated with real world digital signals does lead to spectral leakage, which can affect accuracy of system identification in the frequency domain. Use of windowing functions with overlap can minimize spectral leakage and increase the accuracy of the system.

Another advantage of frequency based system identification is the ease through which in can be implemented. The context of the application can dictate the parameters used in a specified method, such as Welch's method [15] or the Blackmon-Tukey method. In other system identification methods, there can be a significant amount of trial and error to find the model that best fits the data. In a linear regression based model, the number and value of coefficients must be predetermined before the regression is run. Bootstrapping can also be used to add robustness to the model but requires additional effort [7]. In state space identification models, the order of the system that leads to most accurate model often

has to be determined through trial and error. Algorithm choice also plays a key role in determining the best-fit model.

One of the primary disadvantages of frequency based system identification in the context of manual tracking is lack of frequency content in the input. The biological restrictions of the visuomotor system prohibit tracking of high frequency inputs, as the average human response time to visual stimuli young, healthy individuals is approximately 0.25s or 4 Hz [16]. The average response time is most likely greater for PD patients. Most manual tracking experiments do not have reference inputs with frequency content higher than 1 Hz for this reason. In addition, muscle fatigue prevents tracking of high frequency signals for long periods. In an LTI system, input of a range of frequencies is required to obtain a model. However sum of sines inputs often have less than nine sinusoids of varying frequencies, an assumption I make based on my literature survey. This leads to significant gaps in frequency content. Even if a model is sought that would only be valid between 0 and 1 Hz, there is too little frequency content in the input for the model to be valid. Nonetheless, frequency based system identification techniques can be used to extract useful information from the input and output signals.

2.2 Methodology

The methodology I use evaluate the effectiveness of GVS at increasing performance in a manual tracking task utilizes Welch's method for estimating the power spectral density (PSD) of a signal [15]. Once the PSD of both the input and the output are estimated, I calculate the total power by integrating over its length. The difference in

output signal power between trials with GVS and trials without indicates the effectiveness of GVS at increasing tracking performance.

Welch's method requires an analyzed stochastic signal meet the conditions of stationarity [15]. In the case of manual tracking experiments, a subject's performance is not likely to deviate over a short period of time resulting in fixed mean and variance for the magnitude of sub movements. If the experiment required tracking effort over an extended period of time than what would be considered normal for everyday life, performance would likely deviate and sub movements would increase in magnitude as the experiment progresses. This would violate stationarity as the mean and variance of sub movements would change as a function of time. Therefore, I make the assumption that the output is a stationary signal for a short time manual tracking task. The input is not stochastic and can be analyzed without restriction. I will now show how Welch's method can be utilized to estimate the power spectral density (PSD) of the input and output signal.

Assume $U[k], k = 0, 1, \dots, K-1$ is the input to a manual tracking experiment of length K and $Y[k], k = 0, 1, \dots, K-1$ is the stationary output of a manual tracking experiment of length K. Also assume the DC gain has been removed from both the input and the output such that $E[U] = E[Y] = 0$. The first step in Welch's method segments the full length of the signal into N segments that are D units apart and with length L. Hence,

$$U_1 = U[k] \qquad k = 0, 1, \dots, L-1$$
$$U_2 = U[k + D] \qquad k = 0, 1, \dots, L-1$$

and finally

$$U_N = U[k + (N-1)D] \qquad k = 0, 1, \dots, L-1$$

If D < L, the segments are said to overlap. The percentage of overlap, OL, is defined as

$$OL = \frac{(L - D)}{L}$$

Each segment is then multiplied by a windowing function of length L, and the Discrete Fourier Transform (DFT) of each segment is taken. The windowing function is defined as $W[k], k = 0, 1, \ldots L - 1$. The sequence of DFTs, $U_n(f)$ is defined as:

$$U_n(f) = \frac{1}{L}\sum_{k=0}^{L-1} U_n[k]\, W[k] e^{-\frac{j2\pi fk}{L}} \qquad n = 1, 2, \ldots, N$$

The sequence of periodograms for the sequence of DFTs is:

$$I_n(\hat{f}) = \frac{L^2}{\sum_k^{L-1} W^2[k]} |U_n(f)|^2 \qquad n = 1, 2, \ldots, N$$

Where

$$\hat{f} = \frac{f}{L} \qquad f = 0, \ldots, \frac{L}{2}$$

The final estimate is of the power spectral density is:

$$S_{UU}(\hat{f}) = \frac{1}{N}\sum_{n}^{N-1} I_n(\hat{f})$$

The estimate of the PSD for the input function is an average of the sequence of periodograms. The PSD estimate for the output $Y[k]$ is computed in the same fashion. In MATLAB, the `pwelch` function can be used to estimate the PSD.

