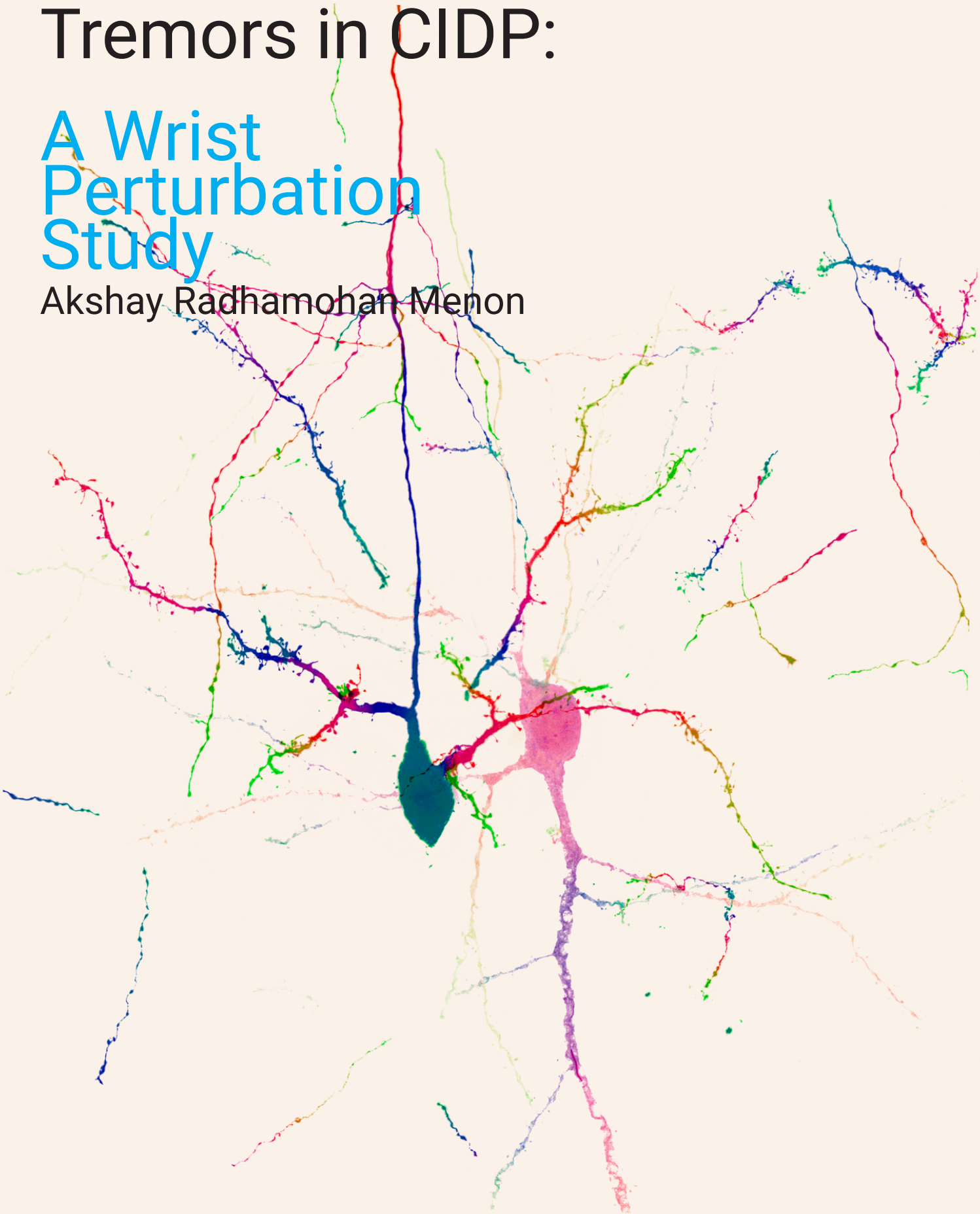
Tremors in CIDP:

A Wrist Perturbation Study

Akshay Radhamohan Menon



Technische Universiteit Delft

TU Delft

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A Wrist Perturbation Study

by

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Dr. L.F. van Rootselaar

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Preface

It has almost been three years of master study at TU Delft. It has been quite a journey. It feels good now. I would like to thank a few who have travelled this bumpy ride of a journey with me.

I would like to extend my sincere gratitude towards my supervisors Alfred Schouten and Winfred Mugge for their enthusiastic guidance and constructive criticism throughout the thesis. I have been through incredibly tough times during my thesis, and I almost feel my supervisors became my second parents. Thank you for helping me find my way.

I extend my gratitude to Fleur van Rootselaar for allowing me to work on this neurophysiology project. Indeed a wonderful experience. I also wish to thank Gabrielle Pallada for getting me started with the experiment protocol, accompanying on every stage of the clinical measurements. Learned a lot!

I had great pleasure of getting to know a few good souls, my friends Siri, Armin, Achinth, Ganesh, the guys at Schiedam, Nina, and my friends in India, to name a few, Vatsan, Chithu, Naresh, and Sanaa. I thank you for your friendship. Thank you Nidhi, you're the special mention. Forever grateful.

Completion of this thesis would not have been possible without the prayers and relentless support of my parents, Anuradha and Radhamohan, and my grandparents, Ammamma, and Surupapa. The past two years have been the toughest for us all, but we faced it together. I guess, it is part and parcel of life. I look forward to the next chapter in our family. Onwards and upwards. God bless everyone.

Akshay Radhamohan Menon
Delft, June 2022

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Tremors in CIDP: A Wrist Perturbation Study

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***Abstract*—Chronic inflammatory demyelinating polyneuropathy (CIDP) is characterized by sensory and motor deficits. Tremor is a frequent and severe symptom in patients suffering from CIDP. There is limited and contradictory data regarding the effect of tremor on treatment of the underlying polyneuropathy, and on treatment specifically aimed at neuropathic tremor. The pathophysiology of the CIDP tremor is unknown, but there are speculations about both a peripheral and central origin. From previous studies, it is seen that if a tremor's frequency is substantially load-independent, entrained exclusively by comparable driving frequencies, and only minimally phase-reset by torque pulses, it is considered to be primarily of central origin. A wrist perturbation study using a wrist manipulator was conducted on CIDP patients, with tremors (n=8) and without tremors (control, n=8) to address these speculations, and to understand the characteristics of this neuropathic tremor. The perturbation study involved studying the effects of entrainment perturbations, spring loading via changing the virtual spring stiffness, ramp-and-hold stretches to evoke stretch reflexes, along with the estimation of admittance. The entrainment task showed subharmonic and superharmonic peaks of power spectral densities of EMG in tremor subjects. Compared to controls, the tremor patients had significantly reduced stiffness, which could be attributed by the loss of muscle strength, and thus the tremor advertently affects muscle activation. No significant difference in M1, and M2 amplitude responses, and reflex latencies were found between the tremor and control group.**

***Index Terms*—Peripheral Neuropathy, Tremors, Stretch Reflex**

I. Introduction

PERIPHERAL neuropathy is a disease of the peripheral nervous system characterized by numbness and paresthesia, as well as weakness and pain [1]. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is the most common inflammatory neuropathy, with a prevalence of 1-7 per 100.000 people [1]. Wasielewska [2] revealed a tremor prevalence of 60% in a patient group of 89 polyneuropathy patients. Neuropathic tremor is more common in demyelinating polyneuropathies than axonal [3], and studies by Cao et al. (2017) [4] have shown that tremors affect 80% of CIDP patients, compared to 35% of patients with other neuromuscular diseases in the control group. Thus, tremor is a common problem in polyneuropathy patients. However, the pathophysiology of the tremor is still unknown.

There are theories about central and peripheral origins of the tremor. Tremors associated with peripheral neuropathies are typically postural and kinetic in nature, with frequencies ranging from 3-6 Hz and amplitudes ranging from moderate to large[3] [5]. Pleading for a central origin, both ET and neuropathic tremor have a delayed second agonist burst and show increased bilateral cerebellar activity during the tremor and at rest [6]. Schwingenschuh [7] found low rates of eyeblink classical conditioning (EBCC) in patients with demyelinating polyneuropathy, supporting a theory of cerebellar dysfunction. Some findings support a peripheral origin of the tremor by indicating a dependency between the tremor and peripheral mechanisms. A link was discovered between prolonged ulnar and median F-wave frequency and tremor disability, lending credence to the role of a stretch reflex mechanism [5]. According to Findley [8], the frequency of reflex generated oscillations is dependent on the transmission delay in the segmental reflex arc, the activation delay, the rise time of reflex generated force, as well as the tuning effects that any external loading and muscle compliances provide. Bain et al. (1996) [9] proposed a peripheral mechanism in which delayed and distorted afferent input causes a cerebellar functional disturbance, resulting in a delayed second agonist burst, of which afferent information is again delayed and distorted, perpetuating the error. The neuropathic tremor could be the result of pre-existing peripheral neuropathy and the resulting distorted afferent information, or it could be the result of an additional malfunction of the cerebellum or related central pathways.

Mechanical oscillations, reflex oscillations, and central oscillations have all been proposed as possible explanations for the presence of tremors in various studies. Mechanical factors, in particular, play an important role in determining the frequency and amplitude of tremors. The perturbation of the tremorous body part to see if the tremor is altered in phase is a formal method for determining whether a tremor is influenced by sensory input [10]. Several previous studies have argued that mechanical perturbations should have a significant impact on a peripheral rhythm while remaining largely unchanged on a central rhythm. The tremor was found to be frequency-shifted towards the driving frequency, i.e., entrained by the imposed movement, but only if the two frequencies differed by less than 1 Hz or were harmonically related. For all other driving frequencies, the tremor rhythm remained unchanged and added to the external drive, such that the resultant limb movement exhibited characteristic 'beats'. These 'beats' were interpreted as evidence that the respective tremors or tremor components were generated by central oscillators and that these oscillators could be somewhat modified by proprioceptive feedback [11]. In a study conducted by Elble [12] on ET patients, frequency entrainment was produced only by forcings at frequencies within +l Hz of the tremor frequency and its second harmonic.

