The design of a new protocol to accurately estimate the passive and active components of the muscle system

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Abstract

For people who have had a stroke holds that after 6 months 63% suffer from some kind of physical aftereffects of stoke. The physical aftereffects can have different symptoms and are mostly caused by an increased joint resistance. The increased resistance can have multiple origins which can be basically divided in two groups: active (neural) and passive (mechanical) origins. Because the treatment options for both of these origins differ, it is important for clinicians to know what the origin is for each individual patient. In the clinic it is not possible to distinguish these origins at the moment. Therefor a biomechanical approach, involving simultaneous capture of joint torque, kinematics and electromyography, is used to measure the resistance of the joint and a neuromuscular model is developed which estimates the passive and active muscle parameters of the flexor and extensor muscle of the wrist.

In this study an existing neuromuscular model is extended and improved, in order to describe the passive and active properties of the muscle more accurate. The disadvantage of the improved model is that the data that is acquired with the current protocol is not rich enough anymore in terms of position, velocity and accelerations in order to estimate all the neuro- and mechanical parameters of the model in a feasible way. Therefore, the goal of this research is to make a new protocol which provides rich enough data in order to estimate all the parameters of the newest model in a feasible way. To achieve this different input signals are evaluated that acquired more information in the position, velocity or acceleration domain and the conditions during the tests of the protocol changed from passive to active.

Concluded was that the passive parameters of the muscle system could be estimated accurately during tests under passive conditions. When the conditions changed from active to passive the estimations deteriorated and all parameters were estimated less accurate than under passive conditions.

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Introduction

Yearly over 47000 people in the Netherlands are hospitalized after having a stroke, which is about 126 persons each day (Vaartjes et al. 2013). About 9000 of the stroke patients die of the effects of stroke. For the remaining patients it is known that after 6 months 63% of the stroke survivors suffer from some kind of physical aftereffects of stoke (Wissel et al. 2009). One of the aftereffects is increased joint resistance in one or more joints. Patients with increased joint resistance often have one or more of the following symptoms: shortened, overactive muscles; velocity-dependent stiffness of joints; increased tendon reflexes; involuntary muscle contractions; weakness of the muscles; reduced range of motion of the joint; and deformations of the limbs, all contributing to the loss of functionality, especially in the fine motor control (Wissel et al. 2009). Increased joint resistance can have multiple causes, which are made visible in Figure 1 (Lieber et al. 2004):

- Increased passive muscle stiffness (soft tissue contracture), which is caused by fibrosis in the muscle tissue, a change in the structure of the muscle tissue or collagen tissue, or an increase in stiffness of the tendon.
- Increased neural mediated reflex stiffness (spasticity), which is defined as a chronic violation of the central execution of the motor command and can be caused by an increased reflex gain or a decreased inhibition of the α-motor neurons.
- Increased active muscle stiffness, which can be caused by an increased number of attached cross-bridges or an increase in stiffness per cross-bridge. Cross bridges form links inside muscle fibres in order to contract the muscle. When more cross bridges are connected the muscle is in a more contracted state and thus stiffer.

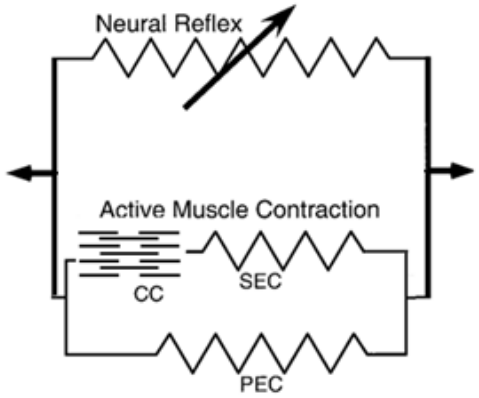

Figure 1: Schematic overview of the different causes of increased joint resistance in stroke. Above the neural mediated reflex stiffness is depictured. Below a schematic representation of the muscle is depictured with a contractile component (CC) (active muscle stiffness), a series elastic component (SEC) and a passive elastic component (PEC) depicture the passive muscle stiffness.

The causes described above show that increased joint resistance can have as well a neural as a non-neural (mechanical) origin.

Diverse treatment options exist for patients who are suffering from increased joint resistance. Examples of treatment methods are physical therapy, surgical intervention or pharmaceutical therapy (Wissel et al. 2009). The therapies are all focused on improving the quality of life as it is not possible at the moment to cure the effects of stroke. With the existing treatment methods either the

neural component or the non-neural origin of increased joint resistance is treated. One option to treat increased joint resistance with pharmaceutics is the injection of Botulinum Toxin, which paralyses the muscle by blocking the synapses at the motor end plates and in that way reduces the muscle activity (Fridman et al. 2010). Casting is an example of physical therapy, which is focused on elongating the muscles by forcing them to be a certain length. With casting the joint should get a larger range of motion (RoM) and deformations are decreased. Casting is an example of a treatment method that is focused on the non-neural components of increased joint resistance (Malhotra et al. 2009).

To choose the right treatment method it is important to know if the origin of the increased joint resistance is neural or non-neural (Meskers et al. 2009). A nowadays often used diagnostic method in the clinic is the (modified) Ashworth score (MAS). The MAS is used to measure the resistance of a limb during a movement through the whole RoM of the limb at the same velocity. The MAS does give information about the severity of the increased joint resistance but does not tell anything about the origin (Alibiglou et al. 2008). Currently, there is no clinical method available that distinguishes the neural components from the non-neural components that are the origin of the increased joint resistance. Diverse research groups around the world are busy developing a biomechanical method to measure and quantify diverse components of the muscle, like stiffness, viscosity, and neural activity (de Vlugt et al. 2010, Mirbagheri et al. 2001, Bar-On et al. 2014, Sinkjaer et al. 1994). With such a biomechanical diagnosis it would be possible to define the origin of the increased joint resistance and would thus help in choosing the right treatment option.

Such a biomechanical method mostly includes of Electromyography (EMG), torque and joint angle measurement, and a mathematical model to parameterize the different neuromechanical components at the joint level. Developing a representative neuromuscular model is a challenging task due to the complexity of the muscle system and the large inter-subject variability. In the LUMC in Leiden a wrist manipulator was used for this study which can apply torque or position perturbations. The neuromuscular optimization model that is developed in collaboration between Leiden and Delft was first published in 2010 (de Vlugt et al. 2010). The model was developed for the ankle joint and includes the mechanical and neural parameters of the joint system (as illustrated in Figure 1) for description of joint resistance. For this study the model was translated to a wrist model which contains two antagonistic muscle models with a passive and an active part. The model is in this study suited to estimate tissue relaxation and optimal muscle lengths. The model will be explained in more detail in the methods section.

The expansion of the neuromuscular model means that the model becomes a better rendition of an actual muscle system, but it also means that the model becomes more and more complex. As properties will be modelled in more detail, the number of parameters will increase accordingly implicating that input data should be enriched in terms of position, velocity and accelerations to be able to reliably estimate all the model parameters. One of the new parameters is the optimal muscle length, which is the length at which maximum muscle force can be generated. In order to estimate the optimal muscle length additional information about the active muscle should be acquired. To get such richer data, a new protocol has to be designed which will give more information about the muscle system as compared to the current protocol.

The current protocol consist of passive movements of the wrist joint through the whole range of motion, at two velocities. The current protocol will be used as a base for the new protocol to be applied to the human wrist joint. The muscle is a highly non-linear system (i.e. to determine stiffness, twice as much stretching does not result in a doubling of the torque) and as the muscle system is evaluated over its whole range of motion and not only around its operating point, the non-linearity of the system has to be taken into account. To be able to estimate the model parameters accurately, the input data should be sufficiently rich in order to excite the dynamic modes of the muscle system and cover the whole amplitude range of interest. In the current protocol the input data does not excite all dynamic modes of the muscle system, as only two velocities are considered and only two states where the velocity is zero (the maximum flexion and extension angle), which can lead to inaccurate parameter estimations (Billings et al. 2008). Also, as the current protocol consist of only passive tasks not enough information about the active state of the muscle system is acquired to estimate the parameters of the active component of the muscle system sufficiently. That is, the active muscle stiffness and viscosity scale with muscle force.

The goal of this study is to develop a new measurement protocol that provides richer data in order to correctly estimate all the parameters of the newest model in a feasible way. Richter data means that the joint system is to be excited in such a way that the neural (active) and the mechanical (passive) components of the joint system can be estimated reliably, i.e. each of the individual parameters is sufficiently excited. As the perception of clinicians is different from technicians the protocol must preferably appeal to the clinicians, while analysis techniques remain sufficiently powerful to estimate the parameters. For clinicians it is important to accurately estimate and distinguish the different active and passive muscle parameters in order to visualize the effect of different treatment methods, compare them and choose the best treatment for each individual patient. The addition of parameters like the optimal muscle length to the muscle model is important for clinicians as this parameter is an anatomical measure.

Methods

2.1 Subjects

Ten healthy subjects (4 male, 6 female), with an age range of 18 - 53 years, with no history of neurological disorders or upper extremity injuries participated in this experiment. All subjects signed an informed consent prior to the experiment. All tests were performed on the right arm.

2.2 Instrumentation

Subjects were seated with both feet on the ground. The arm rest was adjusted in such a way that the shoulder of the subject is relaxed, with an abduction angle as close to zero as possible, and the elbow is flexed at approximately 90°, while the forearm is in horizontal position (Figure 2B). Wrist perturbations were applied using a wrist manipulator: the Wristalyzer® (Moog, Nieuw Vennep, the Netherlands), which is illustrated in Figure 2A. The subjects arm was attached to the device and the hand was attached to a rotating handle with Velcro straps, with the thumb on top of the handle to prevent the subject from pinching. The rotational axis of the wrist was aligned with the rotational axis of the Wristalyzer®, such that the rotation of the handle can directly be translated to wrist flexion and extension. The handle was rotated with a vertically positioned servo motor (Parker SMH100 series). The RoM of the handle was approximately 180^0. Positive rotation was defined as wrist flexion and negative rotation was defined as wrist extension. For this study position perturbations were used.

Muscle activation of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) were measured with the Delsys Bagnoli-8 system (Delsys Inc., Boston, the USA) with bipolar surface electrodes. Two electrodes were placed on FCR and two on the ECR. The EMG signals were sampled at 2048 Hz and off-line rectified and filtered by low pass filtering (3^{rd} order Butterworth) at 20 Hz (fEMG). After filtering the mean of the two fEMG signals from the FCR is taken and the mean of the two fEMG signals of the ECR is taken, in order to get an accurate estimate of the muscle activity. The joint angle and wrist torque were low pass filtered (3^{rd} order Butterworth) at 20 Hz in order to prevent amplifying noise due to differentiation. The wrist torque and angle were also sampled with 2048 Hz. The angular velocity and acceleration were derived by single and double differentiation of the angular position of the wrist.

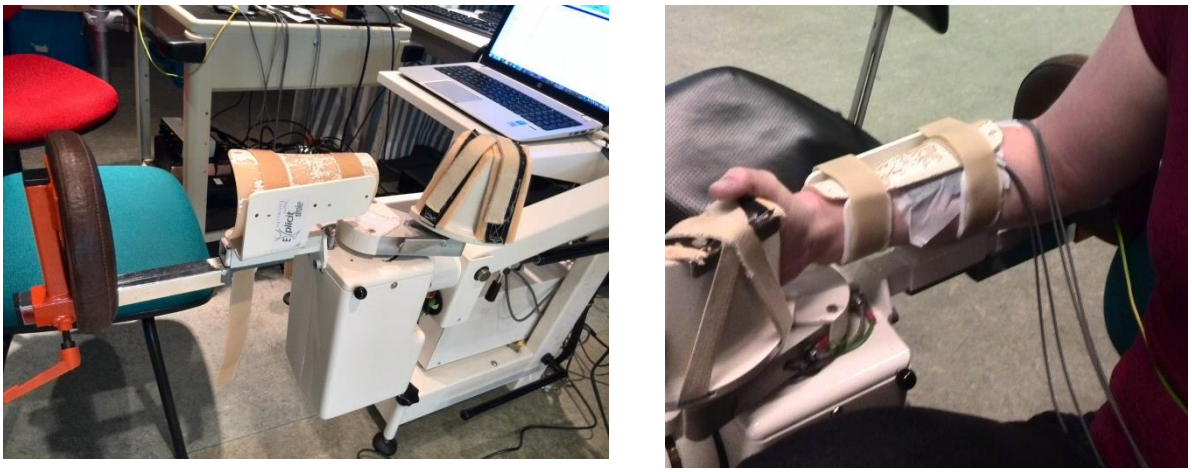

Figure 2: Test setup of the Wristalyzer®. A) The complete setup of the Wristalyzer®. B) Example of a subject attached to the Wristalyzer®, including the electrodes.

2.3 Neuromuscular model

A non-linear neuromuscular model was used to predict the wrist torque. The neuromuscular model optimizes the different parameters by minimizing the quadratic difference between the measured and the modeled torque. Input for the neuromuscular model are the recorded EMG and the joint rotation angle (Figure 3).

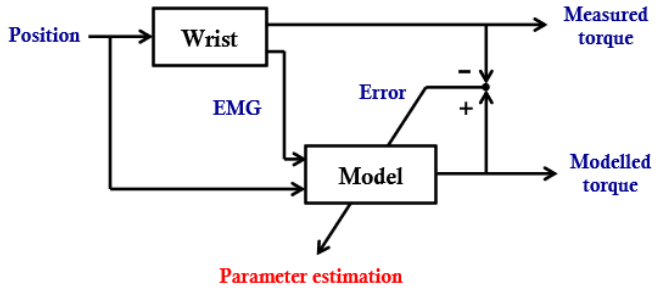

Figure 3: Schematic overview of the model parameterization procedure. Position perturbations are applied to the wrist joint and are, together with the recorded EMG, the input of the neuromuscular model. The neuromuscular model provides an estimate of the torque by minimizing the error between the measured and the modelled torque. To minimize the error the parameters of the model are adapted iteratively.

2.3.1 Outline and adaptations

The neuromuscular model first published in 2010 (de Vlugt et al. 2010) is designed to estimate the ankle torque. The neuromuscular model consist of a passive element for the extensor and an active (Hill type muscle model) element for both extensor and flexor muscle groups. The tendon is assumed to be infinitely stiff compared to the muscle stiffness during the solely passive tasks the protocol consisted of. Since 2010 the neuromuscular model has developed and extended. The neuromuscular model still has recorded EMG and joint rotation angle as input, but is in this study translated into a model for the wrist joint, which consist of a passive element for the flexor and extensor and an active Hill type muscle model element for the flexor and extensor (Figure 4). A Hill type muscle model is a representation of the muscles mechanical response and consists of a contractile element and two linear springs (one is series and one in parallel). With a Hill type muscle model the active part of a muscle is represented as one enlarged muscle fiber. Additionally, relaxation dynamics and optimal muscle length were added to the model as parameters to be optimized and are further explained below. In the neuromuscular model positive rotation is defined as extension, negative rotation is defined as flexion. The model parameters are optimized for every signal by minimizing the quadratic difference between the measured and estimated wrist torque. Parameter estimation and analyzing the results were done in Matlab (The Mathworks Inc., Natrick MA).

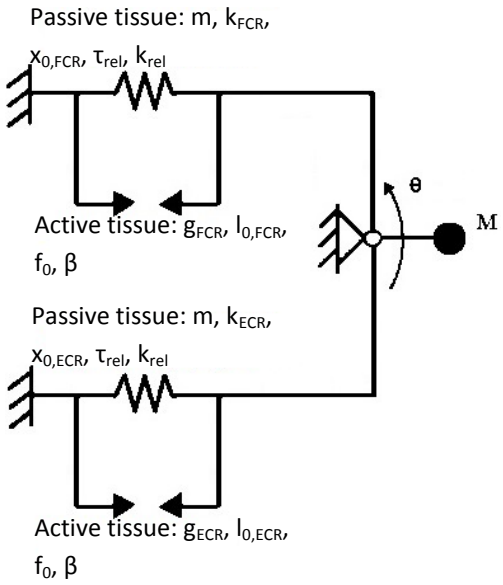

Figure 4: Schematic representation of the neuromuscular model. Above the flexor muscle is depictured, the lower element is the extensor muscle. Both muscles are split in an active and passive tissue part and the corresponding parameters are shown.

External wrist torque $T_{ext}(t)$ is composed by the following main components:

$$T_{ext}(t) = \ddot{\theta} I(t) + T_{FCR}(t) - T_{ECR}(t) \quad \textbf{(1)}$$

Where the external torque is the torque that is measured. For the model is assumed that the modelled torque is equal to the measured torque, and equation 1 becomes:

$$T_{mod}(t) = T_{ext}(t) \quad \textbf{(2)}$$

Where $\ddot{\theta}$ is the angular acceleration, I is the wrist inertia, T_{FCR} the torque generated from the flexor and T_{ECR} is the torque generated from the extensor. T_{FCR} and T_{ECR} are obtained by adding the active and an elastic (passive) muscle force of the respective muscle:

$$T_{ECR}(t) = \left(F_{elastic,ECR} + F_{active,ECR}\right) * r_{ECR} \quad \textbf{(3)}$$

$$T_{FCR}(t) = \left(F_{elastic,FCR} + F_{active,FCR}\right) * r_{FCR} \quad \textbf{(4)}$$

Where $F_{elastic}$ is the elastic (passive) force of the muscle, and F_{active} is the force generated due to muscle activation. The muscle moment arm is represented by r, and is dependent of the joint rotation angle (Gonzalez et al. 1997, Ramsay et al. 2009):

$$r_{FCR}(\theta) = (16.2040 + 0.2 * \theta) * 10^{-3} \quad \textbf{(5)}$$

$$r_{brevis}(\theta) = (16.4337 - 2.1 * \theta) * 10^{-3} \quad \textbf{(6)}$$

$$r_{longus}(\theta) = (10.7166 - 2.3 * \theta) * 10^{-3} \quad \textbf{(7)}$$

$$r_{FCR}(\theta) = (r_{brevis} + r_{longus})/2 \quad \textbf{(8)}$$

Where θ is the wrist joint angle and r_{brevis} and r_{longus} are the moment arms of the extensor carpi radialis brevis and extensor carpi radialis longus respectively. The equations are based on measurements of the moment arms in cadavers.

Passive muscle properties

The elastic force is calculated similarly for the extensor and flexor with (de Vlugt et al. 2010):

$$F_{elastic_0,FCR}(\theta) = e^{(k_{FCR}*(x_{FCR}-x_{0,FCR}))} \quad \textbf{(9)}$$

Where k_{FCR} is the stiffness coefficient, $x_{0,FCR}$ is the slack length of the passive tissue, which is the length of the muscle from which the passive muscle stiffness will increase with increasing muscle length and x_{FCR} is the muscle length (de Vlugt et al. 2010):

$$x_{FCR}(\theta) = l_{0,FCR} + r_{FCR}(\theta) * \theta \quad \textbf{(10)}$$

Where $l_{0,FCR}$ is the optimal muscle length.

When the length of the muscle is kept constant the total force and thus also the total torque will decrease in time. The decrease in torque is called relaxation and should also be taken into account in the neuromuscular model. The relaxation dynamics are calculated as follows :

$$F_{elastic,FCR}(s) = \frac{\tau_{rel}*s+1}{\tau_{rel}*s+1+k_{rel}} * F_{elastic_0,FCR}(s) \quad \textbf{(11)}$$

Where τ_{rel} is the relaxation time constant and k_{rel} is the relaxation factor. The relaxation factor determines the reduction of the elastic force. When k_{rel} is zero, no relaxation is present and the elastic force will stay at the same height. When k_{rel} is e.g. one, the elastic force will reduce with 50% during the time defined by τ_{rel}. Expected was that with the relaxation dynamics also the viscous part of the muscle system could be accurately described, which means that the viscosity dynamics can be taken out of the neuromuscular model. A sensitivity analysis was done during the model testing phase of this study which showed that the viscosity dynamics were indeed accurately described with the relaxation dynamics.

