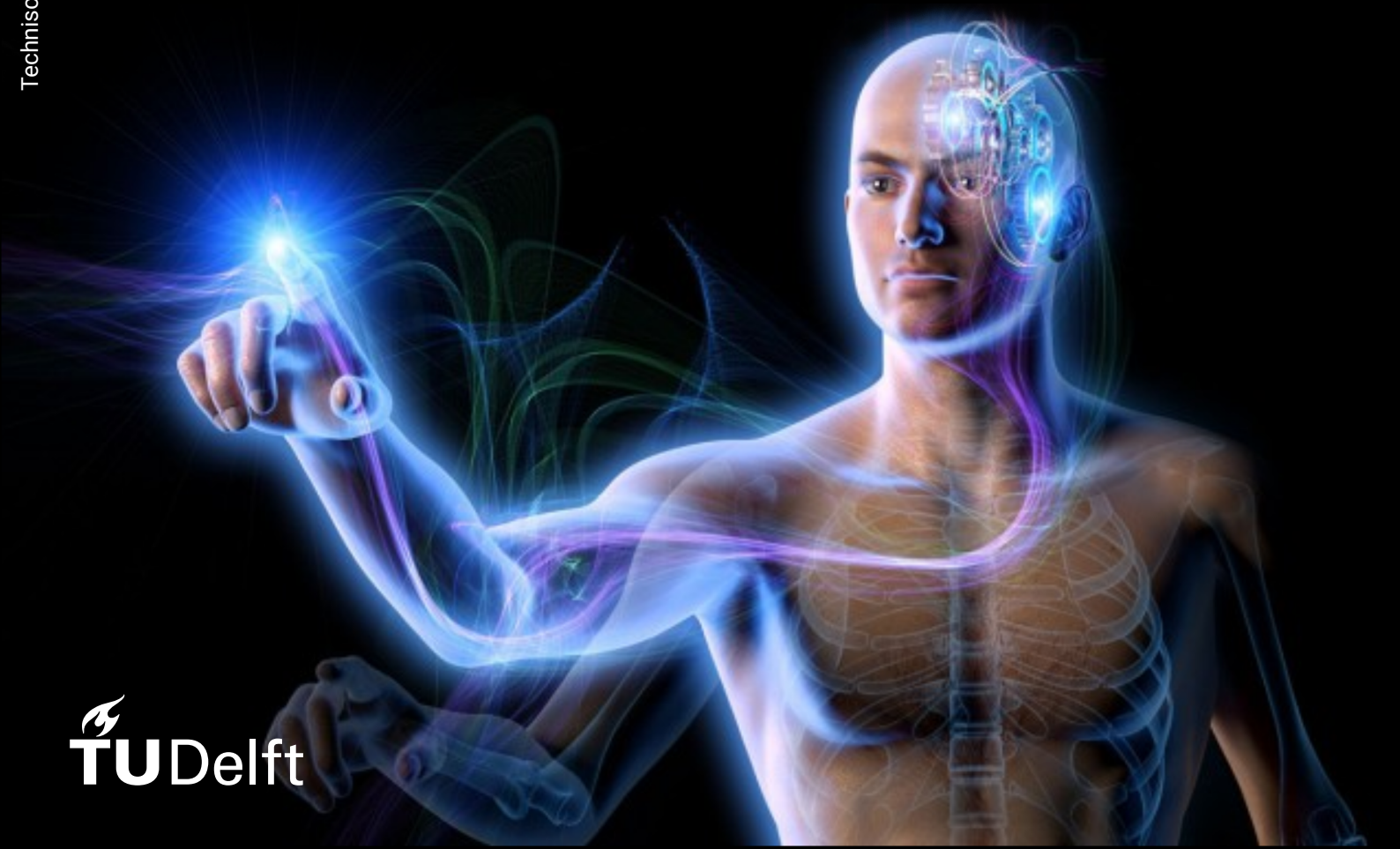
Identifying Behavioural Changes due to Parkinson's Disease Progression in Motor Performance Data

Development of a Tool for Monitoring Treatment of Parkinson's Disease

L. A. Lugtenborg

Technische Universiteit Delft



TU Delft

Identifying Behavioural Changes due to Parkinson's Disease Progression in Motor Performance Data

Development of a Tool for Monitoring Treatment of Parkinson's Disease

MASTER OF SCIENCE THESIS

by

L. A. Lugtenborg

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An electronic version of this thesis is available at `http://repository.tudelft.nl/`.

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The undersigned hereby certify that they have read, and recommend to the Faculty of Aerospace Engineering at Delft University of Technology for acceptance, a thesis entitled: **Identifying Behavioural Changes due to Parkinson's Disease Progression in Motor Performance Data**, submitted by **L.A. Lugtenborg**, in partial fulfilment of the requirements for the award of the degree of **Master of Science**.

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Preface

This thesis report covers the work done in order to obtain my Master of Science (MSc) degree at the Faculty of Aerospace Engineering of the Delft University of Technology. Out of interest in combining different research field and exploring the many different applications of proven models, I chose to further the work in the research collaboration between the department of Neuroscience of the Erasmus Medical Centre (EMC) and the faculty of Aerospace Engineering of the Delft University of Technology in applying models to identify pilot control behaviour to develop methods for aiding the diagnosis of neurological disorders. Part I contains a scientific paper covering the main body of my thesis work. It presents the method, results and discussion for a "proof-of-concept" of the development of a model than can detect changes in motor performance data related to increasing Parkinson's disease symptom severity. In Part II a preliminary graduation report is presented that covers the literature study on Parkinson's disease, the cybernetic approach and trend analysis methods. In Part III, appendices are included that present further results for both the paper and literature review. For the final thesis work related to AE5310 Parts I and III need to be considered, as Part II has previously been graded for AE4020.

I would like to thank my excellent supervisors Daan and Johan for their continued support and feedback on my work. Thank you Max for your interest and new insights during our meetings. Special thanks goes to the secretaries and inhabitants of the group homes for the elderly of Woongroep Hilligersberg, Woongroep het Vlinderhuis and Groepswonen van Ouderen Schiedam, who helped bring my participant group together, as well as the participants who found the time to come to the EMC.

L. A. Lugtenborg
Rotterdam, August 2020

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List of Symbols

Roman

A_f	Sine wave amplitude	$[deg], [px]$
CF	Cost function value	$[-]$
CV	Coefficient of Variance	[%]
df	Degrees of freedom	$[-]$
E, e	Control system error signal	$[px]$
f_d	Disturbance forcing function	$[px]$
f_t	Target forcing function	$[px]$
H_A	Sinusoid amplitude filter	[]
$H_{c,ce}$	Controlled element dynamics	[]
H_n	Remnant dynamics	[]
H_{nms}	Neuromuscular dynamics	[]
$H_{O_{t,e,x}}$	Human controller dynamics	[]
$H_{p,pe}$	Pilot dynamics	[]
$\hat{H}_p$	Estimated pilot dynamics	[]
j	Imaginary number	$[-]$
K_n	Remnant gain	$[-]$
K_p	Pilot gain	$[-]$
K_c	Controlled element dynamics gain	$[-]$
k	Sinusoid index	$[-]$
N, n	Sample size	$[-]$
N_f	Number of excitation frequencies	$[-]$
n	Remnant signal	$[px]$
S_{nn}	Power spectral density of remnant signal	$[\frac{px^2}{rad/s}]$
$S_{uu_{f_{t,n}}}$	Power spectral density of input signal	$[\frac{px^2}{rad/s}]$
T_I	Controller lag time constant	$[s]$
T_L	Controller lead time constant	$[s]$
T_m	Measurement time	$[s]$
T_n	Remnant lag time constant	$[s]$
p	P-value for statistical tests	$[s]$
P_n	Remnant power ratio	[]
t	Time	$[s]$
t	Significance value for student's t-test	$[-]$
U, u	Human controller output signal	$[px]$
u_{sim}	Simulated human controller output signal	$[px]$
W	Significance value for Wilcoxon's test	$[-]$
x	System output signal	$[px]$
X, x_t	Trend predictor variable	$[-]$
y	Control system output signal	$[px]$
y	Trend dependent variable vector of one estimated parameter for y_1, ..., y_t	[]
y_t	Trend dependent variable at time point t	[]
$\mathbf{Y_t}$	Trend dependent variable matrix for all estimated parameters at time point t	[]

Greek

$B, \beta_{0,1}$	Trend intercept and slope	$[-]$
δ	Symptom severity sclaing factor	$[-]$
E, ε_t	Trend error variable	$[px]$
ζ_{nms}	Neuromuscular damping ratio	$[-]$

η_t	Linear predictor	$[-]$
θ	Control parameter vector	$[-]$
μ_t	Data mean at time t	$[px]$
ρ_u^2	Relative remnant	$[-]$
σ_n^2	Remnant signal power	$[px^2]$
σ_u^2	Input signal power	$[px^2]$
σ^2	Data variance	$[px^2]$
τ	Time delay	$[s]$
τ_c	Crossover time delay	$[s]$
ϕ_f	Phase	$[rad]$
χ^2	Significance value for Friedman's ANOVA	$[-]$
ω	Frequency	$[rad/s]$
ω_c	Crossover frequency	$[rad/s]$
ω_f	Excitation frequency	$[rad/s]$
ω_m	Base frequency	$[rad/s]$
ω_{nms}	Neuromuscular frequency	$[rad/s]$

List of Abbreviations

BG	Basal Ganglia
CE	Controlled Element
D	Dominant hand
DND	combined Dominant and Non-dominant hand control
DUECA	Delft University Environment for Communication and Activation
EMC	Erasmus Medical Centre
FCM	Fourier Coefficient Method
GLR	General Linear Regression
GLiR	Generalised Linear Regression
HC	Human Controller
HRQOL	Health-Related Quality Of Life
L-Dopa	Levodopa
LMM	Linear Mixed Models
LSE	Least Squares Estimate
MAD	Mean Absolute Deviation
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
MEM	Mixed Effect Model
MLE	Maximum Likelihood Estimate
MMSE	Mini Mental State Examination
MSc	Master of Science
ND	Non-Dominant hand
PD	Parkinson's Disease
PSD	Power Spectral Density
RMS	Root Mean Squared value
SISO	Single-Input-Single-Output
SLR	Simple Linear Regression
SN	Substantia Nigra
SNR	Signal to Noise Ratio
SOP	Successive Organisation of Perspective
UPDRS	Unified Parkinson's Disease Rating Scale
VAF	Variance Accounted For

I

Scientific article

Identifying Behavioural Changes due to Parkinson's Disease Progression in Motor Performance Data

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***Abstract*—Parkinson's disease can severely affect motor performance and impede in executing daily activities. Treatment can greatly improve patients' quality-of-life, however, disease detection and monitoring is still performed subjectively. Quantification of patients' motor performance and its decline due to increasing symptom severity using tracking tasks could provide a solution and even help in early disease assessment. In order to develop a proof-of-concept for a tool that can be used for the detection of behavioural changes in motor performance data, the longitudinal clinical data are approximated by a combined dataset with experimental data of healthy participants and simulated Parkinson's disease control behaviour. 25 healthy participants in the age range of 55-75 participated in a manual pursuit tracking experiment to identify baseline control behaviour. PD data were simulated by bootstrapping the experimental data and scaling this value based on previous research. The resulting experimental and PD data were combined and a general linear regression model was used to see if a change in control behaviour due to upcoming PD symptoms could be detected with trend analysis. It was found that for the parameters related to a decline in motor performance caused by the disease, for at least 50% of the participants a simulated change in motor behaviour was successfully detected. This means that the developed method is able to detect a trend for half of the population and is a major step forward in the development of a tool that can aid monitoring of disease progression and treatment for Parkinson's disease.**

***Index Terms*—Manual tracking, Parkinson's disease, cybernetic approach, system identification, trend analysis, behavioural changes**

I. Introduction

As people age, everyday tasks that are fundamental for a good quality of life become increasingly difficult to perform due to the natural degeneration of the brain [1]. Moreover, ageing presents an increasing risk of developing a neurodegenerative disease, which can make the simplest daily activities a challenge [2]. Neurodegenerative diseases do not only influence memory, as is the case with Alzheimer's disease [3], they can also seriously impair motor performance [4]. Parkinson's disease (PD), is one of the disorders that affects motor performance, caused by a decrease in dopamine-producing neurons of the Basal Ganglia that hampers the communication in the brain, especially in the motor control area [5]. This leads to symptoms like slowness of movement (bradykinesia), postural instability and involuntary tremors. PD can have an asymmetrical onset, which can make early diagnosis difficult [4]. The disease is progressive and still incurable 200 years after the first proper description of its symptoms, but early diagnosis and correct treatment can greatly improve patients' quality-of-life [4]. As of this moment, diagnosis and monitoring the effects of treatment are done by detecting the motor symptoms related to Parkinson's disease (especially bradykinesia) and using questionnaires [6]. These results are translated in either a low resolution Hoehn and Yahr scale [7] or the more detailed Unified Parkinson's Disease Rating Scale (UPDRS) analysis [8].

A more objective way of determining the effects of PD is to quantitatively measure the decline in motor performance, especially for fine motor skills. The neural network required for fine motor skills, the visuomotor-network, is present throughout the brain and can be severely affected by neurodegeneration. Specific functional losses in this network caused by neurodegeneration leads to loss in performance for eye-hand tasks [9]. One method to analyse fine motor skill and its degradation is with the use of tracking tasks. Much research has been done in finding the influence of PD and its treatment on motor skills by using simple tracking tasks [10–17].

A recent collaborative research project, between the department of Neuroscience of the Erasmus Medical Centre (EMC) and the faculty of Aerospace Engineering of the Delft University of Technology, focuses on developing methods, using cybernetics, to analyse and quantify the effects of neurodegenerative disorders on motor performance. Manual control cybernetics is an approach to model human control behaviour [18]. In a manual tracking task, a dynamic system is perturbed by forcing functions and controlled by a human controller (HC) [19]. The data from these tasks can be used to define a model describing the controller's motor skills. One of the applications of cybernetics is its use in analysing and comparing motor skills of the human controller in order to detect deviating

This research was made possible by the Control and Operations department of the Delft University of Technology and and Neuroscience department of the Erasmus MC by providing all the needed equipment for the experiments and support in the research. Special thanks goes to the secretaries and inhabitants of the group homes for the elderly of Woongroep Hilligersberg, Woongroep het Vlinderhuis and Groepswonen van Ouderen Schiedam, who helped bring the participant group together, as well as the participants who found the time to come to the EMC.

behaviour between groups or systems. Previous research using this approach included testing a tracking task to quantify the loss of motor skills related to Parkinson's disease [20] and cerebellar stroke [21], and the influence of age on eye-hand coordination [22]. These experiments showed that changes in behaviour due to neurological decay can be quantified in isolated situations, such as comparing healthy controls with patients. What is missing, is research in its possible application for individual cases, for example in detection of a decline in motor performance over a longer period of time due to disease progression and increasing severity of symptoms.

Finding anomalies or (behavioural) changes in data, has been the focus of research for quite some time [23–25]. Within Parkinson's disease or medical research, the main focus is again on finding differences between groups, such as identifying Parkinsonism and Parkinson-related symptoms by analysing activity outliers during sleep [26], or outliers in gait monitoring data [27]. Furthermore, research is performed to find clear outliers in hospital-wide data-sets in order to identify people suffering from Parkinson's disease [28] or with other medical issues [29]. To identify more gradual behavioural changes due to disease progression in individual motor performance data, trend analysis is a more applicable method [23]. At this moment, trend analysis finds its main application in financial forecasting and climate monitoring [30,31], however, it is also increasingly used in analysis of longitudinal data from clinical trials [32]. Application of these methods to detect behavioural changes in individual patients' clinical data for early disease assessment and treatment monitoring is still fairly limited. Several methods are being developed for monitoring patients at home to gather data that can be used by clinicians [33,34]. However, these systems and their applications are still in an early stage of development.

Even though many methods are being investigated, so far no objective procedure to evaluate loss in motor skills due to neurological diseases is available, and with an increased focus on providing personalised healthcare, a universally accepted method to quantify decline due to increase in symptom severity is essential. Tracking tasks have proven to be applicable in comparing data-sets and finding differences in behaviour between healthy controls and PD patients, however, its application in analysing changes in motor performance of individual data still needs to be explored. Moreover, detection of these changes using trend analysis methods becomes increasingly complex due to the multivariate nature of the tracking data, where each of the estimated parameters is related to the others. There is no information available on the day-to-day variance in control performance when using tracking tasks. By not knowing this variation bandwidth, and therefore, the data variability, it is unsure how severe symptoms and disease progression need to be before they can be detected by a trend model.

The goal of this research is to develop a methodology for identifying behavioural changes in individual motor performance data due to Parkinson's disease in a combined experimental and simulated data-set by using trend analysis methods. This model could then be used to develop a tool that supports current diagnostic and disease monitoring methods. Time constraints for this study did not allow the longitudinal clinical study (5 years) with Parkinson's patients that would be ideal for defining individual differences in motor performance between healthy and PD affected data. Therefore, focus lay on providing a "proof-of-concept" for the development of a diagnostic tool that can be used in the disease assessment and monitoring of Parkinson's patients.

In order to approximate part of the longitudinal clinical data-set and to analyse natural variability in motor performance, a single-axis manual pursuit tracking task was used to gather motor performance data, spread over five days. The experimental set-up was portable for use in different applications, with a touchscreen input device. The participants were 25 healthy people between the age of 55-75. Measurements were done using both the dominant and non-dominant hand, since PD can manifest itself asymmetrically [4]. With the Fourier Coefficient Method [19] the different control parameters were defined for each measurement and participant. After this, initial regression models were used to correct any learning trends in the experimental data, since an increasing performance related to learning effects may counteract any PD related performance decline. PD data was simulated by bootstrapping a participant's corrected performance data and scaling this with values based on previous research [20]. The experimental and simulated data were combined to resemble motor performance data with a change in control behaviour. Finally, the combined data-set was analysed with a novel approach based on multivariate linear regression models to determine the accuracy with which behavioural changes in the motor performance data can be detected.

This paper is structured as follows. First, the cybernetic method for analysing the experimental data and the hypotheses related to the cybernetic analysis are explored in Section II. This is followed by the methods used for the trend analysis and related hypotheses in Section III. Section IV goes into more detail on the experimental setup used. The results are analysed in Section V and a discussion is provided in Section VI. Finally, Section VII presents the main findings in the conclusion.

II. Cybernetic method

This section will cover the cybernetic approach used in the analysis of the experimental data. With this method, the final 'healthy' part of the combined data to be used in the trend analysis is defined. Furthermore, analysis of control performance parameters will give insight in the variation in control performance for healthy participants and two hypotheses related to this variation are defined at the end of this section.

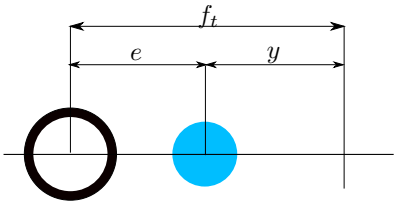


Fig. 1: Pursuit display

A. Control task

Manual control cybernetics is a widely used approach to define human control behaviour [18]. Analysis of how a human controls a dynamic system provides insight in the limitations and performance of the controller in such a way that it can be used to detect 'abnormal' or deviating behaviour. In manual tracking, a human controller is controlling a dynamic system that is perturbed by forcing functions [19]. The data from these tasks provide a detailed measurement of the HC's motor skills.

The human motor performance data for this study were gathered using a horizontal-axis pursuit tracking task, similar to that used in previous research with PD patients [12, 20, 22]. In pursuit tracking the participant is asked to reduce the error e between the system output y (blue dot) and the target signal f_t (black circle), as shown in Figure 1. This means the participant had to control the blue dot so that it was positioned on the black circle at all times. A pursuit task was chosen as the display is thought to ensure the task is sufficiently intuitive for elderly participants [20]. Previous research found that even though preview tasks provide a deeper insight in control behaviour, the task seemed too complex with an excessive workload for cerebellar patients [21], therefore, it was deemed inappropriate for the similarly vulnerable participant group in this research and its future applications for Parkinson's patients. As mentioned in Section I, participants controlled the dynamic system with both the dominant and non-dominant hand as PD can manifest itself asymmetrically [4].

The control scheme used in this study is presented in Figure 2. Here, a quasi-linear human controller is combined with a controlled element H_{ce} in a closed-loop system, excited with forcing function f_t. It was found that when combining a pursuit tracking task with the appropriate controlled element (CE) dynamics, the participant is expected to show compensatory behaviour and the block diagram from Figure 2 was deemed suitable for this task [35]. Based on previous research the participants controlled single integrator CE dynamics in the form of Equation (1). Single integrator dynamics may cause problems with the data analysis due to loss-of-contact with the touchscreen, as the participant is controlling the target velocity, letting go of the screen can cause an abrupt halt to the target. Nonetheless, using those dynamics ensures that enough information is available on control behaviour in the higher frequencies, such as the neuromuscular dynamics [21]. The CE gain K_c was heuristically tuned such that the deflection range of the hand in the control task was within reasonable limits. It was found that a gain of $K_c = 8$ was effective for this setup.

$$H_{ce} = \frac{K_c}{s} \tag{1}$$

B. Identification of human controller dynamics

Identification of human control behaviour from the experimental data, gathered in the tracking task described above, can be done using system identification methods [19]. In general these methods fit a model to the data, corresponding with a defined set of parameters. The HC can be modelled as a quasi-linear controller, a combination of a continuous linear pilot model H_{pe} and the remnant n, which covers the nonlinear behaviour and system noise [37], as shown in Figure 2. The continuous linear mathematical model for the human controller is defined by McRuer and Hex [37] as:

$$H_{pe}(j\omega) = \underbrace{K_p \frac{T_L j\omega + 1}{T_I j\omega + 1}}_{\text{pilot equalisation}} e^{-j\omega\tau} H_{nms}(j\omega) \tag{2}$$

Here, K_p is the controller gain. T_L and T_I describe the controller lead and lag time constants, respectively. τ indicates the time delay and $H_{nms}(j\omega)$ indicates the neuromuscular system dynamics, expanded in in Equation (3). The neuromuscular frequency and damping ratio are indicated with ω_{nms} and ζ_{nms}, respectively.

$$H_{nms}(j\omega) = \frac{\omega_{nms}^2}{(j\omega)^2 + 2\zeta_{nms}\omega_{nms} j\omega + \omega_{nms}^2} \tag{3}$$

The crossover model defined by McRuer et al. states that, generally, any open-loop control system converges to single integrator dynamics [37]. This system is a combination of the HC and CE dynamics. Since the controlled element dynamics are single integrator dynamics, it is expected that the controller will be a proportional controller and will not generate any lead or lag. Therefore, Equation (2) can be simplified to (4).

$$H_{pe}(j\omega) = K_p e^{-j\omega\tau} H_{nms}(j\omega) \tag{4}$$

For the experimental data in this research, the parameters for the controller model defined in Equation 4 were fitted using four different methods, in order to find the most accurate

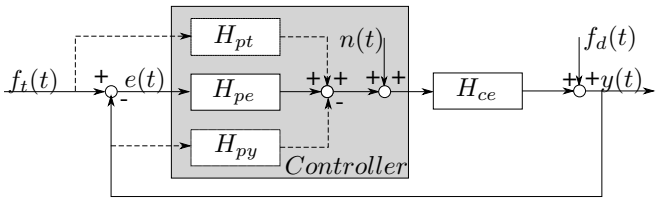


Fig. 2: Pursuit control block diagram, adapted from [36]

control parameter values. One parameter set was defined using a previously developed time-domain method [38], while the other three were fitted in the frequency-domain. These three models include its most basic form, one with a correction for the higher frequencies and a model corrected for the signal to noise ratio. The method for the frequency domain fits is described in this section.

One of the most widely used frequency-domain methods in this research field is the Fourier Coefficient Method (FCM) [19]. A black box method that is applied to estimate the control parameters in a dynamic closed-loop system. The system used for this study is shown in Figure 2. If the the multisine forcing function f_t is designed in such a way that the signal-to-noise ratio (SNR) at the excitation frequencies is high, the contribution of the remnant at those points will be negligible [19]. Human control dynamics at those excitation frequencies can then be estimated with Equation (5). Here $U(j\omega_t)$ and $E(j\omega_t)$ are the Fourier transformed HC output and error signals, analysed at the excitation frequencies, respectively.

$$\hat{H}_{p_e}(j\omega_t) = \frac{U(j\omega_t)}{E(j\omega_t)} \tag{5}$$

The result of the estimated frequency response function (FRF) is an indication of the HC dynamics in this system. The parameters related to human control behaviour, K_p, τ, ζ_{nms} and ω_{nms}, can be estimated by fitting Equation (4) to the estimated FRF data from Equation (5) at the excitation frequencies for each measurement. The model can be fitted by minimising the cost-function defined by Equation (6).

$$CF(\theta) = \sum \left\| \hat{H}_{pe}(j\omega_t) - H_{pe}(j\omega_t;\theta) \right\|^2, \quad \theta = [K_p, \tau, \zeta_{nms}, \omega_{nms}] \tag{6}$$

This is a general version of the cost-function, used for the first fit to the data. As mentioned, three different frequency-domain fits were used to estimate the control parameters for Equation (4). Moreover, a time-domain method was used to determine the last set. From here on, these different fitting methods and their results are indicated as M1-M4 and a more detailed explanation of each approach is provided below.

M1 The first parameter set was defined by fitting the most simple form of the cost-function as shown in Equation (6). This method was a baseline for comparison of the other approaches.

M2 For the second fit, the original cost-function was normalised to emphasise the higher frequencies, in order to get a more accurate estimate of the neuromuscular dynamics, as shown in Equation (7).

M3 Due to the high noise levels in the experimental data, which will be elaborated on in Section II-C, it was opted to fit the model using a cost-function with weights related to the signal-to-noise ratio (SNR). This ensured the model was fitted to the most reliable data points.

M4 Finally, because of the relatively low average quality of the three model fits for the frequency-domain method, a last parameter set was estimated using previously developed time-domain methods [38].

$$CF(\theta) = \sum \frac{\left\| \hat{H}_{pe}(j\omega_t) - H_{pe}(j\omega_t;\theta) \right\|^2}{\left\| \hat{H}_{pe}(j\omega_t) \right\|^2} \tag{7}$$

An indication of goodness of fit can be determined with the Variance Accounted For (VAF) [39]. This metric analyses the difference between the actual and simulated input signals u, as shown in Equation (8). The VAF can range from 0% to 100% where, 100% means a perfect fit to the measured data.

$$\text{VAF} = \left(1 - \frac{\sum_{k=1}^{N} |u(k) - u_{sim}(k)|^2}{\sum_{k=1}^{N} u(k)^2}\right) \times 100\% \tag{8}$$

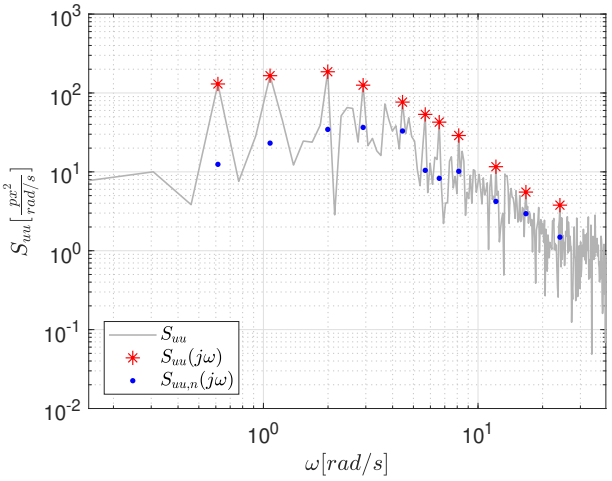
C. Signal-to-noise ratio

Visual inspection of the FRF estimates showed that the data seemed relatively noisy and the quality of the model fits was low when using the original model presented in Equation (6) (M1) or the expanded normalised version (M2). Therefore, it was opted to add a third fitting model with weights related to the signal-to-noise ratio at each frequency.

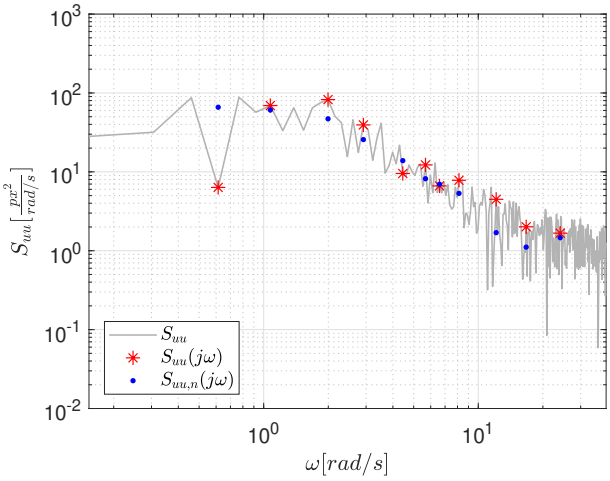
The Power Spectral Density (PSD) for each trial was plotted to visualise the amount of noise in the control signal. Figures 3a and 3b show examples of a good and bad tracking run, respectively. Figure 3a shows that the spectrum of the control signal u has clear peaks above the noise signal, while Figure 3b shows input components that are drowned in noise. This means that the FRF mainly captures noise and the estimate is not a good indication of the actual dynamics.

One metric for the SNR that can be used in weighing the frequencies for the model fit is the relative remnant [40], as shown in Equation (9). Here $\bar{S}_{uu,n}$ indicates the noise power and $\bar{S}_{uu}$ the signal power at the input frequencies. The noise power at each excitation frequency is estimated by averaging the power of three data points before and after the excitation frequency, the locations of the red and blue dots in Figure 3. Generally, the relative remnant has a value between 0 and 1, and a value of 1 indicates a perfectly linear response [40]. However, this value can also become negative when the peak power of the input lies below the noise level. As the relative remnant is used to weigh the frequencies for the model fit, any negative values have been capped at zero.

$$\rho_u^2(j\omega_t) = 1 - \frac{\bar{S}_{uu,n}(j\omega_t)}{S_{uu}(j\omega_t)} \tag{9}$$



(a) Participant 2, D day 5, measurement 1



(b) Participant 3, ND day 2, measurement 2

Fig. 3: Power Spectral Densities showing a high (a) and low (b) signal-to-noise ratio

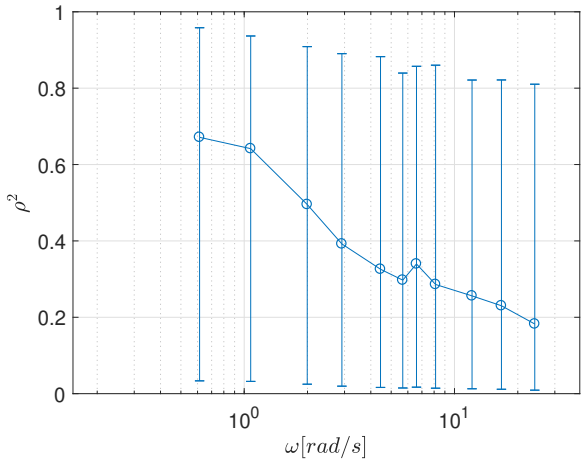


Fig. 4: Relative remnant averaged across participants

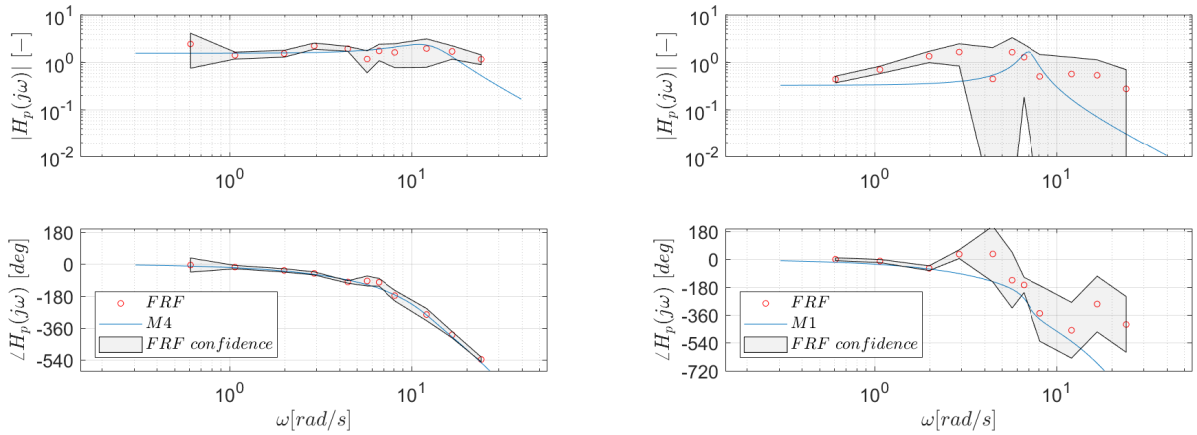
Figure 4 shows the relative remnant averaged across all participants. It can be seen that the relative remnant is good in the lower frequencies while for the higher frequencies the amount of noise in the signal increases. This means the participants have trouble following the higher frequencies of the input signal, which could have an effect on the accuracy of the model fit. As the neuromuscular dynamics are related to the higher excitation frequencies, estimations of ζ_{nms} and ω_{nms} might become unreliable.

Determination of how well the frequency response function estimators fit the data, the FRF confidence limits can be calculated [41]. These limits say something about the expected spread of the estimators and with that in mind, one can critically look at the estimated parameters and their VAF values. Figure 5 shows the FRF confidence limits corresponding to the PSD's of Figure 3. It can be seen that for participants with noisy data, the expected spread of the FRF estimators is large in the higher excitation frequencies. This corresponds to the higher relative remnant. Therefore, an estimate for the neuromuscular dynamics, related to the higher frequencies, might not be completely accurate for these participants.

D. Data analysis

From the data gathered in the experiments, time traces were made and examples related to Figure 3 are shown in Figure 6. The dotted vertical line, at time point 9.06 s, indicates the moment the actual measurements begin, the time before that line is defined as the run-in time. Only the data after the vertical line are taken into consideration for the further analysis. In the figure, the blue line indicates the target position f_t and the red line the system output y, as previously defined in Figure 1.

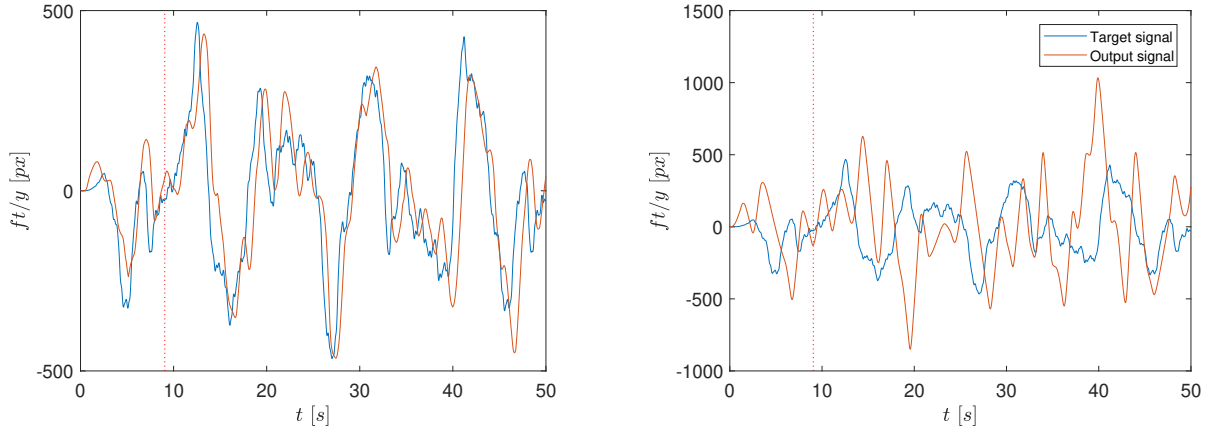
Using the system identification method described in Section II-B, the FRF estimation and four different methods of fitting the data are defined for every measurement and participant. Examples of the fits, corresponding to Figures 3 and 5 are shown in Figure 7. As can be seen in Figure 7a, for a measurement with a good SNR, the four methods have a very similar fit, with only small deviations in the higher frequencies. These similarities are also found when comparing the VAF values for this trial, which are 75.5%, 76.2%, 76.1%, 76.6% for M1 to M4, respectively. Here, M1 to M4 indicate the previously defined fitting methods. However, not all participants had a sufficiently high control performance to get similarly stable model fits. For several participants the data were relatively noisy, resulting in very different model fits as shown in Figure 7b. The VAF values for the models defined by M1 to M4 were 24.7%, 7.4%, 19.2% and 36.9%, respectively. These values are all relatively low and indicate that the fitted models for this trial do not provide a good estimate of the data.



(a) Participant 2, D day 5, measurement 1

(b) Participant 3, ND day 2, measurement 2

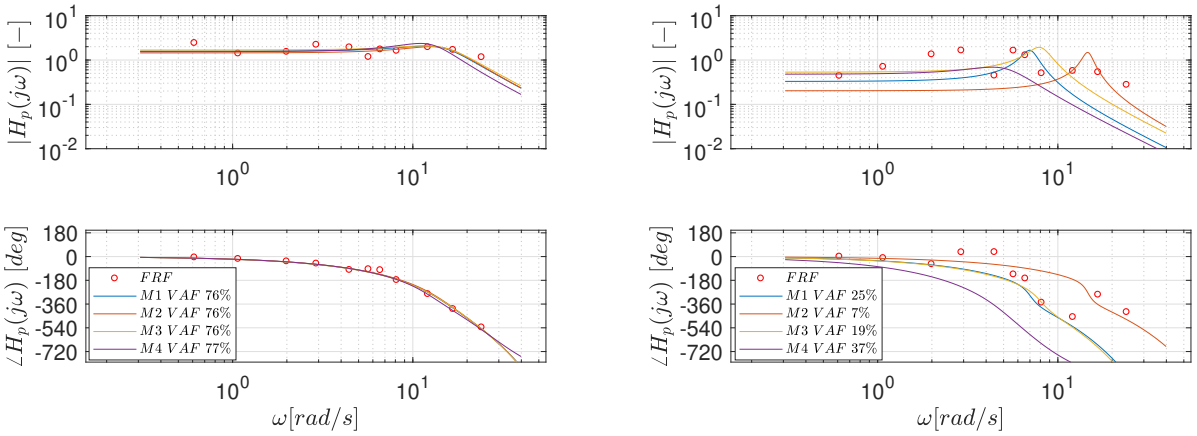
Fig. 5: Confidence limits for FRF showing a small (a) and wide (b) expected spread



(a) Participant 2, D day 5, measurement 1

(b) Participant 3, ND day 2, measurement 2

Fig. 6: Time traces of target and output signal showing high (a) and low (b) tracking performance



(a) Participant 2, D day 5, measurement 1

(b) Participant 3, ND day 2, measurement 2

Fig. 7: Fitted models and FRF estimate for a good (a) and bad (b) model fit

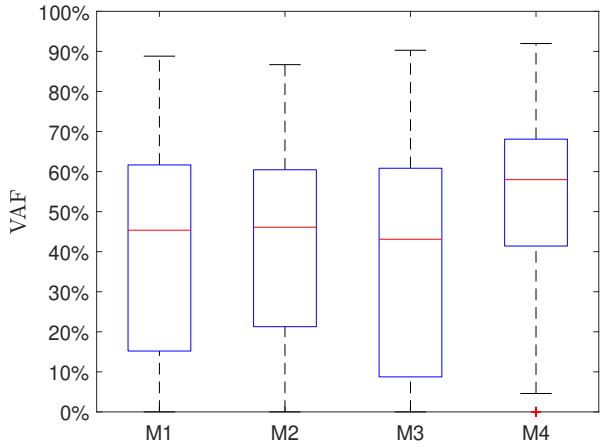


Fig. 8: Overview of VAF values for the different fitting methods

An overview of all calculated VAF values for the four different fitting methods is given in Figure 8, where the box plots show the quartiles and medians, and outliers are indicated with a red asterisk. It can be seen that for the frequency domain models M1-M3 the average VAF lies around 45%, while for the time-domain model M4 the average is almost 60%. In general, it can be concluded that the time-domain methods result in a better fit. This can, however, be explained by the method used, as the time-domain fitting method focuses on directly optimising the VAF value [38], while the frequency-domain functions optimise the cost value as defined in Equation (6). However, the time-domain model was not able to converge for all participant data-sets, therefore, for the final data-set, the best fit was found for each measurement and participant, using the approach of Section II-E.

E. Data selection

From the available model estimations for each participant and each run the final data-sets that will be used as the basis for the trend analysis must be selected. For every measurement four different fitting methods were applied to the data, as described in Section II-D. Figure 8 showed that in general the time-domain model, M4, performed best. However, for some participants M4 did not converge or did not present the best fit. Therefore, the best model for each measurement was chosen based on the highest available VAF value. The corresponding parameters were then selected after visual inspection and only when the criteria defined below were met.

First of all, it was checked if there were any outliers in the control parameters, tracking performance, indicated as RMSe and control activity, marked as RMSu, with MATLAB's function *isoutlier*. That function checks if there are any values that are more than three scaled median absolute deviations (MAD) away from the median. When an outlier is present, but the model has a VAF higher than 60%, it indicates that the model fit is expected to describe the data in a realistic manner [20], so the outlier is considered to be a valid data point. The second check determines if the parameters fall within a realistic range, with values based on literature and previous data [42]. These ranges are presented in Table I.

TABLE I: Parameter range for data selection

Parameter	Range
K_p	$0 < x < 5$
τ	$0 < x < 1$
ζ_{nms}	$0 < x < 1$
ω_{nms}	$0 < x < 25$

If any of the criteria were not met, the model with the second best VAF was checked. When none of the models met the criteria the measurement was defined as a missing value point.

Figure 9 gives an example of the final baseline data-set for Participant 1 with non-dominant hand control. Here the model number in Figure 9a indicates which of the four fitting methods is selected, from the definition presented in Section II-D.

F. Post-analysis

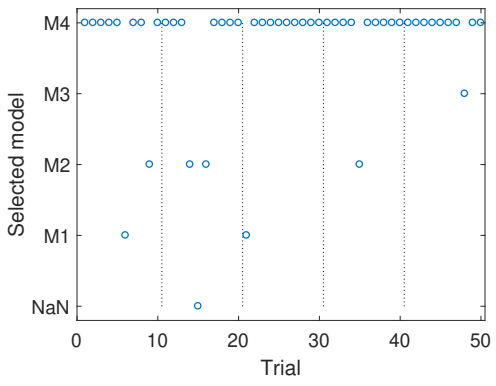
Statistical tests can be used to determine if there is a significant variation in human performance data, both for day-to-day variance and in the case of dominant versus non-dominant hand control. These tests allow an extension of the results to the entire population with statistical models [43].

First the normality and sphericity assumptions of the data-sets were checked. Normality was tested using the Shapiro-Wilk model. The analysis was done for both the whole data-set and each individual participant. It was found that the data did not adhere to the normality assumption for the case of the whole data-set, as well as for 56% of the individual cases. Since the data are not normally distributed, the sphericity assumption does not need to be checked. Since more than half of participants have a non-normal data distribution, it was decided to use Friedman's ANOVA for the analysis of day-to-day variation and the Wilcoxon Matched-Pairs test for dominant and non-dominant analysis and likewise for the post-hoc tests if the day-to-day variance was found to be significant [43].

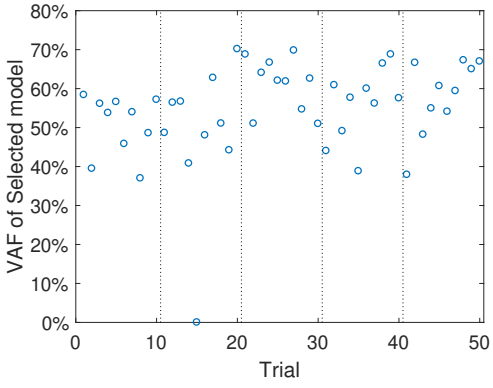
G. Hypotheses

For the experimental data in this research that was analysed using the cybernetic approach, two hypotheses were defined.