Once the PSD is estimated for the input and output, the total power is found by integrating over the length of the PSD. In MATLAB, this is computed using the `bandpower` function. The integral is estimated using the rectangle method. When using the `bandpower` function in MATLAB with a time domain signal as the input, the command utilizes Welch's method as the default method for estimating the PSD that is used to calculate signal power.

In order to apply a paired T-Test between trials with GVS and trials with out, I added the input of a trial with GVS activated to the output of a trial without GVS. Then I added the input of the same trial without GVS to the output of the trial with GVS. This has the effect of normalizing two trials with respect to the input signals. Thus a Paired T-Test will discriminate against signal power contained in the output only. In the application of Welch's method and bandpower calculations to the data from the experiment, I apply my methodology only to the combined input/output signal. However, superposition is a property of the DFT and I felt it was important to treat both the input and the output separately in this description of my methodology.

Chapter 3

Data Application

3.1 Experiment Description

3.1.1 Subjects

Participants in the manual tracking experiment consisted of fourteen control subjects and twelve PD patients recruited from the Pacific Parkinson's Research Center. The PD group consisted of 10 males and 2 females with a mean age of 61.4 ± 6.5 years. Only ten Control and PD subjects recorded data that was used in this experiment. None of the participants reported any vestibular or auditory disorders. Table 1 provides a list of symptom severity for the PD subjects whose data was used in my analysis. All subjects were tested after a 12-hour withdrawal period of L-Dopa medication.

Patient Number	Age (yr)	Sex	Duration since Diagnosis (yr)	UPDRS Motor Score	Hoehn and Yahr Stage	Handedness
1	58	M	4	18	2	R
3	67	M	4	16	2	R
4	56	M	2.5	21	2	L
5	53	M	3	32	2.5	R
6	49	M	7.5	35	2	R
7	65	F	5	32	2	R
8	68	M	1.5	22	2	R
9	66	M	1	24	2	R
10	70	M	1	21	2	R
11	59	M	1.5	10	2	R

Table 1. Characteristics of PD Subjects. UPDRS is Unified Parkinson's Disease Rating Scale. There were originally twelve subjects but only data from ten subjects was used.

3.1.2 Ethics Statement

This study was conducted with approval from the University of British Columbia Clinical Research Ethics Board. All subjects gave written, informed consent prior to participation. Research was conducted according to the principles expressed in the Declaration of Helsinki.

3.1.3 Description of the Manual Tracking Task

Subjects were seated approximately 80 cm from a screen that displayed the reference target and the cursor they controlled. Connecting the reference target and the cursor was a black rod. Figure 3 contains a picture of what the subject would see on the screen. The reference target moved up in down according to a specified target trajectory which was composed by the summation of two sinusoids with frequencies of 0.06 and 0.1 Hz. Subjects were asked to keep the black rod between the target and the cursor straight by controlling the cursor with a joystick.

The tracking error, Δ, was defined as the difference in position between the target and the cursor. The experiment contained two modes in which Δ was scaled by a factor of α. In the 'Better' mode, α was set to 0.3 and in the worse mode, α was set to 2. Thus subjects appeared to perform better or worse depending on the mode of the experiment. My noise power method only utilized data obtained from subjects performing the task in the worse mode. The exaggeration of error in this mode increased sub movement activity, allowing for differences between trials with GVS and without GVS to be more apparent.

Throughout the duration of the experiment, subjects performed eight 90-second trails with a 30-second rest period between each trial. Trials 1, 2, 5 and 8 were conducted with the presence of GVS below sensory threshold while the trials 3, 4, 6 and 7 were conducted without GVS. Each trial was divided into three 30-second blocks that alternated between the better or worse modes. Figure 3 shows the pattern of trials.