Active muscle properties

Neural muscle activity is estimated from corresponding fEMG signals similar for the flexor and extensor according to (de Vlugt et al. 2010):

$$E_{FCR_{EMG}}(t) = g_{FCR} * fEMG_{FCR}(t) \quad \textbf{(12)}$$

Where g_{FCR} is the fEMG weighing factor. The estimated neural activity is then passed through a linear second order filter, which describes the activation process of the muscle. A similar filter is used for the flexor and extensor (de Vlugt et al. 2010):

$$a_{FCR}(s) = \frac{\omega_0^2}{s^2+2*\beta*\omega_0*s+\omega_0^2} * E_{FCR_{EMG}}(s) \quad \textbf{(13)}$$

Where a_{FCR} is the active state of the flexor, β is the relative damping of the activation filter, f_0 is the cut-off frequency of the activation filter, and $\omega_0 = 2\pi f_0$ and s is the Laplace operator. A Hill type muscle model was applied which calculates the active muscle force from the muscle force-velocity-

characteristics, the muscle force-length characteristics and the active state of the muscle (Thelen 2003):

$$F_{active,FCR}(t) = f_v(v_{FCR}) * f(l_{FCR}) * a_{FCR} \quad \textbf{(14)}$$

The force-length and force-velocity characteristics are described with exponential functions:

$$f(l_{ECR}) = e^{-\left(\frac{x_{ECR}-l_{0,ECR})^2}{wfl_{ECR}}\right)} \quad \textbf{(15)}$$

$$f_v(v_{ECR}) = \begin{cases} \frac{v_{ECR}+v_{max,ECR}}{\frac{v_{ECR}}{m_{vsh}}-v_{max,ECR}}; & v_{ECR} < 0 \\ 1 - \frac{(1+m_{vsh}*m_{vshl})*(f_{ecc}-1)*v_{ECR}}{m_{vsh}*m_{vshl}*v_{max,ECR}+v_{ECR}}; & v_{ECR} \geq 0 \end{cases} \quad \textbf{(16)}$$

Where m_{vsh}, m_{vshl} and wfl_{ECR} are a shaping factors, v_{ECR} is the muscle lengthening velocity, $l_{0,ECR}$ is the optimal muscle length, which is the muscle length at which maximum muscle force can be generated, f_{ecc} is the maximum eccentric force which is 1.5 times the isometric force and the isometric force was normalized to 1 since scaling of the force was determined by the fEMG-weighting factors, and $v_{max,ECR}$ is the maximum shortening velocity which is 8 times the optimal muscle length per second.

The initial values of the different parameters were acquired from literature, where the physiological limits were chosen as boundaries (Table 1).

Table 1: Initial values and boundaries of the different parameters.

Parameter	Initial value (lower boundary- upper boundary)
m	1 (0.1-3) kg
k_{FCR}	240 (40-800) 1/m
k_{ECR}	240 (40-800) 1/m
$x_{0,FCR}$	0.04 (-0.1-0.1) m
$x_{0,ECR}$	0.06 (-0.1-0.1) m
τ_{rel}	0.9 (0.01-10) s
k_{rel}	2 (0.01-50)
g_{FCR}	$1*10^4$ ($1-1*10^{11}$) N/Volts
g_{ECR}	$1*10^4$ ($1-1*10^{11}$) N/Volts
$l_{0,FCR}$	0.063 (0.01-0.12) m
$l_{0,FCR}$	0.07 (0.01-0.12) m
f_0	0.4 (0.01-10) Hz
β	0.7 (0.01-20) Ns/m

Table 2 provides an overview of the parameters of the 2010 ankle model and the newest wrist model. Added parameters compared to the 2010 version include; the relaxation dynamics (described with the relaxation factor and the relaxation time constant), optimal muscle lengths and relative damping of the activation filter. The passive viscosity and muscle force shift parameter are removed from the model. As stated before, a sensitivity analysis done in the testing phase of the model showed that the passive viscosity had become superfluous by the addition of the relaxation dynamics. The muscle force shift factor was a compensation for the force that could not be described with the passive force-length characteristic in the model, i.e. the passive muscle force of the antagonist and the relaxation dynamics of the agonist. In the newest model both the passive muscle

force of the antagonist and the relaxation dynamics of the agonist (ant antagonist) are included in the model, which makes the muscle force shift factor superfluous.

Table 2: An overview of the parameters of the first and current neuromuscular model.

Ankle model, 2010 (de Vlugt et al. 2010)				**Wrist model, 2014**			
1	m	Mass (ankle + footplate)	kg	1	m	Mass wrist	kg
2	k_{tri}	Stiffness coefficient	1/m	2	k_{FCR}	Stiffness coefficient flexor	1/m
				3	k_{ECR}	Stiffness coefficient extensor	1/m
3	$x_{0,tri}$	Muscle length shift	m	4	$x_{0,FCR}$	Approximated slack length flexor	m
				5	$x_{0,ECR}$	Approximated slack length extensor	m
4	e_1	IEMG weighting factor for the tibialis anterior	N/Volts	6	g_{FCR}	fEMG weighting factor flexor	N/volts
5	e_2	IEMG weighting factor for the lateral gastrocnemius	N/Volts	7	g_{ECR}	fEMG weighting factor extensor	N/volts
6	e_3	IEMG weighting factor for the soleus	N/Volts				
7	e_4	IEMG weighting factor for the medial gastrocnemius	N/Volts				
8	f	Cut-off frequency activation filter	Hz	8	f_0	Cut-off frequency activation filter	Hz
				9	β	Relative damping activation filter	Ns/m
				10	$l_{0,FCR}$	Optimal muscle length flexor	m
				11	$l_{0,FCR}$	Optimal muscle length extensor	m
				12	τ_{rel}	Relaxation time constant	s
				13	k_{rel}	Relaxation factor	
9	b_{tri}	Viscosity coefficient	Ns/m				
10	F_0	Muscle force shift	N				

2.3.2 Model validation

The model parameters are optimized by minimization of the mean squared model error:

$$e = T_{meas} - T_{mod} \quad \textbf{(17)}$$

With T_{meas} as the measured wrist torque and T_{mod} the estimated wrist torque from the model over the time frame used for parameterization. The error vector is used to calculate the covariance matrix:

$$P = \frac{1}{N} * (J^T * J)^{-1} * e * e^T \quad \textbf{(18)}$$

Where N is the number of time samples used for the estimation of the parameters and J is the Jacobian matrix. The Jacobian is an NxN_p matrix, with N_p = 13, which is the number of estimated parameters, and contains the first derivatives of the final error to each parameter. From the covariance matrix *P,* the standard error of the mean (SEM) for each parameter can be calculated by taking the square root of the auto-covariance (diagonal terms of *P*). The SEM-values are normalized to their corresponding parameter value and are compared between the tests, where a lower SEM-value is considered better. A low SEM means that the particular parameter has a substantial contribution to the total generated wrist torque.

The validity of the complete model was assessed by calculating the variance accounted for (VAF), which is a measure of the model goodness of fit. The VAF is described with:

$$VAF = \left(1 - \frac{\Sigma(T_{meas}(t) - T_{mod}(t))^2}{\Sigma T_{meas}(t)^2}\right) * 100\% \quad \textbf{(19)}$$

2.4 Protocol

The idea is to identify the passive tissue, the active muscle and the reflexive component with the improved neuromuscular model. Therefore, the input signal should be richer in terms of position, velocity and acceleration in order to address all the different active and passive muscle components of the model. When all components of interest are sufficiently stimulated all the parameters of the new, extended model are expected to be accurately estimated.

2.4.1 Development

In this section the different characteristics of the muscle are evaluated and is shown in which way the original protocol fails to sufficiently excite the different characteristics, which will be explained below. The contractile properties and the passive properties of the muscle are of great interest for this research and therefor the input signal should contain a large reach and variety of positions and velocities. Figure 5 represents a schematic representation of the muscle and how the different components are excited. The input (position), the total EMG (reflex and voluntary contraction) and the output torque are measured.

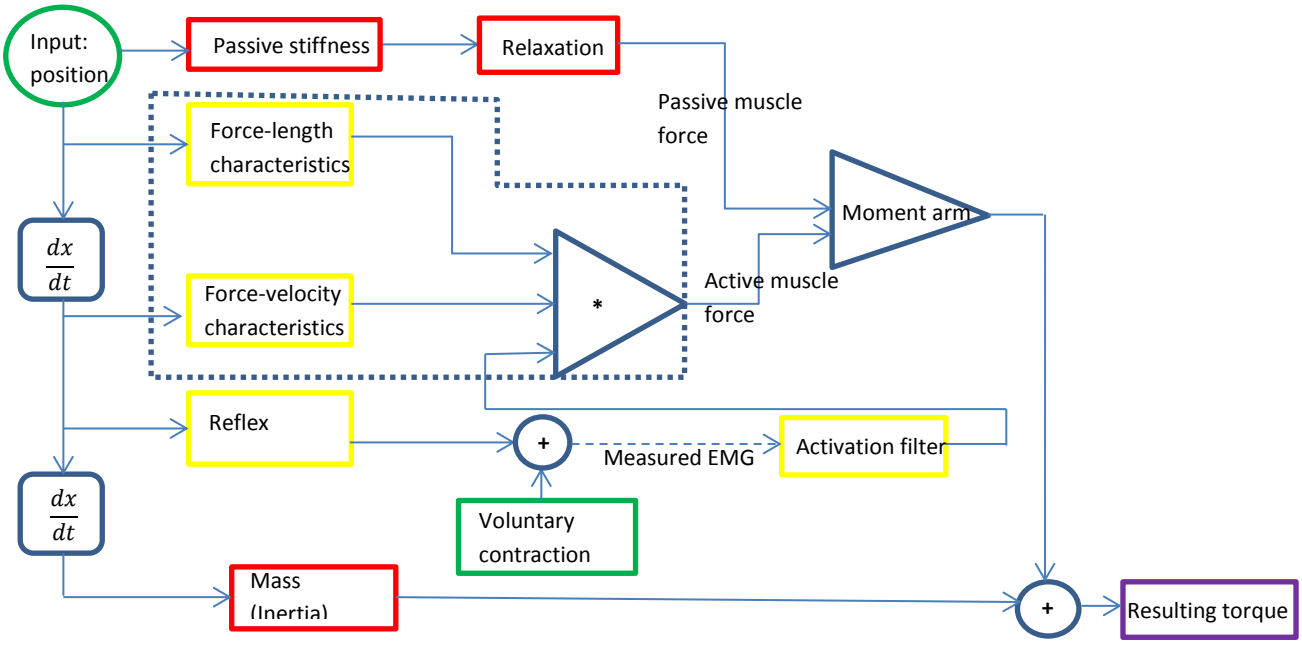

Figure 5: Schematic representation of the muscle system of one muscle. The green blocks are input to the system (only the position is measured), the purple block is the output torque of the system, the red blocks are the passive muscle components and the yellow blocks are the active muscle components.

First the passive muscle component of the neuromuscular model is considered. The original protocol consisted of ramp-and-hold movements at two velocities, a slow velocity and a high velocity in order to evoke a stretch reflex. Figure 6 shows such a ramp-and-hold movement, at slow velocity with a stretch in the flexion direction. The original protocol consisted of only passive tasks.

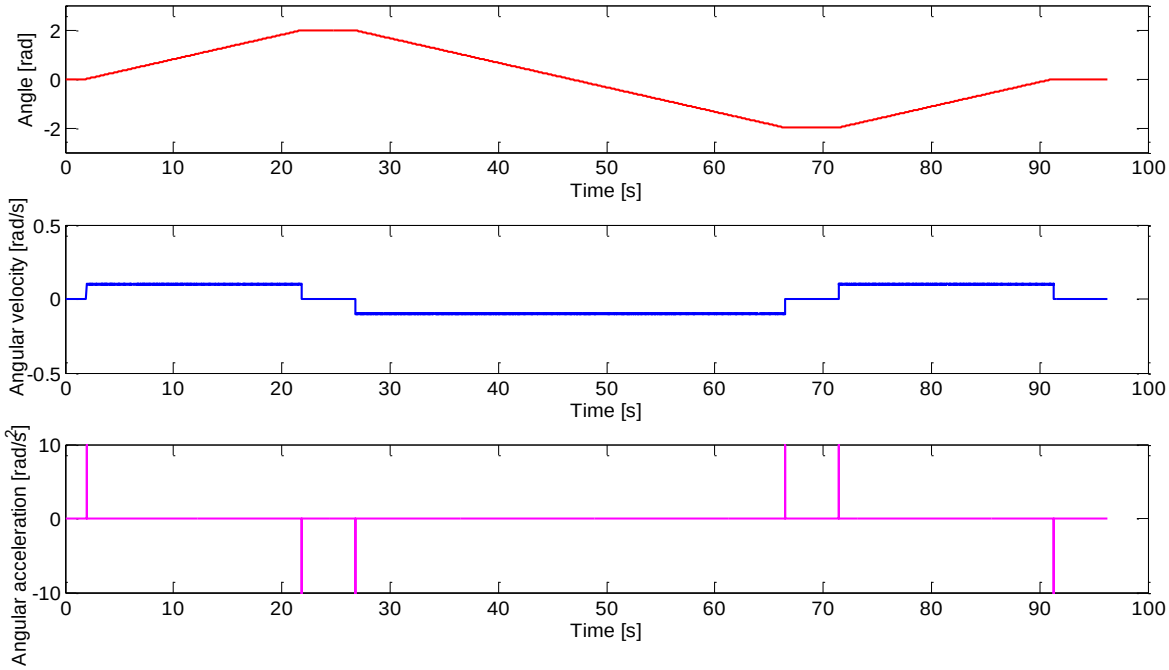

Figure 6: The input (implied rotations onto the wrist) signal in the original protocol. The velocity during the ramps were resp. 1 s and 0.5s for the whole RoM. The red line is the change in angular position over time, the blue line is the change in angular velocity over time, and the magenta line is the change in angular acceleration over time.

The input data for the model acquired with original protocol consisted of two hold phases, at the maximum flexion and extension angle of the wrist. The force –length characteristic of the muscle (active and passive parts), is illustrated in Figure 7a. As there is no movement of the muscle in the hold phases of the signal, the muscle is expected to be the least active in these parts. Apart from any offset EMG and a delayed reflex reaction no activity is expected. When almost no muscle activity is present only passive mechanisms contribute to the total muscle torque. Thus, at the hold phases is expected that the passive muscle parameters, which are k_{ECR}, k_{FCR}, $x_{0,FCR}$, $x_{0,ECR}$, k_{rel} and τ_{rel}, can be estimated accurate as at the hold phases the passive torque is the main contributor to the total torque. At the ramp phases of the signal the passive torque also contributes to the total muscle torque but in the ramp phases also active muscle torque can contribute to the total torque.
In the original protocol two different velocities in the flexion and in the extension direction were used. Thus in total for four velocities and the zero velocity on the force-velocity characteristic of the muscle information is acquired, as is illustrated in Figure 7b. As only one velocity and the zero velocity were included per input signal for the model with the original protocol, not enough points on the force-velocity curve were available to get an accurate estimation of the form of the force-muscle lengthening velocity curve, as is illustrated in Figure 7b.

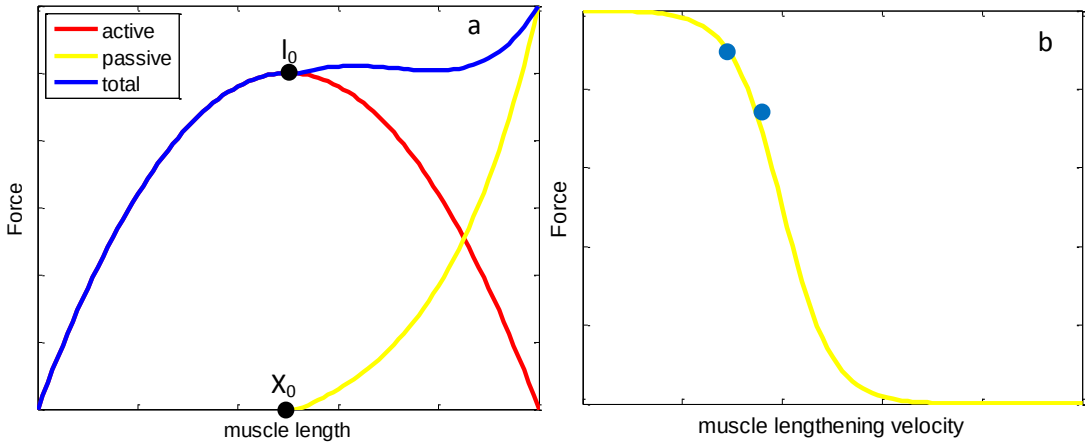

Figure 7: a) An illustration of the muscle Force-muscle lengthening velocity curve. On the curve five points are visible, which represent the 5 different velocities used in the old protocol. b) An illustration of the muscle Force-muscle length curve.

The active muscle part of the force- muscle length curve and the force- muscle lengthening velocity curve are dependent of the activation level, which is illustrated in Figure 8. The activity dependence means that adding active tasks to the originally completely passive protocol will result in a better estimation of $l_{0,EXR}$, $l_{0,FCR}$, β and f_0.

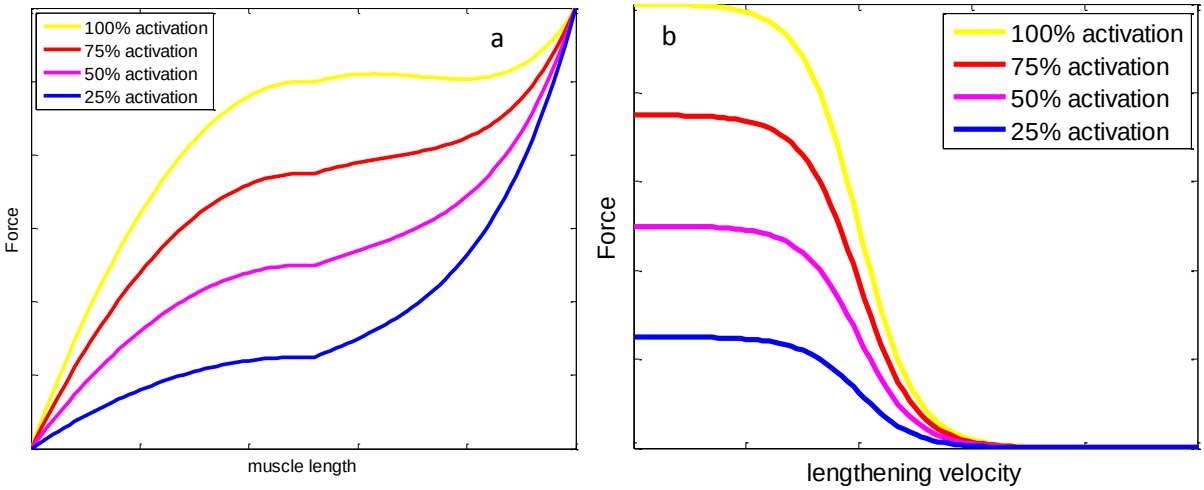

Figure 8: a) The active part of the muscle force-muscle length curve is dependent of the activation level. b) The muscle force-muscle lengthening velocity curve is dependent of the activation level.

Adding an active task also means that the parameters of the active muscle component in the model are not only estimated based on the reflex activity of the muscle, as it is in the original protocol, but can be based on actual, voluntary contraction. With the original protocol reflex activity of the muscle would show as a small peak at a certain position and velocity, which means that the signal to noise ratio is quite low. Expected is that the parameters of the active muscle component are estimated more precise during voluntary contraction because the activation is then visible over a variation of positions and over a variation of velocities which means that the signal to noise ratio has improved compared to the reflex activity during passive task.