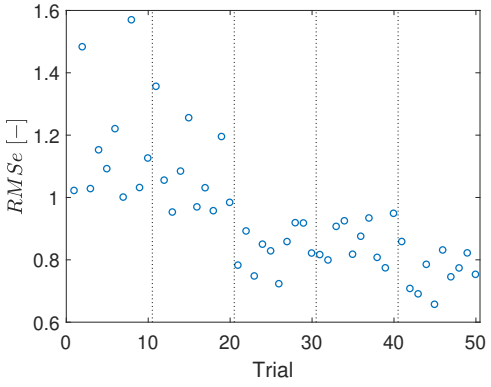
H.I: It is expected that there will be a statistically significant variation in day-to-day motor performance for all control parameters.
Research has shown that elderly people have a higher variability of movement and motor performance, especially regarding reaction time and damping [3]. Additionally, when using manual control tracking tasks it was noted that there is a large group of variables that is ideally kept constant when comparing data of experiments [36]. These so called operator-centered variables, like motivation and fatigue, are, however,



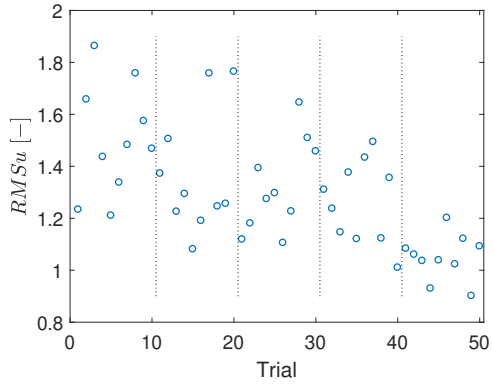
(a) Model nr



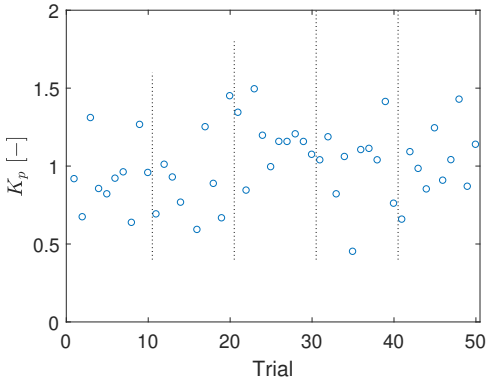
(b) VAF



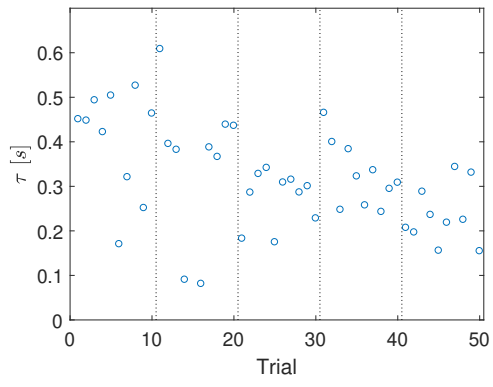
(c) RMSe



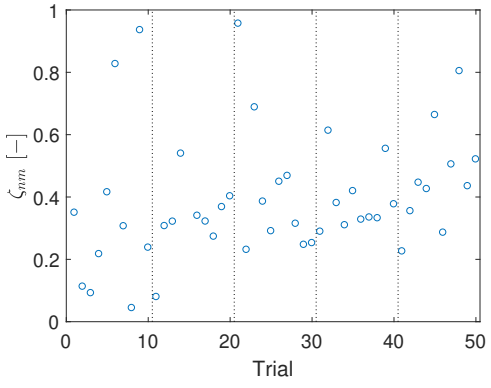
(d) RMSu



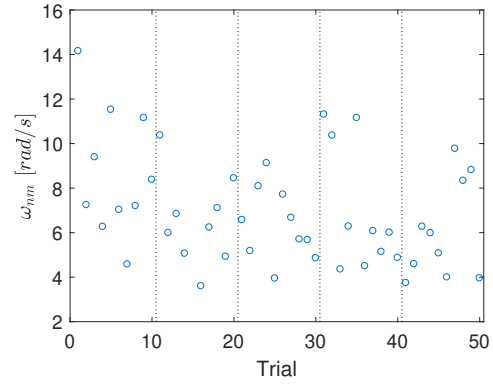
(e) K_p



(f) τ



(g) ζ_{nms}



(h) ω_{nms}

Fig. 9: Selected model for each measurement with corresponding model fit and parameter values, Participant1, ND

extremely difficult to keep steady when measurements are spread over multiple days. Moreover, as the elderly participant group is more vulnerable to changes in these variables, it is expected that there will be a statistically significant day-to-day variation in motor performance, which is visible in all control parameters, especially the time delay τ and damping ratio ζ_{nms}.

H.II. It is expected that the control performance of the dominant hand is better than for non-dominant hand control.
It has been found that regardless of age, the fine motor skill performance of the dominant hand is significantly better that of the non-dominant hand [44]. It is therefore expected to see a difference between motor performance score between the two hands. A better tracking performance, or lower RMSe, typically comes with a higher gain K_p and smaller time delay τ [40]. Furthermore, for the neuromuscular dynamics, it is expected that a higher natural frequency and damping ratio occur. As the fine motor skills in the non-dominant hand are suspected to be less effective, more overshoot is expected.

III. Trend analysis

This section explains the trend analysis methods used in this paper. Regression models are applied to the experimental data to correct for any learning trends, in order to prepare the 'healthy' data-set. Furthermore, PD data are simulated by bootstrapping the data for healthy participants and scaling these values based on previous research [20]. The combined data-set is then analysed using the same multivariate regression models to see if there is a detectable change in control behaviour for the simulated data.

A. Identification of changes in data

The goal of this research is to detect behavioural changes in motor performance data due to Parkinson's disease. As mentioned in Section I, previous research has shown that there is a significant difference in the motor performance of PD patients and a healthy control group [10, 11, 16], as well as in the specific control parameters defined in Section II [20]. To identify these changes, longitudinal clinical data were approximated by gathering data using the cybernetic method described in Section II and adding matched simulated PD data, which will be elaborated on in Section III-C2.

In order to detect changes in behaviour, anomalies in the motor performance data-set need to be found. Many different methods are available for finding changes in data-sets, with the main two methods being outlier and trend analysis [45]. Methods for detecting outliers and trends have many similarities and a close relationship in their utilisation in finding behavioural changes [45], however, due to the nature of its application the focus for this research lies on trend detection. This is because even though an outlier may identify atypical characteristics of a data-set, which can indicate progressing PD symptoms [24], human controllers are not machines and they may have a bad day where performance falls way below the previous average. Trend analysis is defined as finding a more consolidated change in a system over a longer period of time [23]. Multiple anomalies in a row, and ultimately a trend line, can give a more reliable indication that there are changes in performance due to disease progression and not just a one-off incident. Especially regarding a possible future application where a gradual disease progression is expected.

Statistical trend analysis methods can be used to separate underlying behavioural patterns from signal noise [23]. For the application of this research, monotonic trends were expected: gradual changes over time, consistent in direction [46], in other words, a decline in motor performance due to disease progression. Monotonic trends can be analysed using either parametric regression models or non-parametric statistical models [23]. The first are generally preferred as they are more powerful, if the underlying assumptions are valid [23]. Moreover, many different applications of parametric regression models are available to fit the data [31].

B. Regression models

Longitudinal and clinical data are most often analysed using regression models, which estimate the dependency between two variables [47]. Using the experimental motor performance data combined with a simulated data-set, regression models can be fitted to determine if there is a significant trend.

Due to the anticipated natural variance in day-to-day control behaviour, which will lead to relatively noisy data, and the fact that a monotonic decrease or increase was expected, linear regression models were deemed appropriate. Since these models indicate whether or not there is a general trend in the data and give its relative direction, it can be checked if the trend follows the decline in motor performance that is expected from previous research [20].

The linear regression model generally takes the form described by Equation (10). Here the response variable y_t is the parameter measured at each time interval and predictor variable x_t signifies the moment in time. β_0 and β_1 indicate the intercept and slope of the trend line and ε_t is the random error or deviation from the trend fit [23,30,31]. A graphical illustration is given in Figure 10.

$$y_t = \beta_0 + \beta_1 x_t + \varepsilon_t \tag{10}$$

In the case of multiple response variables, which in this paper are the estimated parameters K_p, τ, ζ_{nms}, ω_{nms}, tracking performance RMSe and control activity RMSu, the model is extended to its multivariable form in the general linear regression model (GLR) of Equation (11) [23, 48]. Here the variables indicate the set of related values, for example $\boldsymbol{Y}_t$ gives the set of the six response variables at time point t. Using MATLAB's *mvregress* function, the relation between the response variables was defined using a correlation matrix. For use of this model, any missing data points need to be extrapolated in order to provide a sufficient amount of 'healthy' data.

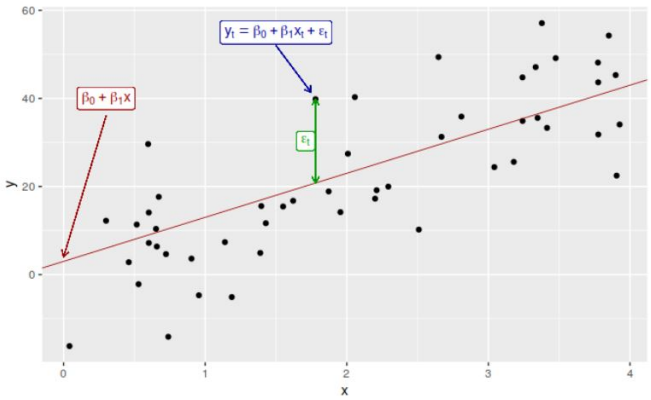


Fig. 10: Example of a simple linear regression model fitted on a random data-set [30]

$$\boldsymbol{Y}_t = \boldsymbol{\beta}_0 + \boldsymbol{\beta}_1 x_t + \boldsymbol{E}_t \tag{11}$$

The underlying assumptions of linear regression models are related to the errors ε_t, also known as the model residuals. One of the most important assumptions is a conditional normal distribution of residuals. Moreover, residuals have to have a zero mean to avoid bias, be unrelated to the predictor variable and not autocorrelated [30].

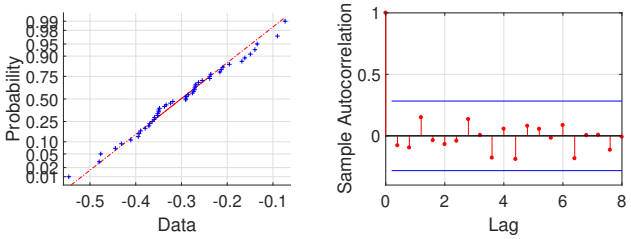
Fitting the regression model was done using least squares estimation (LSE) [23]. The model estimator for the intercept and slope is defined in Equation (12) [31]. The vector variables in this equation are defined in Equation (13). Here, $\mathbf{y}$ indicates the vector of one of the response variable values for all points in time $y_1, \ldots, y_t$.

$$\hat{\boldsymbol{\beta}} = \left(\mathbf{X^T X}\right)^{-1} \mathbf{X}^T \mathbf{y} \tag{12}$$

$$\mathbf{y} = \begin{bmatrix} y_1 \\ \vdots \\ y_n \end{bmatrix}, \ \hat{\boldsymbol{\beta}} = \begin{bmatrix} \hat{\beta}_0 \\ \hat{\beta}_1 \end{bmatrix}, \ \mathbf{X} = \begin{bmatrix} 1 & t_1 \\ \vdots & \vdots \\ 1 & t_n \end{bmatrix} \tag{13}$$

With the parameters of the regression model, a t-test can be used to determine if there is a significant trend in the data. The null hypothesis $H_0 : \beta_1 = 0$ is tested against the alternate hypothesis $H_1 : \beta_1 \neq 0$. This will determine if there is a statistically significant slope in the data-set [23]. The t is determined using Equation (14). If $\beta_1 = 0$ Equation (14) has a t-distribution with n-2 degrees of freedom [31]. where n indicates the sample size. This can be tested using the student's t cumulative distribution function.

$$t = \frac{\hat{\beta}_1}{\sqrt{\frac{\sum\left(y_i - \hat{\beta}_0 - \hat{\beta}_1 x_i\right)^2}{(n-2)}}} \tag{14}$$



(a) Residual normality (b) Residual autocorrelation

Fig. 11: Residual check for learning curve trend analysis for K_p, Participant 1

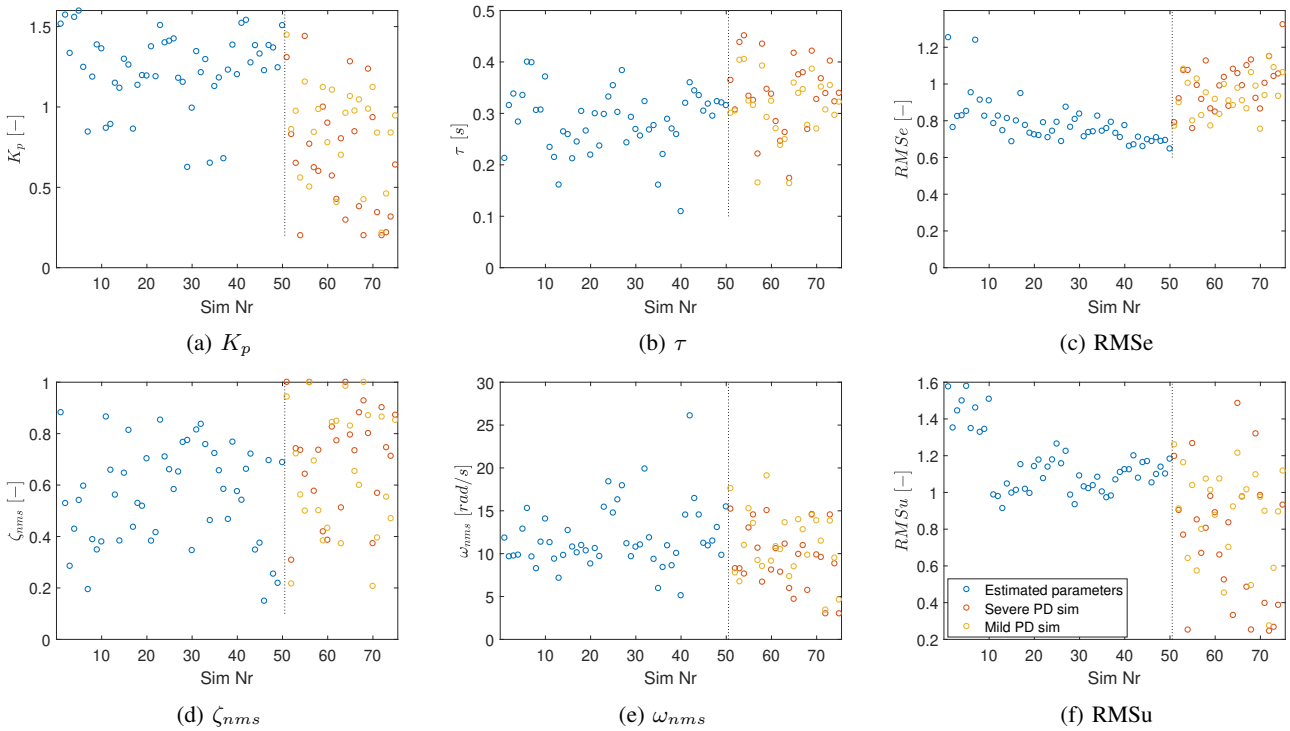
C. Data preparation

Before the trend analysis methods can be applied to the final data-set to identify behavioural changes due to Parkinson's disease progression, the baseline data-set as defined in Section II needs to be prepared. First of all, an initial trend check is performed in order to correct for any learning effects in the data as they can cancel out performance degradation due to PD. Furthermore, the simulated PD data are added to complete the data-set for the final analysis.

1) Learning curve: Even though it is hypothesised that there will not be a significant learning curve in the experimental data due to the simplicity of the task [20,21], the data are analysed for trends. If is a learning trend is found, it can severely affect the trend detection process for the full data-set. As a learning curve is accompanied with increasing performance and disease progression comes with decreasing performance, both trends may cancel each other out.

Using the general linear regression model described in Section III-B, by applying MATLAB's *mvregress* function to the data, any significant trends in the experimental data were detected. The assumptions for the model residuals are checked. With zero-mean correlation with t, no autocorrelation and a normal distribution, the model is found to be valid. An example of the residual check for Participant 1 is presented in Figure 11. After checking if the model assumptions were valid, the data were corrected for the significant trend and a second check was performed so see if the correction was accurate.

2) Simulation of PD data: The data-set is completed by adding data-points related to PD control behaviour. From the original data (50 data points), which have already been corrected for learning trends, 25 new related data points were defined using bootstrapping methods [23] for each participant and hand. These new data were then scaled as representative for PD symptoms, by adding a δ to the bootstrapped value. This δ is randomly selected from the predefined range shown in Table II that is based on differences between PD patients and healthy controls from real experimental data [20]. This variation in scaling allows for differences in symptom severity for good and bad control days and the changing influence of treatment also known as on/off moments [4].



(a) K_p (b) τ (c) RMSe

(d) ζ_{nms} (e) ω_{nms} (f) RMSu

Fig. 12: Estimated and simulated control parameters for Participant 25, D

TABLE II: Parameter Change Range for PD Symptom Simulation

	Mild Symptoms	Severe Symptoms
K_p	$-0.5 < \delta < 0$	$-0.9 < \delta < 0$
τ	$0 < \delta < 0.02$	$0 < \delta < 0.07$
ζ_{nms}	$0 < \delta < 0.2$	$0 < \delta < 0.31$
ω_{nms}	$0 < \delta < 3$	$0 < \delta < 5$

The table shows ranges for mild and severe symptoms. The main analysis is done with severe symptom data, to see if the model is actually able to detect behavioural changes in the data. The mild range will used for the sensitivity analysis so determine the range of symptom severity the model can handle. The PD values for the tracking performance, RMSe, and control activity, RMSu, were obtained by running a simulation model based on Figure 2 with the 4 new pilot parameters in Equation (4). The available data only covered the dominant hand, for this research it was assumed that for the non-dominant hand PD patients experience a similar decline and the same δ range could be used to simulate disease progression. 25 PD related data points were simulated for each participant and hand. This number was chosen to ensure a sufficiently high number of data points for detection of behavioural change, while keeping in mind that detection after many data points might not provide an improvement on current diagnostic methods.

Figure 12 gives an example of the combined experimental and simulated dominant-hand control data-set for Participant 25. Here, the blue dots before the vertical black line indicate the estimated parameters and the yellow and red points are the mild and severe simulated bootstrap data points, respectively.

3) Combined data: From the previous preparation steps, two different data-sets are available for each participant and control hand, the data for healthy participants, corrected for any learning trends, and the simulated PD data related to the previous data-set. These are combined to form the data that will be used in the detection of behavioural changes in motor performance data using the same regression models as for the learning effect analysis.

D. Sensitivity

After the initial trend analysis is performed, the sensitivity of the model needs to be checked. This is done with three tests. First of all the number of data points used in the trend analysis is varied to see how detection performance changes and how many affected data points are required for detection. Second, the severity of the discrepancies in the simulated PD data can be altered to analyse the applicability of the model to different symptom severity levels. Finally, a group of good participants was selected in order to determine how detection performance changes for different controllers.

1) Changing number of data points: Firstly, the number of data points used in the trend analysis is changed. The original model uses 50 'healthy' and 25 simulated PD points. As the disease progression is unique for each participant,

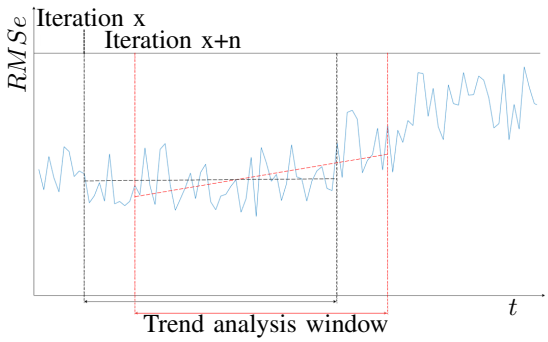


Fig. 13: Example of the sliding window detection method with randomly generated data

the number of baseline data points preceding a behavioural change due to increasing symptom severity is different in each case. Moreover, a longer set of healthy data can balance out any initial trends, needing a higher number of affected data points before a trend is identified. The number of PD data points required for detection of behavioural changes in motor performance data is a good indication of the sensitivity of the model.

The first change to the model was to gradually add data points instead of using the full data-set from the start. The model started off with 50 data points, as that is the amount in the baseline data-set. During each iteration, one of the PD data points is added and the new set is analysed for trends, so that the minimum number of affected data points needed for trend detection can be determined.

Secondly, use was made of a sliding window for the trend detection iterations. In this case a fixed window size is chosen that is shifted every iteration, as shown in Figure 13. This allows for trend detection that is not weighed by a large amount of baseline data, therefore it is expected that the initial decline in performance is detected earlier. In order to pick an appropriate window size, several options were analysed to determine which performed best. Good performance is defined as early trend detection. However, to avoid any false positives, the detection should be stable, with values under the significance threshold, for several consecutive data points.

2) Participant selection: Another aspect in defining the applicability of the trend model to the whole population is to see how the analysis differs for a selection of the participants with a good performance, or in other words to define the percentage of the population for which this model can successfully be applied. The initial analysis is performed for the whole participant group, which could lower the overall performance of the trend detection model due to the difficulty of finding trends in noisy data of participants with a lower motor performance, such as PD patients. When making a selection of good participants, it can be determined if the model only works for high performing participants or if performance does not have

TABLE III: Participant inclusion criteria value range

Inclusion criterion	Value range
RMSe [-]	≤ 1
MMSE [-]	≥ 26
Reaction time simple tap [s]	≤ 0.4
Reaction time screen touch [s]	$0.8 \leq \delta \leq 1.2$
Reaction time space release [s]	$0.2 \leq \delta \leq 0.4$
Taps per second [-]	≥ 4

a significant effect on the accuracy of detection of behavioural changes. The inclusion criteria for the good participants are defined as follows.

First of all, the number of missing data points, as defined in Section II-E, cannot be higher than 10, for each control hand. A higher number would mean that more than one-fifth of the original data are missing. Moreover, missing data points indicate noisy data with a bad system identification model fit, which relates to a lower control performance. If more than 20% of the data are missing, it generally means that the participant did not have adequate control over the system.

Another measure of control performance was defined by the tracking performance, or RMSe parameter. If a participant would not give any input, the RMSe would be 1 for this control task. The parameter indicates whether a participant reduced the tracking error while controlling the system ($\leq$1) or actually increased the error by providing an input ($\geq$ 1). Therefore, a score of 1 or lower was defined as adequate control performance.

The MMSE is a measure of the cognitive functioning of the participants and a MMSE score $\geq$ 26 indicates that a participant does not show cognitive decline [49]. Therefore, this threshold is taken into account when selecting participants with a sufficiently high tracking performance. However, it must be noted that the all participants had a score of 26 or higher. This threshold is, therefore, not a defining factor in the participant selection, but should be taken into account for future research.

Moreover, several baseline tests, developed by the neuroscience department of the EMC [9], were performed before the start of the experiment in order to tests if the participants were able to perform basic motor tasks. These data were used in the selection of the participants with a higher motor performance. From these tests several motor performance parameters were defined, and inclusion criteria thresholds were formed visually, including the majority of participants while excluding obvious outliers. The complete set of ranges for the performance criteria are given in Table III.

The final selection of participants with an adequate control performance included 15 of the original 25 participants, only 60% of the group. The age range of this new group was the same, but the average age was almost three years younger than the complete participant group, ($\mu = 64.07$ years, $\sigma = 6.74$ years). This indicates that age is an important factor in the analysis of the data and applicability of the model.

3) Symptom severity: As already mentioned in Section III-C2, two different severity ranges for the PD data were defined and the general trend analysis was done using the severe symptom range. In order to test the applicability of the model to different ways of disease progression, trend analysis performance with differing symptom severity was compared. It must be noted that the differences between mild and severe symptoms are subjective and taken as averages and extremes of the data from previous research [20], respectively. As the patients in previous research were early stage, the average values were deemed appropriate for milder symptoms and the extremes for severe symptoms. This was chosen so that the simulated data were still based on actual values.

E. Hypotheses

For the trend analysis method, two further hypotheses are defined.

H.III. It is expected that learning effects do not significantly influence motor performance and its parameters.
Previous research indicates that a pursuit task has a lower complexity and workload as compared to preview tasks [21]. Furthermore, patients were able to perform the task after a short amount of practise [20]. Therefore, it is expected that there will be no obvious learning trends in the data.

H.IV. It is expected that significant trends are found when analysing each individual, combined experimental and simulated PD data-set for the gain K_p, damping ratio ζ_{nms} and tracking performance RMSe, for 65% of the participants.
Previous research has shown that there is a significant difference in parameters related to motor performance of patients and an age-matched control group [20]. These differences are the baseline for the simulated PD data and as such it is expected that there will be a visible trend in time, in other words a behavioural change in motor performance, for the combined healthy experimental and simulated PD data-set for these parameters. However, it is unlikely that this will be the case for all participants, due to the variability in performance metrics. Taking into account the participants with a relatively high RMSe, therefore, low performance, and a low relative remnant, which means noisy data, it is expected that for 65% of the participants a detectable change in motor behaviour due to PD symptoms is found.

IV. Experiment

In this section the experimental set-up is discussed. With the described experiment the data used in the cybernetic approach is gathered and these data provide the base for the healthy participant data part used in the detection of behavioural changes in motor performance data.

A. Apparatus

The experiment was performed in several common rooms of group homes for the elderly using a portable experimental set-up. The main experiment ran on a HP laptop with a Linux operating system (Ubuntu 18.04.3 LTS) on the Delft University Environment for Communication and Activation (DUECA) [50]. A Dell P2341T touchscreen was used as input device and was connected to the laptop, as shown in Figure 14. Participants were asked to wear touchscreen gloves in order to reduce friction between the finger and touchscreen. The touchscreen was re-positioned for use with the dominant and non-dominant hand to provide a more natural control position for the hand.

Fig. 14: Experiment test set-up.

Motor performance baseline measurements were done by measuring reaction times and eye-hand coordination using a portable setup from the EMC [9]. The Tobii X2-60 compact eyetracker was positioned below the touchscreen and was combined with the Tobii Pro Studio software to run tests measuring reaction time and control precision. A separate keyboard and the previously mentioned Dell touchscreen were used as input devices for the tests.

B. Target forcing function

To analyse the data using the frequency domain identification method described in Section II-B, a quasi-random multisine forcing function was used as a target function in the pursuit tracking task. The forcing function is defined as the sum of eleven sinusoids with different frequencies, amplitudes and phases, as shown in Equation (15). The frequencies ω_f of the multisine are all integer multiples of the base frequency ω_m, defined by Equation (16), where T_m indicates the measurement time.

$$f(t) = \sum_{k=1}^{N_f} A_f(k) \sin\left(\omega_f(k)t + \phi_f(k)\right) \tag{15}$$

$$\omega_m = \frac{2\pi}{T_m} \tag{16}$$

This multisine described by the eleven sinusoids of Table IV has been used in previous research [20–22]. This combination of sines was found to be able to cover the whole region of interest in human behaviour dynamics and was used in this research for continuity reasons.

TABLE IV: Target Signal Components, obtained from [20]

N_f	ω_f $[rad/s]$	A_f $[deg]$	ϕ_f $[rad]$
4	0.614	1.079	7.239
7	1.074	0.776	0.506
13	1.994	0.391	7.860
19	2.915	0.225	8.184
29	4.449	0.117	9.012
37	5.676	0.082	6.141
43	6.596	0.066	6.776
53	8.130	0.051	6.265
79	12.118	0.035	4.672
109	16.720	0.028	2.672
157	24.084	0.024	8.009

Previous research used a signal length of $50\ s$, of which the first $9.04\ s$ where used as run-in time and the latter $40.96\ s$ as measurement time T_m [20–22]. The sinusoid amplitudes were determined using a second-order low pass filter as described in Equation (17), where $T_{A_1} = 0.1\ s$ and $T_{A_2} = 0.8\ s$. Finally, the phases were selected 'randomly' to achieve an average crest factor [20]. The input signal polarity was switched for every second trial to mitigate learning effects in the experiment.

$$H_A(j\omega) = \frac{(1 + T_{A_1} j\omega)^2}{(1 + T_{A_2} j\omega)^2} \tag{17}$$

C. Dependent measures

During each measurement run, the target signal f_t, control signal u and system output y, as previously defined in Figure 2, were recorded for use in the data analysis. From these signals, the control parameters K_p, τ, ζ_{nms} and ω_{nms} were determined using the approach described in Section II. The tracking performance metric, indicated as RMSe, is defined as the root mean squared (rms) value of the error divided by the rms of the target signal, or $RMS(e)/RMS(f_t)$. Control activity, here defined as RMSu, is defined similarly to the tracking performance as $RMS(e)/RMS(u)$. A high value indicates that the participant is actively controlling the system, while a lower value signifies a more reserved control strategy.

D. Participants

The participant group consisted of 25 healthy people, with an age range of 56-75 years ($\mu = 66.88$ years, $\sigma = 6.77$ years), coinciding with the average age of symptom onset for Parkinson's disease [4]. An overview of the participant information is given in Table V. Moreover, an elderly participant group shows similar, though slightly better, control performance compared to patients on Levodopa treatment [13], which provides a good baseline for the approximated data. Healthy participants included people who did not have any neurological impairments. Minor deficits related to old age, such as slight slowness of movement that did not severely influence motor performance, were allowed as they show the impact of natural neurological degeneration caused by the ageing of the brain. All participants signed a consent form. The experiment was approved by the Delft University of Technology, Human Research Ethics Committee (HREC) with application number 982. The performance variation and trend analyses are performed for the whole participant group. This is followed by the analysis for a selection of the participants in the sensitivity analysis as mentioned in Section III-D.

TABLE V: Overview of participant information

Participant	age	sex	Handedness
1	56	f	r
2	58	m	r
3	75	f	r
4	75	f	r
5	72	f	r
6	74	m	r
7	73	f	r
8	74	f	l
9	75	m	r
10	58	m	r
11	64	f	r
12	64	f	r
13	64	m	r
14	61	f	r
15	67	f	r
16	70	f	r
17	72	f	r
18	62	m	l
19	60	f	r
20	58	f	r
21	69	m	r
22	75	f	r
23	68	f	r
24	72	f	r
25	56	f	r

E. Procedures

To approximate longitudinal clinical data, the experiment was spread over 5 days. During the first day, an elaborate briefing was given on the experiment. This was followed by measurements for both dominant and non-dominant hand control and debriefing. For the follow-up measurement sessions the briefing was shortened and the baseline tests were skipped.

Before the start of the experiment, all participants were asked to perform a Mini Mental State Examination (MMSE) to assess cognitive functioning [49]. A baseline for the motor performance is defined with two short tests, measuring reaction time and eye-hand coordination, using tests developed by the neuroscience department of the Erasmus MC [9], where eye and hand movements are compared to estimate motor performance of participants.

The measurements consisted of two blocks with five practice trials, to re-acquaint themselves with the task and control hand, and 10 measurement trials, with short breaks in between to lessen fatigue of the hand and eyes. For the first day, the training blocks were expanded until the participant showed stable control behaviour. In each block the participant controlled the system with alternately the dominant and non-dominant hand. Learning effects and fatigue were mitigated by changing the order of starting with either D or ND control, per subject and measurement set. 10 trails per hand per measurement day were

chosen to ensure that enough data points for further analysis with trend methods.

V. Results

This section presents the results of this paper. First the outcomes of experimental data analysis for variation in the data are given. After this, the results for the trend analysis are presented, for the learning curve, main trend detection and sensitivity analysis.

A. Experiment

1) Day-to-day variation: To understand how control behaviour is influenced when the measurements are spread over multiple days, the data were analysed for day-to-day variance. Two different situations were defined for the complete experimental data-set, namely separate data for dominant (D) and non-dominant (ND) control. The analysis was performed for all of the estimated parameters and performance and input scores that were calculated in the manner described in Section II. As mentioned, the data did not have a normal distribution, therefore, Friedman's ANOVA was used for the statistical analysis to see if any significant differences were present.

An overview of daily variation in the dominant hand data-set is presented in Figure 15, where a between-subject correction has been applied. The box plots show the quartiles and medians, and outliers are indicated with a red asterisk. Both the data in this figure, as well as the ND set, were not normally distributed in accordance with the Shapiro Wilk test for normality. Upon visual inspection, it can be seen that for the gain, time delay and damping ratio there seems to be a difference between the daily performance. The variation is mainly in a monotonic manner, which could indicate a learning curve; this will be elaborated on in Section V-B1. The difference between days is confirmed by Friedman's ANOVA, where a significant effect between the days was found for all parameters except ω_{nms}, as shown in Table VI.

Using Wilcoxon's test for post hoc analysis, it was determined that for the dominant hand data-set there is a highly significant effect between the majority of days, as shown in Table VII. For ω_{nms} no analysis was performed as the results of Friedman's ANOVA were insignificant. The few relations where no significant effects were found for the estimated parameters K_p, τ and ζ_{nms} generally centered on day 3 with day 2 or 4, or other adjacent days. Similar results were found for the ND sets, with a slightly higher number of significant relations, which means there is a somewhat higher variation in control performance for the non-dominant hand as compared to dominant hand control, though it is very limited.

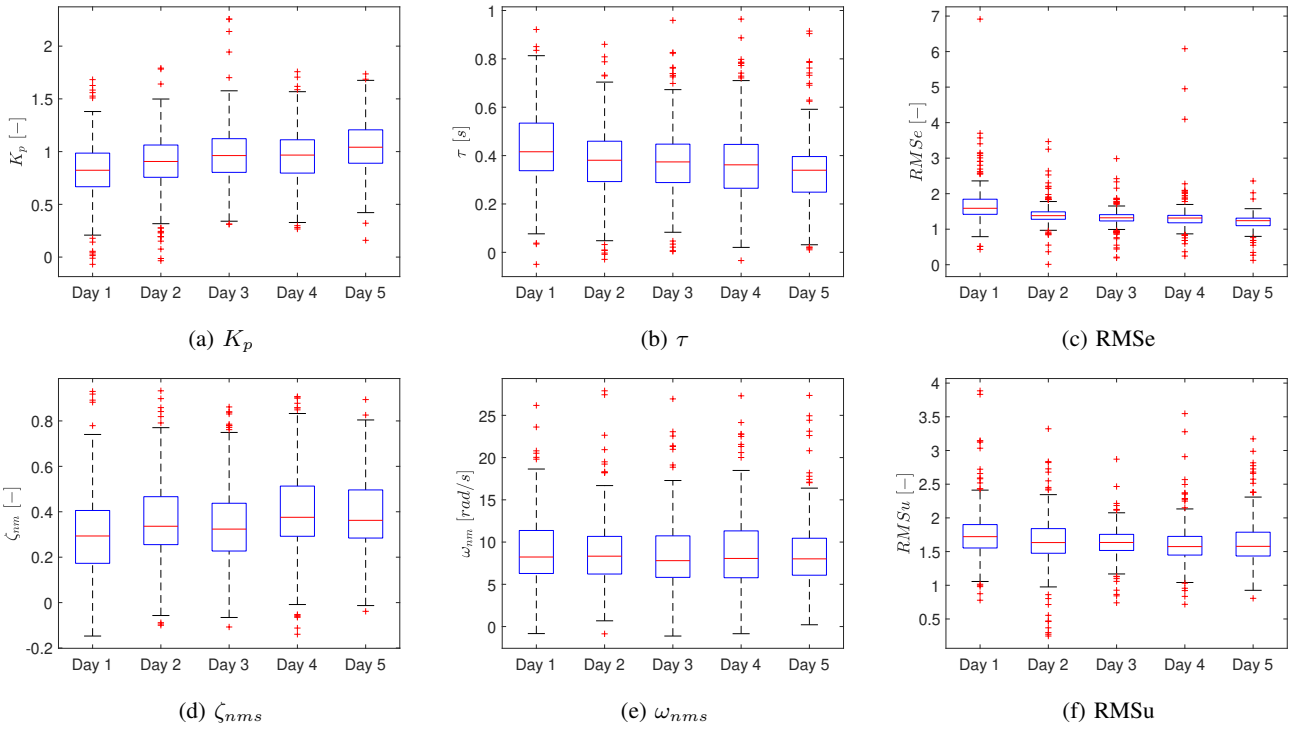
Individual values for the standard deviation in the data and corresponding Coefficient of Variance (CV) are presented in Table VIII. Here, the CV is defined as the percentage of the mean, or $\sigma/\mu * 100\%$ and gives an indication of the relative spread of the data. A higher percentage indicates a larger variation. The individual statistical analysis demonstrated that for the tracking performance and control activity, almost all controllers showed a significant effect in the day-to-day variance, see Table IX. The control parameters, however, have lower percentages. Only for the control gain more than half of the participants have significant differences in day-to-day variance with 56% and 64% respectively. For all other estimated parameters less than half of the participants show a significant difference in the data. Nonetheless, the natural frequency showed the lowest percentage, congruent with the insignificant ANOVA results. Any differences between the two analyses could be attributed to the significantly smaller data-sets in the individual analysis.

2) Dominant and non-dominant hand control: The experimental data were also analysed for differences between dominant and non-dominant hand control motor performance. While in the day-to-day variation no major differences were found between the two control hands, there could still be a difference in participants' control performance. The data were not normally distributed, therefore, the Wilcoxon's matched pairs test was used in the analysis.

Figure 16 shows the results of the analysis of dominant and non-dominant hand control for the complete data-set and all control performance parameters. The results of the statistical test are given in Table X. Highly significant differences ($p \leq 0.01$) were found for all parameters but the time delay and neuromuscular frequency. For the gain, tracking performance and control activity the average for the non-dominant hand was higher and for the damping the average was lower.

Individual analysis showed that there were considerable differences in these results between participants. Table XI shows the results for the individual statistical tests. An upward trend means the average for ND is higher than for D. The majority of participants with a significant result followed the trend found in the main analysis for all parameters, except the time delay. In the combined data-set the time delay did not show any significant differences, while for the individual analysis over half of the participants show major differences. Moreover, several participants showed results which are highly contrasting to the combined data-set. An example of such constrasting results for the tracking performance is given in Figure 17, where Participant 25 has a significantly higher score, thus worse performance, for the non-dominant hand ($W = -4.71$, $p \leq 0.01$), while for Participant 16 this was reversed ($W = 2.08$, $p \leq 0.05$).

Further observations showed that participants generally had a lower performance for the hand they started controlling the system with on the first day. In other words, if the first measurements were done using ND control, the final performance for D control was generally higher, though this is not statistically supported. This could be explained by learning effects, as the participants had more time to understand the system before controlling with the second hand, performance way higher at the end of the measurement day.



