
**Influence of Motor Unit
Characteristics and Behavior
on Surface EMG, Force, and
Their Association**

Influence of Motor Unit Characteristics and Behavior on Surface EMG, Force, and Their Association

PhD Thesis by

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ABSTRACT

Human voluntary movement occurs when muscles generate force in response to patterns of activation from the neural system. The force generated by individual muscles however is difficult to measure experimentally. Therefore, the surface EMG signal is often used as a surrogate measure for the relative muscle force in spite of the differences in the mechanisms underlying these two signals. This PhD thesis focuses on the limitations the association.

To investigate the relation between these two signals, a computational model of adaptations occurring in the neuromuscular system during sustained contractions and the resulting muscle force and surface EMG signal was developed. Simulations of the metabolic accumulation in the muscle was used to control the rate of change for the various neuromuscular adaptations, while a control algorithm estimated the excitatory drive to the muscle needed to maintain a desired contraction level. Using the model, first, the influence of muscle fatigue on the association between contraction level and average rectified surface EMG amplitude was analyzed. Next, the relation between the temporal variability in the surface EMG envelope and the force was assessed.

The simulations indicated that the presence of muscle fatigue potentially introduces a large bias in the relation between the amplitudes of force and surface EMG. This bias is difficult to predict since it depends on multiple adjustments in the neuromuscular behavior. Furthermore, there was little correlation between the surface EMG envelope and the force variability. This lack of correlation was due to the filtering effects related to the process of force generation. These filters implied that only the variability of the common neural input to the motor neuron population was transmitted to force and were not present in the generation of the surface EMG signal.

These results indicate significant limitations in the ability of the surface EMG signal to reflect the characteristics of the force generated by the muscle. Therefore, using this signal as an estimator for force should be done with caution and at a qualitative level only.

ABSTRACT IN DANISH (DANSK RESUMÉ)

Al voluntær bevægelse af den menneskelige krop er resultatet af kraft genereret af musklerne som følge af aktivering fra nervesystemet. Kraften, der genereres af enkelte muskler, er dog vanskelig at måle eksperimentielt. Af denne årsag bruges overflade EMG signalet ofte til at estimere den relative muskelkraft på trods af forskellene i mekanismerne bag disse to signaler. I denne PhD tese fokuseres på begrænsningerne forbundet med at foretage denne sammenligning.

For at undersøge sammenhængen mellem disse to signaler blev en matematisk computermodel af de ændringer, der forekommer i det neuromuskulære system under vedvarende muskelkontraktioner samt den resulterende muskelkraft og overflade EMG signal, udviklet. Simulationer af akkumuleringen af metaboliske stoffer i musklen blev brugt til at kontrollere hastigheden hvormed de neuromuskulære ændringer forekom, mens en kontrolalgoritme genererede det nødvendige niveau af det eksitatoriske neurale input til musklen for at kunne opretholde den ønskede muskelkraft. Ved brug af modellen blev indflydelsen af muskeltræthed på forbindelsen mellem muskelkraften og den gennemsnitlige rektificerede overflade EMG amplitude undersøgt. Dernæst blev sammenhængen mellem den temporale variabilitet i det lav-pas filterede overflade EMG signal og kraften undersøgt.

Simulationerne indikerede at tilstedeværelsen af muskeltræthed potentielt introducerer en stor bias i brugen af overflade EMG amplituden til at estimere muskelkraft. Størrelsen af denne bias er vanskelig at forudsige, da den afhænger af en række forskellige neuromuskulære ændringer. Derudover blev der kun fundet en lav korrelation mellem det lavpas-filterede overflade EMG signal og variabiliteten i muskelkraften. Denne lave korrelation skyldtes en række filtreringsprocesser involveret i produktionen af kraft. Disse filtreringsprocesser betyder, at kun den variabilitet i det neurale input, der er fælles for hele populationen af motoriske enheder, bliver overført til kraften, hvilket ikke er tilfældet for overflade EMG signalet.

Resultaterne påpeger væsentlige begrænsninger i brugen af overflade EMG signalet til at estimere muskelkraftens karakteristika. Derfor bør dette signal kun bruges til at estimere muskelkraft i et begrænset omfang og udelukkende på et kvalitativt niveau.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dario Farina, for his guidance during this PhD project and for encouraging me to join and initiate other research projects throughout the period.

Also, I would like to thank Roger Enoka for being my mentor throughout these years. I am most grateful for this collaboration.

Finally, I would like to thank all my friends and colleagues at Department of Health Science and Technology and at Department of Neurorehabilitation Engineering (Georg-August University, Göttingen, Germany) for excellent company.

The thesis is dedicated to my parents; to my father, Klaus, for his unconditional support and to my late mother, Yrsa, who I wish was here to share this occasion.

TABLE OF CONTENTS

I. Introduction	7
II. Physiological mechanisms behind force and surface EMG	8
III. Computational modeling of motor units, force, and surface EMG	12
IV. Aim of the thesis	15
V. Model implementation and validation	17
VI. Impact of fatigue on the relation between the amplitudes of force and surface EMG	22
VII. Impact of motor neuron population characteristics on the relation between force variability and surface EMG envelope	27
VIII. Discussion	31
References	33

Chapter I:

INTRODUCTION

“We have a brain for one reason and one reason only – and that’s to produce adaptable and complex movements.” Daniel Wolpert

Muscle fibers are the transducers of the electrical signals of the nervous system into mechanical action. Once activated, muscles generate force which is transferred via tendons to the skeletal system, producing movements.

Identical movements may be the results of infinite combinations of patterns of force generated by the different muscles acting on the joints, and unlike joint movements, the forces produced by individual muscles are not easily measured. Externally, muscle force can only be measured in non-dynamic conditions (e.g. isometric or isokinetic contractions), and more importantly, any activity from synergetic or antagonistic muscles, which is present in most movements, disrupts the estimate (Disselhorst-Klug et al. 2009). Alternatively, implantable devices can measure the force applied to the tendons (Fleming and Beynon 2004), however their invasiveness makes this an unattractive option for most applications.

Instead, the electrical signal reflecting the muscle fiber action potentials measured on the skin surface above a muscle (surface EMG) is widely used as surrogate measure of the force it generates (Disselhorst-Klug et al. 2009; Staudenmann et al. 2010). This association has arisen from the notion that both muscle force and muscle fiber action potentials occur as direct consequences of neural muscle activation, and due to the common observation that when a subject increases muscle force linearly, the amplitude of the surface EMG signal increases in a similar linear fashion (Woods and Bigland-Ritchie 1983; Lawrence and De Luca 1983).

The underlying mechanisms behind generation of force and surface EMG however are fundamentally different in several aspects, and both in different ways sensitive to the behavior and the characteristics of the motor unit population, which may limit the similarity of these two signals (Staudenmann et al. 2010). Therefore, the work of this thesis will explore the limits of this association.

Chapter II:

PHYSIOLOGICAL MECHANISMS BEHIND FORCE AND SURFACE EMG

This chapter reviews the mechanisms by which muscles are excited, with special emphasis on the different mechanisms involved in generation of force and the surface EMG signal respectively.

ACTIVATION OF SINGLE MOTOR UNITS

The soma and dendrites of each motor neuron receive tens of thousands of synaptic connections from other neurons (Ulfhake and Cullheim 1988) that each elicits a brief excitatory or inhibitory postsynaptic potential (EPSP/IPSP) that modulates the membrane potential of the motor neuron (Heckman and Enoka 2004). If sufficient excitatory input is received by the motor neuron for its membrane potential at the axon hillock to increase by ~15 mV, an action potential is generated (Kandel et al. 2000). The action potential propagates along the axon and across the neuromuscular junction and activates the muscle fibers in a one-to-one fashion.

The motor neuron receives synaptic input from several different sources, either monosynaptically or via spinal interneurons (Gandevia 2001). A large part of the input related to the volitional command originates at the supraspinal level (Lemon 2008), but afferent sensory fibers also contribute significantly to the synaptic input (Macefield et al. 1993). Although their spinal actions are complex and task-dependent (Hultborn 2001), the most important types of sensory input include type Ia (excitatory) and Ib (inhibitory) from receptors sensitive to muscle stretch and force (Heckman and Enoka 2004).

The relation between the synaptic input received by the motor neuron and the frequency by which it generates action potentials depends highly on its intrinsic properties. Among others, these properties include persistent inward currents that once activated serves to amplify the synaptic input (Lee and Heckman 2000; Hultborn et al. 2003), and the time-dependent decline in motor unit discharge rate to a constant input, known as spike-frequency adaptation (Gorman et al. 2005; Spielmann et al. 1993).

ACTIVATION OF POPULATIONS OF MOTOR UNITS

Muscle activation occurs through the activation of motor neurons that innervate a number of muscle fibers. First recognized by Sherrington and colleagues, one motor neuron exclusively innervates a

group of muscle fibers which constitutes the smallest functional unit of the neuromuscular system (known as the motor unit). Most skeletal muscles are innervated by 100-1000 motor neurons, referred to as the motor neuron population of a muscle (Heckman and Enoka 2004). Although certain sensory inputs are not received homogeneously across the motor unit population (Heckman and Binder 1993), it is generally assumed that the motor neuron population receives approximately the same neural input. The size and membrane resistance of the neurons vary across the population, so that neurons with small soma diameters have the lowest rheobase current and therefore are recruited at a lower level of neural input than larger ones (Henneman 1957; HENNEMAN et al. 1965). The small neurons, that typically constitute the majority of neurons in the population (Gustafsson and Pinter 1984), innervate a smaller number of muscle fibers and thus produce less force. This association between recruitment and force producing capacity of the motor units is generally referred to as Henneman's size principle. This implies that when the motor neuron population is exposed to an increasing level of neural input, more and more larger motor units will become active (recruitment) and the discharge rate of the active units will increase (rate coding).

MECHANISMS UNDERLYING FORCE GENERATION

The arrival of the action potential at the neuromuscular junction causes a brief increase in sarcolemma sodium permeability, generating an electrical impulse that propagates along the muscle fibers. This impulse triggers the release of calcium from the Sarcoplasmic Reticulum that allows the formation of cross-bridges to occur.