2.4.2 Resulting protocol

The measurement protocol starts with three initializing tests, earlier used in the old protocol, which are needed for certain boundary values for the actual protocol. With the first initializing test is tested if the EMG electrodes are placed at the right muscle and in such a position that the electrodes can pick up an electrical signal from the muscle. The second and third initializing tests are used to provide the RoM, as well the active RoM as the passive RoM, which is used as the position boundaries for the real protocol. The main part of the protocol consists of four different tests. Four tests are chosen because all four tests acquire richer information in another domain. By hierarchically separating the different domains can be distinguished which parameters are better estimated in which domain. In the end a signal can be made which combines the different domains that are necessary to accurately estimated all parameters. The four tests are:

1. A ramp and hold signal which consists of multiple hold phases at different locations in the RoM. Acquires more information in the position domain (static muscle information). Expected is that the passive a parameters (k_{ECR}, k_{FCR}, $x_{0,ECR}$, $x_{0,FCR}$, k_{rel} and τ_{rel}) are more accurately estimated than with the ramp and hold signal with only two hold phases at maximum flexion and maximum extension.
2. A signal with a bell-shaped velocity profile. Acquires more information in the velocity domain (dynamic information). Expected is that the high velocities will evoke reflex reactions, which results in more information about the active muscle and the force- muscle lengthening characteristic than with the ramp and hold signal. More data about the active muscle state will result in more accurate estimations of the active parameters (g_{ECR}, $g_{FCR,}$ $l_{0,ECR}$, $l_{0,FCR}$, f_0 and β).
3. A multi sine signal. Acquires more dynamic information by containing a large variation of velocities and accelerations. Expected is that the mass will be more accurately estimated due to the accelerations and that the high velocities will evoke reflex reactions. Due to the reflex reactions more data about the active muscle state and the force- muscle lengthening characteristic is present and thus the active muscle parameters will be estimated more accurate.
4. A ramp and hold signal as in the old protocol, but under active muscle conditions. Acquires more information of the active muscle dynamics by changing the task conditions from passive to active. Expected is that the active parameters are better estimated during active conditions than during the passive conditions of the old protocol, because the signal to noise ratio (SNR) of the active muscle dynamics is higher during passive conditions than during a reflex reaction under passive conditions.

The first test consist of a ramp-and-hold signal with multiple holds (Figure 9, 10 and 11). The holds in the multiple hold signal will add static muscle information at different positions, thus more static observations at different joint angles. The holds will not be addressed in a 'logical' order, but in such a way that the distances between the holds have a large variance. As the timing of the hold phases cannot be expected, subjects do not know what is coming and they will not try to anticipate to the movements. A slow (Figure 9) and a fast version (Figure 10), 0.26 rad/s and 4.67 rad/s respectively, of the multiple hold signal is used in order to evoke a reflex reaction in the ramp phases of the fast parts. The velocities are chosen from literature (Pisano et al. 2000), because 0.26 rad/s is to slow to evoke a reflex reaction at healthy subjects and most patients, and 4.67 rad/s is a velocity of about 1.5 times the muscle length per second.

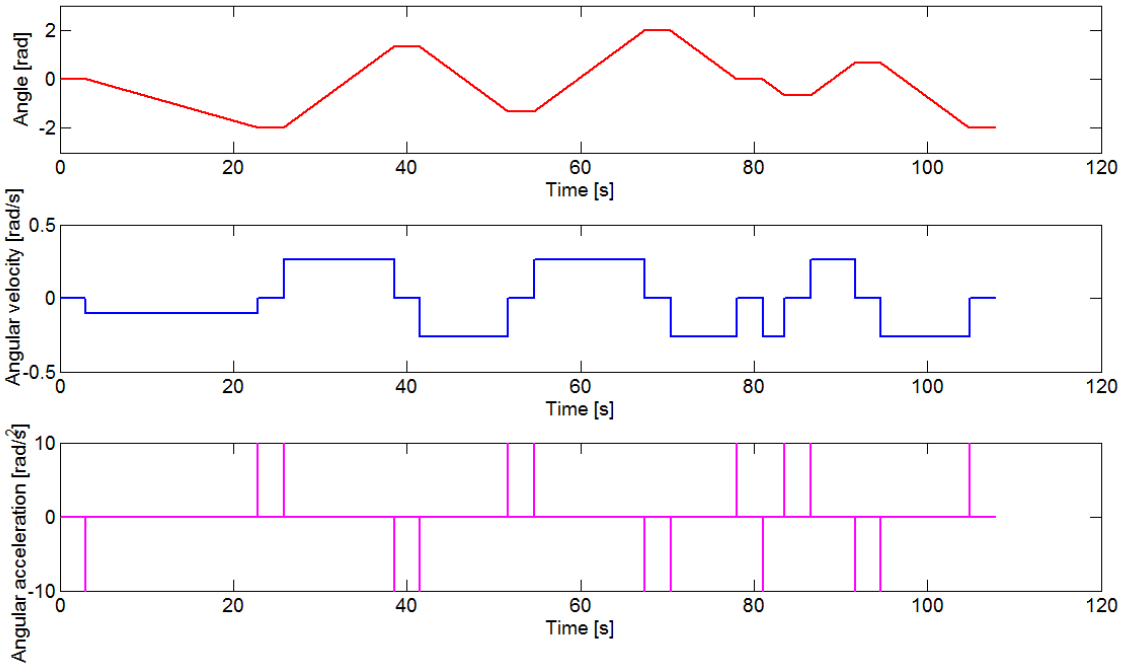

Figure 9: Signal with multiple holds and low velocity. The red line is the change in angular position over time, the blue line is the change in angular velocity over time, and the magenta line is the change in angular acceleration over time.

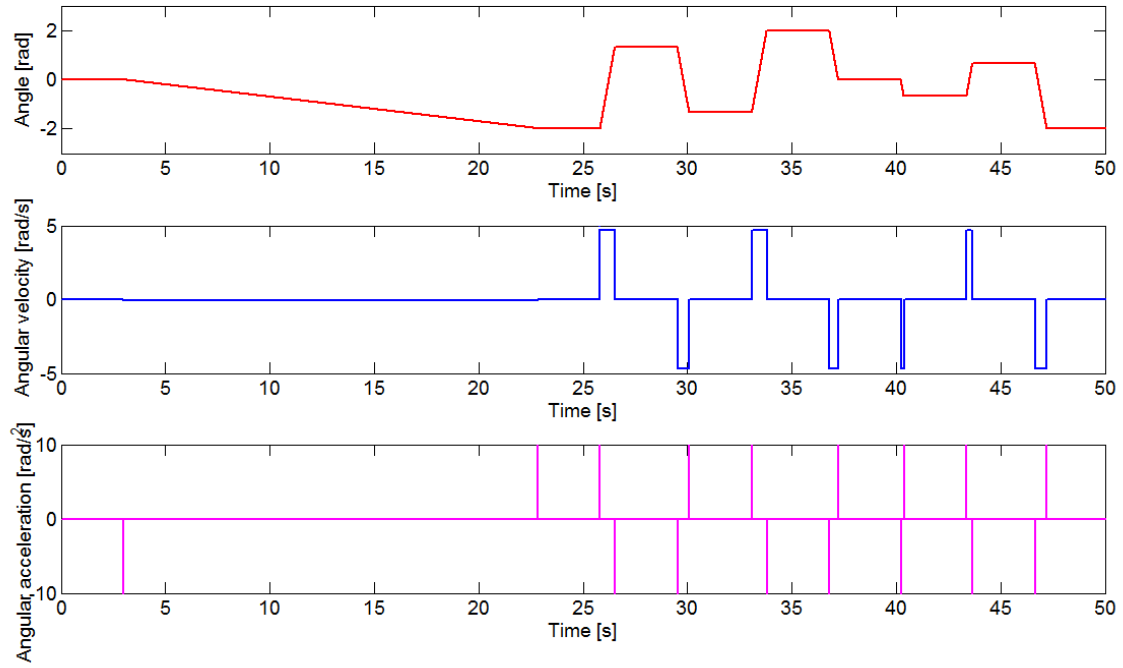

Figure 10: Signal with multiple holds and high velocity. The red line is the change in angular position over time, the blue line is the change in angular velocity over time, and the magenta line is the change in angular acceleration over time.

A third version of the multiple hold signal does have multiple velocities, seven including the zero velocity, and multiple holds at random time instants (Figure 11). The acceleration profiles of the

signals with the multiple hold phases are roughly the same as the acceleration profile of the original protocol, but with more accelerations.

The second test consist of a sigmoid signal, because the sigmoid signal has a bell-shaped velocity profile (Figure 12) and will thus add dynamic (velocity) information to the current protocol. The acceleration profile of the sigmoid signal also shows more variation, which means that the mass should be estimated more accurate.

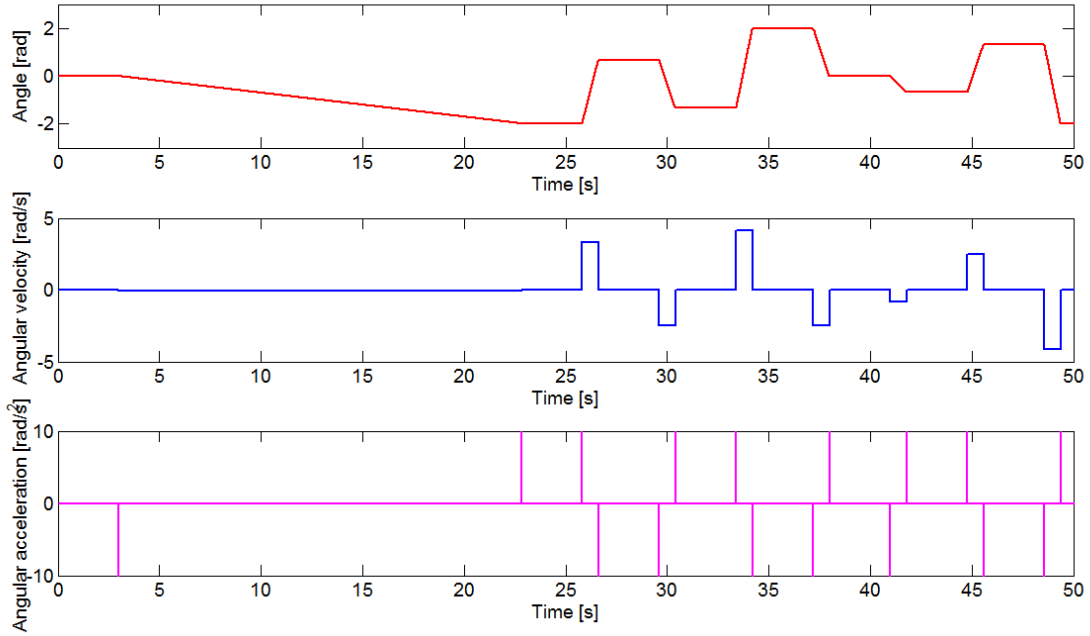

Figure 11: Signal with multiple holds and variable velocities. The red line is the change in angular position over time, the blue line is the change in angular velocity over time, and the magenta line is the change in angular acceleration over time.

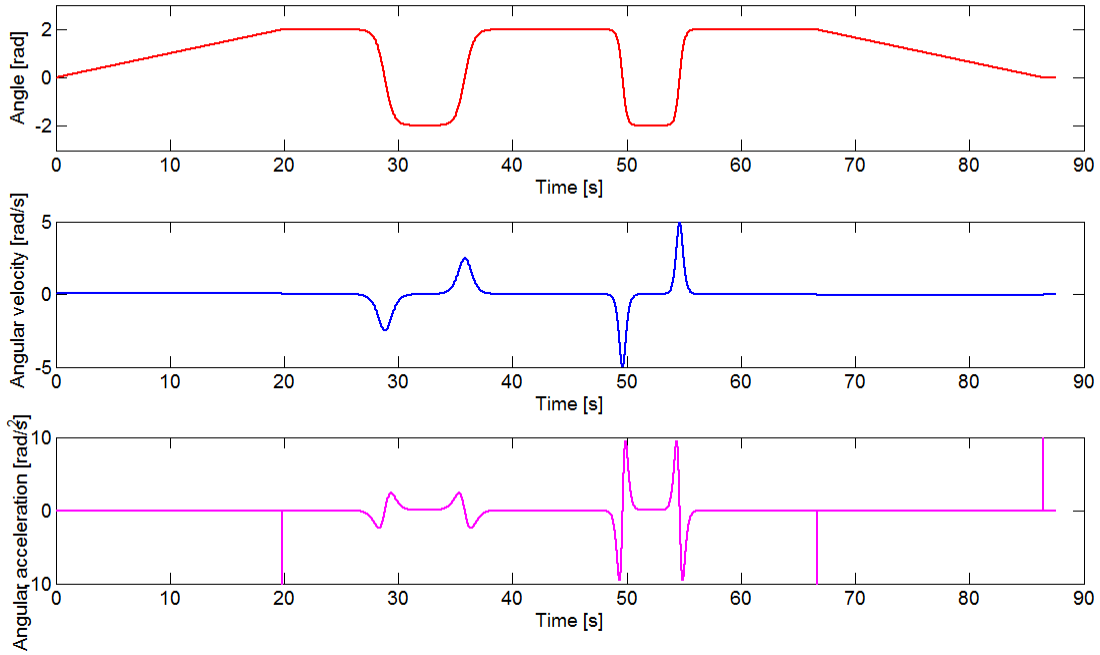

Figure 12: Sigmoid signal with bell shaped velocity profile. The red line is the change in angular position over time, the blue line is the change in angular velocity over time, and the magenta line is the change in angular acceleration over time.

The third test consists of a multi sine signal (Figure 13). A multi sine signal is a logical choice when the original protocol is not taken as the starting point because the signal consist of a lot of different and higher velocities and also various points in time at which the velocity is zero. The acceleration profile also contains multiple variations, so the inertial component of the muscle will be highly excited.

The fourth test is a ramp and hold signal as in the original protocol, but under active muscle conditions. The subject is asked to maintain a certain force level, visual feedback is provided for the subject to be able to see if the right force level is reached. After the subjects has reached the correct force level (during the first few seconds of the experiment) the visual feedback is turned off and the subject is asked to try to maintain the same force level during the test. The visual feedback is turned off to prevent too much correction from the subject. When the subject has visual feedback he might correct in such a way that the output torque is without variance. During pilot tests it became clear that a torque line without any variance is not sufficient enough data for the model to estimate. During the active tasks small position perturbations (of +/- 20^0) are applied to the subject. The perturbations are not through the whole RoM because that makes it very difficult to maintain the same force level. Three different start positions, the zero position, 30^0 of extension, and 30^o of extension, are used so that the initial muscle length will differ and at each start position four different force levels are asked, 0.5Nm and 1Nm in the flexion direction and 0.5Nm and 1Nm in the extension direction. The force levels are chosen after different pilot tests, which showed that 0.5Nm and 1Nm were feasible force levels for as well flexion as extension force. For this research is not investigated if the force levels are also feasible for CVA-patients. Figure 14 shows an example of one of the active signals, here the start position was 30^0 of flexion. To acquire even more varying data a last active test is added in which the subject can decide for himself how much and in which direction he will deliver force and vary his force level during the test. The varying force level means that the muscle activation is completely independent of the position, and the output torque will vary more during the varying force level test in comparison with the other active tests which might lead to a good estimation of the measured output torque.

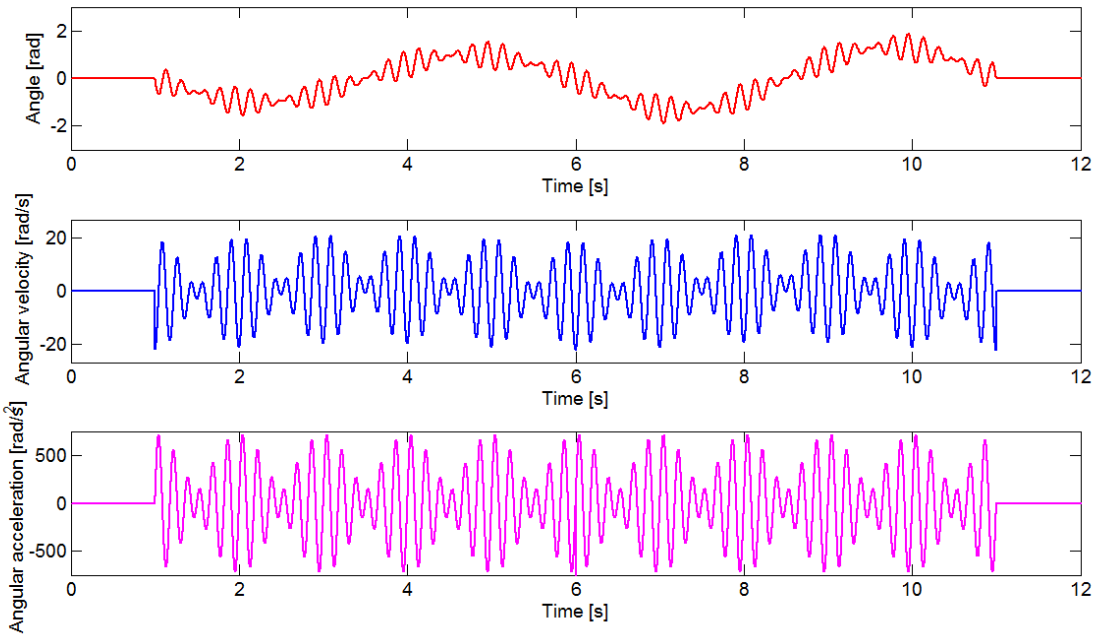

Figure 13: Multi sine signal. The red line is the change in angular position over time, the blue line is the change in angular velocity over time, and the magenta line is the change in angular acceleration over time.

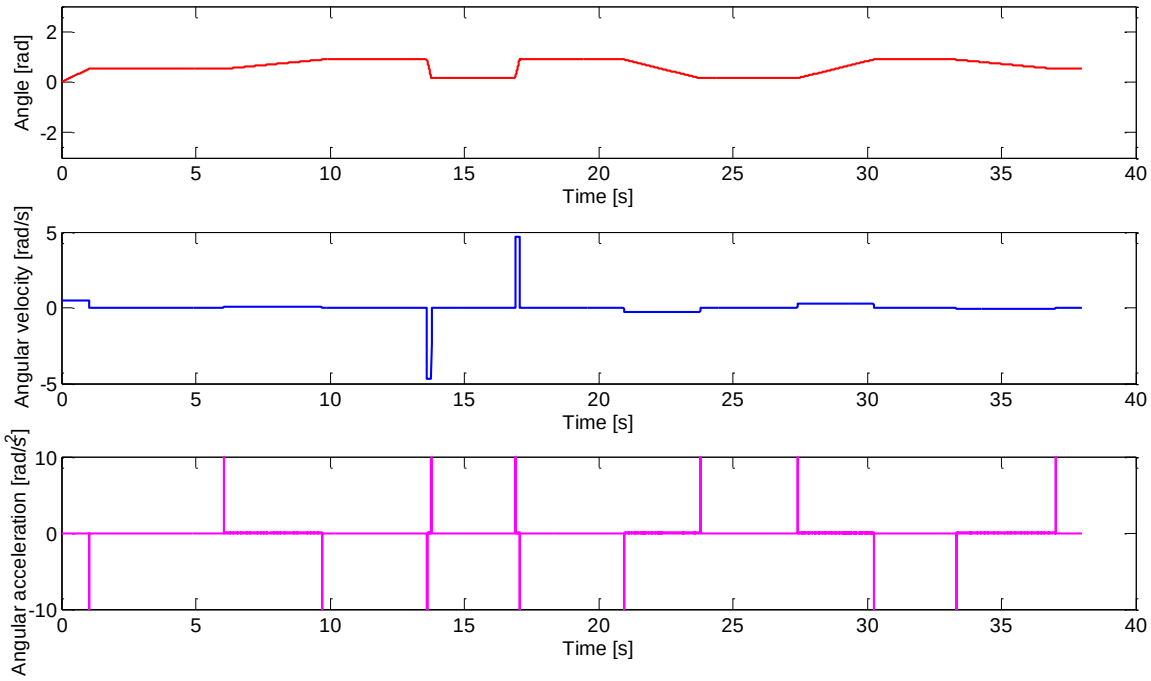

Figure 14: Active task with small position perturbations. The starting position of this signal was 45^0 of flexion. The red line is the change in angular position over time, the blue line is the change in angular velocity over time, and the magenta line is the change in angular acceleration over time.

