Validation of the NeuroFlexor method for obtaining the neural and intrinsic component of wrist hyper-resistance post stroke

Agreement with an EMG-driven optimization method and clinical scales

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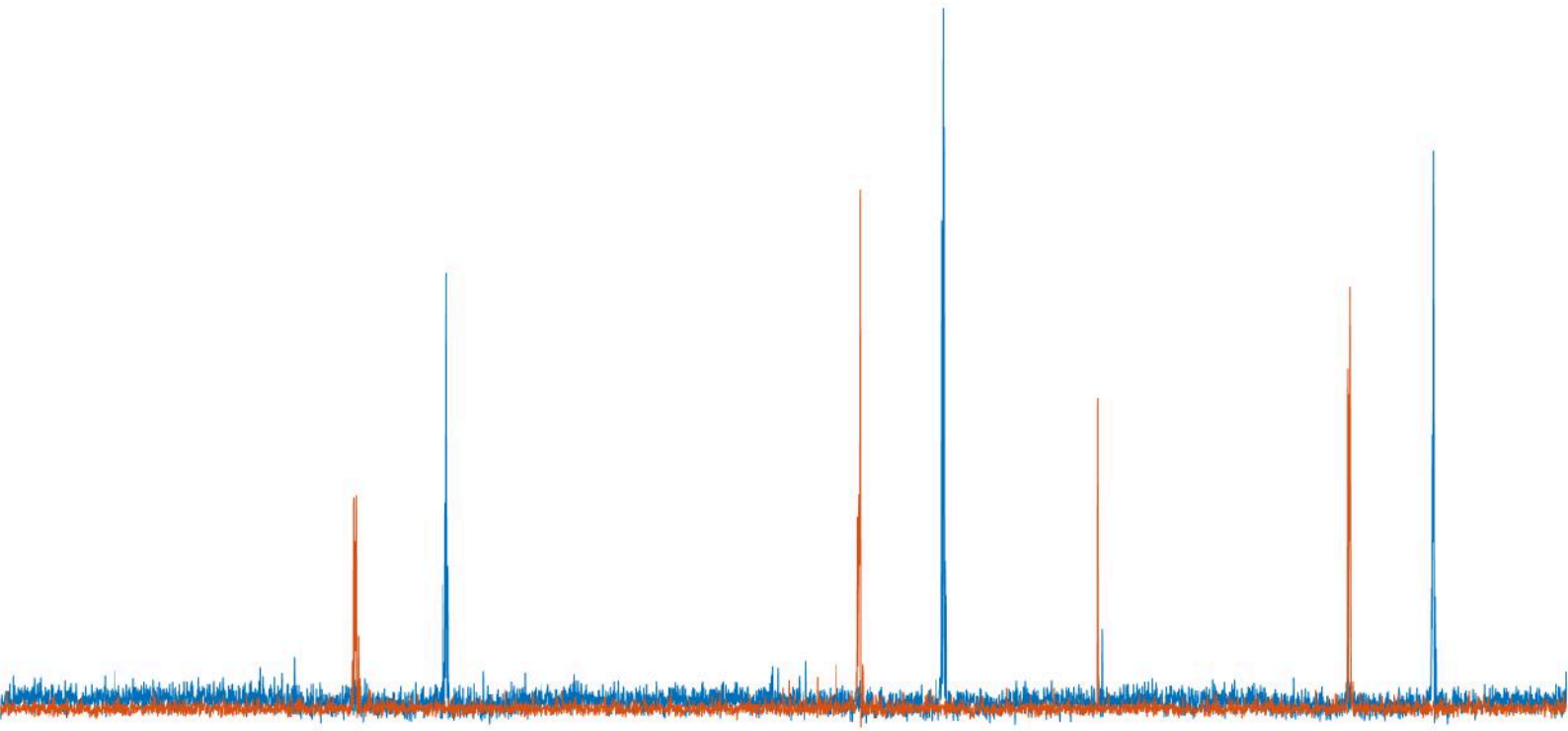

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Validation of the NeuroFlexor method for obtaining the neural and intrinsic component of wrist hyper-resistance post stroke

Agreement with an EMG-driven optimization method and clinical scales

by

Larissa Scholte

in partial fulfillment of the requirements for the degree of

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”Graduation is like a multisine.”

L. SCHOLTE

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Preface

This report titled 'Validation of the NeuroFlexor method for obtaining the neural and intrinsic component of wrist hyper-resistance post stroke: Agreement with an EMG-driven optimization method and clinical scales' is submitted for the Degree of Master of Science at the Delft University of Technology. The thesis project was performed at the VU University Medical Centre under the supervision of Carel Meskers and Aukje Andinga in the Department of Rehabilitation Medicine. Furthermore, this thesis was conducted under the supervision of Alfred Schouten and Winfred Mugge of the Department of Biomechanical Engineering at the Faculty of Mechanical, Maritime and Materials Engineering. With this research I hope to contribute to the improvement of the recovery therapy of stroke survivors.

Amsterdam, March 2018
Larissa Scholte

Glossary

BoNT - A	Botulinum Toxin Type-A
CVA	Cerebrovascular Accident
DOF	Degree of Freedom
EC	Elastic Component of the NeuroFlexor Method
ECR	Extensor Carpi Radialis
EMG	Electromyography
FCR	Flexor Carpi Radialis
ICC	Intra-class Correlation Coefficient
LoA	Limits of Agreement
M	Mean
MAS	Modified Ashworth Scale
MDC	Minimal Detectable Change
MDC%	Minimal Detectable Change percent change
MMSE	Mini-Mental State Examination
NC	Neural Component of the NeuroFlexor Method
NIHSS	National Institutes of Health Stroke Scale
nSEM	Normalized Standard Error of the Mean
OR	Odds Ratio
pROM	Passive Range of Motion
RMS	Root Mean Square
RMSE	Root Mean Square Error
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of the Mean
SIPE	System Identification and Parameter Estimation
TS	Tardieu Scale
VAF	Variance Accounted For
VC	Viscous Component of the NeuroFlexor Method

Validation of the NeuroFlexor method for obtaining the neural and intrinsic component of wrist hyper-resistance post stroke: Agreement with an EMG-driven optimization method and clinical scales

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Half of the long-termed disabled stroke survivors experience increased hyper-resistance of the wrist. Discrimination between the two components of joint hyper-resistance, i.e. the neural reflexive and intrinsic tissue component, is important since the components require a different treatment method. To discriminate between the two components, objective methods are developed that make use of bio-mechanical modeling. This research aimed to address the agreement between a clinically easy applicable modeling method, the NeuroFlexor method, and a more comprehensive optimization method, which both objectively obtain the neural and intrinsic components of joint hyper-resistance. Furthermore, this research study addressed the agreement between the neural and intrinsic components obtained with the NeuroFlexor and optimization method, and the external validation of the two components with clinical rating scales.

Method NeuroFlexor based assessments and instrumented positional wrist perturbations were applied to chronic stroke survivors ($n = 49$) and healthy volunteers ($n = 11$). The neural and intrinsic components were estimated using the NeuroFlexor method, whose method is a force-relationship method, and a nonlinear electromyography driven wrist optimization model. The Modified Ashworth scale (MAS) was rated to all stroke survivors as clinical scale. Correlation analysis was conducted to find the agreement between the components of both methods, and to find the agreement between the MAS and the components. To analyze how well the neural and intrinsic components of both methods were able to predict the MAS, multiple regression analysis with a backward selection procedure was used for both methods separately and both methods together. On the healthy subjects, the optimization model was applied on the NeuroFlexor data to check differences in model structure.

Results The neural components of both the NeuroFlexor method and optimization method had a strong correlation ($r = 0.656$), as well as the intrinsic components ($r = 0.648$). For both methods, the neural and intrinsic components were significant estimators of the MAS, and the NeuroFlexor method and the optimization method were approximately equivalently able to predict the MAS ($r^2 = 0.466$ and $r^2 = 0.519$, respectively). For the multiple regression analysis with the intrinsic and neural component of both methods together, the neural component of the optimization method together with the intrinsic component of the NeuroFlexor method were more able to describe the MAS ($r^2 = 0.605$) than the two components of the methods separately. For healthy patients, the optimization model was not able to reliably estimate the two components from the NeuroFlexor data.

Conclusion This study found evidence to support the use of the NeuroFlexor device for quantification of the neural and intrinsic components of wrist hyper-resistance post-stroke. Further research is needed to establish the validity of the neural component of the NeuroFlexor and the intrinsic component of the optimization method.

Keywords: hyper-resistance, spasticity, stroke, bio-mechanical modeling, system identification

1. Introduction

When someone suddenly has difficulties communicating, numbness of the face, arm or leg, loss of vision, a severe headache and/or trouble with keeping their balance, do not hesitate to contact the doctor, since these are symptoms of a stroke [1]. Each year, 15 million people suffer a stroke worldwide [2]. A cerebrovascular accident (CVA), more commonly called stroke, is a loss of brain function and can be either an ischaemic stroke, caused by blockage of a blood vessel by a clot, or a hemorrhagic stroke, caused by a burst blood vessel [3]. Both cause a blood flow disruption which results in a lack of oxygen and nutrients supply to the brain, resulting in damaged brain tissue. The effects are dependent on the severity and may lead to a neurological movement disorder or even death. About 5 million people who suffer from a stroke remain long-term disabled [2].

About half of the long-term disabled stroke patients experience loss of arm function including increased hyper-resistance of the wrist, wrist contracture and a reduction of the range of motion [4]–[6]. The term hyper-resistance is defined as the impaired neuromuscular response, i.e. increased resistance, to passive stretch. Assessment of joint hyper-resistance can contribute to the recovery in post-stroke rehabilitation [7]. The components causing joint hyper-resistance post-stroke are of neural or non-neural, i.e. intrinsic (tissue), origin [8]. These two components together, i.e. the neural and intrinsic component, are called the neuromechanical parameters.

The neural component of joint hyper-resistance is stretch hyper-reflexia, or more commonly called spasticity, together with an increased baseline activity [9], i.e. involuntary background activation, and synergistic contraction patterns. Lance defined spasticity as [10]:

> "A motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes, i.e. muscle tone, with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex, as a component of the upper motor neuron syndrome."

It is important to discriminate between these components since the neural and intrinsic components require a different treatment method, where therapy is focused on the most dominant contributor [7], [11].

The neural component of joint hyper-resistance is treated with botulinum toxin type-A (BoNT-A) and baclofen to block neuromuscular transmissions [12], [13]. The intrinsic component of joint hyper-resistance are the passive muscle properties, i.e. the stiffness (elasticity) and viscosity of the muscle and connective tissue. When the intrinsic component of muscle hyper-resistance dominates over the neural component, treatment is aimed at stretching of visco-elastic tissue by casting, splinting or surgery [14].

Currently, assessment of wrist hyper-resistance post-stroke is mostly based on subjective clinical measurements of a specialist [15], [16], since they appear to be the easiest applicable [17] and do not require sophisticated measurement devices. Examples of clinical scales are the Modified Ashworth Scale (MAS) and the Tardieu scale (TS). The disadvantage of these clinical scales is that they are subjective, not standardized, have a low validity and a low inter-rater and intra-rater reliability [18], [19], especially when they have been related to objective methods to obtain joint hyper-resistance [15]–[17], [20]. Above that, these clinical scales do not distinguish between the different properties contributing to the movement disorder [17]. Notwithstanding these criticisms, these clinical methods are still used clinically due to the high cost/benefit ratio of bio-mechanical approaches.

At present, existing bio-mechanical methods that identify the neuromechanical parameters, are validated by comparing the outcome parameters with clinical scales [4], [20]–[25]. However, since clinical scales lack validity and reliability, validation of the bio-mechanical methods with clinical scales could lead to conflicting results. Unfortunately, there is no appropriate golden standard yet, forcing to validate the neuromechanical parameters with clinical scales.

Nowadays, existing bio-mechanical methods to obtain the biomechanical parameters are either based on system identification and parameter estimation (SIPE) techniques [4], [22], [24], [26], [27], or on signal analysis [20], [21], [25], the latter are classified as force-relationship methods. The SIPE methods assume a specific model structure that resembles the mechanics of the wrist joint. Parameters are estimated by simulating the measured impedance to the applied perturbation signal with a specific model structure that resembles the mechanics of the joint. The disadvantage of most system identification and parameter estimation based assessments of the neuromechanical parameters is that they are complicated to use clinically. Therefore, it could be advantageous to use force-relationship models that are based on simple signal analysis and which do not require complex off-line data analysis.

The NeuroFlexor model, i.e. a unidirectional wrist model of Lindberg et al. [21], makes use of a force-relationship technique to determine the neuromechanical parameters and is therefore clinically appealing. The NeuroFlexor model makes much general assumptions about muscular structure and is based on three points on the force response curve [21]. To check validity of the NeuroFlexor method, this study compares the neuromechanical parmeters of the NeuroFlexor method with the neuromechanical parameters obtained with a bidirectional nonlinear electromyography driven SIPE model, i.e. the optimization model. The optimization model is more comprehensive than the NeuroFlexor model, and simulates the active and passive mechanics of the wrist joint.

The aim of the present study is to validate the NeuroFlexor method in a cohort of stroke patients, by looking at the agreement between NeuroFlexor based assessments of the neuromechanical parameters and the neuromechanical parameters obtained with the optimization method. First, the test-retest reliability of the NeuroFlexor will be discussed. Next, validity measures of the optimization method will be discussed, together with the robustness of the model. Thereafter, the correlation between the neuromechanical parameters of both methods will be discussed. Depending on the discrepancy between the neuromechanical parameters obtained from both methods we will discuss whether the differences are caused by measurement conditions or the underlying modeling techniques. Therefore, the optimization model will be applied on the NeuroFlexor data to check differences in model structure. Since the MAS does not distinguish between the two components of joint hyper-resistance [17], [28],

a stepwise multiple linear regression analysis will be conducted on the neuromechanical parameters of both the NeuroFlexor method and optimization method separately, to see which parameters are able to describe the MAS. To check which neural or intrinsic component is most able to predict the MAS, a stepwise multiple linear regression analysis was conducted based on the neuromechanical parameters of the NeuroFlexor and optimization method together. Next to that, it will be discussed whether the neuromechanical parameters are able to distinguish between patients with a different MAS.

Our hypothesis is that the optimization method will give a more valid estimation of the neuromechanical parameters than the NeuroFlexor method since the optimization method uses a more comprehensive model based on muscle physiology. Therefore, we assume that there is no strong correlation between the neuromechanical parameters of the NeuroFlexor method and optimization method, i.e. the correlation is less than 0.6 [29], and that the discrepancy will be too large to validate the neuromechanical parameters of the NeuroFlexor method. Furthermore, we hypothesize that the neuromechanical parameters of the optimization method are able to predict the MAS and distinguish between patients with a different MAS more accurately than the neuromechanical parameters of the NeuroFlexor method.

2. Materials and Methods

2.1 Subjects

In total 49 chronic stroke patients and 11 healthy controls participated in this study. Cross-sectional measurements were obtained from 35 chronic patients (at least 6 months post-stroke) with a motor and/or somatosensory upper-limb impairment post stroke as part of the NeuroFlexor study. Next to patients from the cross-sectional study, longitudinal measurements were obtained from 14 acute patients with a motor and/or somatosensory upper-limb impairment post stroke. Four repeated measurements with the NeuroFlexor and Wristalyzer (MOOG, Nieuw Vennep, The Netherlands) were performed in the first six months post-stroke i.e. within 3 weeks, at 5 weeks, 12 weeks, and 26 weeks post stroke. For this study, only data obtained during the 26th week was used.

Clinical tests, i.e. the MAS and the passive range of motion, were assessed once at the impaired wrist of patients by a trained researcher. In total, three observers rated the clinical test during the study. The passive range of motion of the wrist was measured with a goniometer (pROM_g), while the goniometer was fixated to the lowerarm and hand. During determination of the pROM_g the fingers were stretched. The total pROM_g was determined by adding the average maximum flexion angle and the average maximum extension angle out of three measurements. In total four MAS scores were rated at the wrist, i.e. both wrist flexion and extension with their fingers stretched and bent. Finally, the highest rated MAS score was used. Appendix A shows the descriptions of the MAS grading. Patient characteristics are summarized in Table I.

To apply the optimization model on the NeuroFlexor data, NeuroFlexor data was obtained from 11 healthy subjects. For the healthy subjects, only the instrumented measurements were performed. Table II shows the healthy subject characteristics.

2.1.1 Inclusion and exclusion criteria

For the cross-sectional study, we identified patients who survived a first-ever hemorrhagic or ischaemic stroke in an area supplied by the anterior, medial, and/or posterior cerebral arteries. For the longitudinal study, patients were identified which had a first-ever unilateral ischaemic stroke in the past three weeks, in an area supplied by the anterior, medial, and/or posterior cerebral arteries. For both the cross-sectional and longitudinal study other inclusion criteria were: patients had to have an upper limb deficit according to the National Institutes of Health Stroke Scale (NIHSS) 5 a/b score > 0 at the time of inclusion, to be over 18 years and a have mini-mental state examination (MMSE) score larger than 20. Furthermore, the patients had to be able to sit without support for 30 seconds. Exclusion criteria for both the cross-sectional study and longitudinal study were previous existing neurological conditions, previous existing orthopaedic limitations of the impaired upper limb, and not being able to comply with the protocol. Furthermore, the subject should not have used any medication that could influence the upper extremity in the past three months, e.g. botulin-toxin injections. For healthy subjects, the exclusion criteria were neurological deficiencies, orthopedic problems with their wrist and inability to comply with the protocol.

All patients gave their written informed consent to the experiment, which was approved by the Medical Ethical Committee of the VU Medical Centre. Healthy subjects gave their written informed consent to the experiment, which was approved by the Ethical Committee of the Delft University of Technology.

2.2 Instrumentation

2.2.1 NeuroFlexor

The NeuroFlexor is a one degree of freedom (DOF) haptic manipulator, which exerts a positional perturbation in the extension direction of the wrist. It measures the force resistance of the wrist and finger-muscles during passive extension of the wrist [21]. The wrist is moved by moving the hand plate with a step motor. During the movement, the resistance force is measured by a force sensor mounted underneath the hand plate (Figure 1).

During the measurements with healthy patients, also electromyography (EMG) signals were collected (see Subsection 2.2.3). EMG data was obtained with a Mobi system (TMSi B.V., The Netherlands). A trigger signal was extracted from the NeuroFlexor device, such that the data obtained with the NeuroFlexor and the Mobi could be off-line aligned. Matlab R2017b (The MathWorks Inc. Natick, MA) was used to record the EMG signals and the trigger signal, and for off-line data analysis.