Physical objects have mechanical properties that obey the laws of physics, and a joint with its associated muscles can well be recognized as a simple model of a mechanical system consisting of a mass and a spring. The human limb possesses inertia (I) and stiffness (K) so that it acts as a passive

mass-spring system. Such a system oscillates with a natural frequency (ω), defined by the formula 1. The frequency of some tremors (or tremor components) is reduced by a weight load while it increases with a spring load, similar to the effects of such loads on resonant mechanical systems. As a result, it was concluded that such tremors are primarily of peripheral origin [13]–[15]. Other tremors that did not show such load dependence were interpreted as evidence for the involvement of primarily central mechanisms[11]. The load was either a spring that provided elastic resistance to movement or a mass that resisted movement due to its inertia.

$$\omega = \sqrt{(K/I)} \tag{1}$$

Kiers [16] obtained the H-reflexes, F wave mean and minimum latency, mean and maximum amplitude, duration, and persistence in 241 nerves from 78 patients with Guillain-Barre syndrome (GBS) and 162 nerves from 43 patients with chronic inflammatory demyelinating polyneuropathy (CIDP). F wave abnormalities were found in 92% and 95% of nerves from GBS and CIDP patients, respectively, and the most common abnormalities in both groups were the absence of F responses or prolongation of minimum and mean latency. Sabbahi [17] conducted a study to examine H-reflex parameters among the pathophysiologic conditions of essential tremor (ET), Parkinson's disease (PD), combined essential tremor with Parkinson's disease (ETPD), and a control group, and hypothesized that PD patients had less inhibitory effects from the brainstem and cortical inhibition on the spinal output of motor neurons than the other groups, and deemed that the H-reflex approach to be useful in assessing inhibitory pathologies in individuals with Parkinson's disease and ETPD.

Disabling tremor is an under recognized symptom of demyelinating polyneuropathy. There is limited data regarding the effect of tremor on treatment of the underlying polyneuropathy, and on treatment specifically aimed at neuropathic tremor. The current paper aims to determine the pathophysiology of this neuropathic tremor, and its characteristics for development in therapeutic interventions. Literature [12], [13], [18]–[21] indicates that the response to mechanical disturbances distinguishes tremors of central versus peripheral origin. If a tremor's frequency is substantially load-independent, entrained exclusively by comparable driving frequencies, and only minimally phase-reset by torque pulses, it is considered to be primarily of central origin. The current paper contributes to understanding the neuropathic tremor with a wrist perturbation study conducted on 16 CIDP patients, with and without tremors. The wrist perturbation study involved three tasks: 1) Entrainment Task, 2) Loading Task, and 3) Stretch Reflex task. In Section II, we discuss the study population, methods, and the protocol of each tasks in detail. Section III shows the outcome measures of the experiment and results, and Section IV provides a comprehensive discussion on the results. Finally, we present the concluding remarks and future work in Section V.

II. Methods

Participants

Patients (n = 16) diagnosed with CIDP (Table I) were recruited in the Amsterdam Medical Center (AUMC), out of which 8 patients exhibited tremor/myoclonus. These patients were categorized as the 'Tremor' group, and the remaining patients (n = 8) were categorized as the 'Control' group. The tremor was assessed by a neurologist from EMG measurements during rest, posture, movement, and finger-to-nose manoeuvres as part of the tremor registration of the patients taken by Amsterdam Medical Center (AUMC) before the experiment. In the case of the tremor group, measurements were performed on the tremor-affected side or in the case of two tremor-affected arms, on the most affected one. Measurements of the controls were performed on the dominant arm. All subjects gave informed consent, and the medical ethics committee of the Amsterdam Medical Center (AUMC) approved the study.

TABLE I. Patient Information

Patient #	Gender	Age [yrs]	Selected Arm	Tremor Freq.[a] [Hz]	$T_{MVC, flex}$ [Nm]	$T_{MVC, ext}$ [Nm]
CIDP with Tremor/Myoclonus						
167	M	73	Right	3	9.3	7.8
186	F	52	Right	3	6.52	4.62
120	F	68	Right	4	5.68	4.98
177	F	73	Right	5	9.56	4.62
169	M	57	Left	6	3.39	2.58
128	M	54	Left	9	9.97	6.52
143	F	33	Right	10	5.5	3.9
131	M	53	Left	12	17.95	9.88
Mean (SD)		57.9 (13.4)			8.48 (4.48)	5.61 (2.34)
CIDP without Tremor/Myoclonus						
127	M	82	Right	3*	13.19	8.65
104	F	54	Right	3*	8.25	5.48
111	F	60	Right	4*	10.97	4.89
154	F	76	Right	5*	5.52	3.21
101	M	64	Right	8*	19.36	12.19
117	M	70	Right	9*	19.09	13.37
144	F	59	Right	10*	10.34	7.71
149	M	78	Left	12*	5.43	4.93
Mean (SD)		67.9 (10.1)			11.52 (5.44)	7.55 (3.66)

The tremor frequency of control subjects was assigned by matching with tremor subjects based on age and gender [a]

Experimental Setup

The experiment protocol was applied by a wrist manipulator (Wristalyzer, Moog Inc., Nieuw-Vennep, the Netherlands) to assess motor control of the wrist. Subjects sat in a chair holding the handle of the manipulator with their dominant hand. The lower arm was restrained in an arm support such that the axes of rotation of the wrist and the manipulator aligned (Figure 1). The manipulator applied force and position perturbations to the subject's wrist. Torque and angle were available for recording.

Signal Recording

All signals were recorded using a Refa amplifier (TMSi, Oldenzaal, The Netherlands). Signals from the robotic manipulator (recorded and commanded position and force) were recorded via optical isolation amplifiers (TMSi) to ensure participant safety. Surface EMG was recorded with Ag/AgCl surface electrodes placed over the flexor carpi radialis and extensor carpi radialis muscles using maximal voluntary contraction and palpation to identify muscles. A ground electrode was placed on the elbow joint of the ipsilateral hand. The EMG was recorded at a sampling frequency of 2048 Hz together with the force and position output of the wrist manipulator for synchronization purposes. Prior to the perturbations, the maximum voluntary contraction (MVC) of all subjects was measured from the dominant arm using a Hand-held wireless Dynamometer (MICROFET 2, Hoggan Scientific LLC, USA).

Signal Preprocessing

EMG signals were digitally filtered with a high-pass 3rd order Butterworth filter (20 Hz cut-off) to remove motion artefacts, rectified, and then digitally low pass filtered with a 3rd order Butterworth filter (80 Hz cut-off). The 'filtfilt' function in MATLAB that performs zero-phase digital filtering by processing the input data in both the forward and reverse directions was employed for all the filters used.

EMG Obligation

The EMG recordings taken during the experimental protocol were required to fulfil the obligation of possessing less power at 50 Hz and at its harmonics (100 Hz, and 150 Hz), compared to the power at the remaining frequencies up until 148 Hz. For a given trial, the spectral densities of raw EMG were determined using the 'pwelch' function in MATLAB. The sum of the spectral densities in the bandwidths 1-49, 51-99, and 101-149 Hz, multiplied with the frequency resolution, were the compared with that belonging to the bandwidths 49-51, 99-101, and 149-151 Hz. The EMG of a given trial fulfils the obligation if the former value was more than 80% of the latter. EMG recordings that failed to meet this requirement were excluded.

Experiment Protocol

A. Entrainment Task

Task Instruction: At the beginning of the task, subjects were instructed to bring the hand to the neutral position by means of visual position feedback (Figure 1b). Upon aligning, the visual feedback was removed, and subjects were instructed to relax and restrict any voluntary movement. Force perturbations were applied after a short random delay of a minimum of 2 seconds.

Perturbation Signal: Five perturbation signals were designed based on the tremor frequency F_T [Hz] determined for each subject (Table II. Each perturbation signal was a sinusoid of a specific frequency [Hz] and amplitude [Nm] as shown in Table 2. The designed frequencies included frequencies that range from 2 Hz below and above the tremor frequency F_T [Hz] and also its 1:2 Harmonic. In order to eliminate phase effects, the sinusoid signal was designed to slowly ramp up to the final amplitude from '0.15' [Nm] in 2 seconds from start. Based on the wrist-entrainment study done by Elble [12], the sinusoidal forcings at each frequency were applied such that the peak-to-peak amplitude of wrist position, produced by the forcing, was in the range of 7° to 12°. The total duration of the signal was 20 seconds.

Execution: In a single experimental session, a total of 10 sinusoidal forcings were systematically delivered to the wrist with two trials for each designed frequency. The amplitude of forcing ranged from 0.15 to 2 Nm. A training trial was conducted for each subject with a randomly selected design frequency prior to the actual measurement. For the control group, the entrainment protocol was executed with a control frequency F_T [Hz] by matching that of comparatively similar tremor subjects based on age and gender. The power spectral density of the EMG of the Extensor and Flexor, and of the measured position and torque was determined using the 'pwelch' function in MATLAB. The parameters used in the 'pwelch' function were: Hann-window, segment length of 4 seconds and 50% overlap. The spectral densities were averaged over the two trials.

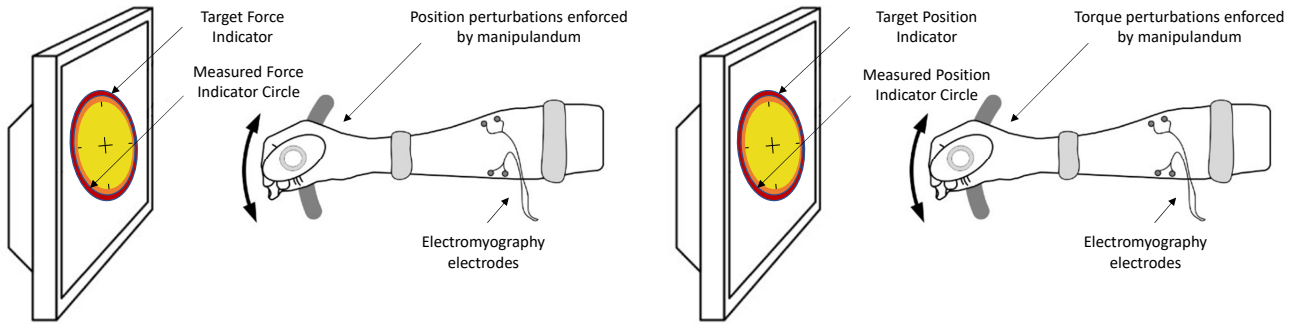
TABLE II. Entrainment Task Information: Frequency and amplitude of perturbation signal used. The amplitude of sinusoidal torque perturbation corresponding to the applied frequency for each subject is provided [a].

