Identification of neural and non-neural contributors to joint stiffness in upper motor neuron disease

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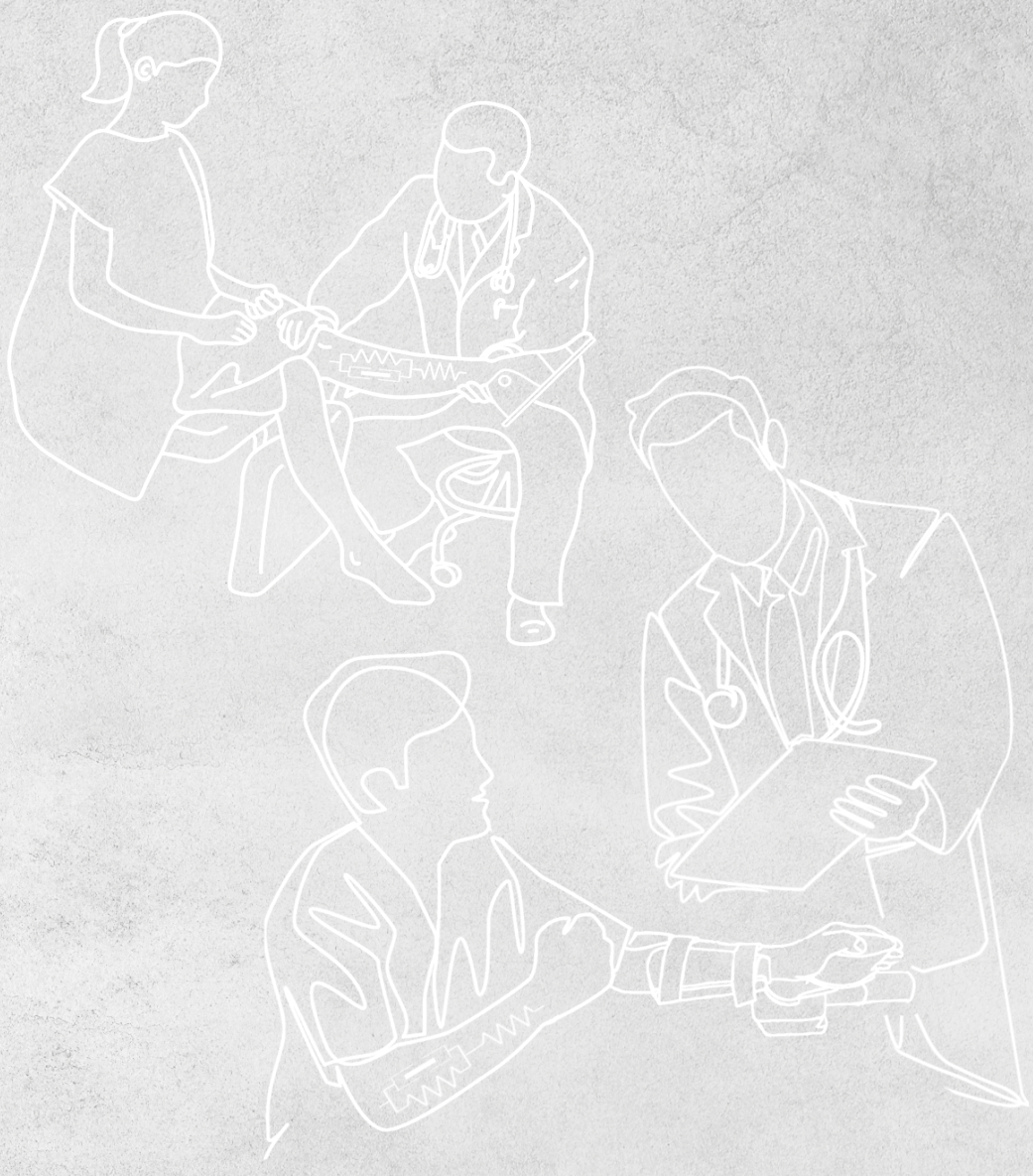
CHAPTER 1

Introduction



In upper motor neuron diseases, like spinal cord injury, multiple sclerosis, cerebral palsy and stroke, motor areas in the brain and/or spinal cord are damaged or fail to develop normally. Cerebral palsy is due to abnormal development or damage in the developing brain and occurs in about 2 per 1000 life births[1;2]. Stroke is now the second leading cause of death worldwide and third most common cause of disability-adjusted life-years[3-5] and the incidence of stroke increases with the graying of the society[6;7]. Improvement in acute stroke care results in a greater proportion of patients surviving stroke, but consequently a larger number of people that needs to deal with stroke related disabilities. Activities of daily living and quality of life are affected by motor, cognitive, speech and language disorders, depression and dementia[8;9]. Interfering motor disorders are stiffness, i.e. increased resistance to movement, decreased range of motion, flexion deformity resulting in a shift of joint rest angle towards flexion and paresis, i.e. the inability to voluntarily and selectively generate muscle strength and power[10].