2.2.2 Optimization method

The Wristalyzer (MOOG, Nieuw Vennep, The Netherlands) was used to collect the data for the optimization model and was located in a van. The van was driven to the patients and the measurement were carried out in the van. The Wristalyzer is a one-DOF haptic manipulator, which allows flexion and extension of the wrist. It measures the mechanical response to an imposed perturbation on the handle (Meester techniek B.V., The Netherlands), with a torque limit of 5.2 Nm. The handle is moved by a vertically positioned servo motor (Parker SMH100

Table I. Patient demographics

	Overall	Classified MAS $_0$	MAS $_1$	MAS $_{1+}$	MAS $_2$	MAS $_3$
	($n = 49$)	($n = 9$)	($n = 11$)	($n = 12$)	($n = 7$)	($n = 10$)
Age [years] (mean ± SD)	59.69 ± 10.01	65.56 ± 6.62	60.36 ± 9.23	60.92 ± 6.95	56.86 ± 11.77	54.20 ± 13.16
Time after stroke [years] (mean ± SD)	5.28 ± 6.35	3.21 ± 3.91	3.57 ± 5.07	7.72 ± 9.68	6.53 ± 5.44	5.19 ± 4.67
Stroke type [ischaemic] (%)	85.71 %	88.89 %	100.00 %	91.67 %	71.43 %	70.00 %
Sex [men] (%)	69.39 %	55.56 %	72.73 %	83.33 %	71.43 %	60.00 %
Weight [kg] (mean ± SD)	80.45 ± 15.72	75.78 ± 22.75	87.73 ± 14.79	80.75 ± 12.45	83.43 ± 9.69	74.20 ± 15.03
pROM$_w$ [deg] (mean ± SD)	118.74 ± 20.09	131.28 ± 12.56	124.32 ± 20.29	118.00 ± 16.65	117.82 ± 23.76	99.65 ± 17.57
pROM$_g$ [deg] (mean ± SD)	172.48 ± 19.28	183.43 ± 15.83	169.45 ± 27.97	173.83 ± 15.41	169.71 ± 12.96	166.71 ± 17.30
Affected body side [right] (%)	40.82 %	55.56 %	54.55 %	33.33 %	57.14 %	10.00 %
Affected hand dominant [yes] (%)	42.86 %	55.56 %	72.72 %	33.33 %	42.86 %	10.00 %

Table II. Healthy subject demographics

	($n = 11$)
Age [years] (mean ± SD)	30.27 ± 10.50
Sex [men] (%)	27.27%
Dominant hand measured [yes] (%)	63.63%
Weight [kg] (mean ± SD)	75.27 ± 9.88

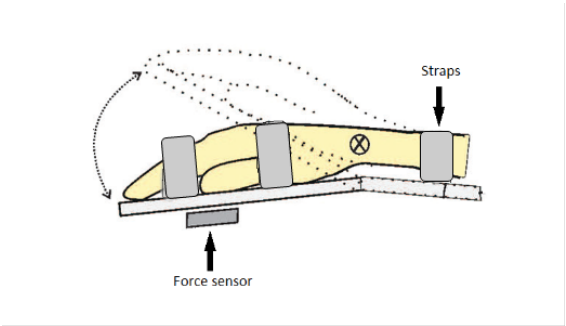


Figure 1. Schematic side view of the NeuroFlexor. Where a force sensor under the handplate measures the resisting force, and the wrist is fastened to the handplate with straps.

series), with a maximum range of -80° to 80°. Furthermore, the motor is equipped with a SinCos encoder to measure the angle (Stegmann SRS50) and the reaction torque was measured with a torque sensor in the handle. The Wristalyzer was force-controlled to determine the passive range of motion (pROM), and position controlled during the determination the neuromechanical measurements. The manipulator is controlled by an inertia-spring-damper system, with a stiffness of 85 Nm/rad. Further information about the Wristalyzer setup is described in Appendix B. Wrist torque, angle and EMG signals were recorded simultaneously at 2048 Hz using a Refa TMSi amplifier (TMSi B.V., The Netherlands). ASA Lab (ASA Lab 4.9.2, ANT Software BV, the Netherlands) was used for recording of the EMG and Wristalyzer signals, while Matlab R2017b (The MathWorks Inc. Natick, MA) was used for control of the Wristalyzer and for off-line data analysis.

2.2.3 Signal processing

For the optimization measurements and NeuroFlexor measurements of healthy subjects, muscle activation of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) of the measurement side was obtained by an EMG with standard disposable surface electrodes from Ambu® (Ambu A/S, Denmark), at a sample frequency of 2048 Hz. The ground electrode was placed on the mastoid process of the subject to keep patient potential and amplifier potential at about the same level.

To reduce background noise and to remove baseline activity, EMG signals were band-pass filtered at [20 - 450] Hz (3th-order Butterworth). Thereafter the EMG signals were full wave rectified and subsequently low-pass filtered (3rd order Butter-worth (20 Hz)), to obtain the linear envelope. Finally, the minimal EMG, defined as the minimal EMG value determined with steps of 8 ms during the whole measurement [4], was subtracted from EMG, to reduce the influence of noise and offset muscle activation.

Angle and force signals were low-pass filtered at 20 Hz (3th-order Butterworth), to avoid noise enlargement while calculating the angular velocity and acceleration. To avoid long computational times of the optimization method, all data obtained with the optimization method was down-sampled to 128 Hz. In case of the healthy subject data on the NeuroFlexor data, EMG data was re-sampled to the sample frequency of the NeuroFlexor.

2.3 NeuroFlexor method

2.3.1 Measurement protocol

To asess test-retest reliability, measurements were performed twice on the same day with the NeuroFlexor. Measurements

were performed on the impaired hand of the stroke patients and on the right hand of the healthy subjects, while the subjects were instructed to "relax and do nothing". The subjects were seated with their arm resting on the device such that their elbow was approximately 90° flexed. The forearm was strapped to the device making minimal displacements possible, the hand was strapped to the handplate and the distal edges of the malleoli of the wrist are placed in line with the rotation axis (Figure 2). The wrist was moved over a range of 50°, i.e. from 20° flexion to 30° extension. First, five slow ramp, hold and release movements in extension direction (5°/s) were executed and thereafter ten fast movements in extension direction (236°/s). The software program NeuroFlexor Scientific v0.06 (AggeroMedTech AB, 2014, Solna, Sweden) was used to control the measurements and to perform the analysis of the obtained data. The first out of five slow movements and the first out of ten fast movements were excluded from the analysis, in order to avoid bias from startle reflexes and mechanical hysteresis [30].

2.3.2 Modeling

An underlying model determines the neuromechanical parameters by calculation steps based on data points on the force curve recorded during the slow and fast sweeps. Appendix D shows the model structure. The passive joint resistance is separated into three components: a neural (NC), an elastic (EC) and a viscous component (VC). Where the NC and EC are called the neuromechanical parameters of the NeuroFlexor method.

2.4 Optimization method

2.4.1 Measurement protocol

Before the measurements, the van was stabilized and the inner temperature was set such that it was comfortable for the subjects. Subjects were seated such that their shoulder was relaxed and their elbow was approximately 90°of flexion. Before the subjects arm was placed in the Wristalyzer, it was checked whether the subject could comfortably rotate their wrist by manually rotating the wrist. The forearm was fixated to a lower arm cuff (Kramer Orthopedie B.V., The Netherlands) and hand was fixated to the handle. EMG electrodes were placed on the bulk of the FCR and the bulk of the ECR. First, the resting position of the subject was set by recording the angle in rest. Thereafter, the passive range of motion (pPROM$_w$) was determined by gradually increasing the torque in both flexion and extension direction, until a torque of 2 Nm was reached. While obtaining the pROM$_w$, subjects were asked to remain maximally relaxed and it was online checked whether no voluntary muscle activation was present in the EMG signal.

After determination of pROM$_w$, the neuromechanical parameters were assessed under passive conditions with positional perturbations. Passive sweep trials were executed over pROM$_w$ minus one degree from the extremities of both the flexion and extension angle, to secure the safety of the subject. During the sweep trial, the subjects were instructed to "relax and not intervene" and the wrist was rotated over pROM$_w$ at four different velocities in both flexion and extension direction. These include a slow sweep at 5 °/s, an Ashworth sweep pROM$_w$/s, a fast sweep 236 °/s, and a preparatory movement to reach the limits of pROM$_w$. The resting time after the preparatory movement and before the flexion movement was 3 seconds, and the resting time between the flexion and extension sweep was 5 seconds. The angle was defined as positive during flexion position and negative during extension. Unlike the movements over the full range of motion, preparatory sweeps are applied over half of the pROM$_w$ to move the robot to flexion or extension extremity of pROM$_w$.

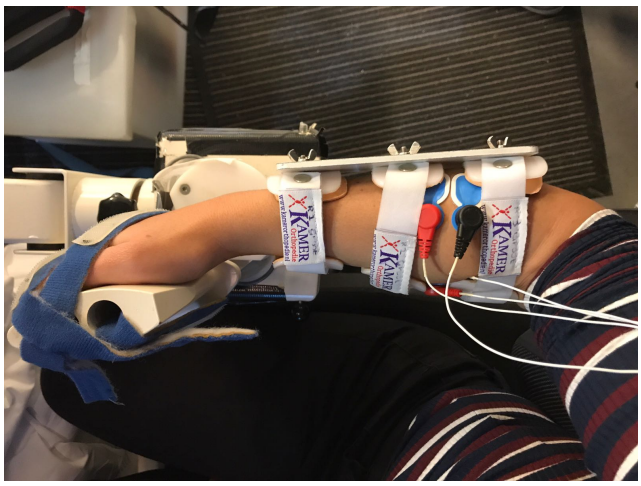


Figure 2. Measurement setup of the optimization method with the Wristalyzer (MOOG, Nieuw Vennep, The Netherlands), where the arm was strapped to a lower arm cuff (Kramer Orthopedie B.V., The Netherlands), the hand was strapped to the handplate and the distal edges of the malleoli of the wrist are placed in line with the rotation axis. EMG surface electrodes are placed on the flexor carpi radialis and extensor carpi radialis (Ambu A/S, Denmark).

2.4.2 Modeling

The optimization model of de Vlugt et al. [26] was extended by de Gooijer - van de Groep et al. to a bidirectional wrist model [4]. The model simulates the physiological mechanisms, which consists of the active and intrinsic muscle contributions. The active contribution is EMG dependent and is based on a Hill-type muscle model [31], i.e. it contains a force-length and force-velocity relationship. Optimal muscle lengths are estimated and the active contribution is based on second order dynamics with a cut-off frequency to mimic activation dynamics. The intrinsic contribution consists of visco-elastic properties of the ECR and FCR muscles, which are represented by a spring system that describes the resistance of the connective tissue as a result of stretching the muscles beyond their slack lengths. Also, relaxation dynamics, i.e. the tension decay of muscles following stress [32], was modeled, where its elastic force will decrease over time. Appendix D. 1.1 shows the full model description.

The input signals for the model are the measured angle θ, the measured torque and the EMG signals of the ECR and FCR. The wrist model simulates the measured wrist torque, by adjusting its model parameters (called the parameter estimation part, a

schematic representation is visible in Appendix C). In total 12 physiological parameters were estimated by the model, which can be separated into passive parameters, i.e. the mass of the hand and handplate (m), the stiffness coefficients of the muscles (k_{ecr} and k_{fcr}), the relaxation time constant (τ_{rel}), the relaxation factor (k_{rel}), tendon slack lengths ($l_{slack,ecr}$ and $l_{slack,fcr}$), and into active parameters, i.e. the EMG weighting coefficients (g_{ecr}) and (g_{fcr}), the optimal muscle lengths ($l_{o,ecr}$) and ($l_{o,fcr}$), and the activation cut-off frequency (f_0). Initial parameter values, together with their lower and upper bounds are presented in Table III.

The parameters of the model were estimated by minimizing the error function, i.e. the difference between the estimated torque and measured torque, by using a nonlinear least squares algorithm. Thus, as cost function (E) the sum of the difference between the modeled and measured torque was minimized over all time samples:

$$E = \sum_{i=1}^{N} \epsilon(\theta, i) \tag{1}$$

$$\epsilon(\theta, i) = \hat{T}(\theta, i) - T(i) \tag{2}$$

where θ is the parameter vector, N the number of time samples, i the index of the time sample, ϵ the error between the modeled torque $\hat{T}$ and the measured torque T.

To test for possible sub-optimal solutions (local minima), a sensitivity analysis was performed in 4 randomly selected patients. Therefore a grid search algorithm was performed on the initial parameters, such that the optimization procedure was started with the most optimal initial parameters obtained by the grid search algorithm. Thereafter, it was checked whether the outcome parameters of the optimization method with the grid search algorithm differed from the parameters obtained with the normal optimization procedure, i.e. without grid search algorithm.

After parameter optimization, i.e. when the final parameters were obtained, stiffness at joint level (K_{joint}) and active torque were calculated. The joint stiffness was taken at an angle that was the same for all subjects, i.e. at angle 0 °[4]. Finally, root mean square (RMS) values of the modeled active torque were calculated as a measure of the neural component [26]. RMS values were taken over the standardized parts visible in Figure 3, resulting in RMS values for respectively the slow part of the modeled active toque ($T_{act,m,slow}$), the Ashworth part ($T_{act,m,Ash}$) and the fast part ($T_{act,m,fast}$) (Where m stands for either the ECR or the FCR). 0.5 seconds before and after the sweep were taken such that it should be enough to catch the stretch reflex [25], [33]. ($T_{act,m,fast}$) was used as the neural outcome parameter ($T_{act,m}$) from the optimization method. So, K_{joint}, $T_{act,ecr}$ and $T_{act,fcr}$ are the main outcome measures of interest and defined as the neuromechanical parameters of the optimization method.

2.4.3 Quality measures

The validity of the model was assessed with the variance accounted for (VAF), which compares the measured torque with the estimated torque and which gives an indication of the goodness of fit of the model.

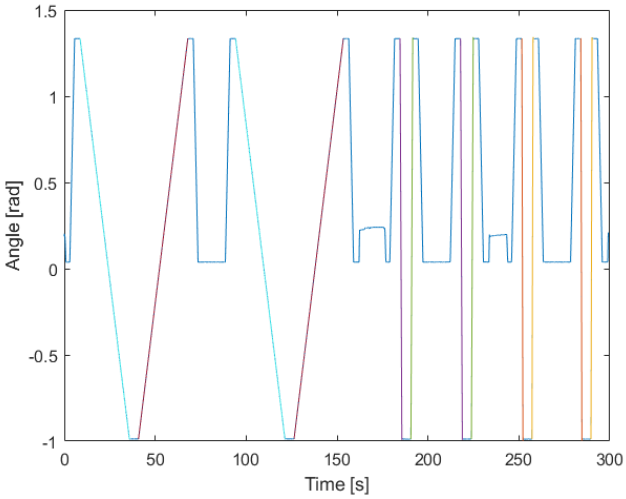


Figure 3. Example of the measured angle of the optimization method, where the angle was defined as positive during flexion and negative during extension. Model parameters are estimated over the time samples of the whole movement. While during the time samples of the light blue curves $T_{act,fcr,slow}$ is calculated, during the brown curve $T_{act,ecr,slow}$, during the purple curve $T_{act,fcr,Ash}$, during the green curve $T_{act,ecr,Ash}$, during the orange curve $T_{act,fcr,fast}$, and finally, during the yellow curve $T_{act,ecr,fast}$.

$$VAF = 1 - \frac{\sum_{i=1}^{N}(T(i) - \hat{T}(\hat{\theta}, i)^2}{\sum_{i=1}^{N}(T(i))^2} \cdot 100\%, \tag{3}$$

with $\hat{\theta}$ the optimized parameter vector, N the total number of time samples, i the index of the time sample, T the measured torque, $\hat{T}$ the estimated torque. A high VAF shows a good performance of the model, while a low VAF shows a bad performance. Estimates with a lower VAF value than 90% were neglected [34].

Next to the VAF, the root mean square error (RMSE) was calculated, as a measure of the difference between the estimated torque and measured torque. The RMSE is calculated by

$$RMSE = \sqrt{\frac{\sum_{i=1}^{N}(T(i) - \hat{T}(\hat{\theta}, i)^2}{N}}, \tag{4}$$

with $\hat{\theta}$ the optimized parameter vector, N the total number of time samples, i the index of the time sample, T the measured torque, $\hat{T}$ the estimated torque. A low RMSE shows a good performance of the model, where an RMSE of 0 shows excellent agreement.

Reliability of the parameters was assessed with the normalized standard error of the mean (nSEM), which is based on the sensitivity of each parameter to the error function [4], [26], [35]. Generally it holds that a parameter with a low normalized

Table III. Parameters optimized by the wrist optimization model

Parameter	Description [unit]	Initial value	Lower bound	Upper bound
Intrinsic parameters				
m	Mass of the hand + handplate [kg]	0.6	0.5	5
k_{ecr}	Stiffness coefficient ECR [1/m]	240	10	800
k_{fcr}	Stiffness coefficient FCR [1/m]	230	10	800
τ_{rel}	Relaxation time constant [s]	0.9	0	10
k_{rel}	Relaxation factor [-]	1	0	50
$l_{slack_{ext}}$	Connective tissue ECR slack length [m]	0.06	-0.1	0.1
$l_{slack_{flex}}$	Connective tissue FCR slack length [m]	0.04	-0.1	0.1
Neural parameters				
G_{ecr}	EMG weighting factor ECR [1/V]	1×10^4	1	1×10^{11}
G_{fcr}	EMG weighting factor FCR [1/V]	1×10^4	1	1×10^{11}
f_0	Activation cutoff frequency [Hz]	3	1	10
$l_{o_{ecr}}$	Optimal muscle length ECR [m]	0.070	0.04	0.11
$l_{o_{fcr}}$	Optimal muscle length FCR [m]	0.063	0.04	0.11

standard error of the mean (nSEM) value has a substantial contribution to the error function. SEM values were calculated using the covariance matrix P:

$$P = \sqrt{\frac{1}{N}(J^T \cdot J)^{-1}\epsilon \cdot \epsilon^T} \tag{5}$$

with N the number of parameters, J the Jacobian matrix (partial derivatives of the prediction error for each parameter), and ϵ the error function. SEM values are calculated by taking the square root of the diagonal terms of P. Thereafter, SEM-values were normalized to their corresponding parameter value.