2.5 Method validation

The first step is to apply the model to all different data sets acquired with the above described tests. The VAF-values are used to assess the goodness of the fit for each test. The SEM-values are used to see which parameters are accurately estimated for each test. When pilot data was analyzed concluded was that the VAF-values should be above 98% to be sufficiently high, the normalized SEM-values should be below 0.1 to be sufficiently low. Expected is that with the tests under passive conditions the VAF-values will be high and that with the passive tests which acquires more position information all passive parameters (m, k_{ECR}, k_{FCR}, $x_{0,ECR}$, $x_{0,FCR,}$ k_{rel} and τ_{rel}) could be estimated accurately. For the test with active conditions there are two options:

1. The VAF-values are high and all SEM-values are low, no further actions are necessary.
2. The VAF-values are low and/or SEM-values are high, in this case further actions are necessary. In order to acquire more accurate estimations the datasets of the flexor and the extensor with the same force level and same start position, e.g. for the neutral start-position the task with a high flexion force level and the task with a high extension force level, will be estimated simultaneously. During the task with a e.g. a high flexion force level the flexor is active and the extensor is passive, during a task with a high extension force level the extensor is active and the flexor is passive. Thus, by estimating a flexor and an extensor task simultaneously they contain information about both the extensor and flexor muscle under active and passive conditions.

After the simultaneous estimation of the datasets of the flexor and the extensor muscle, there are again two options:

1. The VAF-values are high and all SEM-values are low, no further actions are necessary
2. The VAF-values are low and/or SEM-values are high, in this case further actions are necessary. At this point high VAF-values are expected, but high SEM-values are expected for the passive parameters. The high SEM-values are probably because the passive parameters

are not estimated accurately because the datasets do not contain sufficient information about the passive state of the muscle because only a small part of the RoM is described with this data. To cover a bigger part of the range of motion the data of the flexor and extensor muscle with the same force level and different start positions is simulated simultaneously.

After expanding the RoM by combining signals per force level there are again two options:

1. The VAF-values are high and all SEM-values are low, no further actions are necessary.
2. The VAF-values are low and/or SEM-values are high, in this case further actions are necessary. The next step would be to take the passive parameters out of the optimization and set the values of the passive parameters to fixed values which are found with the passive tests.

After taking the passive parameters out of the optimization there are again two options:

1. The VAF-values are high and all SEM-values are low, no further actions are necessary.
2. The VAF-values do not increase after setting the passive parameters to fixed values this probably means that some of the active parameters are dependent of the activity of the muscle. The passive parameters should be put into the optimization again in turn to see if one or more of the passive parameter are dependent of the muscle activity.

When setting the values of passive parameters to fixed values does not work, the next solution would be adding tendons to the model. During passive tests the tendons can be assumed to be much stiffer than the passive muscle tissues, but when the muscle is active the muscle becomes shorter and stiffer due to cross-bridge connections and the assumption might not hold anymore. With the addition of the tendons an extra state is added to the model which compensates for the different way the force is now transferred through the muscle. In Figure 15 can be seen how the schematic representation of Figure 4 changes.

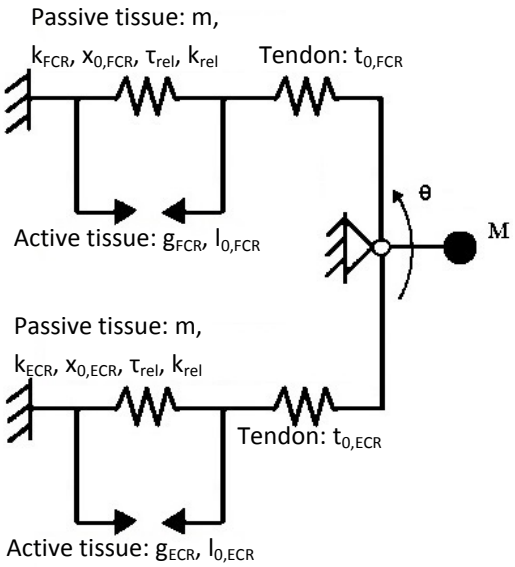

Figure 15: Schematic representation of the neuromuscular model, including the tendons. Above the flexor and its tendon are depictured, below the extensor and its tendon are depictured. Both muscles are split in an active and passive tissue part and the corresponding parameters are shown.

With the addition of the tendon equation **2** will change to:

$$T_{ECR}(t) = F_{Tendon,ECR} * \ r_{ECR} = \left(F_{elastic,ECR} + F_{active,ECR}\right) * r_{ECR} \quad \textbf{(20)}$$

Where $F_{Tendon,ECR}$ is the tendon force calculated with (Thelen 2003):

$$F_{Tendon,ECR} = \begin{cases} \frac{F_{toe,ECR}}{(e^{s_{toe,ECR}}-1)} * \left(e^{\left(s_{toe,ECR}*\frac{lt_{ECR}-t_{0,ECR}}{lt_{toe,ECR}-t_{0,ECR}}\right)} - 1\right); lt_{ECR} \leq lt_{toe,ECR} \\ kt_{lin,ECR} * \left(lt_{ECR} - lt_{toe,ECR}\right) + F_{toe,ECR}; \quad ; lt_{ECR} > \ lt_{toe,ECR} \end{cases} \quad \textbf{(21)}$$

Where $F_{toe,ECR}$ is the tendon force (dependent of the maximum isometric force) and $lt_{toe,ECR}$ is the tendon length after which the tendon force-length behavior transcribes from non-linear to linear, $s_{toe,ECR}$ is an exponential shape factor, $kt_{lin,ECR}$ is a linear shape factor, $t_{0,ECR}$ is the slack length of the tendon, which is the length after which tendon force will be generated due to stretching of the tendon and lt_{ECR} is the length of the tendon:

$$lt_{ECR} = l_{mt,ECR} - x_{ECR} \quad \textbf{(22)}$$

Where $l_{mt,ECR}$ is the length of the muscle-tendon complex. Similar equations are used for the flexor muscle. To be able to add the tendons the model structure had to change from a vector based model to an iterative model because an additional dynamic state is added and therefore not all states could be obtained directly from the measurement anymore. The activation filter also changed in a first order non-linear filter with a different time constant for the activation and deactivation dynamics (calculated in the same way for the flexor and extensor):

$$a_{ECR} = \frac{E_{EMG,ECR} - a_{ECR}}{\tau_a * s} \quad \textbf{(23)}$$

Where τ_a is a time constant which varies with the activation level and whether the muscle activation level is increasing or decreasing (Thelen 2003):

$$\tau_a = \begin{cases} \tau_{act} * (0{,}5 + 1{,}5 * a); \ E_{EMG} > a \\ \frac{\tau_{deact}}{0{,}5+1{,}5*a} \quad ; \ E_{EMG} \leq \ a \end{cases} \quad \textbf{(24)}$$

Where τ_{act} is the activation time constant and τ_{deact} is the deactivation time constant, with values of 15×10^{-3} and 50×10^{-3} respectively, but different values were tried as no consensus about the activation and deactivation time constant was found in literature (Winters et al. 1985, Riek et al. 1999). As the activation and deactivation constant are known, with the new activation filter the relative damping and cut-off frequency parameters will be eliminated. The first order non-linear filter has approximately the same properties as the earlier used linear second order filter. Table 3 gives an overview of the parameters that are now optimized with the new model.

Table 3: An overview of the parameters of the new neuromuscular model which includes the tendon.

Wrist model including tendon, 2015			
1	M	Mass wrist	kg
2	k_{FCR}	Stiffness coefficient flexor	1/m
3	k_{ECR}	Stiffness coefficient extensor	1/m
4	$x_{0,FCR}$	Approximated slack length flexor	m
5	$x_{0,ECR}$	Approximated slack length extensor	m
6	τ_{rel}	Relaxation time constant	s
7	k_{rel}	Relaxation factor	
8	g_{FCR}	fEMG weighting factor flexor	N/volts
9	g_{ECR}	fEMG weighting factor extensor	N/volts
10	$l_{0,FCR}$	Optimal muscle length flexor	m
11	$l_{0,FCR}$	Optimal muscle length extensor	m
12	$t_{0,ECR}$	Tendon slack length extensor	m
13	$t_{0,FCR}$	Tendon slack length flexor	m

Another possible explanation for low VAF- values and high SEM-values that should not be overlooked is that the optimization algorithm has found a local minimum instead of the global minimum. A grid-search will be done for two data sets as an indication if the solution of the estimation is near the global minimum. Grid searches will be performed for the model with and without tendons. Based on this results the best input signal and task description for the protocol will be determined.

Results

For two of the active tests (high flexion force with neutral start position and low flexion force with a start position in extension) and one passive test (multiple hold phases with multiple velocities) the data of 9 subjects was available. For one active test (with the varying force level) data of 4 subjects was available (Table 4).

Table 4: overview of the number of subjects for each test.

Test	Number of subjects
Passive test: Ramp and hold	10
Passive test: Sigmoid	10
Passive test: Multiple holds, low velocity	10
Passive test: Multiple holds, high velocity	10
Passive test: Multiple holds, varying velocity	9
Passive test: Multi sine	10
Active test: low (extension) force level, neutral start-position	10
Active test: low (flexion) force level, neutral start-position	10
Active test: high (extension) force level, neutral start-position	10
Active test: high (flexion) force level, neutral start-position	9
Active test: low (extension) force level, flexion start-position	10
Active test: low (flexion) force level, flexion start-position	10
Active test: high (extension) force level, flexion start-position	10
Active test: high (flexion) force level, flexion start-position	10
Active test: low (extension) force level, extension start-position	10
Active test: low (flexion) force level, extension start-position	9
Active test: high (extension) force level, extension start-position	10
Active test: high (flexion) force level, extension start-position	10
Active test: varying force levels	4

In Appendix A multiple tables can be found which give the mean value and mean SEM-value for each parameter per test, averaged over all subjects for the passive and active tests.

Examples of the results of the model estimations can be seen in Figure 16 and 17. Figure 16 and 17 also show the contribution of the passive muscle torque and the neural muscle torque to the total torque. For the active tests the neural muscle torque (thus the torque of the active muscle) is the most contributing component, while for relaxing tasks the passive muscle component is the main contributor to the total torque. However, for active tasks and passive tasks can be seen that both the neural muscle torque and the passive muscle torque are needed to make up the total torque. When fast movements occur during passive tests reflex reactions can be seen and at those fast slopes the neural muscle torque also contributes to the total torque.

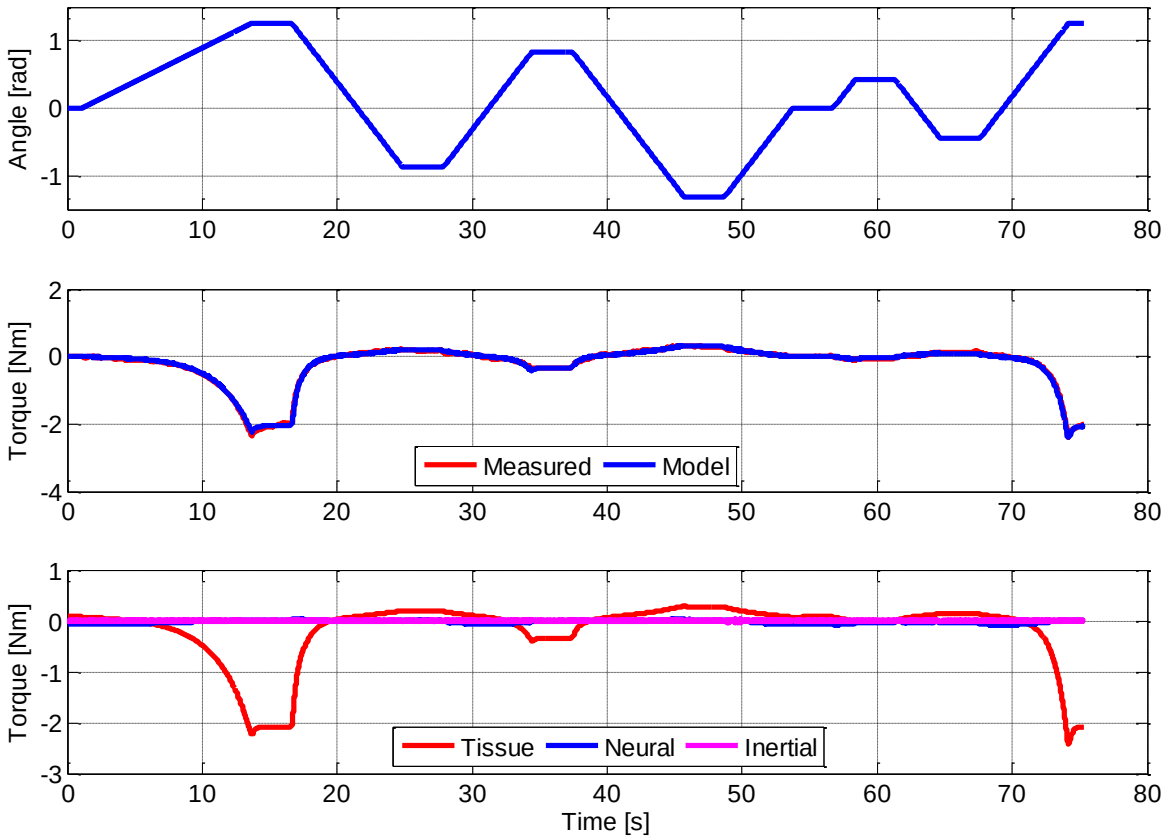

Figure 16: Estimation of the measured torque of the passive test with the multiple hold phases (slow). In the lowest part of the figure the division of the torque in the elastic and neural torque components is depictured.

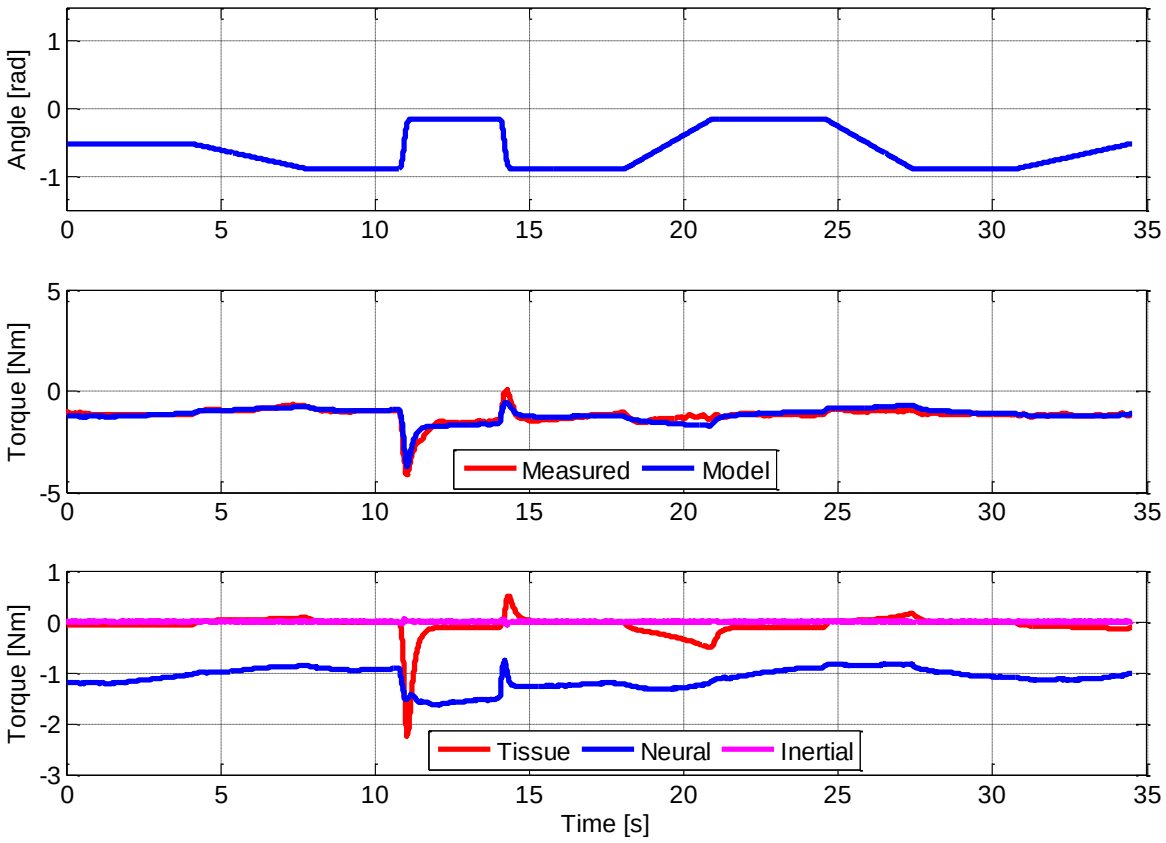

Figure 17: Estimation of the measured torque of an active test with a high flexion force level and a start position in flexion. In the lowest part of the figure the division of the torque in the elastic and neural torque components is depictured.

All the estimations for the passive conditions showed high VAF values. The VAF-values for the active tests were generally lower. The SEM values of the active parameters (g_{ECR}, g_{FCR}, $l_{0,ECR}$, $l_{0,FCR}$, f_0 and β) were lower for the active tasks than for the passive tasks. For all tasks the $x_{0,ECR}$, $l_{0,ECR}$ and βgenerally had higher SEM values.

Passive tests

VAF-values of all passive tests are shown in Figure 18. SEM values are shown in Figure 19. Plots of the different values of the 13 parameters per test, including the standard deviation for each parameter are shown in Figure 20.

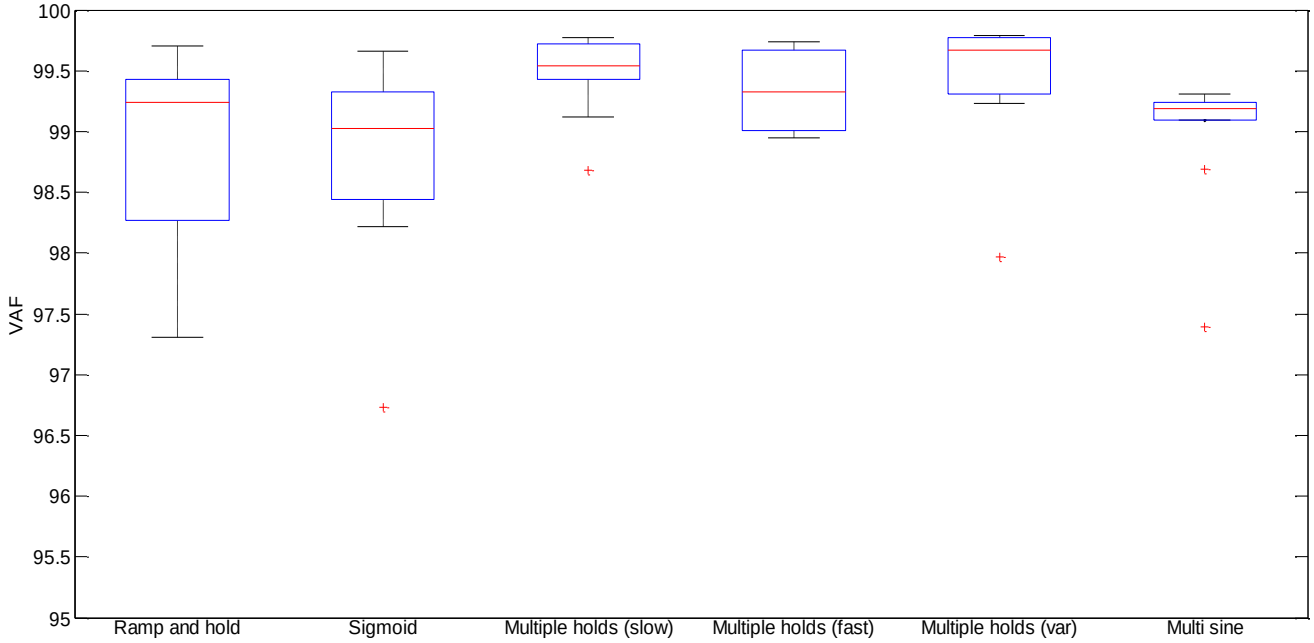

Figure 18: Boxplot of the VAF-values of the different passive tests

All tests had a high mean VAF-value and relatively low variability for the tests with the multiple hold phases (Figure 18). The plots of the SEM-values are plotted on a logarithmic scale (Figure 19), because $x_{0,ECR}$ and $l_{0,ECR}$ would otherwise lie outside the plot. When the SEM-values were evaluated the signal with multiple hold phases and low velocity gives the best estimation of all the individual parameters, except for β. In Figure 20 the consistency of all the parameter values between the passive tests is shown. The relaxation parameters k_{rel} and τ_{rel} were significantly higher for the sigmoid signal, g_{FCR} and g_{ECR} are much higher for the signal with multiple hold phases and low velocity, $x_{0,FCR}$ and $l_{0,FCR}$ were estimated with a large variance for the signal with multiple hold phases and varying velocities, and f_0 and β were estimated with a great variance for the multi hold signal with a high velocity. It was also noticed that during all the passive tests except the multi sine the elastic torque was the main contributor to the total torque. For the multi sine test the inertial torque was the main contributor to the total torque.