Patient #	Tremor Freq. (F_T) [Hz]	F_{T-2} [Hz]	F_{T-1} [Hz]	F_{T+1} [Hz]	F_{T+2} [Hz]	(1:2)F_T [Hz]	Perturbation Amplitude[a] [Nm]
CIDP with Tremor/Myoclonus							
167	3	1*	2*	4	5	6	{n.a., n.a., 0.35, 0.55, 0.75}
186	3	1	2	4	5	6	{0.25, 0.15, 0.35, 0.55, 0.75}
120	4	2	3	5	6	8	{0.15, 0.15, 0.55, 0.75, 1.2}
177	5	3	4	6	7	10	{0.15, 0.15, 0.75, 1, 1.6}
169	6	4	5	7	8	12	{0.35, 0.55, 1, 1.2, 1.6}
128	9	7	8	10	11	4.5	{ 1, 1.2, 1.6, 1.6, 0.35}
143	10	8	9	11	12	5	{ 1.2, 1.3, 1.6, 1.6, 0.55}
131	12	10	11	13	14	6	{ 1.6, 1.6, 1.6, 1.6, 0.75}
Mean (SD)		5 (3.37)	6 (3.37)	7.5 (3.42)	8.5 (3.42)	7.19 (2.62)	
CIDP without Tremor/Myoclonus							
104	3[a]	1	2	4	5	6	{0.25, 0.25, 0.35, 0.55, 0.75
127	3[a]	1	2	4	5	6	{0.25, 0.25, 0.35, 0.55, 0.75
111	4[a]	2	3	5	6	8	{0.15, 0.15, 0.55, 0.75, 1.2
154	5[a]	3	4	6	7	10	{0.15, 0.35, 0.75, 1, 1.6}
101	8[a]	6	7	9	10	4	{0.75, 1, 1.3, 1.6, 0.35}
117	9[a]	7	8	10	11	4.5	{ 1, 1.2, 1.6, 1.6, 0.35}
144	10[a]	8	9	11	12	5	{ 1.2, 1.3, 1.6, 1.6, 0.55}
149	12[a]	10	11	13	14	6	{ 1.6, 1.6, 1.6, 1.6, 0.75}
Mean (SD)		4.75 (3.45)	5.75 (3.45)	7.75 (3.45)	8.75 (3.45)	6.19 (1.96)	

* Subject 167 was not measured at those frequencies

B. Loading Task

Task Instruction: The task instruction was to bring the hand to the neutral position, maintain the position, and restrict any perturbations applied on the wrist. Position feedback was provided for the task (Figure 1a).



(a) (b)

Fig. 1. The subject was seated upright, with the forearm fixed, enabling unrestricted wrist movement. Since the handle's axis of rotation was aligned with the wrist flexion/extension axis, the actuated handle will induce wrist rotations on the subject. A monitor provided feedback on the measured and desired position/force. The neutral position was defined as the position of the neutral axis of the wrist. The fixed red circle was proportionate in radius with the target angle/torque, and the yellow circle was proportionate in radius with the measured angle/torque at the handle. The radius of the yellow circle matching that of the red circle represented 100% of the desired position/force. The width of the red circle represented the ranging from 95% to 105% of the desired angle/torque and was instructed to all the subjects as the target zone for the tasks. (a) Force Task: Force Feedback on External Monitor (b) Position Task: Position Feedback on External Monitor. (figures inspired from Mugge et al. (2012) [22]

Perturbation Signal: A single multi-sine perturbation signal was designed in the frequency domain to have rectangular spectra containing dominant power from 0.1 to 1 Hz. Power was applied to two adjacent frequency points, to enable frequency averaging to reduce estimator variance ([23]). This multi-sine perturbation of 32s was supplemented with a reduced level of power up to 40 Hz, according to the Reduced Power Method [24]. The reduced power level was kept at 2% of the dominant power to ensure a good signal-to-noise ratio for the position task.

Execution: In a single experimental session, the designed perturbation signal was applied to each subject in three different conditions: (1) No load, (2) Spring load of stiffness 0.6 Nm/rad, and (3) Spring load of stiffness 1.2 Nm/rad. Two trials were conducted for each condition. Conditions 2 and 3 were established by setting up a virtual spring in the wrist manipulator which provided a bias torque of 0.21 Nm and 0.42 Nm respectively. A training trial was conducted for each subject for each condition to determine the suitable gain for the perturbation signal. The cross-spectral densities between the measured position and disturbance forcing were averaged over the two trials for each condition, and frequency-averaged over the two adjacent frequency points to determine the frequency response function of mechanical admittance, and coherence.

Non-parametric system identification: A mechanical system can be properly described by its admittance which shows the dynamic behaviour (output movement) in response to a force perturbation input. The admittance was estimated in the frequency domain, using a closed-loop frequency domain identification procedure [25], according to:

$$\hat{\mathbf{H}}_{\mathrm{T}\theta}(f) = \frac{\hat{\mathbf{S}}_{\mathrm{D}\theta}(f)}{\hat{\mathbf{S}}_{\mathrm{DT_c}}(f))} \tag{2}$$

in which $\hat{S}_{D\theta}(f)$ denotes the cross-spectral density of external torque perturbation D(f) and measured wrist angle(f), and $\hat{S}_{DT_c}(f)$ denotes the cross-spectral density of external torque perturbation D(f) and measured wrist torque Tc(f). $\hat{H}_{\mathrm{T}\theta}(f)$ is an estimate of the arm dynamics $H_{\mathrm{T}\theta}(f)$, whereas $\hat{\Gamma}^2_{\mathrm{D}\theta}(f)$ is a measure for the signal to noise ratio. The squared coherence function $\hat{\Gamma}^2_{\mathrm{D}\theta}(f)$ ranges from zero for systems with no linear relation to one for a linear system without noise.

$$\hat{\mathbf{\Gamma}}^2_{\mathrm{D}\theta}(f) = \frac{|\hat{\mathbf{S}}_{\mathrm{D}\theta}(f)|^2}{\hat{\mathbf{S}}_{\mathrm{DD}}(f).\hat{\mathbf{S}}_{\theta\theta}(f))} \tag{3}$$

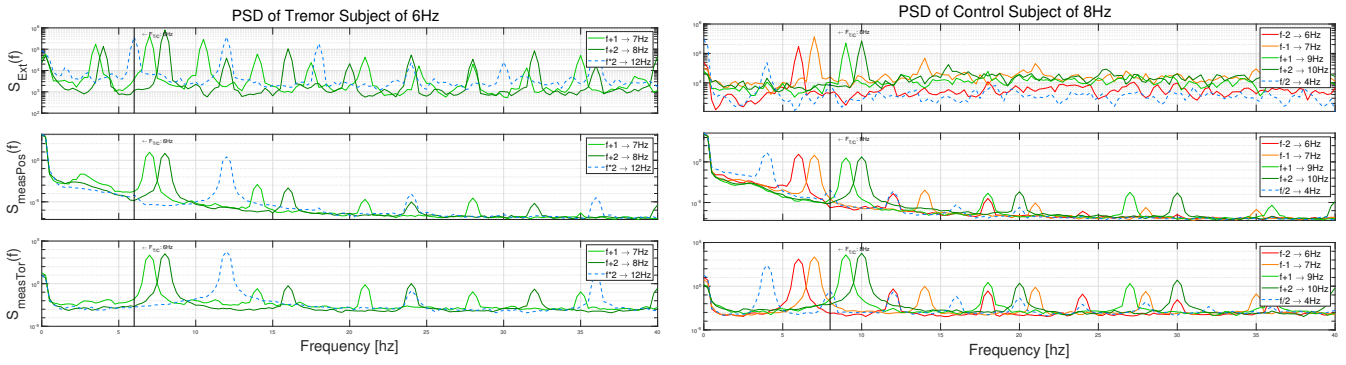
Statistics: The statistical analysis was done with a One-way analysis-of-variance (ANOVA), performed on the magnitude of the FRF at each perturbation frequency point in the bandwidth [0.1-2]Hz, for each loading task across study groups, followed by an unpaired t-test to compare admittance between the study groups. A significance level of 0.05 was used.

C. Reflex Task

Task Instruction: The task instruction was to maintain a force, a task best performed by giving way to the position perturbation. With the wrist in the neutral position, the subject was instructed to maintain a constant contraction at 20% of the 6 Nm (the torque limit of the wrist manipulator) in the flexion direction, while ramp-and-hold perturbations were applied at random intervals.

Perturbation Signal: Four series of nine ramp-and-hold stretch perturbation signals were designed to stretch the flexor muscles. The perturbations were randomly separated in time, however with a minimum of 2 seconds to allow subjects to re-attain the desired background contraction. All the ramp-and-hold perturbation signals were designed with the same parameters: Ramp velocity 2.0 rad/s, Ramp amplitude 0.08 rad (in the extension direction) and hold of 0.75s. After each ramp-up and hold, a smooth return ramp-down to the neutral position was applied. The total duration of the signal was 30 seconds.

Execution: In a single experimental session, the subjects were instructed to attain the desired torque level, and once attained, the 30-seconds-trial commenced. The recordings



(a) (b)

Fig. 2. The Power Spectral Density plots of Extensor EMG of a subject is plotted along with that of measured position and torque in a linear frequency x-axis. The black line represents the tremor frequency/assigned frequency of a tremor/control subject. The red and orange lines represent 2 and 1 Hz below the tremor frequency F_T respectively, the dark and light green represent 2 and 1 Hz above the tremor frequency F_T respectively, and the blue dotted line represents the 2:1 Harmonic of the Tremor Frequency F_T. (a) PSD plot of the 6 Hz Tremor Subject (b) PSD plot of the 8 Hz Control Subject

(EMG, angle and torque) were segmented into parts starting 100 ms prior to and ending 150 ms after the onset of a stretch perturbation. The cross-correlation function in MATLAB was used on the measured position to align the segments relative to the first segment to obtain a precise average. Segments whose mean value of measured torque prior to perturbation (100 ms prior to onset) was below 60% of desired torque were excluded. The accepted rectified segments were averaged over the total number of repetitions to obtain the average. The averaged EMG signal was normalized by its mean background EMG (of the 60 ms prior to the onset of the perturbation, background EMG) using Formula 4.

$$\mathbf{EMG}_{\text{norm}} = \mathbf{EMG}/mean(\mathbf{EMG}_{\text{background}}) \qquad (4)$$

Effectively, the EMG values smaller than 1 indicate depression and values greater than 1 indicate facilitation with respect to the background EMG. The short-latency M1 response was determined as the area-under-the (EMG) curve (AUC) between 20 and 55 ms and the long latency M2 response was determined as the AUC between 55 and 100 ms. Onsets of M1 and M2 were identified as the time when the EMG passed over thrice the standard deviation of the background EMG of the average EMG signal.