2.5 Statistical analysis

For statistical analysis, a disease gradation was defined, ranging from patients with a MAS of zero to patients rated by a MAS of 4. Four groups were discerned, i.e. patients with a MAS equal to zero (MAS_0), a MAS equal to one (MAS_1), a MAS of 1+ (MAS_{1+}), a MAS equal to 2 (MAS_2) and a MAS equal to 3 (MAS_3). None of the patients was rated with a MAS of four. For statistical analysis, patients with a MAS of 1+ were rated with a MAS of 1.5 to maintain equal intervals [19], [28].

For test-retest reliability of the NeuroFlexor, the intra-class correlation coefficients (ICC) were calculated based on absolute-agreement. The ICC was based on a single measure and a 2-way random-effects model was used. Next to that, limits of agreement (LoA) in conjunction with Bland-Altman plots and the minimal detectable change (MDC) were presented. The MDC percentage (MDC%) was thereafter calculated by dividing the MDC by the maximal score of the measure. ICC values above 0.75 where classified as excellent, between 0.75 and 0.4 as fair to good, and below 0.4 as poor [36]. The average out of the two measurements was taken for further analysis.

Correlation between the neuromechanical parameters of the NeuroFlexor and optimization method was assessed using the Pearson correlation coefficient (r). While correlation between the neuromechanical parameters of two methods and the MAS was assessed using the Spearman correlation coefficient (r). Furthermore, correlation between $pROM_g$ and both EC and K_{joint} was assessed using the Pearson correlation coefficient (r). Absolute r-values below 0.2 were classified as very weak, between 0.20 and 0.4 as weak, between 0.40 and 0.60 as moderate, between 0.60 and 0.80 as strong, and above 0.80 as very strong [29].

Also, validation of the neuromechanical parameters of both methods with respect to the MAS is done by using a stepwise linear regression analysis with a backward selection procedure at an alpha of 0.10 [37], to check which parameters are able to describe the MAS. For the stepwise linear regression analysis, the MAS was treated as a continuous variable. To check for multicollinearity, the correlation matrix of the neuromechanical parameters was calculated together with the eigenvalues of the matrix. Moreover, condition numbers K_j were calculated to check for multicollinearity. Condition numbers are defined by [38]

$$K_j = \sqrt{\frac{\lambda_{max}}{\lambda_j}} \tag{6}$$

where j is the index of the parameter number, λ_j the j-th eigenvalue of the correlation matrix, and λ_{max} is the largest eigenvalue. If the condition number is larger then 30, than multicollinearity may be present [39].

A Kruskal-Wallis test with independent samples was performed to compare results of the neuromechanical parameters

between patients with a different MAS. A dependent-samples t-test was conducted to compare the differences in $pROM_g$ and $pROM_w$ and the differences in active torque values with velocity.

Except for the multiple linear regression analysis, all tests of significance were performed at an alpha of 0.05. Statistical analysis was performed with IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1 Measured data

From the 49 included patients, four patients could not comply with the Wristalyzer protocol due to a limited range of the wrist. Furthermore, one patient was excluded from analysis, due to faltering of the NeuroFlexor during the measurements. In total, data from 44 stroke patients (n = 44) was analyzed for comparison of the optimization method and for the NeuroFlexor method. Out of the resulting 44 patients, the range of the NeuroFlexor perturbation was adjusted for two patients, since they were not able to move their wrist from 20° flexion to 30° extension. Next to the excluded subject due to faltering of the NeuroFlexor, another subject was excluded from the test-retest reliability analysis because the second NeuroFlexor measurement could not be performed due to a limitation of time. So that the test-retest reliability was performed with data from 47 stroke patients.

During the Wristalyzer measurements, the measured torque of ten patients exceeded the maximum torque of 5.12 Nm, causing clipping to occur. Since clipping occurred only at the end of the extension movement, with a maximum period of 0.7 sec, parameters were estimated without taking the part were clipping occurred into account. The error vector was in these cases modified such that is was zero at the points where the torque limit was exceeded. A sensitivity analysis was done to see whether the clipping patients did not have any influence on the final outcomes, which was not the case.

One healthy subject could not comply with the protocol for healthy subjects, due to a recently fractured wrist joint. The measurement of this subject was performed on the left wrist.

3.2 NeuroFlexor method

Outcome parameters of the measurements with the NeuroFlexor are shown in Table IV. For the healthy subjects, the outcomes of the single measurement was reported. Where for patients, the mean values out of the two measurements, i.e. the mean value of NC, EC, and VC, was reported.

The ICC for test-retest reliability for NC was 0.944 ($F(46, 46) = 17.646,\ p < 0.001$), indicating excellent reliability. The test-retest of EC was excellent, with an ICC of 0.917 ($F(46, 46) = 11.971,\ p < 0.001$). The ICC for VC was 0.797 ($F(46, 46) = 4.853,\ p < 0.001$), indicating excellent reliability. Bland-Altman plots are presented in Appendix E15 and show a distribution scattered around a mean difference line of approximately 0. Next to that, nearly all values lie between the limits of agreement. Minimal detectable change (MDC) values were 15.282, 3.841, 0.799 for the NC, EC and VC, respectively. Consequently, the MDC% were 31%, 22 % and 59% for the NC, EC and VC, respectively.

3.3 Optimization method

The neuromechanical parameters of the optimization method are shown in Table IV. Furthermore, the 12 parameters estimated by the optimization model are shown in Table V.

Figure 4 shows an example of the modeled data, including the filtered EMG response of the ECR and FCR (top left), the imposed angular position (top right), the normalized force-length and force-velocity curves of the ECR (middle left) and FCR (middle right), including the perturbed range indicated by the red and green curve, and the modelled intrinsic and neural forces from the ECR (bottom left) and FCR (bottom right) muscles.

Data was modeled, such that the error between the modeled torque and measured torque was minimal. Figure 5, shows the corresponding torque fit and Figure 6 shows the development of the passive joint stiffness over angular rotation, both of the same subject as in Figure 4.

The sensitivity analysis of the initial parameters was performed in five randomly selected patients. In all five patients,

Table IV. Neuromechanical parameters of the NeuroFlexor model and optimization model of healthy subjects (n = 11) and patients (n = 44). Where the reported values of the NeuroFlexor method are the mean values out of two measurements for the stroke patients.

Parameter	Value (mean ± SD)					
	Healthy ($n = 11$)	MAS $_0$ ($n = 7$)	MAS $_1$ ($n = 11$)	MAS $_{1+}$ ($n = 12$)	MAS $_2$ ($n = 7$)	MAS $_3$ ($n = 7$)
NC [N]	1.219 ± 1.380	6.064 ± 6.935	10.235 ± 7.429	13.572 ± 10.317	18.710 ± 14.608	32.591 ± 10.223
EC [N]	2.441 ± 0.721	2.848 ± 0.965	4.374 ± 2.065	6.435 ± 3.817	5.756 ± 1.714	11.913 ± 9.605
VC [N]	0.155 ± 0.313	0.189 ± 0.430	0.227 ± 0.484	0.553 ± 0.456	0.433 ± 0.300	0.214 ± 0.482
$T_{act,fcr}$ [Nm]	-	0.247 ± 0.203	0.363 ± 0.308	0.541 ± 0.646	0.945 ± 0.880	1.874 ± 0.610
$T_{act,ecr}$ [Nm]	-	0.072 ± 0.104	0.041 ± 0.069	0.029 ± 0.040	0.062 ± 0.073	0.096 ± 0.138
K_{joint} [Nm/rad]	-	0.734 ± 0.339	1.118 ± 0.868	1.386 ± 0.729	1.830 ± 1.212	2.402 ± 2.268

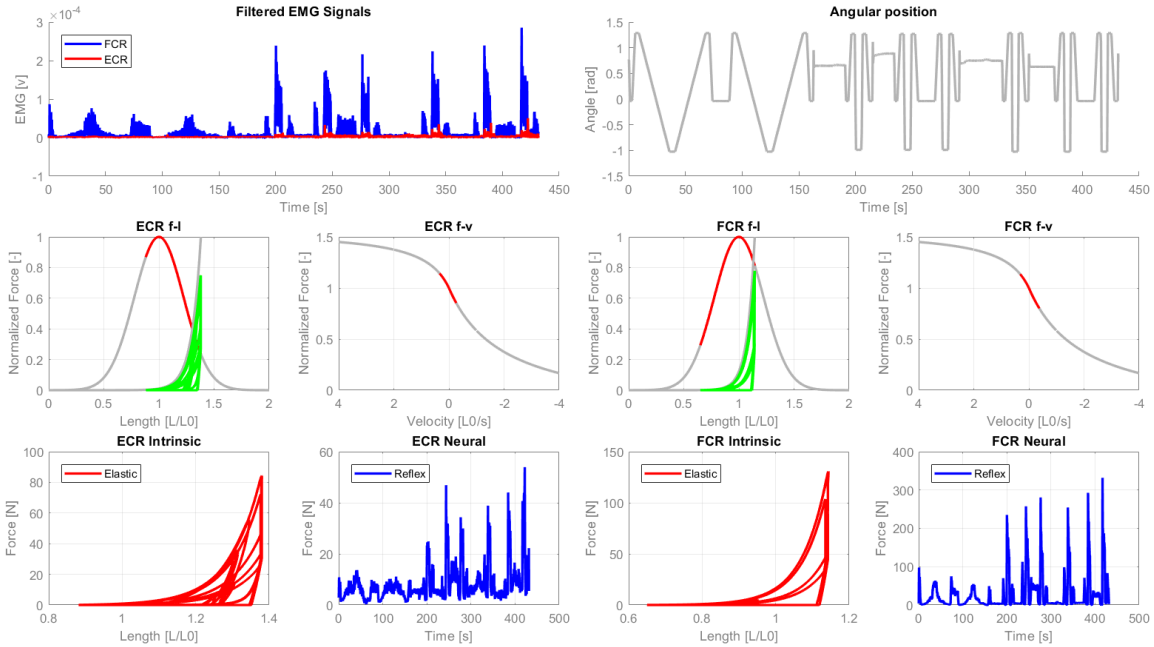


Figure 4. Example of the measured and modeled data for the optimization method for a subject with MAS of 3. EMG response of the ECR and FCR (top left), the imposed angular position (top right), the normalized force-length and force-velocity curves of the ECR (middle left) and FCR (middle right), including the perturbed range indicated by the red and green curve, and the modelled intrinsic and neural forces from the ECR (bottom left) and FCR (bottom right) muscles.

Table V. Parameter results of the optimization method (n = 44).

Parameter	Value (mean ± SD)				
	MAS $_0$ ($n = 7$)	MAS $_1$ ($n = 11$)	MAS $_{1+}$ ($n = 12$)	MAS $_2$ ($n = 7$)	MAS $_3$ ($n = 7$)
Intrinsic					
m [kg]	0.599 ± 0.211	0.624 ± 0.169	0.705 ± 0.159	0.512 ± 0.021	0.610 ± 0.119
k_{ecr} [1/m]	296.006 ± 210.838	345.510 ± 233.405	172.387 ± 76.881	340.484 ± 264.289	266.755 ± 259.940
k_{fcr} [1/m]	180.415 ± 54.594	210.367 ± 34.837	210.997 ± 71.484	173.103 ± 53.687	185.455 ± 83.325
τ_{rel} [s]	3.138 ± 1.615	2.237 ± 1.144	2.824 ± 1.884	2.394 ± 1.156	3.896 ± 3.003
k_{rel} [-]	0.734 ± 0.387	0.904 ± 0.441	1.003 ± 0.508	1.374 ± 1.100	3.083 ± 2.952
$l_{slack_{ext}}$ [m]	0.065 ± 0.019	0.070 ± 0.011	0.068 ± 0.012	0.064 ± 0.019	0.041 ± 0.063
$l_{slack_{flex}}$ [m]	0.044 ± 0.010	0.048 ± 0.006	0.054 ± 0.009	0.038 ± 0.016	0.036 ± 0.017
Neural					
G_{ecr} [1/V]	$(1.79 \pm 2.61) \times 10^6$	$(1.05 \pm 3.22) \times 10^7$	$(3.55 \pm 5.10) \times 10^6$	$(1.40 \pm 1.99) \times 10^6$	$(3.28 \pm 3.78) \times 10^6$
G_{fcr} [1/V]	$(1.05 \pm 1.27) \times 10^7$	$(5.31 \pm 3.83) \times 10^6$	$(2.28 \pm 1.63) \times 10^6$	$(4.34 \pm 2.07) \times 10^6$	$(3.15 \pm 1.86) \times 10^6$
f_0 [Hz]	1.249 ± 0.442	1.584 ± 0.620	3.198 ± 2.617	1.860 ± 0.622	2.006 ± 0.612
$l_{o_{ecr}}$ [m]	0.086 ± 0.031	0.053 ± 0.021	0.071 ± 0.033	0.078 ± 0.033	0.056 ± 0.025
$l_{o_{fcr}}$ [m]	0.058 ± 0.025	0.063 ± 0.024	0.069 ± 0.021	0.058 ± 0.013	0.071 ± 0.014

no noticeable differences were found between the estimated parameters with the elaborate grid search algorithm and the normal optimization procedure, suggesting that the optimization method is not sensitive to local minima.

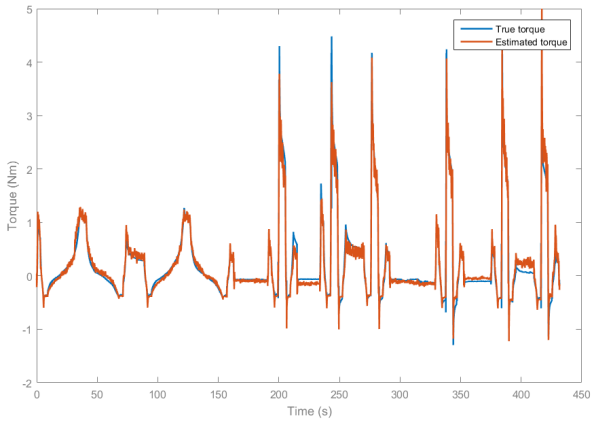


Figure 5. Example of model fit (red) on top of measured torque data (blue) of the optimization method, for a subject with MAS of 3. The VAF for this subject was equal to 96,62%

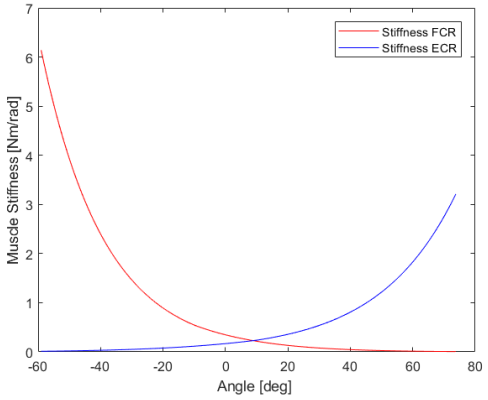


Figure 6. Example of the development of the passive muscle stiffness over angular position of the FCR (red) and ECR (blue) modeled with the optimization model, for a subject with MAS of 3.

3.3.1 Model validity

The Variance Accounted For (VAF) was above 90% in all cases, meaning that the measured wrist torque could be well described by the model. The VAF values of all patients had a mean of 97.528% (SD = 1.524%). Next to that, RMSE values had a mean of 0.095 Nm (SD = 0.033 Nm).

Normalized SEM values for the parameters obtained with the non-linear parametric method are presented in Figure 7. Median nSEM values were less than 1%, except for G_{ecr} and $l_{o_{ecr}}$ (Figure 7).

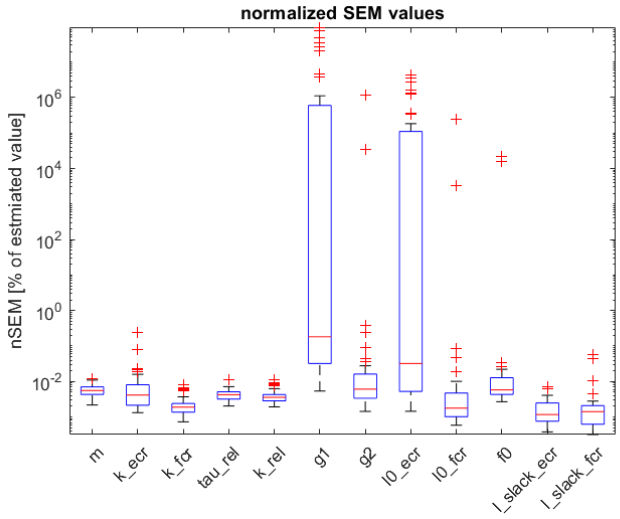


Figure 7. Box plot showing the normalized SEM (nSEM) values for the 12 parameters of the optimization method of the stroke patients (n = 44). In each box (blue), the central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers (black) extend to the most extreme data points not considered outliers, and the outliers are plotted individually using the '+' symbol (red).

3.3.2 Influence of velocity

Since the minimal $pROM_w$ was 83°, the Ashworth sweep (ROM/s) was in none of the cases slower than the slow sweep at 5°/s. Likewise, the maximal $pROM_w$ was 154° for patients. So, the Ashworth sweep does not exceed the velocity of the fast sweep. Active torque of the FCR, increased significantly with speed between the slow (M = 0.114 Nm, SD = 0.133 Nm) and Ashworth sweeps (M = 0.516 Nm, SD = 0.575 Nm), t(43) = -5.541 and $p < 0.001$. Also, the active torque of the FCR increased significantly with speed between the Ashworth (M = 0.516 Nm, SD = 0.575 Nm) and fast sweeps (M = 0.726 Nm, SD = 0.773 Nm), t(43) = -5.581 and $p < 0.001$. Finally, the active torque of the FCR increased significantly with speed between the slow (M = 0.114 Nm, SD = 0.133 Nm) and fast sweeps (M = 0.726 Nm, SD = 0.773 Nm), t(43) = -5.905 and $p < 0.001$.