(a) K_p (b) τ (c) RMSe

(d) ζ_{nms} (e) ω_{nms} (f) RMSu

Fig. 15: Day-to-day variation in motor performance parameters, D

TABLE VI: Results of Friedman's ANOVA for day-to-day variation for all data with either dominant (D), non-dominant (ND) control, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

Friedman's ANOVA		Dependent measures											
		K_p		τ		ζ_{nms}		ω_{nms}		RMSe		RMSu	
Data set	df	χ^2	Sig.	χ^2	Sig.	χ^2	Sig.	χ^2	Sig.	χ^2	Sig.	χ^2	Sig.
D	4	75.32	**	31.91	**	42.03	**	2.40	-	344.23	**	64.37	**
ND	4	119.43	**	38.46	**	48.85	**	4.49	-	313.40	**	61.30	**

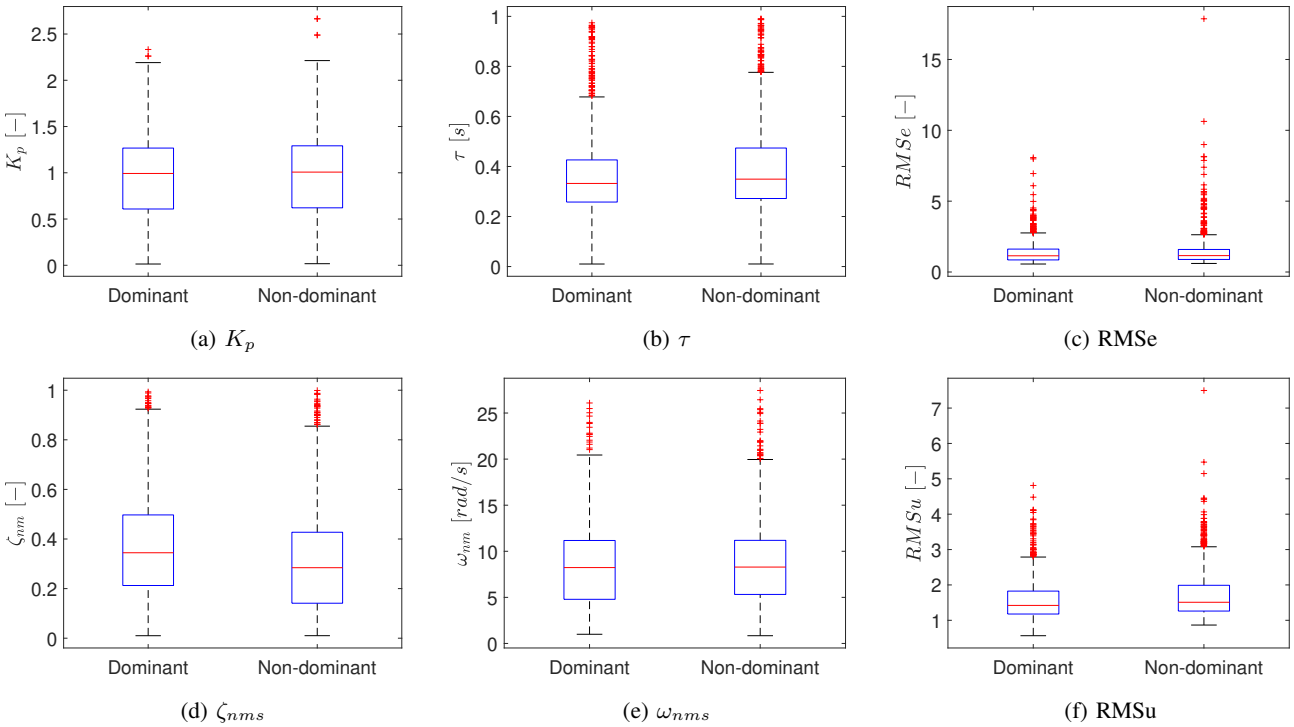
TABLE VII: Results of post hoc Wilcoxon test for day-to-day variation for dominant hand control (D), where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

Wilcoxon - D	Dependent measures											
	K_p		τ		ζ_{nms}		ω_{nms}		RMSe		RMSu	
Data set	W	Sig.	W	Sig.	W	Sig.	W	Sig.	W	Sig.	W	Sig.
Day 1 - Day 2	-3.04	**	1.95	-	-3.27	**	n/a	n/a	8.82	**	3.16	**
Day 1 - Day 3	-4.84	**	1.14	-	-3.12	**	n/a	n/a	10.26	**	4.87	**
Day 1 - Day 4	-5.14	**	2.41	*	-5.13	**	n/a	n/a	10.94	**	5.44	**
Day 1 - Day 5	-7.46	**	5.33	**	-4.31	**	n/a	n/a	12.41	**	4.97	**
Day 2 - Day 3	-1.59	-	0.09	-	0.11	-	n/a	n/a	3.32	**	0.51	-
Day 2 - Day 4	-1.79	-	1.47	-	-2.58	**	n/a	n/a	5.69	**	2.94	**
Day 2 - Day 5	-4.98	**	3.10	**	-1.42	-	n/a	n/a	8.96	**	3.29	**
Day 3 - Day 4	-1.17	-	1.68	-	-3.03	**	n/a	n/a	3.41	**	2.84	**
Day 3 - Day 5	-4.73	**	3.51	**	-3.27	**	n/a	n/a	8.19	**	1.78	-
Day 4 - Day 5	-4.31	**	2.17	*	0.39	-	n/a	n/a	5.11	**	0.45	-

TABLE VIII: Standard deviation and coefficient of variance of control parameters for all participants

	Parameters															
	K_p				τ				ζ_{nms}				ω_{nms}			
Participant	D		ND		D		ND		D		ND		D		ND	
	σ	CV	σ	CV	σ	CV	σ	CV	σ	CV	σ	CV	σ	CV	σ	CV
1	0.20	23	0.24	24	0.13	39	0.12	36	0.17	52	0.20	50	3.68	57	2.45	35
2	0.26	19	0.18	12	0.08	25	0.06	19	0.10	41	0.08	36	3.14	28	3.40	25
3	0.10	84	0.19	47	0.22	62	0.25	40	0.08	108	0.08	73	7.50	70	5.15	70
4	0.16	68	0.21	68	0.31	63	0.25	62	0.09	105	0.18	135	6.78	79	7.35	63
5	0.31	32	0.32	35	0.19	42	0.22	43	0.21	68	0.18	73	4.32	62	4.04	55
6	0.30	49	0.28	39	0.18	46	0.14	38	0.21	42	0.26	74	4.98	61	4.86	52
7	0.25	33	0.34	37	0.15	33	0.12	38	0.25	61	0.25	47	7.15	66	5.86	65
8	0.37	39	0.55	42	0.16	36	0.09	28	0.20	62	0.25	70	3.44	38	3.98	39
9	0.28	24	0.25	19	0.07	21	0.08	25	0.20	67	0.13	56	3.29	31	4.17	39
10	0.24	21	0.24	18	0.06	24	0.05	19	0.20	30	0.18	30	2.66	26	2.98	27
11	0.54	61	0.35	37	0.14	46	0.18	57	0.31	61	0.22	44	4.95	59	4.68	71
12	0.24	51	0.26	58	0.23	52	0.18	55	0.31	75	0.31	81	6.04	73	6.16	65
13	0.17	16	0.28	24	0.07	23	0.14	52	0.17	34	0.21	43	2.00	32	3.07	47
14	0.34	67	0.22	47	0.29	54	0.22	37	0.12	80	0.05	68	5.36	79	4.49	68
15	0.23	32	0.18	39	0.09	33	0.23	51	0.21	51	0.10	72	4.62	45	4.42	51
16	0.36	48	0.39	47	0.14	41	0.17	56	0.31	57	0.25	54	5.75	63	4.27	61
17	0.22	50	0.33	75	0.28	51	0.22	53	0.14	68	0.12	84	6.07	92	6.35	62
18	0.22	16	0.35	25	0.12	51	0.11	42	0.16	35	0.17	37	3.71	45	3.85	42
19	0.22	18	0.21	17	0.08	26	0.06	22	0.13	38	0.07	26	2.87	34	1.54	22
20	0.14	13	0.17	16	0.11	41	0.10	29	0.15	38	0.19	51	3.20	43	3.23	34
21	0.37	27	0.38	39	0.06	20	0.08	23	0.20	33	0.20	53	2.76	30	4.44	36
22	0.34	37	0.37	33	0.13	32	0.08	27	0.25	57	0.25	44	3.73	36	4.18	38
23	0.49	37	0.37	27	0.12	36	0.12	30	0.22	49	0.20	51	3.50	42	3.74	39
24	0.47	38	0.44	39	0.14	37	0.15	32	0.13	48	0.09	51	2.71	50	3.10	40
25	0.25	20	0.16	16	0.07	24	0.09	29	0.22	39	0.23	44	3.69	31	2.90	28

	Parameters							
	RMSe				RMSu			
Participant	D		ND		D		ND	
	σ	CV	σ	CV	σ	CV	σ	CV
1	0.24	23	0.20	21	0.29	22	0.23	18
2	0.16	21	0.14	17	0.24	17	0.29	19
3	0.66	32	0.41	20	0.39	33	0.36	19
4	1.23	36	1.94	46	0.58	26	0.72	30
5	0.35	20	0.33	18	0.63	24	0.73	27
6	0.37	27	0.23	19	0.27	23	0.16	13
7	0.45	32	0.22	18	0.28	20	0.34	22
8	0.36	22	0.25	21	0.35	17	0.84	34
9	0.39	37	0.33	33	0.27	17	0.36	20
10	0.17	20	0.09	11	0.15	13	0.13	11
11	0.20	18	0.29	23	0.27	17	0.30	19
12	0.31	20	0.41	24	0.24	21	0.26	21
13	0.10	11	0.15	18	0.09	8	0.11	9
14	0.57	25	0.99	41	0.57	28	0.69	28
15	0.35	28	0.55	36	0.17	14	0.37	27
16	0.27	21	0.17	14	0.31	23	0.31	22
17	0.91	37	2.39	90	0.54	24	1.04	45
18	0.12	17	0.15	20	0.14	11	0.14	10
19	0.22	26	0.17	19	0.16	13	0.16	11
20	0.10	12	0.18	19	0.16	13	0.15	11
21	0.18	19	0.20	18	0.17	12	0.26	17
22	0.49	35	0.60	40	0.22	13	0.29	17
23	0.21	22	0.17	17	0.32	21	0.23	13
24	0.23	17	0.29	20	0.77	31	0.60	25
25	0.12	15	0.11	13	0.17	15	0.18	15



(a) K_p (b) τ (c) RMSe

(d) ζ_{nms} (e) ω_{nms} (f) RMSu

Fig. 16: Dominant and non-dominant hand control performance parameters

TABLE IX: Percentage of participants with a significant (p<0.05) result for Friedman's ANOVA for day-to-day variation, all estimated parameters

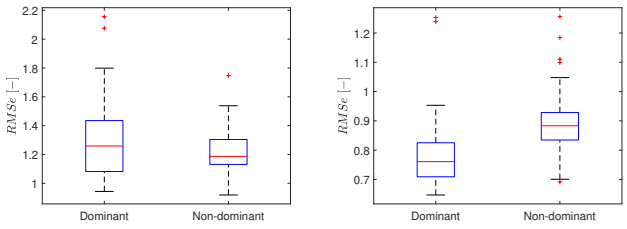
data-set	Dependent measures					
	K_p	τ	ζ_{nms}	ω_{nms}	RMSe	RMSu
D	52%	40%	36%	20%	92%	92%
ND	64%	40%	28%	24%	96%	88%

TABLE X: Results of Wilcoxon's test for dominant and non-dominant hand control analysis, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

Parameter	W	Sig
K_p	−2.85	**
τ	−0.73	-
ζ_{nms}	5.44	**
ω_{nms}	−1.72	-
RMSe	−3.11	**
RMSu	-10.50	**

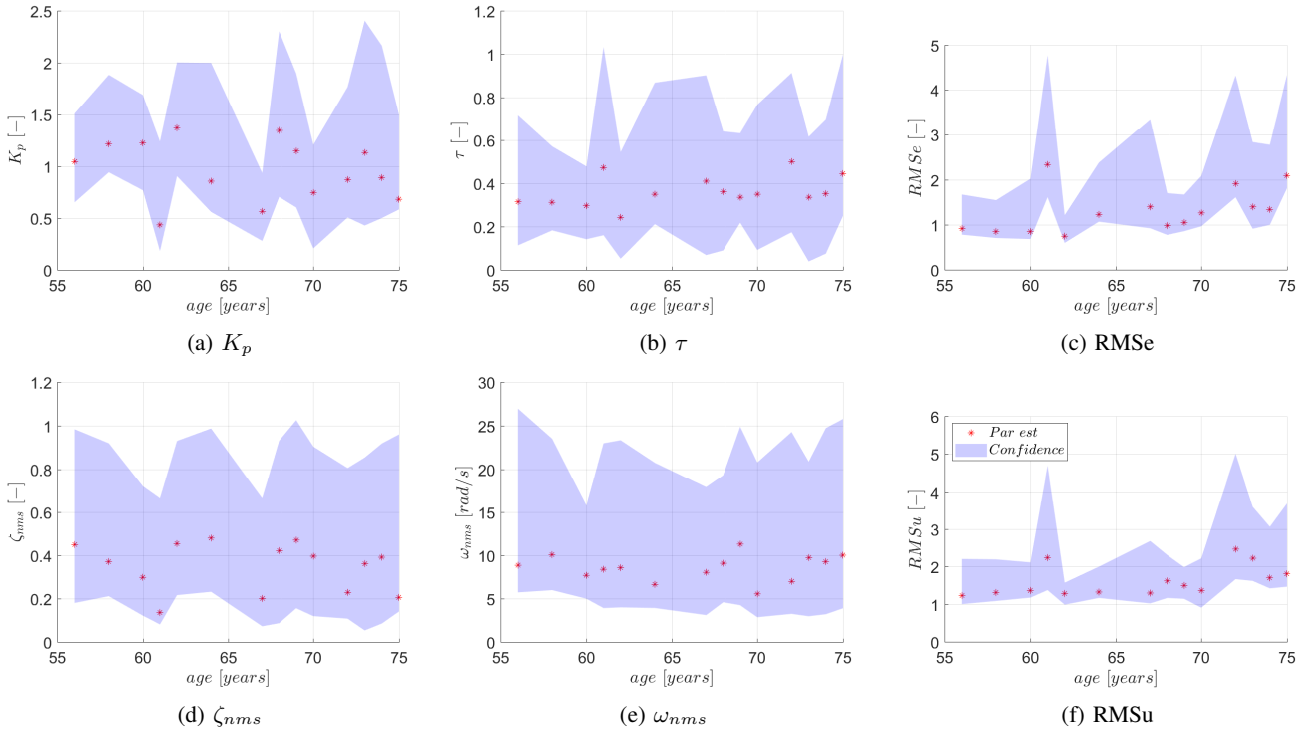
TABLE XI: Percentage of participants with a significant trend ($p < 0.05$) for dominant and non-dominant hand control analysis, and their slope indication, all estimated parameters

Parameter	upward	downward	not significant
K_p	32%	12%	56%
τ	32%	20%	48%
ζ_{nms}	16%	16%	68%
ω_{nms}	16%	12%	72%
RMSe	32%	28%	40%
RMSu	44%	20%	36%



(a) Participant 25 (b) Participant 16

Fig. 17: Comparison of difference in score parameters with D and ND control for two participants



(a) K_p (b) τ (c) RMSe

(d) ζ_{nms} (e) ω_{nms} (f) RMSu

Fig. 18: Learning curves and data correction Participant 23, ND

3) Ageing and performance: It would also be interesting to see how performance can be influenced by increasing age and to define confidence bins for healthy participants. If a future participant would fall outside of these confidence intervals, combined with an initial trend, it could indicate upcoming PD symptoms.

Figure 18 presents all performance metrics values related to the age of the participants. The red asterisks give the average across participants with the same age and the blue fill indicates 95% confidence interval. It must be noted that the number of participants per age group differs significantly. Any clear outliers, such as at age 61, can be explained by a single participant of that age with better or worse than average performance. In general the trend is that the confidence limits become slightly broader and performance, both visible in the RMSe and related control parameters, worsens with age.

B. Trend analysis

1) Learning curve: To determine whether part of the variance in the data found in Section V-A1 can be attributed to learning effects, trend analysis is used. A monotonic upward or downward trend, in combination with improving performance scores, can indicate an learning curve spread over multiple days, where the motor performance of a participant keeps improving.

Table XII gives an overview of the percentage of the participants with a significant trend (p<0.05) in the original experimental data. For the tracking performance RMSe, 84% of the participants showed a significant downward trend, so higher performance, which indicates that, overall, there is a learning curve present. Moreover, the 68% of participants with a significant change in control activity shows that more than half of the participants adapted their control behaviour as they were learning and understanding the system over the five measurement days. For the estimated control parameters K_p, τ, ζ_{nms} and ω_{nms} the percentages are lower, but still indicate that control behaviour changed over time. For all significant trends, the trend lines of RMSe, K_p, and ζ_{nms} were increasing while τ and ω_{nms} decreased, related to an increase in motor performance. For the RMSu trend lines, the slope direction changed between up and downward trends, depending on the changing control strategy of the participant.

TABLE XII: Results of GLR learning curve analysis, percentage of participants with a significant learning curve (p<0.05) in experimental data, all estimated parameters

Parameter	Significance
K_p	64%
τ	48%
ζ_{nms}	54%
ω_{nms}	28%
RMSe	84%
RMSu	68%

Figure 19 shows an example of the results for the learning curve trend analysis for Participant 23, for non-dominant

TABLE XIII: Results of one-sample t-test for learning curve analysis for Participant 23, ND, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

Parameter	df	t	Sig
K_p	48	21.21	**
τ	48	12.05	**
ζ_{nms}	48	7.63	**
ω_{nms}	48	9.39	**
RMSe	48	23.91	**
RMSu	48	30.81	**

hand control. It can be seen that, for this participant, all parameters had a significant trend (red line), with statistical details presented in Table XIII.

For further analysis the significant learning curves have been corrected and a second regression model was fit to the corrected data to check if the correction was done properly. The purple lines in Figure 19 indicate the regression fit for the corrected data, showing no significant remaining trends.

2) Trend analysis: Aside from its application to the experimental data when analysing for learning curves, the general linear regression model as described in Section III was used to determine if there are any detectable trends in the approximated longitudinal clinical data with a simulated disease progression, i.e., the combined experimental (healthy) and simulated (PD) data-sets. After fitting a regression line, a t-test was used to see if the line had a significant slope, which indicates a trend.

Table XIV provides an overview of the percentages of participants with a significant slope for the different metrics, both for the combined data-set and the separate sets. Since the variance had only minor differences in between D and ND control and similar ranges were used for PD parameter simulation, no major differences were expected, this is confirmed by the data. As can be seen in Table XII, the values for the separate D and ND data-sets generally correspond to that of the combined set. Minor deviations, of one or two participants, are found for K_p, ω_{nms}, RMSe and RMSu.

Furthermore, it can be seen that for the gain, time delay, damping ratio, tracking performance and control activity, at least half of the participants have a significant slope in the regression line fitted to the approximated longitudinal data. Finally, as a change in K_p, ζ_{nms} and RMSe is expected from previous research [20], the data were analysed to see how many participants showed change in behaviour for all three PD related control parameters. From the trend analysis it was found that 34% of the participants showed such results.

Figure 20 presents an example of the regression models fitted to the data-set of Participant 25 with dominant hand control. The red lines indicate the model fitted to the estimated and simulated parameters, defined by the blue dots, the dashed purple line gives the regression line fitted to the healthy experimental data and the vertical black line separates the experimental and simulated data. Table XV gives the corresponding t-test results for the null hypothesis (i.e. no significant slope). It can be seen that there is a significant trend for all parameters except the time delay, which corresponds to the results in Figure 20.

TABLE XIV: Results of GLR trend analysis, percentage of participants with a significant trend ($p<0.05$), all estimated parameters

Parameter	Combined	D	ND
K_p	66%	60%	72%
τ	64%	64%	64%
ζ_{nms}	96%	96%	96%
ω_{nms}	46%	44%	48%
RMSe	50%	48%	52%
RMSu	58%	56%	60%

TABLE XV: Results of one-sample t-test for GLR trend analysis for Participant 25, D, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

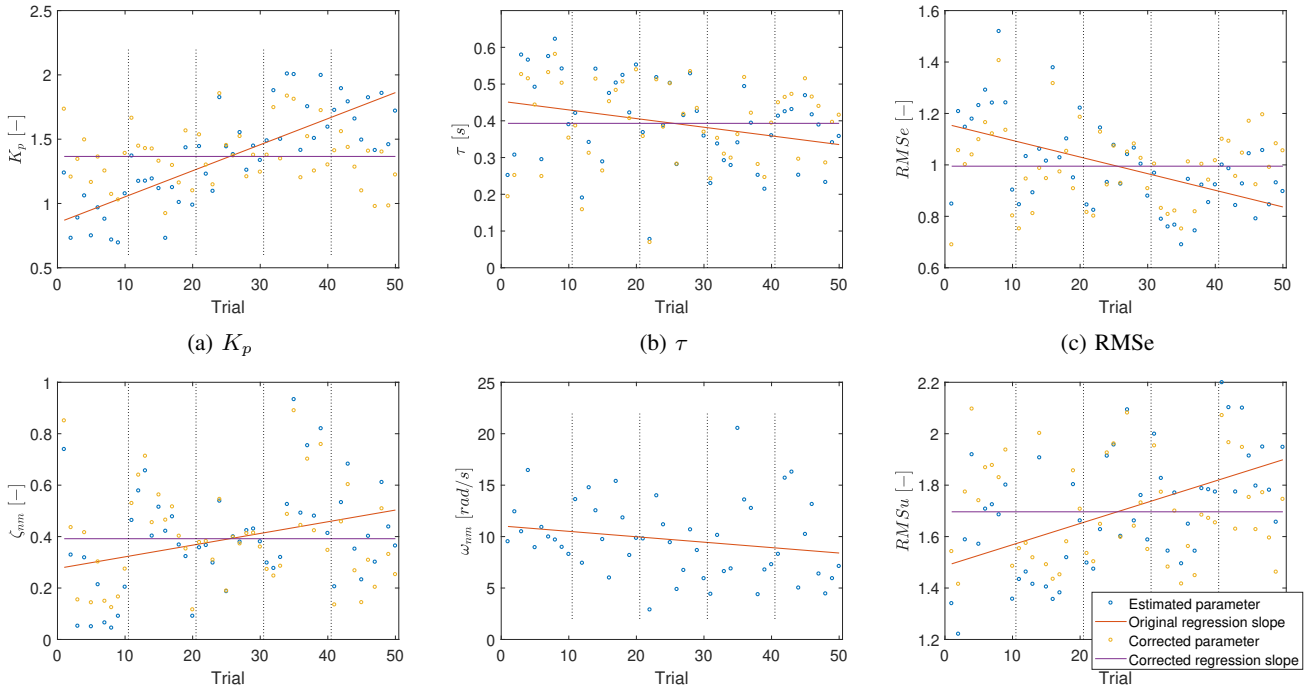
Parameter	df	t	Sig
K_p	73	-4.03	**
τ	73	1.12	-
ζ_{nms}	73	2.07	*
ω_{nms}	73	-2.09	*
RMSe	73	2.74	**
RMSu	73	-3.66	**

C. Sensitivity Analysis

The trend analysis showed that for the expected parameters K_p, ζ_{nms} and RMSe a trend was found for over half of the participants. The analysis might, however, be influenced by the choices made in the method design, such as number of data points in trend analysis, participant inclusion and symptom severity. Therefore, a sensitivity analysis was performed, of which the results are covered in this subsection.

1) Number of data points used: As mentioned in Section III-D, it would be interesting to determine how many PD data points are required before the model detects a trend in the data. For this, two different versions of the trend model are applied, one with an increasing number of data points and the other with a sliding analysis window, as explained in Section III-D. In order to determine which model provides the best application to the whole data-set and future utilisation, the p-values are averaged across all participants.

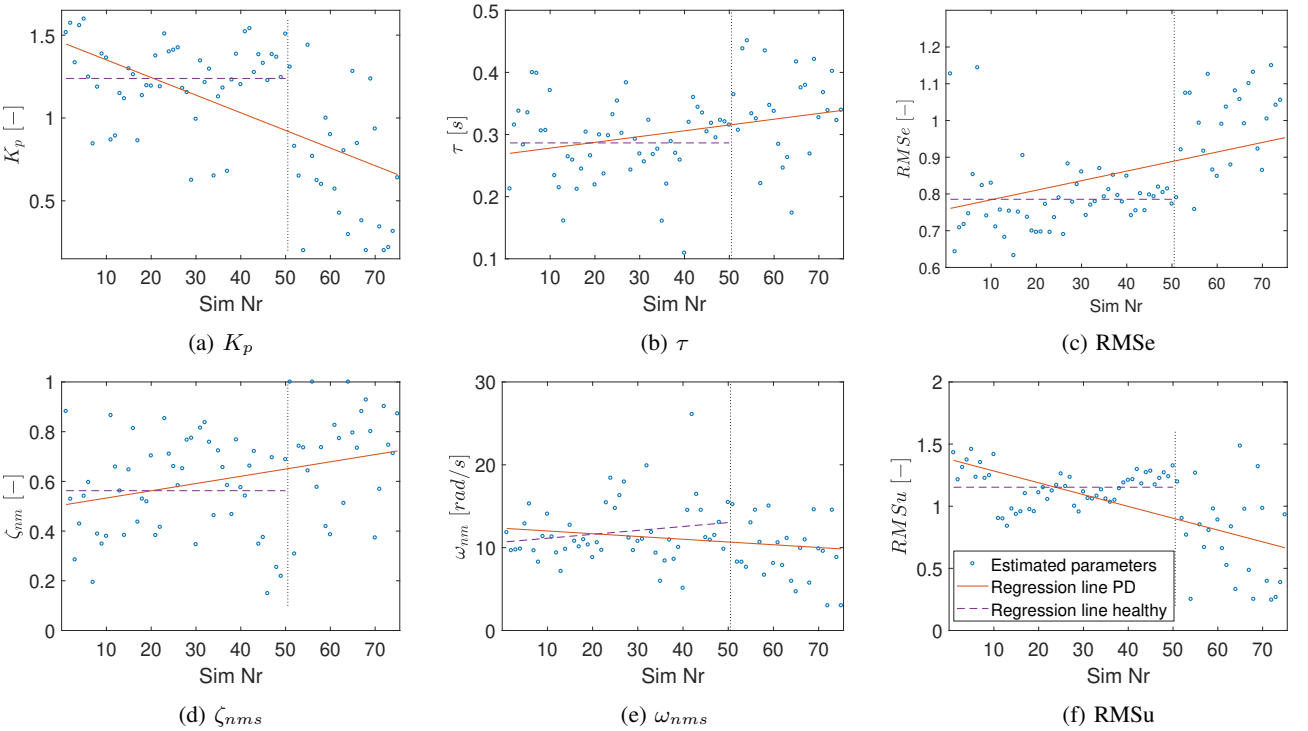
Figure 21 presents the p-values for the trend analysis when changing the number of data points used in the analysis. The horizontal axis signifies the number of iterations done by the model, where each iteration adds or shifts to the following simulated PD value. The dashed horizontal red line marks the p-value threshold ($p \leq 0.05$), and any p-values below this line indicate that a significant trend is detected. It can be seen that only for the damping ratio, the model converges to a significant trend, while for all other parameters no significant



(a) K_p (b) τ (c) RMSe

(d) ζ_{nms} (e) ω_{nms} (f) RMSu

Fig. 19: Learning curves and data correction Participant 23, ND



(a) K_p (b) τ (c) RMSe

(d) ζ_{nms} (e) ω_{nms} (f) RMSu

Fig. 20: Regression lines for Participant 25, D

TABLE XVI: Comparison of GLR trend analysis results, percentage of participants with a significant behavioural change in motor performance ($p<0.05$), all estimated parameters

Parameter	All	Selection
K_p	66%	77%
τ	64%	53%
ζ_{nms}	96%	97%
ω_{nms}	46%	50%
RMSe	50%	53%
RMSu	58%	73%

trend is found in the averaged data for any of the methods. Furthermore, only a stable trend detection, with multiple adjacent significant values, is seen in Figures 21a and 21c.

Figure 21c shows how the significance of the trend evolves if the number of data points increases per iteration, so that for the final iteration the original trend model with 75 data points is used. Only the damping ratio converges to a significant trend after 10 iterations. The values for the gain, tracking performance and control activity do stabilise around 10 iterations, but do not cross the significance threshold.

Figures 21a, 21b, 21d and 21e show the models where a sliding window is used in the analysis, with window sizes 50, 35, 25 and 15 trails, respectively. For all but window size 15, the ζ_{nms} reaches a significant value, but for 25 data points this is only briefly. Sizes 50 and 35 have more subsequent iterations with a significant values, providing a more stable result.

2) Participant selection: All previous results were gathered using the whole participant group. To analyse to what part of the population the model can be applied and how motor performance affect the detection accuracy of the model, the trend analysis is again performed for a selection of the participants with a high control performance. Table XVI gives an overview of the percentage of the good performing participants with a significant trend for each control parameter, as well as the original percentages for comparison. In general, the values for the select group are higher than those of the regular analysis. The exception is for the neuromuscular natural frequency.

Analysing the selection of participants with a higher performance also provides better results for the sliding window analysis, as shown in Figure 22. For the analysis with an increasing data-set, presented in Figure 22c, little is changed compared to the full data-set. However, when using a sliding window to detect the trend, the gain, damping ratio and tracking performance reach significant values.

The smaller windows, 15 and 25, provide earlier detection for K_p and RMSe, however, they move back above the threshold after 1-3 iterations at the point where the majority of the data used in the analysis is simulated PD data, which is not reliable for detection. Windows with 50 and 35 data points provide a more stable analysis. For size 50 the values stay continuously below the threshold, while for 35 eight subsequent iterations show a significant value for all three expected parameters

TABLE XVII: Comparison of GLR trend analysis results, percentage of participants with a significant behavioural change in motor performance ($p<0.05$) for mild and severe symptom simulation, all estimated parameters

Parameter	Severe	Mild
K_p	66%	58%
τ	64%	38%
ζ_{nms}	96%	78%
ω_{nms}	44%	42%
RMSe	50%	44%
RMSu	58%	60%

K_p, ζ_{nms} and RMSe. The detection moment for these parameters with window size 50 lies between 6-10 iterations and for 35 it is at 6-11 iterations.

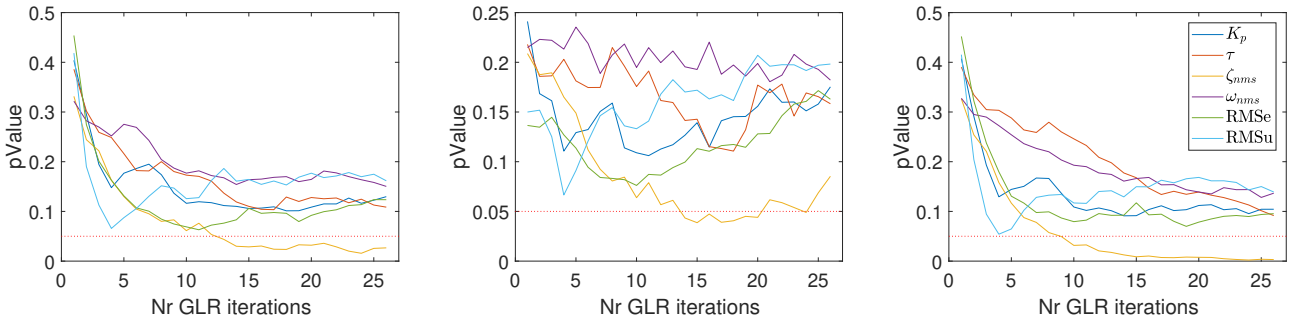
3) Mild and severe symptoms: Finally, it is tested how the trend analysis detection performance is changed for mild and severe symptom simulation. As mentioned in Section III-C2, two different ranges were defined for the PD simulation data and all previous results were obtained with the 'severe' symptom data-set.

Figure 23 shows the comparison of trend significance for the severe and mild data-sets for all data and participants. The dashed horizontal red line marks the threshold for a significant trend ($p\leq0.05$). Using Wilxocon's matched pairs test, as the data are not normally distributed, is can be seen that for the gain, time delay, damping ratio and natural frequency, there is a significant difference in the results for the severe and mild data-sets, while the control activity and tracking performance do not show any significant effects. Generally the trend analysis has a better performance for the severe symptom simulation. Moreover, from Figure 23 it can be seen that the spread in results for the trend significance is generally higher for the mild symptoms, as expected.

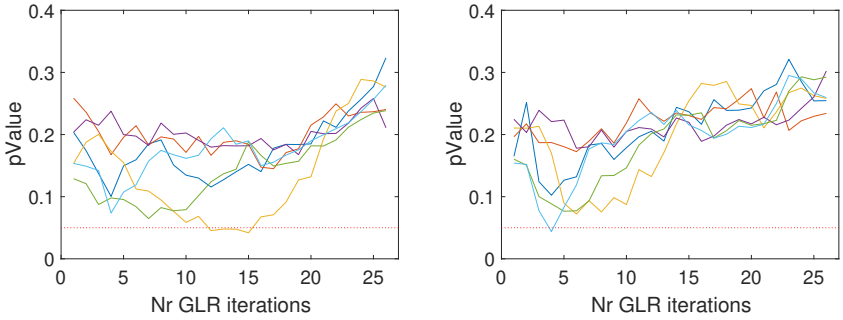
These results are confirmed when looking and the percentages of participants with a significant trend for the different parameters, as presented in Table XVII. In general, the percentages for the mild symptom data-set is lower, except for the RMSu.

An example of the regression models for the two different data-sets is presented in Figure 24. This figure shows the same severe symptom control gain values as in Figure 20a and the mild symptom data-set is added. Furthermore, the two regression lines are shown, from which it can be seen that for the severe set the regression has a steeper slope.

4) Dominant and non-dominant hand control: The majority of the results for the trend analysis part presented in this section focused on the analysis of the combined dominant and non-dominant hand data-set, as no major differences were found in the analysis for D and ND related to the trend results. In general, the trend analysis of the dominant and non-dominant hand data-sets exhibit similar outcomes as the presented results. Minor deviations can occur but the important observations are equivalent.

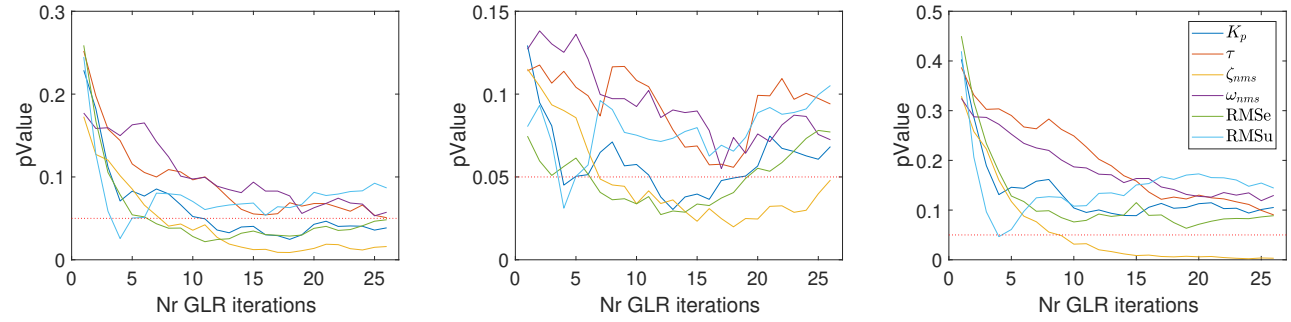


(a) Window size 50 (b) Window size 35 (c) Increasing window size

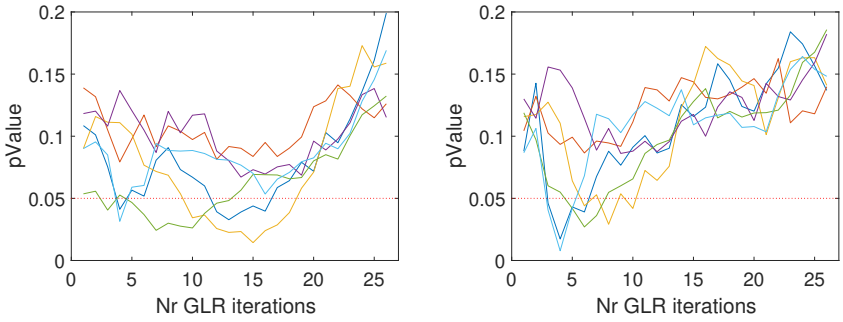


(d) Window size 25 (e) Window size 15

Fig. 21: Sensitivity analysis with changing window size, population averages across all participants

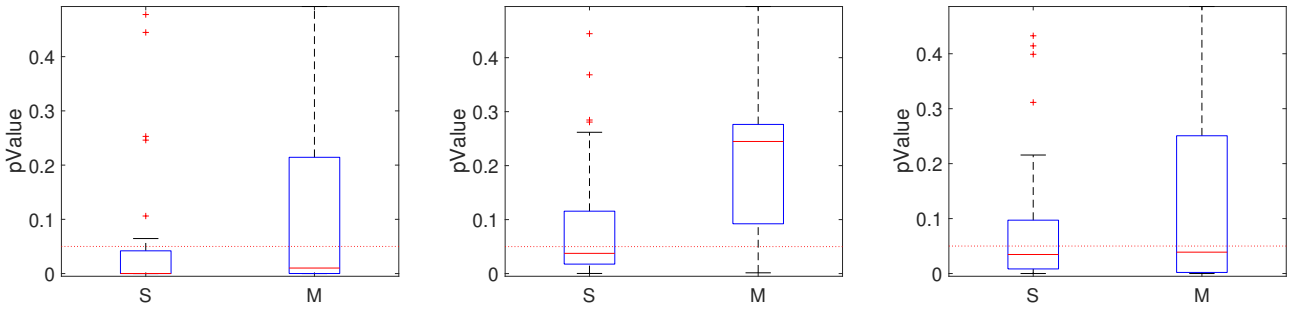


(a) Window size 50 (b) Window size 35 (c) Increasing window size

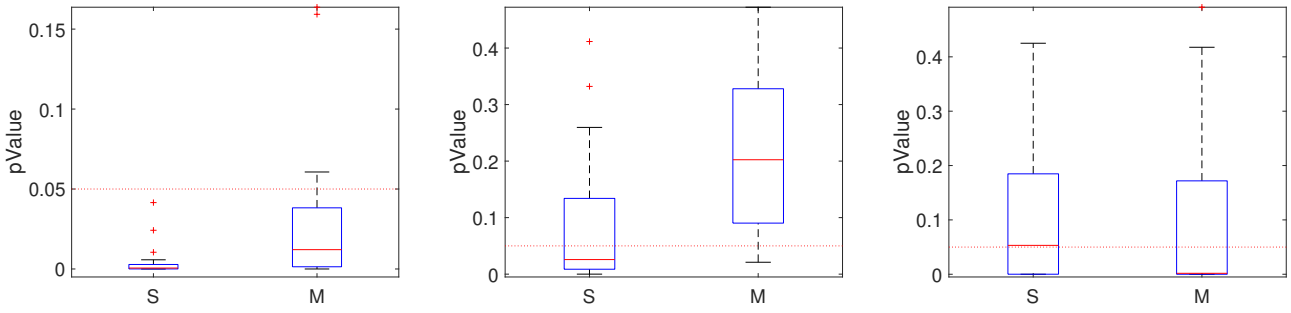


(d) Window size 25 (e) Window size 15

Fig. 22: Sensitivity analysis with changing window size, population averages across good participants



(a) K_p (b) τ (c) RMSe



(d) ζ_{nms} (e) ω_{nms} (f) RMSu

Fig. 23: Trend analysis pValues for mild and severe PD symptom simulation cases, full window size

TABLE XVIII: Results of Wilcoxon's test for mild and severe symptom trend analysis, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

Parameter	W	Sig
K_p	-3.14	**
τ	-3.11	**
ζ_{nms}	-4.62	**
ω_{nms}	-3.46	**
RMSe	-1.12	-
RMSu	1.14	-

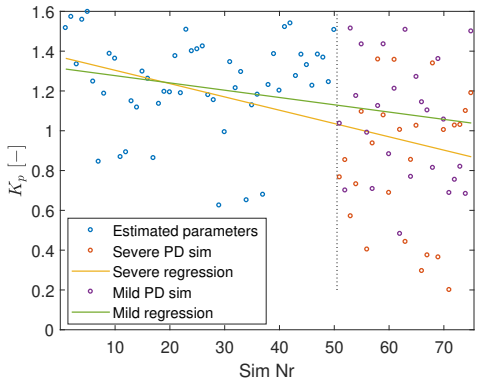


Fig. 24: Example of mild vs severe symptom trend analysis for the control gain, Participant 25, D

D. Detection performance

All in all, it was found that for the complete participant group, the model was able to detect a motor behaviour change for at least 50% of the participants when looking at the individual control parameters of interest, K_p, ζ_{nms} and RMSe. When combining these three parameters, however, only 34% showed a significant behavioural change related to PD. Detection performance increases for high control performance and changing the number of data points used in the trend analysis. Furthermore, to ensure a high detection performance, the PD symptoms need to be highly deviating from the healthy participant data.

VI. Discussion

The aim of this paper was to provide a proof-of-concept for a method that can detect behavioural changes in motor performance data due to Parkinson's disease progression. The data for this study comprised a combination of healthy experimental and simulated PD data to approximate longitudinal clinical data. Separate analyses, e.g. tests for variation in day-to-day and handedness performance, were performed for the experimental data-set and trend analysis methods were used to detect behavioural changes in the combined data-set.

Hypothesis I expected participants to show a variation in day-to-day motor performance. The data presented in Section V-A1 suggest this was true for all analysed parameters except the neuromuscular natural frequency. Highly significant differences were found between the five measurement days,

mainly related to an higher control performance, and post-hoc tests showed that most pairwise comparisons between the days were significant. Part of the variation in the data can be explained by a learning curve, which will be elaborated on later in the discussion. Nonetheless, since the data do not exhibit a monotonic trend, it can be concluded that there is a natural variation in the day-to-day control performance. The fact that this significant variation is not present for ω_{nms}, might be explained by the low quality of model fit for the higher frequencies. Even though they are not directly visible from the figures due to a between-subject correction, the many estimated values above 24 rad/s are dubious as they are higher than the highest excitation frequency, see Table IV. Furthermore, Section II-C showed the low relative remnant and wide confidence limits for the higher frequencies related to the neuromuscular dynamics. The FRF estimate and, therefore, the fitted model might not be an accurate representation of the neuromuscular dynamics.

Parkinson's disease can manifest itself asymmetrically [4], therefore, tracking data of both control hands were analysed. Hypothesis II expected participants to have a worse performance with ND hand control, this was, however, not confirmed by the results. The tracking performance showed better values for ND control and for the individual analysis 32% of participants had a significantly lower ND score, as compared to 28% with a higher score. In line with the better tracking performance [40], ND control showed increased gain values. However, the damping ratio was found to be lower for the non-dominant hand, which indicates more overshoot when controlling the system and thus a lower performance. When looking at the data for the individual participants, the same trend was found as described above, however, some cases strongly contradicted the overall results. When considering that each controller is unique, this spread in the data and the inconsistent results might be explained. All in all, the hypothesis could not be confirmed.

Hypothesis III expected that there would be no significant learning effects in the data, which was disproved by the data analysis. When looking at the data presented in Figure 15, it can be seen that, even though not fully monotonic, the values generally increases or decreases over the multiple measurement days. Using general linear regression models, it was found that for over half of the participants, RMSe and K_p, had a significant slope, corresponding with increasing performance. Furthermore, 48% exhibited a trend with decreasing time delay. The percentages for the neuromuscular dynamics were relatively low with 32% and 28% for ζ_{nms} and ω_{nms}, this might again be attributed to the difficulty of fitting the higher frequencies accurately. Feedback from participants included that controlling the target velocity while positioning their finger on a touchscreen was not very intuitive and for some it took many practise trials to understand and control the system. When comparing this setup to previous research with the same block-diagram, but with a joystick as input device [20], the unexpected learning effect could be explained. All in all, the hypothesis is disproved. This means that for future applications of this model, a longer training period is needed before the data are useful.

Finally, Hypothesis IV expected a significant trend for the control gain K_p, damping ratio ζ_{nms} and tracking performance RMSe, in the combined experimental and simulated data-set and for 65% of the participants. Results show that over half of the participants exhibit a trend in the data, with 66% for K_p, 96% for ζ_{nms} and 50% for RMSe. This was, however, as expected and can be explained by the fact that the simulated data are based on previous research [20]. However, when looking at participants who showed a change in behaviour for all three expected parameters, only 34% of the participants had significant results. While for all three PD related parameters combined, a low number of successful trend detections is found, the results for the single parameter analysis could already provide a doctor with information on changing control behaviour as a support for the current diagnostic methods. With K_p and ζ_{nms} showing a detection success rate above 65%, the hypothesis can partly be confirmed as the expected accuracy was not met for all parameters.

Three different tests were applied to see how the applicability of these trend models adjusts when changing analysis methods. Firstly, the number of data points used in the analysis was changed, both by increasing the data-set for each iteration, as well as using sliding windows with different sizes. When averaging the results across all participants, only the damping ratio reached a significant value consistently, since 96% of the participants had a significant trend for the damping ratio. The insignificant averages for the other parameters could be attributed to participants with a lower control performance, since the results averaged across high performing participants did reach significant values for the expected parameters, see Figure 22. When taking all participants into account, the method with the earliest detection of behavioural changes is obtained with an increasing window size, while for the good participants window sizes of 50 or 35 also show significant values for K_p and RMSe. A window size of 50 provides earlier trend detection. This difference is, however, minimal and might be a result of this particular simulated data-set for the selected 15 well performing participants, since the detection limits differ one iteration. Future analysis with a more elaborate data-set could work on optimising the window range for analysis. Moreover, in order to try and avoid any false positives, stable trend detection is preferred, where multiple consecutive iterations show a results below the significance threshold. A window size of 50 data points provides the most stable detection.

The current selection criteria indicated 60% of the participants had a sufficient control performance. In general the trend detection performance was increased when focusing on the selected participants, nevertheless, excluding almost half of the participants is a harsh measure. This number could, however, possibly be lowered for future applications. In this research,

a significant learning curve was found in the original data that were used for participant selection. When following participants for a longer period of time, the score might still improve and enable the selection of many more participants.

Finally, the analysis for severe and mild symptom simulation showed that for the expected control parameters, K_p, ζ_{nms} and RMSe, still more than half of the participants showed a significant trend with milder symptoms, even though trend detection performance was less than for the severe data-set. This suggests that the trend detection method is applicable for a wider range of symptom severity. It must be noted that the mild and severe symptoms are subjective, as it is unknown what parameter values actually correspond to those symptom levels. Generally, the simulated PD data-set was highly influential to the performance of the trend methods, considering that the simulated parameters were based on previous research [20]. However, those results are limited in the number of participants used and any individual effects are not taken into account as they are a comparison of healthy controls and Parkinson's disease patients. How the values for the control parameters change over time due to disease progression is unique for each patient and, without experimental data, still unknown.

As a proof-of-concept this study shows that trend analysis methods can be used to determine changes in control behaviour, related to Parkinson's disease. However, further research should be done to develop more accurate models. Many of the previously mentioned limitations of this research centre around the used data-set and for future research, gathering actual clinical data on individual Parkinson's disease progression is desirable. Moreover, allowing for more subsequent measurement days and performing the analysis only after a relatively stable score is achieved, could provide more insight in the natural variation of control performance that is not related to a learning curve. This information can then be used to adapt the trend detection methods for the expected noise levels in the data. Finally, for this research linear regression models were used for trend detection. The influence of model type on detection performance should be researched, non-linear models might present a better fit to continuously decreasing control performance. Furthermore, the current method focuses on combining individual metrics, while taking into account the correlation between the different control parameters. Further development could focus on analysing combined metrics. Moreover, the differences between parametric and non-parametric models on trend detection performance could be explored. The assumptions for regression models might be too strict for actual clinical data, so different methods might be needed for the analysis.

VII. Conclusion

This paper presents a proof-of-concept for the application of trend analysis models to identify changes in control behaviour in clinical motor performance data due to Parkinson's disease progression. The data were approximated by combining healthy experimental and simulated PD data. The experimental data were gathered using a single-axis manual pursuit tracking task, conducted by 25 healthy participants in the age range of 55-75. Using system identification methods, four different cybernetic control parameters were estimated (K_p, τ, ζ_{nms} and ω_{nms}) and combined with results for tracking performance and control activity. PD values for these six parameters were simulated based on previous research and combined into a final data-set. Linear regression models were used to detect behavioural trends in the combined data-set and were tested for their capacity for PD symptom detection when altering the number of data points used in the analysis, having a select group of participants or differing levels of PD symptom severity.

In general it was found that the general linear regression models were able to detect behavioural changes in the motor performance data. For the parameters related to Parkinson's disease progression, the control gain K_p, damping ratio ζ_{nms} and tracking performance RMSe, at least 50% of the participants showed a significant trend and a higher detection accuracy was found for participants with a better performance. The model was able to detect different levels of symptom severity and using a sliding window with 50 data points increased overall detection performance and on average, between 6 and 10 iterations with PD data were required before a trend was detected.

Overall, the regression models detected behavioural changes in motor performance for al least half of the population, which shows the potential of the proposed approach within this research field. This study provides exploratory research in the development of a tool that can aid in the objective disease assessment and monitoring of symptom progression for patients with PD to provide optimised treatment.

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II

Preliminary report

1 Introduction

When people get older, performing daily tasks such as walking or eating might become a real challenge due to the natural degeneration of the brain [1]. However, the effects of ageing are not solely limited to this. The risk of developing a neurodegenerative disease significantly increases with age. Neurodegenerative diseases do not only influence memory, as is the case with Alzheimer's disease [2], they can also severely impair motor performance [3]. The neural network required for fine motor skills, the visuomotor-network, is present throughout the brain and can be severely affected by neurodegeneration [4]. This MSc research focuses on a specific neurodegenerative disease that affects motor performance, Parkinson's disease (PD).

Parkinson's disease leads to a decrease in dopamine-producing neurons of the Basal Ganglia that hampers the communication in the brain, especially in the motor control area [5]. This leads to symptoms like slowness of movement (bradykinesia), postural instability and involuntary tremors, which can occur in asymmetrical onset. The disease is progressive and still incurable 200 years after the first proper description of its symptoms, but early diagnosis and correct treatment can greatly improve patients' quality-of-life [3].