Statistics: Unpaired t-tests were used to assess differences in response amplitudes A_{M1} and A_{M2}, and the reflex latencies between the tremor and control group. A significance level of 0.05 was used.

III. Results

A. Entrainment Task

The EMG recordings of subjects 144, 149, 128, 117, 154, and 111 did not fulfil the EMG obligation mentioned in Section II, hence, the entrainment task results for these subjects are not available. The results for the entrainment task comprise power spectral density plots of EMG, along with that of measured position and measured torque. These plots are available for 7 tremor and 3 control subjects. From these plots, we observe peaks, which correspond to those frequencies where the power spectral density is larger than the mean of the power spectral density over the entire frequency range (in this case, up until 40 Hz). The presence of peaks in the EMG power spectrum that do not reflect that of the measured position and torque could indicate reflexive activity due to the entraining force perturbation, and thereby we address these peaks as 'additional peaks'. The presence of additional peaks in the spectral densities of the EMG was observed in two tremor subjects of 6 Hz and 10 Hz and was not visible in other subjects.

For the 6 Hz tremor patient (Figure 2a), the (2:1)F_T harmonic perturbation of 12 Hz shows additional peaks at the tremor frequency and its harmonics (6 Hz, and 18 Hz, 30 Hz, etc.) in the spectral plot of Extensor-EMG. These additional peaks are not reflected in the spectral density plots of measured position and torque. Similarly, the 8 Hz perturbation shows additional peaks at its 2:1 harmonic, 4 Hz, and harmonic frequencies (12 Hz, 20 Hz, 28 Hz, and 36 Hz). These additional peaks are not observed in the corresponding frequency points of the measured position and torque spectral plots.

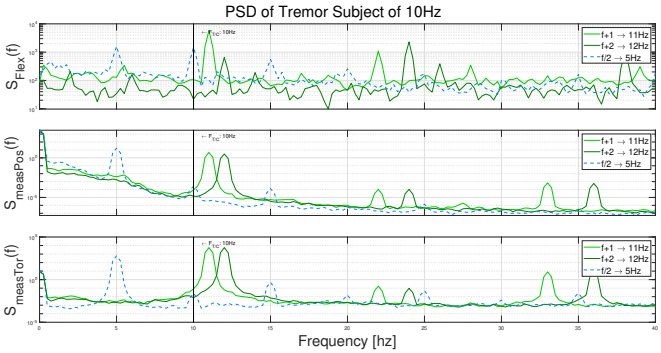
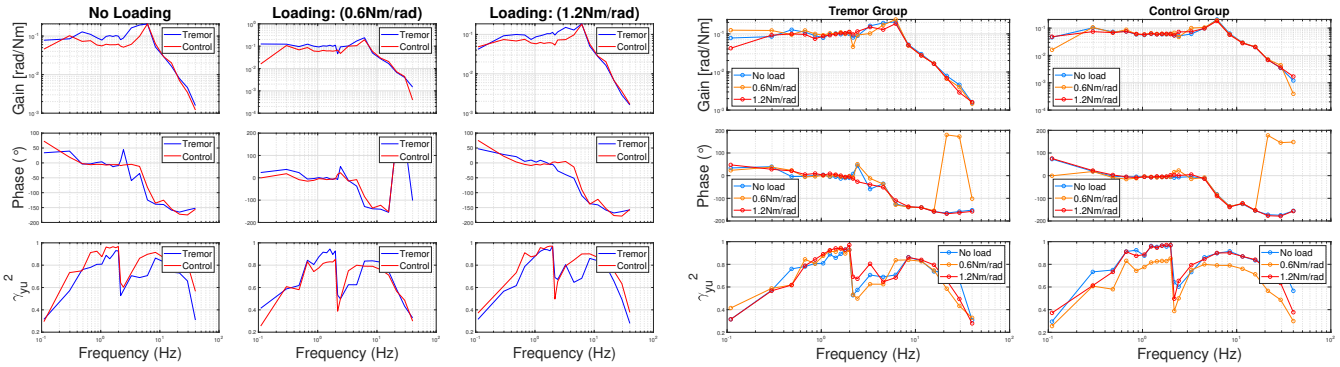


Fig. 3. Power Spectral Density plots of the 10 Hz Tremor subject, where a peak is observed at 26 Hz for the 12 Hz perturbation line in the Flexor-EMG Spectral. The Spectral plots of the Extensor - EMG were not available, as the EMG recordings failed to fulfil the obligation (Section II).



(a) (b)

Fig. 4. Admittance, and coherence were averaged across subjects of each study group. The gain and phase of the estimated FRFs, $\hat{S}_{D\theta}(f)$; and the squared coherence function, $\hat{\Gamma}^2_{D\theta}(f)$, are plotted. (a) Averaged Admittance and Coherence per loading conditions. (b)Averaged Admittance and Coherence per study group over the loading conditions.

For the same 6 Hz tremor patient (Figure 2a), the 7 Hz perturbation shows additional peaks at 3 Hz, 11 Hz, 17 Hz, 24 Hz, and 32 Hz in the spectral plot of Extensor-EMG, which is not reflected in the measured position and torque. The difference between the additional peaks and the perturbation frequency and its harmonics is 3 Hz, which is the 2^{nd} subharmonic of the tremor frequency, F_T, of 6 Hz. For the 10 Hz Tremor patient in Figure 3, the 12 Hz perturbation shows an additional peak at 26 Hz in the spectral plot of Flexor-EMG, 2 Hz after its 2^{nd} harmonic at 24 Hz. The 26 Hz peak is not reflected on the spectral plots of measured position and measured torque, and this 2 Hz difference is the difference between the tremor frequency F_T and the perturbation frequency.

B. Loading Task

The averaged admittance and coherence over subjects of the two groups, tremor and control, were plotted per condition (Figure 4a) and per group over conditions (Figure 4b). From both Figures 4a and 4b, no significant effects of varying stiffness is observed between the conditions. The average admittance across subjects of the tremor group is significantly higher than that of the control group ($p<0.05$) in the frequency bandwidth of [0.1-2] Hz, where the dominant power lies. Figure 5 shows the box plots of admittance in the [0.1-2] Hz bandwidth where the higher admittance level of the tremor group is observed.

C. Reflex Task

The EMG recordings of subjects 104, 111, 117, 128, 131, 144, 149, 167 did not fulfil the EMG obligation mentioned in Section II, hence the results for the reflex task for these subjects are not available. For other subjects, only the accepted EMG recordings have been processed, and the M1, M2 response and the M1 Onset time were determined. The reflex task results are available for 5 tremor and 3 control subjects. No significant effect of tremor condition was found for the M1 and M2 reflex responses and M1 reflex onsets (unpaired t-test, Table IV).

TABLE III. Results of Loading Task. Results are presented in means with standard deviations in parentheses. The mean is obtained from the absolute values of admittance in the bandwidth of [0.1-2] Hz across subjects of each study group.

Loading Results in the Frequency Bandwidth: [0.1 - 2] Hz	Tremor n=8	Control n=8	p_value
Condition 1: No loading			
Average Admittance [rad/Nm]	0.825 (0.17)	0.495 (0.13)	0.0016
Condition 2: Virtual Spring load (0.6 Nm/rad)			
Average Admittance [rad/Nm]	0.886 (0.15)	0.507 (0.12)	0.0012
Condition 3: Virtual Spring load (1.2 Nm/rad)			
Average Admittance [rad/Nm]	0.84 (0.1)	0.496 (0.07)	<0.001

Mean (S.D)

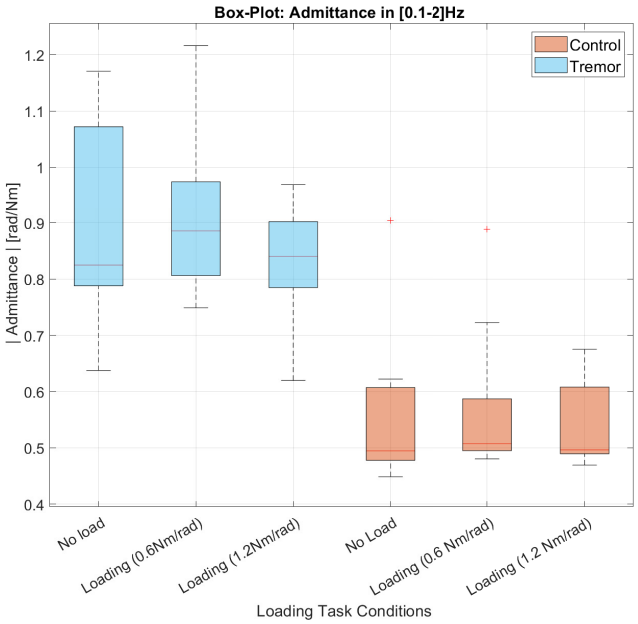


Fig. 5. Box plots of the absolute values of admittance in the bandwidth of [0.1-2] Hz across subjects of each study group, for each loading condition..