For the ECR, the active torque between the slow sweep (M = 0.026, SD = 0.045 Nm) and Ashworth sweep (M = 0.041 Nm, SD = 0.063 Nm) increased significantly, t(43) = -2.271 and p = 0.028. Likewise, the active torque of the ECR increased significantly with speed between the Ashworth (M = 0.041 Nm, SD = 0.063 Nm) and fast sweeps (M = 0.055 Nm, SD = 0.084 Nm), t(43) = -2.739 and p = 0.009. Finally, the active torque of the

ECR also increased significantly with speed between the slow (M = 0.026 Nm, SD = 0.045 Nm) and fast sweeps (M = 0.055 Nm, SD = 0.084 Nm), t(43) = -2.956 and p = 0.005. Box-plots of the active torque values of the FCR and the ECR separated with movement velocity are presented in Figure 8a respectively Figure 8b.

3.4 Agreement between methods

Pearson correlation between the neural component of the FCR, $T_{act,fcr}$ and the neural component of the NeuroFlexor, NC, was strong: r = 0.656 (p < 0.001, Figure 9). While the correlation between the neural component of the ECR, $T_{act,ecr}$ and the neural component of the NeuroFlexor, NC, was very weak: r = -0.021 (p = 0.8937, Figure 9). Whereas no correlation is expected between NC and $T_{act,ecr}$, since the NeuroFlexor determines its neuromechanical parameters during an extension movement. The correlation between the elastic component of the optimization method, K_{joint} and the elastic component of the NeuroFlexor EC, showed strong correlation: r = 0.648 (p < 0.001, Figure 9).

3.5 Agreement with clinical scales

3.5.1 Agreement with MAS

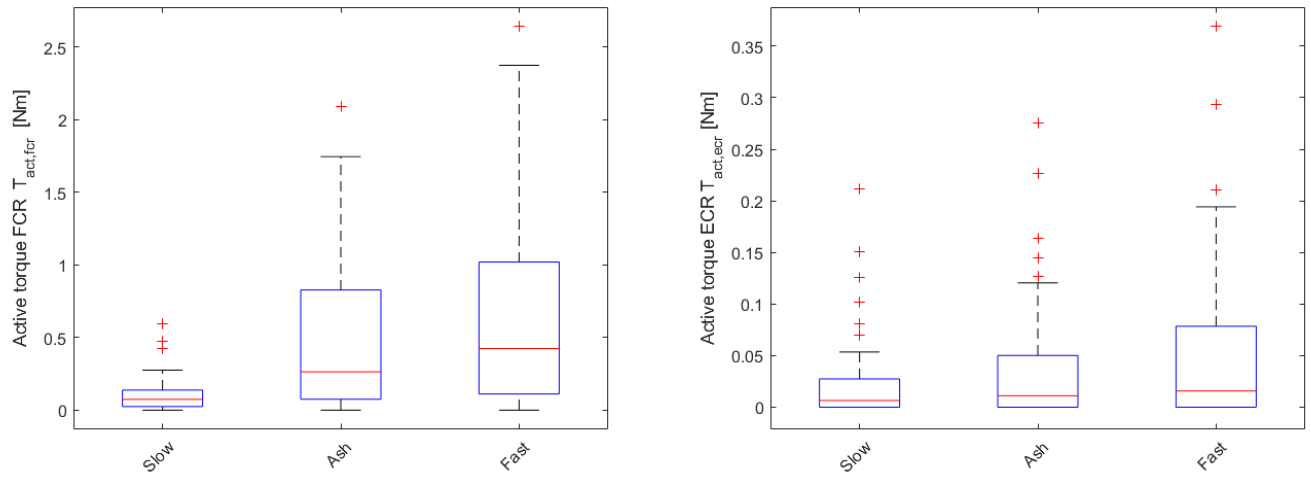
First, outcome parameters of both methods were compared to the MAS individually. The Spearman correlation between the neural contribution of the FCR, $T_{act,fcr}$, and the MAS, was moderate (ρ = 0.548, p < 0.001). Whereas the correlation between the neural contribution of the ECR, $T_{act,ecr}$, and the MAS, was very weak (ρ = -0.010, p = 0.948). Wrist joint stiffness, K_{joint} correlated moderately with the MAS (ρ = 0.406, p = 0.006).

The neural component NC and MAS were moderately correlated (ρ = 0.600, p < 0.001). Also, the correlation between elastic component EC and the MAS was moderate (ρ = 0.581, p < 0.001). Whereas correlation between the viscous component (VC) and the MAS was very weak (ρ = 0.168, p = 0.267). All plots can be seen in Figure 10.

Stepwise linear regression analysis was calculated to predict the MAS based on NC, EC, and VC. A significant regression equation was found (P(2,41) = 17.882, p < 0.001) with a R^2 of 0.466. NC (β = 0.490, p < 0.001) and EC (β = 0.307, p = 0.020) were significant estimators of the MAS, while VC was not a significant estimator (Table VI). From the standardized coefficients, we see that NC contributes more to the MAS than EC.

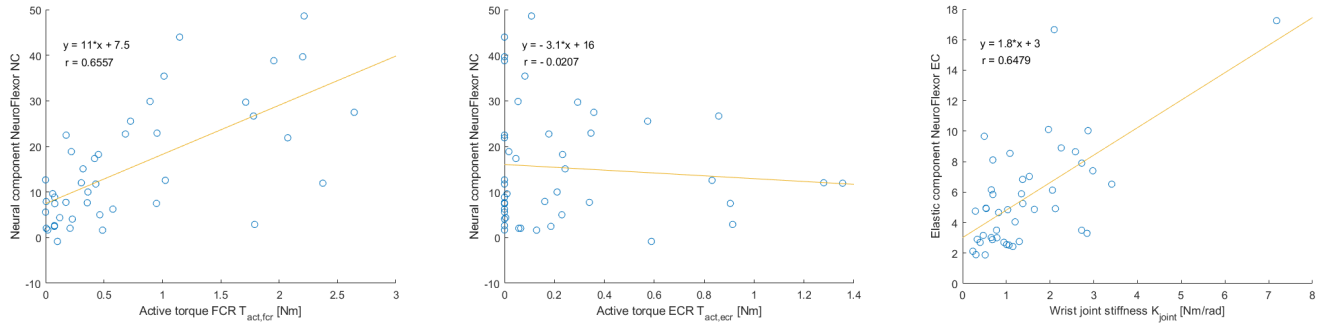
Stepwise linear regression analysis was conducted to predict the MAS based on K_{joint}, $T_{act,fcr}$, and $T_{act,ecr}$. A significant regression equation was found (P(2,41) = 22,161 p < 0.001) with a R^2 of 0.519. K_{joint} (β = 0.310, p = 0.008) and $T_{act,fcr}$ (β = 0.594, p < 0.001) were significant estimators of the MAS, while $T_{act,ecr}$ was not a significant estimator (Table VII). From the standardized coefficients, we see that $T_{act,frc}$ contributes about twice as much as K_{joint}.

To see whether the neural component of the NeuroFlexor method or the neural components of the optimization method were more able to predict the MAS, a stepwise linear regression analysis was conducted to predict the MAS based on NC, EC, VC, K_{joint}, $T_{act,fcr}$, and $T_{act,ecr}$. A significant regression equation was found (P(2,41) = 31.417, p < 0.001) with a R^2 of 0.605. EC (β = 0.428, p < 0.001) and $T_{act,fcr}$ (β = 0.584, p < 0.001) were significant estimators of the MAS, while $T_{act,ecr}$ was not a significant estimator (Table VIII). From the standardized coefficients, we see that $T_{act,fcr}$ contributes more than the EC .



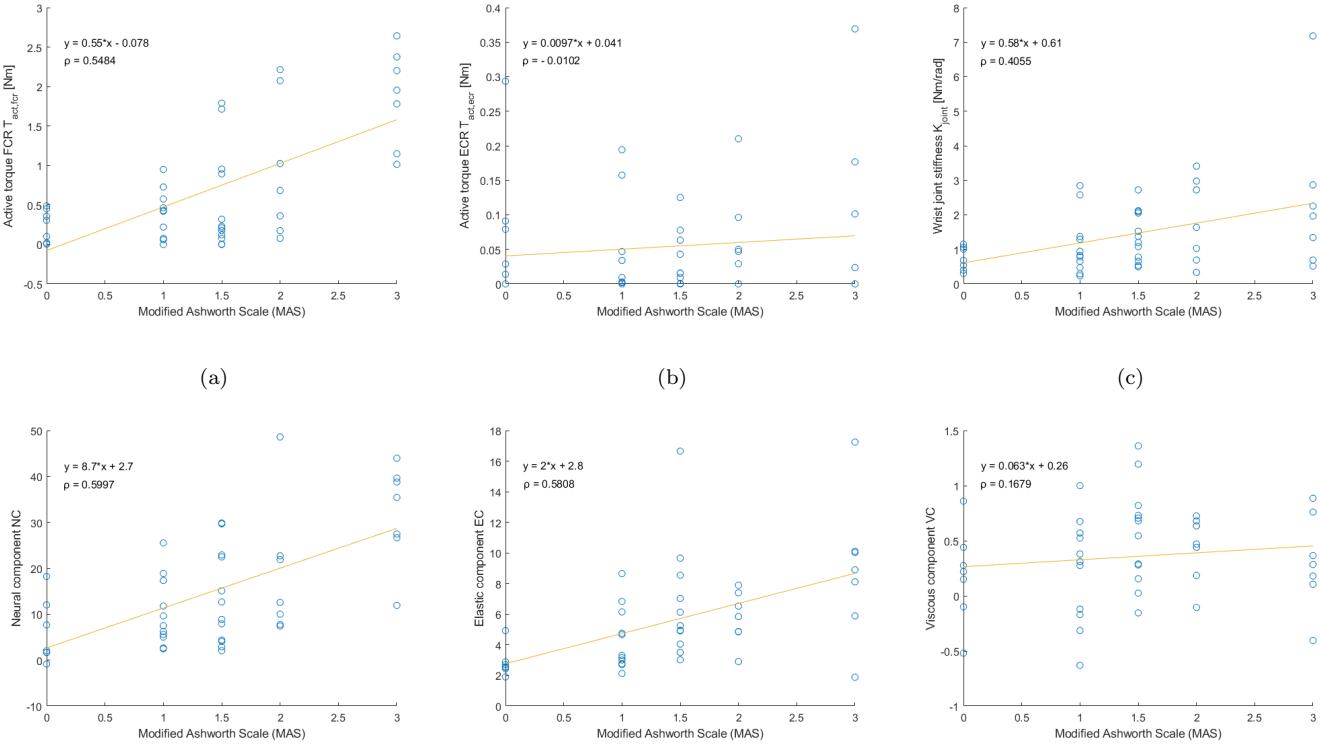
(a) FCR (b) ECR

Figure 8. Box plot showing the root mean square values (RMS) of the active torque of the FCR (a) and the ECR (b) during the slow, Ashworth and fast part of the optimization method. In each box (blue), the central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers (black) extend to the most extreme data points not considered outliers, and the outliers are plotted individually using the '+' symbol (red).



(a) (b) (c)

Figure 9. Scatter plots with the linear equation and Pearson correlation coefficient r, which show the relationship between the neuromechanical parameters of the NeuroFlexor method and optimization method. (a) Relationship between $T_{act,fcr}$ and NC. (b) Relationship between $T_{act,ecr}$ and NC. (c) Relationship between K_{joint} and EC.



(a) (b) (c)

(d) (e) (f)

Figure 10. Linear relationship between the MAS and (a) $T_{act,fcr}$, (b) $T_{act,ecr}$, (c) K_{joint}, (d) NC, (e) EC, and (f) VC. Where ρ is the Spearman correlation coefficient.

To check for multicollinearity, the correlation matrix of the neuromechanical parameters is presented in Table F3 (Appendix F), and the eigenvalues with their condition numbers in Table F4 (Appendix F). Since the condition numbers are all below 30, we can conclude that no multicollinearity was present.

Finally, to evaluate whether parameter outcomes of the optimization model could improve the prediction of the MAS,

Table VI. Backward prediction model of the multiple linear regression analysis for the NeuroFlexor method. Where B is the unstandardized coefficient and β the standardized coefficient.

Variables	Model 1			Model 2		
	B	β	p-value	B	β	p-value
(Constant)	0.482		0.031	0.459		0.032
NC	0.036	0.507	0.031	0.035	0.490	0.000
EC	0.081	0.305	0.001	0.081	0.307	0.020
VC	-0.110	-0.053	0.664	-	-	-
R^2	0.468			0.466		
R^2_{adj}	0.429			0.440		

Table VII. Backward prediction model of the multiple regression analysis for the optimization method. Where B is the unstandardized coefficient and β the standardized coefficient.

Variables	Model 1			Model 2		
	B	β	p-value	B	β	p-value
(Constant)	0.641		0.001	0.641		0.001
$T_{act,fcr}$	0.725	0.614	0.000	0.702	0.594	0.000
K_{joint}	0.219	0.296	0.015	0.296	0.310	0.008
$T_{act,ecr}$	-0.538	-0.049	0.689	-	-	
R^2	0.521			0.519		
R^2_{adj}	0.486			0.496		

stepwise linear regression analysis was conducted to predict the MAS based on the neuromechanical parameters of the NeuroFlexor and optimization method, together with the parameters outcomes of the optimization model. A significant regression equation was found ($P(3,40) = 27.634$, $p < 0.001$) with a R^2 of 0.675. NC ($\beta = 0.395$, $p < 0.001$) , $T_{act,fcr}$ ($\beta = 0.574$, $p < 0.001$) and G_{fcr} ($\beta = -0.266$, $p = 0.006$) were significant estimators of the MAS. From the standardized coefficients, we can conclude that $T_{act,fcr}$ contributed more than NC and G_{fcr}. The model summary is presented in Table F5 in Appendix F.

From the Kruskal-Wallis analysis it followed that the patients with a different MAS significantly differed for NC ($H(4) = 16.753$, $p = 0.002$) and EC ($H(4) = 16.233$, $p = 0.003$). The viscous component did not significantly differ for patients ($H(4) = 3.900$, $p = 0.420$). For the optimization method, $T_{act,fcr}$ significantly differed with disease grade ($H(4) = 16.730$, $p = 0.002$), while $T_{act,ecr}$ ($H(4) = 1.229$, $p = 0.873$) and K_{joint} ($H(4) = 7.252$, $p = 0.123$) did not significantly differ.

3.5.2 Relation with pROM

Since the pROM was dependent on the measurement technique, i.e. measured with the goniometer or measured with the Wristalyzer, it was checked which measurement technique had a higher correlation with the elastic components of the NeuroFlexor method and the optimization method. In 34 patients, the $pROM_w$ measurement was limited during flexion of the wrist by the hardware stops of the Wristalyzer, resulting in a lower $pROM_w$ than the actual passive range of motion.

$pROM_g$ correlated very weak with EC ($r = -0.148$, $p = 0.338$), and weak with K_{joint} ($r = -0.328$, $p = 0.030$). While $pROM_w$ correlated strong with EC ($r = -0.606$, $p < 0.001$) and strong with k_{joint} ($r = -0.742$, $p < 0.001$). Scatter plots with the linear regression line are depicted in Appendix I18.

Furthermore, the agreement between the passive range of motion measured subjectively with the goniometer and the passive range of motion measured with the Wristalyzer was checked. The mean value of $pROM_g$ ($M = 172.477°$, $SD = 19.284°$) was significantly larger than $pROM_w$ ($M = 118.744°$, $SD = 20.091°$), $t(43) = -18.2568$, $p < 0.001$. This is confirmed by the Bland-Altman plot presented in Appendix G, where a bias of approximately 53° is visible. Besides significant difference in the means, the linear correlation between $pROM_g$ and $pROM_w$ was moderate: ($r = 0.5090$, $p < 0.001$, Figure I19).

3.6 Healthy subject data

Model outcomes of one healthy subject are summarized in Appendix H, which shows the model outcomes of one healthy subject. VAF values of the slow measurements were above 90% (M = 96.811%, SD = 0.684%), meaning that the measured wrist torque could be described the model. However, VAF values from the fast measurement were very low (M = 4.896 %, SD = 3.650%), implicating that the model structure was not able to describe the measured force by the assumed dynamics of the wrist joint. Next to that, normalized SEM values were high (Table H7). During the slow stretch, τ_{rel}, k_{rel}, G_{fcr} and $l_{o_{fcr}}$ had high nSEM values. While during the fast stretch, τ_{rel}, k_{rel}, $l_{slack_{ext}}$, $l_{slack_{flex}}$, G_{ecr}, G_{fcr}, f_0, $l_{o_{ecr}}$, and $l_{o_{fcr}}$ had high nSEM values, meaning that neither the intrinsic nor neural component could be less reliably estimated.

Table VIII. Backward prediction model of the linear regression analysis for the neuromechanical parameters of the NeuroFlexor method and optimization method. Where B is the unstandardized coefficient and β the standardized coefficient.

Variables	Model 1			Model 2			Model 3			Model 4			Model 5		
	B	β	p-value	B	β	p-value	B	β	p-value	B	β	p-value	B	β	p-value
(Constant)	0.303		0.173	0.302		0.169	0.328		0.094	0.306		0.102	0.314		0.092
$T_{act,fcr}$	0.592	0.501	0.003	0.585	0.494	0.003	0.607	0.513	0.000	0.691	0.514	0.000	0.691	0.584	0.000
EC	0.100	0.377	0.010	0.104	0.393	0.002	0.102	0.386	0.002	0.103	0.388	0.001	0.113	0.428	0.000
NC	0.009	0.128	0.460	0.010	0.142	0.372	0.008	0.133	0.387	0.008	0.117	0.429	-	-	-
VC	-0.101	-0.049	0.660	-0.093	-0.045	0.678	-0.100	-0.048	0.650	-	-	-	-	-	-
$T_{act,ecr}$	.350	0.032	0.791	0.352	0.032	0.678	-	-	-	-	-	-	-	-	-
K_{joint}	0.024	0.033	0.828	-	-	-	-	-	-	-	-	-			
R^2	0.615			0.614			0.613			0.611			0.605		
R^2_{adj}	0.552			0.563			0.574			0.582			0.586		

4. Discussion

The study addressed the agreement between the neural and intrinsic components obtained with the NeuroFlexor and optimization method, to validate the NeuroFlexor method. Contradicting our hypothesis, we found a strong correlation between the neural component of the NeuroFlexor method and neural component of the optimization method, as well as for the intrinsic component of the optimization method and NeuroFlexor method. As a secondary objective, the study addressed at the external validation of the neuromechanical parameters with the MAS. Where the present study showed that the neuromechanical parameters of the two methods together were better able to describe the MAS than the neuromechanical parameters of both methods separately. From the healthy subject data, we were not able to obtain reliable neuromechanical parameters with the optimization model on the NeuroFlexor data.