As of this moment, diagnosis and monitoring the effects of treatment are done by identifying the motor symptoms related to Parkinson's disease (especially bradykinesia) and using questionnaires [6]. These results are translated in either a low resolution Hoehn and Yahr scale or the more detailed UPDRS (Unified Parkinson's Disease Rating Scale) analysis [7, 8]. Currently, treatment is provided by restoring dopamine levels in the brain, which mainly leads to improved motor function. Non-motor symptoms are, however, barely suppressed and a high dose or long term medication can lead to severe side effects such as hallucinations [3]. Treatment monitoring is subjectively done by neurologists. Thus far, no objective method to evaluate loss in motor skills due to neurological diseases is available, and a universally accepted method to quantify improvement due to medication, or decline due to increase in symptom severity, is desirable.

One method to analyse fine motor skill and its degradation is with the use of tracking tasks. A lot of research has been done in finding the influence of PD and its treatment on motor skills by using simple tracking tasks [9–16]. A recent collaborative research project, between the department of Neuroscience of the Erasmus Medical Centre (EMC) and the faculty of Aerospace Engineering of the Delft University of Technology, focuses on developing methods to analyse and quantify the effects of neurodegenerative disorders. Previous steps included testing a tracking task to quantify the loss of motor skills related to Parkinson's disease and cerebellar stroke, respectively [17, 18] and the influence of age on eye-hand coordination [19]. These experiments proved that changes in behaviour due to neurological decay can be quantified in isolated situations, when comparing two sets of data. The next step is to investigate the possible application for individual treatment monitoring, for example in identifying a decline in motor performance over a longer period of time due to disease progression and increasing severity of symptoms.

However, there is a lack of available information on the natural variability of human performance over time and the visibility of gradual change due to neurological symptoms. Furthermore, due to not knowing this variation bandwidth, it is unknown how severe the symptoms need to be to be detectable. Identifying a change in behaviour from the motor performance data with trend analysis is an extremely complex task in this application due to its multivariate nature. Moreover, time constraints for this study do not allow the longitudinal clinical study with Parkinson's patients that would be ideal for the analysis. Therefore, this research will focus on providing a "proof-of-concept" for the development of a diagnostic tool that can be used in the monitoring of Parkinson's patients.

The objective of this thesis is to:

'Identify behavioural changes in motor performance due to Parkinson's disease in a combined experimental and simulated data-set by using trend analysis methods.'

In order to approximate the longitudinal clinical data-set and to quantify natural variability in motor performance, a manual tracking experiment with an elderly control group will be performed. These data will be combined with simulated PD control behaviour, based on previous research [17], to resemble a motor performance data-set including a change in control behaviour.

This report is a preliminary literature study, covering the background and current research on the topic. First, information on Parkinson's disease is provided in Chapter 2. This is followed by an analysis of the influence of ageing on neurodegeneration and its relation to PD in Chapter 3. Chapter 4 will cover the basics of manual tracking tasks and Chapter 5 will discuss the different models that are available for analysing trends in data-sets. Finally, an experiment and data analysis proposal is defined in Chapter 6 and a conclusion on this literature study is given in Chapter 7.

2

Parkinson's Disease

This chapter will cover the different aspects related to Parkinson's disease (PD) that are of interest in the research scope discussed in Chapter 1. First, a short introduction to PD is given in Section 2.1 and its influence on the brain is discussed in Section 2.2. Section 2.3 covers the current diagnosis and treatment methods and their shortcomings. Finally, an overview is given on how PD affects motor control and how this has been determined thus far in Section 2.4. Finally the key takeaways for this chapter are presented in Section 2.5.

2.1. Introduction to Parkinson's Disease

Over 200 years ago, the first proper description of disorders related to Parkinson's disease was given by J. Parkinson, but, at this point, there is still a lot unknown about the disease and its causes [20]. What is known, is that PD is a progressive, age-related, neurodegenerative disorder and second most common after Alzheimer's disease [5].

PD occurs predominantly in middle and older aged people and the incidence rises with age. For people aged between 50 and 59 years, the incidence lies at 17.4 patients per 100.000. This increases to 93.1 in 100.000 for ages between 70 and 79 [3]. It is still generally unknown what causes PD, therefore, the disease is often labelled as idiopathic. The only consistently found risk factors in many studies are related to age and smoking. Research has been focusing on finding genetic risk factors, however this still needs to mature. Thus far, it is thought genetics play a role in only 10% of PD cases, this means the cause is exceedingly unknown [5].

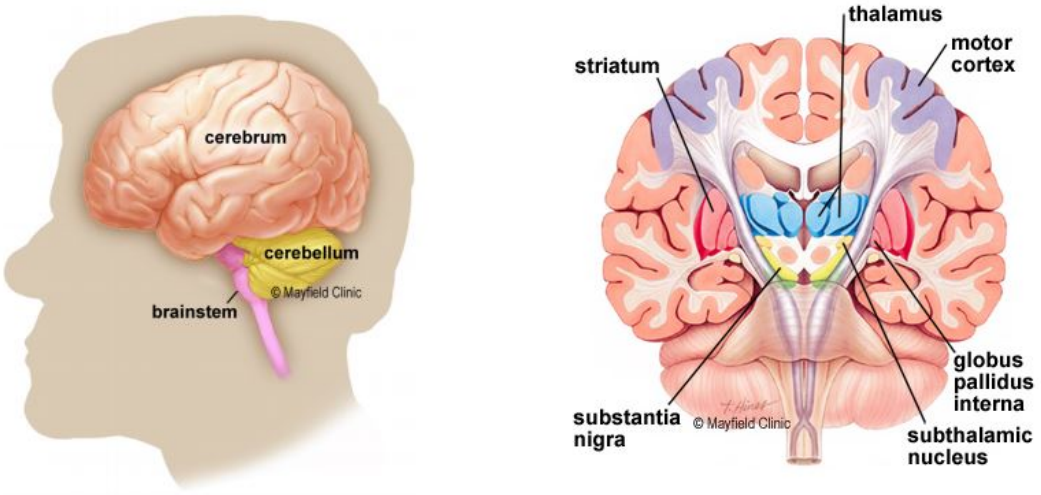
The disease typically presents itself with loss of motor control, mainly in the form of bradykinesia (unusually slow movements), rigidity, tremor and impaired balance. The onset of the disease usually starts at one side of the body and affects the other side in a later stage [21]. However, depending on the patient and stage of the disease, non-motor symptoms can also occur in the form of loss of smell and taste, mood changes and sleep problems [22]. At this moment, a diagnosis is generally made by using rating scales, and the most common treatment is the use of the dopaminergic medication Levodopa [3]. Even though treatment is generally done with Levodopa, it can result in severe side motor- and non-motor complications, this will be elaborated on in Section 2.3.

There is a significant difference found in symptoms and disease progression when comparing the age of onset. In early onset PD (people aged 45-50) the main symptom that occurs is tremor. Furthermore, the disease has a slow progression rate, but Levodopa-induced side effects develop faster. Late onset PD (age 70+) defines itself with more severe motor symptoms, a faster progression of the disease and less pronounced Levodopa-related side effects [23]. One thing both early and late onset PD have in common is that the symptoms are caused by the degeneration of brain cells.

2.2. Neurodegeneration and Parkinson's Disease: Effect on the Brain

The brain has three primary parts, the cerebrum, cerebellum and brain stem, as shown in Figure 2.1a. Within the cerebrum, the basal ganglia (BG) are found, which communicate with the cerebellum to complete some crucial functions. These include action selection, action gating, reward based learning, preparation and timing of (fine) motor actions, as well as non-motor aspects like emotion control [24].

For this study the main focus lies on the basal ganglia's ability to control voluntary movement and develop fine motor skills [26]. The substantia nigra (SN) is part of the BG as shown in Figure 2.1b. The neurotransmitter



(a) Main parts of the brain

(b) Basal Ganglia structures

Figure 2.1: Overview of the brain and functions related to PD [25]

dopamine is produced in the SN nerve cells. Neurotransmitters are used to relay messages in the brain that plan and control body movement. A simplified scheme of the neural pathways used for eye-hand coordination are shown in Figure 2.2. It is shown that for cognitive motor decisions, needed for (fine) motor skills, the information has to pass through the BG.

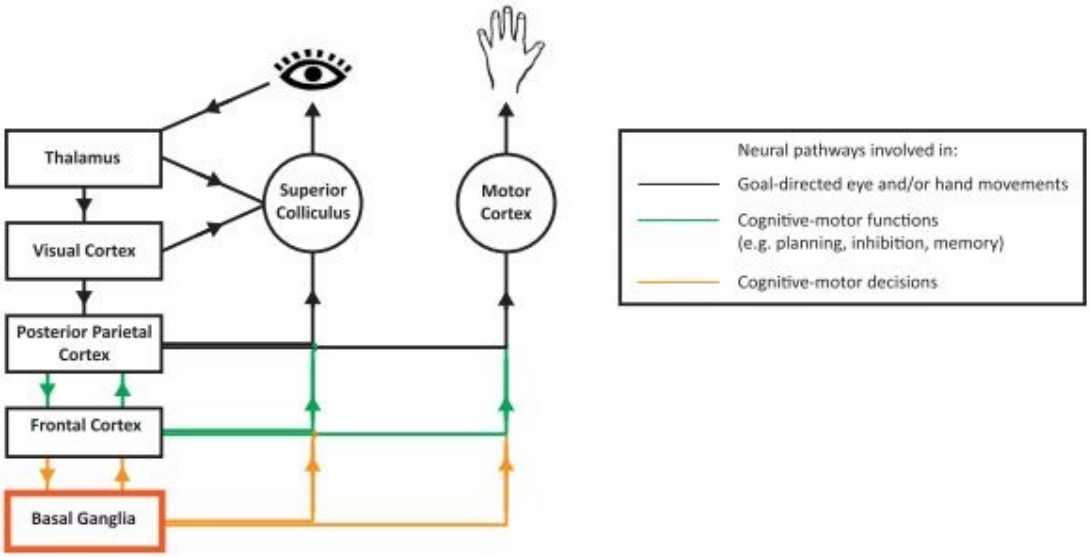


Figure 2.2: Simplified scheme of the neural pathways involved in generation of eye-and hand movements [4]

Parkinson's disease causes the death of the dopamine producing nerve cells in the SN for unknown reasons. While initial motor symptoms become evident with 30-70% cell loss [27], from a loss of more than 80% real communication problems in the brain occur in the form of all aforementioned PD symptoms [25, 26]. The neurological communication paths related to eye-hand coordination are highly dependent on the basal ganglia [4], a dysfunctional BG is therefore very likely to influence eye-hand coordination.

2.3. Diagnosis and Treatment

Parkinson's disease is a progressive non-curable disease. After diagnosis, symptoms can only be repressed, not slowed down. The most widely used treatment for PD significantly increases quality of life for the first stages of the disease, but can also induce a broad range of complications. This section will focus on each of the aspects related to disease progression. Subsection 2.3.1 will give an overview of how PD is diagnosed, while Subsection 2.3.2 covers the current treatment methods and complications. Finally the available clinical rating scales is discussed in Subsection 2.3.3.

2.3.1. Diagnosis

At this moment, there are no definitive tests to positively identify idiopathic PD in a patient. Detection of the disease is mostly done through various methods and observation of early symptoms by doctors. This includes an extensive medical history, rating scales, which will be discussed in Subsection 2.3.3, and multiple motor tests. The disease cannot be diagnosed without clear presence of bradykinesia [3, 6].

Bradykinesia is decidedly most commonly caused by Parkinsonian symptoms [3], however, care must be taken to avoid confusion of PD and Parkinsonism. PD is one of many neurological disorders that are described by the term Parkinsonism. An early stage diagnosis for Idiopathic PD can be difficult to distinguish from other Parkinsonian disorders due to similarities in the form of loss of dopamine and the resulting bradykinesia. The distinction is important as PD is a progressive non-curable disease while some forms of Parkinsonism can be cured. Distinction between the two can be made since Parkinsonian syndromes tend to have a more rapid progression and additional symptoms. Moreover, most syndromes do not have the same positive response to the most common PD treatment available [28].

Idiopathic Parkinson's disease is therefore the appropriate diagnosis if a patient displays a slow progression of bradykinesia, no symptoms related to other neurodegenerative diseased related with Parkinsonism and several other supportive criteria defined in the 'UK Parkinson's Disease Society Brain Bank's clinical criteria for the diagnosis of probable Parkinson's disease" [29].

Currently, a lot of research is done to improve the early diagnosis of Parkinson's disease as this is key to ensuring patients' quality of life. A wide variety of methods is explored in order to objectively diagnose PD. One of these is identification of biomarkers related to PD [30]. Moreover, focus is laid on home monitoring using smartphones and online access [31, 32]. More applicable to this research is the analysis of fine motor skills, for example with line drawing skills [33]. Finally a manual pursuit tracking task was proposed for detection of early stage PD [17], this last method could possibly be used for objective monitoring of treatment effects and will be elaborated on, later in this research study. It must be noted that all methods mentioned in this paragraph are still being developed and not part of routine clinical applications.

2.3.2. Treatment

As mentioned, idiopathic Parkinson's disease is still incurable, therefore, treatment focuses on the improvement of patients' quality of life and functional capacity. This part describes the main treatment method that is currently used, its results and the complications related to the medicine.

Dopaminergic Medications

First introduced over half a century ago, Levodopa (L-Dopa) is still the go-to drug for the treatment of Parkinson's disease symptoms [34]. The drug is the standard treatment for most patients with PD and even for some other forms of Parkinsonism. Dopamine agonists can be introduced if a patient shows early complications with L-Dopa, this is especially the case for early-onset PD. However, most patients using dopamine agonists will need to switch to Levodopa within the first five years of treatment [3, 27].

Levodopa treatment focuses mainly on the suppression of classical motor symptoms related with Parkinson's disease, namely bradykinesia and rigidity. While the response to the drug is different in each patient, motor symptoms are suppressed and skill improvement of 20-70% is found after initial treatment and this keeps improving over time with prolonged treatment [3].

Levodopa Complications

Even though Levodopa can be seen as the most effective drug to counter PD related motor symptoms, several complications occur during long-term treatment. As the disease progresses and becomes steadily worse, the dosage of L-Dopa needs to be increased, bringing several complications.

The initial complication is related with the wearing-off of the positive effects of the drug, also known as ON and OFF phases. This results in re-emerging motor symptoms between the scheduled drug doses. This can be as extreme as initially being able to move freely, while a minute later assistance is needed to rise from a chair [27, 35].

Moreover, chronic or high-dose L-Dopa treatment leads to a high chance of developing dyskinesias (unwanted and intrusive repetitive movements) and motor fluctuations (unexpected deviations in motor response). 40-50% of the patients develop these drug-related symptoms within the first five years of chronic treatment, this increases to 70-80% after 10 years. Many patients do prefer to live with these symptoms as the PD-related motor symptoms are perceived to have a more negative effect on the quality of life [27].

Levodopa treatment also causes several non-motor complications. Early-stage treatment can cause nausea, faintness and anorexia, however, this is rare in most patients as initial drug toleration is relatively high. Chronic or high-dose treatment can have more extreme symptoms. These include insomnia, depression, psychosis and hallucinations, urinary complications and pain. Such symptoms severely affect patients' quality of life [3].

Finally, after long years of treatment, the major causes of morbidity and mortality are found in the non-motor symptoms related to advanced PD, autonomic failure, loss of balance and most critically, dementia. These symptoms are unaffected by Levodopa treatment and often end up being more disabling to patients than dyskinesia and other motor symptoms [36].

2.3.3. Treatment Monitoring

The progression of Parkinson's disease is unique in each patient and there are no fully standardised and objective treatment methods. Even though a lot of research is being done to improve the monitoring of PD patients, the treatment planning and clinical information are still determined with the use of subjective rating scales and diaries [27]. This section will discuss the currently used clinical rating scales and the monitoring methods that are being researched.

Clinical Rating Scales

As mentioned, the most commonly used method to assess PD progression in patients and derive treatment plans is with the use of clinical rating scales. Many of these scales are available and the most common methods are discussed in this part.

The *Hoehn and Yahr Rating Scale* is to this moment the most widely known and used rating scale in the assessment of PD and monitoring of treatment. First described in 1967, its simplicity, universal acceptance and ease of use are the reason its still predominantly used so many years later. This simplicity also has its disadvantages, because of its non-linearity and the mixing of impairment and disability. It does not fully cover all motor related symptoms of PD, and does not include non-motor symptoms at all [7, 35]. Even though the latter is less relevant to this research, it does have a significant effect on patients' quality of life. An adapted scale with half scores was proposed to increase applicability [35]. The gradations are:

Gradation 0.0	No indication of the disease
Gradation 1.0	Unilateral involvement only
Gradation 1.5	Unilateral and axial involvement
Gradation 2.0	Bilateral involvement without impairment of balance
Gradation 2.5	Mild bilateral disease with recovery on pull test
Gradation 3.0	Mild to moderate bilateral disease; some postural instability; physically independent
Gradation 4.0	Severe disability; still able to walk or stand unassisted
Gradation 5.0	Wheelchair bound or bedridden unless aided

The *(MDS-)UPDRS* or (Movement Disorder Society-sponsored revision of the) Unified Parkinson Disease Rating Scale is widely accepted as a tool to monitor patients and evaluate interventions. This scale is more extensive and covers many different aspects of PD. The first version was presented in 1987 by Fahn and Elton [37] and Goetz et al. proposed an update in 2007. This scale was ultimately released in 2009 and includes the non-motor symptoms of PD and daily living aspects, as well as complications related to treatment [8]. The main parts of the MDS-UPDRS are presented below.

Furthermore there are several health-related quality of life (*HRQOL*) scales, as this is considered one of the most important aspects for patients [38]. Since these scales indicate treatment effects on patients' daily life

Part I Non-motor experiences of daily living
Part II Motor experiences of daily living
Part III Motor examination
Part IV Motor Complications

and activities, such as mobility and social activity, disease progression is assessed from their point of view and is therefore extremely subjective [38].

There is no one best scale, each has its advantages and disadvantages. For each patient and assessment goal, the most appropriate test must be selected. There are, however, quite some general disadvantages to these methods. First of all, rating scales are subjective and do not always provide a correct view of all symptoms. Moreover, Levodopa treatment predominantly influences the motor skills, and as discussed in Subsection 2.3.2 can have severe complications, from dyskinesias to ON-OFF moments. These symptoms are variable through the day and the moment of the test can greatly influence the outcome.

Home-Based Monitoring Systems

A lot of research done at this moment focuses on the development of home-based monitoring systems in order to overcome the main limitations of the rating scales [39]. The progress of technology these days allows for the use of wearables that monitor physical performance in daily life. However, there are still a lot of uncertainties and problems regarding the efficiency, reliability and specific application of these devices [39]. This research field is still in early stages and many obstacles have to be overcome to allow application of home-based monitoring systems.

Monitoring using Tracking Tasks

One of the measures to monitor treatment effects in patients with a neurodegenerative disorder is by analysing motor performance and the decline in fine motor skills over time. The current clinically accepted rating scales and tests are, however, not objective and sensitive enough. Assessment of motor performance in patients has been a research field in itself for many years and will be explored in Section 2.4.

Previous research has shown that manual tracking methods are able to differentiate between PD patients and healthy participants by objectively quantifying motor performance. The first results of this study (n=6) show significant differences in performance, control gain and neuromuscular damping [17]. Further possible applications of tracking tasks could be long-term performance monitoring. This study focuses on providing a proof-of-concept for its application to monitoring gradual disease progression by analysing the motor performance over a longer period of time.

2.4. Parkinson's disease and Motor Performance

In order to properly monitor gradual disease progression in PD, it needs to be known how symptoms affect fine motor skills. A lot of research has been done previously to analyse motor performance and the influence of Levodopa medication in patients. Much of the research done uses manual tracking methods similar to the set-up used in the TU Delft-EMC research collaboration, only with simpler input signals. Details on how tracking tasks are designed are discussed in Chapter 4.

Flowers [10] found that patients had difficulties in controlling continuous movements and timing in simple sinusoid pursuit tracking tasks. Furthermore, when using multisine signals, patients were visibly slower than the age-matched control group [10]. Other experiments also showed a significant decrease in peak movement velocities and gains [40]. In preview tasks it was shown that patients have reduced prediction capabilities and do not use the preview information as much as the control group [9, 15].

Levodopa and other dopaminergic drugs are used to suppress motor symptoms in Parkinson's patients. The effects on measurable motor skills do differ significantly. An aspect found Parkinson's patients during motor experiments, is the tendency to reduce the amplitude of the movements and even restrict them to a limited range, even while on Levodopa treatment [12]. On the other hand, overshooting, or a reduced damping ratio, is found to be significantly reduced when patients are using dopaminergic medicines [14]. For both the damping ratio and natural frequency, it was found that the value range became more similar to that of controls after medication. Another significant effect of L-dopa treatment is that patients on medication were able to perform better after practice, while patients off medication did not show significant learning effects [13].

Finally, the Erasmus MC has been working on methods of measuring motor performance caused by neurodegeneration in the brain. A set-up developed at the department of Neuroscience uses fine motor tapping tasks to measure the reaction time and accuracy of participants. In these tests PD patients have again shown the slower limb movements [4].

Aside from that, the joint research collaboration between the EMC and TU Delft has also given insight in the quantification of the loss of motor skill in PD patients. Using a pursuit manual tracking task with system identification methods, it was shown that patients have a significantly worse performance and higher control variability than age matched controls. Furthermore, an increased control gain and higher damping was found in patients [17].

2.5. Conclusion

This chapter explored the workings of Parkinson's disease, its treatment, the current disease monitoring methods and its severe influence on human motor performance. It is clear that, even though, the disease has been around for a long time, there is still no commonly accepted, objective, clinical method to diagnose and monitor PD. Furthermore, PD progresses uniquely for each patient and the available rating scales are not ideal in defining appropriate medical dosage or for application in treatment monitoring.

Furthermore, this chapter has provided information on how PD affects motor performance and the wide range of research already done to define the influence of the disease on motor skills. However, at this point there is still no official method that objectively quantifies degeneration in motor skills due to PD. This MSc research focuses on the proof-of-concept of a method to objectively identify changes in motor performance for application in disease progression monitoring, for now focused on Parkinson's disease. Simulation of motor performance influenced by PD, which includes increased neuromuscular damping, decreased control gain and higher control variability, will be used to test how trend analysis methods can detect changes in control behaviour.

3

Ageing and Neurodegeneration

In Chapter 2, the difficulties related to PD and neurodegenerative diseases have been covered as well as their influence on motor performance. However, as discussed in Chapter 1, due to the nature of this MSc research and corresponding time constraint, it is opted to approximate the longitudinal motor performance data with elderly participants. It is not just diseases that affect the brain and human motor performance, ageing brings its own complications when the brain suffers from natural degeneration. This chapter will briefly discuss the influence of ageing on the brain in Section 3.1. This is followed by an analysis of the relation between ageing and Parkinson's disease in Section 3.2 and a short conclusion of this chapter is given in Section 3.3

3.1. Effects of the Natural Ageing Process on the Brain

This section discusses the effects of natural neurodegeneration related to ageing of the brain. First the physical changes are briefly discussed in Subsection 3.1.1. This is followed by the cognitive changes related to ageing, amongst which its influence on motor performance, in Subsection 3.1.2.

3.1.1. Physical Changes

After the age of 40, it is found that brain volume steadily reduces at a rate of about 5% per decade. This decline is often attributed to neuronal cell death, however, whether it is the only and main cause is still unsure [2, 41]. The reductions are mostly found in the grey matter and prefrontal cortex. The neurodegeneration due to ageing typically follows a distinct course, where cholinergic and dopaminergic neural systems are thought to be more significantly affected as compared to other neurotransmitters [41].

3.1.2. Cognitive Changes

The brain consists of many neural networks. While the brainstem stores information of reflexive and simple motor programs, the higher order cortical processes are related to decision-making processes and they form the networks for amongst other, language and memory [2]. The gradual reduction of the brain volume affects neurological processes, such as changes in cognitive behaviour. The symptom most widely known and commonly associated with age is loss of memory. Memory can be divided into four sections, working, procedural, episodic and semantic memory. Ageing affects two of those, namely episodic memory, related to the location and method of information gathering and semantic memory, which is defined as the meaning and relation between things. Similarities in ageing and neurodegenerative orders can be seen as the most common neurodegenerative disorder, Alzheimer's disease, also influences episodic memory. This loss in memory may also be partly due to lower attention levels, slower processing speeds and impairment in sensory or perceptual functions [2].

Aside from memory loss, another significant change in the ageing brain is found in the dopamine levels. It is believed that ageing causes a weakening in the neurons and often influences the dopamine and serotonin neurotransmitters [42]. Dopamine levels are found to be declining with approximately 10% per decade [2]. This results in the appearance of classical motor symptoms often related to dopamine level decline, such as difficulties with coordination, raised variability in motor skills, slowing of movement velocities and problems with balance and gait. Levodopa is, therefore, a drug that in some cases can be used to counteract ageing symptoms in the elderly [43].

Research has shown that when comparing to a young control group, elderly people have an increased neuro-

muscular damping ratio [19]. Aside from this, one of the most common motor symptoms related to ageing is slower reaction times to inputs [2, 44, 45]. Fine motor performance and movement speed significantly decrease with increasing age, though, in some cases this can be attributed to the fact that elderly people tend to focus on accuracy instead of speed [43]. However, regardless of age, fine motor performance is significantly better in the dominant hand [45]. Aside from movement speed, elderly people are also found to suffer from lower attention levels, increasing error, and increasing variability of movement [2, 43].

The effect of ageing in the brain is often not noticed at a younger age. This is because the brain is able to adapt its internal process to overcome ageing symptoms. For example it is able to recruit a larger neural substrate to solve problems [41].

3.2. Ageing and its Relation to Parkinson's Disease

As evident from Chapter 2 and Subsection 3.1.2, there are some similarities found between ageing and neurodegenerative disorders. Since the focus of this study is on PD, this section will discuss the likeness and relation of ageing and PD.

First of all, it was found that age is the main and sole definite risk factor of Parkinson's disease [6]. Even though there are some rare early onset cases, PD is predominantly a mid-to-late-onset disease [3]. Generally the age of onset is thought to define the disease progression, which indicates a relation between ageing and PD.

Both processes include a decay of the dopaminergic system, resulting in a loss of dopamine levels. However, the rate of decline for ageing at 10% per decade, does not reach the same levels as in Parkinson's disease. It is found that initial motor symptoms become evident with 30-70% decline in levels, while some PD symptoms are only visible with more than 80% cell loss [26, 27]. It is clear that the average decline due to ageing will not reach the levels associated with PD.

Some literature defines ageing as a vulnerable pre-PD state [23]. It is thought that because of natural ageing effects, the neurons in the substantia nigra are weakened and lose the ability to compensate for further degradation. This means any degradation in brain cells is worsened when influenced by age [42]. Therefore, the aged brain is more susceptible to PD.

To some extent, ageing and PD show similar motor symptoms. It is even found that natural ageing is the cause of mild Parkinsonian symptoms distinguished by an absence of rest tremor, symmetrical onset and lack of response to other dopaminergic therapy [1]. Furthermore, it was observed that elderly people have an increased neuromuscular damping ratio, similar to PD patients [19]. On the other hand, there are also aspects found to be uniquely related to PD bradykinesia instead of physiological bradykinesia of old age. These include movement range and velocities [12].

Even though the exact pathological connections between PD and ageing are still unknown, many similarities between the two are found with regards to brain decline and symptoms. Increasing age does not necessarily mean the development of Parkinson's disease, but age is thought to have a large influence on the disease onset and progression.

3.3. Conclusion

In this chapter the influence of natural ageing on motor performance and its similarities and differences with Parkinson's disease are discussed. This is of interest due to the time constraint related to this MSc research, that does not allow for a longitudinal study with patients, resulting in the need to approximate the data with age-matched participants for a proof-of-concept. This chapter gives insight in how motor performance is affected by natural ageing of the brain, leading to slower reaction times, increased neuromuscular damping ratio and increasing variability of movement. Information that will be used when defining hypotheses for the manual tracking experiment. Furthermore, the differences between motor skills of elderly people and PD patients will be taken into account when simulating the PD motor performance data, as described in Chapter 1.

4

Manual Control Tracking Tasks

Analysing motor performance in human controllers has been a focus of research for a long time. One of the available methods is using the cybernetics approach, a widely applied method using manual control tracking tasks. These applications range from analysing a pilots behaviour during flight or determining a change in motor performance due to neurological disorders. This chapter will discuss the basics of manual tracking tasks in Section 4.1. The human controller and its control behaviour are elaborated on in Sections 4.2 and 4.3, respectively. An explanation of the different aspects that relate to designing a tracking task is given in Section 4.4. Lastly, Section 4.5 covers the methods used to identify the control dynamics and a short conclusion is given in Section 4.6.

4.1. Introduction to Manual Tracking

In manual tracking, a human controller (HC) is controlling a dynamic system which is perturbed by forcing functions [46]. The ultimate goal of the tracking tasks is to minimise the error between the target signal and the system to be controlled. A commonly used example of such a task is following a curving road in a car or rejecting disturbances in an airplane. In a much simpler form, the task can also be following a moving target on a touchscreen or with a joystick.

Analysing HC behaviour can give great insight in how humans approach a task. It can help in the development of interfaces that aid humans in controlling complex dynamic systems. Moreover, it can be used to detect 'abnormal' or deviating behaviour, for example in motor control affecting neurodegenerative diseases like Parkinson's disease. McRuer et al. were the first to present a comprehensive overview and method to describe HC dynamics [47]. This material is still widely used to support research on human controller behaviour.

4.2. Human Controller

Investigation of HC behaviour would be much more streamlined if every human acts identical to others. Furthermore, ideally one model could describe HC behaviour over a range of tasks. However, a HC is a *multimode, adaptive, learning controller* [48]. HCs learn new skills and adapt their behaviour to the controlled system. Depending on the presented task, human controllers use a variety of control strategies. If designed carefully, a specific manual tracking task can be used to assess and compare human behaviour.

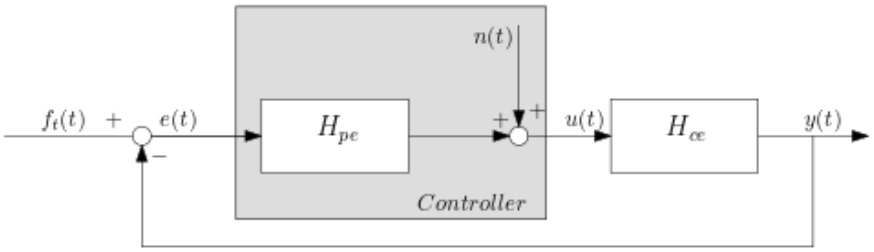


Figure 4.1: Compensatory control block diagram , adapted from [49]

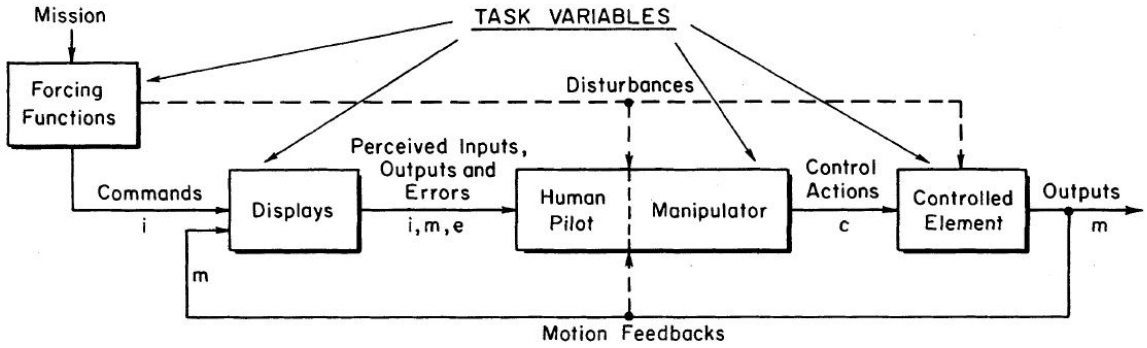
An example of a simple compensatory tracking task is given in the closed-loop block diagram of Figure 4.1.

The human controller is indicated as *controller* in the grey box of Figure 4.1 and its behaviour is defined as a continuous linear mathematical model, H_{pe}, in combination with a remnant signal n [46]. This latter signal is included to cover the non-linear behaviour and noise in the system [48]. The HC output u is fed into the controlled system, H_{ce}. Finally the error signal e is defined as the difference between the target f_t and system output y.

Figure 4.2 presents a more general overview of the manual tracking task and the variables that influence control behaviour. It shows the four main task variables which define the manual control tracking task. The *forcing functions* define the task input and allow for closed loop identification of HC behaviour [46]. The signals can take many forms, but the most common set-up is to have a multisine *target* and a *disturbance* signal, this will be further elaborated on in Subsection 4.4.1. The *display* type also highly influences behaviour and will be discussed in detail in Subsection 4.3.2. The *manipulator dynamics* present the dynamics of the hardware used to provide HC input and the *controlled element* describes the system that needs to be controlled, it has a direct influence on the strategy of the HC [48].

The three other variable sets define the setting of the experiment and should be kept as constant as possible. The presented *environmental variables* in Figure 4.2 are defined for aerospace related experiments, but can be applied in a certain extent to this research. Temperature and the test environment should be relatively constant. However, in future applications of this research, that might be difficult as an ideal hand-held set-up should be usable in many different surroundings, such as doctor waiting rooms. Though, as long as these variables are kept as constant as possible for individual patients the longitudinal data should be usable. *Procedural variables* include training and instructions. These should be identical amongst all participants to improve comparability of the results. This is, however, less important than the other factors as focus is on variability within participants, not between participants.

Finally, *operator-centered variables* are the most difficult to keep constant, while being especially important for this research scope. Aside from obvious factors related to ageing and PD, mentioned in Chapters 2 and 3, motivation and fatigue are also likely to play an important role in deviations between participant groups. Young people are prone to be more motivated to perform at their best while older people and PD patients are more susceptible to fatigue and stress. Furthermore, in a longitudinal study, human performance variability is highly influenced by these factors as they cannot be kept fully constant over a longer period of time, which is expected to result in natural variability in motor skills.



ENVIRONMENTAL VARIABLES:	OPERATOR-CENTERED VARIABLES:	PROCEDURAL VARIABLES:
In-Flight vs. Fixed-Base	Motivation	Instructions
Vibration	Stress	Practice
G-Level	Workload	Experimental Design
Temperature	Training	Order of Presentation
Atmospheric Conditions	Fatigue	Etc.
Etc.	Etc.	

Figure 4.2: Variables affecting human control behaviour [48]

4.3. Tracking Behaviour

This section will cover the control behaviour of the HC and how this behaviour is influenced by selecting the appropriate experimental set-up. First, Subsection 4.3.1 will discuss the three main control classifications for the HC. This is followed by an explanation of how displays influence control strategies in Subsection 4.3.2 and the pursuit display is elaborated on in Subsection 4.3.3

4.3.1. Successive Organisation of Perception

As mentioned, HC behaviour can be analysed for specific manual control tasks, since humans show different control behaviour in certain tasks. These were first discussed by Krendel and McRuer [50]. The Successive Organisation of Perspective (SOP) is a hierarchical scheme that describes three different control classifications; compensatory, pursuit and precognitive control [50].

In *compensatory* tracking tasks, only the error between the system target and output $e(t) = f_t(t) - x(t)$ is shown to the controller. The goal is to keep the error as close to the zero-reference as possible, so the target and output signals are similar. This can be related to disturbance rejection in aircraft.

The *pursuit* tracking task shows the systems target and output, the human controllers can therefore derive the error themselves. Any knowledge about and predictability of the target signal will be used by the HC to try and improve performance.

Finally, in the highest hierarchical level, *precognitive control* the human controller has full knowledge about the target and necessary input. For this reason the error signal is not required and it is effectively open-loop control. This indicates the highest skill level of the controller.

4.3.2. Displays

Section 4.3.1 defines three main control strategies a human controller can use. The selection of the control strategy is highly dependent on the used display. The three typically used displays are the compensatory, pursuit and preview displays and are shown in Figure 4.3.

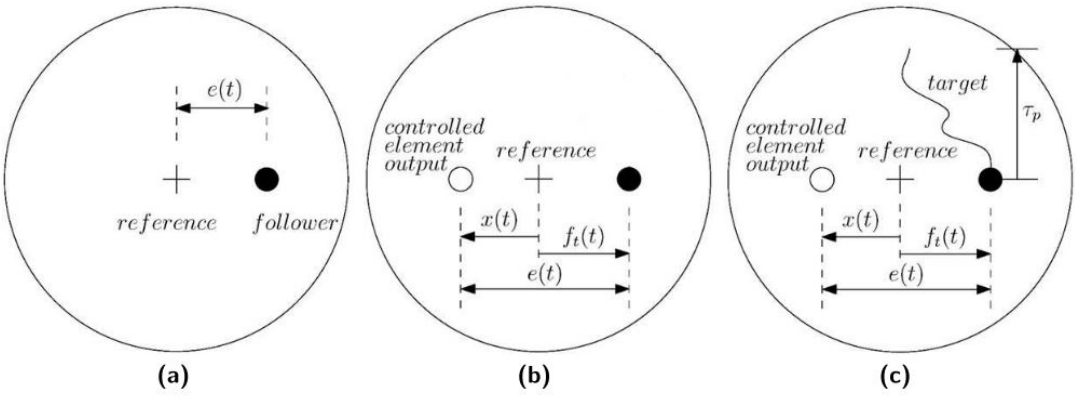


Figure 4.3: Compensatory, pursuit and preview displays [49]

First, the compensatory display is shown in Figure 4.3a. This display provides information on the error between the target and controlled element. The HC is expected to display compensatory tracking behaviour. However, if the target signal is sufficiently predictable, pursuit behaviour can be achieved [51].

Figure 4.3b shows a pursuit tracking display. In this display the target and system output are presented and since $e(t) = f_t(t) - x(t)$, the HC can derive the error. The increase in information can be an advantage for the HC. An example is the increase in predictability and understanding of the dynamics as the controlled element output is shown explicitly. Furthermore, mistakes are easier to identify for the HC. However, a pursuit display does not necessarily induce pursuit behaviour. In certain settings, the HC was found to display compensatory behaviour.

Finally, a preview display is shown in Figure 4.3c. The pursuit display is extended to show a future path of the target signal. The HC can decrease his delay by using the preview information. Similar to the pursuit

display, a preview display does not necessarily invoke the same behaviour in all controllers. The HC may invoke compensatory or pursuit behaviour depending on the signals used in information processing and the available amount of preview [51].

In previous research it was shown that both pursuit and preview displays can be used to identify and quantify neurological impairment based on the control behaviour [17, 18]. Depending on the participant pool and required information, the appropriate display needs to be selected. It was found that when using pursuit instead of preview display, the task is easier, however the diagnostic capacity is lower as some deeper insight in manual tracking behaviour is lost [18]. This research focuses on elderly people and future applications in monitoring Parkinson's disease, therefore, the pursuit display is deemed more appropriate due to its lower complexity and workload.

4.3.3. Pursuit Tracking

As mentioned above, the pursuit display introduces three information sources to the HC, indicated in Figure 4.3b. The resulting closed-loop system is shown in the block diagram of Figure 4.4. In this set-up the HC is tasked to align the *target* with a combination of the *controlled element output* and a *disturbance signal*.

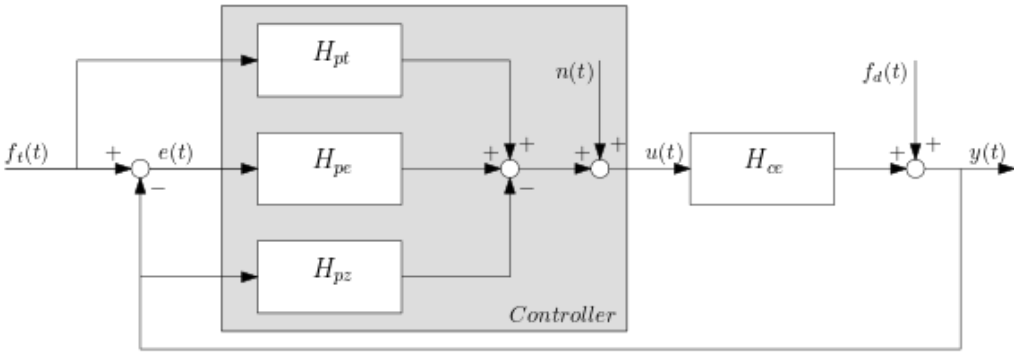


Figure 4.4: Pursuit control block diagram displays, adapted from [49]

Similar to the system in Figure 4.1, the human controller is indicated as *controller* in the grey box of Figure 4.4. However in this case, the control behaviour is influenced by the remnant signal n and three information sources, the controlled element, target and due to the signal dependency, the error. This relation results in an overdetermined system, which can be reduced to a two channel model. The reduced pursuit model is most often described without the H_{pz} channel, in other words, the HC is expected to use the error and target signals. Another simplification of the model can be made since the HC does not use the target input function with single integrator controlled element dynamics H_{ce}[51]. This means the model can be reduced to a SISO (single-input-single-output) system, as shown in Figure 4.1, which is effectively a compensatory tracking task. Because the model is reduced to a single channel model, the disturbance forcing function is not needed for identifying the controller dynamics.

4.4. Tracking Task Design

In order to evoke the required human controller behaviour, more than just the proper display selection needs to be considered. Figure 4.2 shows the different aspects that need to be taken into account when designing manual tracking experiments. Display selection has already been covered in Subsection 4.3.2. This section will cover the other task variables. Subsection 4.4.1 will cover the design of the forcing functions of the system. The manipulator and controlled element dynamics are briefly discussed in Subsection 4.4.2. Finally the remnant, as part of the human controller, is considered in Subsection 4.4.3.

4.4.1. Forcing Functions

As mentioned in Section 4.2, the forcing functions define the input of the experiment and when properly defined, they can be used to identify HC behaviour. To ensure the desired behaviour in the controller and avoid target anticipation, the signal must appear to be random [52]. This is achieved with the use of quasi-random multisine signals, a combination of multiple sines with frequencies in the range of interest.

$$f(t) = \sum_{k=1}^{N_f} A_f(k) \sin\left(\omega_f(k)\, t + \phi_f(k)\right) \tag{4.1}$$

Equation (4.1) describes the general form of such a multisine forcing function. The target signal is the sum of N_f sines with a defined amplitude A_f, frequency ω_f and phase ϕ_f. The frequencies are an integer multiple of the base frequency, preferably a prime multiple to avoid harmonics. The starting phase is chosen randomly, but the final signal needs to be checked for unfortunate disturbing peaks [46].

4.4.2. Manipulator and Controlled Element Dynamics

The manipulator and neuromuscular dynamics are often combined in a single, lumped, low-order model, usually as an underdamped second- or third-order low-pass transfer function [52]. This means that when identifying human controller behaviour, the manipulator dynamics are included.

As for the controlled element dynamics, they directly influence HC behaviour and are therefore chosen to try to evoke the preferred control behaviour, which is influenced by a combination of the level of task difficulty and behaviour in high and low frequencies. The crossover model states that the whole system generally converges to single integrator dynamics, as presented in Equation (4.2) [48] and the system dynamics are often in the form of a gain, single or double integrator.

$$H_p(j\omega) H_{ce}(j\omega) = \frac{\omega_c}{j\omega} e^{-j\omega\tau_c} \tag{4.2}$$

4.4.3. Remnant

To complete the diagram shown in Figure 4.1 the remnant signal needs to be defined. It is used to cover any non-linear aspects of human control behaviour and in order to have a correct model to simulate PD behaviour in a manual tracking task, the remnant signal needs to be taken into account.