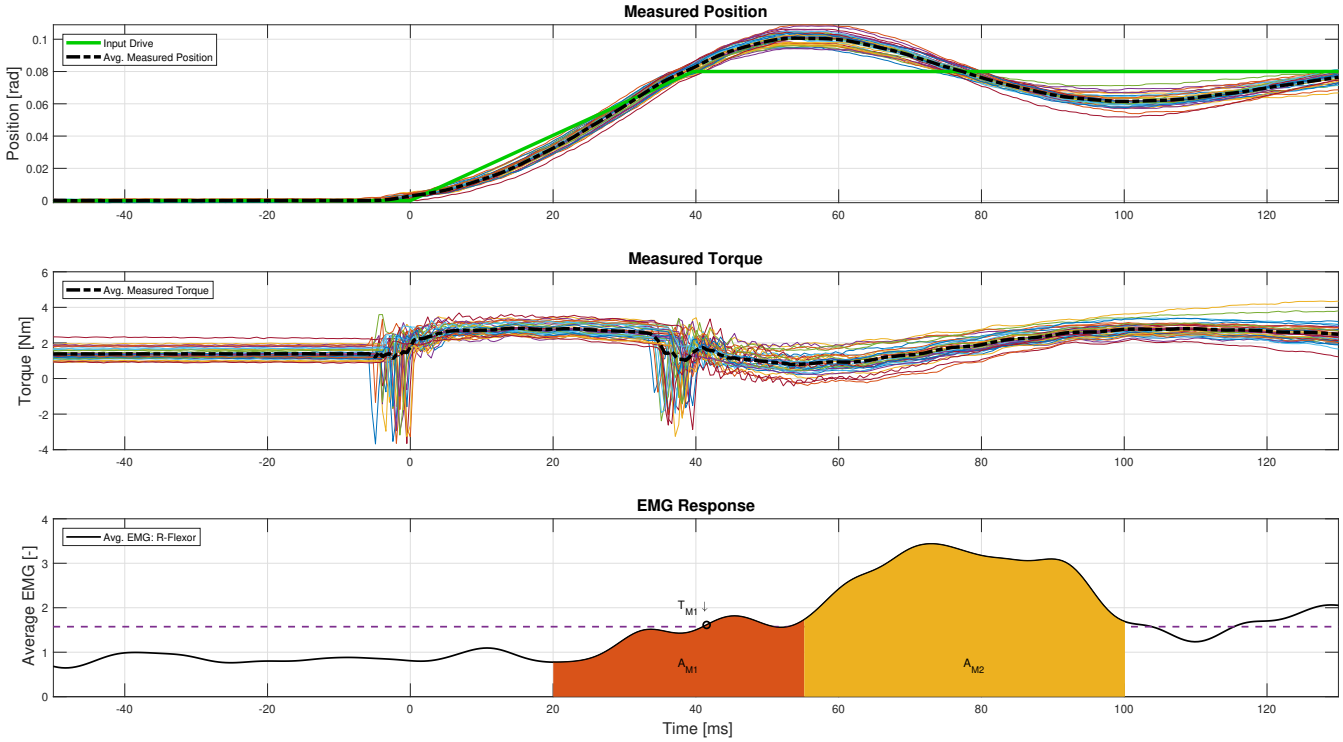


Fig. 6. Typical recording of a ramp-and-hold perturbation for a subject. Top: the measured position over each ramp, the green line indicating applied position perturbation, the dotted black line indicating averaged measured position over all the ramps; middle: measured torque, the black dotted line indicating measured torque over all the ramps ; bottom: flexor EMG, normalized to background EMG. Orange area designates the M1 time window (from 20 to 55 ms after perturbation onset) and the red area designates the M2 time window (from 55 to 100 ms after perturbation onset). T_{M1} indicates the onset time of the M1 response and A_{M1} and A_{M2} the magnitudes of the M1 and M2 response, respectively (mean amplitude of EMG)

TABLE IV. Results of Reflex Task. Results are presented in means with standard deviations in parentheses

Result	Tremor n=5	Control n=3	p_value
M1 Response Extension [-]	1.69 (0.93)	1.47 (0.21)	0.71
M2 Response Extension [-]	2.95 (1.95)	2.14 (0.61)	0.52
M1 Onset Extension [ms]	36.38 (16.88)	38.57 (4.14)	0.87
Mean (S.D)			

IV. Discussion

A. Entrainment Task

The additional peaks observed in the entrainment results (section III-A) could be reflex-induced EMG modulation, that seemed to occur only when the tremor amplitude spontaneously declined. The entrainment of motor unit activity by CIDP tremor is observed to prevent reflex-induced modulation of EMG by sinusoidal forcings that are in the range of 4 to 15 Hz. Reflecting on findings of previous studies on essential tremors [26], where the response of the stretch reflex to wrist oscillation was reduced in patients with essential tremors, entrainment effects on EMG modulation could enhance or inhibit stretch reflexes in CIDP patients associated with tremor. Due to the unavailability of enough EMG recordings, a precise conclusion on entertainment effects on CIDP tremor cannot be made.

The amplitude and frequency of CIDP tremors are shown to have a variable relationship; amplitudes associated with high-frequency tremors being lower or greater than those associated with low-frequency tremors. These dramatic fluctuations in tremor amplitude might be explained by resonance effects related with frequency entrainment [27]. At the same time, the tremor frequencies and joint mechanics exhibit a contrast that indicates subharmonic or superharmonic entrainment effects. These effects could result in a more symptomatic tremor. The 16 to 20 Hz motor-unit entrainment of orthostatic tremor producing an 8 Hz bodily oscillation is probably an example of such phenomena [28]–[30]. Just as the CIDP tremor and stretch reflex are capable of mutual entrainment, similar entrainment of other parts of the nervous system is possible such as a physiological central oscillator, the inferior olive being the most likely candidate [27], [29], [31].

B. Loading Task

Significantly higher average admittance of the tremor group in the [0.1-2] Hz bandwidth show that the tremor subjects exhibit lower stiffness than the control subjects. The active stiffness of muscles due to an external perturbation includes intrinsic and reflex components [32]. Thus, the restorative forces for the loading task are provided both by the intrinsic stiffness and reflexive activity. The decrease in stiffness, by the CIDP tremor, could be attributed by the loss of muscle strength, perhaps due to decreased number of active cross

bridges caused by the stretch reflex. We can conclude that tremor in CIDP advertently affects the activation of muscles.

C. Reflex Task

The reflex task, though insignificant, showed higher M1, M2 responses by the tremor group than the control group, along with a small reduction in onset. Heightened sensitivity would correspond with such higher-amplitude reflex response and shorter latency. However, this would be in contrast to the lower active stiffness of tremor group, as a study by Blackburn [33] suggest that greater stiffness enhance spinal stretch reflex sensitivity by improving mechanical coupling of the muscle spindle and the stretch stimulus. The loss in sample size of EMG recordings for reflex task analysis could have affected the results.

V. Conclusion

In this study, we conducted three experiment protocols to investigate the pathophysiology of the tremor associated with CIDP, and its characteristics. The EMG recordings that fulfiled the obligation varied, and hence hindered the significance of the results. The entrainment experiment showed sub-harmonic/super-harmonic peaks in the EMG power spectral density plots, that could indicate EMG modulation due to reflexive activity. The tremor subjects were characterized to have lower active stiffness than the control group, attributed by the loss in muscle strength. The reflex experiment results were not significant.

References

[1] R. Hanewinckel, M. Ikram, and P. Van Doorn, "Peripheral neuropathies," *Handbook of clinical neurology*, vol. 138, pp. 263–282, 2016.

[2] A. Wasielewska, M. Rudzińska, T. Tomaszewski, *et al.*, "Tremor in neuropathies of different origin," *Neurologia i neurochirurgia polska*, vol. 47, no. 6, pp. 525–533, 2013.

[3] M. C. Dalakas, H. Teräväinen, and W. K. Engel, "Tremor as a feature of chronic relapsing and dysgammaglobulinemic polyneuropathies: Incidence and management," *Archives of neurology*, vol. 41, no. 7, pp. 711–714, 1984.

[4] Y. Cao, P. Menon, F. Ching-Fen Chang, *et al.*, "Postural tremor and chronic inflammatory demyelinating polyneuropathy," *Muscle & nerve*, vol. 55, no. 3, pp. 338–343, 2017.

[5] T. A. Saifee, P. Schwingenschuh, M. M. Reilly, *et al.*, "Tremor in inflammatory neuropathies," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 84, no. 11, pp. 1282–1287, 2013.

[6] G. Deuschl, R. Wenzelburger, K. Löffler, J. Raethjen, and H. Stolze, "Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor," *Brain*, vol. 123, no. 8, pp. 1568–1580, 2000.

[7] P. Schwingenschuh, T. A. Saifee, P. Katschnig-Winter, *et al.*, "Cerebellar learning distinguishes inflammatory neuropathy with and without tremor," *Neurology*, vol. 80, no. 20, pp. 1867–1873, 2013.

[8] L. J. Findley and R. Capildeo, *Movement disorders: tremor*. Springer, 1984.

[9] P. Bain, T. Britton, I. Jenkins, *et al.*, "Tremor associated with benign igm paraproteinaemic neuropathy," *Brain*, vol. 119, no. 3, pp. 789–799, 1996.

[10] M. Hallett, "Overview of human tremor physiology," *Movement disorders*, vol. 13, no. S3, pp. 43–48, 1998.

[11] O. Bock and N. Wenderoth, "Dependence of peripheral tremor on mechanical perturbations: A modeling study," *Biological cybernetics*, vol. 80, no. 2, pp. 103–108, 1999.

[12] R. J. Elble, C. Higgins, and L. Hughes, "Phase resetting and frequency entrainment of essential tremor," *Experimental neurology*, vol. 116, no. 3, pp. 355–361, 1992.

[13] G. C. Joyce and P. M. H. Rack, "The effects of load and force on tremor at the normal human elbow joint," *The Journal of Physiology*, vol. 240, no. 2, pp. 375–396, 1974. DOI: 10.1113/jphysiol.1974.sp010615.

[14] R. J. Elble, "Physiologic and essential tremor," *Neurology*, vol. 36, no. 2, pp. 225–225, 1986.

[15] P. M. H. Rack and H. F. Ross, "The role of reflexes in the resting tremor of parkinsons disease," *Brain*, vol. 109, no. 1, pp. 115–141, 1986. DOI: 10.1093/brain/109.1.115.

[16] L. Kiers, P. Clouston, G. Zuniga, and D. Cros, "Quantitative studies of f responses in guillain-barre syndrome and chronic inflammatory demyelinating polyneuropathy," *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, vol. 93, no. 4, pp. 255–264, 1994.

[17] M. Sabbahi, B. Etnyre, I. Al-Jawayed, and J. Jankovic, "H-reflex recovery curves differentiate essential tremor, parkinson's disease, and the combination of essential tremor and parkinson's disease," *Journal of clinical neurophysiology*, vol. 19, no. 3, pp. 245–251, 2002.

[18] R. G. Lee and R. B. Stein, "Resetting of tremor by mechanical perturbations: A comparison of essential tremor and parkinsonian tremor," *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, vol. 10, no. 6, pp. 523–531, 1981.

[19] A. Gollhofer and W. Rapp, "Recovery of stretch reflex responses following mechanical stimulation," *European journal of applied physiology and occupational physiology*, vol. 66, no. 5, pp. 415–420, 1993.

[20] J. McAuley, J. Rothwell, and C. Marsden, "Frequency peaks of tremor, muscle vibration and electromyographic activity at 10 hz, 20 hz and 40 hz during human finger muscle contraction may reflect rhythmicities of central neural firing," *Experimental brain research*, vol. 114, no. 3, pp. 525–541, 1997.