4.1 Reliability NeuroFlexor

Our study showed that the NeuroFlexor is a reliable instrument for measuring the components of wrist hyper-resistance since the NC, EC, and VC from the NeuroFlexor method showed excellent test-retest reliability. This agrees what is published earlier, although they found slightly lower test-retest reliability for EC (ICC 0.79-0.88) and slightly higher results for VC (ICC 0.88-0.90) [30]. So we can conclude that the NeuroFlexor method is a reliable method to obtain the neuromechanical parameters.

4.2 Validity and model fit optimization model

For the patient group, VAF values were above 90% for the optimization model, indicating that the measured wrist torque could be well described by the model. High VAF values are in line with previous publications of the optimization model [4], [8]. Low nSEM values (Figure 7), indicate the absence of redundancy and that the estimation was sufficiently accurate. However, nSEM values of the EMG weighting factor of the ECR (g_{ecr}) and the optimal muscle length of the ECR (lo_{ecr}) were high compared to the nSEM values of the other parameters, indicating that g_{ecr} and lo_{ecr} had little to no contribution to the total modeled output torque and the active torque of the ECR is less reliably estimated. Therefore, the active torque of the FCR ($T_{act,fcr}$) has to be used as a measure for the neural component of the optimization method rather than the active torque of the ECR ($T_{act,ecr}$).

Although our study included patients with a more severe MAS than the study of de Gooijer - van de Groep et al., they found higher values of the joint stiffness (K_{joint}) with the optimization model at an angle of zero, e.g. values for joint stiffness of approximately 0 - 17 Nm/rad [4]. Next to that, prior measurements of passive wrist stiffness were reported in the range of <0.15 - 3 Nm/rad [40]–[44]. Whereas Klomp et al. found a stiffness for a paretic stroke patient at the rest angle of 2.8 Nm/rad [11]. No further information about the passive wrist stiffness in stroke patients is yet available. However, the passive joint stiffness (K_{joint}) found this study falls in the range of measurements from most prior studies [11], [40]–[44].

Difference in modelled joint stiffness with earlier reported joint stiffness of the model can be caused by the fact that we applied the optimization procedure over a comprehensive movement, i.e. with multiple flexion and extension sweeps at multiple velocities, while earlier publications applied the optimization procedure over extension and flexion angles separately, while fast and slow stretch velocities were separated for the optimization procedure [4], [8], [26].

Since spasticity is highly dependent on velocity, inclusion of multiple velocities gives a better estimate of the neural component, e.g. parameters as the optimum muscle length and the activation cutoff frequency can be better estimated. Our study showed that the modeled active component was velocity dependent, i.e. the active torque of both the flexor and extensor muscles increased with speed. For the NeuroFlexor method, Lindberg et al. reported that the neural component was also velocity dependent in patients [21]. So, the fact that the neural components of both methods increase with velocity, indicates that $T_{act,fcr}$, $T_{act,ecr}$, and NC are a measure of spasticity, as defined by Lance [10].

We found a higher active torque for the FCR ($T_{act,fcr}$) for patients rated with a MAS of 3 than earlier reported with the optimization method [4], which can be attributed to the fact that our study included more severely affected patients. Whereas we found lower values for the active torque of the ECR $T_{act,ecr}$, which can be due to the high nSEM values of g_{ecr} and lo_{ecr} .

Since estimated parameters represent the physiology of the subjects, other publications also used the parameters estimated by the model (Table V) to discriminate between healthy subjects and stroke patients, e.g. the slack length of the connective tissue and optimal muscle length [4], or to compare results pre- and post-treatment [45]. However, we found evidence that the neuromechanical parameters of both methods were better able to separate patients with disease severity than the slack length or optimal muscle length (Appendix F). Since the EMG weighting factor of the FCR improved the prediction of the MAS, it would be better to use the EMG weighting factor of the FCR as a measure for the neural component rather than the slack length of the connective tissue.

4.3 Agreement of the two methods

Since the neuromechanical parameters of the NeuroFlexor are expressed in Newton [21], while the joint stiffness of the optimization method is expressed in Nm/rad, and the neural components in Nm, no absolute agreement of the parameters is expected. According to Bland and Altman, the use of correlation is misleading for assessing the agreement between two methods of clinical measurement [46]. However, we are interested in the strength of the relation (i.e. association) between the neural components or the elastic components of both methods instead of absolute agreement, so correlation analysis is best applicable to determine the agreement between the neuromechanical parameters of both methods.

The fact that Pearson correlation between NC and $T_{act,fcr}$ was strong, while the correlation of the NC with $T_{act,ecr}$ was very weak, was in line with our expectations since the NeuroFlexor device only applies a movement in flexion direction and thus will

be incapable of measuring the active component of the ECR. Next to that, $T_{act,ecr}$ was assumed to be the least valid due to the low nSEM values of g_{ecr} and lo_{ecr}.

Since the Pearson correlation between the elastic component of the NeuroFlexor and K_{joint} was strong, the NeuroFlexor method is able to determine the elastic component when only perturbing the wrist in the extension direction.

Unfortunately, any modeling or device defects that limit the validity of one method will affect the validity analysis of the other. Due to a lack of a gold standard, we discussed the content validity, i.e. the degree to which the instrument logically appears to measure the neuromechanical parameters, to conclude which method causes the discrepancies and in which method a bias might be present.

To calculate the neural component, Lindberg et al. [21] take the second force peak (P2, Figure D14) and subtract the inertia, viscosity and elastic force from the total force. Therefore, any errors in the preceding force components will lead to an error in the neural component (NC), leading to a less reliable neural component.

The force peak used to calculate the neural component (P2) is taken 211 ms after the initial stretch. However, an average stretch reflex latency of the wrist of stroke survivors of 41 ms was reported [25], while others report a long latency time of 55 − 100 ms after the onset of the displacement [47], [48]. Although the stretch reflex might have an influence on the oscillation of the device, this will not have a direct relationship with the force peak P2. Moreover, the inertia of the device was calculated with a constant acceleration of 21 m/s^2 for each patient [21], which may also differ for each patient and thus has an influence on the neural component (Equations D3 − D6). So we can conclude that the NeuroFlexor model makes general assumptions about muscle physiology for estimating the neural component and thus, the neural component lacks content validity.

In contradiction, the optimization method takes into account the EMG activity, together with the torque response to predict whether there is active torque present. Therefore, we assume that the discrepancy between the neural components, i.e. NC and $T_{act,fcr}$, can be attributed to the lack of content validity of the NeuroFlexor method.

Since the amount of force at the end of the slow movement is equal to EC, the elastic component of the NeuroFlexor method is just an instrumented way of measuring the passive resistance to motion. Although there is not made a distinction between the neural and intrinsic component during the quantification of EC, the neural component is thought to contribute little during the slow stretch [25], [49]. The the optimization method tries to declare the intrinsic component by modelling the passive stiffness of the muscles while taking into account the muscle mechanics and the force response. So neither the intrinsic component (EC) of the NeuroFlexor, or the intrinsic component of the optimization method (K_{joint}) lacks content validity.

Next to our content validity analysis, we are not able to conclude which method is more able to estimate valid neuromechanical parameters due to the absence of a golden standard. So, regarding the validity of both methods, none of them would be preferred with our current knowledge.

4.4 Agreement with clinical measures

Since the MAS has a low validity and reliability [15]–[20], one should be careful when interpreting the results of the multiple linear regression analysis for describing the MAS. Unfortunately, we were forced to validate the neuromechanical parameters by comparing them to the MAS since no appropriate golden standard is yet present. The main purpose was to compare the MAS ratings with the components of wrist hyper-resistance.

In this study, we found that the neural component (NC) and the elastic component (EC) of the NeuroFlexor method increased with the MAS, where they were moderately correlated. This agrees with an earlier validation study with the MAS, whereas the correlation between NC and the MAS found during this study was slightly less strong then found earlier (r $>$ 0.6) [21]. In this study, we also found increased values for K_{joint} and $T_{act,fcr}$ with elevated MAS, which are comparable with results found earlier [4], [26]. Our results showed a more detailed distinction with disease severity, which provides more insight into the development of wrist hyper-resistance with increasing disease severity.

From the stepwise linear regression analysis we found that both NC and EC were significant estimators of the MAS for the NeuroFlexor method. Likewise, we found that $T_{act,fcr}$ and K_{joint} were significant estimators for the optimization method. This agrees with the fact that the MAS does not distinguish between the two components [17], [28] and thus the MAS is spread out over the elastic component and the neural component. Both methods were able to describe the MAS by their neural and elastic component at a similar degree (($r^2 = 0.466$ of the NeuroFlexor method vs. a $r^2 = 0.519$ of the optimization method). The fact that the neuromechanical parameters of the optimization method are slightly more able to declare the variance of the MAS than the NeuroFlexor method, which was as we hypothesized, can be attributed to the fact that the neural component of the optimization method contributes more to the MAS than the neural component of the NeuroFlexor method ($\beta = 0.594$ vs. $\beta = 0.490$, respectively), while the intrinsic components contributed about the same ($\beta = 0.310$ vs $\beta = 0.307$, respectively). However when the methods are used separately, none of the methods would be advantageous in terms of validity with the MAS since both methods were able to describe the declared variance of the MAS at an approximately similar degree.

When we look at how well the neuromechanical parameters of the two methods simultaneously are able to describe the MAS, we found that EC and $T_{act,fcr}$ together are more able to predict the MAS than the neuromechanical parameters of the methods separately. This indicates that EC is more able to describe the MAS than K_{joint}. Likewise, $T_{act,fcr}$ is more able to describe the MAS than NC. However, EC is just an instrumented way of measuring the MAS, and thus it is expected that the EC describes the MAS more than K_{joint}. The fact that $T_{act,fcr}$ contributes the most when predicting the MAS (Table VII, Table VIII and Table F5), implies that the neural component obtained with the optimization method is the best estimate of the neural component of joint hyper-resistance. Though the Spearman correlation coefficients of the NC and EC where higher than the coefficient of $T_{act,fcr}$, we conclude from the multiple regression analysis that most information is given by $T_{act,fcr}$. Therefore, the neural component of the optimization method is expected to be more

valid than the neural component of the NeuroFlexor method, which agrees with our conclusion about the construct validity of the NeuroFlexor. We can conclude that the neural component can be estimated more accurately with the optimization method, and thus addition of EMG signals would contribute to a valid estimation of the neural component.

From the Kruskal-Wallis analysis we can conclude that both methods are able to discriminate between the neural component of joint hyper-resistance with disease grade. Whereas the NeuroFlexor method is more able to discriminate between the intrinsic component with different MAS than the optimization method. So questions arise about the validity of K_{joint}. An earlier study reported significant difference between K_{joint} with the MAS grade [4]. However, they only made distinction between a MAS of zero and MAS greater or equal to 1 [4].

In this study, a clear example was provided of why biomechanical measurement methods are preferred over subjective clinical scales. Namely, since we expect that the pROM decreases with increasing stiffness, the poor correlation of pROM_g with EC and K_{joint}, and the strong correlation of pROM_w with EC and K_{joint} indicate that pROM_g lacks validity. The lack of agreement between pROM_g and pROM_w can be caused by inconsistent forces used in assessing the pROM, the positioning of the goniometer or due to the lack of reliability between different raters [50].

4.5 Healthy subject data

To discuss whether the model structure of the NeuroFlexor method is able to quantify valid neuromechanical parameters, the neuromechanical parameters were estimated by applying the optimization model on the data obtained from 11 healthy subjects with the NeuroFlexor device. The low VAF values for the fast stretch are caused by the fact that the remaining force response (Figure H17) shows an oscillation and thus does not represent the expected force response to passive stretch, which was modeled as an exponentially increasing function with increasing angle in the optimization method. Since the angle is not oscillating and thus represents the applied angle, the optimization model is not able to model the inertia of the device. From this, we can conclude that position of the NeuroFlexor device is not controlled properly and that the estimated parameters are based on the oscillation amplitude of the NeuroFlexor. Although the joint stiffness could be determined from the slow stretch, a fast stretch is minimally needed to determine the neural component [51]. So, we were not able to determine the neural component of wrist hyper-resistance from the NeuroFlexor data with the optimization method. Yet, joint stiffness of the healthy subject was lower than the joint stiffness of stroke survivors.

Our findings do not agree with an earlier published article of Wang et al. [52], were they also applied a neuromusculoskeletal model (optimization model) on data obtained with the NeuroFlexor. Contradicting to our low VAF values for the fast stretch, they found high VAF values for both the slow stretch and fast stretch [52]. However, the optimization was only performed for a selected part of the force curve from the fast movement (from the second force peak, P2, to the third force peak, P3), i.e. during which the angular velocity remained stable. From this, we conclude that the method of Wang et al. for determining the neuromechanical parameters during the fast stretch is too generalized, and our low VAF values are correct.

4.6 Strengths and limitations

Since no appropriate golden standard is available that discriminates between the neural and intrinsic components of joint hyper-resistance, the validation with the MAS should be treated with caution and we are not able to conclude which neuromechanical parameters are valid regarding the current knowledge. Despite, our results showed a more detailed distinction of the neuromechanical parameters with disease severity.

During our study, the entire clinically meaningful measurement range was not completely covered, since a MAS score of 4 is lacking. However with a MAS score of 4, one is probably not able to participate with the NeuroFlexor and Wristalyzer measurement due to the limited range of motion, since a MAS score of 4 is equivalent with a rigid joint. In case of the NeuroFlexor measurements, a minimum wrist range of 50° is necessary, while during the optimization method the extension angle of the pROM_w had to be larger than 0° to perform the sweep protocol. So for both measurement techniques, patients with a severe contracted wrist are thus excluded.

Although the MAS was rated by experienced physicians, we were not able to grade the MAS by the same physician and in total three different persons rated the MAS. So intra-rater differences could be present between the MAS of different patients.

The forearm was pronated during the NeuroFlexor measurement, while the forearm was in neutral position during the measurement of the optimization method with the Wristalyzer. Since Kane et al. showed that there is no statistically significant difference in the position of the forearm and the passive ROM of the wrist [53] and since the sarcomere length of the ECR does not vary with forearm position [54], we assumed that the position of the forearm did not influence the neuromechanical parameters.

For the assessment of the contribution of the neuromechanical parameters to the MAS, we used a multiple linear regression model. This model assumes that the dependent variable is a continuous variable, which is not the case for MAS. Although the MAS has been treated as a continuous scale in earlier publications [18], [55], [56], Pandyan et al. stated that the MAS should be used as ordinal scale [28]. Therefore also an ordinal logistic regression analysis with a backward prediction model was conducted. This analysis is presented in Appendix J. From this analysis, we see that that for both methods separately, the neural and intrinsic component are significant estimators, which we also found in the multiple linear regression analysis. Also, we found that EC and $T_{act,fcr}$ were significant estimators of the MAS, where the active torque of FCR ($T_{act,fcr}$ of the optimization method was the strongest predictor and contributed most to the odds of having a higher MAS value. Furthermore, the strength of association between the MAS and independent variables was about the same for the linear regression model and the ordinal logistic model for the NeuroFlexor method (R^2_N of 0.483 vs. a R^2 of 0.440), the optimization method (R^2_N of 0.503 vs. a R^2 of 0.496), and for the NeuroFlexor and optimization

method together (R^2_N of 0.597 vs. a R^2 of 0.586). Although we did not found a reliable model with the ordinal logistic regression analysis when the additional parameters of the optimization method where added, we can conclude that the multiple linear regression method and ordinal logistic regression method give the same results when comparing the neuromechanical parameters of both methods. This implies that our results of the multiple linear regression analysis are justified.

Sensitivity analysis of the optimization method to local minima was only performed at five randomly selected patients. However, since modeled parameters did not differ from the parameters obtained with the original procedure, we concluded that the model is not sensitive to the initial parameter values.

4.6.1 EMG signals

The EMG signal is assumed to consist out of varying muscle activation, offset muscle activation and measurement noise (Figure 11). Varying muscle activation consists of reflexive responses to the imposed positional perturbation and voluntary activation. Whereas the offset activation is the constant neural firing of muscles, defining the minimum muscle contraction.

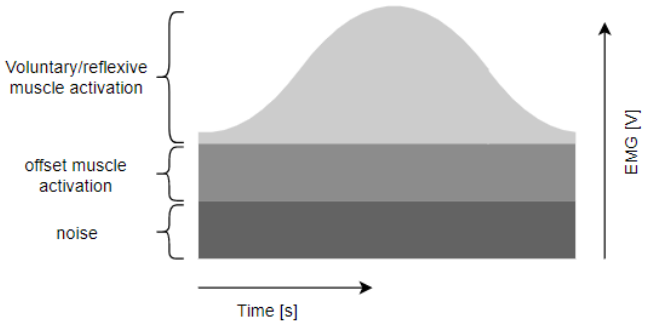


Figure 11. Composition of the EMG signal; offset muscle activation, voluntary / reflexive muscle activation and measurement noise.

The model has to take offset muscle activity into account to estimate active forces caused by offset muscle activity. When all offset muscle activity would be removed, the active torque may be underestimated. Unfortunately, measurement noise and background muscle activity are difficult to distinguish from each other. Therefore, not all background noise will be eliminated that may be present in the EMG signals. Despite that, the active components still increase with increasing velocity, meaning that the active torque mainly describes the reflexive torque. Therefore, we assumed that the influences of the measurement noise are small and had a negligible influence on the neuromechanical parameters of the optimization method.

Although, EMG signals are highly variable and may be influenced by placement of the EMG electrodes, tissue characteristics, e.g. skin differences, activity of other neighboring muscles, and background/environment noise [57], our results demonstrated that measurement of EMG activity contributes to the quantification of the neural component of joint hyper resistance.

4.6.2 Determination of the pROM$_w$

In the optimization method, the ramp-and-hold movements were performed over the whole pROM$_w$. However, in some patients, the pROM$_w$ was larger than could be measured due to the hardware stops of the Wristalyzer. Next to that, stretch-induced muscle activity might have affected the pROM$_w$ measurement. Since the EMG signal increased at 2 Nm extension compared to the EMG signal at zero torque. However, EMG increments during the pROM$_w$ measurements were small compared to EMG increments during the RaH measurements. Thus, the increased EMG signal during the pROM$_w$ measurement is considered to have a negligible effect on the reported pROM$_w$ values.