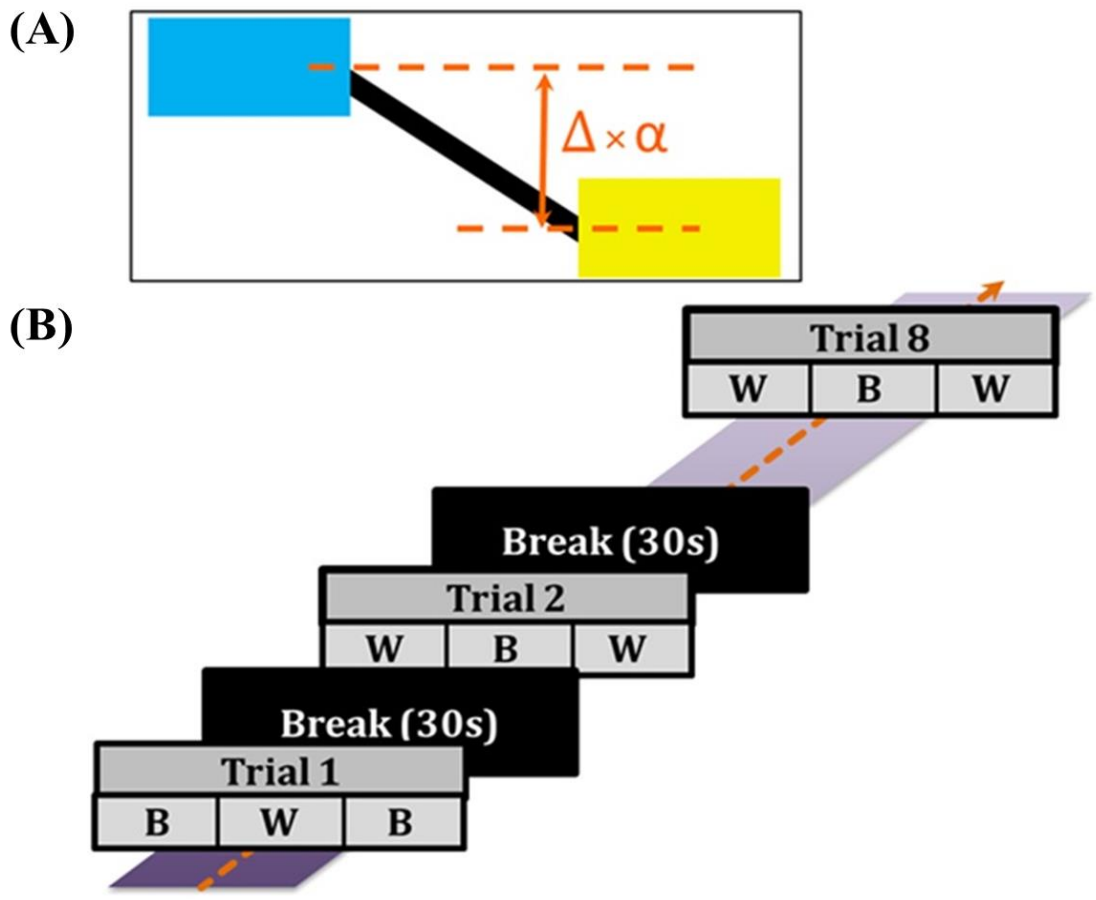

Fig. 3. Set up of the switching manual tracking task. (A) The main objective of the task was to keep the black rod connecting the blue target and the yellow cursor in a horizontal position. The tracking error, Δ, was scaled by $\alpha = 0.3$ for the 'Better' condition and $\alpha = 2$ for the 'Worse' condition. (B) Sequence of trials followed by rest. GVS was applied in four trials. Imagine from [7]

The normal control subjects performed the set of 8 trials once. PD subjects performed the set of 8 trials twice. The first set of trials was performed after a 12 hour overnight withdrawal period from L-Dopa. After the trial concluded, the PD subjects were given a single dose of fast acting L-Dopa. After the effects of this dose were felt by the subjects, they completed another set of the 8 trials.

3.1.4 Stimulus

GVS was applied through 17 cm^2 carbon rubber electrodes in a bilateral and bipolar fashion. An electrode was placed over the mastoid process behind each ear of the subject and coated with Tac gel (Pharmaceutical Innovations) to optimize adhesiveness and conductivity. The average impedance of the subjects was approximately 1 kΩ. The GVS signals were digitally generated on a computer using MATLAB. The digital signals were then converted to analog signals using a NI USB-6221 BNC (National Instruments) digital acquisition module. The analog signals were then subsequently passed to Model DS5 (Digitimer) constant current stimulator.

The GVS signals were zero-mean, linearly detrended, noisy currents with a 1/f-type power spectrum. The stimulus signals generated were between 0.1 and 10 Hz applied according to a Gaussian probability density function. Figure 2 contains an example of the GVS single in addition to the probability density function. GVS was applied at a level below sensory threshold so that subjects were not bothered by any sensation while conducting the manual tracking task.