[21] G. Joyce and P. M. Rack, "The effects of load and force on tremor at the normal human elbow joint," *The Journal of Physiology*, vol. 240, no. 2, pp. 375–396, 1974.

[22] W. Mugge, A. C. Schouten, G. J. Bast, J. Schuurmans, J. J. van Hilten, and F. C. van der Helm, "Stretch reflex responses in complex regional pain syndrome-

Bibliography

Use letters for the chapter numbers of the appendices.

related dystonia are not characterized by hyperreflexia," *Clinical neurophysiology*, vol. 123, no. 3, pp. 569–576, 2012.

[23] W. Mugge, D. A. Abbink, A. C. Schouten, J. P. Dewald, and F. C. Van Der Helm, "A rigorous model of reflex function indicates that position and force feedback are flexibly tuned to position and force tasks," *Experimental brain research*, vol. 200, no. 3, pp. 325–340, 2010.

[24] W. Mugge, D. A. Abbink, and F. C. van der Helm, "Reduced power method: How to evoke low-bandwidth behaviour while estimating full-bandwidth dynamics," in *2007 IEEE 10th International Conference on Rehabilitation Robotics*, IEEE, 2007, pp. 575–581.

[25] F. C. Van der Helm, A. C. Schouten, E. de Vlugt, and G. G. Brouwn, "Identification of intrinsic and reflexive components of human arm dynamics during postural control," *Journal of neuroscience methods*, vol. 119, no. 1, pp. 1–14, 2002.

[26] P. Matthews, "Muscle spindles and their motor control," *Physiological Reviews*, vol. 44, no. 2, pp. 219–288, 1964.

[27] R. J. Elble, "Central mechanisms of tremor," *Journal of clinical neurophysiology*, vol. 13, no. 2, pp. 133–144, 1996.

[28] J. J. Kelly and F. W. Sharbrough, "Emg in orthostatic termor," *Neurology*, vol. 37, no. 8, pp. 1434–1434, 1987.

[29] J. Colebatch, R. Frackowiak, D. Brooks, L. Findley, and C. Marsden, "Preliminary report: Activation of the cerebellum in essential tremor," *The Lancet*, vol. 336, no. 8722, pp. 1028–1030, 1990.

[30] P. Thompson, J. Rothwell, B. Day, *et al.*, "The physiology of orthostatic tremor," *Archives of neurology*, vol. 43, no. 6, pp. 584–587, 1986.

[31] R. J. Elble, "Inhibition of forearm emg by palatal myoclonus," *Movement Disorders: Official Journal of the Movement Disorder Society*, vol. 6, no. 4, pp. 324–329, 1991.

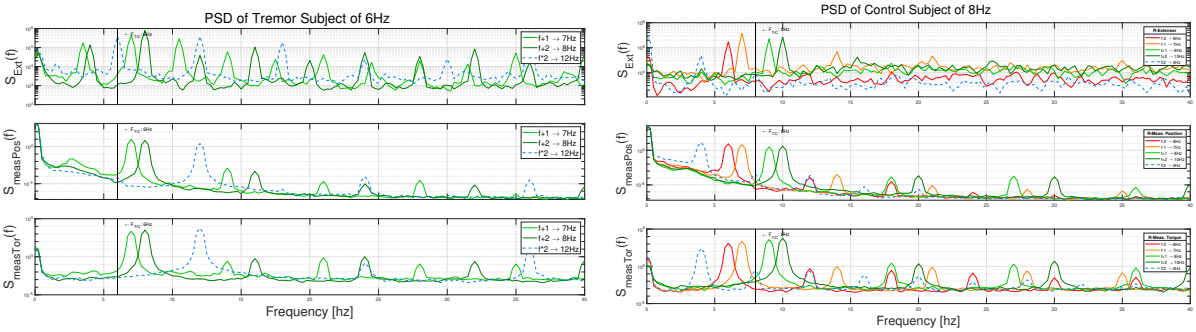
[32] T. Nichols and J. Houk, "Improvement in linearity and regulation of stiffness that results from actions of stretch reflex," *journal of Neurophysiology*, vol. 39, no. 1, pp. 119–142, 1976.

[33] J. T. Blackburn, D. A. Padua, and K. M. Guskiewicz, "Muscle stiffness and spinal stretch reflex sensitivity in the triceps surae," *Journal of athletic training*, vol. 43, no. 1, pp. 29–36, 2008.

2

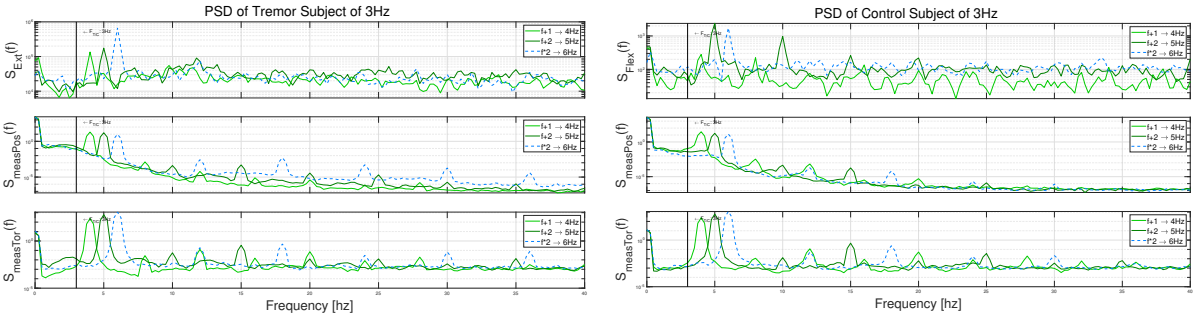
Appendix - A: Entrainment Task

Power Spectral Density Plots of the Study Population



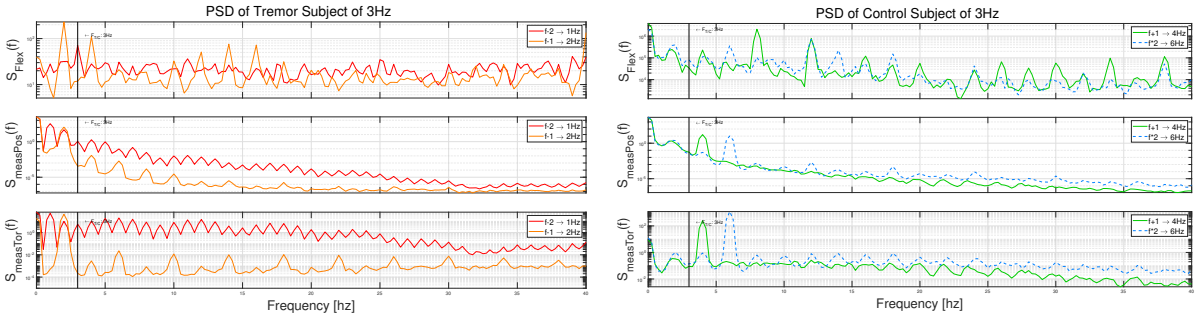
(a) (b)

Figure 2.1



(a) (b)

Figure 2.2



(a) (b)

Figure 2.3

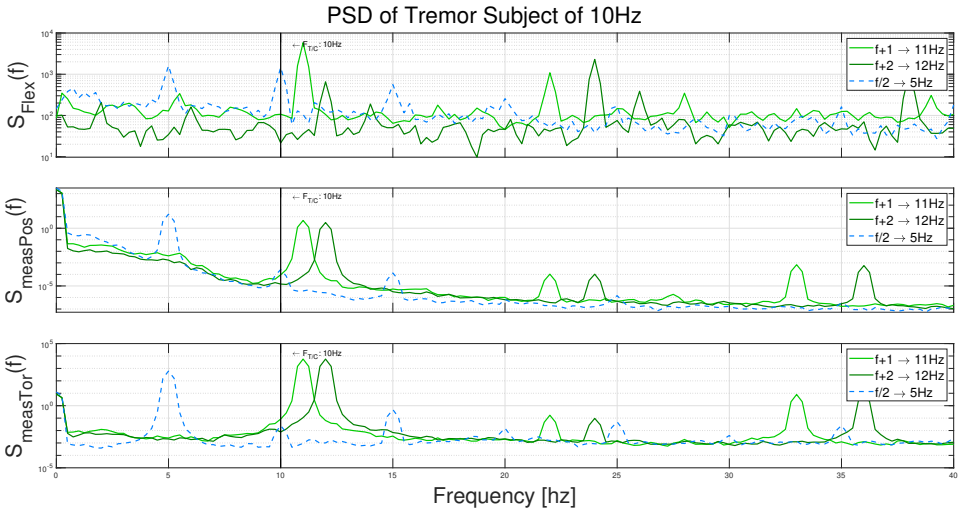
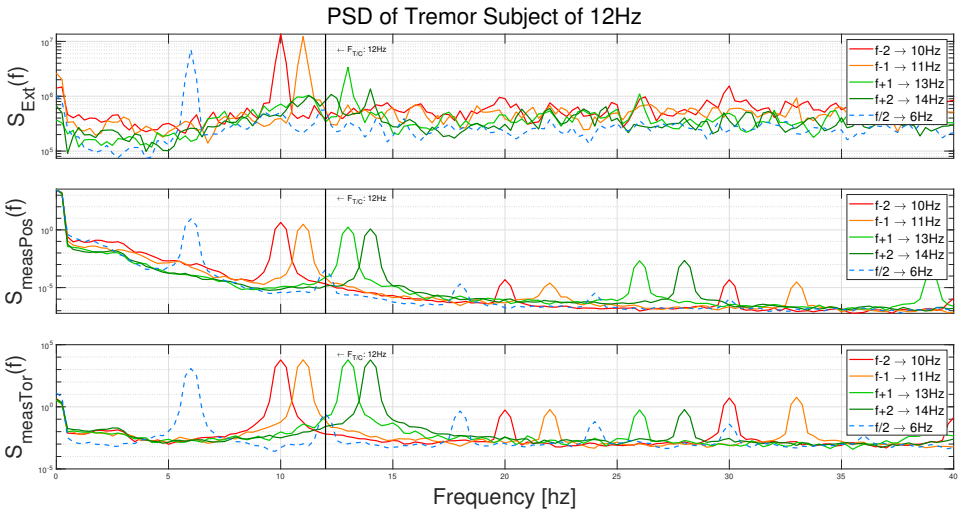