4.7 Clinical implications

The NeuroFlexor method and optimization method used in this study, with separation of the neuromuscular components contributing to the joint hyper-resistance, improve the diagnosis of impaired wrist functioning following stroke. By separation of the intrinsic and neural components, the clinician would have a better indication for the optimal treatment. Since the MAS does not discriminate between the two components contributing to joint hyper-resistance, our results show that the bio-mechanical modelling devices provide a better alternative then the MAS. Next to that, biomechanical measurement methods are more reliable than clinical measurements.

The NeuroFlexor method and optimization method showed strong correlation. This is highly beneficial for clinical purpose, since the NeuroFlexor device is easy applicable, e.g. the measurement takes little time and the device is more portable. Furthermore, no EMG-recording is required. Next to that, the optimization method needs time consuming off-line data analysis, while the neuromechanical parameters from the NeuroFlexor measurement can be directly calculated after the measurements. With direct results of the NeuroFlexor a clinician should be directly able to start the treatment.

4.8 Implications for future work

For future research, a method that can distinguish between offset muscle activation and reflexive muscle activation would be desirable such that only the reflexive muscle activation is a measure of the neural component. Since during this study, baseline activity also contributed to the neural component of the optimization model.

During this study, the sensitivity of the outcome parameters to variability and uncertainty in model structure of the optimization method is not explored systematically. To quantify the sensitivity of the outcome parameters of the optimization method to variability Monte Carlo approaches could be used, as has been done before in other biomechanical modeling studies [58]–[60]. Next to that, the optimization model could be expanded by taking into account the thixotropic properties of a muscle. Therefore

a history-dependent model should be built, since 15 s of rest following a stirring manoeuvre is needed to restore most of the initial short-range stiffness [42].

To check whether the model structure of the NeuroFlexor method is comprehensive enough, neuromechanical parameters could be determined from the NeuroFlexor data with the optimization model. Therefore, the optimization model should be expanded by a mass-spring-damper system such that the oscillation and damping of the device are separately modeled. Hereby you would be able to compare the neuromechanical parameters when no measurement or device differences are present. Although addition of EMG signals makes the device less clinically appealing, this would lead to better validation of the neural component and tell us whether EMG provides more information when determining the neural component.

Although our study contributed to the validation of biomechanical modeling methods and is a step in the right direction, still no appropriate golden standard is available that discriminates between the neural and intrinsic components of joint hyper-resistance. Further research needs to be done on validation of the two components of wrist hyper-resistance and on optimization of the methods. Since the active component of the flexor carpi radialis, modelled with the optimization model, and the elastic component of the NeuroFlexor method are more able to describe the MAS than the neuromechanical parameters of the two methods separately, questions arise whether the neural component of the optimization model and the elastic component of the NeuroFlexor are more valid. Therefore, more research is necessary for the validation of the neural component of the NeuroFlexor and the elastic component of the optimization method.

To check the responsiveness of both methods, i.e. to check whether the methods are sensitive to changes, the neuromechanical parameters could be estimated over a longitudinal data set and it could be checked whether the neuromechanical parameters of both methods are sensitive to treatment.

4.9 Recommendations

The use of biomechanical techniques for quantifying the neuromechanical parameters makes it possible to separate the neural and mechanical components. Furthermore, we found that the NeuroFlexor is a reliable method to obtain the neuromechanical parameters of wrist hyper-resistance. Since the neuromechanical parameters of both methods were strongly correlated, the NeuroFlexor method is easier applicable, we advocate the use of the NeuroFlexor device for clinical purposes.

5. Conclusion

The NeuroFlexor method and optimization method enabled us to estimate the neural and intrinsic component of wrist hyper-resistance. Conclusions are summarized as follows:

- The NeuroFlexor method reliably estimates the neuromechanical parameters of wrist hyper-resistance.
- Both the neural components and the intrinsic components of the Neuroflexor and optimization method were strongly correlated.
- For both methods separately, both the neural and intrinsic component were significant predictors of the MAS.
- The neural component of the optimization method together with the intrinsic component of the NeuroFlexor method were more able to predict the MAS than the methods separately.
- The active component of the optimization method contributed the most out of all parameters in predicting the MAS, so addition of muscle EMG contributes to a valid estimation of the neural component.
- Patients with an elevated MAS differed through an increased neural and intrinsic component of the NeuroFlexor, and though an increased neural component of the optimization method.
- Further research is needed to establish the validity of the neural component of the NeuroFlexor method and the intrinsic component of the optimization method.

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A Modified Ashworth Scale

Table A1. The MAS grades muscle hyper-resistance according to six ordinal levels.

Grade	Description
0	no increase in muscle tone
1	slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	more marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	considerable increase in muscle tone, passive movement difficult
4	affected part(s) rigid in flexion or extension

B Data Acquisition with the Wristalyzer

Information about the Wristalyzer setup for acquisition of the EMG, torque, and angular signals is depicted in Figure B12. Furthermore, additional parameters of the Wristalyzer control settings are described in Table B2.

Table B2. Wristalyzer settings

Parameter	Value
Stiffness [Nm/rad]	85
Damping factor [Nm · s/rad]	1
Max damping [Nm · s /rad]	0.5
Counter-force factor [N]	0.99

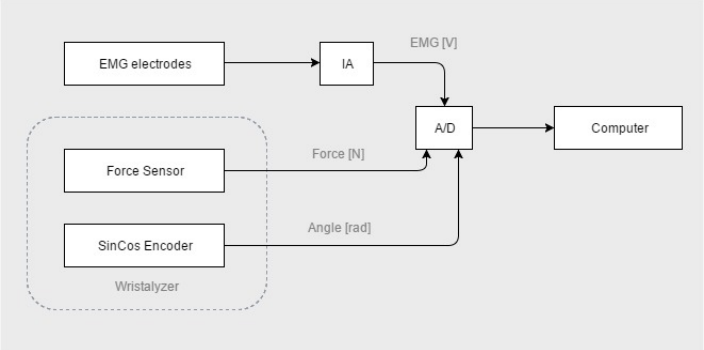


Figure B12. Data Acquisition during Wristalyzer measurement. EMG signals were recorded by making use of surface electrodes, which was thereafter amplified by an instrumented amplifier (IA). The exerted force on the Wristalyzer was measured by a force sensor and the angle was recorded by the SinCos encoder. The EMG signals, the force signal and the angle of the Wristalyzer were sent to an A/D converter and thereafter sent to the computer.

C System identification and parameter optimization procedure

The non-linear parametrical method estimates the model parameters by minimizing the error function between the measured torque and estimated torque. The error function is defined as

$$\mathbf{e} = \mathbf{T} - \hat{\mathbf{T}}, \tag{C1}$$

of which $\mathbf{e}$ is the error vector, $\mathbf{T}$ the true outcome signal and $\hat{\mathbf{T}}$ the modeled outcome parameter. Reducing the error function goes as follows;

I. First guess of initial parameters for the model.
II. Give upper bound and lower bound for the parameters.
III. Minimize the error function $\mathbf{e}$ between the true output signal and estimated output.
IV. If the total error is less than the default value, then quit and the parameters are optimal. Else, repeat step III until the total error is reduced.

This system identification and parameter optimization method is visualized in Figure C13.

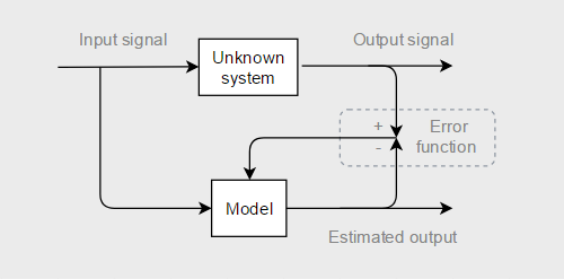


Figure C13. Schematic view of the system identification and parameter estimation method.

D Model descriptions

D. 1 *Neuroflexor model*

In the model of Lindberg et al. the total resisting force F is the summation of passive elastic force F_p, viscous force F_v, inertial forces of the limb and device F_{in} and reflexive force F_{act}

$$F(\theta) = F_p(\theta) + F_v(\theta) + F_{act}(\theta) + F_{in}(\theta), \tag{D2}$$

where θ denotes the angle of the device [21].

Firstly, the elastic component (EC) was recorded at the end of the slow movement, such that the length-dependent elasticity is estimated while minimizing the contribution of the stretch reflex. The EC corresponds to P3, i.e. the fully stretched position during the slow movement (Figure D14).

The inertia component (IC) corresponds to the force resisting to the acceleration of the hand and was calculated in the model as

$$IC = m \times a, \tag{D3}$$

where IC is the inertia, m the mass of the platform and hand, and a the angular acceleration of the device, equal to 21 m/s^2 [21]. The mass of the hand was estimated as 0.6% of the total body weight.

The viscosity is produced by the friction from tissues, and increases with increasing velocity. Lindberg et al. assumed that the viscosity component (VC) is highest during the initial acceleration and continues at a lower level during further stretching. P1 is defined as the maximum of the first force peak during the initial acceleration (Figure D14). To calculate the viscosity component, first, the early viscosity component (VC_{P1}) was calculated

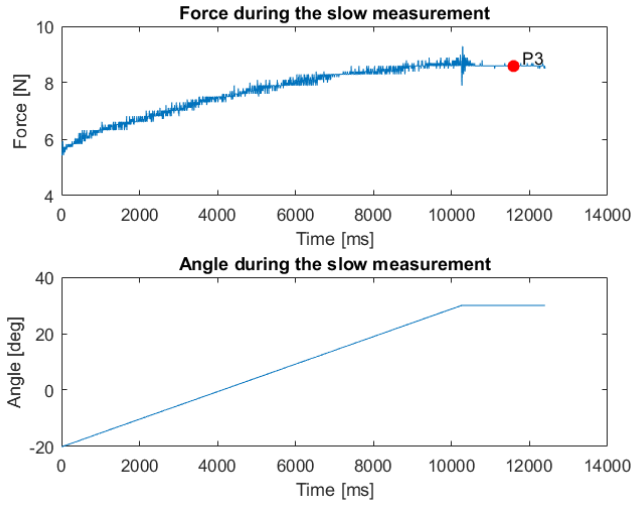
$$VC_{P1} = Totalforce_{P1} - IC, \tag{D4}$$

where $Totalforce_{P1}$ is the maximum force at P1 (Figure D14), and IC the inertial component calculated as above [21]. Since there is a comparatively stable relationship between the early and late viscosity, where Lindberg et al. assumed the late viscosity is approximately 20% of the early viscosity [21], [61]

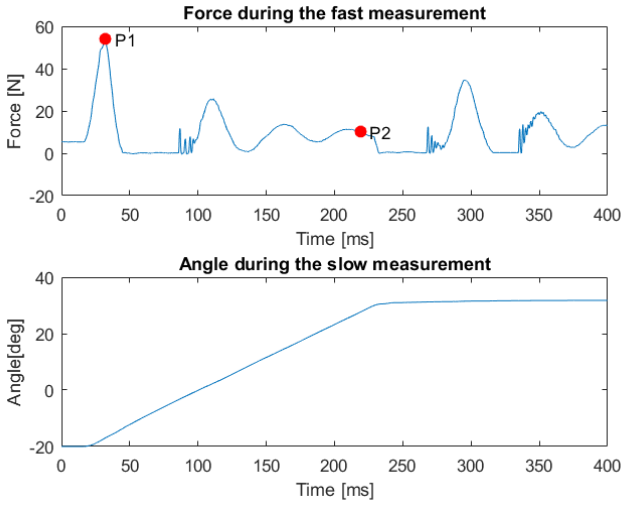
$$VC = VC_{P1} \times 0.2. \tag{D5}$$

Finally, P2 is defined as the late force peak during the stretch (Figure D14) and consists of the neural, viscous and elastic component together. Thus, the neural component (NC) was estimated by

$$NC = Totalforce_{P2} - (EC + VC). \tag{D6}$$



(a) Slow measurement



(b) Fast measurement

Figure D14. Neuroflexor measurement: (a) Graph of total force over time during a slow (5°/s) movement (upper graph) and a graph of the angle of the device during a slow measurement (lower graph). (b) Graph of total force over time during a fast (236°/s) movement (upper graph) and a graph of the angle of the device during a fast measurement (lower graph). Where P1 stands for the first force peak of the fast movement, P2 for the late peak during stretch, and P3 at the fully stretched position during the slow movement.

D. 1.1 *Optimization model*

The model used in this study is based on the ankle model of de Vlugt et al. [26], which is later on extended by de Gooijer et al. to a bidirectional wrist model [4]. The torque generated during passive RaH movements of the wrist was modeled by

$$\hat{T}(t) = I\ddot{\theta}(t) + T_{ext}(t) - T_{flex}(t), \tag{D7}$$

with t the time in seconds $[s]$, $\hat{T}$ the modeled wrist torque $[Nm]$, I the inertia of the wrist and handle $[kg \cdot m^2]$, $\ddot{\theta}$ the angular acceleration $[rad/s^2]$, T_{ext} the torque generated by the extensor carpi radialis $[Nm]$ and T_{flex} the torque generated by the flexor carpi radialis $[Nm]$. Muscle torques were divided in torques generated by the elastic force of the connective tissues (F_e) and the active muscle forces (F_{act}):

$$\begin{aligned} T_{ext}(\theta,t) &= (F_{e,ecr}(l_{ecr}) + F_{act,ecr}(v_{ecr}, l_{ecr}, \alpha_{ecr}))r_{ecr}(\theta) \\ T_{flex}(\theta,t) &= (F_{e,fcr}(l_{fcr}) + F_{act,fcr}(v_{fcr}, l_{fcr}, \alpha_{fcr}))r_{fcr}(\theta), \end{aligned} \tag{D8}$$

with T_{ext} and T_{flex} the modeled torque $[Nm]$, $F_{e,ecr}$ and $F_{e,fcr}$ the elastic (passive) force $[N]$, v_{ecr} and v_{fcr} the lengthening velocity $[m/s]$, l_{ecr} and l_{fcr} the muscle length $[m]$, α_{ecr} and α_{fcr} the active state $[-]$, r_{ecr} and r_{fcr} the moment arm of the tendon $[m]$, of the ECR resp. the FCR, and θ the angular position of the Wristalyzer $[rad]$.

Passive properties The elastic force, i.e. $F_{e_0,ecr}$ and $F_{e_0,fcr}$ of the muscles were modeled as follows

$$\begin{aligned} F_{e_0,ecr}(t) &= e^{k_{ecr}(l_{ecr}(\theta) - l_{slack,ecr})} \\ F_{e_0,fcr}(t) &= e^{k_{fcr}(l_{fcr}(\theta) - l_{slack,fcr})}, \end{aligned} \tag{D9}$$

where k_{ecr} and k_{ecr} are the stiffness coefficients of the ECR resp. the FCR $[1/m]$, $l_{slack,ecr}$ and $l_{slack,fcr}$ the estimated slack lengths of the connective tissue of the ECR resp the FCR $[m]$, and x_{ecr} and x_{fcr} the muscle length of the ECR resp. the FCR $[m]$. Increased tissue stiffness can be described by Equation D9 as a steeper (or shifted) force-length relationship.

The relaxation dynamics were modeled by a first order filter, resulting in elastic forces modeled by

$$\begin{aligned} F_{e,ecr}(t) &= \frac{\tau_{rel}s + 1}{\tau_{rel} + 1 + k_{rel}} \cdot F_{e_0,ecr}(s) \\ F_{e,fcr}(t) &= \frac{\tau_{rel}s + 1}{\tau_{rel} + 1 + k_{rel}} \cdot F_{e_0,fcr}(s), \end{aligned} \tag{D10}$$

with k_{rel} the estimated relaxation factor $[-]$ of the tissue, s the Laplace operator, and τ_{rel} the estimated tissue relaxation time $[s]$. Finally, elastic forces in negative direction were set to zero, as the tissue can only exert pulling forces.

The muscle length of the extensor carpi radialis (ECR) and flexor carpi radialis (FCR) were determined by

$$l_{ecr} = l_{0*,ecr} + r_{ecr}(\theta)\theta \tag{D11}$$

$$l_{fcr} = l_{0*,fcr} - r_{fcr}(\theta)\theta, \tag{D12}$$

with l_{ecr} and l_{fcr} the length of the ECR respectively FCR $[m]$, $l_{0*,ecr}$ and $l_{0*,fcr}$ the muscle lengths of the ECR respectively FCR at zero degrees wrist angle position (handle in line with the forearm). The zero muscle lengths are 6.3 cm for the FCR and 7.0 cm for the ECR (average of ECR longus and brevis, optimal fiber lengths from [4], [62], [63]. Positive values for θ [rad] denote flexion direction, and thus positive values for θ denote lengthening of the extensor carpi radialis and shortening of the flexor carpi radialis.

The moment arms of the extensor carpi radialis (r_{ecr}) and the flexor carpi radials (r_{fcr}) were assumed to scale linearly with joint angle, and defined using the equations of Ramsay et al. [4], [64].

$$r_{ecr,brevis} = (13.4337 - 2.1411\theta) \cdot 10^{-3} \quad \text{for } \theta < 10° \tag{D13}$$

$$r_{ecr,longus} = (11.7166 - 2.2850\theta) \cdot 10^{-3} \quad \text{for } \theta > 10° \tag{D14}$$

$$r_{ecr} = (r_{ecr,brevis} + r_{ecr,longus})/2 \tag{D15}$$

$$r_{fcr} = (13.2040 + 1.5995\theta) \cdot 10^{-3} \quad \text{for } \theta > -10°, \tag{D16}$$

Active properties To compute the active force generated by the extensor carpi radialis ($F_{act,ecr}$) and flexor carpi radialis ($F_{act,fcr}$), a Hill-type muscle model was used

$$F_{act,ecr} = f_{v,ecr}(v_{ecr}) f_{l,ecr}(l_{ecr}, l_{o,ecr}) \alpha_{ecr} \tag{D17}$$

$$F_{act,fcr} = f_{v,fcr}(v_{fcr}) f_{l,fcr}(l_{fcr}, l_{o,fcr}) \alpha_{fcr}, \tag{D18}$$

where $f_{v,ecr}$ and $f_{v,fcr}$ are the force-velocity relationships, $f_{l,ecr}$ and $f_{l,fcr}$ the force-length relationships, $l_{o,ecr}$ and $l_{o,fcr}$ the estimated optimal muscle lengths $[m]$ and α_{ecr} and α_{fcr} the active state of the muscle $[-]$, of the ECR resp. the FCR [4]. The force-length relationship was dependent on whether the muscle lengthened $v > 0$ or shortened $v < 0$ [65]:

$$f_{v,ecr}(v_{ecr}) = \begin{cases} 1 - \frac{(1 + m_{vsh} \cdot m_{vshl}) \cdot (f_{ecc} - 1) \cdot v_{ecr}}{m_{vsh} \cdot m_{vshl} \cdot v_{max,ecr} + v_{ecr}} & \text{if } v_{ecr} \geq 0 \\ \frac{v_{ecr} + v_{max,ecr}}{\frac{v_{ecr}}{m_{vsh}} - v_{max,ecr}} & \text{if } v_{ecr} < 0 \end{cases} \tag{D19}$$

$$f_{v,fcr}(v_{fcr}) = \begin{cases} 1 - \frac{(1 + m_{vsh} \cdot m_{vshl}) \cdot (f_{ecc} - 1) \cdot v_{fcr}}{m_{vsh} \cdot m_{vshl} \cdot v_{max,fcr} + v_{fcr}} & \text{if } v_{fcr} \geq 0 \\ \frac{v_{fcr} + v_{max,fcr}}{\frac{v_{fcr}}{m_{vsh}} - v_{max,fcr}} & \text{if } v_{fcr} < 0 \end{cases} \tag{D20}$$

with $m_{max,ecr}$ the maximum shortening velocity, which was 8 times the optimal muscle length [4], [65], the maximum eccentric force f_{ecc} was 1.5 times the isometric force and the isometric force was normalized to 1 because the force had been scaled by the weighting factors EMG weighing factors g_{ecr} and g_{fcr}. Furthermore, m_{vsh} and m_{vshl} are shaping factors with values 0.25 and 0.5 respectively.