The signal is usually modelled as coloured noise by passing white noise trough a filter. The model described by Levison [53] is widely used to approximate the remnant signal and is described by Equation (4.3). This function, originally designed for compensatory tasks, was also found to be applicable for pursuit tracking tasks [54].

$$H_n(j\omega) = K_n \frac{1}{1 + T_n j\omega} \tag{4.3}$$

In this equation, T_n is a lag time constant. The value for the gain K_n can be tuned to obtain the desired noise power ratio, as shown in Equation (4.4), which is related to the power-spectral densities of the control output and the noise signal, defined in Equation (4.5).

$$P_n = \frac{\sigma_n^2}{\sigma_u^2} \approx 0.25 \tag{4.4}$$

$$\frac{\sigma_n^2}{\sigma_u^2} = \frac{\int_0^\infty S_{nn}(j\omega)\, d\omega}{\int_0^\infty S_{uu}(j\omega)\, d\omega} = \frac{\int_0^\infty S_{nn}(j\omega)\, d\omega}{\int_0^\infty \left(S_{uu_{f_t}}(j\omega) + S_{uu_n}(j\omega)\right) d\omega} \tag{4.5}$$

4.5. System Identification and Parameter Estimation

To identify the human control dynamics, system identification methods can be used. The Fourier Coefficient Method (FCM) is a widely used black box method, which analyses the data in the frequency domain [46]. The multisine forcing function described in Subsection 4.4.1 is designed such that the signal-to-noise ratio at the excitation frequencies is high. As the contribution of the remnant is small at those frequencies, it can be neglected and the human control dynamics, $\hat{H}_{p_e}$, can be estimated with Equation (4.6). Here $U\left(j\omega_t\right)$ and $E\left(j\omega_t\right)$ are the Fourier transformed HC output and error signals, analysed at the excitation frequencies, respectively.

$$\hat{H}_{p_e}(j\omega_t) = \frac{U(j\omega_t)}{E(j\omega_t)} \tag{4.6}$$

The HC dynamics are dependent on the pilot, or controller, model. The HC model has been defined by McRuer and Hex [48], as a combination of a linear model and the nonlinear remnant. This relation can be seen in Figure 4.1, and the controller equivalent dynamics are described in Equation (4.7). Here K_p is the controller gain. T_L and T_I describe the controller lead and lag time constants, respectively. τ indicates the time delay and the neuromuscular frequency and damping ratio are indicated with ω_{nms} and ζ_{nms}, respectively.

$$H_p(j\omega) = \underbrace{K_p \frac{T_L j\omega + 1}{T_I j\omega + 1}}_{\text{pilot equalisation}} e^{-j\omega\tau} \underbrace{\frac{\omega_{nms}^2}{(j\omega)^2 + 2\zeta_{nms}\omega_{nms} j\omega + \omega_{nms}^2}}_{\text{neuromuscular dynamics}} \tag{4.7}$$

To estimate the pilot parameters corresponding to a measured data-set, the cost function defined in Equation (4.8) will be minimised. This function will find parameters so that the pilot estimation of Equation (4.7) is the most optimal fit to the data defined in Equation (4.6). The function is normalised to allow a better fit in the higher frequencies. Estimation is done by providing different initial solutions and selecting the optimal fit.

$$CF(\theta) = \sum \frac{\left\| \hat{H}_p(j\omega_t) - H_p(j\omega_t;\theta) \right\|^2}{\left\| \hat{H}_p(j\omega_t) \right\|^2}, \qquad \theta = [K_p, \tau, \zeta_{nms}, \omega_{nms}] \tag{4.8}$$

Finally, for an indication of how well the model fits to the data, the Variance Accounted For (VAF) can be used [55]. This method analyses the difference between the actual and simulated input signals u, as shown in Equation (4.9). The VAF can range from 0% to 100% where, 100% means a perfect fit to the measured data.

$$\text{VAF} = \left(1 - \frac{\sum |u - u_{sim}|^2}{\sum u^2}\right) \times 100\% \tag{4.9}$$

4.6. Conclusion

This chapter reviewed the cybernetic approach to modelling human control behaviour. A pursuit tracking task is chosen to analyse HC performance because of the method's use for elderly participants and possible future use for patients. Even though a pursuit display lacks deeper insight in control behaviour compared to preview displays, the lower complexity of the task is deemed more appropriate. Moreover, it was found that when applying single integrator control dynamics in a pursuit tracking task, the HC shows compensatory tracking behaviour, which simplifies the system identification process. The Fourier Coefficient Method will be used to analyse the data in the frequency domain and parameters will be estimated by minimising a cost function. Day-to-day variation in control performance is expected as operator-centered variables, such as motivation, fatigue and stress, cannot be kept fully constant.

5
Trend Analysis

As mentioned in Chapter 2, one of the measures to monitor treatment effects in patients with a neurodegenerative disorder is motor performance. A decline in fine motor skills can indicate disease progression and an increase in severity of fine motor skills, while improving performance might indicate proper suppression of the symptoms with medication. This chapter will explore statistical methods that are able to find and possibly even predict such changes in the data, trend analysis. In Section 5.1 an introduction to trend analysis is given. This is followed by an explanation of two main aspects of the data-set in Section 5.2. An overview of the different models that are available is given in Section 5.3. Lastly, a short conclusion is presented in Section 5.4.

5.1. Introduction to Trend Analysis

Trend analysis is defined as finding a change in a system over a longer period of time [56]. It is a widely used statistical method to identify patterns in time-series or longitudinal data-sets. Trends are characterised as long-term increasing or decreasing data, which are not necessarily linear [57]. These methods are often used to determine if the changing behaviour differs from random behaviour from a statistical point of view.

Trend analysis methods are often used in economic problems where trends are defined in order to try and estimate future outcomes, this is a special branch of statistics that uses the idea that the past acts as an indication of the future [57]. It also finds many applications in the analysis of clinical data, usually gathered in longitudinal studies [58].

When using trend analysis methods, care must be taken to avoid their weaknesses. Data are very likely to be influenced by measurement errors, which can be confused with a trend. It is generally assumed when analysing time-series, that the data consist of the systematic pattern and noise, therefore, it is often required to apply some sort of filter before searching for trends [59]. Moreover, a lot of time-series data have some form of autocorrelation where errors transfer from one period to the other, there are several statistical tests available to test for autocorrelation in the data [56].

Furthermore, even in the most random data, short-term trends can be found if the data-set is small. On the other hand, when no trend is found, it is not necessarily the case that there is no trend. It could be that the data-set used is incomplete and unable to show the existing trend [60].

Another aspect to take into account is the effect of other variables on the measured data. Applying the latter to the scope of this research requires thinking about possible learning or fatigue effects in the data. If this happens, it might be necessary to correct the data before analysis [56].

5.2. The Data-set

This section will cover two different aspects of the data-set that are important to consider when selecting a trend analysis method. First the sample size is discussed in Subsection 5.2.1. After this, the difference between time-series and longitudinal data is explained in Subsection 5.2.2.

5.2.1. Sample Size

In trend analysis, the sample size is an extremely important factor. When using a small data-set, the regression result can lead to overfitting and an inaccurate trend model [57]. There is no clear rule of thumb regarding the data-set size that the majority of literature can agree on, it ranges from 10 observations for each estimation

term, to having a sample size of at least 50, plus 8 observations per predictor variable [56, 61]. In general it depends on the number of predictor variables and the noise level in the data, and simpler trend models are advised when the data-set is small [57].

One way of counteracting the negative effects that come with a small sample size is the use of bootstrapping methods. This group of methods creates new artificial data-sets resampled from the experiment data or fitted models, by sampling with replacement [56]. Bootstrapping allows for the simulation of many instances of one data-set and provides an estimate of the p-value as well as providing confidence intervals for small data-sets [62]. One difficulty arising with bootstrapping methods is its application to time-series data. More often than not, it is important to take into account the autocorrelation generally present in time-series, which means the resampling cannot be done in a fully randomised way. There are, however, different bootstrap methods available for these kind of problems [63].

5.2.2. Time-series and Longitudinal Data

Trend analysis finds its application in the analysis of longitudinal or time-series data. Even though both define data gathered over a longer time, there is a difference between the two, both in definition and in the models required to analyse the data.

Time-series data are defined as anything that is observed sequentially over time [57], an example being the measured temperature in one city on the first day of each year. This can either be in a regular (i.e., monthly) or irregular time frame. Most methods used in trend analysis, assume regularly spaced data, while data gathered in clinical experiments are usually irregularly spaced and dependent on the patient's availability. This results in the need for models that can be applied to unevenly spaced data [64].

Longitudinal data or panel data are a specific subset of time-series data, also known as cross-sectional time-series data. Longitudinal data combine time-series and cross-sectional data, where the latter indicate a collection of observations for multiple participants or entities at a single point in time, for example, a one time measurement of temperatures in multiple cities. In longitudinal data analysis the relation between the participants is taken into account when finding trends in the data, therefore complicating the analysis [58].

5.3. Available Models

There are many different models available to find trends in data, each with its own applications, advantages and disadvantages. Most models used in defining trends make use of regression analysis, which estimates the relationship between dependent and independent variables [56]. This section covers the different models that have a potential application in this research and are often applied to longitudinal or time-series data of clinical nature. In Subsection 5.3.1 the simplest form of regression analysis is discussed and Subsection 5.3.2 explores the application to a multivariate data-set. Models that are commonly applied to longitudinal data are explored in Subsection 5.3.3 and the difficulties of working with irregularly spaced observation data are considered in Subsection 5.3.4. Finally, Subsection 5.3.5 shortly names two possible extensions of the aforementioned models in case their underlying assumptions are invalid.

5.3.1. Simple Linear Regression

One of the most basic forms of trend analysis is simple linear regression (SLR). SLR finds its application in simple experiments or observations where the observed variables do not depend on each other and can be analysed separately from the rest. In a SLR model, there is only one response variable y_t and one parameter, or predictor variable x_t as shown in equation (5.1). Here β_0 and β_1 indicate the intercept and slope of the trend and ε_t is the random error or deviation from the trend fit [56, 57].

$$y_t = \beta_0 + \beta_1 x_t + \varepsilon_t \tag{5.1}$$

The main assumptions made when using linear regression models are related to the errors ε_t. First of all they have a zero mean to avoid bias. Furthermore, they are unrelated to the predictor variables and not autocorrelated. If these assumptions are not met, there would be more information available in the data-set which should be included in the model [57].

Model fitting is generally done using least squared estimation (LSE) due to its intuitive and easy application. There are two other models that are also widely applied in statistics, namely, Bayesian analysis and maximum

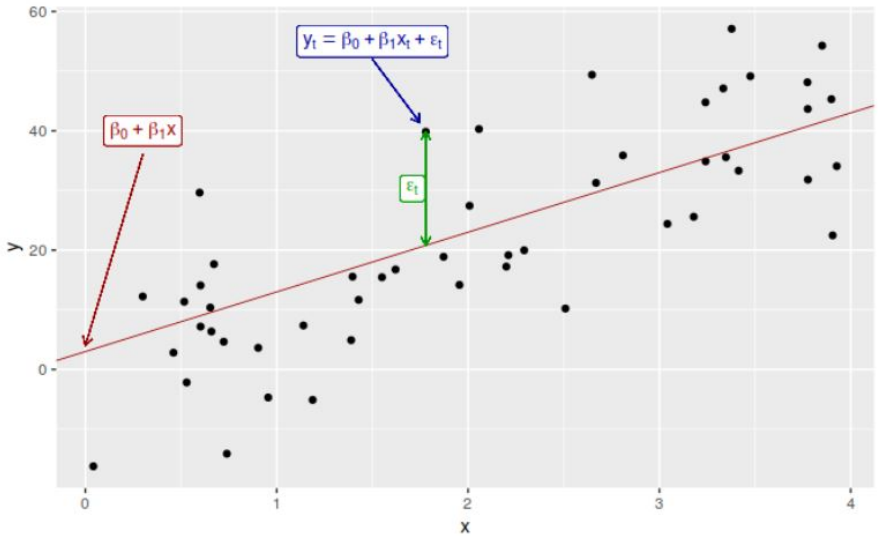


Figure 5.1: Example of a simple linear regression model fitted on a data-set [57]

likelihood estimation (MLE) [56]. However, the LSE is still the most common and easily applied method [56].

When the errors have a normal distribution and the data-set is sufficiently large, a t test can be done on the LSE model to test a null hypothesis $H_0 : \beta_1 = 0$. This will determine if there is a statistically significant slope in the data-set [56].

It is important to note that only when the trend parameters in the regression equation are in a linear form like in Equation (5.1), the regression model can be considered to be linear. This should not be confused with a linear trend, which refers to the time variation and not the equation parameters [56].

5.3.2. Multivariate and Multivariable Linear Regression

An extension of SLR comes in the form of analysing multiple, possibly related predictor and response variables, and a distinction is made between *multivariable* and *multivariate* analysis. The former indicates a system where multiple predictor variables $x_{n,t}$ are related to a single response variable y_t as shown in Equation (5.2) [57, 65].

$$y_t = \beta_0 + \beta_1 x_{1,t} + \beta_2 x_{2,t} + \cdots + \beta_k x_{k,t} + \varepsilon_t \tag{5.2}$$

However, for this research it is more interesting to look into multivariate analysis, or the general linear regression model (GLR). This allows for analysing common trends in related parameters of time-series data, such as the different estimated parameters of the pilot model. The GLR model is given in Equation (5.3). This model analyses the relationship between the multiple response variables $\boldsymbol{Y}$ and their related predictor variables $\boldsymbol{X}$ and errors $\boldsymbol{E}$ for time-series data with multiple parameters related to one observation.

$$\boldsymbol{Y}_{n\times p,t} = \boldsymbol{X}_{n\times n+1,t}, \boldsymbol{\beta}_{(k+1)\times p} + \boldsymbol{E}_t \tag{5.3}$$

One of the most important assumptions for using this model is a conditional normal distribution of residuals. If this assumption is too strict for the data-set, a different, related model can be used which will be shortly considered in Subsection 5.3.5, the generalised linear regression model (GLiR) [56, 66].

GLR analysis is a more elaborate version of SLR, in that the parameter estimation is most commonly done using LSE [56] and the corresponding statistical tests can be done either as independent univariate tests, which is effectively simple linear analysis, or as combined multivariate tests. Testing for trends can be done in a similar way as described in Subsection 5.3.1. The slope parameter can be tested for significance using a null hypothesis where $H_0 : \boldsymbol{\beta_1} = 0$ and $\boldsymbol{\beta_1}$ is a vector containing trend slope parameters for each response-predictor couple [66].

It must be noted that GLR is only applicable to analysis of time-series data where an individual instance is observed over time, or for the individual analysis of instances or participants gathered with longitudinal studies. To analyse possible relations between instances, the mixed effect model (MEM) is more appropriate [56]. This will be elaborated on in the next subsection.

5.3.3. Mixed Effect Models

As already mentioned in Subsection 5.3.2 mixed effect models or linear mixed models (LMM) are generally used when analysing longitudinal data, since GLR models are only applicable in analysing long-term data of a single participant. Even though the ultimate goal of the research collaboration is to design a tool that aids treatment monitoring in individuals, as PD progression is unique for each patient. It might be interesting to learn from other patients and to see if there are general trends in age groups and onset types. Furthermore, in longitudinal studies the participant group is chosen such that they represent a specific part of the population that is to be analysed. Analysing individual data, especially in a proof-of-concept set-up like this study, might therefore not present the full picture related to the population and thus the most interesting information.

Mixed effect models are used to incorporate both global level information as well as individual information and a general model is given in Equation (5.4). Here the individual observations are given by $Y_{i,j}$, where j indicates the measurement number and i the participant. $X_{i,j}$ gives the predictor variables, β_0 and β_1 present the regression parameters and ε_{ij} the error, just like in SLR and GLR. The terms $b_{i,0}$ and $b_{i,1}$ represent deviation from the population average in the form of $b_{i,0} = \left(\beta_{i,0} - \beta_0\right)$ and $b_{i,1} = \left(\beta_{i,1} - \beta_1\right)$ [67].

$$Y_{ij} = \beta_0 + \beta_1 \cdot X_{ij} + \underbrace{b_{i,0} + b_{i,1} \cdot X_{ij}}_{\text{between-subject}} + \underbrace{\varepsilon_{ij}}_{\text{within-subject}} \tag{5.4}$$

The parameters of LMM are generally estimated using maximum likelihood estimation instead of LSE in order to minimise bias [56]. In this method, the parameter estimates are determined by maximising the joint probability or density of the observations. It can also be simplified to maximising the log-likelihood function. An advantage of using MLE is its application to incomplete data-sets. Even if the longitudinal data have some missing or faulty data-points, MLE can still be used to find an estimate to the regression model [56, 67].

5.3.4. Models for Irregularly Spaced Data

Thus far, all described models can be used under the assumption of evenly spaced data on the time axis, without inter-dependencies. In irregular spaced (clinical) data, there is typically a dependence between successive observations that varies with the separation in time, for example, the day-to-day variance between sets of motor performance data, which are influenced by the moment the measurements are taken. This inter-dependency is not easily applied in a model such as Equation (5.4) and research is done to develop methods that can be applied to these data-sets [56]. Most clinical observations and longitudinal studies, participants are observed at irregular intervals and the different participants are often measured on different days.

The most commonly used method for analysis of unevenly spaced data is to transform it to equally spaced data, often using linear interpolation methods [56]. With this new data-set the models discussed above can be easily applied. However, there are several disadvantages that come with the interpolation. The estimates of covariances and autocorrelation can be influenced by a bias which is hard to quantify. Furthermore, there is often a causal relationship between parameters in multivariate time series, that can get lost when interpolating data. Moreover, the information available in the data-set can get diluted with added points for far spaced observations or removed points for closely timed observations [64].

Current research focuses on finding methods that are directly applicable to unevenly spaced data, however, these methods are still in their early stages and do not cover estimation methods for trend analysis [64]. For the scope of this project, any unevenly spaced data will therefore be interpolated if necessary, while keeping the disadvantages in mind for further statistical analysis. This will be tested with simulation data.

5.3.5. Other Models

Depending on the final data-set, its distribution and underlying parameter relations, it might be that the aforementioned models are not appropriate for trend analysis. In this subsection some possible extensions of SLR and GLR that can overcome these problems are briefly noted.

Polynomial and Nonlinear Regression and Trends
In special cases, non-linear trends can be properly analysed using linear regression models. Depending on the definition used, polynomials are actually linear regression models even though the trend they may describe is not. Regression models are categorised as linear if the parameters $\beta_0, ..., \beta_n$ are linearly entered into the model [56]. Due to the combination of the possible natural variance in the estimated control parameters and the fact that for this application the data-set is simulated to show increasing symptom severity, it is expected that that a linear model will be sufficient to analyse for trends.

There are, however, cases where linear models cannot appropriately describe a trend in the data. One example can be a very aggressive disease progression with exponentially increasing severity of symptoms. In general, the regression analysis can be done similar to linear models by using LSE, as long as the underlying assumptions hold. The difficulty lies in the large sample set required, and often there is no one optimal solution to the estimation problem [56]. Other solutions include approximating the model with a linear version, by transforming the data with the logarithm or making the function piecewise linear [57].

Generalised Linear Regression
The models discussed in the previous subsections are only valid under the assumption that the residuals have a normal distribution. This assumption can, however, be relaxed when using generalised linear regression models (GLiM). It uses a more general notation of the regression function based on the distribution of the response variable, as shown in Equation (5.5), which allows for a non-normal distribution and nonlinear relationship between the linear predictor η_t and mean μ_t. The only limitation in these models, is that the distribution must be one of the exponential family [56].

$$Y_t \sim N\left(\mu_t, \sigma^2\right), \quad \text{where} \quad \mu_t = \beta_0 + \sum_{i=1}^{p} \beta_i x_{it} = \eta_t \tag{5.5}$$

5.4. Conclusion
In this chapter the general concept of trend analysis methods, as well as the different available models are explored. The most widely used method of trend analysis is regression analysis, which estimates the dependencies between two variables. Regression analysis has many applications and this MSc research focuses on how those methods can be applied to analyse changes in manual control behaviour due to the progression of neurological disorders like PD.

Ideally, the data for this research would be in the form of longitudinal clinical data of Parkinson's patients, however for this proof of concept the longitudinal data are approximated by analysing motor performance of age-matched controls, as will be further elaborated on in Section 6.2. The use of (approximated) longitudinal data does not allow for application of the simplest forms of regression analysis. For finding individual trends, such as possible learning effects, the GLR model is applicable. However, when looking for a widely applicable method to analyse changes in motor control behaviour due to PD, the global effects of the whole participant group need to be taken into account and mixed effect models are more appropriate.

6

Experiment Proposal and Data Analysis

In this chapter, a proposal is presented for the manual pursuit tracking experiment and the subsequent data analysis steps to be taken in this MSc research project. First, in Section 6.1 the main research questions and hypotheses are defined. This is followed by a detailed explanation of all aspects related to the design of the proposed experiment in Section 6.2. A short overview of the approach to the data analysis is given in Section 6.3. Finally, a brief conclusion is given in Section 6.4.

6.1. Research Question and Hypotheses

As already mentioned in Chapter 1, one of the focus areas of the research collaboration between the TU Delft and EMC is the development of a tool that aids treatment monitoring of Parkinson's patients. Ideally the gathered motor performance data for this research are from a longitudinal clinical study following Parkinson's patients on a set time interval. However, these data would only be complete, and usable in this study, if both the suppression by medication and the gradual increase in symptom severity can be captured. Due to time constraints for this MSc research this cannot realistically be achieved. However, to approximate these kinds of data and to be able to prepare key data analysis steps, measurements can be done with healthy participants, distributed over several days. Patient data can be simulated to generate data that approaches motor degradation due to disease progression, for a proof-of-concept of the methods. With that in mind, the research question is defined as:

'How can a change in motor behaviour due to Parkinson's disease symptoms be identified in naturally varying human controller data?'

This research question can be split into two main questions stated below. The first, with two related subquestions, is connected to the gathering and analysis of data with the experiment that will be discussed in Section 6.2, the last question concerns the use of simulated data based on previous research [17] and the application of trend analysis methods, which will be briefly mentioned in Section 6.3.

1. *Is there a significant natural variation in day-to-day motor performance of healthy elderly people?*
    1.1. *Do learning effects, induced by repeating the measurements over multiple days, influence motor performance and its variability?*
    1.2. *Is there a difference in motor performance and its variation bandwidth between dominant and non-dominant hand control input?*
2. *Is it possible to detect trends in combined experimental and simulated motor performance data?*

From literature, the following hypotheses are defined related to these questions:

1. It is expected that there will be variation in day-to-day motor performance. Research has shown that elderly people have a higher variability of movement and motor performance [2]. Additionally, in Section 4.2 it was noted that there is a large group of variables that is ideally kept constant when comparing data of experiments. These operator-centered variables, like motivation and fatigue, are however extremely difficult to keep steady when measurements are spread over multiple days. Moreover, as the elderly participant group is more vulnerable to changes in these variables, it is expected that there will be a day-to-day variation in motor performance.

1.1. It is expected that learning effects do not significantly influence motor performance. Previous research indicates that a pursuit task has a lower complexity and workload as compared to preview [18]. Furthermore, patients were able to perform the task after a short amount of practise [17].

1.2. It has been found that regardless of age, the fine motor skill performance of the dominant hand is significantly better that of the non-dominant hand [45]. It is therefore expected to see a difference between motor performance score and variation.

2. Previous research has shown that there is a significant difference in parameters related to motor performance of patients and an age-matched control group [17]. It is therefore expected that there will be a visible trend in time for the combined healthy experimental and simulated PD data-set.

6.2. Experiment Design

In this section the different aspects related to the design of a manual pursuit tracking experiment are discussed. First, participant selection is explained in Subsection 6.2.1. This is followed by a detailed description of the control task in Subsection 6.2.2 and the apparatus in Subsection 6.2.3. Lastly, Subsection 6.2.4 describes the experiment procedures.

6.2.1. Participants

Ideally, the experiment follows Parkinson's patients during their regular check-ups to be able to use accurate data in the development of a diagnostic tool. However, due to time constraints related to this research project, it was opted to approximate the patient data for a proof-of-concept.

It is proposed to have a participant group of 25 healthy elderly people, with an age range of 55-75 years. This age range is deemed appropriate as it is the average age of symptom onset for Parkinson's disease [3]. Furthermore, elderly people are expected to show control behaviour closer to that of PD patients, as compared to younger participants. The results are expected provide information on the natural variation bandwidth of motor performance, before symptoms are present, but including any natural neurological degeneration caused by the ageing of the brain. This allows for comparison with simulated and real PD data in following stages of this research.

Healthy participants include people who do not have any neurological impairments. Furthermore, no major visual impairment is allowed due to the nature of the tracking task, where information is provided using a visual stimulant. Preferably, the age and genders are equally distributed, however, this is not a strict requirement for this experiment. In order to find enough participants, a collaboration with group homes for elderly is proposed. Measurements can take place in the common room in order to reduce the burden for participating.

6.2.2. Control Task

In this subsection the different aspects relating to the design of the control task will be elaborated on. First the methods used to define a cognitive and motor baseline for each participant are presented. This is followed by an elaboration on the task description of the main experiment and the display. After this, the input signal the controlled element are described.

Baseline Determination

Before the start of the experiment, all participants are asked to perform a Mini Mental State Examination (MMSE) to assess cognitive functioning [68]. A baseline for the motor performance is defined with two short test, measuring reaction time and eye-hand coordination, using tests developed by the neuroscience department of the Erasmus MC, where eye and hand movements are compared to estimate motor performance of participants.

Task Description

The task to be performed by the participants is a simple horizontal-axis pursuit-tracking task. The goal is to keep the system output as close as possible to the target signal.

In order to approximate longitudinal tracking data and allow for natural variations in performance, the measurements are spread over 5 days. Ideally the time division between measurement sets is equal for all participants, however, this is not a strict requirement as the focus lies on individual day-to-day variation and not the influence of specific time intervals between measurements.

The task consists of two conditions where the participant is asked to follow a target on a touchscreen, using

both the *dominant* and *non-dominant hand* as control input. This set-up is chosen as PD can manifest itself asymmetrically [21]. It is expected that this set-up will provide information on motor performance and any possible differences in the variation bandwidth between controlling with the dominant and non-dominant hand. This can give insight in the possibility of requiring more severe PD symptoms before they can be identified with trend analysis models if a higher variation is present in the non-dominant hand.

Display

For this research purpose, it is opted to select a pursuit display. This display is more intuitive for participants, therefore, it is easier to use. Furthermore, Haartsen observed that a preview task might not be suitable in applications with participants suffering from neurodegeneration due to the higher complexity and workload [18]. Even though more extensive information on manual performance and tracking behaviour could be available when using a preview display, care must be taken to develop a method that is suitable for monitoring PD in vulnerable participants.

The display that will be used is an adaptation of that presented in Figure 4.3b and that used in research by De Vries [17] and is shown in Figure 6.1. The left half shows the controls for the experimenter and the right half the display visible for the participant. The black circle indicates the target signal position, while the blue dot shows the controlled element output. The black box indicates the area where the control input may be applied to prevent blocking the visual stimulus with the hand.

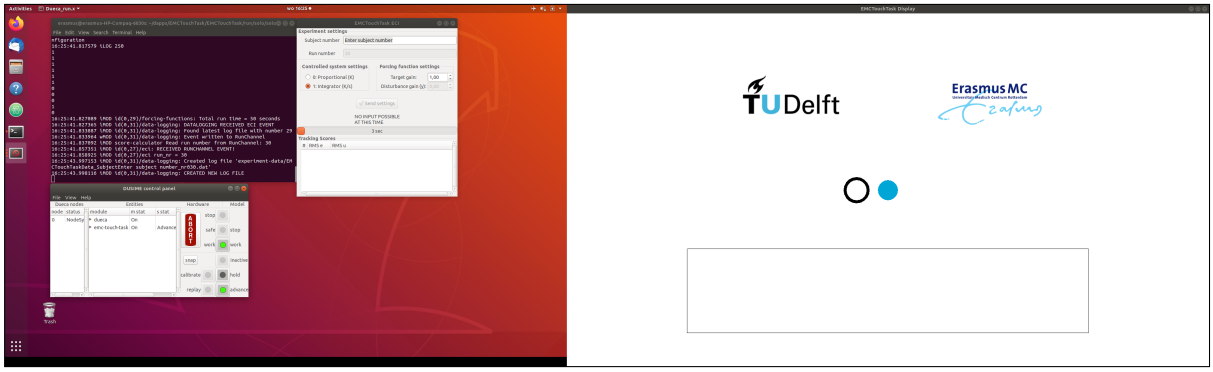


Figure 6.1: Display to be used in experiments

Input signal

As was already discussed in Section 4.3.3, when using a simplified version of the pursuit tracking task, compensatory control behaviour is achieved. This means that only a *target forcing function* is required and the disturbance forcing function is not necessary for the system identification process.

Previous research in the department made use of the multisine described by the 11 sinusoids of Table 6.1 for manual tracking tasks [17–19]. This combination of sines was able to cover the whole region of interest in human behaviour dynamics and, for continuity reasons, will be used in this research.

Table 6.1: Target signal components, obtained from [17]

N_f	ω_f $[rad/s]$	A_f $[deg]$	ϕ_f $[rad]$
4	0.614	1.079	7.239
7	1.074	0.776	0.506
13	1.994	0.391	7.860
19	2.915	0.225	8.184
29	4.449	0.117	9.012
37	5.676	0.082	6.141
43	6.596	0.066	6.776
53	8.130	0.051	6.265
79	12.118	0.035	4.672
109	16.720	0.028	2.672
157	24.084	0.024	8.009

The frequencies ω_f of the multisine are all a multiple of the base frequency. The base frequency ω_m is defined by Equation (6.1), where T_m indicates the measurement time. Previous research incorporated a signal length of 50 s, of which the first 9.04 s where used as run-in time and the latter 40.96 s as T_m. The sinusoid amplitudes were determined using a second-order low pass filter as described in Equation (6.2), where $T_{A_1} = 0.1$ and $T_{A_2} = 0.8$. Finally the phases were selected 'randomly' to achieve an average crest factor [17].

$$\omega_m = \frac{2\pi}{T_m} \tag{6.1}$$

$$H_A(j\omega) = \frac{\left(1 + T_{A_1} j\omega\right)^2}{\left(1 + T_{A_2} j\omega\right)^2} \tag{6.2}$$

In order to reduce learning effects in the experiments, the input signal is flipped for every second trial.

Controlled Element Dynamics
The controlled element dynamics need to be chosen such that the participant shows the preferred tracking behaviour. As mentioned in Section 4.3.3, the HC will display compensatory behaviour if single integrator controlled element dynamics are chosen during pursuit tracking [51], which simplifies data analysis. Furthermore, even though using those dynamics with a touchscreen application might result in the rise of complications with data analysis resulting from loss-of-contact with the screen, it is opted to have single integrator dynamics to ensure enough information on control behaviour in the higher frequencies, (i.e. neuromuscular dynamics) for proper data analysis [18].

6.2.3. Apparatus

As mentioned in Section 6.2.1, in order to find enough participants who are willing to perform the experiment spread over 5 days, it would be easier to operate from the common rooms of group homes for the elderly. For this, the experiment setup is required to be portable.

The experiment will run on a HP laptop with a Linux operating system (Ubuntu 18.04.3 LTS) on the Delft University Environment for Communication and Activation (DUECA). A Dell P2341T touchscreen will be used as input device and will be connected to the laptop. Participants are asked to wear touchscreen gloves in order to reduce friction between the finger and touchscreen. The touchscreen will be re-positioned for use with the dominant and non-dominant hand to provide a more natural control position for the hand.

For the motor performance baseline measurements, a portable setup from the EMC is used. The Tobii X2-60 compact eyetracker is used, in combination with tests running on Tobii Pro Studio software, to measure reaction times and eye-hand coordination. A separate keyboard and the previously mentioned Dell touchscreen are input devices.

6.2.4. Experimental Procedures

The experiment is spread over 5 days, where the first day differs slightly from the others in experimental procedures. The procedures for the first session are shown in Figure 6.2 and include the briefing, baseline tests, measurements for both dominant and non-dominant hand control and debriefing. For the follow-up measurement sessions, the briefing is shortened significantly and the baseline tests are skipped.

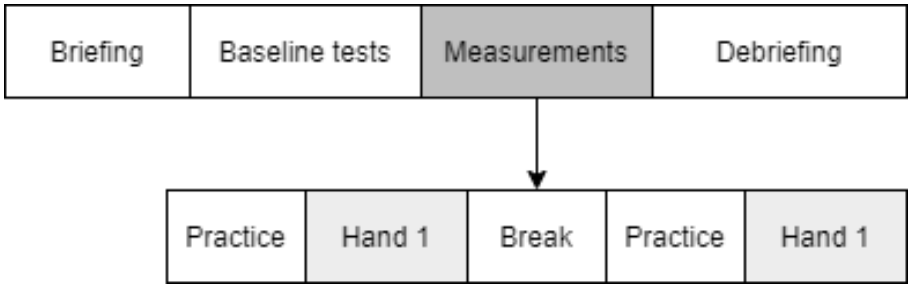


Figure 6.2: Experiment procedures

The initial briefing includes discussion of the information document presented in Appendix B and signing of the consent form, shown in Appendix C. During the baseline tests the participants cognitive and motor performance baseline is determined using the tests described in Subsection 6.2.2.

During the measurements, five practise trails are performed in order to get familiar with the task and control hand. This is followed by 10 measurement trails for the first condition, with a short break halfway to relax the hand and eyes. After another short break, the practice and measurements are repeated for the second condition. Here the conditions define the hand used for the control input, so dominant (D) or non-dominant (ND). Since the participants are elderly and it is expected they tire faster that a young participant group, extra breaks are possible upon request.

In order to mitigate any possible influences of fatigue and/or learning, the order of starting with the dominant or non-dominant hand is changed per subject and measurement set. This is shown in Table 6.2.

Table 6.2: Testing order, D = dominant hand, ND = non-dominant hand

Participant	Set 1		Set 2		Set 3		Set 4		Set 5	
1-13	D	ND	D	ND	D	ND	D	ND	D	ND
14-25	ND	D	ND	D	ND	D	ND	D	ND	D

6.3. Data Analysis

Analysis of trends in time-series and longitudinal data allows for the identification of gradual changes. In applying trend analysis to motor performance data, it might be possible to detect changes in HC behaviour due to PD progression. A trend can indicate if the general direction of the data is increasing or decreasing. Furthermore, analysis can identify changes in trend direction, where a patient initially might have been improving due to treatment, symptoms can resurface and change the direction of the trend. After the experiment is finished there are several steps to be taken before a statistical trend analysis can be done. This section will present a short overview of these steps.

1) Measurement Data Analysis and Preparation

After the experiments are concluded, the raw data will be visualised in order to find corrupt data points and outliers. Furthermore, a parameter estimation will be performed for all participants to estimate the control parameters. The method presented in Section 4.5 will be used. First the FCM is applied to estimate the human control dynamics. After this, the parameters are estimated by minimising Equation (4.8) where a modified version of Equation (4.7) is implemented. As described in Subsection 4.4.2, the controller generally adapts its behaviour to allow for single integrator system dynamics. Keeping this in mind, combined with the selected single integrator controlled element dynamics, the HC is expected to show only a gain in the pilot equalisation equation. Therefore Equation (4.7) can be simplified to Equation (6.3). The estimated control parameters (K_p, τ, ζ_{nms}, ω_{nms}) and performance score will ultimately be used as indicators for a trend in the data.

$$H_p(j\omega_f) = K_p e^{-j\omega_f \tau} \frac{\omega_{nms}^2}{(j\omega_f)^2 + 2\zeta_{nms}\omega_{nms} j\omega + \omega_{nms}^2} \tag{6.3}$$

Furthermore, the measurement data should be analysed for any initial trends. Even though it is hypothesised that there will not be a learning curve due to the task simplicity [17, 18], there might be a visible increase in motor performance. If the residuals are normally distributed, the general linear regression model, described in Subsection 5.3.2, can be applied to test for trends in the data for each individual participant. When a significant trend is present, the data should be corrected.

Finally, in order to test the applicability of the trend analysis models to the whole population group, the proof-of-concept for this method, the healthy data should be bootstrapped to create multiple 'estimates' of the original data-set. This allows for the generation of a more complete data range that more closely represents the whole population group of interest.

2) Simulation of PD Data

The next step is to simulate data from Parkinson's patients, with human control parameters and performance

scores based on previous research [17]. The range can be varied to simulate mild or severe symptoms in order to test the sensitivity of the trend analysis model.

3) Preparation of Combined Data-set
Subsequently, the experimental and simulation data will be combined to form the final data-set. This set will be tested to see which trend analysis model is applicable, using autocorrelation test and validation of the assumptions. If the data-set is found to be too small, further bootstrapping can be used in order to provide confidence intervals and an estimation of the p-value.

4) Trend Analysis
Finally, trend analysis will be performed on the prepared and combined data-set. A mixed effect regression model can be used, either the standard or the generalised version, depending on the residual distribution. The mixed effect model allows for individual participant analysis, while taking into account the global information of all participants. This results in a general trend analysis that determines if there is a significant trend in the individual data-sets, as well as the determination of the general applicability of trend analysis for monitoring disease progression in PD.

The performance of the trend algorithm is usually defined as the number of times a trend is properly detected and how many times the the shape is correctly determined, upon visual inspection [69]. Due to the expected natural variance in the data and simulated decrease in performance due to PD symptoms, a linear trend model is used, so the shape parameter is not of interest. By using the bootstrapped data, it can be tested how often the trend is correctly detected for a large number of data-sets. Furthermore, sensitivity of the model can be tested by changing the 'severity' of the simulated PD data, number of simulated data points and the natural variance in motor performance.

6.4. Conclusion

In this chapter proposals are presented for an experiment and the subsequent data analysis. A pursuit tracking task is suggested for gathering data on natural variation of motor performance of elderly participants, spread over 5 days. These data will be combined with simulated PD control behaviour in order to approximate longitudinal clinical data of increasing PD severity. Trend analysis methods will be applied to indicate how those methods can be used to identify changes in motor performance due to disease progression.

7

Conclusion

Neurodegenerative disorders can have a significant effect on the quality of live for patients. In spite of the huge amount of research done, there is still no single, universally applied method to objectively quantify the impact of brain degeneration on motor performance and measure the effect of treatment methods.

Previous research has shown that a decline in motor performance due to neurodegenerative diseases can be determined with the use of manual tracking tasks when comparing patients to a control group. However, there is little information available on how individual motor performance changes due to increasing symptom severity, which would be interesting for treatment monitoring. This study will focus on quantifying the natural variation in human motor performance and identifying changes in control behaviour related to neurodegeneration caused by Parkinson's disease using manual tracking tasks and trend analysis methods.

With a manual control tracking task, the natural motor performance variation for 25 elderly participants will be determined, spread over five days. A pursuit tracking task with single integrator dynamics is chosen in order to ensure sufficient information on neuromuscular dynamics, while keeping the task simple enough for elderly participants and possible further use with PD patients. Human control parameters will be estimated from the data, using the Fourier coefficient method, and will be combined with simulated data for Parkinson's patients. This combined data-set will then be analysed using statistical trend analysis methods to see if there is a significant change in behaviour from healthy to PD data and how this would be best detected.

Results from the experiment, simulation and data analysis will indicate how trend analysis methods can be used to identify behavioural changes in motor performance data. This will be a next step in the development of a treatment monitoring tool for neurodegenerative diseases.

III

Paper appendices

A

Method flowchart

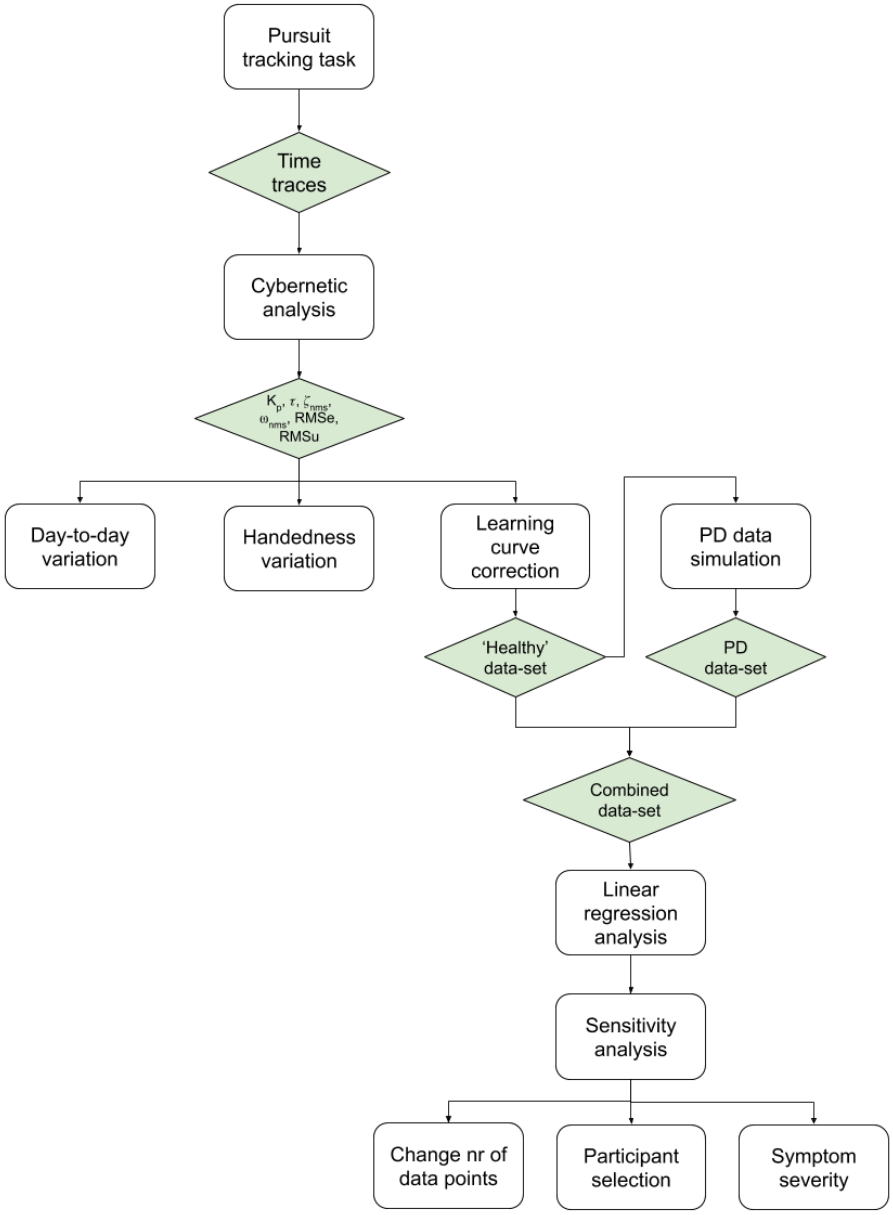


Figure A.1: Method flowchart

B

Briefing Document

This appendix includes the briefing document provided to and discussed with the participants before the start of the experiments. The document is in Dutch, as all participants were Dutch. It has been based on the standard information package and is adapted for this particular experiment.

INFORMATIE VOOR DEELNAME AAN HET ONDERZOEK:

Kwantificeren van natuurlijke variatie in motorische vaardigheden

Geachte heer/mevrouw,

Wij vragen u vriendelijk om mee te doen aan een onderzoek (zie titel). U beslist zelf of u wilt meedoen. Voordat u de beslissing neemt, is het belangrijk om meer te weten over het onderzoek. Lees deze informatiebrief rustig door. Bespreek het met partner, vrienden of familie.

Hebt u na het lezen van de informatie nog vragen? Dan kunt u terecht bij de onderzoeker, achteraan dit document zijn de contactgegevens te vinden.

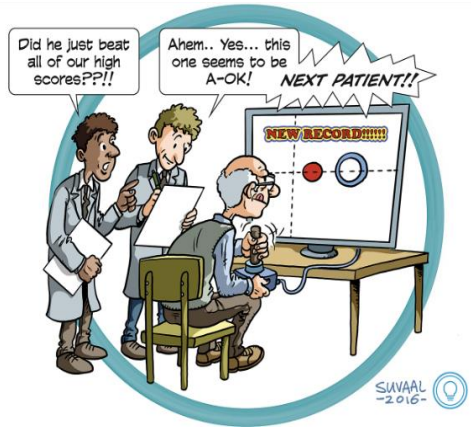
1. KORTE SAMENVATTING EN DOEL VAN HET ONDERZOEK

Ouderdom komt met gebreken is een bekend gezegde. Dit kan onder meer leiden tot teruggang in motorische vaardigheden, wat doorgaans een grote invloed heeft op de kwaliteit van leven. Dezelfde motorische beperkingen kunnen al eerder ontstaan bij mensen met een neurologische aandoening. Met medicatie kunnen deze vaardigheden onder controle gehouden worden, maar voor een effectief behandelplan is een gedetailleerde bepaling van de motorische vaardigheden nodig. Om geleidelijke achteruitgang in deze vaardigheden aan te kunnen tonen is de eerste stap om bij een grote groep gezonde mensen de natuurlijke variatie in stuurprestaties te meten. Het doel van dit project is om deze data te verzamelen.