Figure 2.4



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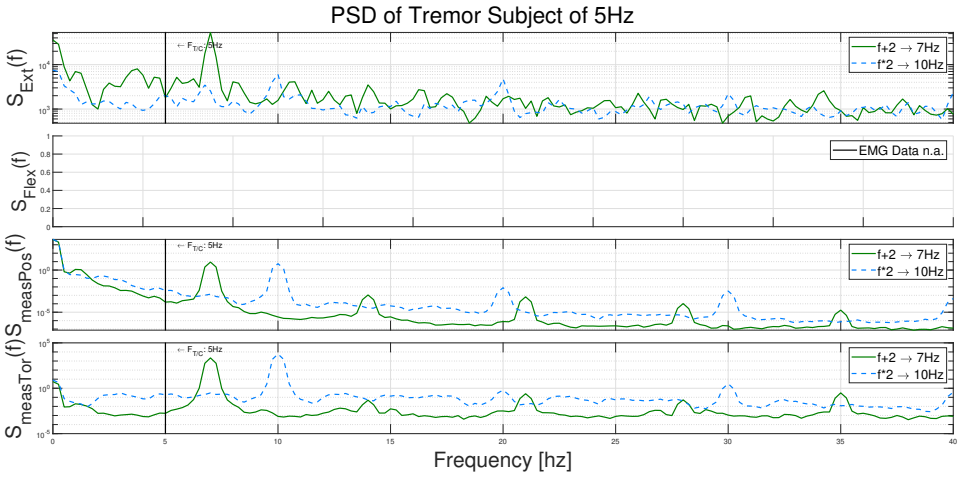

Figure 2.6

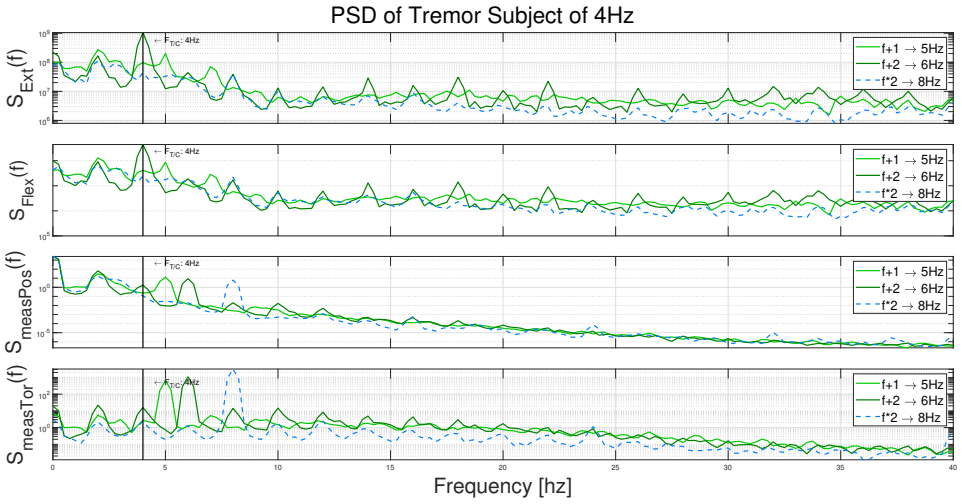

Figure 2.7

3

Appendix - B: Reflex Task

Recording of a Ramp-and Hold Perturbation for the Study Population

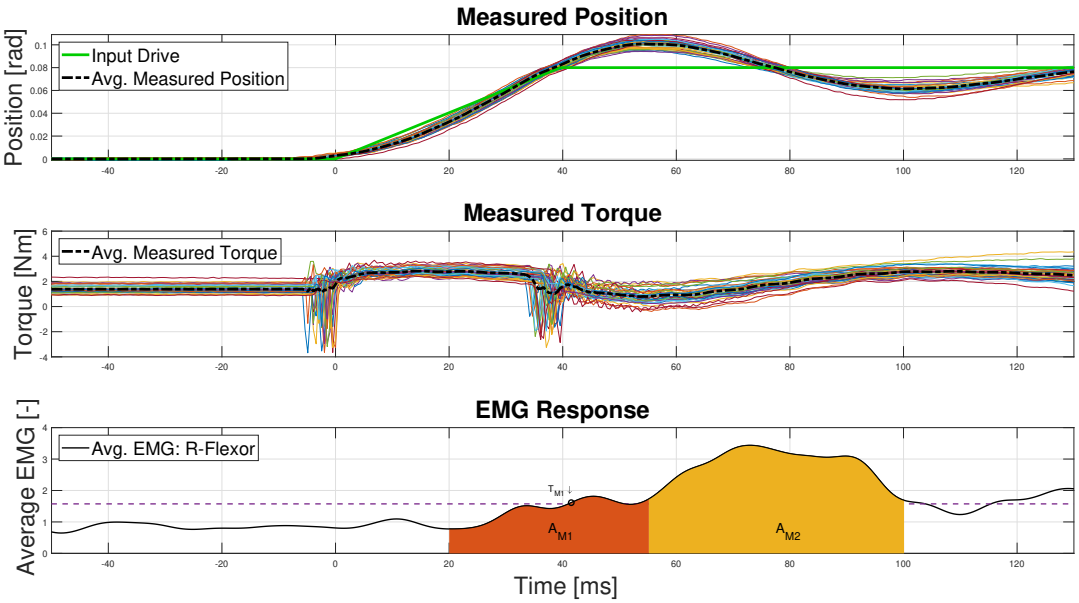

Figure 3.1. Reflex Plot of Control Subject (8Hz)

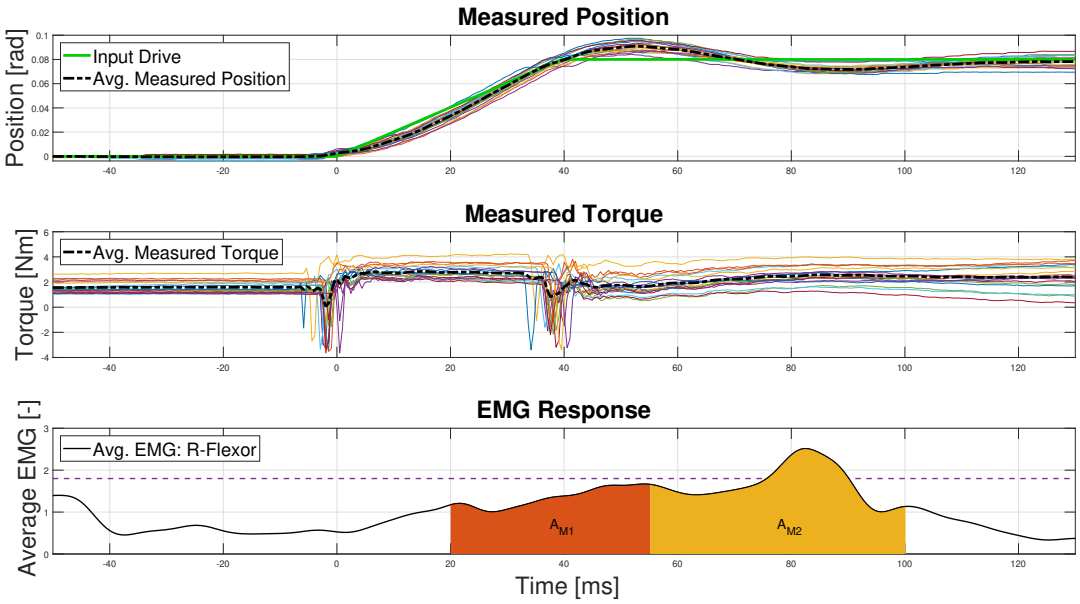

Figure 3.2. Reflex Plot of Control Subject (3Hz)

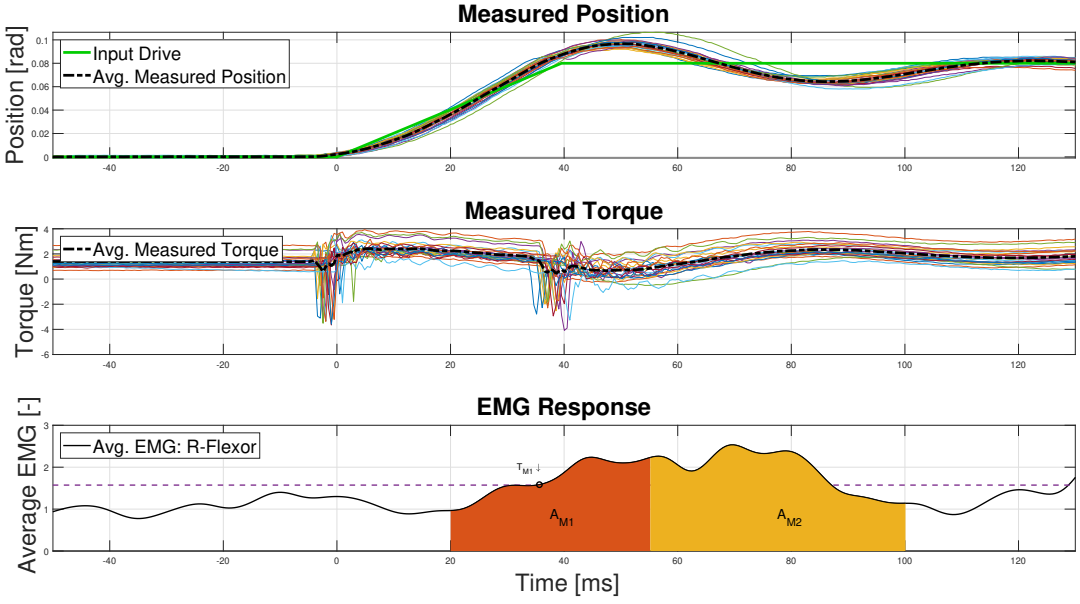

Figure 3.3. Reflex Plot of Control Subject (5Hz)