The optimal muscle lengths were used to estimate the force-length relationship.

$$f_{l,ecr}(l_{ecr}, l_{o,ecr}) = e^{-(l_{ecr} - l_{o,ecr})^2 / w_{ecr}} \tag{D21}$$

$$f_{l,fcr}(l_{fcr}, l_{o,fcr}) = e^{-(l_{fcr} - l_{o,fcr})^2 / w_{fcr}}, \tag{D22}$$

with w_{ecr} and w_{fcr} the shape factors, defined as:

$$w_{ecr} = cf \cdot l_{o,ecr}^2 \tag{D23}$$

$$w_{fcr} = cf \cdot l_{o,fcr}^2 \tag{D24}$$

with cf the shape parameter of the force-length relationship with value 0.1 to resemble the force-generating range of the FCR

and ECR. The active state of the muscle was obtained by filtering the weighted EMG signals by a linear second order filter

$$\alpha_{ecr}(t) = \frac{\omega_0^2}{s^2 + 2\beta\omega_0 s + \omega_0^2} g_{ecr} EMG_{ecr}(s) \tag{D25}$$

$$\alpha_{fcr}(t) = \frac{\omega_0^2}{s^2 + 2\beta\omega_0 s + \omega_0^2} g_{fcr} EMG_{fcr}(s), \tag{D26}$$

$$\tag{D27}$$

where $\omega_0 = 2\pi f_0$, with f_0 the estimated cut off frequency of the activation filter, g_{ecr} and g_{fcr} are the estimated EMG weights of the ECR resp. the FCR, and EMG_{ecr} and EMG_{fcr} are the filtered EMG signals of the ECR resp. the FCR [v].

Finally, the inertial component I was modeled as follows

$$I = ml_a^2, \tag{D28}$$

with m the estimated mass of the handle and hand [kg] and l_a the distance from the rotation axis [m].

After parameter optimization, i.e. when the final parameters were obtained, stiffness at joint level (K_{joint}) and reflexive torque were calculated. The joint stiffness was taken at an angle that was the same for all subjects (θ^*), i.e. at angle 0 °.

$$K_{joint,m} = \frac{dT_{e,m}}{d\theta} = \frac{dF_{e,m} r(\theta^*)}{dx/r(\theta^*)} \tag{D29}$$

$$K_{joint,flex} = k_{fcr} e^{k_{fcr}(l_{flex}(\theta^*) - l_{slack,fcr})} r^2(\theta^*) \tag{D30}$$

$$K_{joint,ext} = k_{ecr} e^{k_{ecr}(l_{ext}(\theta^*) - l_{slack,ecr})} r^2(\theta^*) \tag{D31}$$

$$K_{joint} = K_{joint,flex} + K_{joint,ext} \tag{D32}$$

with $K_{joint,flex}$ the contribution of the FCR to the stiffness at joint level, $K_{joint,ext}$ the contribution of the ECR to the stiffness at joint level and $l_{flex}(\theta^*)$ and $l_{ext}(\theta^*)$ the muscle lengths corresponding (θ^*), m either the ECR or the FCR.

Finally, root mean square (RMS) values of parts of the modeled reflex torque (T_{act}) were calculated as a measure of the neural component

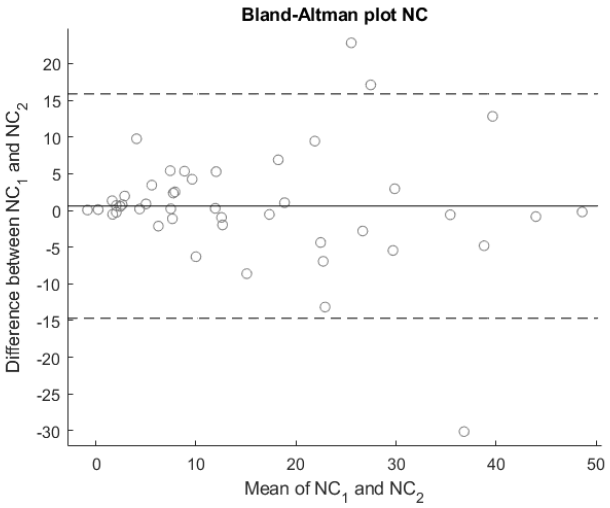
$$T_{act,ecr} = \sqrt{\frac{1}{N} \int (F_{act,ecr} r_{ecr})^2} \tag{D33}$$

$$T_{act,fcr} = \sqrt{\frac{1}{N} \int (F_{act,fcr} r_{fcr})^2}, \tag{D34}$$

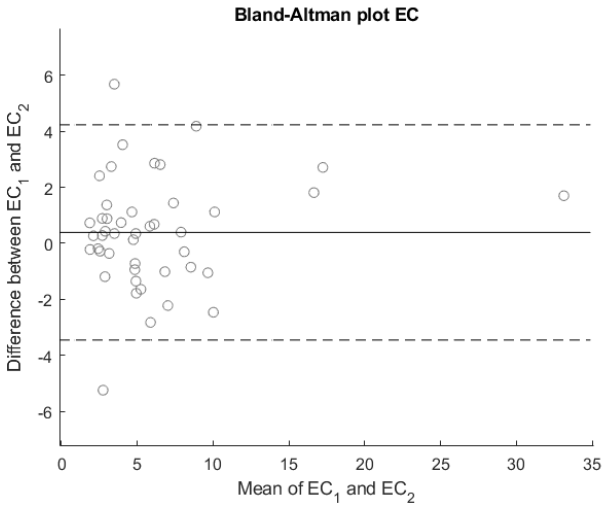
where N are the number of data points.

E Test-retest reliability NeuroFlexor method

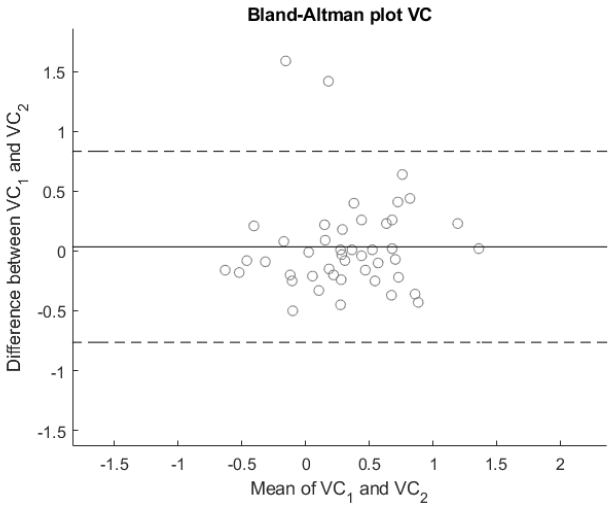
To analyse the agreement between two different measurements of NC, EC and VC, Bland-Altman plots are presented in Figure E15. Minimal detectable change (MDC) values were 15.282, 3.841, 0.799 for the NC, EC and VC, respectively. Consequently, the MDC% were 31%, 22 % and 59% for the NC, EC and VC, respectively.



(a) Neural component



(b) Elastic component



(c) Viscous component

Figure E15. Bland-Altman plots of the NeuroFlexor outcome parameters. With (a) the NC, (b) the EC and (c) the VC.

F Multiple linear regression model

To check for multicollinearity, the correlation matrix of the neuromechanical parameters was calculated. The correlation matrix is presented in Figure F3. The eigenvalues of the correlation matrix, together with their condition number K_j are presented in Table F4. The low condition numbers indicate the absence of multicollinearity.

Table F3. Correlation matrix of the neuromechanical parameters of the NeuroFlexor and optimization method (n=44).

	NC	EC	VC	$T_{act,ecr}$	$T_{act,fcr}$	K_{joint}
NC	1.000*	0.532*	0.338*	-0.021	0.656*	0.549*
EC	0.532*	1.000*	0.162	-0.258	0.161	0.648*
VC	0.338*	0.162	1.000*	-0.094	0.194	0.261
$T_{act,fcr}$	-0.021	-0.258	-0.094	1.000*	0.352*	-0.204
$T_{act,ecr}$	0.656*	0.161	0.194	0.352*	1.000*	0.193
K_{joint}	0.549*	0.648*	0.261	-0.204	0.193	1.000*

*Outcomes are statistical significant ($p < 0.05$).

Table F4. Eigenvalues λ_j of the correlation matrix, together with their condition number K_j.

j	λ_j	K_j
1	0.197	3.605
2	0.339	2.750
3	0.549	2.162
4	0.879	1.709
5	1.470	1.321
6	2.566	1.000

In Table F5, the backward prediction model of the multiple regression analysis for the neuromechanical parameters of the NeuroFlexor method and optimization method, together with the parameter outcomes of the optimization method is presented. Where B is the unstandardized coefficient and β the standardized coefficient. To save space, only the coefficients for the final model, i.e. model 16, are presented. In the previous models, a 'x' denotes that the parameter is a predictor for the model.

Table F5. Backward prediction model of the multiple regression analysis for the neuromechanical parameters of the NeuroFlexor method and optimization method, together with the parameter outcomes of the optimization method. Where B is the unstandardized coefficient and β the standardized coefficient. 'x' denotes that the parameter is a predictor for the model.

Model	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
																	B	β	p
(constant)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.569		0.004
$T_{act,fcr}$	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.678	0.574	0.000
EC	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.105	0.395	0.000
G_{fcr}	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-4.09E-05	-0.266	0.006
NC	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
f_0	x	x	x	x	x	x	x	x	x	x	x	x	x	x					
VC	x	x	x	x	x	x	x	x	x	x	x	x	x						
$T_{act,ecr}$	x	x	x	x	x	x	x	x	x	x	x	x							
$l_{o,fcr}$	x	x	x	x	x	x	x	x	x	x	x								
$l_{o,ecr}$	x	x	x	x	x	x	x	x	x	x									
$l_{slack,ecr}$	x	x	x	x	x	x	x	x	x										
$l_{slack,fcr}$	x	x	x	x	x	x	x	x											
K_{joint}	x	x	x	x	x	x	x												
m	x	x	x	x	x	x													
τ_{rel}	x	x	x	x	x														
k_{fcr}	x	x	x	x															
G_{ecr}	x	x	x																
k_{ecr}	x	x																	
k_{rel}	x																		
R^2	0.772	0.772	0.772	0.771	0.769	0.765	0.757	0.751	0.746	0.742	0.735	0.728	0.722	0.710	0.69	0.675			
R^2_{adj}	0.608	0.623	0.637	0.648	0.658	0.663	0.663	0.665	0.669	0.674	0.675	0.676	0.677	0.672	0.658	0.650			

G Bland-Altman plot pROM

To check the agreement between the passive range of motion measured subjectively with the goniometer and the passive range of motion measured with the Wristalyzer, the Bland-Altman plot was made. The Bland-Altman plot is depicted in Figure G16, where a bias of approximately 53° is visible.

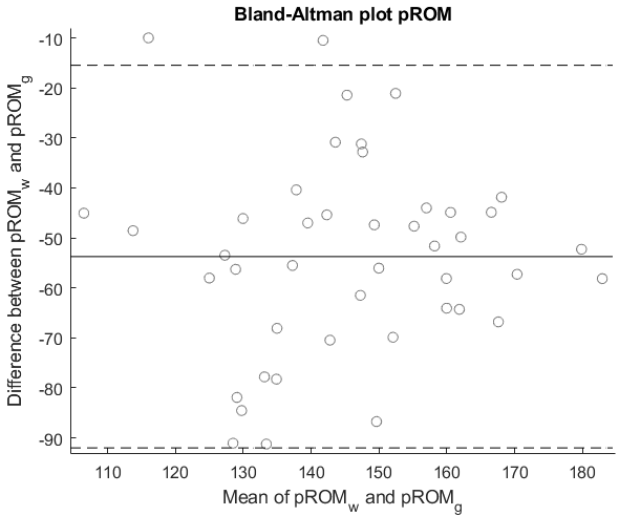
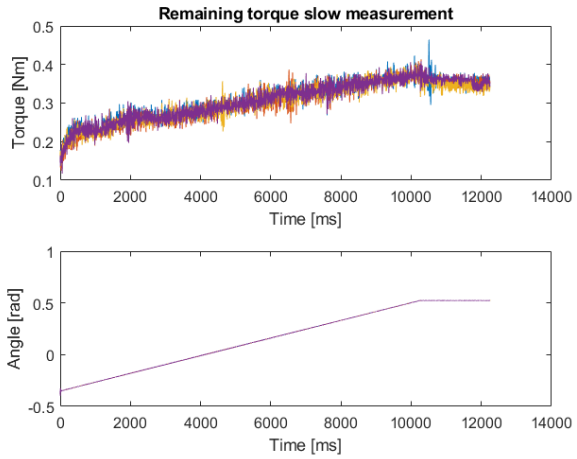


Figure G16. Bland-Altman plots of the pROM measured with the Wristalyzer (pROM$_w$) and goniometer (pROM$_g$).

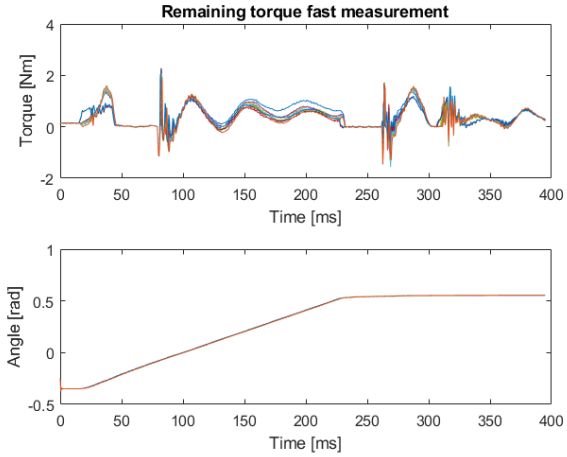
H Optimization model on NeuroFlexor data

Table H6. Neuromechanical parameters of the slow measurement

	Value (mean ± SD)
K_{joint}	0,264 ± 0,037
$T_{act,ecr}$	0,007 ± 0,004
$T_{act,fcr}$	(2,242 ± 2,495) × 10^{-9}



(a) Slow measurements



(b) Fast measurements

Figure H17. Graphs of input signals for the optimization model of the Neuroflexor data (a) Upper graph: the four remaining torque signals, i.e. the torques measured with hand minus the torque signal of the device without hand, during the slow (5°/s) stretch. Bottom graph: the angle of the device during a slow measurement. (b) Upper graph: the 9 remaining torque signals, i.e. the torques measured with hand minus the torque signal of the device without hand, during the fast (236 °/s) stretch. Bottom graph: the angles of the device during the 9 fast measurement.

Table H7. Results of the wrist optimization model on the NeuroFlexor data of one healthy subject (n=1).