The force generated in response to one motor unit action potential is referred to as the twitch. Mathematically the twitch can be approximated by a critically dampened, second-order system (Stein et al. 1972). While the twitch amplitude depends on the number of cross-bridges generated, and thus largely on the number of muscle fibers in the motor unit, the duration of the twitch depends on the predominant muscle fiber type of the motor unit (slow/fast; twitch rising phase duration from 30 ms to 90 ms). When successive action potentials arrive before the completion of the relaxation phase, the twitches begin to sum and the force generated by the motor unit force increases. As the motor unit discharge rate increases, the summated force increases non-linearly until a maximum level (tetanus) (Bawa and Stein 1976). The force generated by the whole muscle is the algebraic sum of forces generated by its motor units.

In sustained contractions, motor units consisting predominantly of fast muscle fibers exhibit a decline in the amplitude and an increase in the duration of the twitch (Burke et al. 1973). Although the slowing of the twitch allows complete tetanus to be reached at a lower discharge rate, the tetanic force of these fast motor units can be reduced by more than 50% (Thomas et al. 1991).

MECHANISMS OF GENERATION OF THE SURFACE EMG SIGNAL

The action potential propagates along the sarcolemma via rapid changes in the ion conductivity of its membrane. These depolarizing currents are the source of an electric field that can be detected on the surface of the skin as it passes under an electrode due to the conductive properties of the biological tissue. Typically, action potential propagates along the sarcolemma at a velocity of 3-5 m/s (Andreassen and Arendt-Nielsen 1987). As the conduction velocity determines the time the action potential takes to pass the below the electrode, this velocity and the recorded electrical field duration are inversely related (Lindstrom and Magnusson 1977).

In sustained contractions the shape of the intracellular action potential changes, presumably due to disturbances in intra- and extracellular Calcium concentrations (Dimitrova and Dimitrov 2003). Most notably, these changes involve decreased amplitude (by up to 50%) and increased depolarization and repolarization periods (by 200-300%).

The electrical field can be approximated as the second spatial derivate of the intracellular action potential (Andreassen and Rosenfalck 1981). The tissue between the source and the electrode acts as a low-pass filter of the electrical field, reducing the influence of distant fibers compared to those closer to the electrode (Nandedkar et al. 1985). In this way, in a simulation study 50% of the amplitude of the evoked surface EMG potential in an intrinsic hand muscle was produced by only 7% of the motor units (Keenan et al. 2006b). Furthermore, the configuration of the detection system (electrode size and position) has been found to have a significant impact on the temporal and spectral characteristics of the surface EMG (Fuglevand et al. 1992; Farina et al. 2002; Dimitrova and Dimitrov 2002; Keenan et al. 2005; Kleine et al. 2001).

As the action potential waveform consists of both positive and negative components, simultaneous activity of multiple motor units will inevitably involve temporal overlap of both these components. When this happens these components will partly or completely cancel each other out, and thereby reduce the amplitude of the surface EMG signal (Day and Hulliger 2001). This is referred to as

amplitude cancelation, which can reduce the surface EMG amplitude by up to 60% at maximal activation.

Chapter III:

COMPUTATIONAL MODELING OF MOTOR UNITS, FORCE AND SURFACE EMG

This chapter explains the advantages of using computational models as a tool for understanding the impact of the underlying neuromuscular mechanisms on surface EMG and force, and reviews the current state of the art within this field.

The activity of single motor units is commonly identified by insertion of wire electrodes into the muscle, although recently techniques for identification of single motor unit discharge patterns based on recordings of networks of surface EMG electrodes have been proposed (Holobar et al. 2009; Nawab et al. 2010). By applying template matching techniques on the interference pattern recorded from intramuscular recording, the contributions of individual motor units and thus their discharge pattern can be identified (LeFever and De Luca 1982; Stashuk and Qu 1996; Stashuk 2001; McGill et al. 2005; Katsis et al. 2007).

Several limitations however are related to the study of the behavior of populations of motor units. Only the activity of motor units with muscle fibers located in close proximity of the uninsulated tip of the wire can be detected. Typically this implies that the discharge pattern of a small proportion of the motor unit population (less than 10 motor units) can be detected from each insertion site (Merletti and Farina 2009). Furthermore, at contraction levels above 50% of MVC the density of motor unit action potentials recorded by the intramuscular wire electrode obstructs valid identification of the contribution from single units (Merletti and Farina 2009).

In part to overcome these limitations, a popular way to study motor unit behavior is by computational models. These models are made up of mathematical descriptions of the physiological processes involved from motor neuron excitation to generation of force. Whereas computational models of smaller and more distinct neural systems, such as single neurons (Rudolph-Lilith et al. 2012) or distinct type of receptors (for example muscle spindles (Mileusnic et al. 2006)) often have higher complexity, more simplified models are usually preferred for larger systems, as populations of motor units, to reduce the number of parameter needed to be identified and the computational burden of the simulations. The model of motor unit recruitment, rate coding, and force generation developed by Fuglevand and colleagues (Fuglevand et al. 1993) has been widely applied for various purposes since its development (e.g. (Herbert and Gandevia 1999; Taylor et al. 2002; Keenan et al.

2006a; Revill and Fuglevand 2011)). In this model, motor unit recruitment and rate coding is determined by an excitatory drive uniformly delivered to the motor neuron pool. Recruitment threshold and the relation between excitation level and discharge rate varies across the motor units depending on motor unit force-producing capacity. Based on the complete discharge pattern the force generated by the whole muscle is simulated. By combining this model with models of the single fiber action potentials as recorded on the skin surface (Fuglevand et al. 1992; Dimitrov and Dimitrova 1998; Farina et al. 2004a), the equivalent surface EMG signal has been simulated.

Unlike in experimental studies the use of such models not only provides the complete discharge pattern of the motor unit population at all contraction levels, but since all parameters (included in the model) can be controlled and manipulated of the model settings they also allow for systematic investigation of the influence of motor unit characteristics on model outputs. The studies applying such computational models to study the impact of motor unit behavior on surface EMG and force can be divided into two groups; studies using an inverse or a forward approach.

Studies using the inverse approach aim to identify specific characteristics of motor unit behavior not easily measured experimentally by finding the configuration for which the resulting model outputs provide the best match with experimental findings. For example, it was found that to reproduce a linear relation between surface EMG and force, a proportional relation between motor unit twitch force and motor unit action potential amplitude (Zhou and Rymer 2004) as well as a broad recruitment range (Fuglevand et al. 1993) were required. The latter observation was confirmed using Monte Carlo simulations varying multiple model parameters, which further indicated that motor units with high recruitment thresholds exhibit a higher peak discharge rates than low threshold units (Keenan and Valero-Cuevas 2007). Furthermore, a number of studies found that appropriate levels of variability in the inter-spike intervals of motor unit discharges was necessary for simulations of realistic force steadiness (Jones et al. 2002; Taylor et al. 2003; Moritz et al. 2005; Barry et al. 2007).

Studies using the forward approach aim to assess the sensitivity of the model outputs to variations in the motor unit characteristics. In this way, it was found that the characteristics of the surface EMG are highly sensitive to fatigue-related changes in the shape of the motor unit action potential. The root mean square of the surface EMG can increase more than two-fold at the same contraction level when the action potentials shapes are adjusted to reflect severe fatigue (Arabadzhev et al. 2010), and these changes are also reflected in a compression of the spectral content of the surface

EMG (Dimitrov et al. 2008). Furthermore, these changes in the shape of the action potentials serves to increase the level of amplitude cancelation, which to a lesser extend is also affected by the ranges of discharge range exhibited by the motor unit population (Keenan et al. 2005). Although, the level of motor unit short-term synchronization was found to reduce force steadiness and increase surface EMG amplitude (Yao et al. 2000), its impact on the surface EMG is relatively small (Keenan et al. 2005; Zhou and Rymer 2004; Arabadzhiev et al. 2010).

Chapter IV:

AIM OF THE THESIS

This chapter describes the motivation to perform the studies in this thesis and the objectives that has been addressed.

As explained in the previous chapters the surface EMG signal amplitude is often used as an estimate of the force produced by that muscle, although the underlying mechanisms of generation of force and EMG are very different. Therefore, the aim of the thesis is to provide a better understanding of the impact of motor unit characteristics and behavior on the relation between surface EMG and isometric force using computational models. This relation was investigated at two levels. First, on a large-scale level, the influence of the motor unit population adaptations to muscle fatigue on the relation between the amplitudes of the two signals was analyzed. Second, on a small-scale level, the influence of the motor unit population characteristics on the relation between the EMG envelope and force variability was addressed.

This thesis collected the work performed in four scientific studies:

I) Dideriksen JL, Farina D, Bækgaard M, Enoka RM (2010)

An Integrative Model of Motor Unit Activity during Sustained Submaximal Contractions. *Journal of Applied Physiology* 108: 1550-1562, 2010, doi: 10.1152/jappphysiol.01017.2009

II) Dideriksen JL, Farina D, Enoka RM (2010)

Influence of Fatigue on the Simulated Relation between the Amplitude of the Surface Electromyogram and Muscle Force. *Philosophical Transactions of The Royal Society A. Mathematical, Physical & Engineering Sciences* 368, 2765-2781, 2010, doi: 10.1098/rsta.2010.0094

III) Dideriksen JL, Enoka RM, Farina D (2011)

Neuromuscular Adjustments that Constrain Submaximal EMG Amplitude at Task Failure of Sustained Isometric Contractions. *Journal of Applied Physiology* 11: 485-494, 2011, doi: 10.1152/jappphysiol.00186.2011

IV) Dideriksen JL, Negro F, Enoka RM, Farina D (2012)

Motor Unit Recruitment Strategies and Muscle Properties Determine the Influence of Synaptic Noise on Force Steadiness. *Journal of Neurophysiology* 107, 3357-3369, 2012, doi: 10.1152/jn.00938.2011

Chapter V:

MODEL IMPLEMENTATION AND VALIDATION

This chapter summarizes the implementation of the model as described in detail in Study I, including the extension of the model to include simulations of surface EMG described in Study III.