Sensory threshold was determined by using a systematic procedure for determining the minimum level of current detectable by the subject. Subjects were given a test stimuli

of 20 μA for 20 seconds. If the subject did not detect the current after the initial 20 seconds, an additional 20 μA was applied for another 20-second duration. The process was repeated until the subject detected the current. After detection, the current was decreased by a 20 μA level until the subject no longer felt the stimulus. Then the current was increased again to confirm sensory threshold. A 30-second rest period occurred between each stimulus test in order to prevent effects due to hysteresis. GVS was applied at 90% of sensory threshold value during the manual tracking experiment.

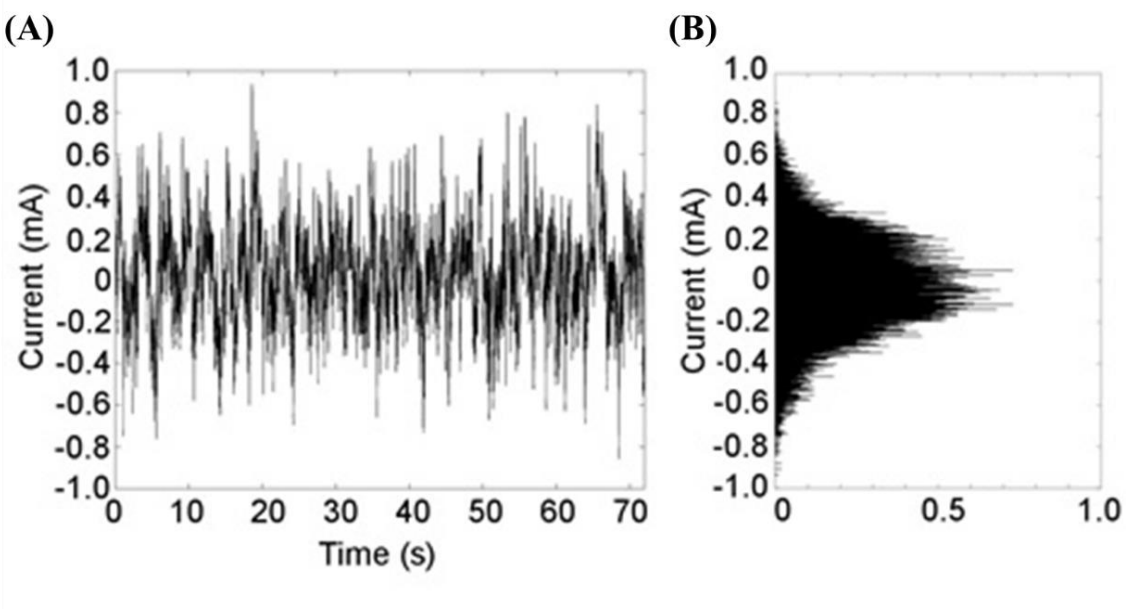

Fig. 4. Characteristics of the GVS signal. (A) An example of the GVS signal during a trial. This is the highest level current intensity used in the experiment. (B) The Gaussian probability density function of the GVS signal. Image from [7].

3.2 Preprocessing

Although my analysis requires the raw data to be intact, some preprocessing steps are necessary in order for Welch's method to be applied. The raw position data collected from the target and cursor display positions in the experiment were not collected at a uniform sampling rate. With the `interp1` function in MATLAB, I used linear interpolation with extrapolation to apply a uniform sampling rate of 55 Hz. The position data also contained a DC gain component which I removed using the `detrend` function.

The 30-second 'worse' mode sections were separated from the 90-second trial blocks. I created a pairing of GVS on and GVS off sections in order to facilitate a paired T-Test. This pairing is outlined in Table 2. In order to normalize signal power occurring from tracking the reference target, I added the target signal to the cursor display signal of the other section in the pair. This had the effect of eliminating any signal power differences that were due to tracking. Each section contained the signal power that resulted from tracking both inputs. The only difference between the two signals now occurs in the high frequency noise component. As a result, I was easily able to determine statistically significant differences in performance related to frequency and magnitude of sub movements.

	GVS On Trial	**GVS Off Trial**
Pair 1	Trial 1 Section 2	Trial 3 Section 2
Pair 2	Trial 2 Section 1	Trial 4 Section 1
Pair 3	Trial 2 Section 3	Trial 4 Section 3
Pair 4	Trial 5 Section 2	Trial 7 Section 2
Pair 5	Trial 8 Section 1	Trial 6 Section 1
Pair 6	Trial 8 Section 3	Trial 6 Section 3

Table 2. GVS On and GVS Off pairs.