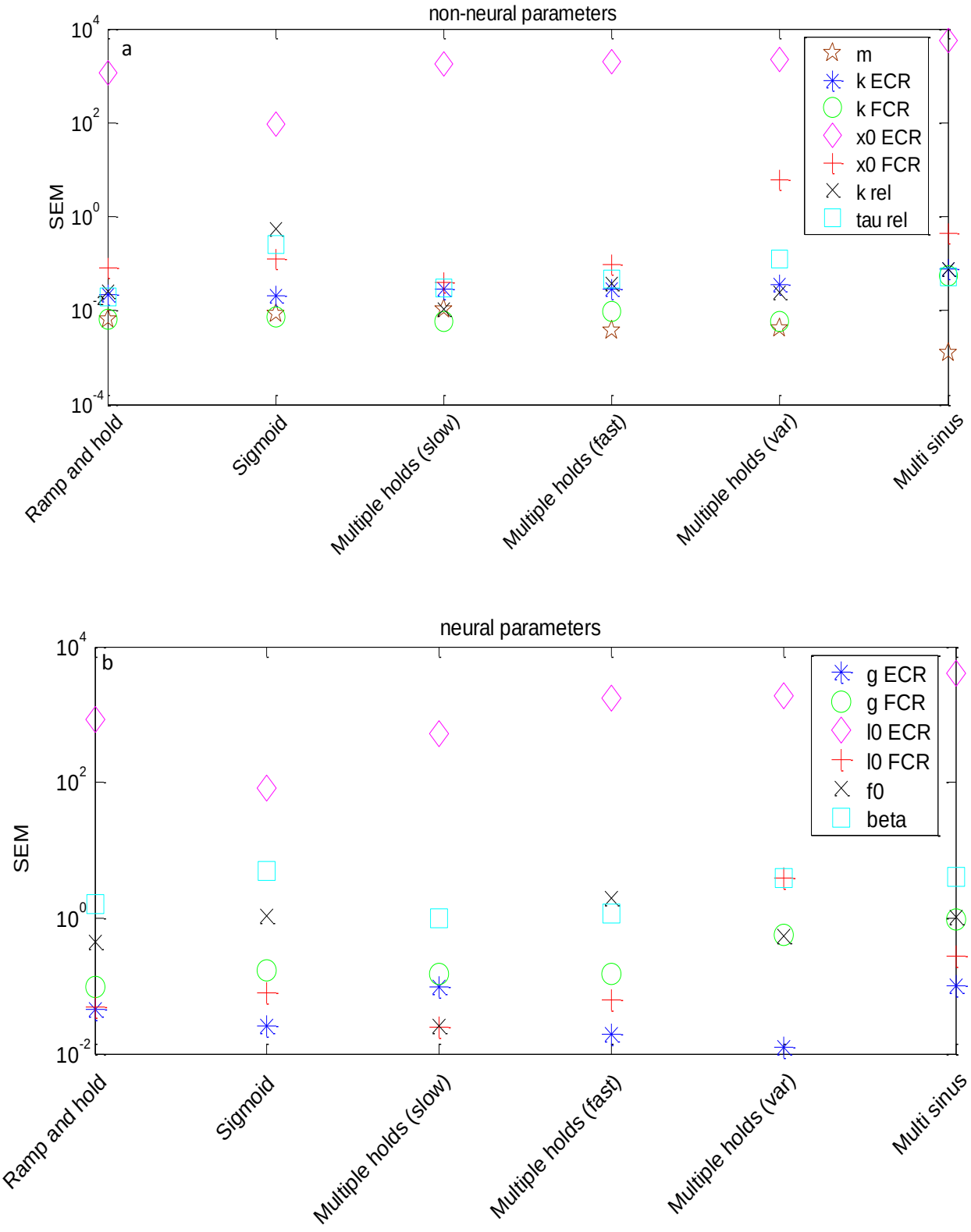

Figure 19: a) SEM values of the passive parameters of the passive tests; b) SEM values of the active parameters of the passive tests.

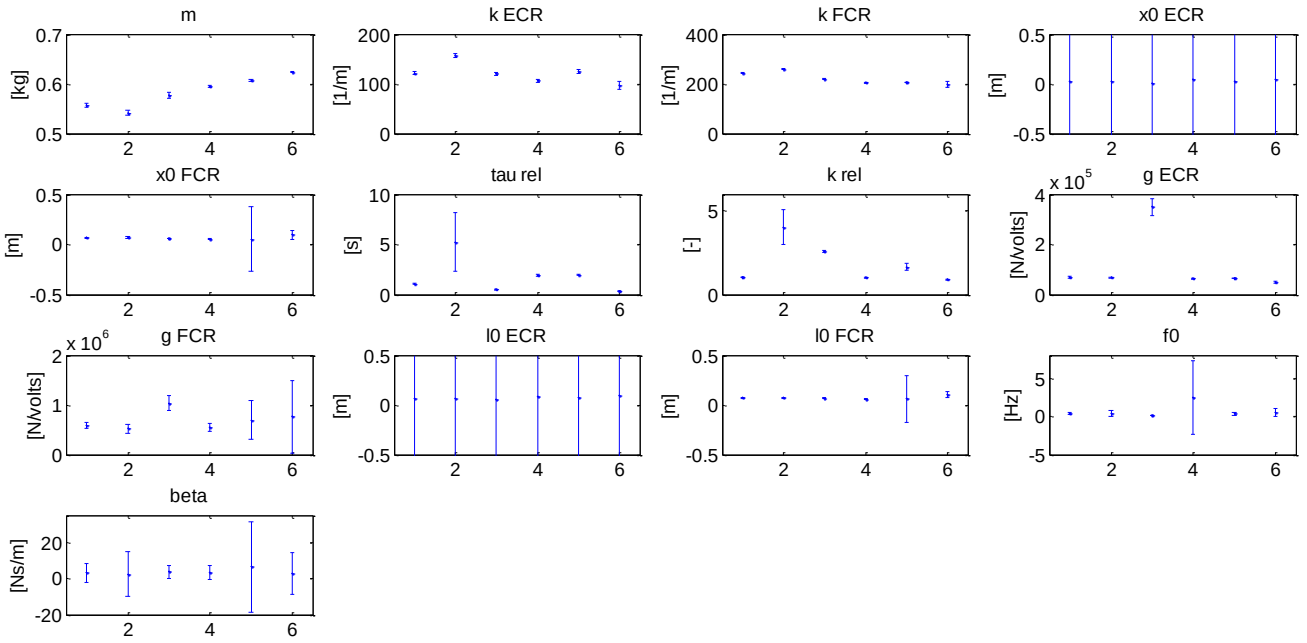

Figure 20: Plots of the values and their standard deviation of each parameter for all the passive tests. (1 = ramp and hold; 2 = Sigmoid; 3 = multiple holds (slow); 4 = multiple holds (fast); 5 = multiple holds (multiple velocities); 6 = multi sinus).

Active tests

VAF-values of all active tests are shown in Figure 21. Corresponding SEM values are shown in Figure 22.

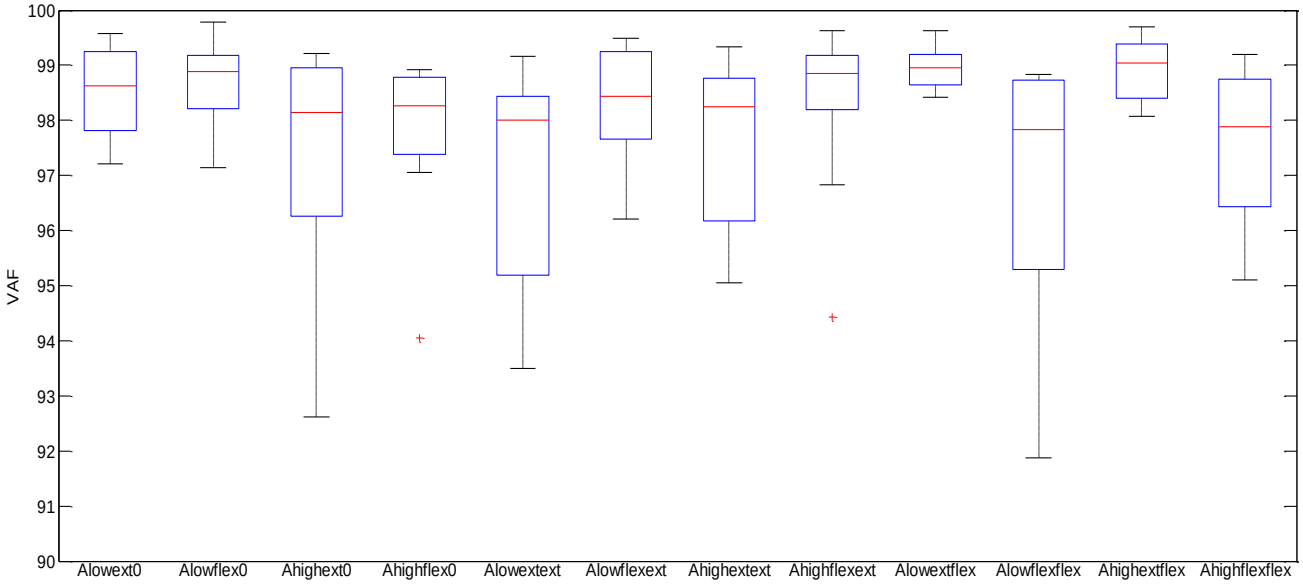

Figure 21: Boxplot off the VAF-values off all the active test. Low or high describes the force level (low = 0.5Nm, high = 1Nm). The flex or ext term directly after the force level describes if the force is applied in the flexion or extension direction respectively. The last term (0, flex or ext) describes the start position of the test, which is respectivly the neutral position in flexion or in extension.

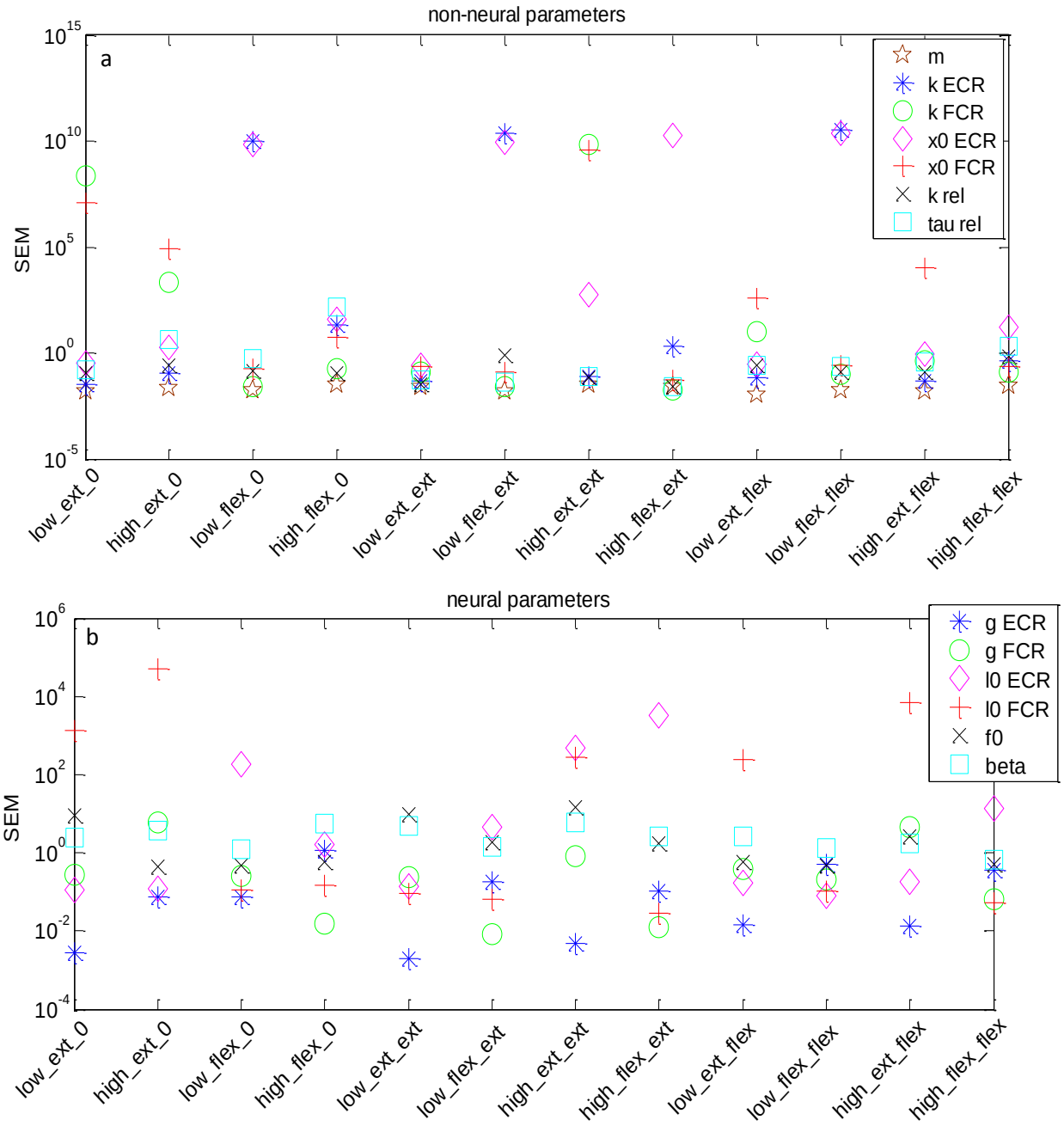

Figure 22: a) SEM values of the passive parameters of the active tests; b) SEM values of the active parameters of the active tests. Low or high describes the force level (low = 0.5Nm, high = 1Nm). The flex or ext term directly after the force level describes if the force is applied in the flexion or extension direction respectively. The last term (0, flex or ext) describes the start position of the test, which is respectivly the neutral position in flexion or in extension.

The VAF-values vary a lot between the different active tests. Some of the tests had a large variation on their VAF-values. Especially the tests with an extension force with a start position in the flexion direction resulted in the highest VAF values (Figure 21), with the least deviations, indicating that the model structure fits best. For tests with an extension force the flexion parameters were less accurate estimated and vice versa (Figure 22). A flexion force with a start position in flexion and an extension force with a start position in extension is difficult to estimate.

Varying activation level

When the activation level is varying and thus completely independent of the movement the VAF-values were very low and SEM-values were very high in comparison with the other tests. An overview of the SEM - and VAF-values is given in Table 5. For f_0 and β the estimated values are not credible, which is illustrated by the high SEM-values for f_0 and β. The mean VAF of the active tests with a varying activation level was 48,4. An estimation of the measured torque can be seen in Figure 23.

Table 5: Mean values and mean SEM-values of the active test with a varying activation level.

Parameter	Mean Value	Mean SEM
m	0,439	0,133
k_{FCR}	582	1,54(x10^3)
k_{ECR}	118	0,117
$x_{0,FCR}$	0,0639	33,6
$x_{0,ECR}$	-0,00549	2,68(x10^6)
τ_{rel}	0,400	1,92(x10^4)
k_{rel}	7,53	2,87(x10^9)
g_{FCR}	6,49(x10^4)	0,0180
g_{ECR}	2,03(x10^4)	0,00617
$l_{0.FCR}$	0,0602	0,801
$l_{0,FCR}$	0,0964	0,665
f_0	13,7	117
β	14,0	175
VAF	48,4	--

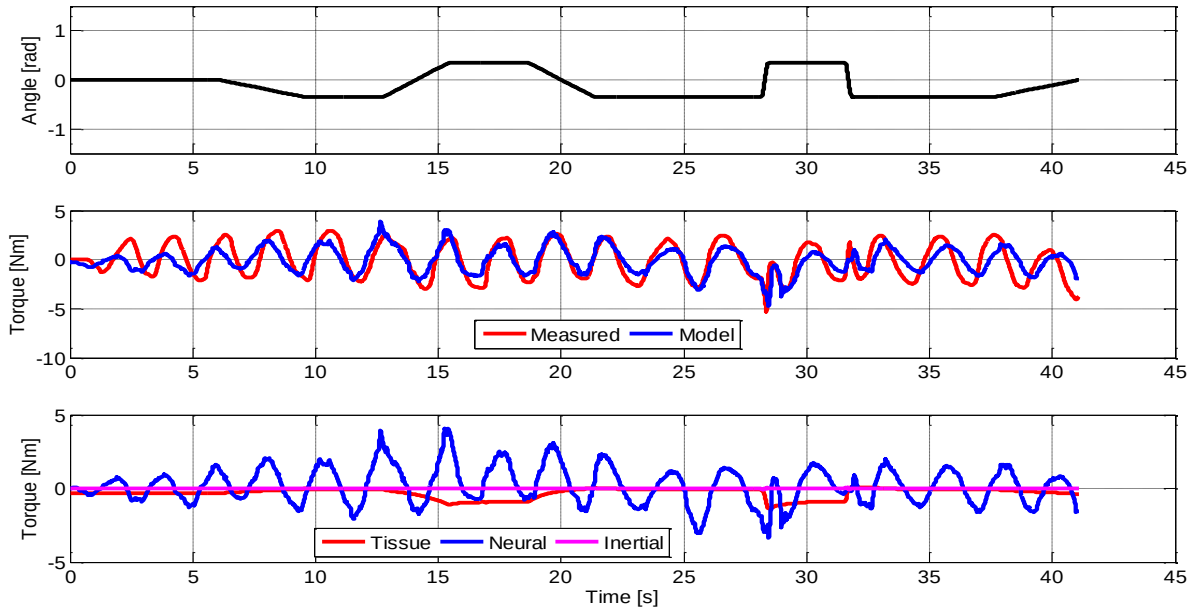

Figure 23: Estimation of the measured torque of the active test with a varying activation level.

Parameter change

To compare the parameter values during the different force tasks (high flexion force, low flexion force, relaxed, low extension force, high extension force), the mean was taken of the force tasks for

the three different start positions for all subjects, such that every force level has one mean value. For the relaxing task the values of the multi holds test with slow velocity is taken. The values are plotted together with their standard deviation in Figure 24.

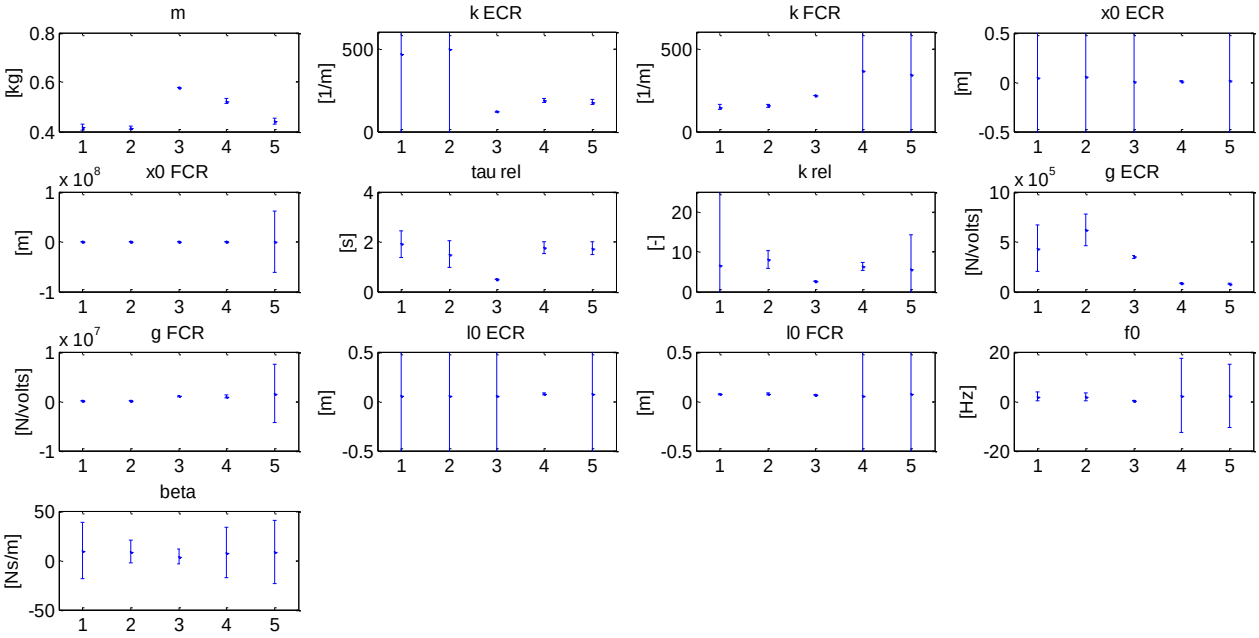

Figure 24: Plots of the values and their standard deviation of each parameter for all the active tests, grouped per activation level. (1 = high flexion force; 2 = low flexion force; 3 = relaxed; 4 =low extension force; 5 = high extension force.