In order for the model to allow comparison of the impact of muscle fatigue on force and the surface EMG signal at any level of fatigue, it had to be able to continuously reflect the progressive adjustments in the motor unit adaptations influencing the two signals. Therefore, the level of the various motor unit adaptations could not be predefined as in the traditional forward modeling approaches, but instead had to depend directly on the simulated contraction itself.

To achieve this, the adopted model of motor unit activity and force production (Fuglevand et al. 1993) needed to be extended in two ways. 1) A set of variables keeping track of the level of muscle fatigue as a direct consequence of muscle contraction history had to be implemented to be used to determine the rate of change for the various motor unit adaptations to fatigue. 2) The appropriate level of excitatory drive to the motor unit population had to be automatically adjusted in order for a constant contraction level to be maintained while the discharge pattern and contractile properties of the motor unit population adapted to fatigue.

For the model to fulfill the first requirement, a model of the metabolic concentrations in the intra- and extracellular environment of the muscle was developed (Fig. 1). This model did not aim to fully reflect the complex underlying mechanisms behind muscle energetics (Tsianos et al. 2012). Instead it was inspired by the basic principles of muscle metabolic dynamics in a way that allowed it to act as a sufficiently flexible and robust indicator of the instantaneous state of the muscle in the simplest possible way. The model was implemented as a compartment model, with one compartment representing each motor unit and one compartment representing the extracellular space of the muscle. Each motor unit discharge was associated with the production of metabolites into the compartment of that motor unit. Depending on the concentration gradient, the metabolites could diffuse across the cell membrane, in and out of the extracellular space. Blood flow removed metabolites from the extracellular space, but was compromised at contraction levels above 30% MVC (de Ruiter et al. 2007; Sjogaard et al. 1988). In this way, this model structure reflected several general experimental observations during fatigue, including the gradual recovery of muscle function

after fatigue (Woods et al. 1987) and the “spreading” of fatigue-related adaptations from active to non-active motor units (Gazzoni et al. 2005; Kostyukov et al. 2002).

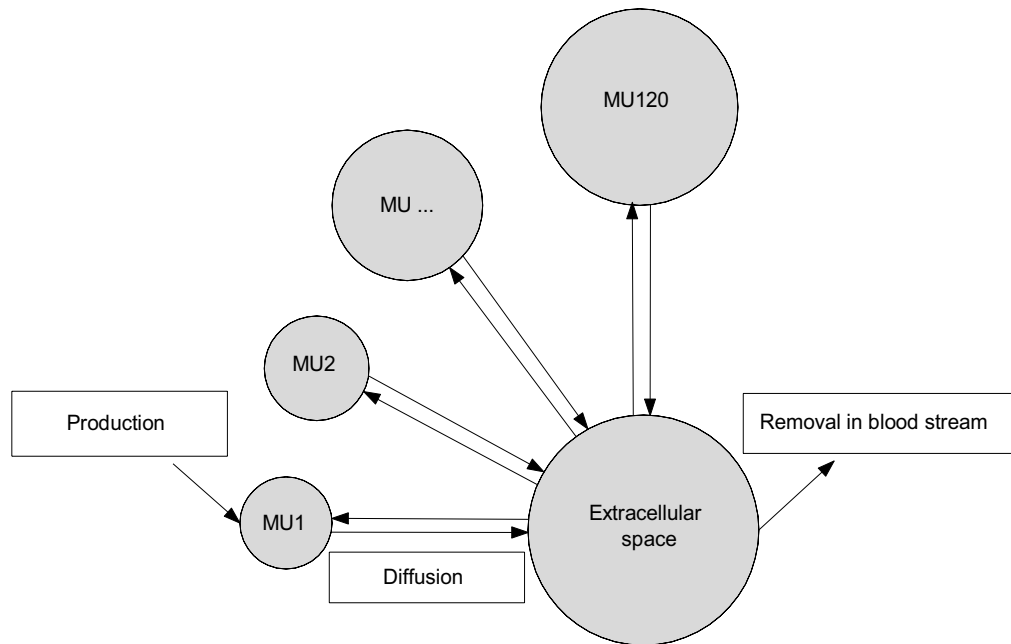


Figure 1. The compartment model for the distribution and transport of metabolites. Circles indicate compartments and arrows indicate transport of substances in and out of compartments. The compartment sizes are not drawn to scale. There was a ~20-fold difference in volume of the smallest and largest compartment, representing the differences in motor neuron innervation number. The compartment representing the extracellular space was ~15 times larger than the largest motor unit compartment.

As the metabolite concentration increased, tetanic motor unit force amplitude was reduced and the tetanic force relaxation time was prolonged. These changes occurred non-uniformly across the motor unit population, in a way where the largest motor units exhibited the largest changes (Burke et al. 1973; Thomas et al. 1991; Fuglevand et al. 1999). Furthermore, the metabolite concentration determined the level of inhibitory afferent feedback, reducing motor unit peak discharge rates (Woods et al. 1987; Garland et al. 1994; De Luca et al. 1996). Again, the largest motor units were affected the most by the inhibitory afferent feedback, potentially reducing their discharge rate by up to 40% (Bigland Ritchie et al. 1983). Finally, the motor unit conduction velocity was inversely related to the metabolite concentration (Farina et al. 2004b; Klaver-Król et al. 2007), but also related to motor unit size (Andreassen and Arendt-Nielsen 1987) and instantaneous motor unit discharge rate (Nishizono et al. 1989).

For the model to fulfill the second requirement, a PID (proportional, integral, derivative) control algorithm was implemented. With a bandwidth of 3 Hz (Loram et al. 2011), this algorithm estimated the level of excitatory drive to the muscle that minimized the error between the simulated and the predefined target contraction level. In this way, the PID algorithm imitated the volitional control of force and made a closed loop in the model, with the target contraction level as the sole input.

Finally, the model was combined with a model for surface EMG generation (Farina et al. 2004a). Anatomical and physiological settings were adopted from a previous simulation study (Keenan et al. 2006a) and the simulated motor unit conduction velocity determined the shape of the intracellular action potential (Dimitrova and Dimitrov 2003). The full model structure is depicted in Figure 2.

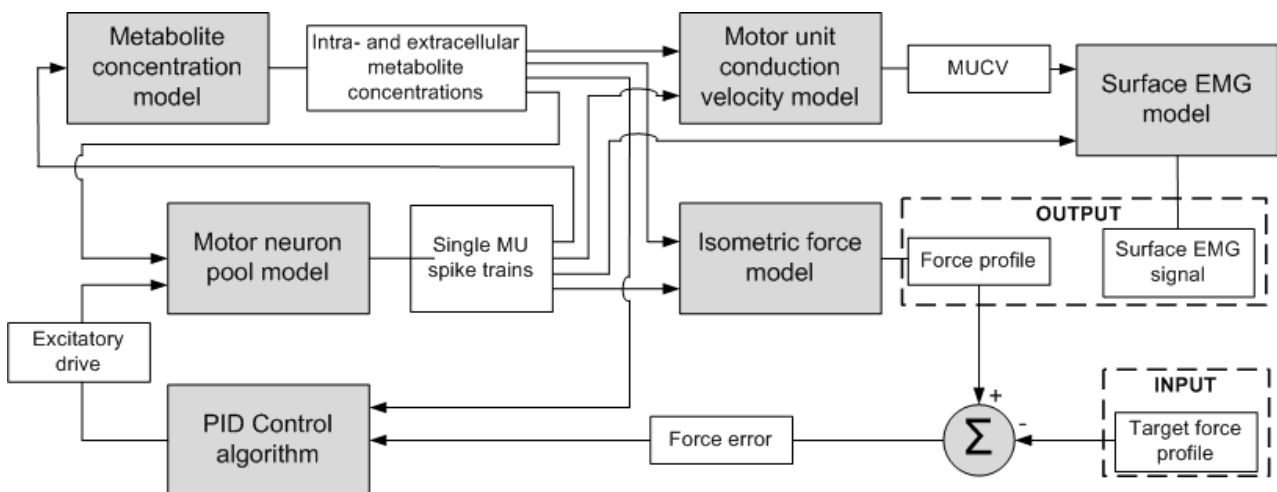


Figure 2. Model structure. The gray boxes indicate the components of the model, and the white boxed denotes the type of data transmitted between the gray boxes. Based on the simulated force, the PID control algorithm determines the excitatory drive, which is the input to the motor neuron population model. The metabolite concentrations are simulated based on the motor unit spike trains and affects the performance of the various sub-models. Surface EMG is simulated using the motor unit conduction velocity and the motor unit spike trains.

MODEL VALIDATION

Model validation was aimed to be based on comparison with experimental findings, reflecting the combined effect of various implemented adjustments to fatigue. However, due to the relative

sparsity of experimental studies exploring fatigue-related changes in muscle behavior, most available data were used to adjust the model parameters. For example, reported times to task failure (Fuglevand et al. 1993; Zijdwind et al. 1999; Maluf et al. 2005) were used to adjust the relation between metabolite concentration and inhibitory afferent feedback, and could therefore not be used for validation. Instead, model validation relied on the change in motor unit recruitment threshold and the surface EMG amplitude at task failure.

The recruitment threshold of a motor unit indicates the force generated by the muscle at the time where it is recruited. This measure is therefore sensitive to both discharge rates and the force-producing capacity of the motor unit population. Figure 3 depicts motor unit recruitment thresholds before and after a fatiguing contraction. For all but very low-threshold motor units, the recruitment threshold decreases in muscle fatigue. These changes were highly similar to experimentally observed (Garland et al. 1994).