In een gezamenlijk onderzoeksproject tussen de TU Delft (Faculteit Luchtvaart- en Ruimtevaarttechniek) en het Erasmus Medisch Centrum (afdeling Neurowetenschappen) is een effectieve methode bedacht voor het gedetailleerd meten van de motorische vaardigheden. De methode gebruikt een eenvoudige stuurtaak in combinatie met een wiskundig model om de motorische vaardigheden daarin te kwantificeren. Deze aanpak is afgeleid van, een methode die aan de TU Delft succesvol is toegepast voor het meten van de stuurprestaties van piloten. De eerste bevindingen van deze unieke samenwerking zijn veelbelovend en het gedetailleerd meten van motorische vaardigheden kan een doorbraak betekenen voor het volgen van de ontwikkeling daarvan in ouderen en patiënten en het opstellen van een passend individueel behandelplan.

2. HOE HET ONDERZOEK WORDT UITGEVOERD

Het experiment bestaat uit het meten van stuurgedrag bij deelnemers aan de hand van een simpele stuurtaak (zie cartoon). Deze metingen worden voor elke deelnemer over 5 (niet noodzakelijk opeenvolgende) dagen verspreid om de natuurlijke variatie in sturen vast te kunnen leggen. Elke sessie zal bestaan uit 25 metingen, wat in totaal ongeveer een uur zal kosten. Verder zal tijdens de eerste meetdag een aantal standaard testjes worden uitgevoerd om een referentie punt voor de prestaties te bepalen. Dit zal bestaan uit een "tapping-taak" voor een motorisch referentie punt. De mini-mental-state-Exam voor het cognitief functioneren en met een Snellenkaart wordt de gezichtsscherpte bepaald.



De benodigde materialen (computer en touchscreen voor uitvoeren van de stuurtaak) zullen door ons worden meegenomen naar de gemeenschappelijke ruimte of andere geschikte locatie, zodat u in uw woonomgeving of tijdens de dagbesteding kan deelnemen aan het project.

3. WAT WORDT ER VAN U VERWACHT

Van u wordt verwacht dat u zo goed mogelijk uw best doet tijdens de testen en zo goed mogelijk de aanwijzingen van de onderzoeker opvolgt. Ook verwachten wij dat u de gemaakte afspraken nakomt en aanwezig bent op de besproken tijd en locatie.

4. MOGELIJKE VOOR- EN NADELEN

Er zijn voor u geen directe voordelen van dit onderzoek te verwachten. U helpt wel mee in de ontwikkeling van een methode om in de toekomst een beter behandelplan op te kunnen zetten voor mensen met een motorische beperkingen door neurologische aandoeningen. Meedoen aan het onderzoek brengt géén risico voor uw gezondheid met zich mee.

Een nadeel van het onderzoek is dat er van u een kleine tijdsinvestering wordt verwacht. Het onderzoek duurt ongeveer vijf uur per persoon, verspreid in blokken van een uur per dag. Om de belasting voor u zo minimaal mogelijk te houden streven wij ernaar om het onderzoek in uw directe omgeving uit te voeren zoals bij uw aanleunwoning of dagbesteding locatie.

5. ALS U NIET WIL MEEDOEN OF WILT STOPPEN MET HET ONDERZOEK

U beslist zelf of u meedoet aan het onderzoek. Deelname is vrijwillig. Als u besluit niet mee te doen, hoeft u verder niets te doen. U hoeft niets te tekenen. U hoeft ook niet te zeggen waarom u niet wilt meedoen. Als u wel meedoet, kunt u zich altijd bedenken en toch stoppen. Ook tijdens het onderzoek. Hiervoor hoef u ook geen reden op te geven.

6. EINDE VAN HET ONDERZOEK

Uw deelname aan het onderzoek stopt als

- de onderzoeken zijn afgerond
- u zelf kiest om te stoppen

Het hele onderzoek is afgelopen als alle deelnemers klaar zijn.

7. GEBRUIK VAN UW GEGEVENS

De meetgegevens die verzameld worden voor dit onderzoek zijn volledig anoniem en zullen vertrouwelijk worden behandeld. Dit betekent dat de onderzoeker de gegevens mogen gebruiken voor dit onderzoek, maar zij mogen deze gegevens alleen bekend maken zonder daarbij uw naam of andere persoonlijke gegevens te vermelden. Uw identiteit blijft dus altijd geheim. De onderzoeker bewaart de gegevens met een code. Dit betekent dat op de studie-documenten in plaats van uw naam enkel een letter-cijfercode staat. Alleen de onderzoeker houdt een lijst bij waarop staat welke letter- cijfercode bij welke naam hoort.

8. EXTRA KOSTEN / VERGOEDING VOOR DEELNAME

De testen voor het onderzoek kosten u niets. Wij streven ernaar om het onderzoek plaats te laten vinden in uw directe omgeving waardoor u geen (extra) reiskosten hoeft te maken. U wordt niet betaald voor het meedoen aan dit onderzoek.

9. HEEFT U VRAGEN?

Bij vragen kunt u contact opnemen met het onderzoeksteam met onderstaande informatie. Bij klachten kunt u het beste terecht bij de ethische commissie van de Technische Universiteit Delft (HREC), deze kunt u bereiken door te mailen naar hrec@tudelft.nl.

Contact informatie onderzoeker:	Contact informatie onderzoeksbegeleiders:	
Lieke Lugtenborg	dr. ir. Daan Pool	dr.ir. Johan Pel
L.A.Lugtenborg@student.tudelft.nl	d.m.pool@tudelft.nl	j.pel@erasmusmc.nl
06 43714371	015 2789611	010 7043385
	TU Delft	Erasmus MC

C

Participant Consent Form

This appendix includes the consent form which is to be signed by the participants before the start of the experiments. The document is in Dutch, as all participants were Dutch. It has been based on the standard consent forms and is adapted for this particular experiment.

TOESTEMMINGSFORMULIER VOOR DEELNAME AAN HET ONDERZOEK:

Kwantificeren van natuurlijke variatie in motorische vaardigheden

Hierbij bevestig ik, door middel van het aanvinken van de boxen, dat:

Ik als vrijwilliger mee doe in het experiment opgezet door de onderzoeker (**Lieke Lugtenborg**) onder toezicht van **dr.ir. Daan Pool** van de Technische Universiteit Delft, faculteit Luchtvaart- en Ruimtevaarttechniek en **dr.ir. Johan Pel** van het Erasmus Medisch Centrum, afdeling neurowetenschappen. ☐

Ik de informatiebrief voor de proefpersoon heb gelezen. Ik kon aanvullende vragen stellen. Mijn vragen zijn genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe. ☐

Ik weet dat meedoen helemaal vrijwillig is. Ik weet dat ik op ieder moment kan beslissen om toch niet mee te doen. Daarvoor hoef ik geen reden te geven. ☐

Ik begrijp dat het deelnemen aan het onderzoek inhoudt dat ik een simpele stuurtaak uitvoer op een touchscreen. ☐

Ik begrijp dat de onderzoeker alle data zal anonimiseren en mij niet bij naam zal noemen in verslagen en/of publicaties die uit dit onderzoek kunnen voortkomen. ☐

Ik toestemming geef om de data die verzameld wordt te gebruiken voor de doelen die in de informatiebrief staan. ☐

Ik begrijp dat dit experiment is beoordeeld en goedgekeurd door de TU Delft Human Research Ethics Committee (HREC). Als ik problemen betreffende mijn deelname aan dit experiment wil melden, weet ik dat ik de onderzoekers met onderstaande informatie kan benaderen, of indien nodig het HREC (hrec@tudelft.nl). ☐

Naam proefpersoon:

Handtekening: Datum: __ / __ / __

Ik verklaar hierbij dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek. Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Naam onderzoeker:

Handtekening: Datum: __ / __ / __

Contact informatie onderzoeker:	Contact informatie onderzoeksbegeleiders:	
Lieke Lugtenborg	dr. ir. Daan Pool	dr.ir. Johan Pel
L.A.Lugtenborg@student.tudelft.nl	d.m.pool@tudelft.nl	j.pel@erasmusmc.nl
06 43714371	015 2789611	010 7043385
	TU Delft	Erasmus MC

D

Participant information

Table D.1 provides an overview of the parameters and their handedness and scores. The maximum MMSE score is 30 and a score lower than 26 is related to cognitive decline [68]. The Baseline pass parameter indicates whether the participant passed all criteria related to the EMC baseline tests, as defined in Table E.1. Best RMSe gives the score for the best tracking performance and Best hand indicates with which hand this score was obtained. Good participants indicates whether a participant has a sufficiently high performance for the select group in the sensitivity analysis.

Table D.1: Overview of participant information

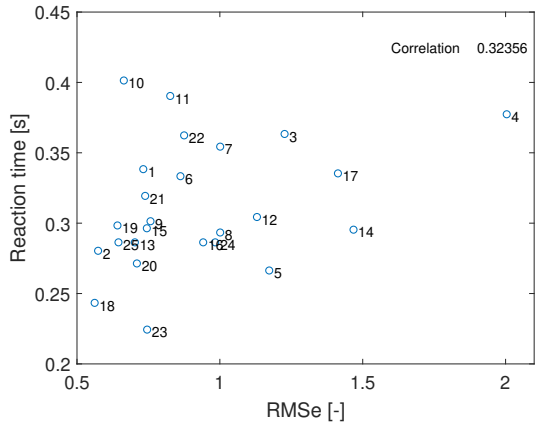
Participant	age	sex	Handedness	MMSE	Baseline pass	Best RMSe	Best hand	Good participant
1	56	f	r	30	*	0.66	ND	*
2	58	m	r	30	*	0.58	D	*
3	75	f	r	30		1.27	D	
4	75	f	r	30	*	1.59	ND	
5	72	f	r	28		1.17	D	
6	74	m	r	27	*	0.82	ND	*
7	73	f	r	30	*	0.87	ND	*
8	74	f	l	30		0.95	ND	
9	75	m	r	28	*	0.69	ND	*
10	58	m	r	30	*	0.61	D	*
11	64	f	r	30		0.80	D	
12	64	f	r	30	*	1.01	ND	
13	64	m	r	30	*	0.67	ND	*
14	61	f	r	30	*	1.36	ND	
15	67	f	r	30	*	0.75	D	*
16	70	f	r	30		0.91	D	
17	72	f	r	30		1.37	ND	
18	62	m	l	26	*	0.53	ND	*
19	60	f	r	30	*	0.64	D	*
20	58	f	r	30	*	0.68	D	*
21	69	m	r	29	*	0.74	D	*
22	75	f	r	29	*	0.86	ND	
23	68	f	r	30	*	0.69	ND	*
24	72	f	r	28	*	0.99	D	*
25	56	f	r	30	*	0.65	D	*

Table D.2: Overview of skipped measurements in data analysis for each participant

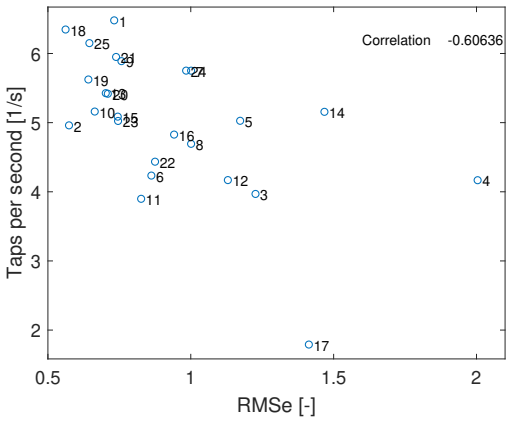
Participant	Nr of missing	Missing runs D	Missing runs ND
1	1	-	15
2	2	-	5, 21
3	33	1, 2, 3, 11, 12, 15, 18, 23, 24, 26, 27, 28, 33, 34, 36, 37, 39, 40, 45, 48, 49	1, 2, 3, 4, 6, 9, 14, 17, 19, 23, 26, 33
4	24	1, 6, 7, 14, 15, 26, 30, 34, 41, 48	2, 4, 6, 8, 14, 19, 20, 21, 33, 38, 43, 47, 49, 50
5	10	17, 21, 34, 35, 44	1, 10, 31, 32, 33
6	18	1, 3, 16, 26, 27, 28, 36, 39, 41, 43	9, 12, 41 ,42 ,45 ,46 ,48, 50
7	17	14, 25, 26, 30, 31, 32, 36, 39, 43, 45, 48	6, 14, 22, 35, 39, 47
8	17	14, 25, 26, 30, 31, 32, 36, 39, 43, 45, 48	6, 14, 22, 35, 39, 47
9	3	28, 42, 46	-
10	4	4, 6, 14, 22	-
11	27	1, 11, 13, 16, 18, 20, 25, 26, 27, 28, 45, 46	5, 6, 8, 10, 12, 18, 19, 25, 33, 35, 36, 39, 40, 42, 45
12	18	11, 12, 22, 27, 37, 41, 42, 45	7, 14, 17, 18, 22, 24, 32, 34, 37, 38
13	2	22	1
14	20	8, 10, 13, 17, 22, 26	4, 14, 19, 23, 24, 25, 27, 32, 33, 34, 37, 39, 40, 49
15	6	-	7, 14, 15, 30, 44, 47
16	14	1, 5, 6, 7, 30, 41, 42, 49	1, 10, 25, 37, 40, 41
17	7	4, 23	3, 4, 10, 15, 33
18	5	1, 31	1, 8, 43
19	1	7	-
20	0	-	-
21	11	8, 9, 29	9, 13, 20, 37, 38, 39, 43, 50
22	8	5, 8, 25, 27, 39	4, 29, 32
23	2	21, 30	-
24	0	-	-
25	5	-	23, 24, 37, 39, 42

E

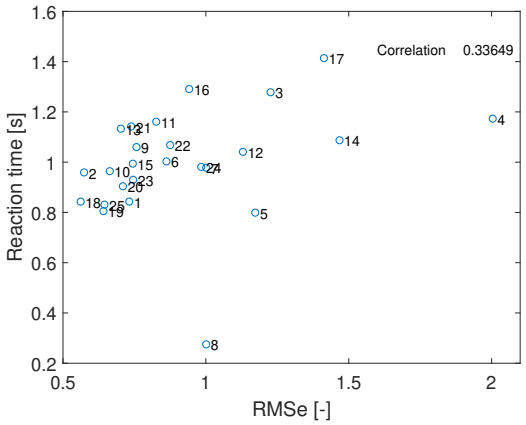
EMC baseline test results



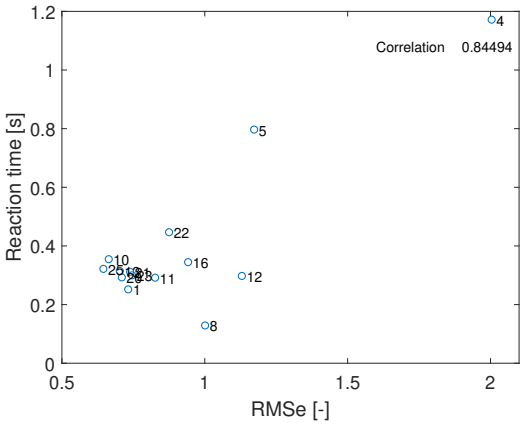
(a) Reaction time simple tap



(b) Taps per second



(c) Reaction time protap touch



(d) Reaction time protap space

Figure E.1: EMC baseline test performance

Table E.1: Participant inclusion criteria value range related to EMC baseline tests

Inclusion criterion		Value range
Reaction time simple tap [s]	Figure E.1a	≤ 0.4
Taps per second [-]	Figure E.1b	≥ 4
Reaction time screen touch [s]	Figure E.1c	$0.8 \leq \delta \leq 1.2$
Reaction time space release [s]	Figure E.1d	$0.2 \leq \delta \leq 0.4$

F

Supporting results experimental data analysis of scientific paper

F.1. Shapiro-Wilk normality test results

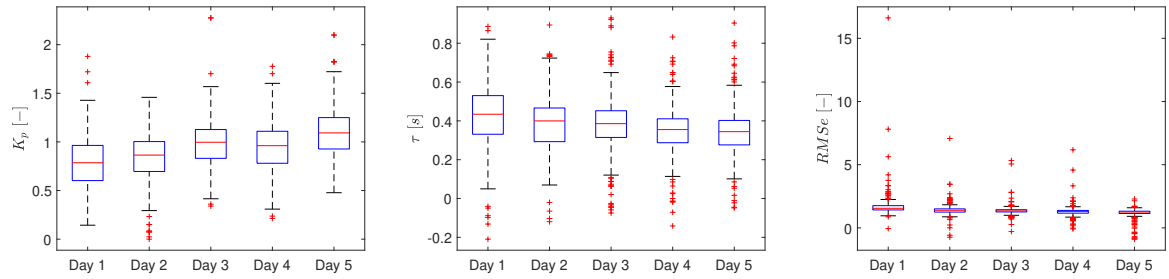
Table F.1: Results of Shapiro-Wilk normality test complete data-sets, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

Shapiro-Wilk	Dependent measures											
	K_p		τ		ζ_{nms}		ω_{nms}		RMSe		RMSu	
Data set	W	Sig.	W	Sig.	W	Sig.	W	Sig.	W	Sig.	W	Sig.
D	0.99	**	0.92	**	0.96	**	0.94	**	0.75	**	0.85	**
ND	0.99	**	0.94	**	0.94	**	0.94	**	0.56	**	0.83	**

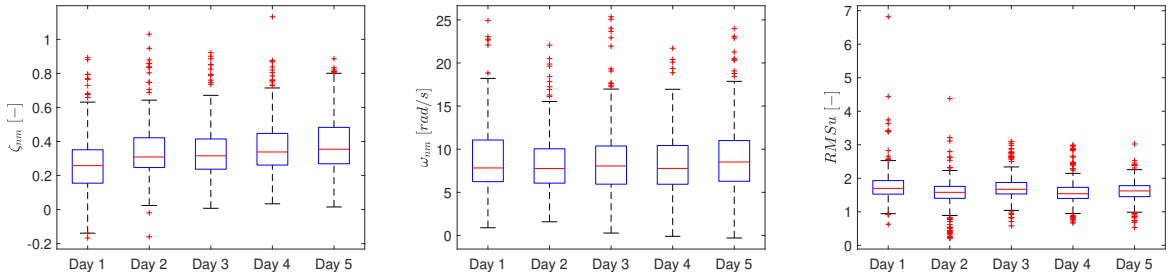
Table F.2: Results of Shapiro-Wilk normality test for individual analysis, where * indicates the data was not normally distributed for that parameter and control hand

Shapiro-Wilk	Dependent measures											
	K_p		τ		ζ_{nms}		ω_{nms}		RMSe		RMSu	
participant	D	ND	D	ND	D	ND	D	ND	D	ND	D	ND
all	56%	60%	56%	56%	56%	60%	76%	60%	72%	56%	64%	56%
1		*			*	*	*	*	*	*	*	
2		*	*	*		*	*	*			*	
3	*				*	*	*		*		*	*
4	*	*	*		*	*	*		*	*	*	*
5	*	*	*				*	*			*	*
6	*	*		*		*	*	*	*	*	*	
7			*	*			*	*	*			*
8	*	*	*	*		*	*		*	*		
9		*		*	*	*	*	*	*	*	*	*
10	*		*	*					*		*	
11								*	*		*	*
12	*	*	*	*	*	*	*	*	*	*	*	*
13	*	*		*	*	*			*		*	*
14	*	*	*		*		*	*		*	*	*
15			*	*	*	*	*			*	*	*
16	*	*		*	*			*	*	*		*
17		*	*			*	*	*	*	*	*	*
18			*	*	*	*	*			*		
19					*		*		*	*	*	*
20				*	*	*		*				
20	*	*	*	*		*		*			*	
22			*	*			*		*	*		
23	*	*			*	*	*	*	*			*
24	*				*		*		*	*		
25	*	*	*				*	*	*			

F.2. Day-to-day variation, non-dominant hand



(a) K_p (b) τ (c) RMSe



(d) ζ_{nms} (e) ω_{nms} (f) RMSu

Figure F.1: Day-to-day variation in motor performance parameters, ND

Table F.3: Results of post hoc Wilcoxon test for day-to-day variation for non-dominant hand control (ND), where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

Wilcoxon - ND	Dependent measures											
	K_p		τ		ζ_{nms}		ω_{nms}		RMSe		RMSu	
Data set	W	Sig.	W	Sig.	W	Sig.	W	Sig.	W	Sig.	W	Sig.
Day 1 - Day 2	-2.68	**	1.98	-	-3.74	**	n/a	n/a	7.54	**	5.09	**
Day 1 - Day 3	-5.76	**	2.41	*	-2.70	**	n/a	n/a	9.77	**	2.91	**
Day 1 - Day 4	-4.93	**	4.64	**	-4.15	**	n/a	n/a	10.39	**	5.78	**
Day 1 - Day 5	-8.64	**	4.16	**	-5.69	**	n/a	n/a	12.67	**	4.32	**
Day 2 - Day 3	-4.07	**	1.39	-	1.46	-	n/a	n/a	2.23	*	-2.71	**
Day 2 - Day 4	-3.80	**	3.58	**	-1.62	-	n/a	n/a	5.89	**	1.34	-
Day 2 - Day 5	-6.92	**	4.07	**	-2.46	*	n/a	n/a	8.40	**	-0.64	-
Day 3 - Day 4	-0.29	-	2.52	*	-2.19	*	n/a	n/a	3.98	**	4.89	**
Day 3 - Day 5	-4.73	**	2.98	**	-3.04	**	n/a	n/a	8.45	**	2.45	*
Day 4 - Day 5	-5.09	**	1.53	-	-0.94	-	n/a	n/a	4.14	**	-2.43	*

F.3. Standard deviation and Coefficient of Variance Corrected data

The table below gives the Standard deviation and Coefficient of Variance for the data which have been corrected for the learning curve.

Table F.4: Standard deviation and Coefficient of Variance of control parameters for all participants, data corrected for learning effects

	Parameters															
	K_p				τ				ζ_{nms}				ω_{nms}			
Participant	D		ND		D		ND		D		ND		D		ND	
	σ	CV	σ	CV	σ	CV	σ	CV	σ	CV	σ	CV	σ	CV	σ	CV
1	0.20	23	0.24	24	0.12	35	0.10	32	0.15	47	0.20	50	3.68	57	2.32	33
2	0.26	19	0.18	12	0.06	19	0.05	16	0.10	38	0.08	36	3.14	28	3.40	28
3	0.10	84	0.16	42	0.22	62	0.25	40	0.08	108	0.08	73	7.5	70	4.94	64
4	0.16	68	0.21	68	0.31	63	0.25	62	0.09	105	0.18	135	6.78	79	7.35	63
5	0.31	32	0.32	35	0.19	42	0.22	43	0.20	64	0.18	73	4.32	62	4.04	55
6	0.25	40	0.27	37	0.17	44	0.13	37	0.21	42	0.25	69	4.98	61	4.86	52
7	0.24	32	0.31	33	0.15	33	0.12	38	0.24	58	0.23	44	7.15	66	5.86	65
8	0.33	35	0.45	34	0.16	36	0.09	28	0.20	62	0.25	70	3.32	37	3.49	34
9	0.27	22	0.23	17	0.07	21	0.07	22	0.20	67	0.13	56	3.29	31	3.99	37
10	0.24	21	0.24	18	0.06	24	0.05	19	0.20	30	0.18	30	2.66	26	2.98	27
11	0.54	61	0.35	37	0.14	46	0.17	52	0.31	61	0.22	44	4.95	59	4.35	64
12	0.24	51	0.25	55	0.22	51	0.18	55	0.31	75	0.26	71	6.04	73	6.16	65
13	0.17	16	0.24	21	0.07	23	0.14	52	0.17	34	0.21	43	1.87	30	3.07	47
14	0.34	67	0.21	44	0.29	54	0.22	37	0.12	80	0.05	68	5.36	79	4.49	68
15	0.23	32	0.18	39	0.09	32	0.23	51	0.21	51	0.10	72	4.62	45	4.42	51
16	0.36	48	0.39	47	0.14	41	0.17	54	0.28	54	0.25	54	5.75	63	4.27	61
17	0.22	50	0.30	65	0.28	51	0.22	53	0.14	68	0.12	84	6.07	92	6.35	62
18	0.16	12	0.27	20	0.11	46	0.11	42	0.16	35	0.17	37	3.71	45	3.85	42
19	0.18	15	0.18	14	0.07	23	0.06	20	0.13	38	0.07	26	2.87	34	1.54	22
20	0.14	13	0.16	15	0.11	40	0.09	26	0.15	37	0.19	51	3.20	43	3.23	34
21	0.31	23	0.28	28	0.06	20	0.08	23	0.20	33	0.20	51	2.76	30	4.44	36
22	0.27	29	0.31	28	0.13	32	0.08	27	0.25	57	0.25	44	3.73	36	4.18	38
23	0.32	24	0.23	16	0.12	35	0.11	29	0.22	49	0.19	48	3.50	42	3.74	39
24	0.39	32	0.29	26	0.14	36	0.13	28	0.13	48	0.08	46	2.71	50	2.92	37
25	0.24	19	0.16	16	0.06	21	0.09	28	0.19	34	0.20	37	3.69	31	2.90	28

	Parameters							
	RMSe				RMSu			
Participant	D		ND		D		ND	
	σ	CV	σ	CV	σ	CV	σ	CV
1	0.20	20	0.13	14	0.26	19	0.19	14
2	0.13	16	0.10	12	0.18	13	0.19	13
3	0.57	28	0.34	16	0.38	32	0.35	19
4	1.23	36	1.94	46	0.56	25	0.72	30
5	0.29	17	0.29	16	0.50	19	0.70	26
6	0.30	22	0.22	19	0.25	22	0.16	13
7	0.38	27	0.22	18	0.20	14	0.31	21
8	0.34	22	0.25	21	0.22	11	0.73	30
9	0.34	32	0.27	27	0.24	15	0.28	15
10	0.13	15	0.06	8	0.12	10	0.11	9
11	0.16	14	0.21	17	0.19	12	0.25	16
12	0.29	19	0.39	23	0.21	18	0.26	21
13	0.10	11	0.11	13	0.09	8	0.11	9
14	0.48	22	0.95	39	0.57	28	0.69	28
15	0.19	15	0.48	31	0.13	11	0.30	22
16	0.22	17	0.17	14	0.28	21	0.31	22
17	0.84	34	2.22	84	0.44	20	0.78	34
18	0.08	12	0.11	14	0.14	11	0.13	10
19	0.20	23	0.15	17	0.16	13	0.16	11
20	0.07	8	0.12	12	0.12	10	0.11	8
21	0.14	15	0.18	15	0.15	10	0.18	11
22	0.36	26	0.47	32	0.20	12	0.29	17
23	0.16	17	0.15	15	0.23	15	0.19	11
24	0.23	17	0.24	16	0.69	27	0.50	21
25	0.09	12	0.10	11	0.15	13	0.15	13

F.4. Dominant vs non-dominant hand slope, participant overview

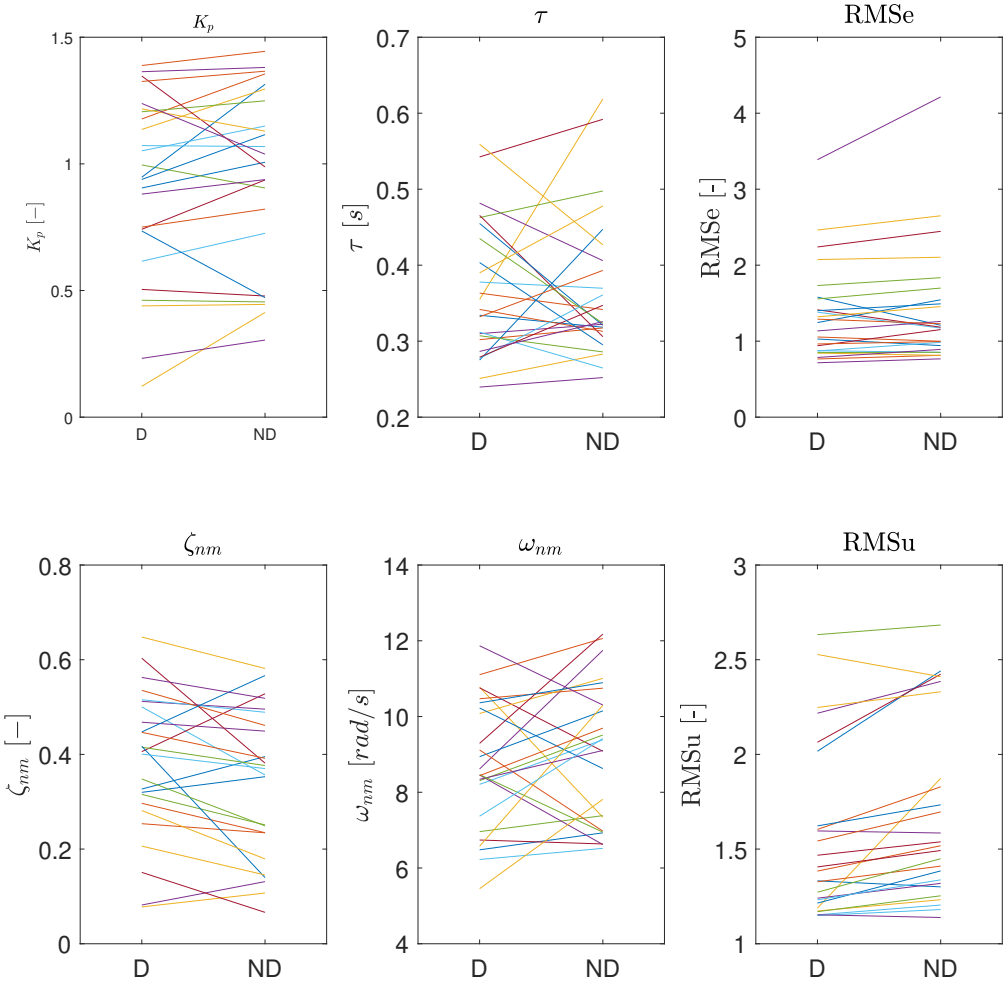


Figure F.2: Dominant versus non-dominant hand control participant means and slope direction

G

Correlation matrix of motor performance metrics for use in GLR trend analysis

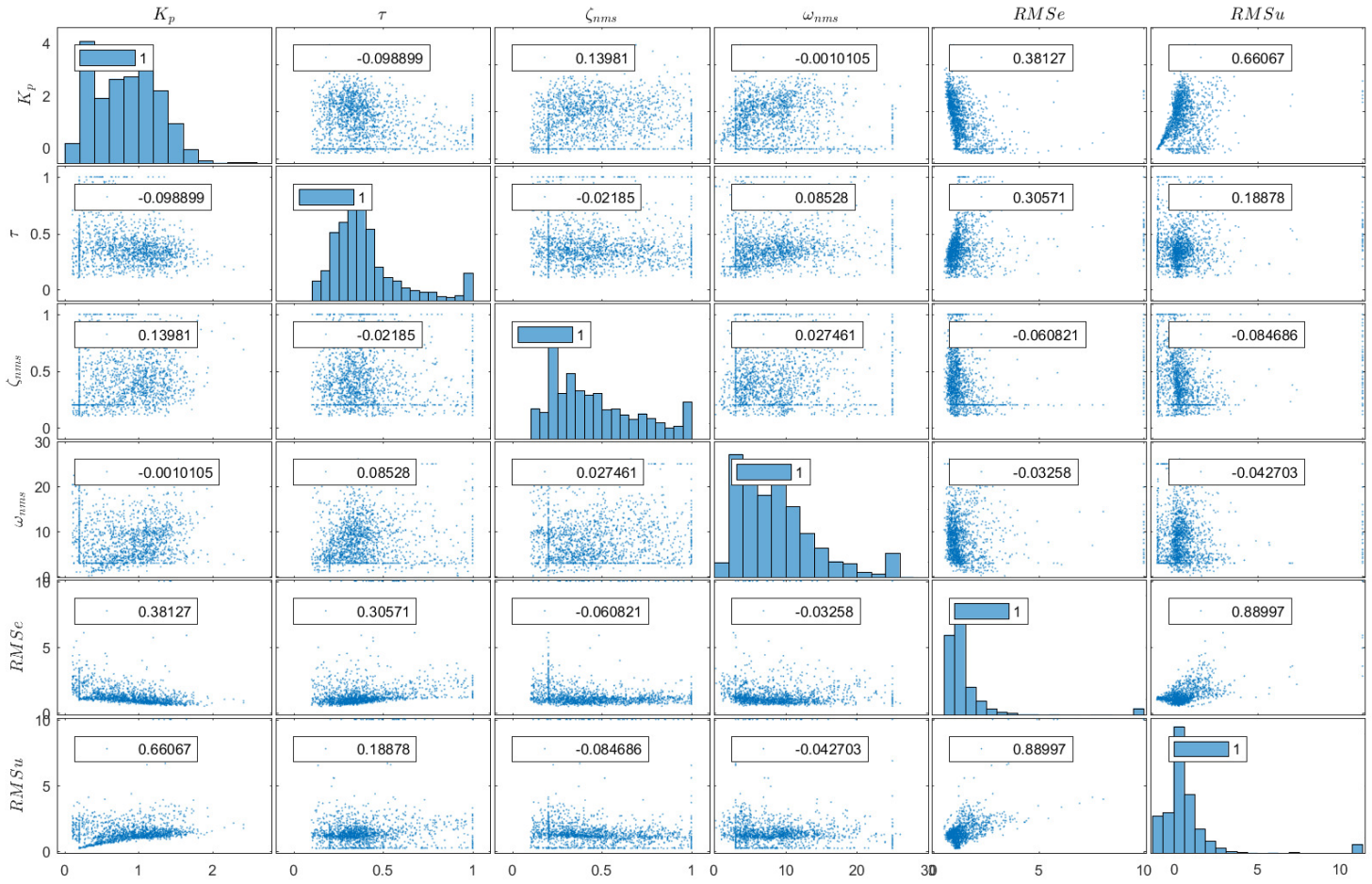


Figure G.1: Correlation matrix for motor performance metrics

H

Individual trend analysis results

H.1 Participant 1

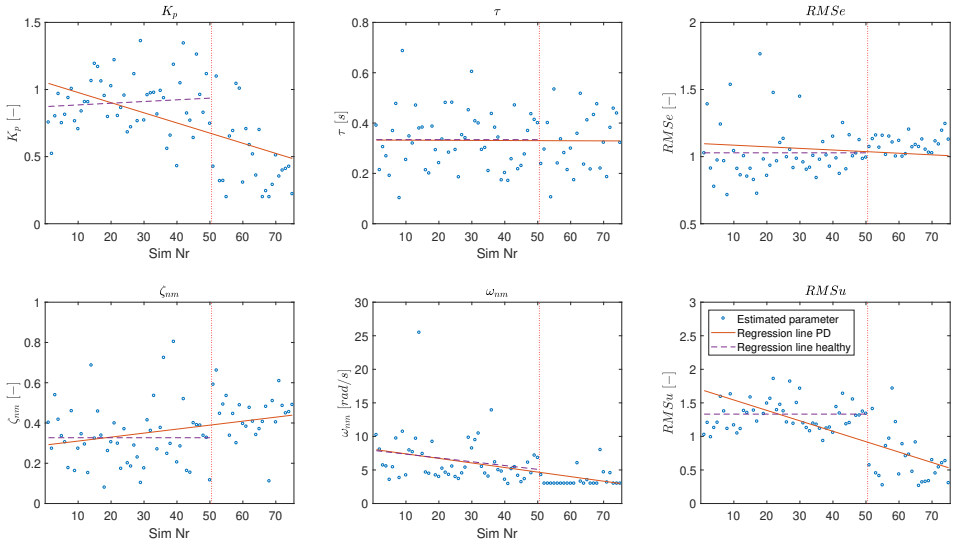


Figure H.1: Results of GLR trend analysis, Participant 1, Dominant hand

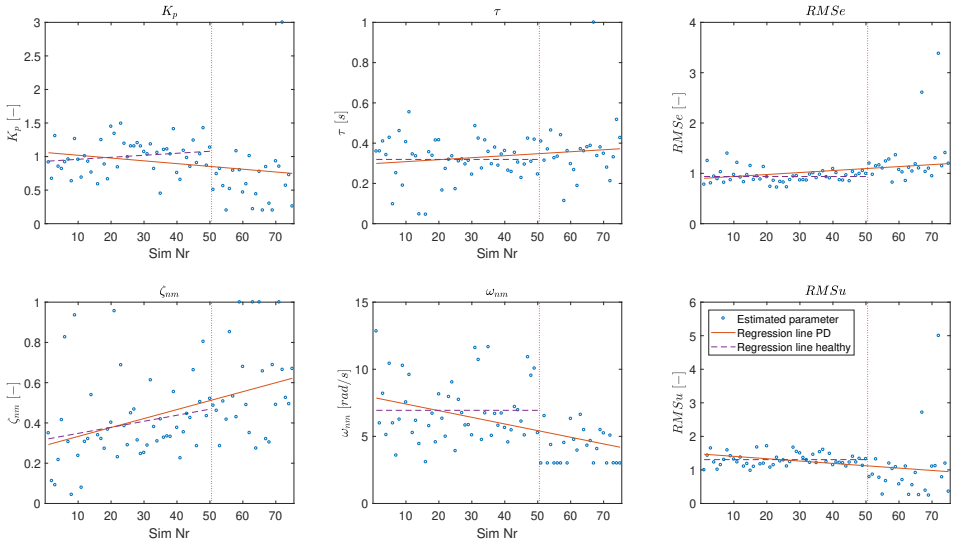


Figure H.2: Results of GLR trend analysis, Participant 1, Non-dominant hand

Table H.1: Results of one-sample t-test for GLR trend analysis for Participant 1, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-5.71	**	-2.00	*
τ	73	-0.07	-	1.50	-
ζ_{nms}	73	2.60	**	4.03	**
ω_{nms}	73	-4.23	**	-4.31	**
RMSe	73	-1.14	-	1.96	*
RMSu	73	-9.88	**	-2.24	**

H.2 Participant 2

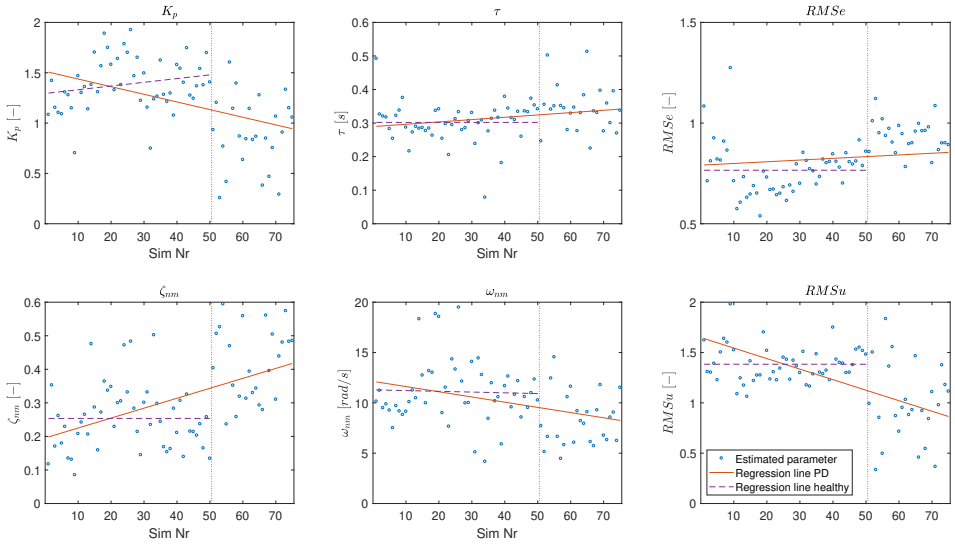


Figure H.3: Results of GLR trend analysis, Participant 2, Dominant hand

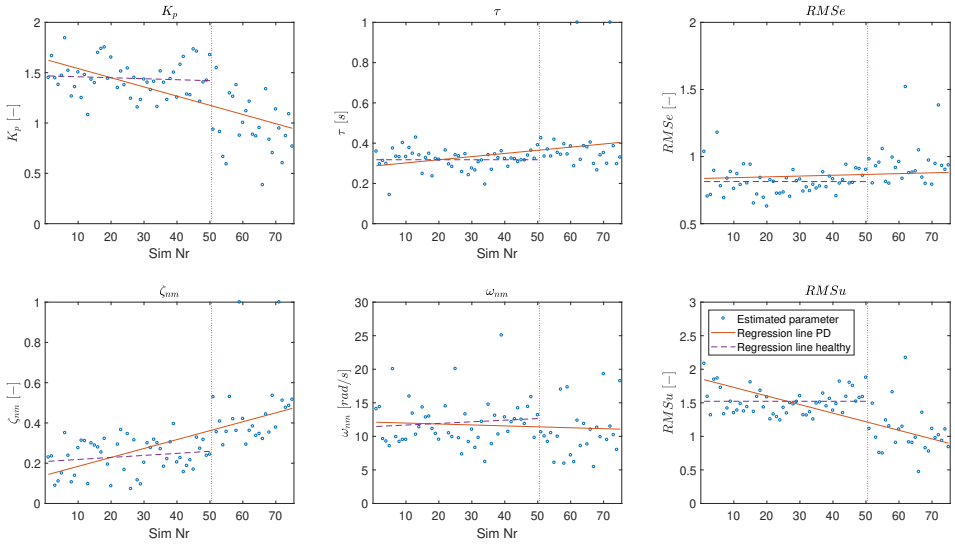


Figure H.4: Results of GLR trend analysis, Participant 2, Non-dominant hand

Table H.2: Results of one-sample t-test for GLR trend analysis for Participant 2, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-4.29	**	-7.17	**
τ	73	2.09	*	2.55	**
ζ_{nms}	73	5.11	**	6.34	**
ω_{nms}	73	-3.21	**	-0.73	-
RMSe	73	0.99	-	0.70	-
RMSu	73	-7.49	**	-9.78	**

H.3 Participant 3

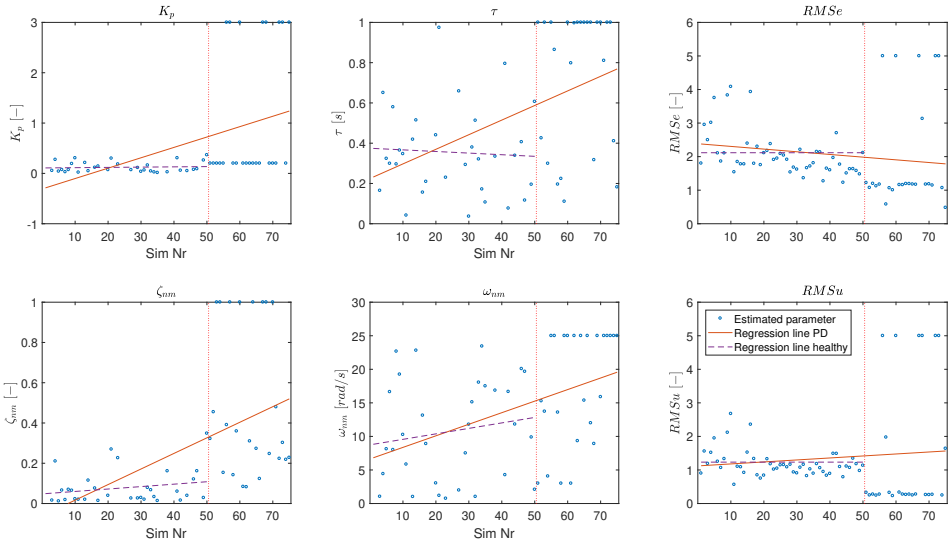


Figure H.5: Results of GLR trend analysis, Participant 3, Dominant hand

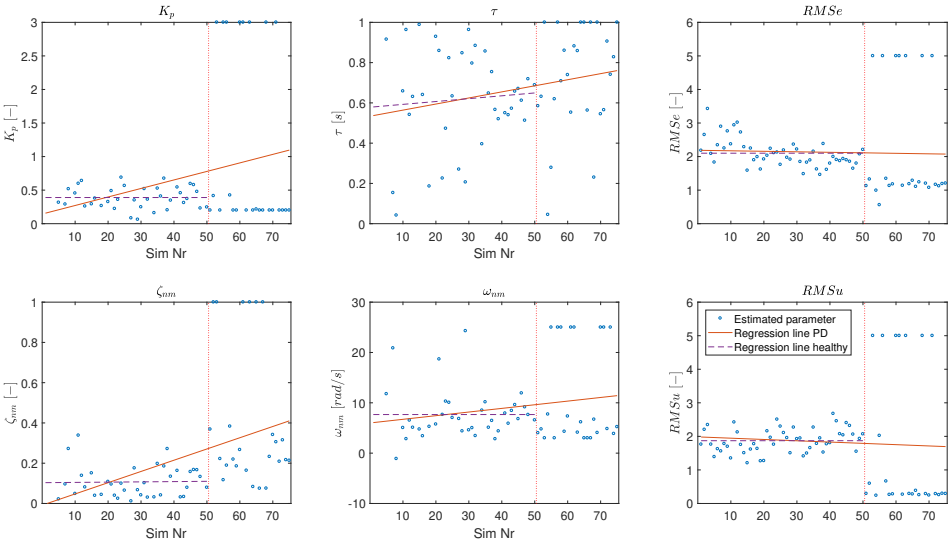


Figure H.6: Results of GLR trend analysis, Participant 3, Non-dominant hand

Table H.3: Results of one-sample t-test for GLR trend analysis for Participant 3, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	3.97	**	2.33	*
τ	73	4.17	**	1.93	*
ζ_{nms}	73	4.85	**	3.63	**
ω_{nms}	73	3.83	**	1.59	-
RMSe	73	-1.14	-	-0.21	-
RMSu	73	0.73	-	-0.45	-