3.3 Characteristics and Outliers

I screened for outliers on two different levels. The first screening for outliers was done by a visual inspection of the data plots from each trial. By using the `subplot` function in MATLAB, I was able to quickly scan all eight trials conducted by each subject in the three subject populations. One of the prominent visual issues I overserved was saturation. Due to hardware limitations, some subjects achieved saturation as they attempted to track the reference input. This occurs when the subject uses the joystick to move the cursor in a position beyond the position detection limits of the hardware. An example of saturation is seen in figure 5. In several instances, saturation occurs in periods of multiple seconds.

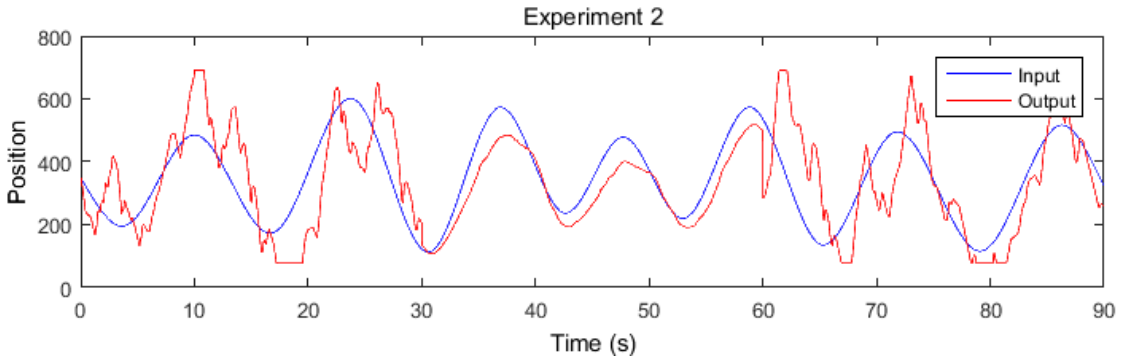

Fig. 5. Saturation occurs in multiple instances in this trial. Just before the 20 second mark and during the 80 second mark, saturation is held for several seconds. This degree of saturation renders this data unusable.

Saturation is an issue because it skews results by artificially creating high frequency content. Computing the DFT in a section with saturation would be similar to computing the DFT of a rectangular function. Data that contains large amounts of saturation was not utilized in my analysis. Unfortunately, the definition of what constitutes a large amount of

saturation is somewhat subjective. However, there was a clear distinction in the amount of saturation contained in data from Parkinson's subjects 2 and 12. Their data was not used in my analysis.

Visual screening also detected outliners in the form of significant deviation of the tracking objective by the subject. Figure 6 shows a trial that contains this type of outlier. This significant deviation could have possibly been the result of some external factor, which renders the data unusable. It also renders useless the normalization of the input trajectory that is necessary for pairing trials. I considered significant long periods of cursor movement in the opposite direction of the target to be significant deviation from the tracking objective.

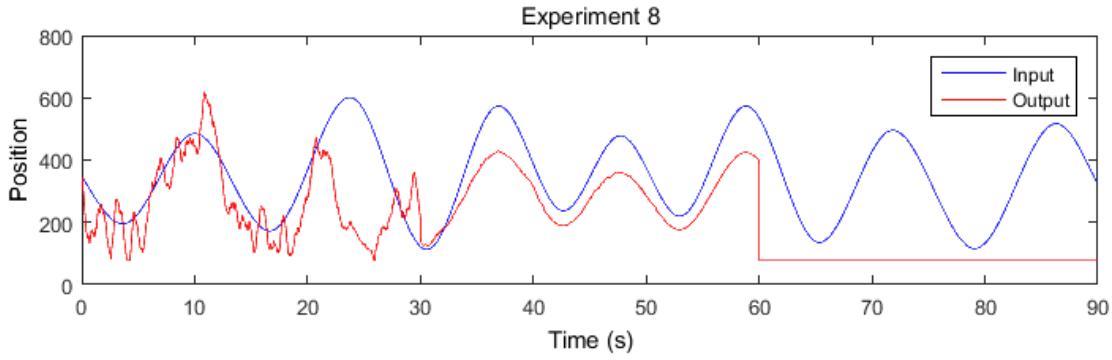

Fig. 6. The first 30-second block contains significant deviation from the tracking objective starting shortly after the 20-second mark. This deviation may have been due to external factors, which is likely given the relatively poor performance in the 'better' section from 30 to 60 seconds, and the lack of data in the second 'worse' block from 60 to 90 seconds.