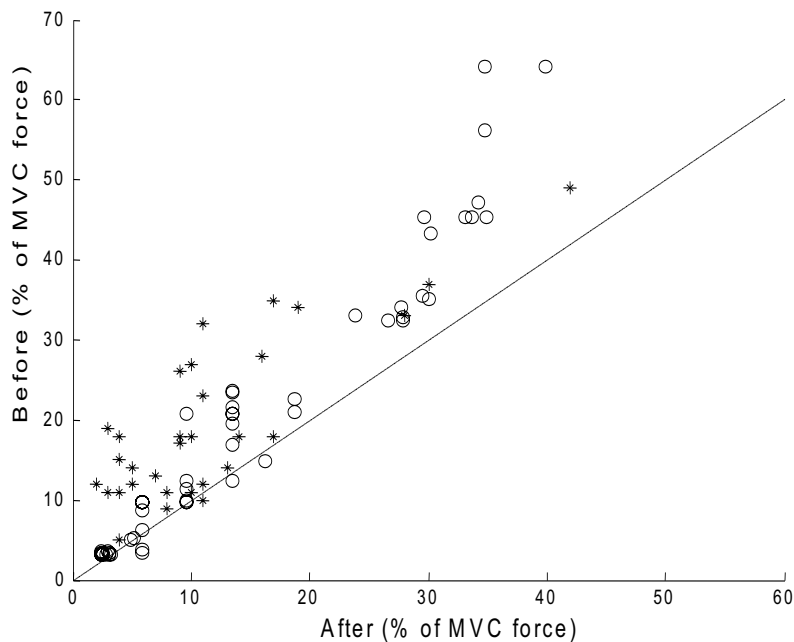


Figure 3. Scatterplot of the simulated recruitment thresholds for motor units measured before and after a sustained fatiguing contraction (o), at a contraction level of 25% MVC for the motor units with an initial recruitment threshold below this level and at 50% MVC for motor units with initial recruitment threshold above this level. The asterisks indicate the experimental data reported by Garland et al. [1994]

Figure 4 depicts the simulated average rectified surface EMG amplitude at task failure at contraction levels of 20, 40, and 60% MVC respectively. The value reflects both the muscle

activation level, as well as changes in the shape of the motor unit action potential waveforms. Across all contraction levels, the simulated surface EMG amplitudes were within the confidence interval of the results of three experimental studies (Fuglevand et al. 1993; Maluf et al. 2005; Carpentier et al. 2001).

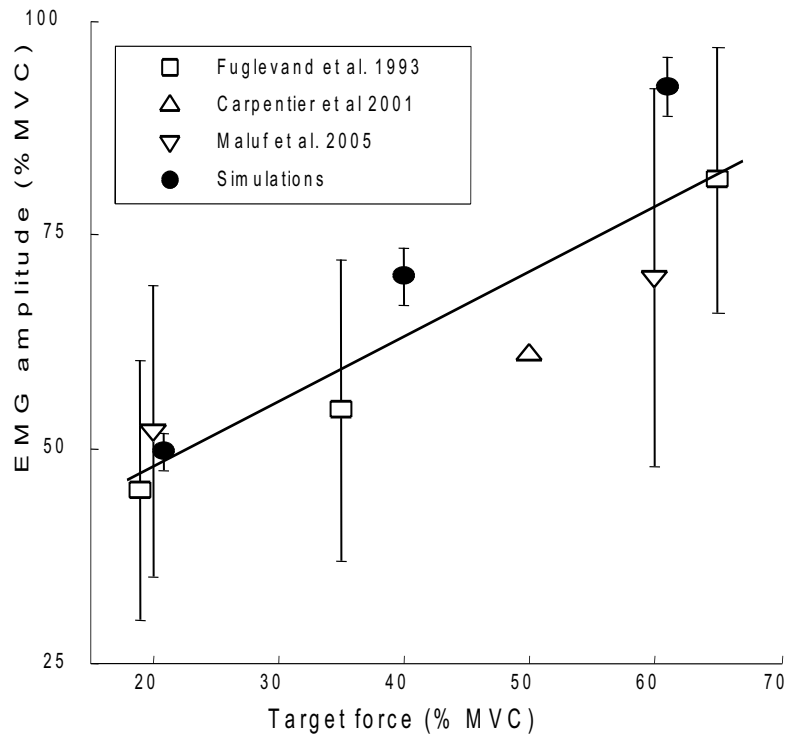


Figure 4. Relation between surface EMG amplitude at task failure for each target force as predicted by the model (filled circles) and those reported in three experimental studies from the FDI. The line indicate the best fit between the experimental and simulated data ($y=0.76x+32.54$).

Summary: Models of the motor unit activity, force production and surface EMG signal were extended to continuously reflect the adaptations occurring in sustained contractions. The model was validated by comparing simulation results with experimental observations from multiple experimental studies.

Chapter VI:

IMPACT OF FATIGUE ON THE RELATION BETWEEN THE AMPLITUDES OF FORCE AND SURFACE EMG

This chapter summarizes the simulation results described in detail in Study II and Study III.

To investigate the influence of muscle fatigue on the relation between the amplitude of force and of the surface EMG signal, a series of simulations imposing different levels of fatigue in the muscle were performed. In study II three different contraction paradigms were applied: 1) 19 repeated 17 s ramp contractions to from zero to maximal efforts with 3 s pause between each ramp, 2) sustained contractions at 30 and 60% MVC for 120 and 60 s respectively followed by a ramp contraction from zero to maximal efforts, and 3) sustained contractions at 20, 35, 50, 65, and 80% MVC for intervals beyond the point of task failure (600 s for 20% MVC, 180 s for 80% MVC).

Figure 5 summarizes the relations between simulated force and surface EMG amplitude (average rectified value in 1 s windows) for the three paradigms. The thin lines indicate the relations obtained during each simulation paradigm, while the bold, broken lines indicate curve-fits of lower (non-fatigue) and upper bound (fatigue) of the relations. The distance between these two curves indicate the magnitude of the impact on fatigue on the relation between force and surface EMG. For example, an surface EMG amplitude of 60% MVC may correspond to contraction levels ranging from 10 to almost 50% MVC depending on the level of fatigue in the muscle. The repeatability of the single-simulation curves was highest at contraction levels below 20% MVC. At this particular contraction level the contraction needed to be sustained for more than 7 minutes in order for the corresponding surface EMG amplitude to exceed the range of 27-35% MVC.

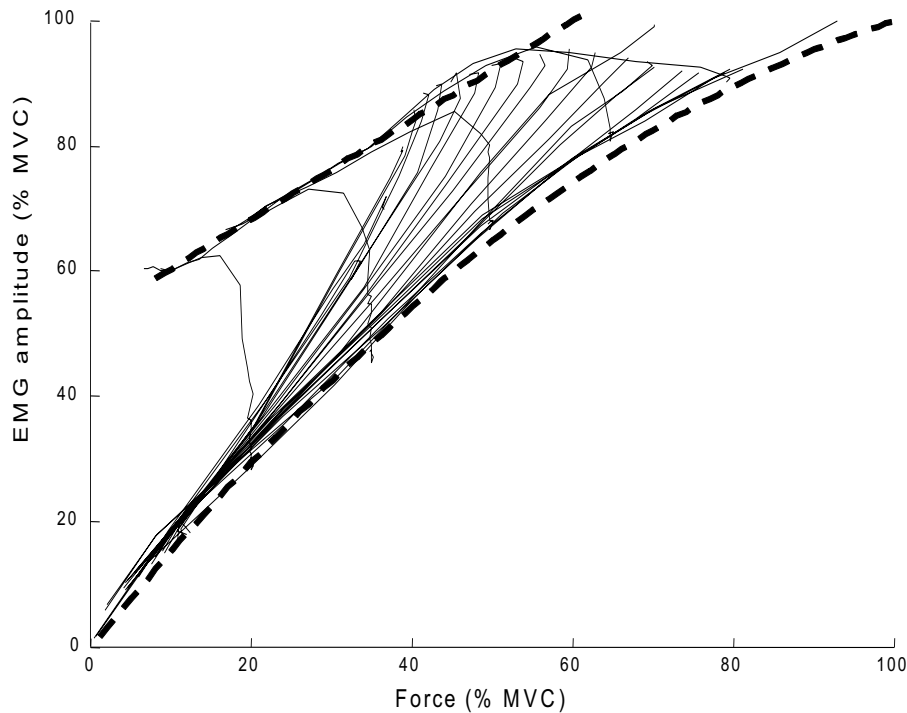


Figure 5. The relations between surface EMG amplitude and muscle force obtained from the three different simulation paradigms. Fatigue shifted the curve to the left. The magnitude of this shift depended on the task that was simulated and the level of fatigue experienced by the muscle. The dashed lines indicate the approximate bounds for the EMG-force relations. The density of the area between the two bounds indicates the difficulty in predicting the influence of fatigue.

To explain which mechanisms are responsible for this discrepancy, Study III systematically investigated the influences of muscle activation level (number of instantaneous muscle fiber discharges) and motor unit conduction velocity on the surface EMG amplitude in sustained contractions at constant contraction levels. First, three contractions at 20, 40, and 60% MVC were simulated until task failure (520, 200, 80 s respectively). The muscle activation level and the motor unit conduction velocity in these contractions are depicted in figure 6. Initially, the muscle activation level declines slightly for all contraction levels, reflecting that the prolongation in motor unit twitch contraction time allows for the force to be maintained with fewer motor unit discharges. Eventually, the decline in motor unit twitch amplitudes forces the muscle activation to increase up to the maximum value, determined by the amount of inhibitory afferent feedback. Motor unit conduction velocity decreased at the highest rate for the 60% MVC contraction, but due to the longer endurance time for the 20% MVC contraction the largest decline occurred for this contraction level.