	Parameters slow (mean ± SD)		Parameters fast (mean ± SD)	
	value	nSEM	value	nSEM
Intrinsic				
m	0.500 ± 0.000	0.028 ± 0.001	0.500 ± 0.000	0.056 ± 0.022
k_{ecr}	159.604 ± 15.347	0.113 ± 0.009	797.085 ± 8.744	1.750 ± 0.923
k_{fcr}	20.893 ± 0.982	0.178 ± 0.027	21.327 ± 0.637	1.550 ± 0.801
τ_{rel}	10.000 ± 0.000	(1.544 ± 2.847) × 10^6	6.633 ± 4.296	(1.053 ± 3.160) × 10^{22}
k_{rel}	0.132 ± 0.179	(1.583 ± 2.926) × 10^6	0.000 ± 0.000	(1.453 ± 2.892) × 10^{13}
$l_{slack_{ext}}$	0.059 ± 0.002	1.114 ± 0.256	0.067 ± 0.000	(1.386 ± 4.158) × 10^3
$l_{slack_{flex}}$	-0.100 ± 0.000	-4.888 ± 0.633	-0.100 ± 0.000	(-3.551 ± 1.065) × 10^5
Neural				
G_{ecr}	(2.182 ± 1.310) × 10^7	0.537 ± 0.571	(4.014 ± 1.204) × 10^7	(1.679 ± 1.036) × 10^8
G_{fcr}	2.422 ± 2.608	(1.417 ± 7.975) × 10^6	(6.508 ± 1.952) × 10^5	(2.147 ± 1.348) × 10^8
f_0	7.750 ± 4.500	23.786 ± 23.488	10.000 ± 0.000	(9.220 ± 7.565) × 10^8
$l_{o_{ecr}}$	0.040 ± 0.000	0.029 ± 0.031	0.102 ± 0.023	(3.497 ± 2.143) × 10^7
$l_{o_{fcr}}$	0.058 ± 0.035	(1.793 ± 1.973) × 10^5	0.048 ± 0.023	(1.258 ± 6.456) × 10^6

I Agreement pROM with elastic components

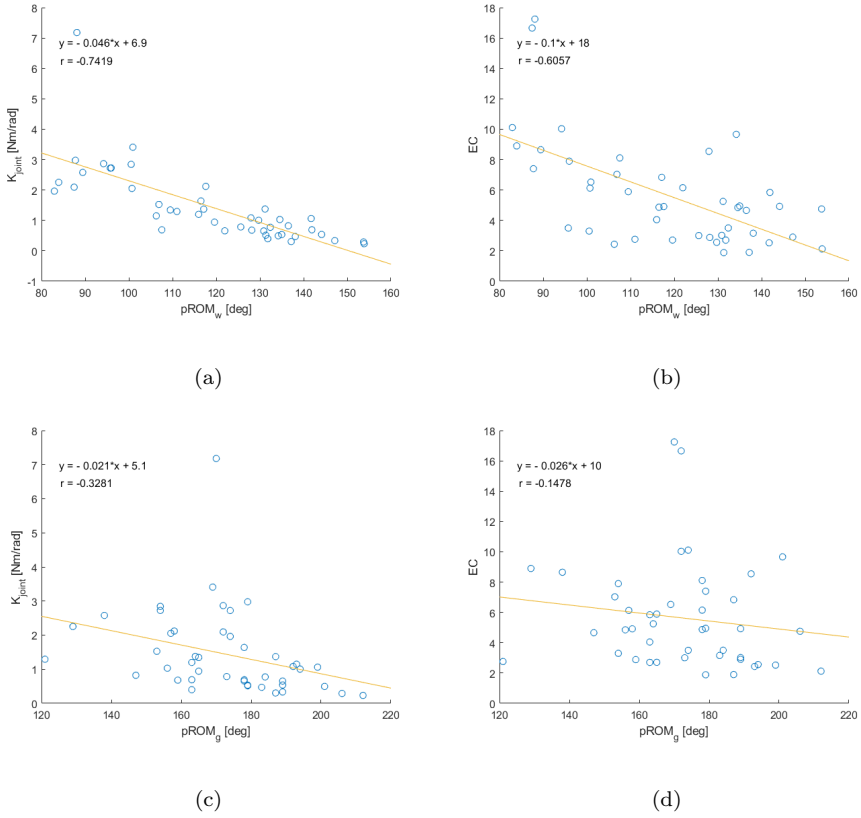


Figure I18. Linear relationship between the elastic component of the optimization method and the passive range of motions. Where (a) depicts the relation between K_{joint} and pROM$_w$, (b) the relation between EC and pROM$_w$, (c) the relation between K_{joint} and pROM$_g$, and (d) the relation between EC and pROM$_w$.

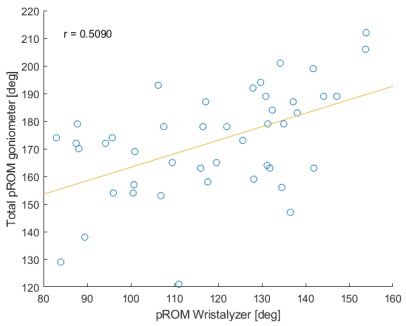


Figure I19. Linear relationship between pROM$_g$ and pROM$_w$.

J Ordinal logistic regression model

Despite we made use of a multiple linear regression model to identify the effect of the values of the neuromechanical parameters on the MAS, we also could have made use of an ordinal logistic regression model with a backwards selection procedure. The ordinal logistic regression model, is an extension of the logistic model to ordinal categorical data and takes into account the ordering of the outcome variable [66].

In an ordinal logistic regression model, the cumulative odds ratio (OR), is the only directly estimated measure of association. The OR is the ratio of cumulative odds for different predictor values. The odds for an event reflect the likelihood that the event will take place, and is calculated by the ratio of the probability that the event will occur over the probability that the same event will not occur, i.e. the cumulative odds θ_j are expressed by [67]

$$\theta_j = \frac{P(Y \leq j)}{1 - P(Y \leq j)} \tag{J35}$$

with Y the ordered dependent variable, $j \in \{1, \dots J-1\}$, and J the number of levels of Y.

Since our MAS scales are approximately evenly distributed, we use of the logit function, which is a transformation of the cumulative probabilities that allows estimation of the model. The cumulative logits are defined by [67]

$$logit(P(Y \leq j|X_1, \dots, X_n)) = \ln \frac{P(Y \leq j|X_1, \dots, X_n)}{1 - P(Y \leq j|X_1, \dots, X_n)} \tag{J36}$$

where Y is the dependent variable, $j \in \{1, \dots, J-1\}$, with J the number of scales for the dependent variable, X_n the n-th independent variable, with $n \in \{1, \dots, N\}$, with N the number of independent variables. The ordinal logistic regression model is stated as follows

$$logit(P(Y \leq j|X_1, \dots, X_n)) = \alpha_j - \sum \beta_n X_n \tag{J37}$$

where Y is the dependent variable, $j \in \{1, \dots, J-1\}$, with J the number of scales for the dependent variable, X_n the n-th independent variable, with $n \in \{1, \dots, N\}$, with N the number of independent variables, α_j represent baseline logits of conditional response probabilities, and β_n are the log odds ratios relating components of X_n to the ordered response Y.

The ordinal logistic regression model assumes that the effect of the independent variable is the same for different logit functions. That means that the results are a set of parallel planes. To check whether the final model meets this assumption, a likelihood ratio test of parallel planes was performed.

Since ordinal logistic regression does not have an equivalent to the R-squared as in linear regression, we used the pseudo R^2 of Nagelkerke (R^2_N) [68] to describe the strength of the association between the MAS and the independent variables.

Stepwise ordinal logistic regression analysis was conducted to investigate whether the NC, EC and VC predict the MAS. Table J8 shows the backward selection procedure. The final predictors accounted for a significant amount of variance in the outcome, likelihood ratio $\chi^2(2) = 27.296$, $p < 0.001$. NC ($\beta = 0.095$, SE = 0.029, OR = 1.100, p = 0.001) and EC ($\beta = 0.279$, SE = 0.107, OR = 1.321, p = 0.009) were final predictors. Each unit increase of the NC was associated with about 10% increase in the odds of the MAS having a higher value. Overall the model accounted for approximately 48% of the variance in the outcome, $R^2_N = 0.483$. The assumption of parallel planes does appear justified as the score statistic for parallel planes is small (χ^2 (6) = 1.771, p = 0.940). From the odds ratios (ORs) we can conclude that EC contributed slightly more to the odds of the MAS having a higher value than NC.

Table J8. Backward prediction model of the ordinal logistic regression analysis for predicting the MAS with the neuromechanical parameters of the NeuroFlexor method.

Variables		Model 1		Model 2	
		β	p-value	β	p-value
(Const.)	MAS_0	0.575	0.390	0.598	0.365
	MAS_1	2.333	0.001	2.362	0.001
	MAS_{1+}	3.978	0.000	4.010	0.000
	MAS_2	5.439	0.000	5.463	0.000
NC		0.096	0.001	0.095	0.001
EC		0.277	0.010	0.279	0.009
VC		-0.103	0.878	-	-
R^2_N		0.483		0.483	

Likewise, stepwise ordinal logistic regression analysis was conducted to investigate whether K_{joint}, $T_{act,fcr}$, and $T_{act,ecr}$ could predict the MAS. Table J9 shows the backward selection procedure. The final predictors accounted for a significant amount of variance in the outcome, likelihood ratio $\chi^2(2) = 28.896$, $p < 0.001$. $T_{act,fcr}$ ($\beta = 1.850$, SE = 0.475, OR = 6.360, $p < 0.001$) and K_{joint} ($\beta = 0.725$, SE = 0.305, OR = 2.065, p = 0.018) predicted the frequency of the MAS. Overall the model accounted for approximately 50% of the variance in the outcome, $R^2_N = 0.503$. The assumption of parallel planes does appear justified as the score statistic for parallel planes is small (χ^2 (7) = 4.223, p = 0.647). From the ORs we can conclude that $T_{act,fcr}$ contributed more to the odds of the MAS having a higher value than K_{joint}.

Table J9. Backward prediction model of the ordinal logistic regression analysis for predicting the MAS with the neuromechanical parameters of the optimization method.

Variables		Model 1		Model 2	
		β	p-value	β	p-value
(Const.)	MAS_0	-0.082	0.890	-0.027	0.002
	MAS_1	1.549	0.011	1.599	0.005
	MAS_{1+}	3.281	0.000	3.334	0.000
	MAS_2	4.923	0.000	4.974	0.000
K_{joint}		0.704	0.025	0.725	0.018
$T_{act,fcr}$		1.908	0.000	1.850	0.000
$T_{act,ecr}$		-1.288	0.735	-	-
R^2_N		0.504		0.503	

Thereafter, a stepwise ordinal logistic regression analysis was conducted to investigate whether NC, EC, VC, K_{joint}, $T_{act,fcr}$, and $T_{act,ecr}$ could predict the MAS. Table J10 shows the backward selection procedure. The final predictors accounted for a significant amount of variance in the outcome, likelihood ratio $\chi^2(2) = 37.253$, $p < 0.001$. Only EC ($\beta = 0.374$, SE = 0.108, OR

= 1.454, p = 0.001) and $T_{act,fcr}$ (β = 2.160, SE = 0.519, OR = 8.671, p < 0.001) were significant estimators. Overall the model accounted for approximately 60% of the variance in the outcome, $R^2_N = 0.597$. The assumption of parallel planes does appear justified as the score statistic for parallel planes is small (χ^2 (6) = 4.861, p = 0.562). From the ORs we can conclude that $T_{act,fcr}$ contributed more to the odds of the MAS having a higher value than EC.

Thereafter, a stepwise ordinal logistic regression analysis was conducted to investigate whether the neuromechanical parameters of the NeuroFlexor and optimization model together with the additional parameters could predict the MAS. Table J11 shows the backward selection procedure. The final predictors accounted for a significant amount of variance in the outcome, likelihood ratio $\chi^2(7) = 48.247$, p < 0.001. $T_{act,ecr}$ (β = 11.439, SE = 4.304, OR = 92874.092, p = 0.008), K_{joint} (β = 1.420, SE = 0.501, OR = 4.137, p = 0.005), NC (β = 0.132, SE = 0.035 , OR = 1.141, p < 0.001), m (β = -7.401, SE = 2.451, OR = 0.000, p = 0.003), $l_{slack,ecr}$ (β = -50.736, SE = 23.346 , OR = 0.000 , p =0.030), g_{fcr} (β = -2.429e-7 , SE = 1.021e-7 OR = 1.000, p = 0.017) and $l_{o,ecr}$ (β =-31.613, SE = 12.444, OR = 0.000, p =0.011) were significant estimators. Overall the model accounted for approximately 70% of the variance in the outcome, $R^2_N = 0.696$. Since the assumption of parallel planes does not appear justified, as the score statistic for parallel planes is large (χ^2 (6) = 48.247, p < 0.001), the log odds ratios β_j are not equal for each value of the dependent variable. From this we concluded that the ordinal logistic regression does not give valid results when the additional parameters are added as estimator.

Table J10. Backward prediction model of the ordinal logistic regression analysis for predicting the MAS with the neuromechanical parameters of the NeuroFlexor and optimization method.

		Model 1		Model 2		Model 3		Model 4		Model 5	
Variables		β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
(Const.)	MAS_0	1.125	0.152	1.023	0.160	0.937	0.185	0.996	0.153	0.934	0.175
	MAS_1	3.004	0.000	2.902	0.000	2.805	0.000	2.889	0.000	2.799	0.000
	MAS_{1+}	4.943	0.000	4.833	0.000	4.734	0.000	4.817	0.000	4.721	0.000
	MAS_2	6.965	0.000	6.848	0.000	6.742	0.000	6.729	0.000	6.576	0.000
$T_{act,fcr}$		1.891	0.006	1.989	0.001	1.929	0.002	1.859	0.002	2.160	0.000
EC		0.328	0.009	0.319	0.009	0.342	0.003	0.343	0.003	0.364	0.001
NC		0.032	0.408	0.029	0.443	0.038	0.291	0.0032	0.361	-	-
VC		-0.605	0.404	-0.631	0.381	-0.524	0.448	-	-	-	-
K_{joint}		0.274	0.505	0.270	0.509	-	-	-	-	-	-
$T_{act,ecr}$		1.530	0.708	-	-	-	-	-	-	-	-
R^2_N		0.615		0.614		0.610		0.605		0.597	

Table J11. Backward prediction model of the multiple regression analysis for the neuromechanical parameters of the NeuroFlexor method and optimization method, together with the parameter outcomes of the optimization method. 'x' denotes that the parameter is a predictor for the model.

	Model	1	2	3	4	5	6	7	8	9	10	11	12		
Variables														β	p-value
(Const.)	MAS_0	x	x	x	x	x	x	x	x	x	x	x	x	-9.777	0.000
	MAS_1	x	x	x	x	x	x	x	x	x	x	x	x	-7.407	0.004
	MAS_{1+}	x	x	x	x	x	x	x	x	x	x	x	x	-5.156	0.035
	MAS_2	x	x	x	x	x	x	x	x	x	x	x	x	-3.161	0.191
$T_{act,ecr}$		x	x	x	x	x	x	x	x	x	x	x	x	11.439	0.008
K_{joint}		x	x	x	x	x	x	x	x	x	x	x	x	1.420	0.005
NC		x	x	x	x	x	x	x	x	x	x	x	x	0.132	0.000
m		x	x	x	x	x	x	x	x	x	x	x	x	-7.401	0.003
$l_{slack,ecr}$		x	x	x	x	x	x	x	x	x	x	x	x	-50.736	0.030
g_{fcr}		x	x	x	x	x	x	x	x	x	x	x	x	-2.429E-7	0.017
$l_{o,ecr}$		x	x	x	x	x	x	x	x	x	x	x	x	-31.613	0.011
τ_{rel}		x	x	x	x	x	x	x	x	x	x	x			
f_0		x	x	x	x	x	x	x	x	x	x				
$l_{o,fcr}$		x	x	x	x	x	x	x	x	x					
VC		x	x	x	x	x	x	x	x						
$T_{act,fcr}$		x	x	x	x	x	x	x							
k_{ecr}		x	x	x	x	x	x								
EC		x	x	x	x	x									
$l_{slack,fcr}$		x	x	x	x										
k_{fcr}		x	x	x											
k_{rel}		x	x												
g_{ecr}		x													
R^2_N		0.813	0.812	0.806	0.800	0.794	0.788	0.776	0.758	0.743	0.730	0.717	0.696		

K TU Delft ethical approval

Date 13-12-2017
Contact person Ir. J.B.J. Groot Kormelink, secretary HREC
Telephone +31 152783260
E-mail j.b.j.grootkormelink@tudelft.nl

Human Research Ethics Committee
TU Delft
(http://hrec.tudelft.nl/)

Visiting address
Jaffalaan 5 (building 31)
2628 BX Delft

Postal address
P.O. Box 5015 2600 GA Delft
The Netherlands

Ethics Approval Application: Identification of the neural and intrinsic component of wrist hyper-resistance.
Applicant: Boessenkool, Henri

Dear Henri Boessenkool,

It is a pleasure to inform you that your application mentioned above has been approved.

Good luck with your research!

Sincerely,

Prof. Dr. Sabine Roeser
Chair Human Research Ethics Committee TU Delft

Prof.dr. Sabine Roeser
TU Delft
Head of the Ethics and Philosophy of Technology Section
Department of Values, Technology, and Innovation
Faculty of Technology, Policy and Management
Jaffalaan 5
2628 BX Delft
The Netherlands
+31 (0) 15 2788779
S.Roeser@tudelft.nl
www.tbm.tudelft.nl/sroeser

L Participant Consent Form

TU Delft

PARTICIPANT CONSENT FORM

Study Title	**Identification of the neural and intrinsic component of wrist hyper-resistance.**		
Participant Name:		**Date:**	
Researcher Name:	Larissa Scholte		

This section to be completed by the participant:

Please tick the box at the end of each statement if you agree with it.

1. I confirm that I have read and understood the Information Sheet for the above study. ☐
2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
3. I understand that my participation is voluntary and that I am free to withdraw from the study, without giving any reason. ☐
4. I agree to the storage and use of personal information for the purposes of this study. ☐
5. I agree to take part in the above study. ☐

Signed:

Name in capitals:

Date:

This section to be completed by the researcher

I certify that this participant has read, properly completed and signed the screening and consent forms, witnessed by myself:

Signed:

Date:

Please note: All data arising from this study will be held and used in accordance with the Data Protection Act. The results of the study will not be made available in a way that could reveal the identity of individuals.

M Participant Information Sheet

PARTICIPANT INFORMATION SHEET

For a study investigating the neural and intrinsic component of wrist hyper-resistance, using two haptic perturbators, electromyography (EMG) and advanced data analysis methods

Date 24-11-2017, Version 1.0

Dear Madam/Sir,

You have been asked to participate in a study which examines the neural and intrinsic component of wrist hyper-resistance, using two haptic manipulators, electromyography (EMG) and advanced data analysis methods. This information sheet provides some detailed information about the study. Any questions, please get in touch with any of the researchers mentioned at the end of this information sheet,

Study background
Increased hyper-resistance of a joint, is major source of disability in UMNS that arises after a CVA. The different components causing joint hyper-resistance post stroke are of neural or mechanical, i.e. intrinsic, origin. Current clinical assessment of joint hyper-resistance is restricted to observer-perceived ordinal rating scales, such as the (Modified) Ashworth Scale (MAS). However, these measures are insensitive and unreliable (Fleuren et al. 2010) and intrinsically incapable of discriminating between the neural and tissue related sources of increased joint hyper-resistance. A measurement technique, which can be used in daily clinical management for the quantification of joint stiffness in the wrist, named 'NeuroFlexor', has been developed and reported to be reliable and valid (Lindberg 2011, Gäverth 2013).

Study goal
The study you are asked to participate in aims to validate the NeuroFlexor, by comparing outcome values obtained by the Wristalyzer device and biomechanical modelling.

What does participating involve?
To separate both components contributing to joint hyper-resistance, biomechanical methods are necessary. To determine the both components of wrist hyper-resistance, the wrist muscles need to stretched at two velocities by moving the hand from flexion to extension direction. The study will be performed with the Wristalyzer device and the Neuroflexor device, which are both commercially on the market. You will be asked to relax your wrist while the devices passively move the wrist from 20 degree flexion to 30 degree extension. Muscle activity will be measured using surface electrodes stuck on different muscles of the arm. You won't notice the recording of muscle activity. You can request a short pause anytime throughout the experiment. The two experiments together will take about 1h.

The study takes place in the measurement van of the VU medical centre within the department of rehabilitation medicine.

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