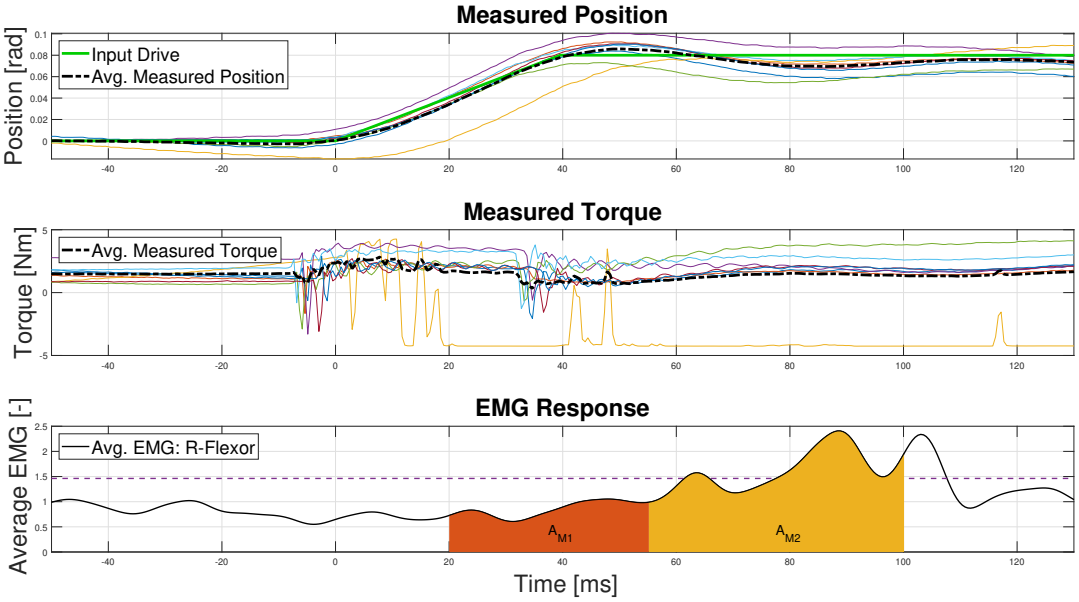

Figure 3.4. Reflex Plot of Tremor Subject (4Hz)

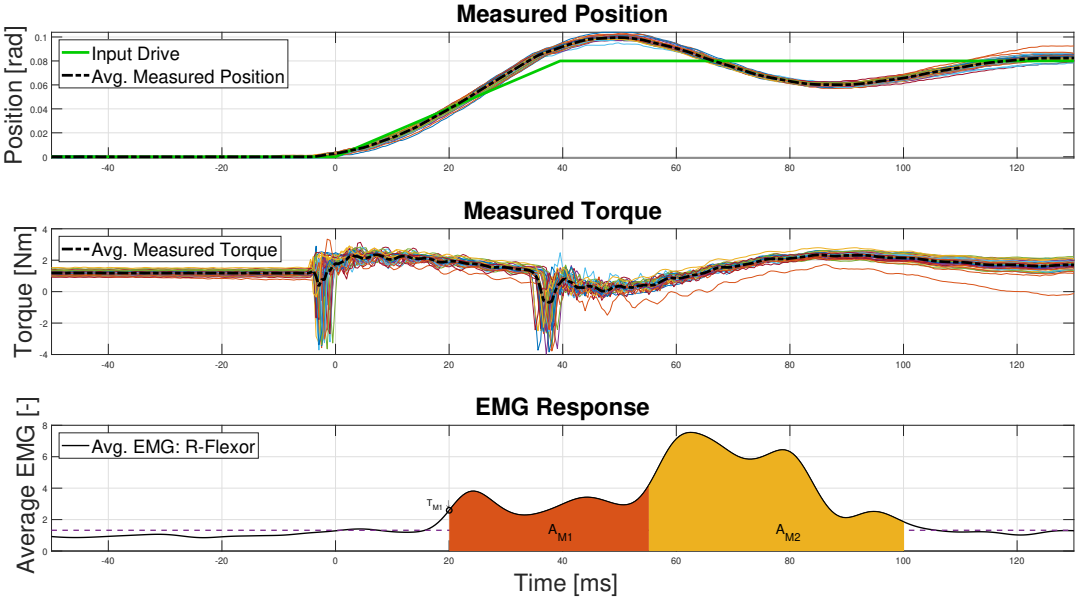

Figure 3.5. Reflex Plot of Tremor Subject (10Hz)

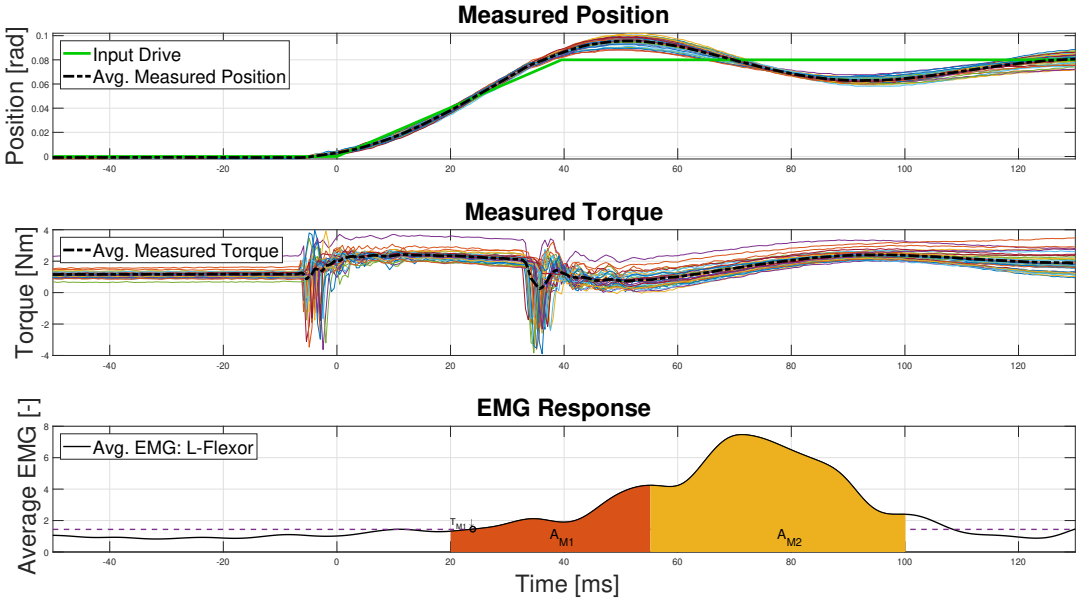

Figure 3.6. Reflex Plot of Tremor Subject (6Hz)

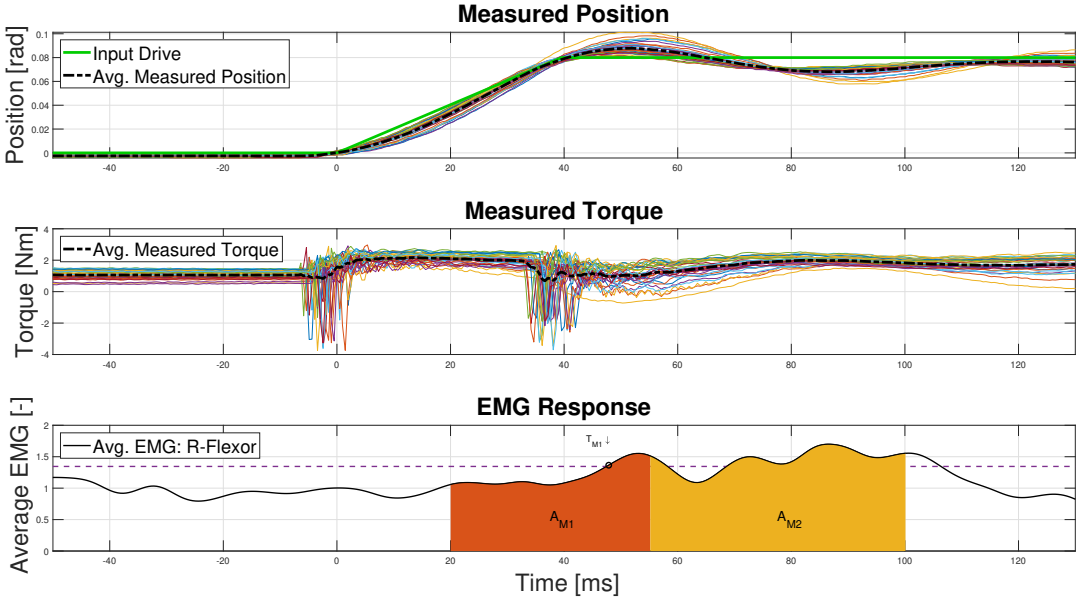

Figure 3.7. Reflex Plot of Tremor Subject (5Hz)

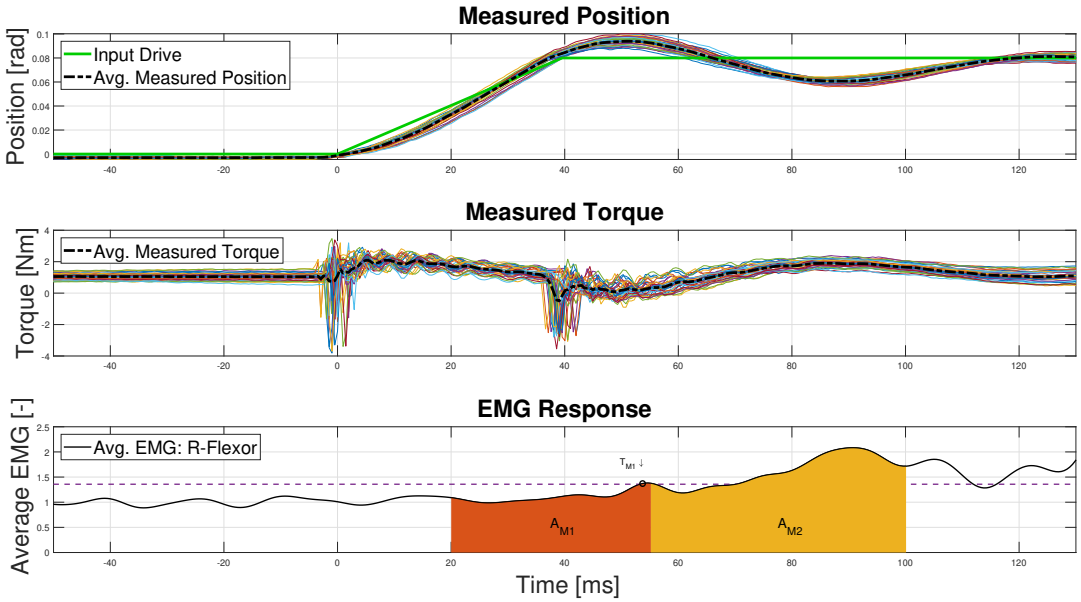

Figure 3.8. Reflex Plot of Tremor Subject (3Hz)