H.4 Participant 4

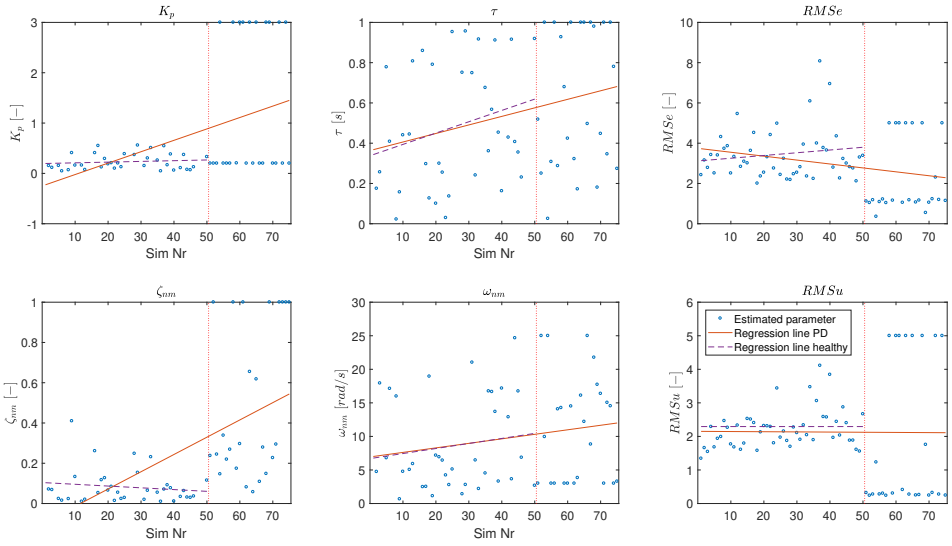


Figure H.7: Results of GLR trend analysis, Participant 4, Dominant hand

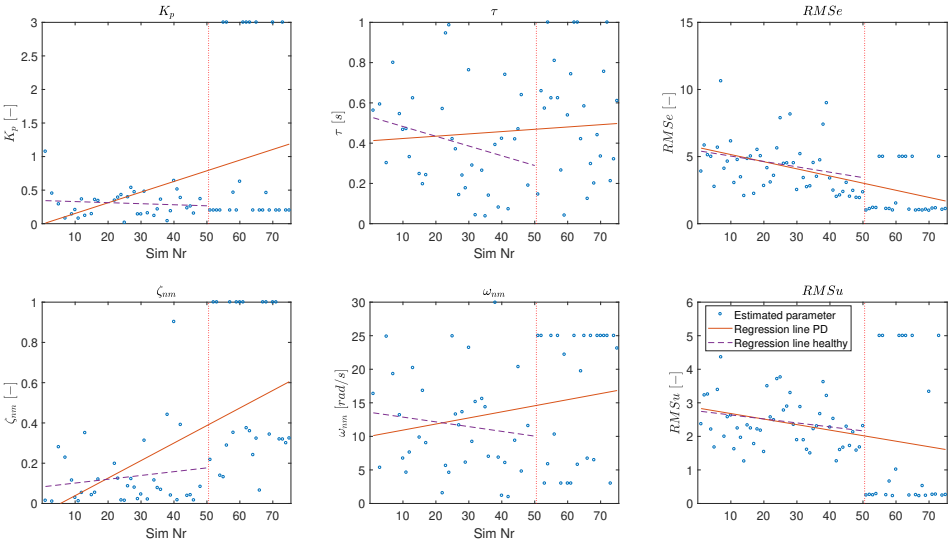


Figure H.8: Results of GLR trend analysis, Participant 4, Non-dominant hand

Table H.4: Results of one-sample t-test for GLR trend analysis for Participant 4, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	4.21	**	3.04	**
τ	73	2.31	*	0.70	-
ζ_{nms}	73	5.61	**	5.03	**
ω_{nms}	73	1.61	-	1.79	*
RMSe	73	-2.09	*	-4.64	**
RMSu	73	-0.06	-	-1.88	*

H.5 Participant 5

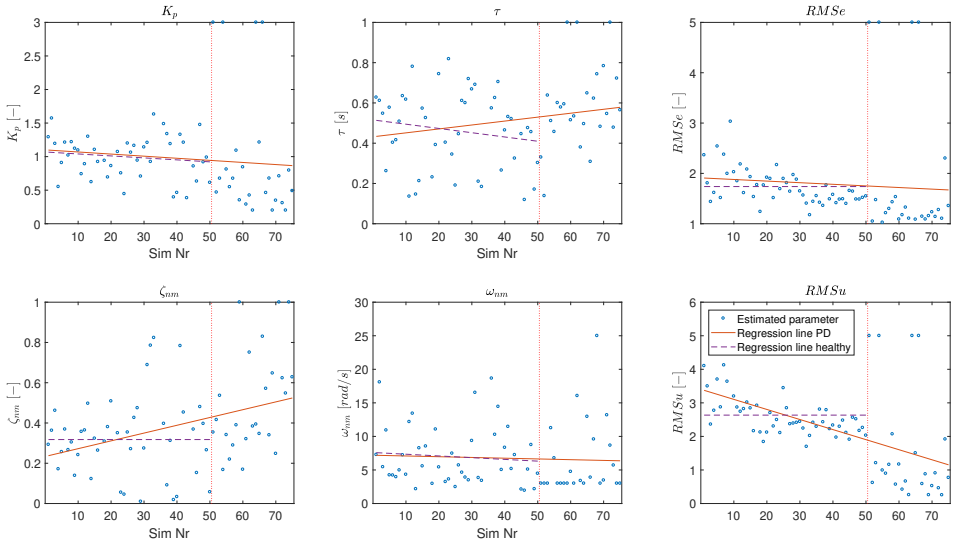


Figure H.9: Results of GLR trend analysis, Participant 5, Dominant hand

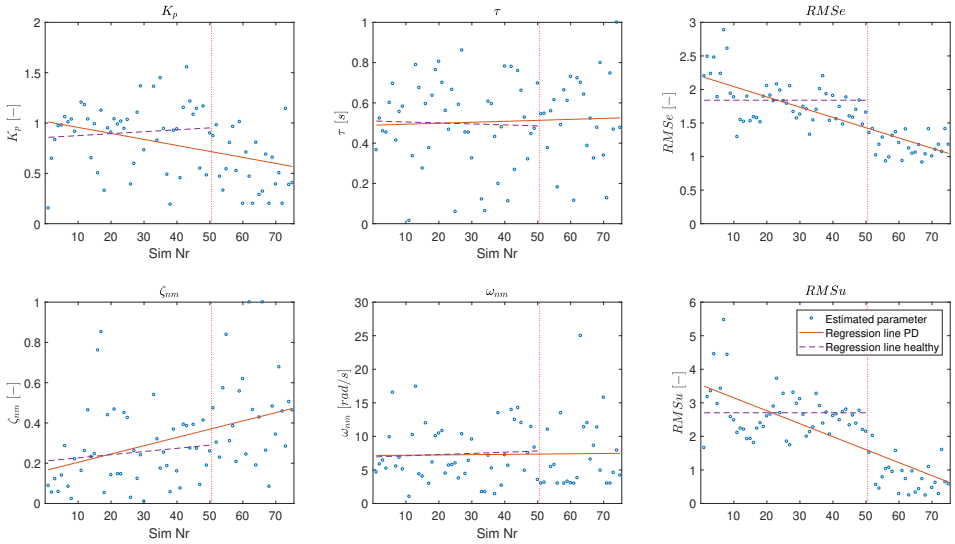


Figure H.10: Results of GLR trend analysis, Participant 5, Non-dominant hand

Table H.5: Results of one-sample t-test for GLR trend analysis for Participant 5, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-0.96	-	-3.47	**
τ	73	1.80	*	0.42	-
ζ_{nms}	73	3.24	**	3.73	**
ω_{nms}	73	-0.43	-	0.18	-
RMSe	73	-0.67	-	-10.45	**
RMSu	73	-5.51	**	-9.82	**

H.6 Participant 6

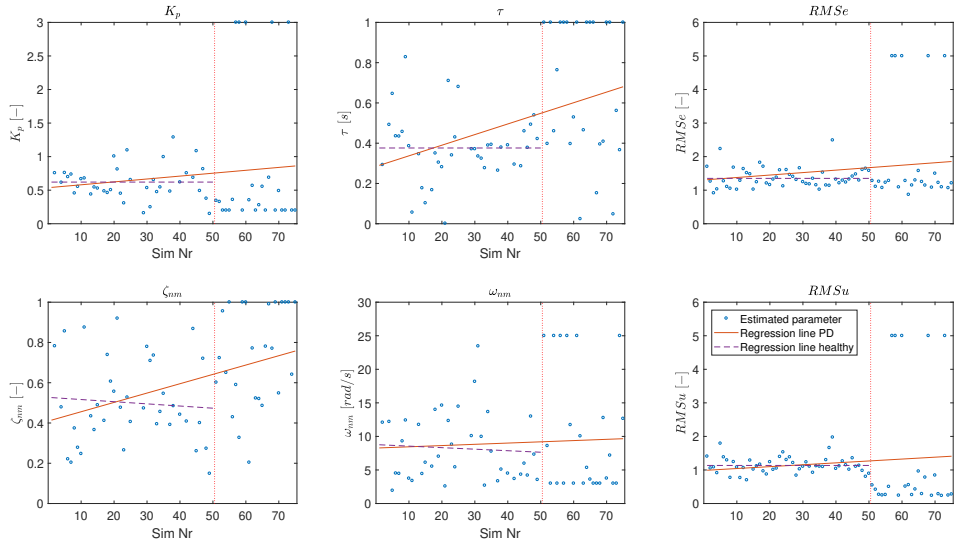


Figure H.11: Results of GLR trend analysis, Participant 6, Dominant hand

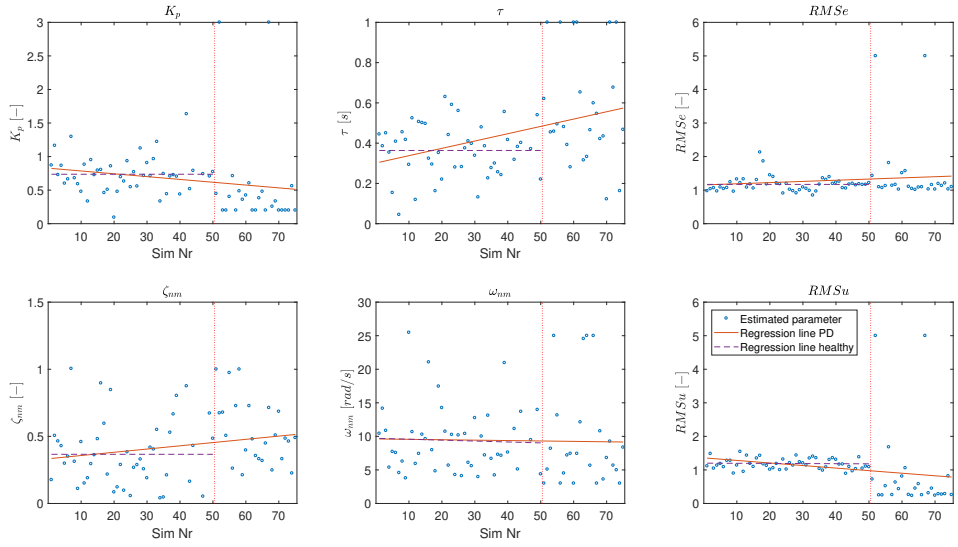


Figure H.12: Results of GLR trend analysis, Participant 6, Non-dominant hand

Table H.6: Results of one-sample t-test for GLR trend analysis for Participant 6, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	1.06	-	-1.61	-
τ	73	3.47	**	3.37	**
ζ_{nms}	73	3.54	**	1.81	*
ω_{nms}	73	0.47	-	-0.20	-
RMSe	73	1.24	-	0.99	-
RMSu	73	0.84	-	-1.87	*

H.7 Participant 7

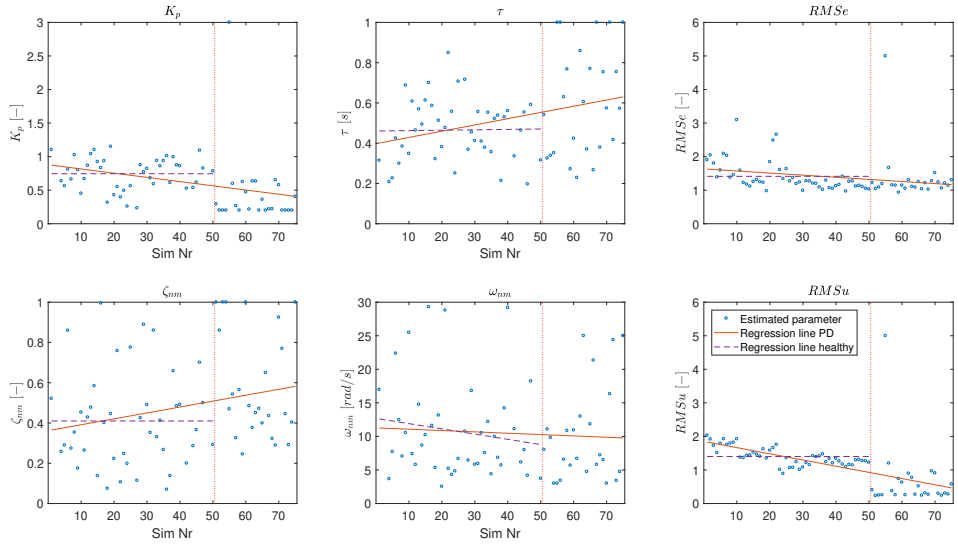


Figure H.13: Results of GLR trend analysis, Participant 7, Dominant hand

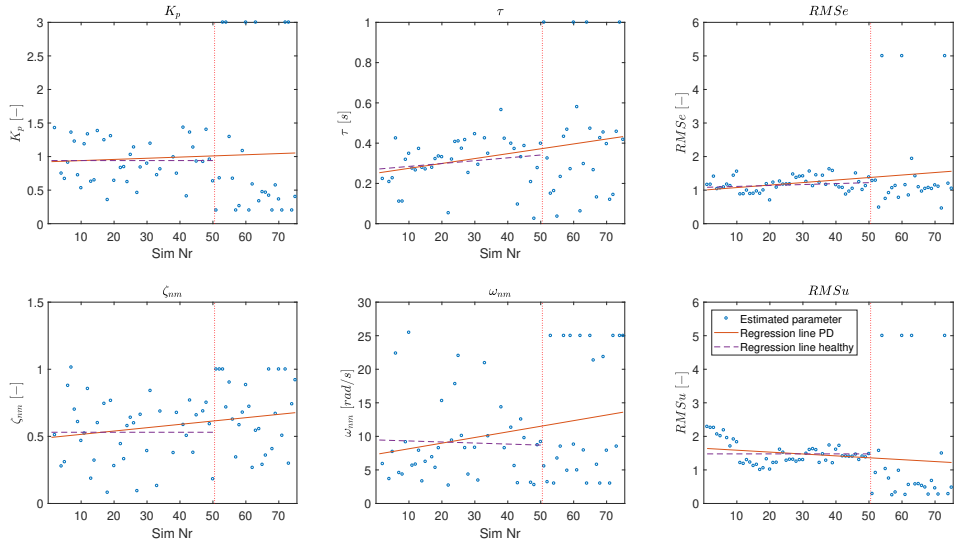


Figure H.14: Results of GLR trend analysis, Participant 7, Non-dominant hand

Table H.7: Results of one-sample t-test for GLR trend analysis for Participant 7, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-0.96	**	0.42	-
τ	73	1.80	**	2.11	**
ζ_{nms}	73	3.24	*	1.80	*
ω_{nms}	73	-0.43	-	2.00	*
RMSe	73	-0.67	*	1.57	-
RMSu	73	-5.51	**	-0.95	-

H.8 Participant 8

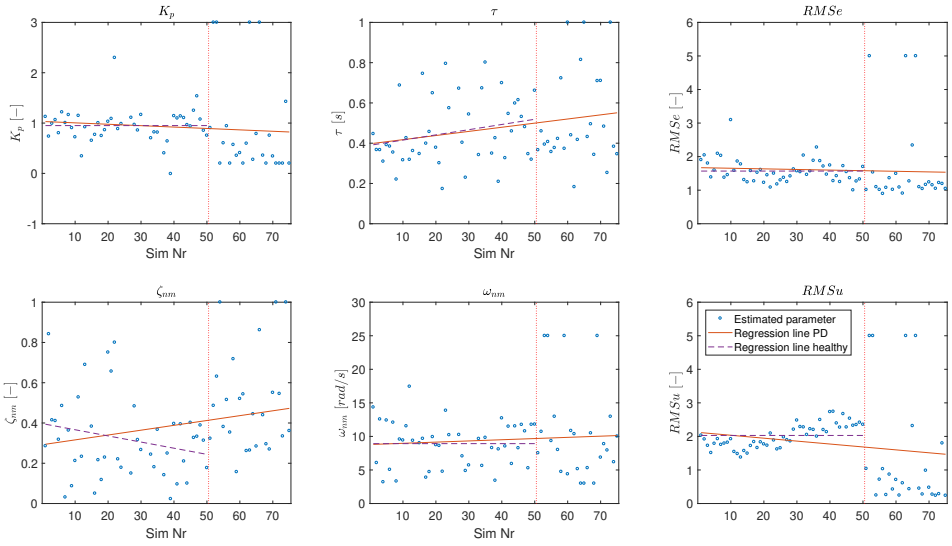


Figure H.15: Results of GLR trend analysis, Participant 8, Dominant hand

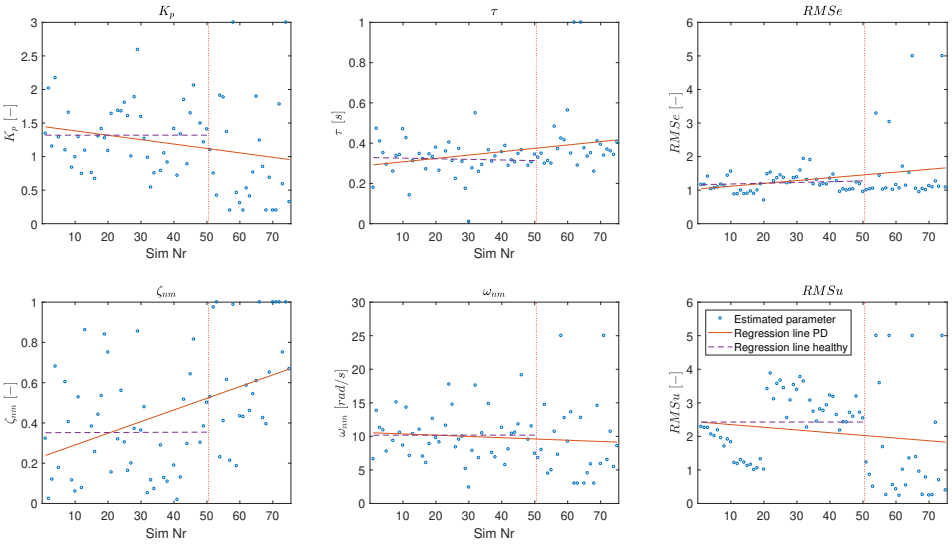


Figure H.16: Results of GLR trend analysis, Participant 8, Non-dominant hand

Table H.8: Results of one-sample t-test for GLR trend analysis for Participant 8, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-0.80	-	-1.94	*
τ	73	2.04	*	2.28	*
ζ_{nms}	73	1.98	*	4.03	**
ω_{nms}	73	0.66	-	-0.75	-
RMSe	73	-0.41	-	2.11	*
RMSu	73	-1.50	-	-1.16	-

H.9 Participant 9

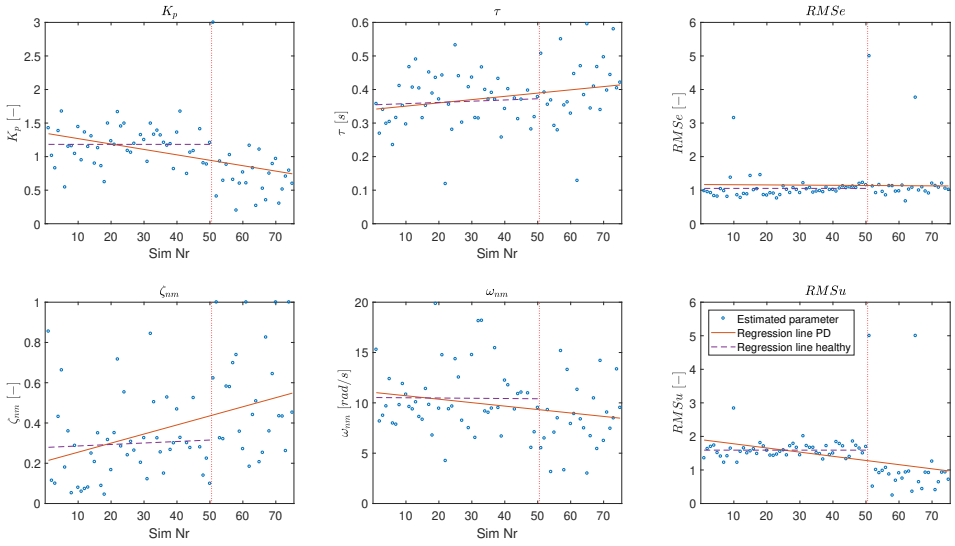


Figure H.17: Results of GLR trend analysis, Participant 9, Dominant hand

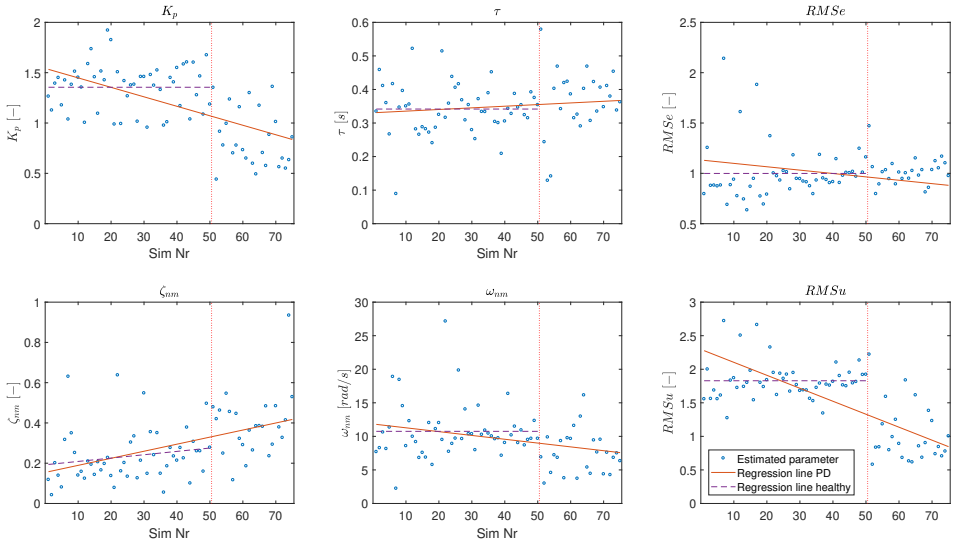


Figure H.18: Results of GLR trend analysis, Participant 9, Non-dominant hand

Table H.9: Results of one-sample t-test for GLR trend analysis for Participant 9, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-3.98	**	-6.31	**
τ	73	2.18	*	1.12	-
ζ_{nms}	73	3.70	**	4.78	**
ω_{nms}	73	-1.94	*	-2.81	**
RMSe	73	-0.16	-	-2.37	*
RMSu	73	-3.28	**	-11.08	**

H.10 Participant 10

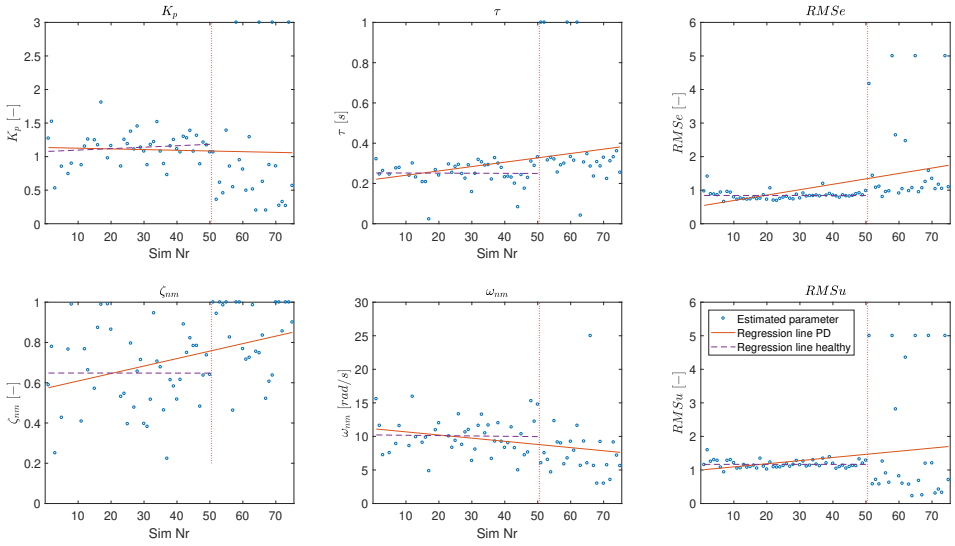


Figure H.19: Results of GLR trend analysis, Participant 10, Dominant hand

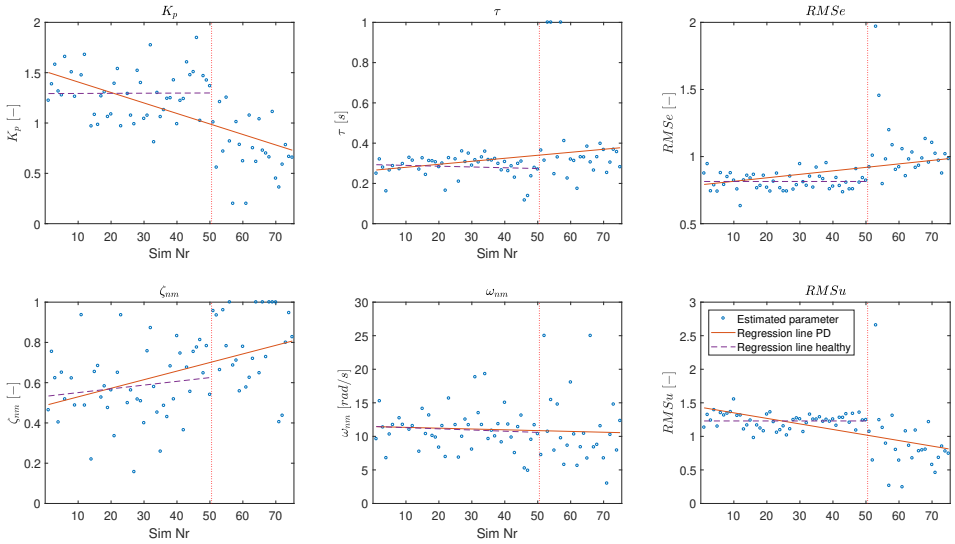


Figure H.20: Results of GLR trend analysis, Participant 10, Non-dominant hand

Table H.10: Results of one-sample t-test for GLR trend analysis for Participant 10, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-0.30	-	-6.53	**
τ	73	2.06	*	1.80	*
ζ_{nms}	73	3.30	**	4.22	**
ω_{nms}	73	-2.39	**	-0.55	-
RMSe	73	3.01	**	2.59	**
RMSu	73	1.40	-	-5.45	**

H.11 Participant 11

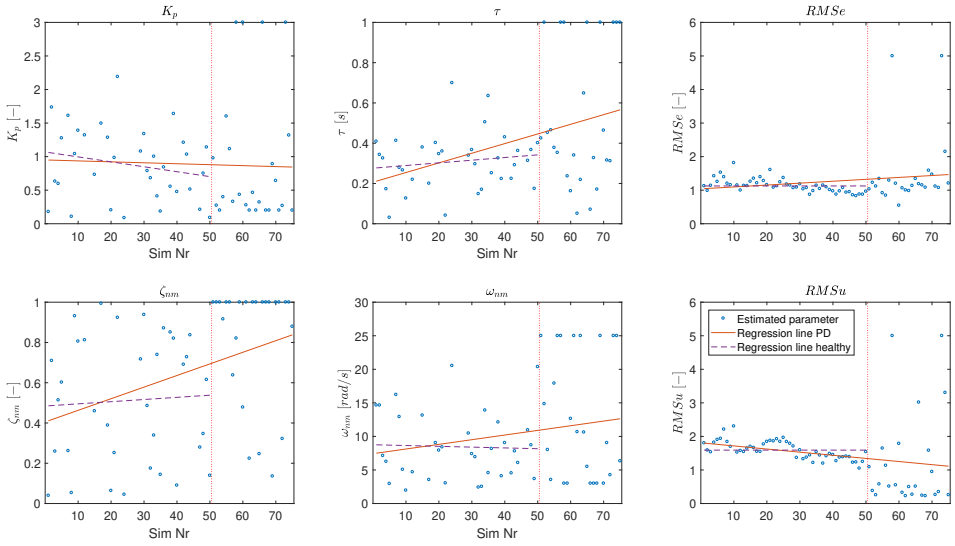


Figure H.21: Results of GLR trend analysis, Participant 11, Dominant hand

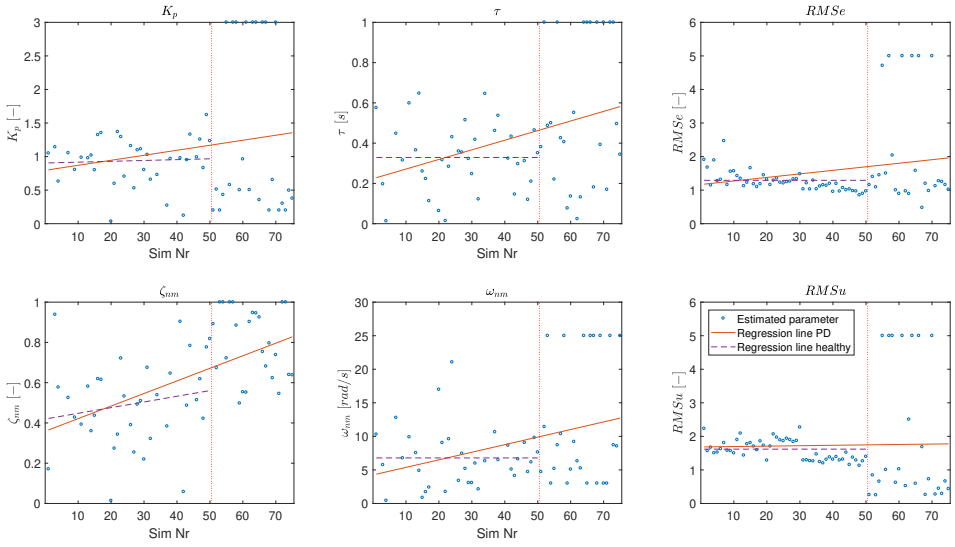


Figure H.22: Results of GLR trend analysis, Participant 11, Non-dominant hand

Table H.11: Results of one-sample t-test for GLR trend analysis for Participant 11, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-0.32	-	1.44	-
τ	73	3.35	**	2.94	**
ζ_{nms}	73	3.18	**	4.96	**
ω_{nms}	73	1.67	*	2.73	**
RMSe	73	1.36	-	1.54	-
RMSu	73	-1.75	*	0.16	-

H.12 Participant 12

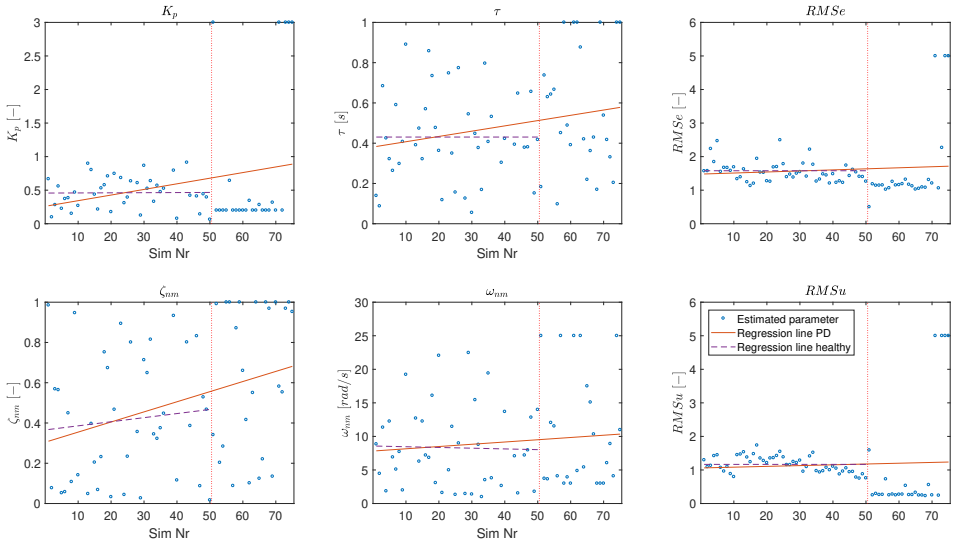


Figure H.23: Results of GLR trend analysis, Participant 12, Dominant hand

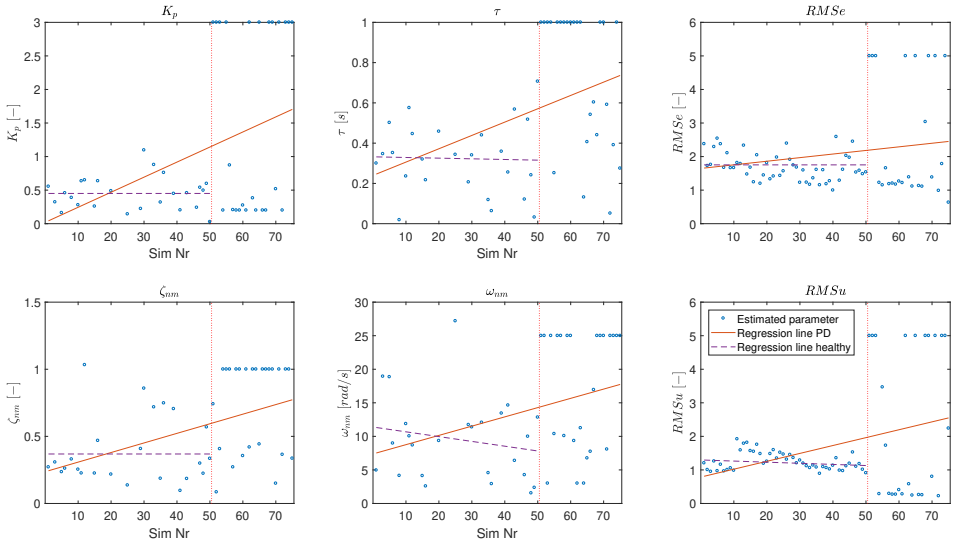


Figure H.24: Results of GLR trend analysis, Participant 12, Non-dominant hand

Table H.12: Results of one-sample t-test for GLR trend analysis for Participant 12, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	2.18	*	3.48	**
τ	73	1.88	*	3.42	**
ζ_{nms}	73	2.82	**	3.59	**
ω_{nms}	73	0.88	-	2.72	**
RMSe	73	0.69	-	1.28	-
RMSu	73	0.40	-	2.31	*

H.13 Participant 13

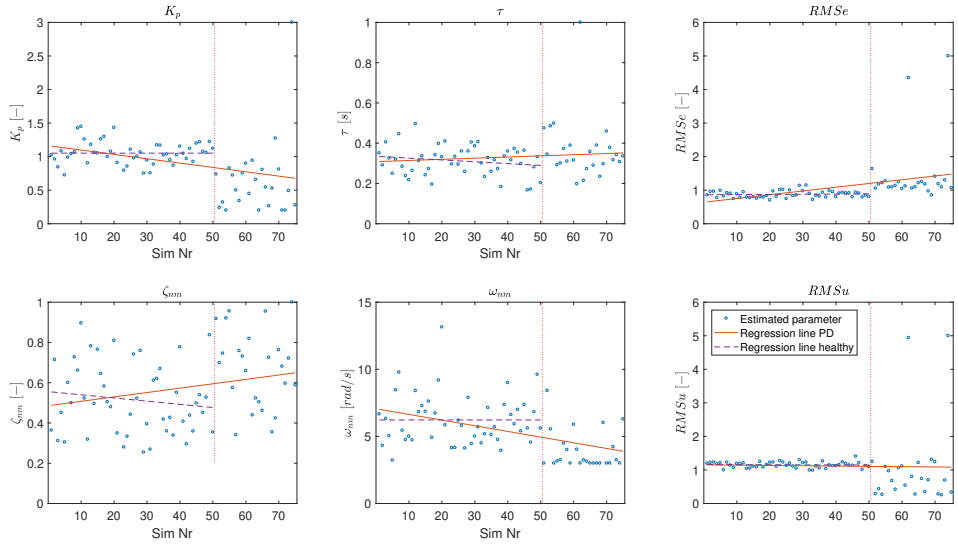


Figure H.25: Results of GLR trend analysis, Participant 13, Dominant hand

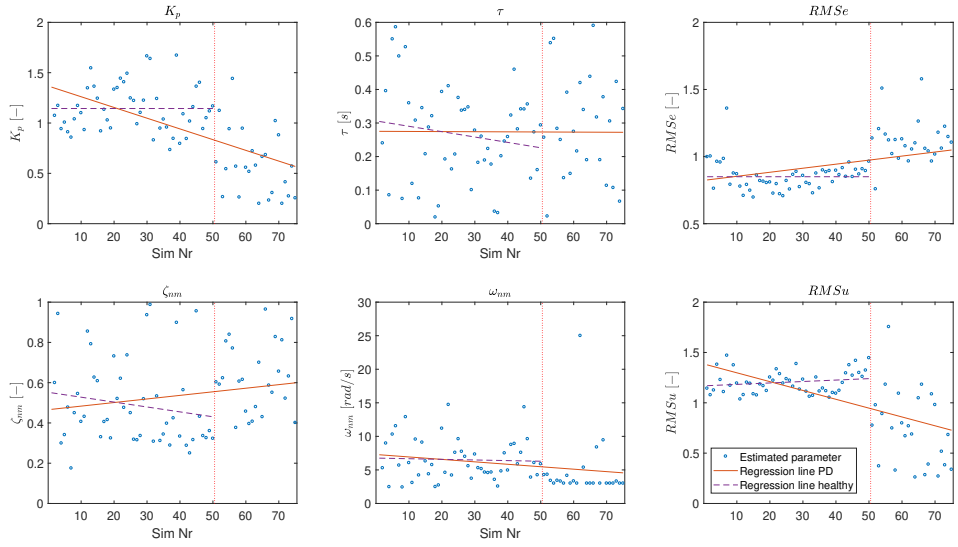


Figure H.26: Results of GLR trend analysis, Participant 13, Non-dominant hand

Table H.13: Results of one-sample t-test for GLR trend analysis for Participant 13, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-3.23	**	-6.64	**
τ	73	1.00	-	-0.05	-
ζ_{nms}	73	2.18	*	1.61	-
ω_{nms}	73	-4.36	**	-1.86	*
RMSe	73	3.60	**	2.97	**
RMSu	73	-0.24	-	-6.22	**

H.14 Participant 14

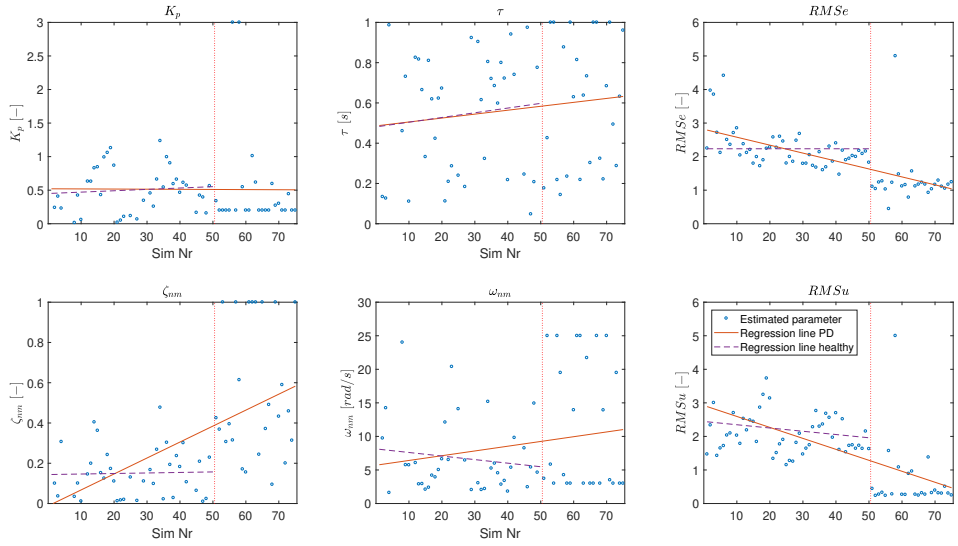


Figure H.27: Results of GLR trend analysis, Participant 14, Dominant hand

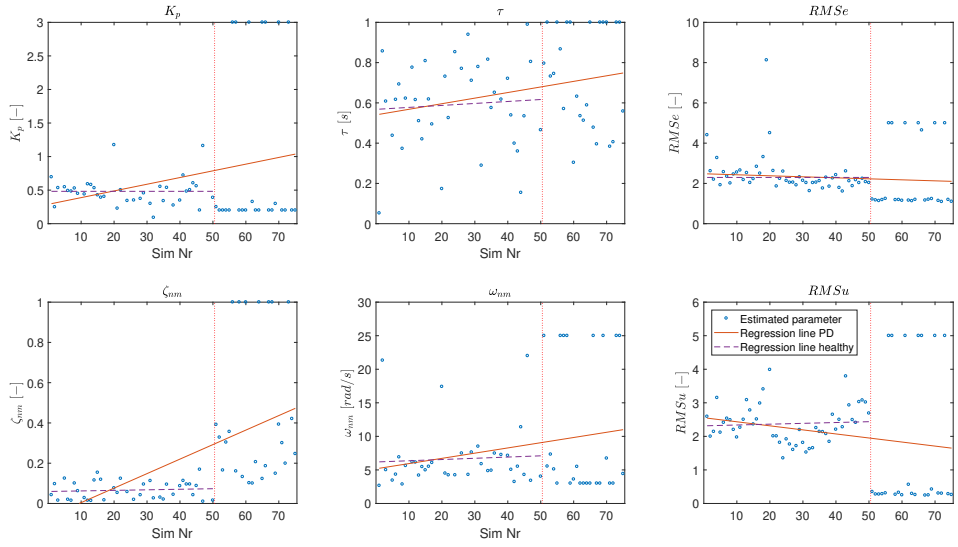


Figure H.28: Results of GLR trend analysis, Participant 14, Non-dominant hand

Table H.14: Results of one-sample t-test for GLR trend analysis for Participant 14, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-0.06	-	2.16	*
τ	73	1.10	-	2.12	*
ζ_{nms}	73	5.42	**	5.17	**
ω_{nms}	73	1.61	-	1.91	*
RMSe	73	-6.68	**	-0.76	-
RMSu	73	-6.93	**	-1.50	-