The second level of screening for outliers occurred when I examined the numerical data obtained from my analysis. I examined the data to see if any of the paired GVS on and GVS off sections had values that differed by more than an order of magnitude. Any data points that met these criteria would have required additional visual scrutiny of the

manual tracking plots and the MATLAB code. Fortunately, I did not find any outliers as a result of this screening. Finally, statistical outliers in the data were noted but not removed.

3.4 Results

The results of my analysis are indicated in Table 3. The GVS was significantly ($p < 0.05$) associated with reductions in high frequency noise in the both the combined PD subject group and the PD subject group that performed the experiment after receiving a dose of fast acting L-dopa. While GVS was associated with reductions in high frequency noise in both the Parkinson's before L-dopa population and the control population, the results were not statistically significant. Finally, GVS was associated with an increase in standard deviation among all populations when it was applied. Only the PD group after L-dopa showed a reduction in standard deviation when GVS was on.

Total Signal Power					
		Normal	**Parkinsons**	**Parkinsons Before L-Dopa**	**Parkinsons After L-Dopa**
GVS ON	AVG	42521.5703	48506.86435	49731.0142	47192.0368
	SD	35067.0070	37738.22179	39831.1046	35679.7902
GVS OFF	AVG	44262.8828	52319.01327	52969.1211	51620.7493
	SD	32432.5225	35950.91901	36171.6414	36038.5210
	T Test	0.3466	0.02235	0.2132	0.0333

Table 3. The results of my analysis indicate $p < 0.05$ (highlighted values), which for the combined PD population and the PD population on fast acting L-Dopa when tested against the GVS condition. Units for the results are square of the position units utilized during the experiment.

3.5 Discussion

The results indicate the presence of GVS has a beneficial effect on a subject's manual tracking task performance. The boxplot in figure 7 displays the distribution of the difference between noise power between the GVS off and GVS on paired trials. A positive difference would indicate a larger noise power value in the in the GVS off trial. Two key differences between the GVS off and GVS on populations are the difference in skew and the number of outliers. The GVS on population has a more positive skew as indicated by the value of the 75th percentile boundary. The positive skew indicates GVS had a beneficial impact on sub movement reduction as there are more positive values in the distribution.

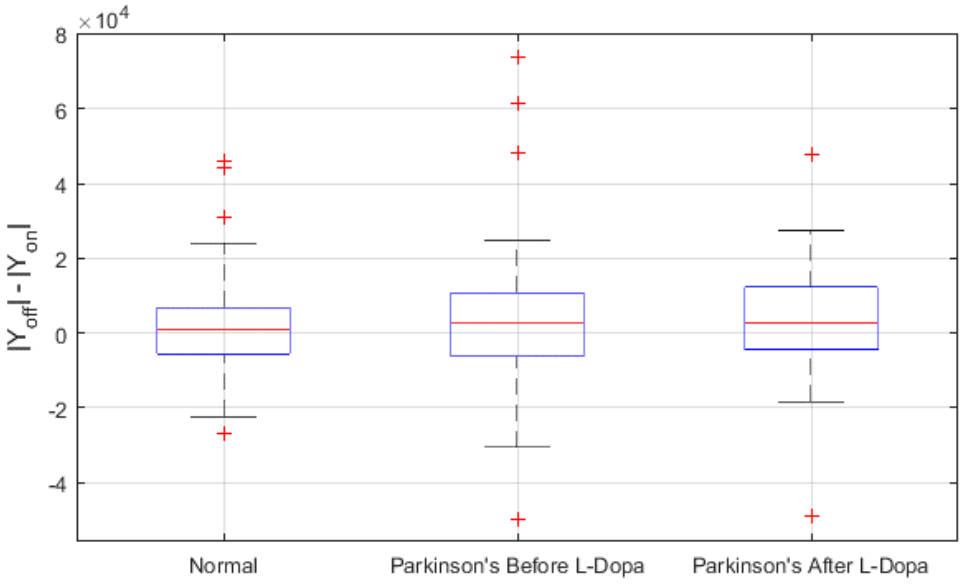

Fig. 7. The box plots of the three populations. The red line indicates the median of the population. The upper and lower edges of the box represent the boundaries of the 75th and 25th quartiles respectively. The whiskers indicate the range of values not considered outliers. The red crosses are outliers, which are data points outside of 2.7 standard deviations.

One suggestion for the beneficial effect of GVS involves a concept known as stochastic facilitation. Previous studies indicated additive stochastic biological noise had a wide range of benefits in the non-linear nervous system. Several studies detected an increase in signal to noise ratio in EEG readings, while another study identified improved sensorimotor performance in patients with chronic stroke. Stochastic facilitation in relation to manual tracking tasks most likely relates to modulation of brain rhythms in the basal ganglia. The difference in performance between a trial with GVS off and GVS on, as displayed in figure 8, may be indicative of this modulation as it relates to reduction of sub-movements.