When the parameters were evaluated for the different activation levels, the standard deviations were low for the parameters of the extensor and high for the parameters of the flexor during an extension force task. The opposite holds for a flexion task. The cut-off frequency of the activation filter was less accurate estimated during an extension force task. The optimal muscle length and approximated slack length of the extensor muscle ($l_{0,ECR}$ and $x_{0,ECR}$ respectively) were only accurately estimated during a low extensor force task. The mass has the highest estimate for a relaxing task and the lowest estimate for flexion task. For the passive stiffness coefficient k_{ECR} accounts that it was higher during an extension force task than during a relaxing task. For the passive stiffness coefficient k_{FCR} accounts that it was lower during a flexion force task than during a relaxing task. The relaxation time constant τ_{rel} was higher during active tasks than during a relaxing task. The EMG weighing factor of the extensor was high during a low flexion force task, lower during a relaxing task and lowest during an extension force task (about the same values for a low and high extension force task). The EMG weighing factor of the flexor was low during a flexion force task and higher during a relaxing task and a low extension force task.

Relation between EMG and VAF

Because the VAF-values are lower for active tests than for passive tests the option is explored if the VAF-value is dependent of the amount, median, mean or maximum EMG values. The relation between the median EMG value and the VAF-value is shown in Figure 25. No (linear) relation between the amount, median, mean or maximum EMG value and the VAF was found, as is represented by the red line in Figure 25. When the outliers of Figure 25 are removed (the point with

a VAF-value of 86% and the point with an EMG value of 0.015N/Volt) there is also no relation between median EMG and VAF visible.

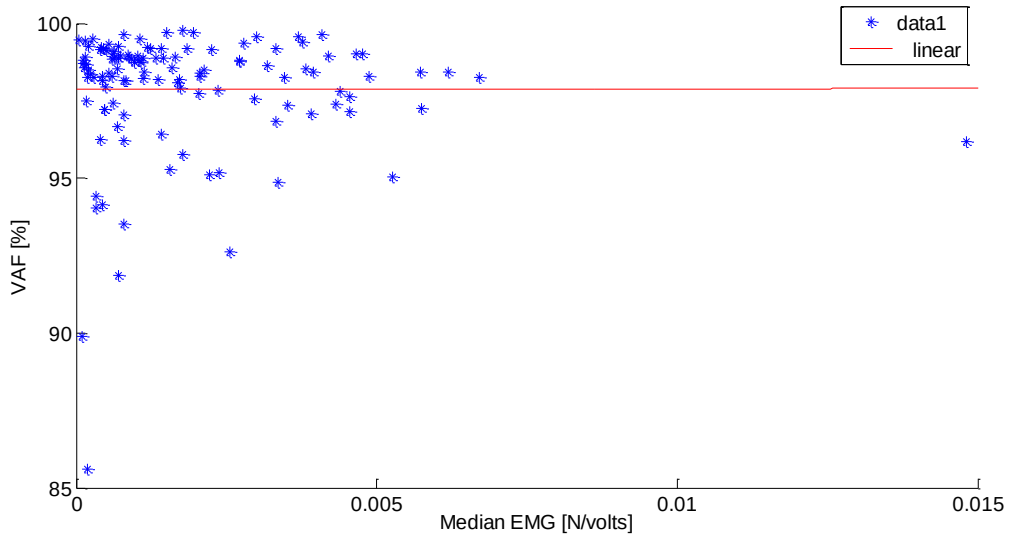

Figure 25: Relation between median EMG and VAF. The blue asterisks are the data points and the red line represents the regression line.

Estimating the active tests simultaneously for the same force levels and start positions

As the VAF-values were not high enough and the SEM-values were very high for some of the parameters during the active tasks, the next step was to simultaneously estimate the parameters for tasks with the same start position and same (but opposite because a flexion and extension force were combined) force level. The data of the low force tasks are plotted together (per start position) and the data of the high force tasks are plotted together (per start position). VAF-values of all the combined tests are shown in Figure 26. Corresponding SEM values are shown in Figure 27.

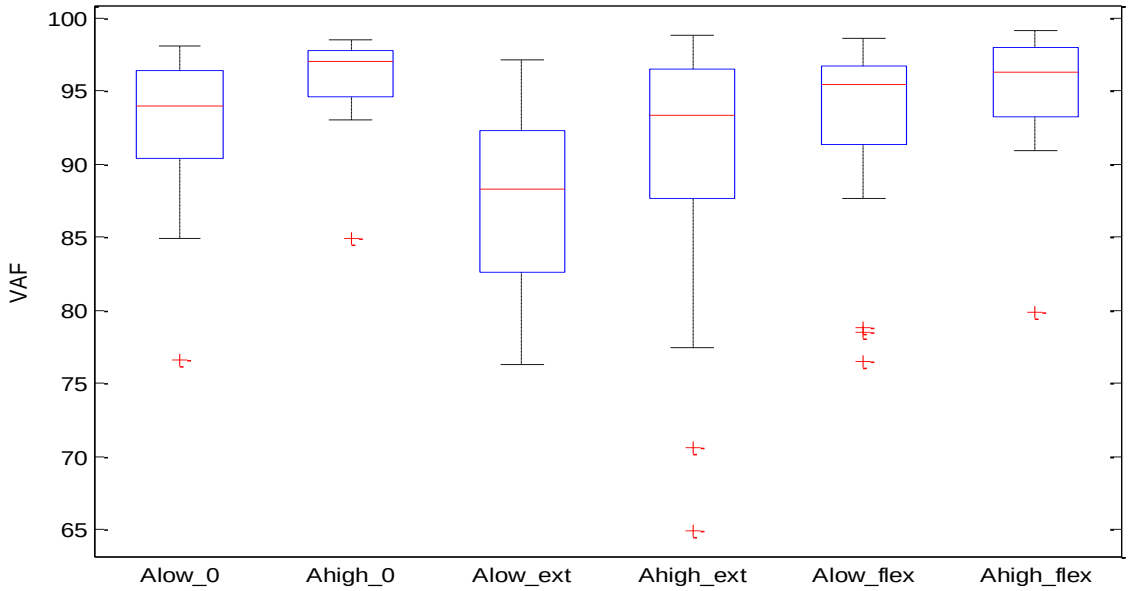

Figure 26: Boxplot of the VAF-values for the different active tests when the forces in flexion and extension direction are simultaneously estimated by the model. Low or high describes the force level (low = 0.5Nm, high = 1Nm), of the flexor and extensor muscle that are simultaneously estimated. The last term (0, flex or ext) describes the start position of the test, which is respectivly the neutral position in flexion or in extension.

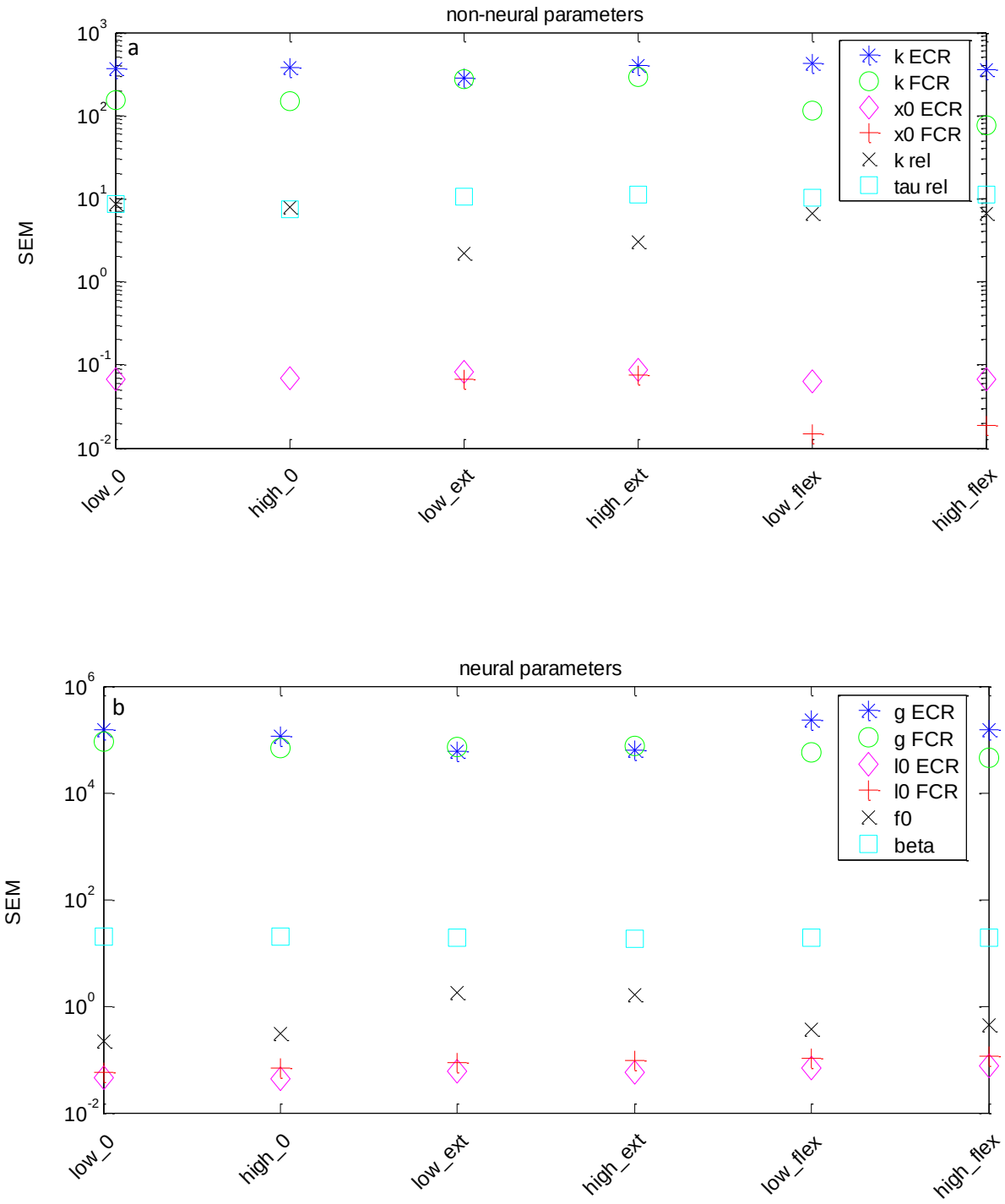

Figure 27: a) SEM values of the passive parameters of the active tests when the forces in flexion and extension direction are simultaneously estimated by the model.; b) SEM values of the active parameters of the active tests when the forces in flexion and extension direction are simultaneously estimated by the model. Low or high describes the force level (low = 0.5Nm, high = 1Nm), of the flexor and extensor muscle that are simultaneously estimated. The last term (0, flex or ext) describes the start position of the test, which is respectivly the neutral position in flexion or in extension.

When the flexion and extension force were estimated together for the two different force levels (high and low) and for the three different start positions, the VAF-values were high for a high force level with a neutral start position and for the low and high fore level with a start position in flexion (Figure 26). When the SEM-values are considered k_{ECR} and $x_{0,ECR}$ were not accurately estimated with the high force with a neutral start position. With a high force level and a start position in flexion most parameters were accurately estimated, except β (Figure 27). Two test that were individually not very good estimated (a high flexion and extension force with a start position in flexion) resulted in a good estimate when the parameters are estimated on the recorded data for both tasks together. In Table 6 an overview is given of the estimated mean values of the single estimations of the active tests compared with the mean values of the parallel estimated active tests. In the parallel estimations $x_{0,ECR}$ was estimated twice as high, the relaxation parameters were estimated higher, g_{FCR} is a factor 10 lower than in the single estimation and β is estimated twice as high.

Table 6: Mean values of the parallel estimations of the active tests compared to the mean values of the single estimated active tests.

Parameters	Mean value parallel estimation		Mean value single estimation	
	Mean	SEM	Mean	SEM
m	--	--	0,450	0,0220
k_{FCR}	364	$4{,}26\text{x}10^{4}$	335	$5{,}62\text{x}10^{9}$
k_{ECR}	176	$1{,}64\text{x}10^{4}$	254	$6{,}20\text{x}10^{8}$
$x_{0,FCR}$	0,0728	0,000470	0,0337	$4{,}83\text{x}10^{9}$
$x_{0,ECR}$	0,0280	0,00177	0,0359	$2{,}98\text{x}10^{8}$
τ_{rel}	5,83	10,1	1,72	0,228
k_{rel}	9,90	31,3	6,645	13,4
g_{FCR}	$1{,}28\text{x}10^{5}$	$2{,}46\text{x}10^{10}$	$3{,}05\text{x}10^{5}$	0,207
g_{ECR}	$6{,}85\text{x}10^{4}$	$2{,}25\text{x}10^{9}$	$6{,}59\text{x}10^{5}$	1,07
$l_{0,FCR}$	0,0586	0,00106	0,0640	330
$l_{0,FCR}$	0,0886	0,000770	0,0698	$4{,}94\text{x}10^{3}$
f_0	0,794	1,15	2,07	3,55
β	19,3	1,62	8,72	2,81740

Secure passive parameters to earlier found values

Expected was that the best results would be acquired when all active tests with the same force level (thus all different start-positions) were combined as one big data set to estimate the different active parameters. Thus, one estimation was done for all tests with a low force level and one estimation was done for all tests with a high force level. Good results were expected because all tasks combined would give information about different muscle lengths and a bigger part of the RoM. However, the resulting VAF-values were below zero. Therefor tasks were again combined per force level and per start-position for the estimation.

The next step was to take the passive parameters out of the optimization and set the passive parameters to fixed values found during the passive tests. From Figure 19a the conclusion was drawn that the passive muscle parameters were consistent and thus that the passive values could be used to set as fixed values for the optimization of the active tests. The fixed parameters were m, k_{ECR}, k_{FCR}, $x_{0,ECR}$, $x_{0,FCR}$, k_{rel} and τ_{rel}. VAF-values of the active tests with the fixed passive parameters are shown in Figure 28. The VAF-values of the tests with a low and high force level and a neutral start-position stayed the same, the VAF-value of the test with a low force level and a start-position in extension increased and the VAF-values of the test with a high force level and a start-position in extension and

the tests for both force levels with a start-position in flexion decreased. Though the SEM-values of the relaxation parameters were a lot higher during active tasks than during passive tasks, it was visible that the values for τ_{rel} and k_{rel} are higher during active tasks than during passive tasks (Figure 24). Therefore, the relaxation parameters were also released and estimated in the model the mean VAF-values of all tests increased (Figure 29). As the relaxation is depended of the stiffness, first was tried to release the stiffness coefficient parameters, which leaded to an increase in the mean VAF-values of the tasks with a high force level and a start-position in flexion or extension. The EMG gain of the extensor (g_{ECR}) and the cut-off frequency and relative damping of the activation filter (f_0 and β) had much higher SEM-values for the active tests with the fixed passive parameters (Figure 30) than when all parameters are optimized by the model (Figure 27b). For the SEM-values it did not matter if the stiffness coefficients or the relaxation parameters were released and optimized in the model, they stayed high.

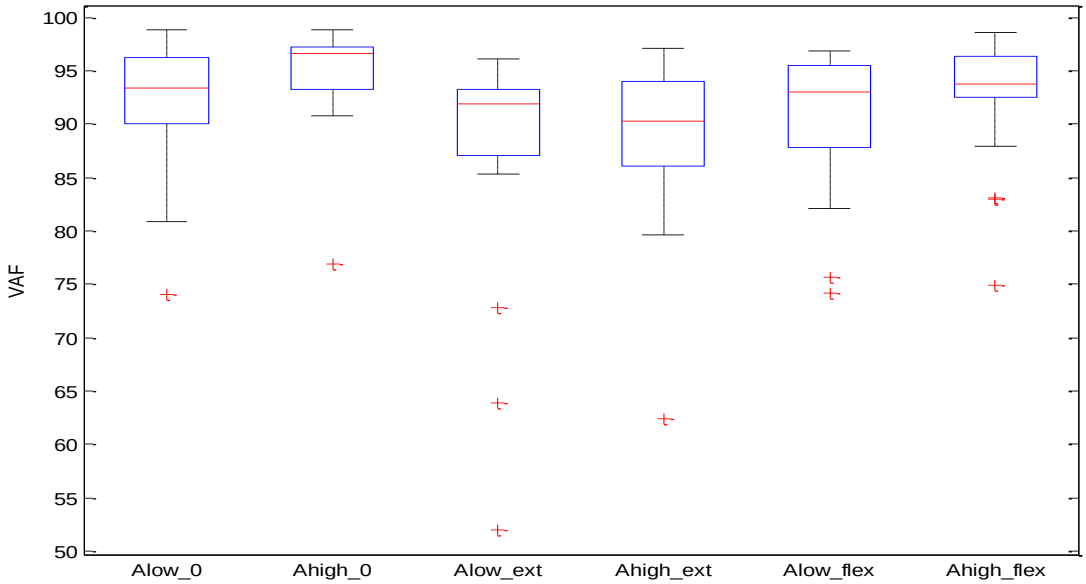

Figure 28: Boxplot off the VAF-values for the different active tests when the forces in flexion and extension direction are parallel simulated by the model and the passive parameters are set as fixed parameters. Low or high describes the force level (low = 0.5Nm, high = 1Nm), of the flexor and extensor muscle that are simultaneously estimated. The last term (0, flex or ext) describes the start position of the test, which is respectivly the neutral position in flexion or in extension.

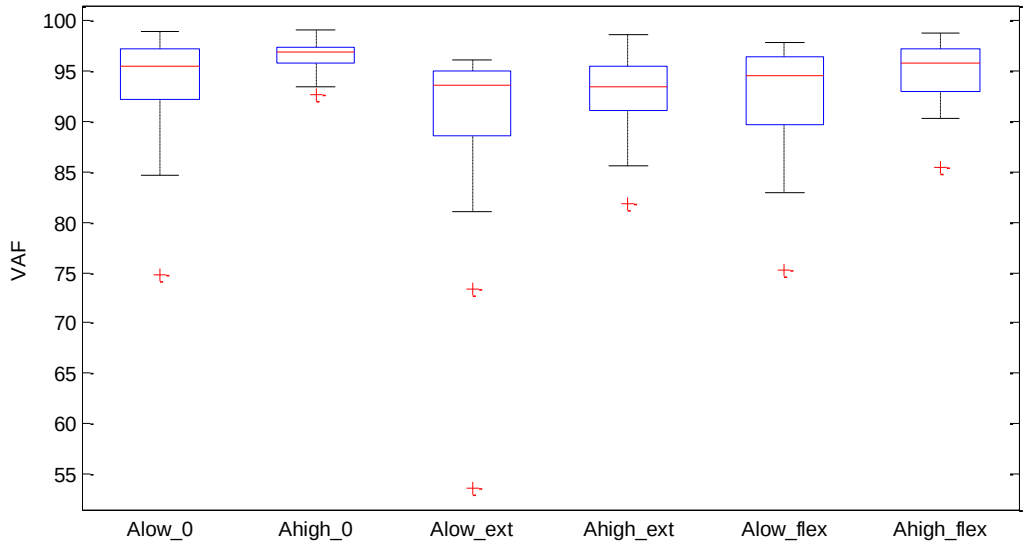

Figure 29: Boxplot off the VAF-values for the different active tests when the forces in flexion and extension direction are parallel simulated by the model and the passive parameters are set as fixed parameters, except k_{rel} and τ_{rel}. Low or high describes the force level (low = 0.5Nm, high = 1Nm), of the flexor and extensor muscle that are simultaneously estimated. The last term (0, flex or ext) describes the start position of the test, which is respectivly the neutral position in flexion or in extension.