Rehabilitation interventions at the ICF[11] level of body functions and structures focus on reduction of stiffness and maintenance or increasing joint range of motions and correction of abnormal joint rest angle shifts. Clinically, the combination of stiffness and muscle over-activity is often called “spasticity”, but the definition is under debate[10;12]. In stroke about 20-30% of all patients suffer from spasticity[13]. Spasticity was assumed to originate from neurally induced reflexive stiffness, i.e. velocity dependent resistance of joint to passive stretching, according to the definition of Lance[14]. However nowadays it becomes accepted that in “spasticity”, the neural and non-neural components intermingle[15-17]. Neural and non-neural tissue components continuously interact within a closed loop: The tight coupling between afferent sensory information, the central neural system, efferent commands and motor properties[16;18]. Neural activity may modulate tissue properties; tissue shortening may alter reflexive thresholds. Moreover, the neural and non-neural properties are environment- and task dependent[10;16].

This poses a challenge to assess and quantify the neural, i.e. reflexive stiffness and involuntary background activation, and non-neural, i.e. muscle shortening and stiffening, components[15;19]. At these contributors selective treatment should be aimed, i.e. either targeted at the neural component or at the non-neural component. The clinical Ashworth and Tardieu tests[20-22] are applied to quantify the joint stiffness by the observer while manually rotating the joint throughout its range of motion. These clinical tests do not differentiate between the neural

reflexive and non-neural tissue components, besides being notoriously insensitive, ordinal and insufficient valid and reliable as a measure for spasticity[16;23;24].

The neural and non-neural components can be disentangled using a system identification and parameter estimation approach (SIPE). System identification uses robotic devices to deliver precise force and position perturbations to a joint to allow for assessment of input- output relations which can be used to describe the properties of a system[18;25-27]. Subsequent neuromuscular modeling allows for describing the neuromuscular system into clinically interpretable parameters. Linear SIPE techniques have been applied for analysis of the underlying neuromuscular system in patients with dystonia and stroke[28;29] and analysis of standing balance in Parkinson's disease and healthy elderly[30-32]. In these SIPE techniques, the non-linearity, e.g. increased resistance against movement near the maximal range of motion, of the (neuromuscular) system is described by a linear technique. Use of these linear techniques requires small deviations of e.g. joint angle and muscle contraction. These small deviations in movements and contraction do not resemble functional movement. Furthermore, the non-linear force-length and force-velocity properties of the connective and contractile tissue and the quantification of thresholds of spinal reflexes require non-linear methods[16;33;34]. Non-linear models were applied to predict recorded forces from ramp-and-hold joint perturbations by optimizing parameter values of the model of the wrist and ankle in healthy subjects and to discriminate groups of patient with stroke from controls[35;36].

Non-linear models are necessary to quantify underlying neural and non-neural contributors of increased joint stiffness, diminished range of motion and shift of joint rest angle. This quantification is important for understanding of underlying mechanisms of functional recovery and the effect of therapy on the underlying components to diminish or eventually prevent impairments of movement function.

The aim of the present thesis is:

1. To quantify neural reflexive and non-neural tissue contributors in patients with upper motor neuron disease to understand underlying pathophysiological mechanism of increased joint stiffness, diminished range of motion and shifted joint rest angle. Therefore, an instrumented and EMG driven non-linear neuromuscular modeling approach is developed and validated that allows for high precision quantification of behavior of the neuromuscular system and by disentanglement of its underlying components (chapter 2, 3 and 4).
2. The method will be used to understand underlying mechanisms of functional recovery and the effect of therapy in stroke:
    a) The development of aforementioned components over time will be analyzed in the sub-acute phase post-stroke to address possible targeted preventive measures and to improve understanding of underlying mechanisms of functional recovery (chapter 5).
    b) The effect of botulinum toxin A treatment on the neural reflexive and non-neural tissue properties in patients post-stroke will be determined to make a first step in predicting which patients will benefit from this therapy (chapter 6).

The present thesis was founded on two research projects, i.e. ROBIN (STW) and Explicit Stroke (ZonMw). ROBIN (ROBot aided system identification: novel tools for diagnosis and assessment in Neurological rehabilitation) aimed to develop the required tools for applying SIPE techniques to clinical practice. The techniques developed in ROBIN were applied to clinical data obtained in Explicit-Stroke. The Explicit-Stroke project was a multi-center randomized controlled trial which studied the effect of early therapy on post-stroke recovery of the upper limb[37;38]. It further aimed to understand the underlying mechanisms of upper extremity functional recovery, encompassing brain plasticity by fMRI[39] and end-point wrist neuromechanics by haptic robotics[40;41].

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