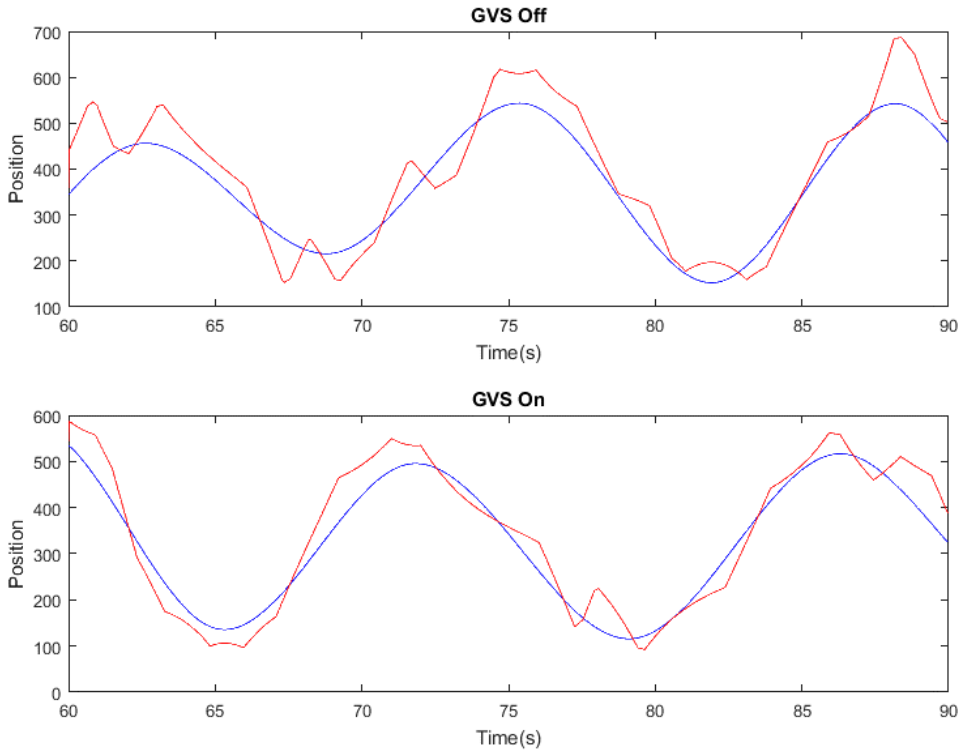

Fig. 8. Two paired trails form the after L-dopa population. The decreased frequency and magnitude of sub-movements in the GVS on trial could be indicative of stochastic facilitation. Not all paired trials contained easily recognizable sub-movement reduction.

While statistical significance was only detected in both the combined group of PD patients and the group of PD patients on L-dopa medication, the trend of GVS reducing high frequency sub-movements is present throughout all groups. Additional data may be able to determine with statistical significance if GVS improves performance in the control group and in the group of PD patients after L-dopa withdrawal. However, the increased standard deviation associated with GVS in concerning. Because the only group that experienced a reduction in standard deviation were the PD patients on L-dopa, the inference is that medication is required in order for all PD patients to benefit from GVS. Otherwise some PD patients benefit while others do not. Additional scrutiny of the data is needed to determine if any of the subject demographics of the PD patients are correlated to better performance when they are off medication and under stimulation by GVS.

Chapter 4

Evaluating Other Data Sets

4.1 Time and Frequency Localized Approaches

All approaches to system identification and performance evaluation of manual tracking tasks so far discussed have not included approaches localized to both time and frequency. While frequency based techniques provide a solid foundation in providing performance metrics for manual pursuit tracking tasks, they can only be applied to linear deterministic or stationary stochastic signals. The presence of nonlinearities in a signal necessitates the use of additional techniques that are localized in both the time and frequency domains.

4.1.1 Wavelets

A wavelet-based approach has been used in multiple studies related to analysis of EEG signals in PD patients. Wavelets are well suited to the study of biological rhythms due to their multiresolution analysis capabilities [17][18][19]. In general, biological signals are often nonlinear and nonstationary in nature. In my analysis of sub movements in manual tracking tasks, I made the assumption that sub movements over a short term period were equivalent to stationary noise. Relaxing this assumption would require an analysis that was localized in both the frequency and time domains.