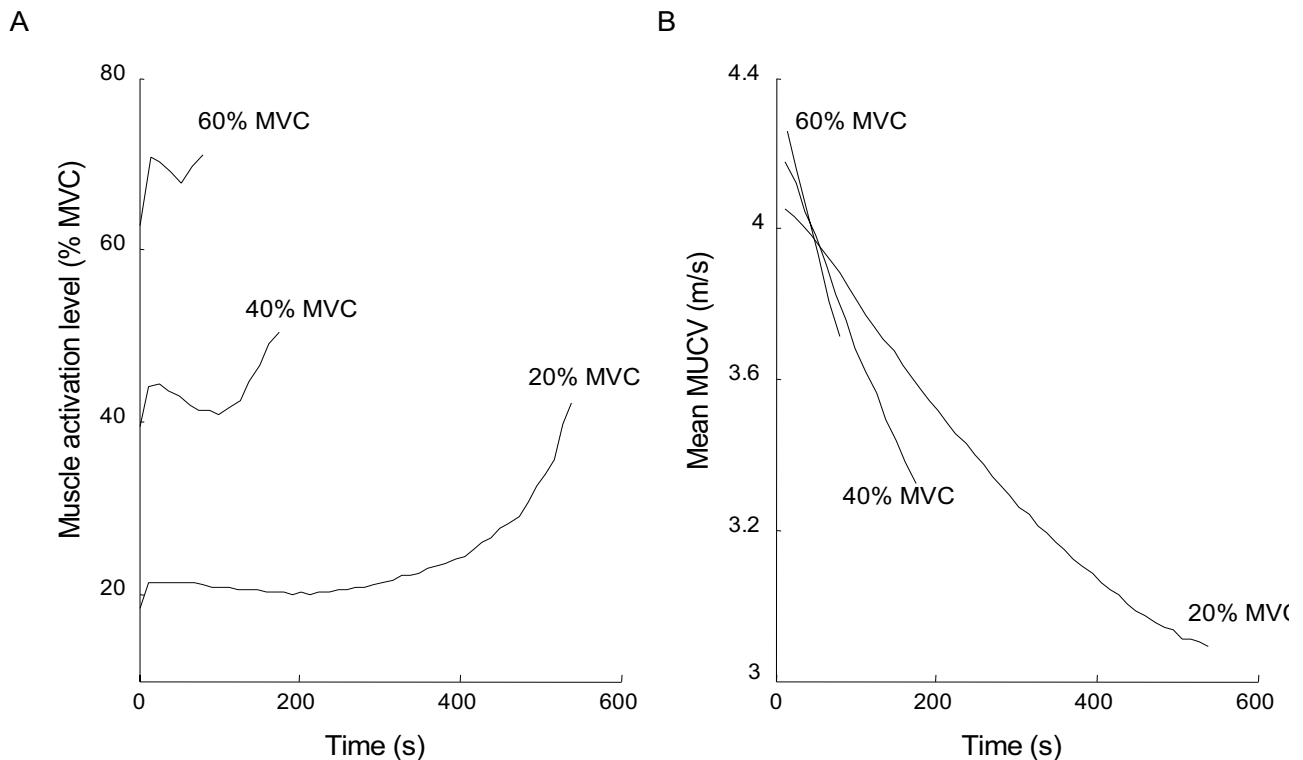


Figure 6. Muscle activation level (muscle fiber action potentials) (A), and average motor unit conduction velocity (B) during the 3 sustained contractions. The muscle activation level were normalized to the values obtained during maximal efforts in the absence of fatigue.

To understand the impact of these observations on the surface EMG signal, a second set of simulations were performed. In these simulations, a single 30 s ramp contraction from zero to maximal efforts were repeated with different imposed levels of average motor unit conduction velocity ranging from 5 m/s (no-fatigue) to 2.7 m/s (severe fatigue). In this way, the surface EMG was simulated for all combinations of muscle activation level and motor unit conduction velocities, making it possible to derive the separate influence of each of these parameters on the surface EMG amplitude. These relations are depicted in figure 7. Muscle activation is closely related to the surface EMG amplitude in a slightly curve-linear fashion, with the gain of this relation being determined by the motor unit conduction velocity. Motor unit conduction velocity on the other hand is less significantly and non-linearly related to the surface EMG amplitude, with the highest surface EMG amplitudes achieved at ~3.3 m/s (moderate to severe fatigue). Furthermore, figure 7 shows the level of surface EMG amplitude cancellation occurring across simulation conditions. While amplitude cancellation increases monotonically as motor unit conduction velocity decreases, it is highly sensitive to muscle activation levels below 20%.

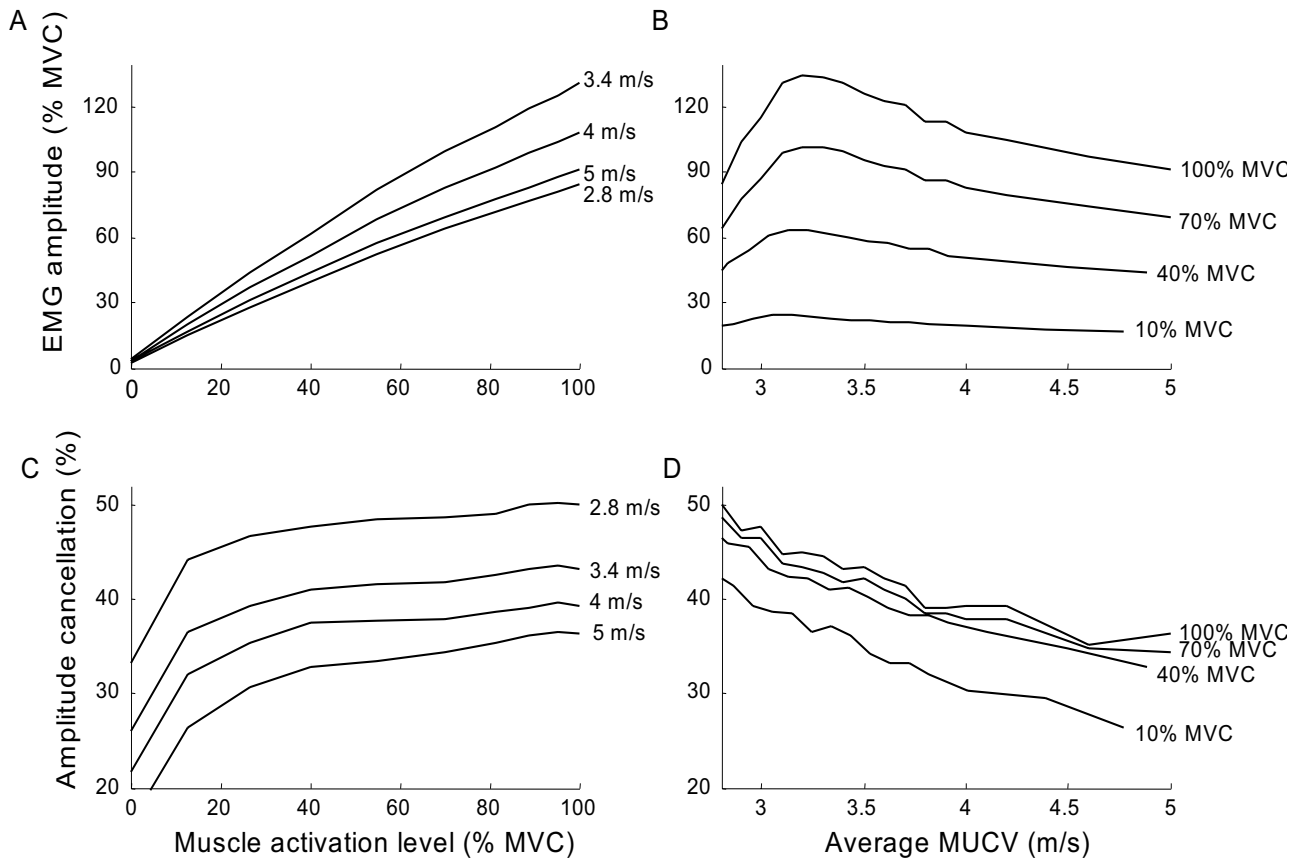


Figure 7. A: derived relations between average rectified EMG amplitude and muscle activation level (number of muscle fiber action potentials). B: relations between EMG amplitude and mean motor unit conduction velocity of the active motor units. C: relations between EMG amplitude cancellation and muscle activation level. D: relations between EMG amplitude cancellation and mean motor unit conduction velocity (MUCV). Each line indicates different levels of mean motor unit conduction velocity (A, C) or different levels of muscle activation level (B, D). The values of conduction velocity were imposed to simulate the EMG in all combinations of muscle activation (0–100%) and conduction velocity (3–5 m/s).

The information provided in figure 6 and 7 indicates that in sustained contractions at 20% MVC, the changes in muscle activation level required to maintain the contraction level involves a large increase in the surface EMG amplitude, while changes in the motor unit action potential waveforms (determined by motor unit conduction velocity) causes a slightly smaller increase in the surface EMG (due to the lower gain of this relation). At higher contraction levels, the muscle activation level increases less, indicating that the changes in surface EMG amplitude can be mainly attributed to changes in the action potential waveforms.

Summary: The results showed that the relation between force and surface EMG amplitude is heavily influenced by the presence of muscle fatigue, and that this relation is not easily predicted as it depends on multiple neuromuscular adaptations.

Chapter VII:

IMPACT OF MOTOR NEURON POPULATION CHARACTERISTICS ON THE RELATION BETWEEN FORCE VARIABILITY AND SURFACE EMG ENVELOPE

This chapter summarizes the simulation results described in detail in Study IV. These results were extended in this chapter by including simulations of the surface EMG signal using the same methodology as in Study II and III.

To investigate the similarity between the temporal variability in the force and in the surface EMG envelope (rectified and low-passed filtered with 400 ms Hann window), the two signals were compared using cross-correlation analysis across contraction levels ranging from 0.5-20% MVC. This analysis revealed a low correlation between the two signals that increased from ~ 0.3 at the low contraction levels to ~ 0.5 at 20% MVC. As force and the surface EMG signal both arise as a consequence of neural activation of the muscle, the underlying reasons for the lack of correlation between the two signals was assessed by investigating the correlation between each of the signals and this activation signal.

The motor unit composite spike train (CST) is defined as the sum of the individual spike trains of all active motor units of the muscle. In this way, CST represents the neural drive to the muscle resulting from all synaptic input received by the entire motor unit population. By applying different low-pass filters (cut-off frequency: 3-15 Hz) to the CST and calculating its correlation with force and the surface EMG signal respectively, it was estimated how the spectral content of the neural drive is reflected in the two signals. Figure 8 depicts these correlations for contraction levels from 0.5 to 20% MVC. These results show that the correlation between force and all low-passed filtered CST was high at low contraction levels, indicating that in these conditions a wide range of the spectrum of the neural drive was transmitted to force. However, as the contraction level increased, primarily the low frequencies (< 3 Hz) of the neural drive were reflected in the force variability. For the surface EMG signal, the correlations were much lower and did not exhibit any trend across the simulated contraction levels, indicating little similarity between the two signals.