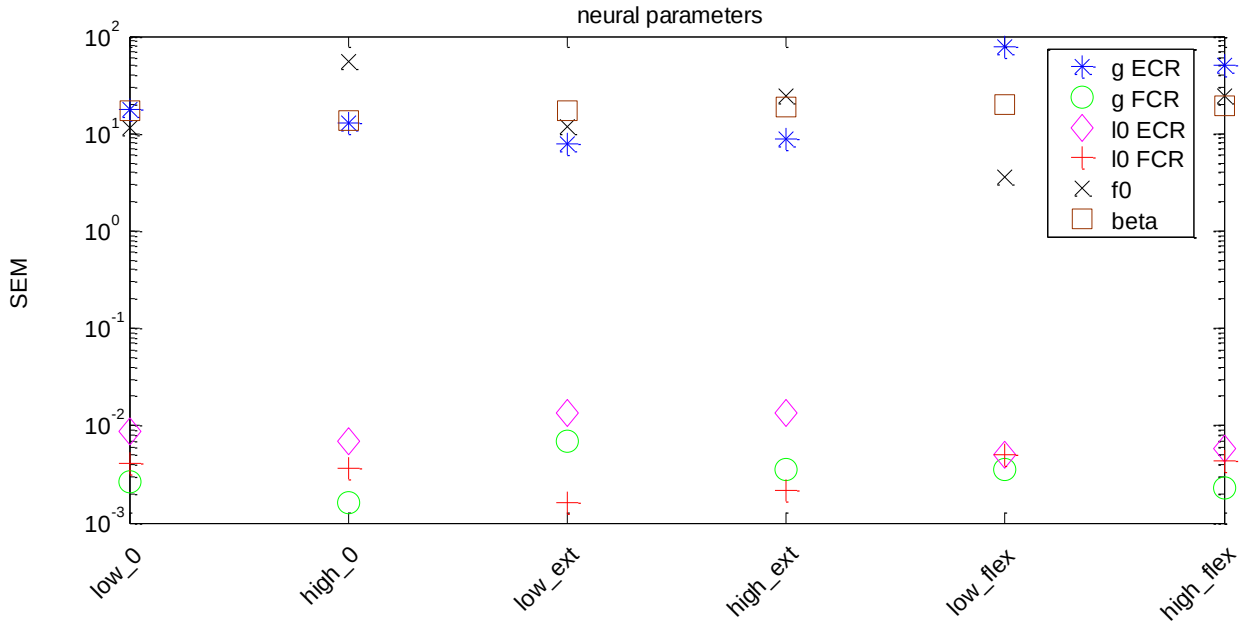

Figure 30: SEM values of the active parameters of the active tests when the forces in flexion and extension direction are parallel simulated by the model and the passive parameters are set as fixed parameters. Low or high describes the force level (low = 0.5Nm, high = 1Nm), of the flexor and extensor muscle that are simultaneously estimated. The last term (0, flex or ext) describes the start position of the test, which is respectivly the neutral position in flexion or in extension.

To ensure that a global minimum was found and not a local minimum a grid search was performed for the task with a high force level and a start position in flexion. The parameter values found with the grid search were equal to the values found with the optimization algorithm, and thus is assumed that the optimization algorithm finds the global minimum and not the local minimum. The mean values and mean SEM-values for the different parameters for the above described methods can be found in appendix A.

Muscle model with tendon

After setting the passive parameters to fixed values, the VAF-values were still not sufficiently high and not all SEM-values were sufficiently low. In order to increase the VAF-values of the active tests tendons were added to the existing neuromuscular model. However, the addition of the tendon did not lead to higher VAF-values, the VAF-values were generally lower than in any of the previous tests. When one test of one subject was considered, high VAF-values could be obtained by changing the shape parameters of the tendon or the initial values of the different parameters. However, when the found values were applied to another signal of the same subject or the same test the VAF-values decreased again.

In order to obtain high VAF-values different strategies were explored:

- a grid search for the parameters that determine the exponential and linear force-length behavior of the tendon (tendon length, maximum isometric force, absolute elongation of the tendon during maximum isometric force and the two shape factors).
- a grid search for the parameters which were sensitive for the outcome of the model (k_{ECR}, k_{FCR}, $x_{0,ECR}$, $x_{0,FCR}$, $t_{0,ECR}$, $t_{0,FCR}$).
- set the passive parameters to fixed values found with the old model and only estimate the active parameters in the model.

- set all parameters to fixed values found with the old model, such that the only parameters to estimate where $t_{0,ECR}$ and $t_{0,FCR}$. By setting all parameters to values found with the old model was tried to recreate the results found with the old model.
- varying the moment arms of both muscles.
- varying the activation and deactivation time constants.

None of the above tried options lead to a model which could be applied to all signals and obtain high VAF-values.

Discussion

The goal of this research was to develop a protocol which acquires rich enough data in terms of position, velocity and accelerations such that all the non-neural and neural parameters of the agonist and antagonist muscle of the wrist in the newest neuromuscular model can be accurately estimated. Based on the results on quality parameters of model estimation, there can be concluded that the model can accurately estimate the measured torque during passive tests; the VAF-values are high indicating that the difference between the measured and the modelled torque is minimal and SEM-values of the passive parameters are low during passive tests, indicating that the parameters are estimated accurately. The VAF-values of the active test are lower indicating that there is a larger difference between the measured torque and the modelled torque than during the passive test and SEM-values of all the parameters are higher during the active tests, indicating that the parameters are less accurately estimated than for the passive tests. In this study diverse options were explored in order to increase the VAF-values and decrease the SEM-values of the active parameters during active tests, but a sufficient explanation has not been found.

Expected was that adding more information in the position domain (the input signals with the multiple hold phases) would result in a more accurate estimation of the passive parameters (k_{ECR}, k_{FCR}, $x_{0,ECR}$, $x_{0,FCR}$, k_{rel} and τ_{rel}). Adding more information in the velocity domain (the input signal with the bell shaped velocity profile and the input signal with the multiple hold phases and varying velocities) would result in more information about the active muscle by evoking reflex reactions and thus would thus result in a more accurate estimation of the active parameters of the muscle (g_{ECR}, g_{FCR}, $l_{0,ECR}$, $l_{0,FCR}$, f_0 and β). Adding more dynamic information by adding varying accelerations and velocities (the multi sine input signal) would also result in more information about the active muscle due to reflex reaction and thus result in a more accurate estimation of the active muscle parameters. Finally, by changing the conditions of the test from passive to active more information about the voluntary active muscle is obtained. Because the SNR of the active muscle dynamics is higher during active conditions than with a reflex reaction during passive conditions a more accurate estimate of the active muscle parameters is expected.

The discussion is structured in the same way as section 2.5 of the methods, first the passive tests are discussed, then the active tests are discussed with the different analyzing methods used to try to acquire higher VAF-values and lower SEM-values for the tests. In order to acquire better results for the active tests the following steps are taken (in this order):

1. Applying the model to the active tests in the same way as for the passive tests.
2. Combining flexion and extension force for the active tests per force level and per start position (e.g. for the neutral start position the high flexion and extension force are combined) and estimate the torque for these signals simultaneously in such a way that one value for each parameter is obtained, with a different SEM-value for both the flexion and extension signal.
3. Combining the active tests only per force level in such a way that one estimation is done for all signals with a high force level and one estimation is done for all signals with a low force level.
4. Set the passive parameters of the active tests to a fixed value found during the passive test in such a way that only the active parameters are estimated in the model.
5. Adding a tendon to the neuromuscular model.

Passive tests

The results showed that the mean VAF-values of all the passive tests were high (above 99%). When the SEM-values are considered, both the optimal muscle length and slack length of the extensor carpi radialis ($x_{0,ECR}$ and $l_{0,ECR}$) were inaccurately estimated. The inaccurate estimates are probably caused by the physical limits of the Wristalyzer®, which prevent that the wrist can move as far in flexion as possible, leading to a not fully stretched extensor. The extensor can thus never reach be fully stretched during the tests and therefor the optimal muscle length and slack length are difficult to estimate.

The parameters f_0 and β have the highest SEM-values and also g_{FCR} has higher SEM-values in comparison with the other parameters. Because the test is applied during relaxing conditions it is expected that the active parameters (i.e. g_{ECR}, g_{FCR}, $l_{0,ECR}$, $l_{0,FCR}$, f_0 and β) have not as good estimates as the passive parameters (i.e. m, k_{ECR}, k_{FCR}, $x_{0,ECR}$, $x_{0,FCR}$, k_{rel} and τ_{rel}).

The consistency plots (Figure 20) show that the consistency of the parameters is good for the parameters, except for $x_{0,ECR}$ and $l_{0,ECR}$ for the above mentioned reasons. K_{rel} and τ_{rel} are higher for the sigmoid input signal in comparison with the other input signals, but as the SEM-values of k_{rel} and τ_{rel} also increase the difference is not significant. The sigmoid signal especially enriches the data on the dynamic front by adding multiple velocities. The relaxation parameters are best estimated when the static position information of the input data is enriched, which explains the higher SEM-values for the relaxation parameters during the test with the sigmoid input signal. The sigmoid signal did not give the better results that were expected from the bell-shaped velocity profile which is probably caused by taking the damping out of the model. The damping is velocity dependent, and now the only velocity dependent component in the model are the force-velocity characteristics, which help identifying the neural parameters and not the passive (non-neural) parameters.

Both the EMG gains (g_{ECR} and g_{FCR}) are estimated higher for the signal with the multiple hold phases and low velocity. Because the multiple hold phases with low velocity signal has a low velocity almost no EMG activity is expected during the measurement of healthy persons, as especially the position (static) information of the input data is enriched. The signal with multiple holds and a low velocity has almost no dynamic components as the velocity is too low to evoke a reflex response. The absence of EMG signal causes the EMG gain to be higher. The last point that can be seen in the consistency graphs is that f_0 and β have a high variance during the test with the multiple hold phases and high velocity. Expected was that more information about the active components of the muscle was available in the signal with the multiple holds and the high velocity, as reflex reactions would be evoked due to the high velocities. When more information about the active muscle component is present in the signal expected is that the parameters of this component have better estimates, so worse estimates for f_0 and β are in contradiction with the expectations.

During the multi sine test the inertia is a much bigger contributor to the total torque than during the other passive tests, which is caused by the quick changes in acceleration during the multi sine test. As inertia is only dependent of the mass, this signal does not provide additional information about the passive and active muscle components, and is thus less interesting for this study. Based on all the results of the passive tests can be concluded that with a test under passive conditions the passive parameters of the muscle are accurately estimated. The signal with the multiple hold phases and low velocity enriches the position (static) information of the input signal,

and reduces the amount of active muscle information due to the low velocity and is thus ideal to accurately estimate the passive parameters of the muscle.

Active tests

The next step is to try to also accurately estimate the active parameters of the muscle. Therefor active tests are added to the protocol during which the subject was asked to maintain a certain force level. The same model was applied to this data as to the data of the tests under passive conditions. When the active signals were estimated individually, the VAF-values of showed large variations. The model has a less accurate estimation of the measured torque when the direction of the force and start position are the same (e.g. a flexion force and a start position in flexion), which is probably caused by the fact that when the wrist is already in flexion the flexor muscle must be more contracted in order to deliver the same flexion force as when the start position of the wrist is in extension. The passive components of the antagonist muscle have to be compensated and the agonist muscle has to work against its own force-length characteristics, which is not the ideal situation and makes it more difficult to optimally estimate the measured torque.

When evaluating the SEM-values it is clear that when an extension force is delivered the flexor parameters have high SEM-values and vice versa. The high SEM-values can be explained by looking at the contribution of the neural torque to the total torque, for an active task the neural torque is the main contributor to the total torque. As the antagonist muscle is relaxed and the passive parameters are of minor importance the parameters of the antagonist cannot be accurately estimated. In general can be seen that the EMG gains (g_{ECR} and g_{FCR}) and the optimal muscle lengths ($l_{0,ECR}$ and $l_{0,FCR}$) have low SEM-values if the muscle the parameters belong to is active. β and f_0 are still not optimally estimated, in contradiction with the expectation that all active parameters would be accurately estimated during active tests.

The next step in order to obtain high VAF-values and low SEM-values with the active tests was to simultaneously optimize the parameters of the tests with the same start-position and the same (high or low) force level. With the simultaneous optimization as well passive as active data of both muscles is available at the same time. Expected was that during the parallel estimation the VAF-values would be higher than during the simulation of passive tasks, as every modelled muscle process is now addressed with the data. However, the combined estimation did not result in higher VAF-values but it did result in lower SEM-values. The mass could not be estimated anymore with the combined method, and f_0 and β still have quite high SEM-values. When the values are compared between the estimation of the estimated torque of two active input signals simultaneously and estimating just one active input signal it can be seen that $x_{0,ECR}$, τ_{rel}, k_{rel} and g_{FCR} have different values when they are estimated in parallel, which is probably because passive and active information of both muscles is now represented in the data. Especially g_{FCR} was estimated very high during extension tasks when the active tasks were single estimated, probably because the EMG activity of the flexor muscle was then close to zero, which explains why g_{FCR} is estimated a factor 10 lower during parallel estimation. The other parameters, $x_{0,ECR}$, τ_{rel} and k_{rel} also had high SEM-values during the single estimation, which explains why during parallel simulation the mean values differ.
The parameters of the activation filter still do not have low SEM-values when the active tests are estimated in parallel. During not one of the tests the activation filter parameters were estimated accurate, which is a striking problem. The non-accurate estimates could be caused by the type of

task, it might be better to use an EMG-task with position perturbations or a position task with force perturbations as both result in different reflex reactions (Forbes et al. 2011), but it can also be caused by the activation filter itself, that the filter is not sufficient to translate the EMG-signal to force. The deficiency of the activation filter might be underwritten by the results of the test with the varying force levels, the torque of the test could not be estimated accurately by the model, even though the resulting torque was (almost) completely uncoupled from the position.

The next step in order to obtain high VAF-values and low SEM-values for the active tests is simultaneously estimating the torque of the data with different start-positions and the same force level, such that data about the whole RoM is included in the optimization. The simultaneous simulation of 6 signals at once did not lead to high VAF-values or low SEM-values.

From the passive tests can be concluded that the estimated passive parameters are consistent for the different subjects (low SEM-values), and thus the next step was to set the passive parameters to fixed values during the simulation of the active tests. The SEM-values of the active tests showed that the stiffness coefficients and relaxation parameters were not estimated accurately. By taking the passive values out of the optimization the idea was that better estimates could be found for the active parameters. Setting the passive parameters to fixed values did not lead to better VAF-values in all cases. Some VAF-values increased, but some others decreased. The SEM-values of the EMG gain of the ECR and the cut-off frequency and relative damping of the activation filter increased. When the relaxation parameters were also optimized by the model, as they were proven to be dependent by the activation level, the VAF-values did increase but the SEM-values stayed the same. As the desired VAF-values and SEM-values are still not found with the above explorations the assumption is made that a state is missing in the model. A next step would be to add a tendon to the model, which should solve the problem of the missing state. During passive tasks the tendon can be assumed to be infinitely stiff, but when the muscle becomes active the stiffness of the muscle and the way in which the force is led through the muscle changes due to attached cross-bridges. Adding a tendon might compensate for this. However, the results of the new muscle model with the added tendons are worse than the results found with the old model, even after diverse attempts with grid-searches and fixing certain active or passive parameter values the results did not improve.

The model with the added tendons requires more anatomical information than the model without the tendons. The model with the tendons requires information about the maximum isometric muscle force, the shape parameters of the exponential and linear region of the length-force graph of the tendon and the absolute tendon elongation at maximum isometric muscle force. The slack length of the tendon is the parameter that is optimized with the model, but this parameter can change a lot, even between measurements for the same subject. The tendon length (and thus also the slack length) can be the length between the muscle and the wrist, but it can also be that the full tendon length including the tendons in the fingers is the right length. The insecurity about all the anatomical variables will lead to a worse estimation (Gerus et al. 2012, Ackland et al. 2012). When all these anatomical variables are systematically adapted for each signal a good estimation can be acquired, but the values that are then found for the anatomical variables have to change again for the next test signal, even if it is a test of the same subject.

The insecurity about the anatomical variables could be the reason of the worse estimation of the model with the added tendons. However, as the anatomical variables have to change even for the

same subject to obtain good estimations, they might not be the main reason for the worse estimations. Another option would be the coupling between the measured EMG and the generated force. The relation between EMG and force is still not clear nowadays and is very difficult to determine because the exact force generated but the muscle cannot be measured in vivo in humans (Woods et al. 1983). When only passive conditions are examined the contribution of the EMG dependent force to the total torque is negligible, which explains why the model works for passive tasks. However, when the relation between EMG and VAF was explored, no relation was found, while expected was that the VAF would decrease with an increase of EMG. The only indication found in this research for a flaw in the description of the relation between force and EMG is that the parameters of the activation filter are not accurately estimated (i.e. have high SEM-values) during active tests.

At the moment, not much research is done to the optimization of muscle parameters during active tasks. One of the problems could be that action potentials are measurable for a short time period (about 3ms) but the force rise during twitch may take up to 100ms, which is now not included in the model and would lead to higher force peaks due to a smaller amount of EMG. In the hill-type model the active muscle component is represented as it is one enlarged muscle fiber, instead of a lot of fibers which are packed in motor-units. The motor units can be activated separately, and are not all active during an active task. The motor units also have different characteristics, as they can be slow or fast and large or small. The properties of the separate muscle fibers and motor units are not included in the hill-type model. Research that is done to goats (Biewener et al. 2014, Wakeling et al. 2012) has found that EMG-signals contain information about the recruitment patterns. The neuromuscular model that they used is driven by the active states of the fast and slow motor units, and has better the neural torque during active tasks than a Hill-type model. If the low VAF-values are owing to the insufficient description of the relation between EMG and force in the model, this would also explain the not representative values and high SEM-values for the relative damping and cut-off frequency during active tests with the model without tendons.

Expected was that with the model with the added tendons it should at least be possible to recreate the results that were obtained with the model without tendons. The current study did not succeed in finding general settings such that for all input signals a good estimation of the torque could be found. However, the general opinion is that when every signal is analyzed individually and different options for certain initial values and shape parameters are tried a good estimate for every signal can be found. As analyzing each signal individually is very time consuming and probably means that the outcome parameters are not very accurate, this method is not desired. As above is suggested that the relation between EMG and force is not modelled in the correct way, expected is that it should be possible to regenerate the results of the passive tests with the model with the added tendons. An explanation why regenerating the results of the passive tests did not work could be that by taking the active component out of the muscle model by reducing the active input, the model basically consists of two springs in series (Figure 31). During slow perturbations it will it will be impossible to separately identify the two springs and thus also to estimate the measured torque and the different passive parameters. Adding a mass which represents the muscle mass between the two springs will solve the problem and is expected to result in better estimations for the passive tests.

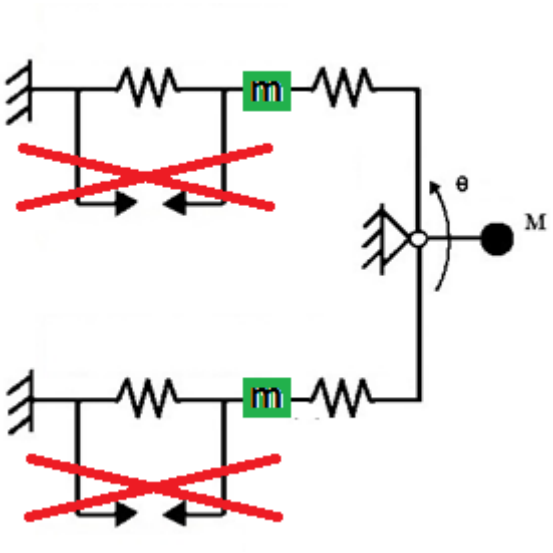

Figure 31: The muscle model with the tendons. The red cross shows that by taking out the active component the muscle model reduces to a model with two springs in series which are difficult to separate individually. A solution could be to add a mass between the two springs, which is represented with the green block.