One of the manual tracking sets I was working on contained a chirp signal that was corrupted by noise. Subjects were asked to pursue the chirp signal while disregarding the

noise corruption. Because I was unable to use standard frequency domain based techniques due to the nonlinear chirp target signal, I instead utilized the Short Time Fourier Transform (STFT) to perform the analysis. However, the main drawback with using the STFT is the sacrifice between time resolution and frequency resolution. The wavelet transform dos not have the same limitations. Both continuous and discrete versions of the wavelet transform can be performed in MATLAB using the `cwt` and `dwt` functions respectively. Selecting the right wavelet and parameters for the intended application is essential to performing a quality analysis.

4.1.2 Fractional Fourier Transform

The Fractional Fourier Transform (FrFT) has recently seen an increase in use for digital signal and imaging applications. However, my review of the literature has found little use in biomedical applications. There are a few papers highlighting its use in medical imaging applications in ultrasound and x-ray [20][21]. The main benefit of the FrFT is that it transforms signals into a domain that is between time and frequency. Linear chirps in signals are easily identified in this domain which would be very useful in the manual tracking data set I was working on that future a linear chirp. A linear chirp is transformed in to a delta function in the Fractional Fourier domain, much like a sinusoid would be in the frequency domain [21].

To study a PD patient's ability to track a signal consisting of a linear chirp corrupted by noise, as indicated in figure 7, FrFT could be utilized to compare the delta functions for both the input and the output. The resulting comparison could provide a measure for how well the subject rejected the noise and tracked the underlying target input.

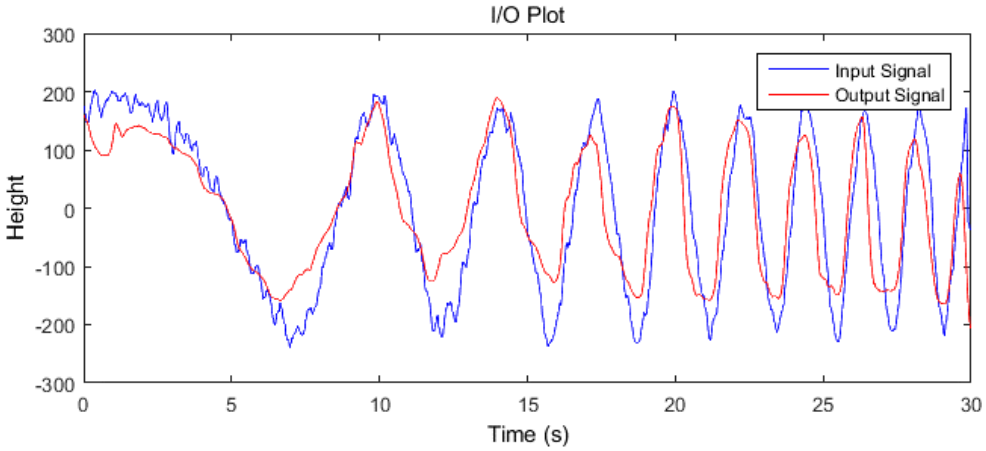

Fig. 9. Application of the fractional Fourier transform could provide quantifiable assessment of performance for tasks involving chirp signals such as this one.

Chapter 5

Conclusion

5.1 Summary

Throughout this thesis, I have discussed the importance of using manual tracking tasks to develop new treatments for the visuomotor symptoms associated with PD. Although these manual tracking tasks are performed in a lab environment, in many ways these tasks are proxies for the everyday tasks they perform in outside environment. Promising new non-invasive treatments such as GVS may be able to improve the quality of life for sufferers of PD. Researchers invest a tremendous amount of effort into understanding the effect GVS has on PD patients performing these manual tracking tasks. While there are a breadth of other methods for assessing performance, frequency domain based analysis can provide a quick and reliable metric for determining how well an individual performed the task. This is based on the premise that less power in frequencies higher than the input is reflective of fewer and weaker sub-movements and better tracking performance. Determining improved performance is vital to proving the efficacy of treatments such as GVS.

5.2 Directions for Future Work

The assumption that sub-movement generation is stationary over the length of the trial for every patient is necessary to make in order to apply my method. It is also an assumption that may not hold for longer trials. In reality, every individual, PD or otherwise, fatigues at different rates, varying attention spans and varying physiologies. Humans and the biological signals they generate are inherently nonlinear. To provide assessment for a more robust set of tracking tasks under more robust conditions, methods which are localized in both the frequency and time domains must be explored. Applications of the wavelet and fractional Fourier transforms can bridge the nonlinearity gap and provide quantifiable assessments of performance.

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