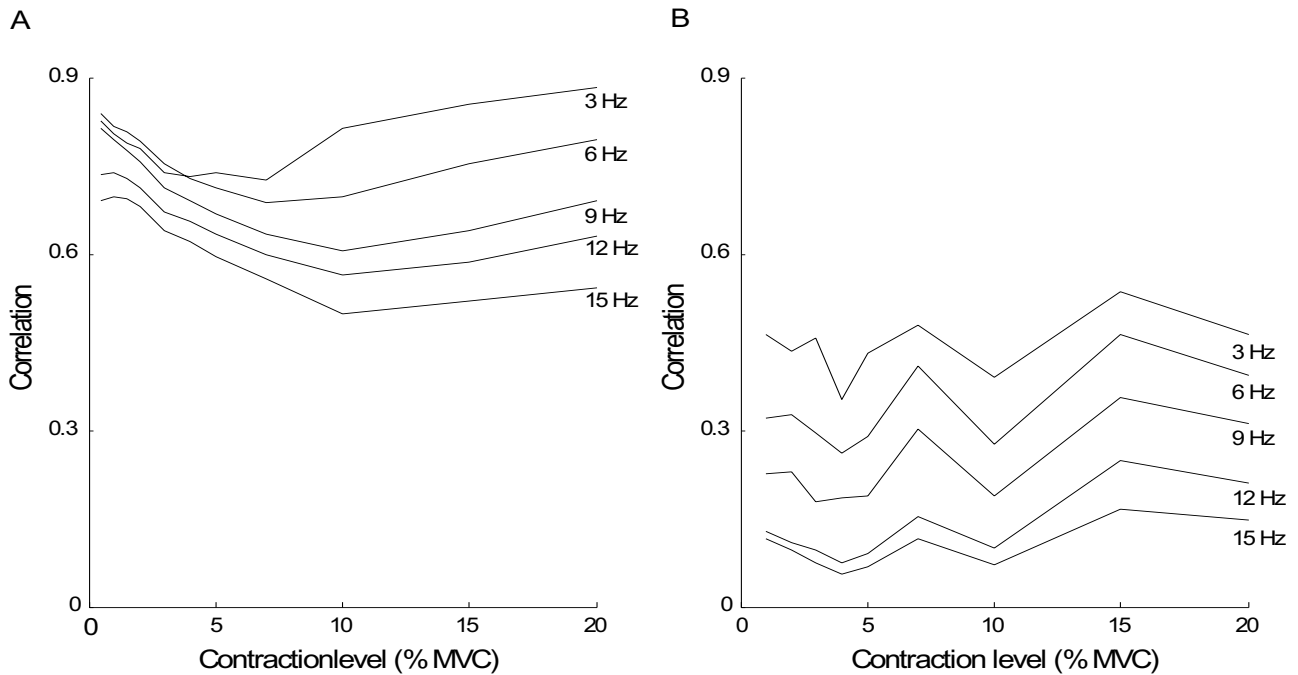


Figure 8. Average peak correlations between the low-pass filtered composite spike train (CST) (cutoff frequencies of 3, 6, 9, 12, and 15 Hz) and the fluctuations in force (A) and the surface EMG envelope (B) respectively, for target forces from 0.5–20% MVC.

Analytical derivations of the generation of force (Study IV) indicated that two low-pass filtering effects implied that only the low-frequency content of the motor unit discharge rate variability is transduced into muscle force. The first filter was related to the convolution of the single motor unit spike trains with the motor unit force twitches (temporal filter) and implied that only discharge rate variability at frequencies below the cut-off frequency determined by the twitch duration (Baldissera et al. 1998) was reflected in the force. The second filter was related to the summation of the force from all active motor units (spatial filter), and implied that variability at all frequencies except DC and those that are common to the entire motor unit population were attenuated as the number of motor units contributed to force increased. In the model, the common variability result from fluctuations in the output of the PID control algorithm, and is experimentally observed as the common drive (De Luca et al. 1982).

Together, these filtering effects of force generation explained the high correlation between the low-frequencies of the neural drive and force. Unlike force, these filtering effects do not occur for the surface EMG signal. Due to the short duration of the motor unit action potentials, the cut-off frequency of the temporal filter related to the motor unit action potential waveform is very high, and

will only provide little effect on the transmission of the neural drive into the surface EMG signal. Furthermore, as the action potential unlike motor unit twitches has no DC-component, the effect of the spatial filter would also be diminished. For these reasons, it is not unexpected that the correlation between the neural drive and the surface EMG signal is relatively low.

When increasing the motor unit twitch duration, as occurs in fatigue (Thomas et al. 1991), the degree of filtering increased, causing the correlation at low frequencies to rise at even lower contraction levels. The fatigue-induced increase in the motor unit action potential waveform (Dimitrova and Dimitrov 2003) however was not sufficient to change the correlation between surface EMG and the neural drive.

To elaborate on the practical effect of these filters in force generation, the influence of the random synaptic noise arising from the thousands of synaptic inputs received by the motor neuron and resulting in the experimentally observable motor unit inter-spike interval variability on muscle force was investigated. For this analysis, a new set of simulations were generated, where the gain of the synaptic noise was varied so that each simulation condition was repeated with coefficients of variation (CoV) for the motor unit inter-spike intervals ranging from 5 to 30% (spanning the physiological range (Clamann 1969; Matthews 1996)). In this way, the impact of this variability on force steadiness for each simulation condition was estimated using linear regression. A slope of the best linear fit <0.1 , indicating that an increase of 10% in the CoV for the inter-spike interval implied an increase of less than 1% in the CoV for force, was set as the lower limit for an insignificant relation between the two parameters. Simulation conditions varied the number of motor units (100-500) and the upper limit for recruitment (40-70% MVC). Figure 9 depicts the highest contraction level at which the relation between discharge rate variability and force steadiness was significant for all simulation conditions. In the majority of conditions the above-mentioned filtering effects of force generation implied that the motor unit discharge rate variability had an influence on force steadiness at very low contraction levels only ($<5\%$ MVC). This effect occurred at higher contraction levels only when very few motor units were available to contribute to the force (low total number of motor units or high upper limit for recruitment).

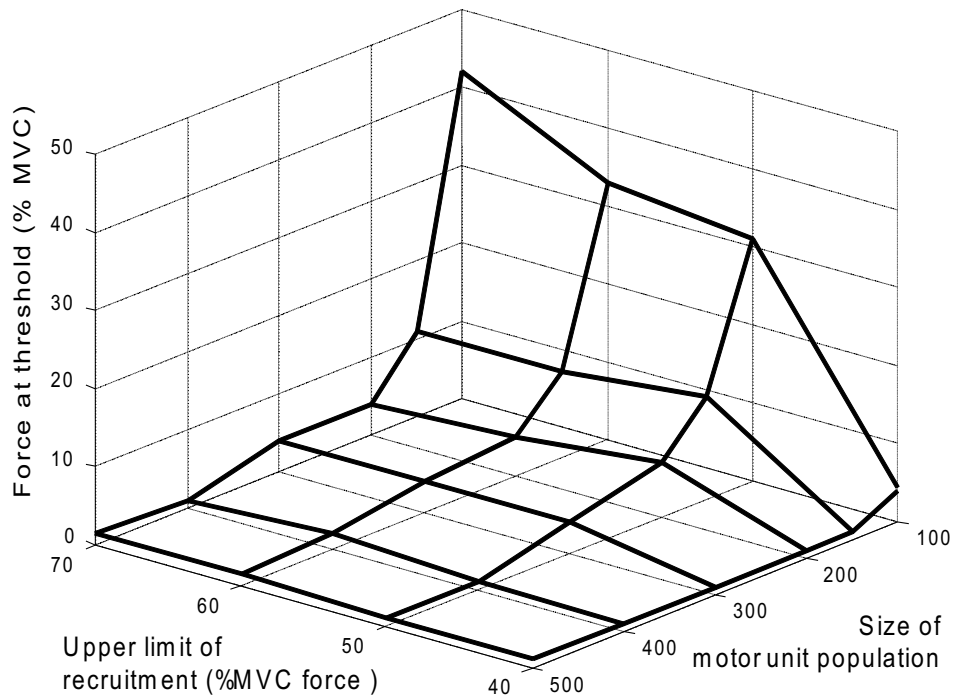


Figure 9. Greatest target forces at which the slope of the linear relation between CoV for ISI and CoV for force was higher than 0.1 for all combinations of motor unit population size (100, 150, 200, 300, 400, and 500) and upper limits of motor unit recruitment (40%, 50%, 60%, and 70% MVC).

Summary: The results showed that the correlation between the force variability and the surface EMG envelope is low, since the filtering effects related to force generation allows it to reflect only the common neural input to the motor neuron population.

Chapter VIII:

DISCUSSION

This chapter discusses the implications of the results of the preceding chapters and summarizes the main findings in the conclusion.

The simulation results presented in Chapter VI indicate that muscle fatigue potentially have a significant impact on the relation between the force level and surface EMG amplitude. For example, these results indicated that depending on the level of muscle fatigue, a given level of surface EMG amplitude may correspond to forces within a range of up to as much as 40% MVC. The simulations revealed that the changes in the number of muscle fiber action potentials required to oppose the loss of motor unit contractile capacity have the largest influence at low contraction levels, whereas the fatigue-related changes in the motor unit action potential waveform are the main determinant at higher contraction levels. Furthermore, the simulations showed that the alteration of the relation between the amplitudes of force and surface EMG depended in complex ways on how muscle fatigue was induced. This underlines the difficulty of predicting the how the relation changes.