H.15 Participant 15

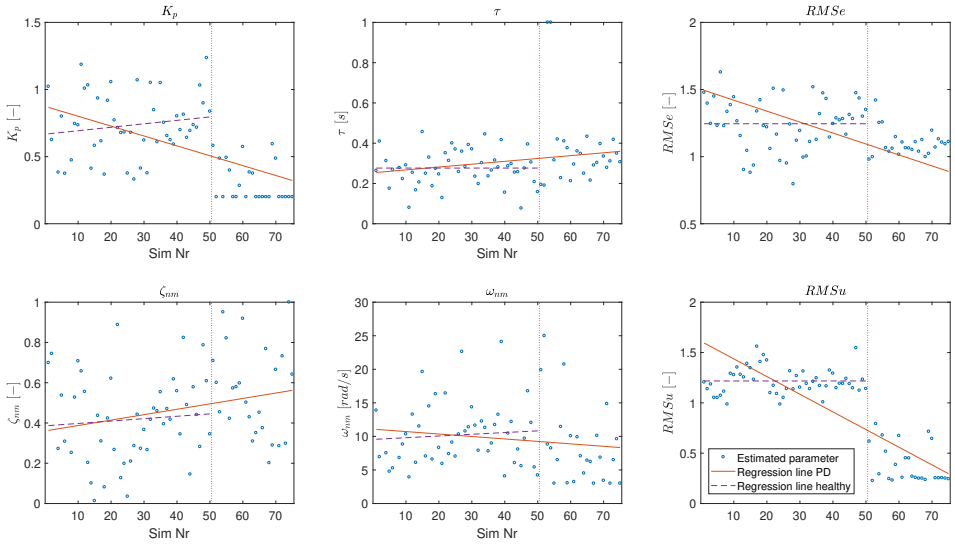


Figure H.29: Results of GLR trend analysis, Participant 15, Dominant hand

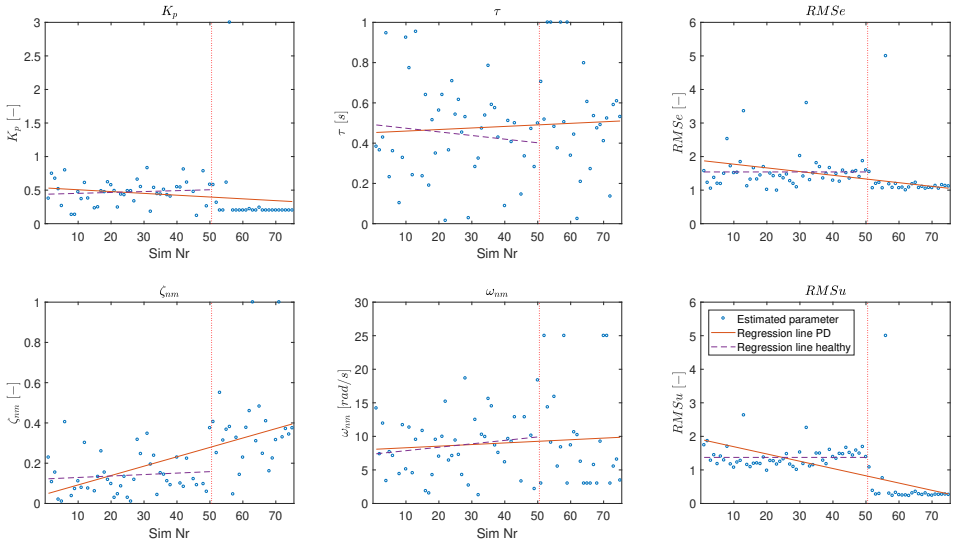


Figure H.30: Results of GLR trend analysis, Participant 15, Non-dominant hand

Table H.15: Results of one-sample t-test for GLR trend analysis for Participant 15, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-5.48	**	-1.37	-
τ	73	1.83	*	0.58	-
ζ_{nms}	73	2.26	*	5.37	**
ω_{nms}	73	-1.32	*	0.77	-
RMSe	73	-6.46	**	-3.28	**
RMSu	73	-15.15	**	-6.62	**

H.16 Participant 16

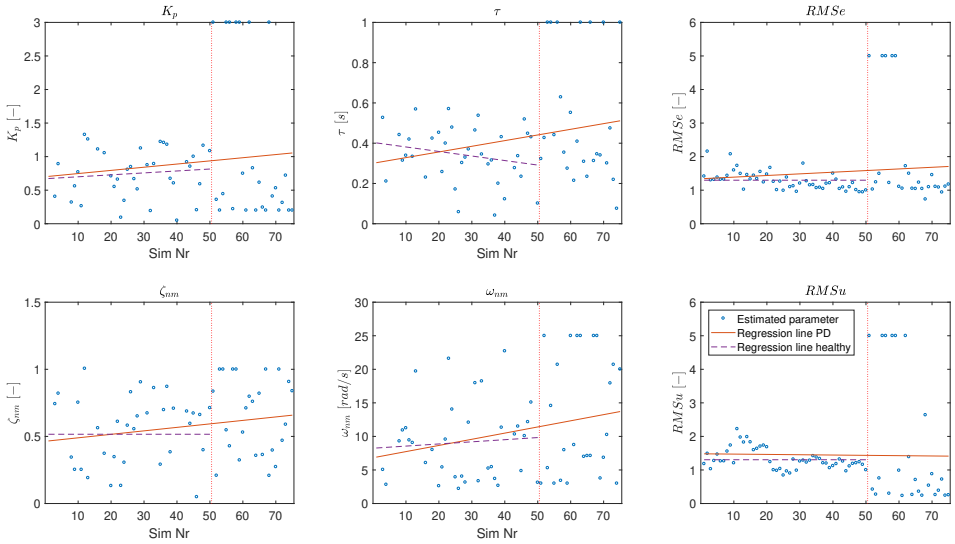


Figure H.31: Results of GLR trend analysis, Participant 16, Dominant hand

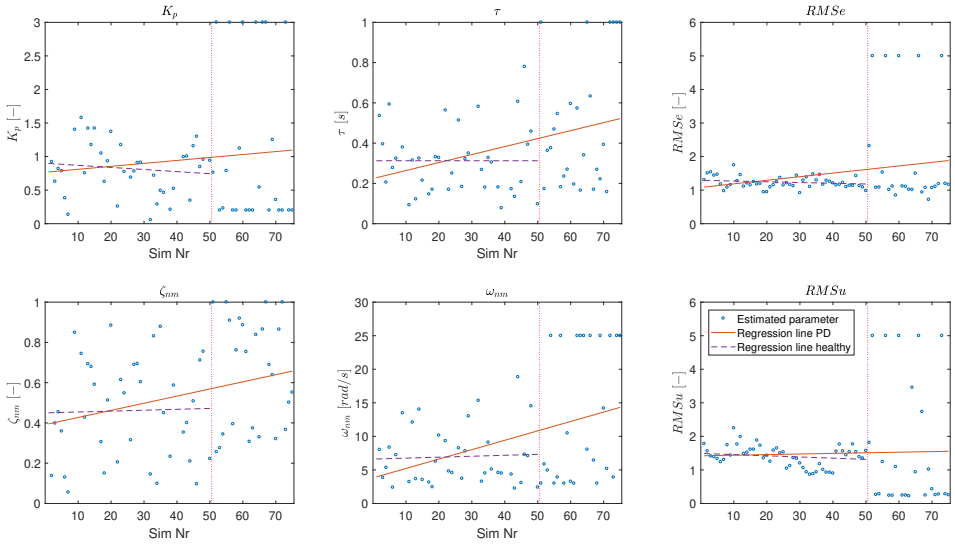


Figure H.32: Results of GLR trend analysis, Participant 16, Non-dominant hand

Table H.16: Results of one-sample t-test for GLR trend analysis for Participant 16, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	0.92	-	0.94	-
τ	73	1.92	*	2.92	**
ζ_{nms}	73	1.51	-	2.38	**
ω_{nms}	73	2.11	*	3.48	**
RMSe	73	0.75	-	1.86	*
RMSu	73	-0.12	-	0.23	-

H.17 Participant 17

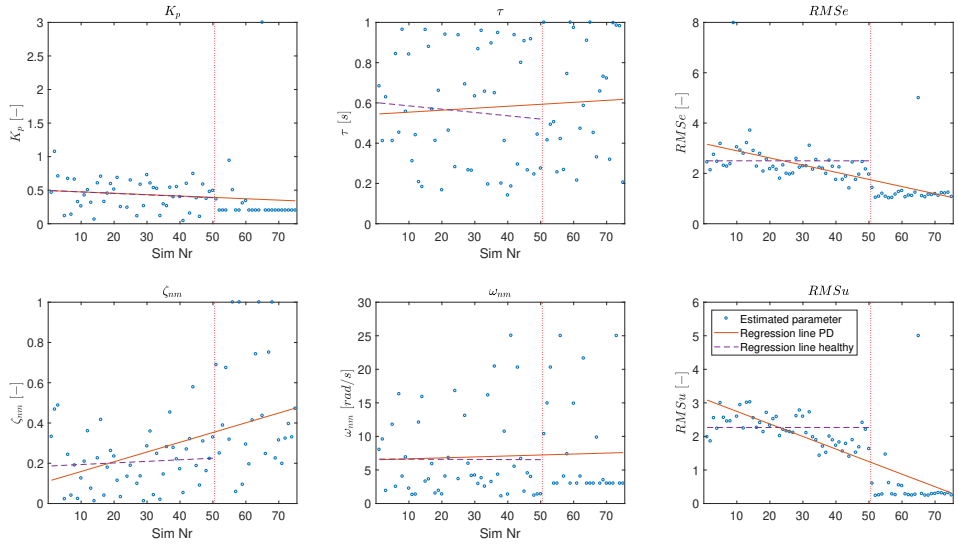


Figure H.33: Results of GLR trend analysis, Participant 17, Dominant hand

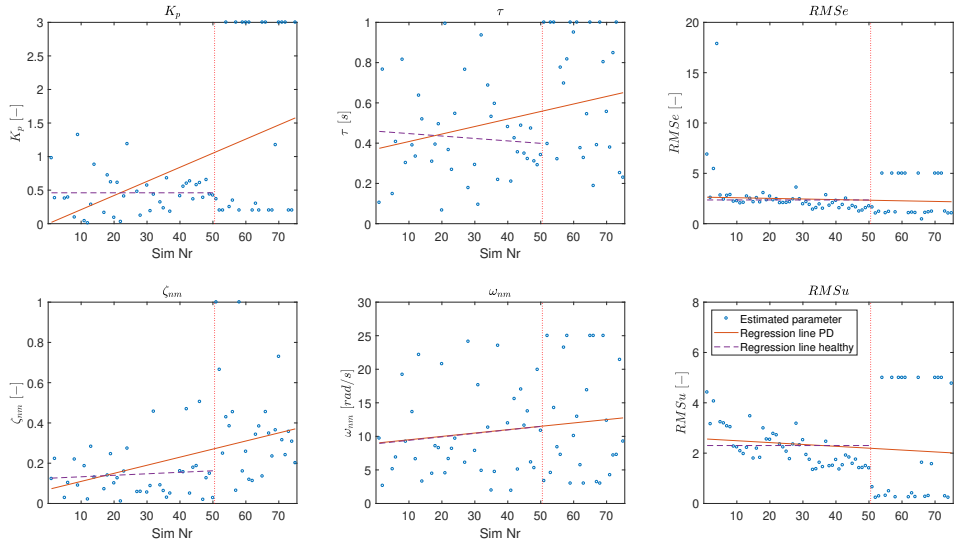


Figure H.34: Results of GLR trend analysis, Participant 17, Non-dominant hand

Table H.17: Results of one-sample t-test for GLR trend analysis for Participant 17, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-1.00	-	3.92	**
τ	73	0.63	-	2.34	*
ζ_{nms}	73	4.08	**	3.55	**
ω_{nms}	73	0.40	-	1.19	-
RMSe	73	-6.28	**	-0.75	-
RMSu	73	-9.64	**	-0.84	-

H.18 Participant 18

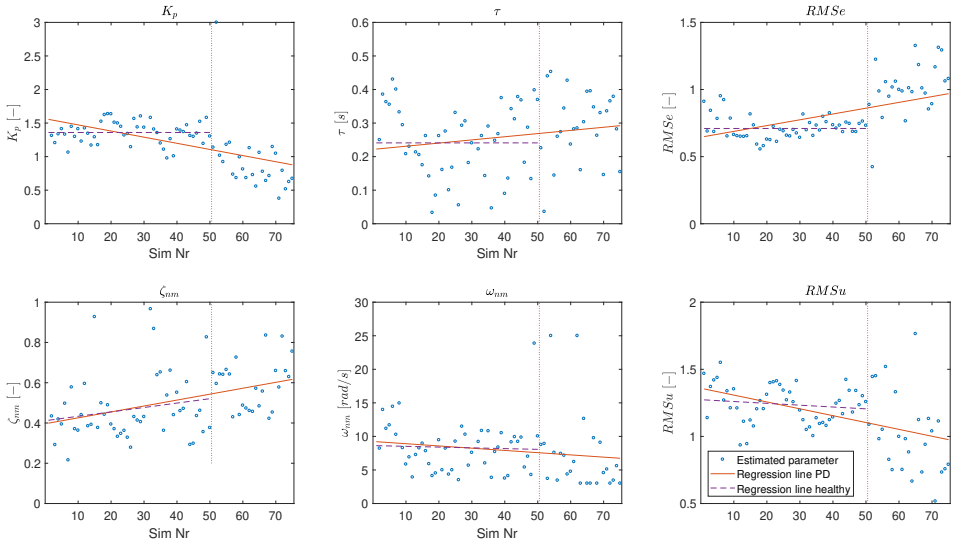


Figure H.35: Results of GLR trend analysis, Participant 18, Dominant hand

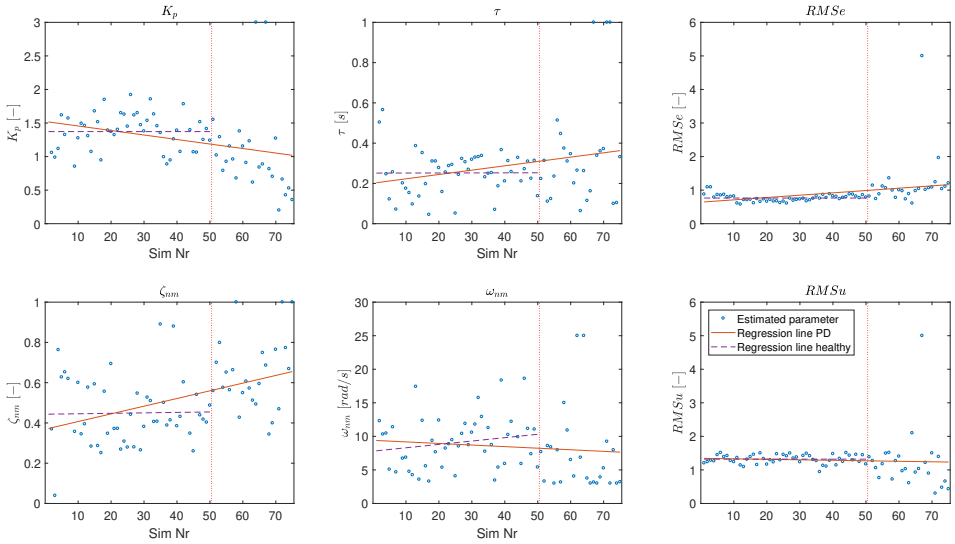


Figure H.36: Results of GLR trend analysis, Participant 18, Non-dominant hand

Table H.18: Results of one-sample t-test for GLR trend analysis for Participant 18, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-5.33	**	-2.73	**
τ	73	1.60	-	2.19	*
ζ_{nms}	73	3.66	**	3.96	**
ω_{nms}	73	-1.36	-	-0.90	-
RMSe	73	4.38	**	2.44	**
RMSu	73	-4.60	**	-0.51	-

H.19 Participant 19

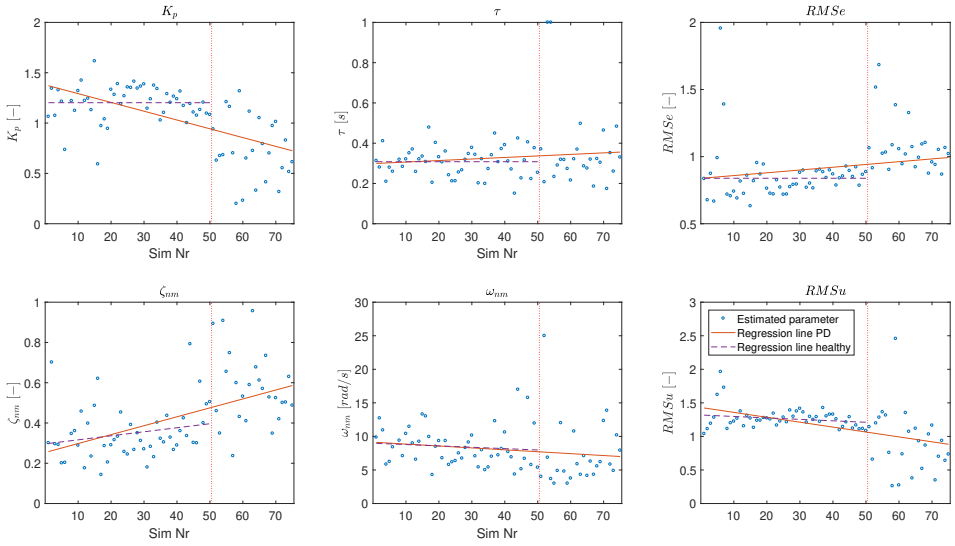


Figure H.37: Results of GLR trend analysis, Participant 19, Dominant hand

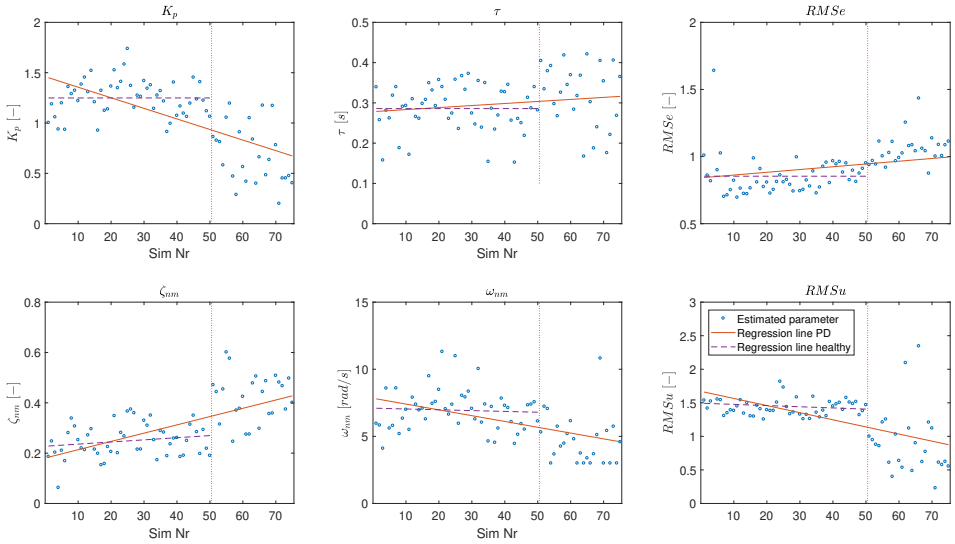


Figure H.38: Results of GLR trend analysis, Participant 19, Non-dominant hand

Table H.19: Results of one-sample t-test for GLR trend analysis for Participant 19, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-6.33	**	-7.61	**
τ	73	1.05	-	1.47	-
ζ_{nms}	73	5.31	**	7.37	**
ω_{nms}	73	-1.47	-	-4.79	**
RMSe	73	1.69	*	2.27	*
RMSu	73	-4.64	**	-6.14	**

H.20 Participant 20

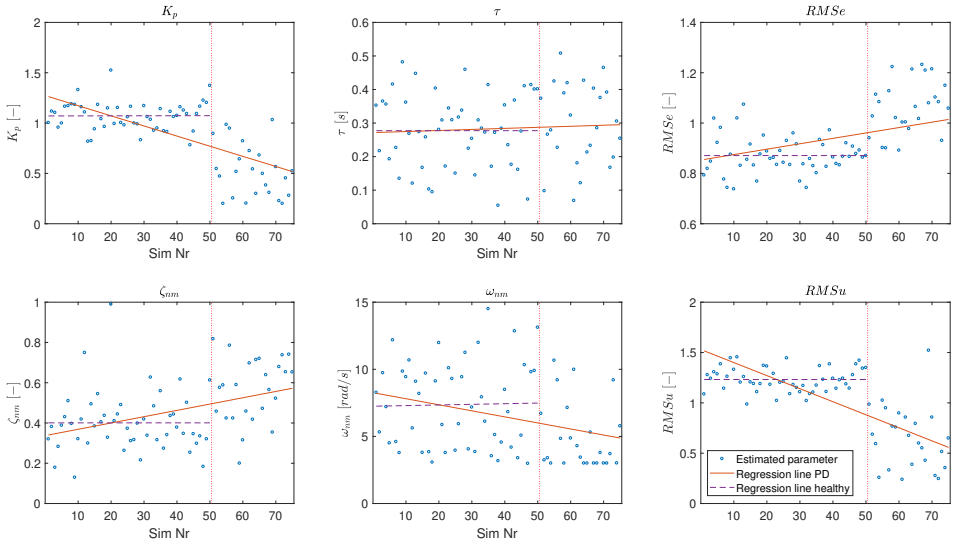


Figure H.39: Results of GLR trend analysis, Participant 20, Dominant hand

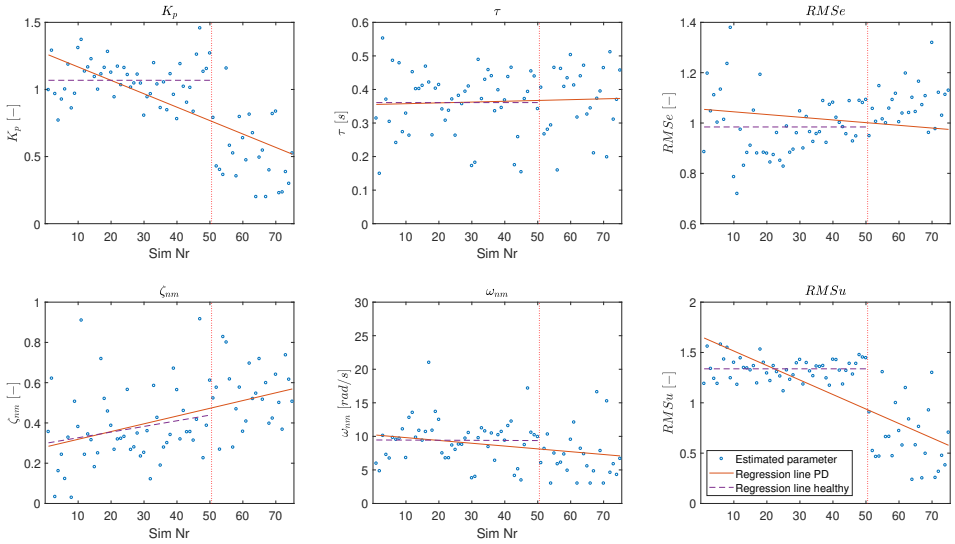


Figure H.40: Results of GLR trend analysis, Participant 20, Non-dominant hand

Table H.20: Results of one-sample t-test for GLR trend analysis for Participant 20, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-8.19	**	-8.15	**
τ	73	0.53	-	0.49	-
ζ_{nms}	73	3.79	**	4.18	**
ω_{nms}	73	-2.81	**	-2.35	*
RMSe	73	3.16	**	-1.26	-
RMSu	73	-11.52	**	-12.09	**

H.21 Participant 21

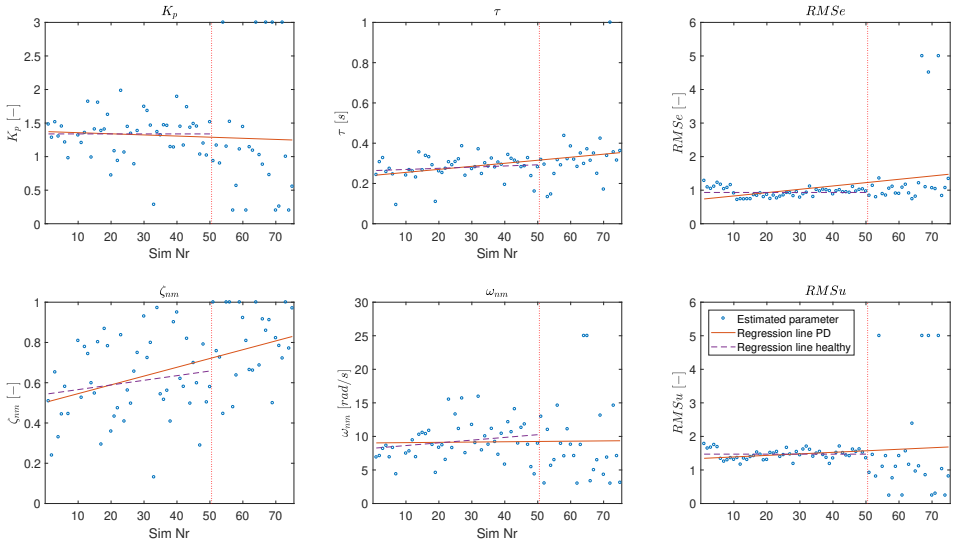


Figure H.41: Results of GLR trend analysis, Participant 21, Dominant hand

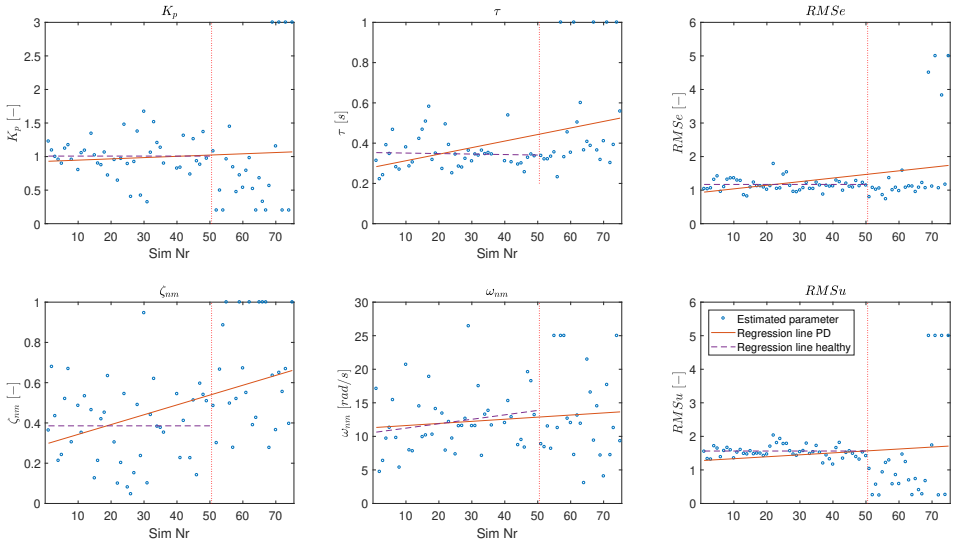


Figure H.42: Results of GLR trend analysis, Participant 21, Non-dominant hand

Table H.21: Results of one-sample t-test for GLR trend analysis for Participant 21, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-0.50	-	0.56	-
τ	73	2.75	**	3.44	**
ζ_{nms}	73	4.21	**	3.86	**
ω_{nms}	73	0.19	-	1.08	-
RMSe	73	2.36	*	2.41	**
RMSu	73	0.89	-	1.05	-

H.22 Participant 22

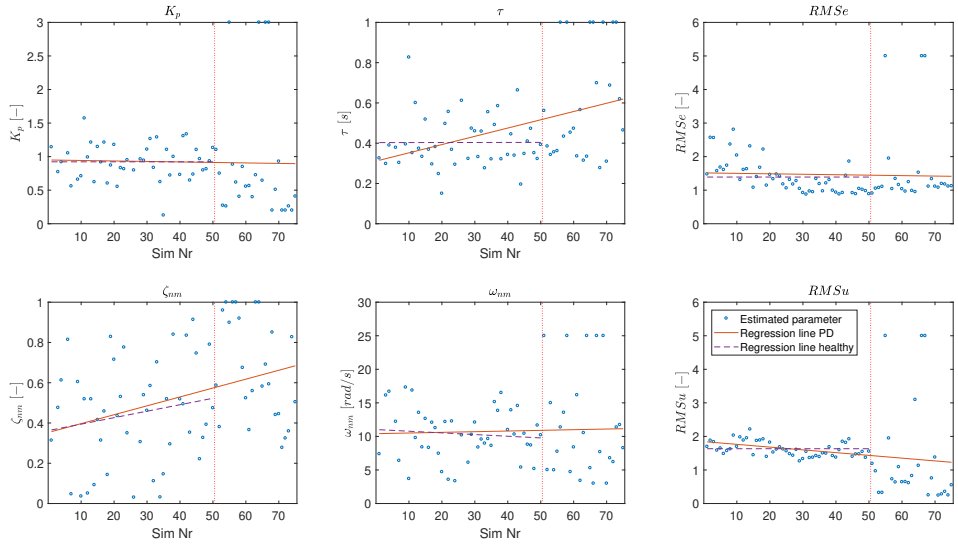


Figure H.43: Results of GLR trend analysis, Participant 22, Dominant hand

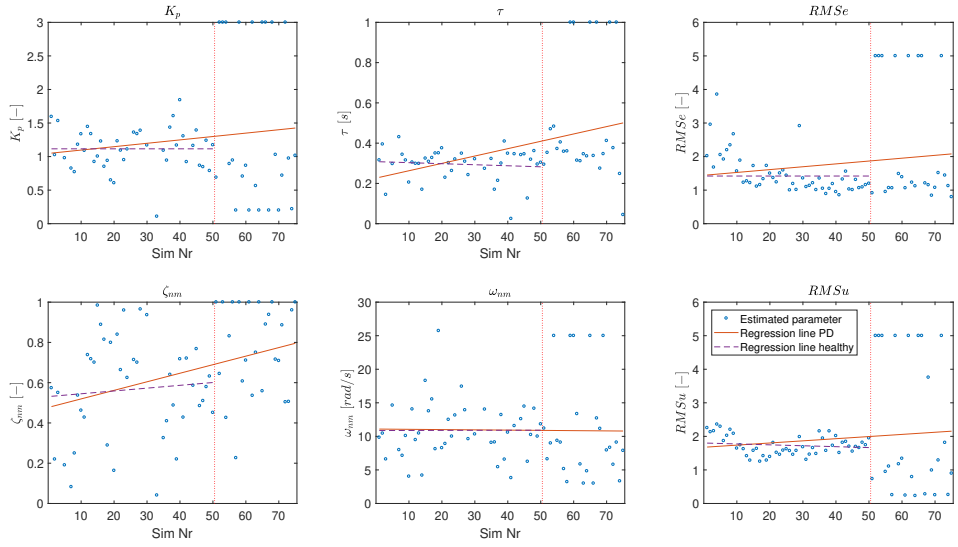


Figure H.44: Results of GLR trend analysis, Participant 22, Non-dominant hand

Table H.22: Results of one-sample t-test for GLR trend analysis for Participant 22, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-0.21	-	1.18	-
τ	73	3.71	**	3.33	**
ζ_{nms}	73	3.06	**	3.18	**
ω_{nms}	73	0.32	-	-0.12	-
RMSe	73	-0.28	-	1.23	-
RMSu	73	-1.61	-	0.91	-

H.23 Participant 23

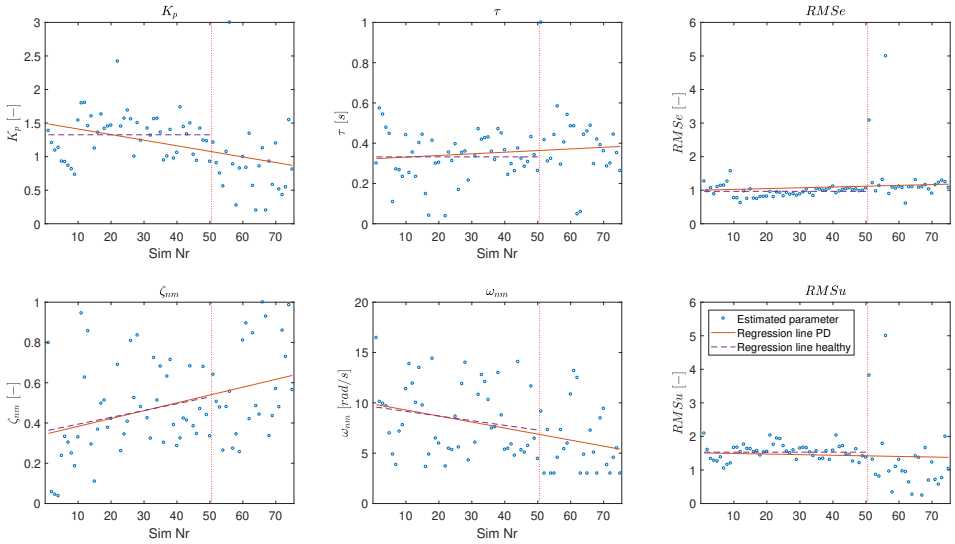


Figure H.45: Results of GLR trend analysis, Participant 23, Dominant hand

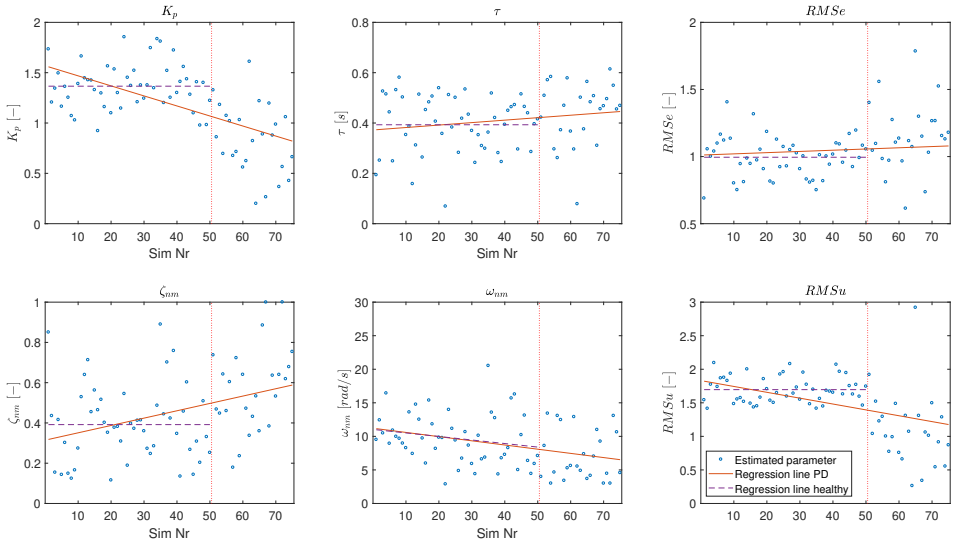


Figure H.46: Results of GLR trend analysis, Participant 23, Non-dominant hand

Table H.23: Results of one-sample t-test for GLR trend analysis for Participant 23, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-3.66	**	-6.35	**
τ	73	1.08	-	1.57	-
ζ_{nms}	73	3.38	**	3.49	**
ω_{nms}	73	-3.40	**	-3.21	**
RMSe	73	0.80	-	0.80	-
RMSu	73	-0.49	-	-3.97	**

H.24 Participant 24

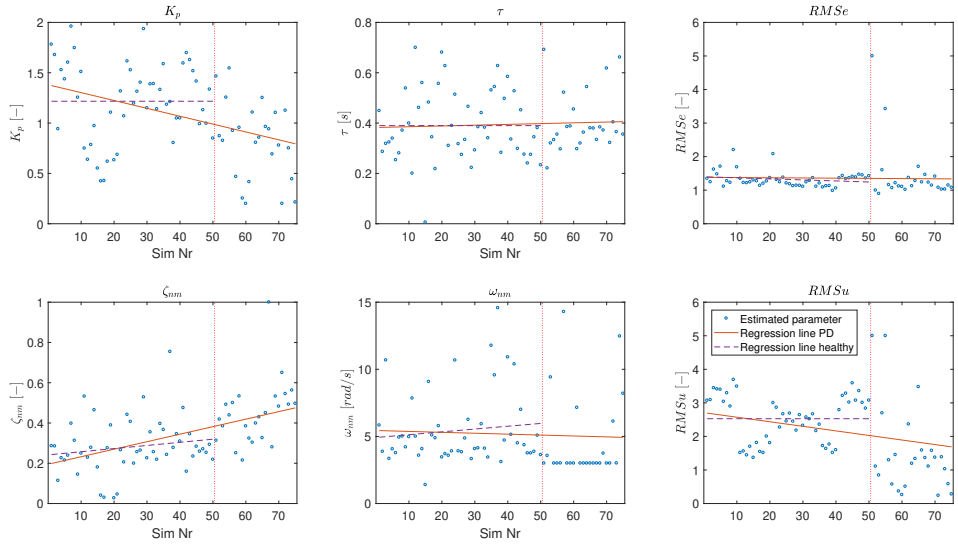


Figure H.47: Results of GLR trend analysis, Participant 24, Dominant hand

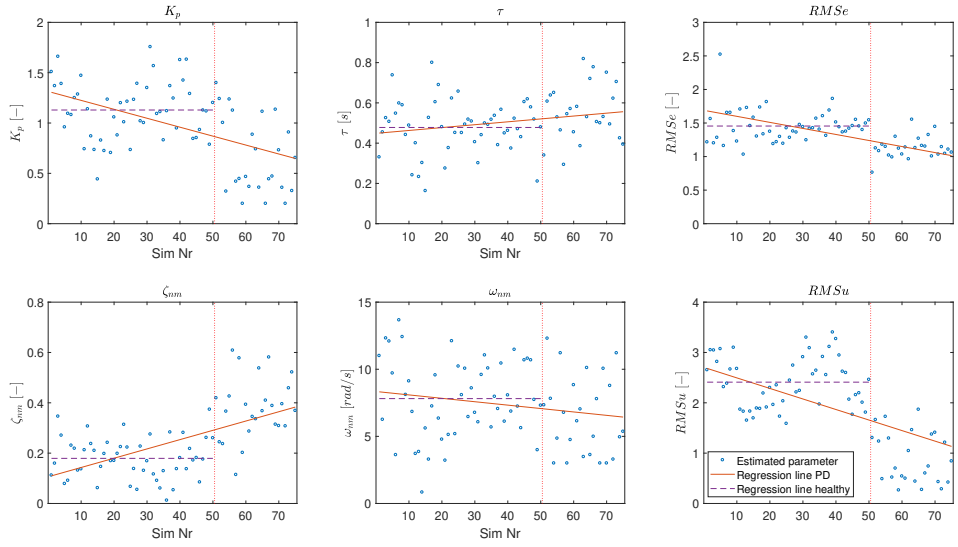


Figure H.48: Results of GLR trend analysis, Participant 24, Non-dominant hand

Table H.24: Results of one-sample t-test for GLR trend analysis for Participant 24, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-3.72	**	-4.99	**
τ	73	0.44	-	2.03	*
ζ_{nms}	73	5.04	**	6.37	**
ω_{nms}	73	-0.44	-	-1.64	-
RMSe	73	-0.21	-	-7.66	**
RMSu	73	-2.47	**	-5.02	**

H.25 Participant 25

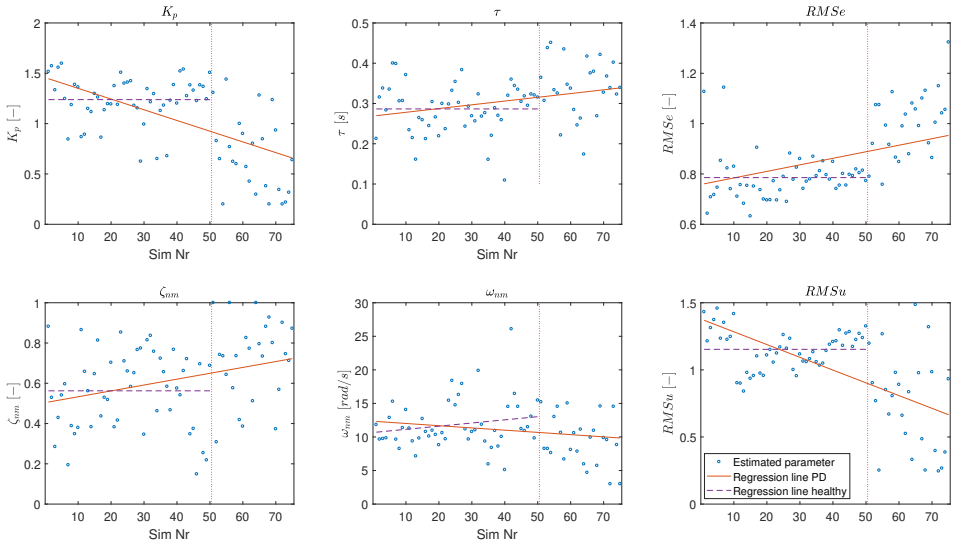


Figure H.49: Results of GLR trend analysis, Participant 25, Dominant hand

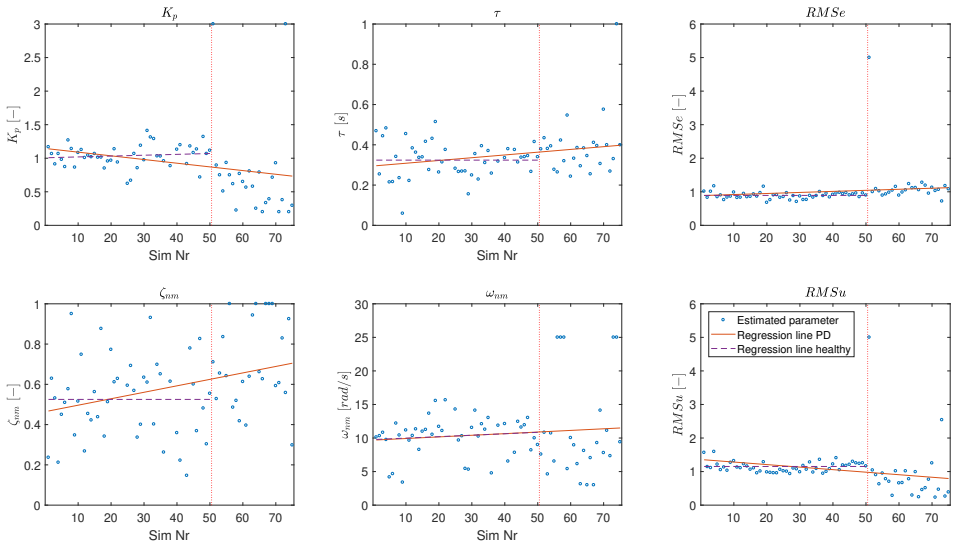
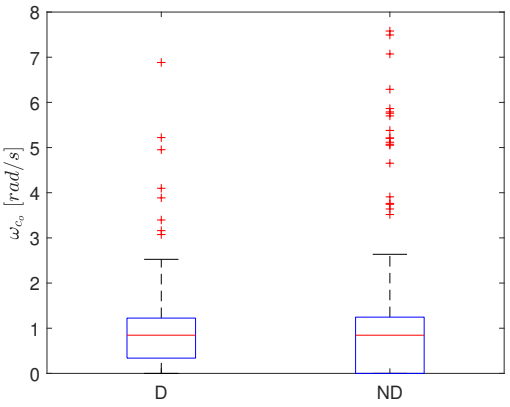


Figure H.50: Results of GLR trend analysis, Participant25, Non-dominant hand

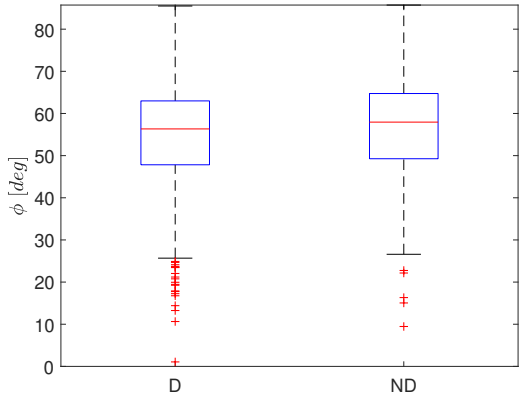
Table H.25: Results of one-sample t-test for GLR trend analysis for Participant 25, where ** is highly significant ($p < 0.01$), * is significant ($0.01 \leq p \leq 0.05$), and - is not significant ($p \geq 0.05$)

		Dominant		Non-dominant	
Parameter	df	t	Sig	t	Sig
K_p	73	-6.38	**	-2.29	*
τ	73	2.71	**	2.25	*
ζ_{nms}	73	2.78	**	2.92	**
ω_{nms}	73	-1.67	-	0.91	-
RMSe	73	3.31	**	1.18	-
RMSu	73	-7.59	**	-2.45	**

Crossover frequencies and phase margin



(a) Crossover frequencies



(b) Phase margin

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