Comparison to literature

Research is done in order to try to separate the neural origin of increased joint stiffness from the non-neural origin of increased joint stiffness. Some research groups are working with the ankle instead of the wrist (Mirbagheri et al. 2000). A big difference between their research and this research is that they also quantified the reflex contribution during active tests, where in this research all the activation (reflex and voluntary activation) is kept together.

Other research has been done into the influence of the type of perturbation and active task on the neural parameters (Van der Helm et al. 2002), they found that position tasks with force perturbations give the most information about functional reflexes. A difference with this research is that this research is not focused on functional outcome, but pure on diagnostic information. From a diagnostic point of view, the force tasks with position perturbations of this research provide sufficient information.
Not much research is done to active tasks, as it is difficult to measure exact muscle force in vivo in humans. Wakeling et. al. has done research to estimate the torque of active tasks with goats, and found that the active torque is difficult to estimate with a hill-type muscle model (Wakeling et al. 2012).
Research about the wrist joint and the estimation of the measured torque during active tasks was not found.

Implications for the clinic

For the clinic it would be helpful to be able to identify the different passive and active parameters of the muscles. With a protocol that includes active and passive tasks all muscle components are evoked and with a neuromuscular model all active and passive parameters could be identified. The protocol and model are a diagnostic tool to view changes in as well the neural as the non-neural parameters of the wrist muscles. For instance, the changes on muscle level due to a certain treatment can be visualized, or the changes on muscle level in the first few months after the stroke can be shown. With the protocol it can also be found out if treatments that on functional level do not

seem to have any effect might have an effect on one or multiple parameters in the muscle. Knowing what the effect of treatment is on certain muscle parameters could be helpful because it might make it easier to find out which combination of treatment options does have an effect on the functional level.
At this point with the current protocol and model it is possible to accurately estimate the different passive parameters of the muscle. However, more research has to be done in order to also accurately estimate the active muscle parameters.

Limitations of this research

A more physical limitation is the RoM of the Wristalyzer®. It would give much better estimates of the optimal muscle length and muscle slack length of the extensor muscle if it was possible to reach the lengthening limits of the extensor during the passive tests. It would also be better if the arm could be fastened in another way in the arm rest of the Wristalyzer® because subjects could now feel their arm move during some of the tests, which also means that the weight of the underarm is also estimated by the model.

During the active tests subjects were asked to maintain a certain force level without any form of feedback. The instruction is very subjective as every subjects interprets the instruction in his own way and some subjects were better at maintaining the right force level than others. As visual feedback in the screen in the form of seeing how much torque is delivered made the data poor in such a way that the model could not estimate the torque anymore because the torque had (almost) become a flat line, another form of visual feedback should be sought. An idea might be to display the measured EMG on the screen and ask the subjects to keep the EMG close to zero for one muscle and above a certain value for another muscle might be a good idea, but has a few flaws. A initializing task has to be added were the subject gives maximum power for as well his flexor as extensor muscle in order to acquire a (linear) scale for the amount of EMG and the force level. Also, a research done by Forbes et al. (Forbes et al. 2011) found that during EMG tasks the subjects decrease their amount of afferent feedback. They recommend a position task in combination with force perturbations, which would be difficult for this study because the neuromuscular model should than be adapted to torque input.
Another limitation of this research is that during active tests the amount of reflexive torque is not quantified. During passive tasks it is assumed that all present EMG activity is background noise and reflex activity, but as the muscle is supposed to be active during an active task there is also an voluntary activity component here. For patients it is important to be able to quantify the amount of reflex activity as it says something about the severity of the spasticity. An estimate of the amount of spasticity might be acquired by taking the mean of the EMG signal and multiplying the mean with the force length and force velocity characteristics to acquire the muscle force. When the mean muscle force is subtracted from the total active muscle force the muscle force due to reflexes will remain. Only healthy subjects are measured for this research. The protocol still has to be tested on stroke patients to be sure that the protocol is also doable for them and to verify if the muscle parameters of the neuromuscular model can also be accurately estimated for stroke patients.
For the model which includes tendons it would be helpful if anatomical information, like forearm length and maximum isometric force, was acquired during the test. When more anatomical information is available some of the insecurities of the model with the tendons will disappear.

Future research

With this research is shown that the passive parameters of the muscles can all be estimated accurately during passive tests and are also consistent over the different subjects. However, the active part is still not included in an optimal way in the neuromuscular model. A next step would be the further exploration of the relation between measured EMG and force. Because the parameters of the activation filter cannot be accurately estimated during active tasks, the assumption is made that the relation between force and EMG is not included in a correct way in the model. During passive tests the contribution of the force due to EMG to the total torque will be small enough to be negligible, but during active tests the force due to EMG is an important contributor to the total torque. A model which takes the differences between slow and fast motor units into account and which takes into account that the length of the action potential can be much shorter than the force rise during twitch might be a good next step.

For future research the model without tendons would be the best point to start improving the relation between measured EMG and force. In the model without tendons less anatomical information is included and the best results are for now acquired with the model without tendons. When additional research is done with the model with tendons a good first step would be to add a mass which represents muscle mass between the passive muscle stiffness and the muscle tendon, as is depictured in Figure 31.

Conclusion

In this research a new protocol was developed which acquires rich enough data in terms of position, velocity and acceleration such that all the non-neural parameters of the agonist and antagonist muscle of the wrist in the newest neuromuscular model can be accurately estimated. A passive tests which consists of multiple hold phases and moves the wrist through the whole RoM with a low velocity such that reflex activity is minimized gives in combination with the newest neuromuscular model a good estimation of the passive stiffness, mass, slack length and relaxation dynamics of as well the flexor as the extensor muscle. The active parameters of the muscle system cannot yet be accurately estimated even when the amount of active information in the input for the neuromuscular model was increased, which is assumed to be caused by an insufficient description of the relation between measured EMG and muscle force.

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Appendix A

Mean values of the parameters and the corresponding SEM-values for the passive tests:

Parameter	Ramp and Hold		Sigmoid		Multiple holds (low velocity)		Multiple holds (high velocity)		Multiple holds (multiple velocities)		Multi sine	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
m	0,557	0,00637	0,542	0,00842	0,577	0,0107	0,594	0,00378	0,607	0,00423	0,623	0,00126
k_{FCR}	122	0,0218	157	0,0205	120	0,0290	107	0,0284	125	0,0358	97,1	0,0761
k_{ECR}	243	0,00641	258	0,00715	219	0,00577	204	0,00963	206	0,00599	197	0,0555
$x_{0,FCR}$	0,0211	$1,181x10^{3}$	0,0237	95,5	0,00691	$1,83x10^{3}$	0,0426	$2,05x10^{3}$	0,0259	$2,24x10^{3}$	0,0487	$5,61x10^{3}$
$x_{0,ECR}$	0,0670	0,0808	0,0694	0,125	0,0616	0,0407	0,0519	0,0980	0,0533	6,03	0,0963	0,444
τ_{rel}	1,09	0,0251	5,22	0,562	0,498	0,0109	1,96	0,0382	1,93	0,0249	0,355	0,0748
k_{rel}	1,05	0,0191	4,03	0,257	2,58	0,0308	1,01	0,0458	1,650	0,126	0,895	0,0525
g_{FCR} (Mean$x10^{4}$)	7,05	0,0453	6,79	0,0253	34,9	0,0949	6,41	0,0197	6,58	0,0127	4,88	0,0989
g_{ECR} (Mean$x10^{5}$)	5,84	0,0959	5,29	0,173	10,4	0,150	5,44	0,152	7,00	0,568	7,67	0,951
$l_{0.FCR}$	0,0611	844	0,0672	81,7	0,0510	525	0,08107	$1,75x10^{3}$	0,0769	$1,92x10^{3}$	0,0901	$4,00x10^{3}$
$l_{0,FCR}$	0,0709	0,0498	0,0717	0,0782	0,0688	0,0252	0,0585	0,061	0,0613	3,83	0,104	0,278
f_0	0,359	0,436	0,366	1,06	0,122	0,0260	2,49	1,93	0,332	0,537	0,493	1,05
β	3,27	1,62	2,54	4,93	3,73	0,980	3,44	1,17	6,43	3,927	2,77	4,10
VAF	98,9		98,8		99,5		99,3		99,4		99,0	

Mean values of the parameters and the corresponding SEM-values for the active tests:

Parameter	low (extension) force level, neutral start-position		low (flexion) force level, neutral start-position		high (extension) force level, neutral start-position		high (flexion) force level, neutral start-position		low (extension) force level, flexion start-position		low (flexion) force level, flexion start-position	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
m	0,565	0,0164	0,407	0,0173	0,401	0,0223	0,438	0,0314	0,470	0,0112	0,470	0,0176
k_{FCR}	147	0,0321	535	$9{,}59\text{x}10^{9}$	173	0,106	462	20,0	253	0,0705	486	$3{,}45\text{x}10^{10}$
k_{ECR}	425	$2{,}23\text{x}10^{8}$	208	0,0247	251	$2{,}26\text{x}10^{3}$	146	0,173	397	10,7	118	0,0950
$x_{0,FCR}$	-0,00195	0,352	0,0559	$7{,}15\text{x}10^{9}$	0,0157	1,80	0,0562	40,5	0,0374	0,309	0,0483	$2{,}34\text{x}10^{10}$
$x_{0,ECR}$	0,0460	$1{,}26\text{x}10^{7}$	0,00805	0,187	0,0336	$8{,}04\text{x}10^{4}$	0,0113	5,35	0,0383	392	0,0204	0,249
τ_{rel}	2,41	0,109	1,57	0,147	2,45	0,248	1,49	0,107	1,87	0,258	2,34	0,127
k_{rel}	7,73	0,152	9,53	0,547	8,17	4,11	7,39	153	7,65	0,267	10,8	0,228
g_{FCR} (Meanx10^{4})	6,90	0,00281	23,2	0,0721	8,11	0,0724	47,2	1,13	16,1	0,0140	53,1	0,509
g_{ECR} (Meanx10^{5})	5,42	0,270	0,649	0,259	12,8	5,95	0,550	0,0159	10,5	0,386	0,540	0,205
$l_{0.FCR}$	0,0645	0,111	0,0530	186	0,0671	0,124	0,0719	1,65	0,0803	0,166	0,0368	0,0781
$l_{0,FCR}$	0,0539	$1{,}37\text{x}10^{3}$	0,0540	0,113	0,0763	$5{,}03\text{x}10^{4}$	0,0706	0,146	0,0645	247	0,0923	0,107
f_0	3,06	8,89	0,971	0,483	1,51	0,435	1,23	0,563	0,957	0,592	1,35	0,460
β	8,32	2,47	7,51	1,23	8,78	3,70	12,5	5,41	8,08	2,57	10,1	1,30
VAF	98,5		96,3		98,7		97,8		99,0		97,0	

Mean values of the parameters and the corresponding SEM-values for the active tests:

Parameter	high (extension) force level, flexion start-position		high (flexion) force level, flexion start-position		low (extension) force level, extension start-position		low (flexion) force level, extension start-position		high (extension) force level, extension start-position		high (flexion) force level, extension start-position	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
m	0,492	0,0166	0,477	0,0300	0,533	0,0260	0,3704	0,0157	0,431	0,0330	0,342)	0,0259
k_{FCR}	204	0,0491	417	0,426	167	0,0470	483	$2,33x10^{10}$	163	0,0743	534	2,16
k_{ECR}	305	0,428	133	0,133	288	0,123	142	0,0265	471	$7,22x10^{9}$	167	0,0181
$x_{0,FCR}$	0,0470	0,866	0,0360	16,2	-0,00888	0,260	0,0686	$9,15x10^{9}$	-0,00481	561	0,0545	$1,83x10^{10}$
$x_{0,ECR}$	0,0528	$1,11x10^{4}$	0,00931	0,233	0,0524	0,222	0,0447	0,133	0,0704	$3,56x10^{9}$	0,0436	0,0548
τ_{rel}	1,51	0,123	3,47	0,712	0,968	0,0320	0,590)	0,780	1,26	0,0648	0,758	0,0264
k_{rel}	5,26	0,357	9,36	2,00	3,46	0,0556	3,86	0,0441	3,44	0,0732	3,17	0,0262
g_{FCR} (Mean$x10^{4}$)	12,3	0,0132	62,4	0,367	2,93	0,00194	109	0,184	3,16	0,00491	20,5	0,108
g_{ECR} (Mean$x10^{5}$)	14,2	4,60	0,942	0,0642	11,8	0,240	0,900	0,00846	19,9	0,843	0,627	0,0128
$l_{0.FCR}$	0,0833	0,176	0,0410	13,4	0,0714	0,135	0,0645	4,62	0,0771	481	0,0571	$3,28x10^{3}$
$l_{0,FCR}$	0,0813	$7,06x10^{3}$	0,093	0,0520	0,0584	0,0939	0,0767	0,0641	0,0628	277	0,0677	0,0285
f_0	1,71	2,69	1,52	0,517	3,02	9,52	3,19	1,88	3,17	14,8	3,11	1,76
β	10,1	1,78	7,27	0,671	6,99	4,71	8,69	1,41	6,60	5,88	9,73	2,67
VAF	98,9		97,6		97,1		97,5		97,7		98,3	

Mean values of the parameters and the corresponding SEM-values for the active tests when the extensor and flexor are combined per force level and start-position and estimated simultaneously:

Parameter	Low force level, neutral start-position		High force level, neutral start-position		Low force level, extension start-position		High force level, extension start-position		Low force level, flexion start-position		High force level, flexion start-position	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
m	--	--	--	--	--	--	--	--	--	--	--	--
k_{FCR}	364	$3,87x10^{8}$	373	$3,12x10^{10}$	282	$4,77x10^{8}$	395	$2,91x10^{10}$	420	$1,97x10^{4}$	352	0,2563
k_{ECR}	153	0,00812	148	0,00920	271	0,0254	294	0,0149	114	$8,81x10^{4}$	77,0	0,00569
$x_{0,FCR}$	0,0666	$2,22x10^{8}$	0,0686	$1,80x10^{10}$	0,0834	$3,48x10^{8}$	0,0880	$1,85x10^{10}$	0,0637	$8,10x10^{3}$	0,0664	0,0950
$x_{0,ECR}$	-0,00124	0,0547	-0,00801	0,0794	0,0671	0,109	0,0765	0,0528	0,0148	$2,81x10^{4}$	0,0188	0,0950
τ_{rel}	8,52	0,0869	7,98	0,0876	2,18	0,0686	3,01	0,0663	6,59	$1,16x10^{4}$	6,69	0,132
k_{rel}	8,68	0,0325	7,52	0,0342	10,6	0,484	11,2	0,925	10,2	$5,41x10^{5}$	11,1	0,0843
g_{FCR} (Meanx10^{4})	14,9	0,000720	11,3	0,000250	5,87	0,000210	6,22	0,000140	23,2	0,00228	15,5	0,000620
g_{ECR} (Meanx10^{5})	0,919	0,00329	0,688	0,00218	0,733	0,00317	0,740	0,00271	0.566	0,00186	0,464	0,00221
$l_{0.FCR}$	0,0452	0,0516	0,0437	0,0111	0,0587	0,0440	0,0581	0,0316	0,0687	0,0294	0,0773	0,0326
$l_{0,FCR}$	0,0567	0,0300	0,0690	0,0477	0,0889	0,0274	0,0947	0,0339	0,107	0,0314	0,115	0,0344
f_0	0,223	0,138	0,308	0,197	1,79	2,06	1,63	2,52	0,364	0,259	0,444	0,348
β	19,8	1,155	19,9	1,13	19,4	2,16	18,4	1,90	19,1	1,22	19,2	1,34
VAF	92,4		95,9		87,8		90,1		92,6		95,2	

Mean values of the parameters and the corresponding SEM-values for the active tests when the extensor and flexor are combined per force level and start-position and estimated simultaneously and the passive parameters are set to fixed values:

Parameter	Low force level, neutral start-position		High force level, neutral start-position		Low force level, extension start-position		High force level, extension start-position		Low force level, flexion start-position		High force level, flexion start-position	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
g_{FCR} (Meanx10^{4})	8,09	17,7	7,05	13,0	5,69	7,79	4,75	8,74	16,3	78,3	10,6	51,0
g_{ECR} (Meanx10^{5})	1,50	0,00263	1,11	0,00164	2,59	0,00684	1,53	0,00350	2,24	0,00359	1,48	0,00227
$l_{0.FCR}$	0,0567	0,00884	0,0545	0,00688	0,0593	0,0133	0,0653	0,0133	0,0480	0,00495	0,0511	0,00580
$l_{0,FCR}$	0,0661	0,00405	0,0641	0,00368	0,0692	0,00162	0,0630	0,00214	0,0736	0,00498	0,0744	0,00431
f_0	0,787	11,3	1,31	55,7	2,24	12,0	2,12	24,6	0,622	3,57	1,06	24,4
β	20,0	17,0	18,7	13,5	18,1	17,0	18,0	19,0	18,5	20,0	20,0	19,2
VAF	91,8		94,7		86,9		88,6		90,6		92,4	

Mean values of the parameters and the corresponding SEM-values for the active tests when the extensor and flexor are combined per force level and start-position and estimated simultaneously and the passive parameters are set to fixed values (except the relaxation parameters):

Parameter	Low force level, neutral start-position		High force level, neutral start-position		Low force level, extension start-position		High force level, extension start-position		Low force level, flexion start-position		High force level, flexion start-position	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
τ_{rel}	4,25	0,342	4,09	0,466	2,32	0,797	2,71	0,287	2,14	0,334	4,19	0,476
k_{rel}	10,1	0,264	8,90469	0,279	10,7	0,865	12,4	0,769	13,0	0,540	13,7	0,371
g_{FCR} (Meanx10^4)	10,9	16,5	8,72	13,6	5,86	9,49	5,37	10,8	14,3	52,4	11,7	22,2
g_{ECR} (Meanx10^5)	1,45	0,00198	2,03	0,00229	3,03	0,00530	1,33	0,00232	2,15	0,00336	1,48	0,00192
$l_{0.FCR}$	0,0674	0,0103	0,0763	0,00885	0,0677	0,0209	0,0771	0,0169	0,0609	0,0157	0,0646	0,00756
$l_{0,FCR}$	0,0740	0,00429	0,0764	0,00464	0,0749	0,00574	0,0745	0,00571	0,0818	0,00530	0,0815	0,00385
f_0	0,774	10,7	1,34	32,7	2,27	18,1	2,35	26,0	1,12	7,44	0,718	13,0
β	20,0	16,2	20,0	13,3	18,6	18,5	18,2	17,9	19,9	20,2	20,0	17,03
VAF	93,5		96,6		89,2		92,6		92,3		94,9	

Mean values of the parameters and the corresponding SEM-values for the active tests when the extensor and flexor are combined per force level and start-position and estimated simultaneously and the passive parameters are set to fixed values (except the stiffness parameters):

Parameter	Low force level, neutral start-position		High force level, neutral start-position		Low force level, extension start-position		High force level, extension start-position		Low force level, flexion start-position		High force level, flexion start-position	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
k_{FCR}	173	0,468	172	0,0673	45,8	1,90	119	1,77x10^4	115	87,06317	120	19,1
k_{ECR}	138	1,30	203	0,843	121	1,47	93,7	0,0330	124	2,,07x10^5	142	1,62x10^6
g_{FCR} (Meanx10^4)	9,88	21,0	8,98	17,8	6,16	12,2	5,32	10,5	15,5	85,6	14,5	47,1
g_{ECR} (Meanx10^5)	1,45	0,00818	1,07	0,00223	2,33	0,00840	1,32	0,00397	1,30	0,00295	1,28	0,00399
$l_{0.FCR}$	0,0510	0,0248	0,0475	0,0286	0,0981	0,186	0,102	0,185	0,0508	0,0591	0,0686	0,0702
$l_{0,FCR}$	0,0807	0,0382	0,0597	0,0194	0,0926	0,0343	0,106	0,0308	0,0971	0,0282	0,1103	0,0351
f_0	1,35	135	0,672	5,23	1,34	15,0	1,16	33,9	0,990	6,98	0,5088	16,2
β	19,7	15,0	15,8	10,51	19,8	21,0	19,2	15,9	19,0	17,6	18,7	13,1
VAF	91,9		93,6		88,5		93,6		92,0		95,1	