Doing this prediction is further troubled by the high sensitivity of the surface EMG signal to differences across muscles and across subjects. For example, it is well-known that muscle fiber type composition determining the muscle fatigue-resistance varies across muscles (Enoka and Fuglevand 2001). Changing these properties in the model would clearly change the results, including those presented in figure 6. Furthermore, although neuromuscular properties is far from known for all muscles findings indicate that parameters such as peak discharge rate (Farina and Falla 2009) and upper limit for recruitment (Kukulka and Clamann 1981) varies across muscles, and that the relation between surface EMG and force is sensitive to these parameters (Zhou and Rymer 2004; Keenan and Valero-Cuevas 2007). Finally, the great variability in EMG amplitude across subject performing the same task (for example indicated by the magnitude of the error-bars in the experimental data reported in figure 4 (Fuglevand et al. 1993; Maluf et al. 2005)), likely in part due to differences in the thickness of the fat-layer between the muscle and electrode (Farina et al. 2002), indicates in inherent uncertainty in the relation between surface EMG amplitude and force.

As shown in Chapter VII, the envelope of the surface EMG signal during an isometric contraction with a constant contraction level is far from the perfect estimator of the temporal variability in force. This lack of correlation between the two signals was due to the filtering effects inherent in

generation of force that is not present in the generation of the surface EMG signal. These filters implied that the force variability in most conditions closely resembled the common drive to the motor unit population, whereas the surface EMG reflected the entire synaptic input to the motor units, including the synaptic noise arising from the many synaptic inputs received by the motor units. These observations are supported by recent experimental findings, indicating that the variability in the neural drive to the muscle are better associated to the force variability than to the surface EMG signal variations (Negro et al. 2009).

It should be noted that the current simulation results reflect the simplest possible conditions; isometric contractions at a constant force level. In force-varying and/or dynamic contractions a series of other physiological properties may further confound the relation between the force variability and the surface EMG envelope. Such properties include for example force-length and force-velocity relations (Zajac 1989), that affects force but not the surface EMG (Staudenmann et al. 2010). Furthermore, the inherent delay in force generation in response to rapid changes in motor neuron excitation level related to the progressive summation of single force twitches is not reflected in the surface EMG signal. On the other hand, in dynamic contractions, the skin (and thus the surface EMG electrode) would move relative to the underlying muscle, potentially changing the characteristics of the recorded surface EMG signal due to its large sensitivity to electrode location with respect to the innervation zone and tendon regions (Masuda et al. 1985).

CONCLUSION

The relation between force and the surface EMG signal was investigated using a novel computational model of neuromuscular activity, force generation and the surface EMG signal in sustained contractions. The simulation results indicated that the presence of muscle fatigue confounds the relation between the amplitudes of force and the surface EMG signal to a degree where the surface EMG amplitude at best can be used as a qualitative indicator of the rough level of force generated by the muscle. Furthermore, the simulations showed that the envelope of the surface EMG signal is a poor estimator of the temporal variability in the force generated by the muscle.

REFERENCES:

Andreassen S and Arendt-Nielsen L. Muscle fibre conduction velocity in motor units of the human anterior tibial muscle: A new size principle parameter. *J Physiol (Lond)* 391: 561-571, 1987.

Andreassen S and Rosenfalck A. Relationship of intracellular and extracellular action potentials of skeletal muscle fibers. *Crit Rev Bioeng* 6: 4: 267-306, 1981.

Arabadzhev TI, Dimitrov VG, Dimitrova NA and Dimitrov GV. Influence of motor unit synchronization on amplitude characteristics of surface and intramuscularly recorded EMG signals. *Eur J Appl Physiol* 108: 2: 227-237, 2010.

Baldissera F, Cavallari P and Cerri G. Motoneuronal pre-compensation for the low-pass filter characteristics of muscle. A quantitative appraisal in cat muscle units. *J Physiol* 511 (Pt 2): Pt 2: 611-627, 1998.

Barry BK, Pascoe MA, Jesunathadas M and Enoka RM. Rate coding is compressed but variability is unaltered for motor units in a hand muscle of old adults. *J Neurophysiol* 97: 5: 3206-3218, 2007.

Bawa P and Stein RB. Frequency response of human soleus muscle. *J Neurophysiol* 39: 4: 788-793, 1976.

Bigland Ritchie B, Johansson R and Lippold OCJ. Changes in motoneurone firing rates during sustained maximal voluntary contractions. *J Physiol (Lond)* Vol. 340: 335-346, 1983.

Burke RE, Levine DN, Tsairis P and Zajac FE,3rd. Physiological types and histochemical profiles in motor units of the cat gastrocnemius. *J Physiol* 234: 3: 723-748, 1973.

Carpentier A, Duchateau J and Hainaut K. Motor unit behaviour and contractile changes during fatigue in the human first dorsal interosseus. *J Physiol (Lond)* 534: 3: 903-912, 2001.

Clamann HP. Statistical analysis of motor unit firing patterns in a human skeletal muscle. *Biophys J* 9: 10: 1233-1251, 1969.

Day SJ and Hulliger M. Experimental simulation of cat electromyogram: Evidence for algebraic summation of motor-unit action-potential trains. *J Neurophysiol* 86: 5: 2144-2158, 2001.

De Luca CJ, Foley PJ and Erim Z. Motor unit control properties in constant-force isometric contractions. *J Neurophysiol* 76: 3: 1503-1516, 1996.

De Luca CJ, LeFever RS, McCue MP and Xenakis AP. Control scheme governing concurrently active human motor units during voluntary contractions. *J Physiol* 329: 129-142, 1982.

de Ruyter CJ, Goudsmit JF, Van Tricht JA and de Haan A. The isometric torque at which knee-extensor muscle reoxygenation stops. *Med Sci Sports Exerc* 39: 3: 443-453, 2007.

Dimitrov GV, Arabadzhiev TI, Hogrel J- and Dimitrova NA. Simulation analysis of interference EMG during fatiguing voluntary contractions. Part II - Changes in amplitude and spectral characteristics. 18: 1: 35-43, 2008.

Dimitrov GV and Dimitrova NA. Precise and fast calculation of the motor unit potentials detected by a point and rectangular plate electrode. *Med Eng Phys* 20: 5: 374-381, 1998.

Dimitrova NA and Dimitrov GV. Interpretation of EMG changes with fatigue: Facts, pitfalls, and fallacies. *13: 1: 13-36*, 2003.

Dimitrova NA and Dimitrov GV. Amplitude-related characteristics of motor unit and M-wave potentials during fatigue. A simulation study using literature data on intracellular potential changes found in vitro. *J Electromyogr Kinesiol* 12: 5: 339-349, 2002.

Disselhorst-Klug C, Schmitz-Rode T and Rau G. Surface electromyography and muscle force: limits in sEMG-force relationship and new approaches for applications. *Clin Biomech (Bristol, Avon)* 24: 3: 225-235, 2009.

Enoka RM and Fuglevand AJ. Motor unit physiology: some unresolved issues. *Muscle Nerve* 24: 1: 4-17, 2001.

Farina D, Cescon C and Merletti R. Influence of anatomical, physical, and detection-system parameters on surface EMG. *Biol Cybern* 86: 6: 445-456, 2002.

Farina D and Falla D. Discharge rate of sternohyoid motor units activated with surface EMG feedback. *J Neurophysiol* 101: 2: 624-632, 2009.

Farina D, Mesin L, Martina S and Merletti R. A Surface EMG Generation Model with Multilayer Cylindrical Description of the Volume Conductor. *51: 3: 415-426*, 2004a.

Farina D, Pozzo M, Merlo E, Bottin A and Merletti R. Assessment of average muscle fiber conduction velocity from surface EMG signals during fatiguing dynamic contractions. *51: 8: 1383-1393*, 2004b.

Fleming BC and Beynnon BD. In vivo measurement of ligament/tendon strains and forces: a review. *Ann Biomed Eng* 32: 3: 318-328, 2004.

Fuglevand AJ, Macefield VG and Bigland-Ritchie B. Force-frequency and fatigue properties of motor units in muscles that control digits of the human hand. *J Neurophysiol* 81: 4: 1718-1729, 1999.

Fuglevand AJ, Winter DA and Patla AE. Models of recruitment and rate coding organization in motor-unit pools. *J Neurophysiol* 70: 6: 2470-2488, 1993.

Fuglevand AJ, Winter DA, Patla AE and Stashuk D. Detection of motor unit action potentials with surface electrodes: influence of electrode size and spacing. *Biol Cybern* 67: 2: 143-153, 1992.

Fuglevand AJ, Zackowski KM, Huey KA and Enoka RM. Impairment of neuromuscular propagation during human fatiguing contractions at submaximal forces. *J Physiol (Lond)* 460: 549-572, 1993.

Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev* 81: 4: 1725-1789, 2001.

Garland SJ, Enoka RM, Serrano LP and Robinson GA. Behavior of motor units in human biceps brachii during a submaximal fatiguing contraction. *J Appl Physiol* 76: 6: 2411-2419, 1994.

Gazzoni M, Camelia F and Farina D. Conduction velocity of quiescent muscle fibers decreases during sustained contraction. *J Neurophysiol* 94: 1: 387-394, 2005.

Gorman RB, McDonagh JC, Hornby TG, Reinking RM and Stuart DG. Measurement and nature of firing rate adaptation in turtle spinal neurons. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 191: 7: 583-603, 2005.

Gustafsson B and Pinter MJ. An investigation of threshold properties among cat spinal alpha-motoneurons. *J Physiol* 357: 453-483, 1984.

Heckman CJ and Enoka RM. Physiology of the motor neuron and the motor unit. In: *Neurophysiology of Motor Neuron Diseases, Handbook of Clinical Neurophysiology, vol. 4*, edited by Eisen A. Amsterdam: Elsevier B V, 2004, p. 119-147.

Heckman CJ and Binder MD. Computer simulations of the effects of different synaptic input systems on motor unit recruitment. *J Neurophysiol* 70: 5: 1827-1840, 1993.

Henneman E. Relation between size of neurons and their susceptibility to discharge. *Science* 126: 3287: 1345-1347, 1957.

HENNEMAN E, SOMJEN G and CARPENTER DO. Functional Significance of Cell Size in Spinal Motoneurons. *J Neurophysiol* 28: 560-580, 1965.

Herbert RD and Gandevia SC. Twitch interpolation in human muscles: mechanisms and implications for measurement of voluntary activation. *J Neurophysiol* 82: 5: 2271-2283, 1999.

Holobar A, Farina D, Gazzoni M, Merletti R and Zazula D. Estimating motor unit discharge patterns from high-density surface electromyogram. 120: 3: 551-562, 2009.

Hultborn H. State-dependent modulation of sensory feedback. *J Physiol* 533: Pt 1: 5-13, 2001.

Hultborn H, Denton ME, Wienecke J and Nielsen JB. Variable amplification of synaptic input to cat spinal motoneurons by dendritic persistent inward current. *J Physiol* 552: Pt 3: 945-952, 2003.

Jones KE, Hamilton AF and Wolpert DM. Sources of signal-dependent noise during isometric force production. *J Neurophysiol* 88: 3: 1533-1544, 2002.

Kandel ER, Schwartz JH and Jessell TM. *Principles of neural science*. New York: McGraw-Hill, Health Professions Division, 2000, p. 1414.

Katsis CD, Exarchos TP, Papaloukas C, Goletsis Y, Fotiadis DI and Sarmas I. A two-stage method for MUAP classification based on EMG decomposition. *Comput Biol Med* 37: 9: 1232-1240, 2007.

Keenan KG, Farina D, Maluf KS, Merletti R and Enoka RM. Influence of amplitude cancellation on the simulated surface electromyogram. *J Appl Physiol* 98: 1: 120-131, 2005.

Keenan KG, Farina D, Merletti R and Enoka RM. Amplitude cancellation reduces the size of motor unit potentials averaged from the surface EMG. *J Appl Physiol* 100: 6: 1928-1937, 2006a.

Keenan KG, Farina D, Merletti R and Enoka RM. Influence of motor unit properties on the size of the simulated evoked surface EMG potential. 169: 1: 37-49, 2006b.

Keenan KG and Valero-Cuevas FJ. Experimentally valid predictions of muscle force and EMG in models of motor-unit function are most sensitive to neural properties. *J Neurophysiol* 98: 3: 1581-1590, 2007.

Klaver-Król EG, Henriquez NR, Oosterloo SJ, Klaver P, Bos JM and Zwarts MJ. Distribution of motor unit potential velocities in short static and prolonged dynamic contractions at low forces:

Use of the within-subject's skewness and standard deviation variables. *Eur J Appl Physiol* 101: 5: 647-658, 2007.

Kleine BU, Stegeman DF, Mund D and Anders C. Influence of motoneuron firing synchronization on SEMG characteristics in dependence of electrode position. *J Appl Physiol* 91: 4: 1588-1599, 2001.

Kostyukov AI, Kalezic I, Serenko SG, Ljubisavljevic M, Windhorst U and Johansson H. Spreading of fatigue-related effects from active to inactive parts in the medial gastrocnemius muscle of the cat. *Eur J Appl Physiol* 86: 4: 295-307, 2002.

Kukulka CG and Clamann HP. Comparison of the recruitment and discharge properties of motor units in human brachial biceps and adductor pollicis during isometric contractions. *Brain Res* 219: 1: 45-55, 1981.

Lawrence JH and De Luca CJ. Myoelectric signal versus force relationship in different human muscles. *J Appl Physiol* 54: 6: 1653-1659, 1983.

Lee RH and Heckman CJ. Adjustable amplification of synaptic input in the dendrites of spinal motoneurons in vivo. *J Neurosci* 20: 17: 6734-6740, 2000.

LeFever RS and De Luca CJ. A procedure for decomposing the myoelectric signal into its constituent action potentials--Part I: Technique, theory, and implementation. *IEEE Trans Biomed Eng* 29: 3: 149-157, 1982.

Lemon RN. Descending pathways in motor control. *Annu Rev Neurosci* 31: 195-218, 2008.

Lindstrom LH and Magnusson RI. Interpretation of myoelectric power spectra: A model and its applications. *Proceedings of the IEEE* 65: 5: 653-662, 1977.

Loram ID, Gollee H, Lakie M and Gawthrop PJ. Human control of an inverted pendulum: is continuous control necessary? Is intermittent control effective? Is intermittent control physiological? *J Physiol* 589: Pt 2: 307-324, 2011.

Macefield VG, Gandevia SC, Bigland-Ritchie B, Gorman RB and Burke D. The firing rates of human motoneurons voluntarily activated in the absence of muscle afferent feedback. *J Physiol (Lond)* 471: 429-443, 1993.

Maluf KS, Shinohara M, Stephenson JL and Enoka RM. Muscle activation and time to task failure differ with load type and contraction intensity for a human hand muscle. *J Neurophysiol* 167: 2: 165-177, 2005.

Masuda T, Miyano H and Sadoyama T. The position of innervation zones in the biceps brachii investigated by surface electromyography. *IEEE Trans Biomed Eng* 32: 1: 36-42, 1985.

Matthews PB. Relationship of firing intervals of human motor units to the trajectory of post-spike after-hyperpolarization and synaptic noise. *J Physiol* 492 (Pt 2): Pt 2: 597-628, 1996.

McGill KC, Lateva ZC and Marateb HR. EMGLAB: An interactive EMG decomposition program. *J Neurosci Methods* 149: 2: 121-133, 2005.

Merletti R and Farina D. Analysis of intramuscular electromyogram signals. *Philos Transact A Math Phys Eng Sci* 367: 1887: 357-368, 2009.

Mileusnic MP, Brown IE, Lan N and Loeb GE. Mathematical models of proprioceptors. I. Control and transduction in the muscle spindle. *J Neurophysiol* 96: 4: 1772-1788, 2006.

Moritz CT, Barry BK, Pascoe MA and Enoka RM. Discharge rate variability influences the variation in force fluctuations across the working range of a hand muscle. *J Neurophysiol* 93: 5: 2449-2459, 2005.

Nandedkar SD, Sanders DB and Stalberg EV. Selectivity of electromyographic recording techniques: a simulation study. *Med Biol Eng Comput* 23: 6: 536-540, 1985.

Nawab SH, Chang SS and De Luca CJ. High-yield decomposition of surface EMG signals. *Clin Neurophysiol* 121: 10: 1602-1615, 2010.

Negro F, Holobar A and Farina D. Fluctuations in isometric muscle force can be described by one linear projection of low-frequency components of motor unit discharge rates. *J Physiol* 587: Pt 24: 5925-5938, 2009.

Nishizono H, Kurata H and Miyashita M. Muscle fiber conduction velocity related to stimulation rate. *Electroencephalogr Clin Neurophysiol* 72: 6: 529-534, 1989.

Revill AL and Fuglevand AJ. Effects of persistent inward currents, accommodation, and adaptation on motor unit behavior: a simulation study. *J Neurophysiol* 106: 3: 1467-1479, 2011.

Rudolph-Lilith M, Dubois M and Destexhe A. Analytical Integrate-and-Fire Neuron Models with Conductance-Based Dynamics and Realistic Postsynaptic Potential Time Course for Event-Driven Simulation Strategies. *Neural Comput* 24: 6: 1426-1461, 2012.

Sjogaard G, Savard G and Juel C. Muscle blood flow during isometric activity and its relation to muscle fatigue. *Eur J Appl Physiol Occup Physiol* 57: 3: 327-335, 1988.

Spielmann JM, Laouris Y, Nordstrom MA, Robinson GA, Reinking RM and Stuart DG.

Adaptation of cat motoneurons to sustained and intermittent extracellular activation. *J Physiol* 464: 75-120, 1993.

Stashuk D. EMG signal decomposition: how can it be accomplished and used? *J Electromyogr Kinesiol* 11: 3: 151-173, 2001.

Stashuk D and Qu Y. Robust method for estimating motor unit firing-pattern statistics. *Med Biol Eng Comput* 34: 1: 50-57, 1996.

Staudenmann D, Roeleveld K, Stegeman DF and van Dieen JH. Methodological aspects of SEMG recordings for force estimation--a tutorial and review. *J Electromyogr Kinesiol* 20: 3: 375-387, 2010.

Stein RB, French AS, Mannard A and Yemm R. New methods for analysing motor function in man and animals. *Brain Res* 40: 1: 187-192, 1972.

Taylor AM, Christou EA and Enoka RM. Multiple features of motor-unit activity influence force fluctuations during isometric contractions. *J Neurophysiol* 90: 2: 1350-1361, 2003.

Taylor AM, Steege JW and Enoka RM. Motor-unit synchronization alters spike-triggered average force in simulated contractions. *J Neurophysiol* 88: 1: 265-276, 2002.

Thomas CK, Johansson RS and Bigland-Ritchie B. Attempts to physiologically classify human thenar motor units. *J Neurophysiol* 65: 6: 1501-1508, 1991.

Tsianos GA, Rustin C and Loeb GE. Mammalian muscle model for predicting force and energetics during physiological behaviors. *IEEE Trans Neural Syst Rehabil Eng* 20: 2: 117-133, 2012.

Ulfhake B and Cullheim S. Postnatal development of cat hind limb motoneurons. III: Changes in size of motoneurons supplying the triceps surae muscle. *J Comp Neurol* 278: 1: 103-120, 1988.

Woods JJ and Bigland-Ritchie B. Linear and non-linear surface EMG/force relationships in human muscles. An anatomical/functional argument for the existence of both. *Am J Phys Med* 62: 6: 287-299, 1983.

Woods JJ, Furbush F and Bigland-Ritchie B. Evidence for a fatigue-induced reflex inhibition of motoneuron firing rates. *J Neurophysiol* 58: 1: 125-137, 1987.

Yao W, Fuglevand AJ and Enoka RM. Motor-unit synchronization increases EMG amplitude and decreases force steadiness of simulated contractions. *J Neurophysiol* 83: 1: 441-452, 2000.

Zajac FE. Muscle and tendon: properties, models, scaling, and application to biomechanics and motor control. *Crit Rev Biomed Eng* 17: 4: 359-411, 1989.

Zhou P and Rymer WZ. Factors governing the form of the relation between muscle force and the EMG: a simulation study. *J Neurophysiol* 92: 5: 2878-2886, 2004.

Zijdewind I, Zwarts MJ and Kernell D. Fatigue-associated changes in the electromyogram of the human first dorsal interosseous muscle. *J Neurophysiol* 22: 10: 1432-1436, 1999.