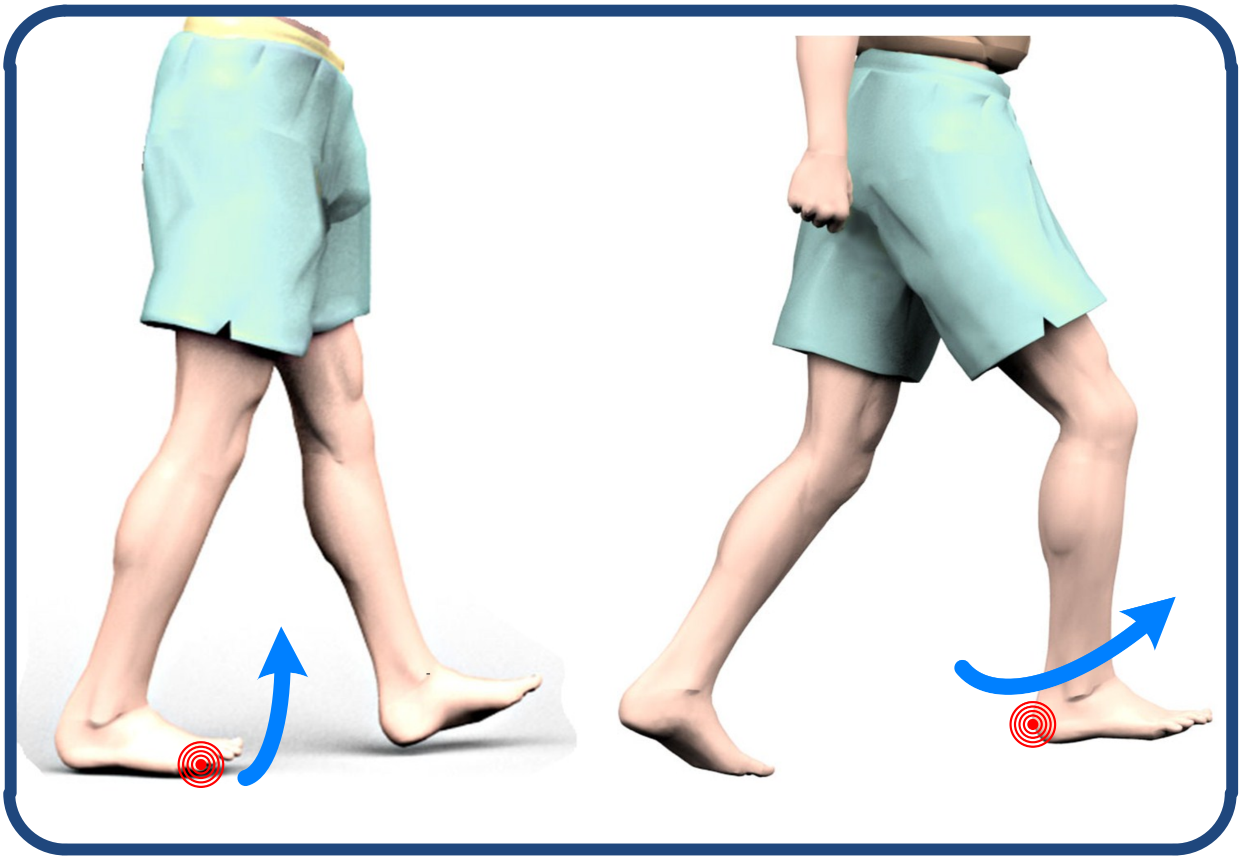
Modulation of the nociceptive withdrawal reflex and its use in rehabilitation of gait of stroke patients

BY

JONAS EMBORG



DISSERTATION SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

CENTER FOR SENSORY-MOTOR INTERACTION (SMI)

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Preface

This thesis is based on the following articles:

- Withdrawal reflex responses evoked by repetitive painful stimulation delivered on the sole of the foot during late stance: site, phase, and frequency modulation. E. G. Spaich, J. Emborg, T. Collet, L. Arendt-Nielsen, and O. K. Andersen, Exp. Brain Res., vol. 194, no. 3, pp. 359-368, Apr.2009. DOI: 10.1007/s00221-009-1705-9 http://dx.doi.org/10.1007/s00221-009-1705-9

- Withdrawal reflexes examined during human gait by ground reaction forces: site and gait phase dependency. J. Emborg, E. G. Spaich, and O. K. Andersen, Med Biol Eng Comput 2009;vol. 4, pp 29-39, Jan 2009. DOI: 10.1007/s11517-008-0396-x http://dx.doi.org/10.1007/s11517-008-0396-x

- Design and test of a novel closed-loop system that exploits the nociceptive withdrawal reflex for swing phase support of the hemiparetic gait. J. Emborg, Z. Matjačić, J. D. Bendtsen, E.G. Spaich, I. Cikajlo, N. Goljar, O.K. Andersen. IEEE Transactions on Biomedical Engineering. Accepted for publication December 2010. DOI:10.1109/TBME.2010.2096507 http://dx.doi.org/10.1109/TBME.2010.2096507

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Commonly used abbreviations

BF	biceps femoris
CVA	cerebro vascular accident
EMG	electromyography
FES	functional electrical stimulation
FET	functional electrical therapy
FPS	fixed pattern of stimulation control
FRA	flexor reflex afferents
FSR	force sensing resistor
GRF	ground reaction force
MA	moving average
MRAC	model reference adaptive control
NP	neural prosthesis
NWR	nociceptive withdrawal reflex
PFC	peak force change
RMS	root mean square
RRF	reflex receptive field
SOL	soleus
TA	tibialis anterior
VL	vastus lateralis

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Jonas Emborg
Aalborg, 2010

Table of contents

1. Introduction

The idea behind this PhD study was to utilise some of the findings obtained in basic studies of the mechanisms of the nociceptive withdrawal reflex organisation and modulation and apply them in the field of rehabilitation engineering. More specifically within gait rehabilitation of patients with upper neuron lesions caused by a cerebrovascular accident (stroke).

Patients who have suffered a cerebral stroke often have problems moving one or more limbs on primarily one side of the body. However, also the contralateral side of the body can also be affected. A stroke might affect the patient's ability to perform relative simple movements used in daily living such as walking, reaching and grasping. Every year, approximately 700,000 European citizens are affected by a stroke, which is nearly one new disabled person *per* minute. The total number of persons with hemiplegia in the European Union is estimated at 3,500,000 (Sinkjaer and Popovic 2005). In Denmark, the prevalence of strokes per year is around 0.3% (15.500 cases), and between 30.000 to 40.000 persons live with the consequences of a stroke (http: and hjernesagen.dk 2009). Approximately 60% of these suffer from decreased functionality and depend on assistance to perform many daily activities, and about 35% have major problems when walking. The functional prognosis is heavily dependent on the initial condition. Thus, less than one tenth of patients with severe pareses in the lower extremity immediately after the stroke obtain fully independent gait function (Pedersen and Olsen 2007). Restoring the ability to perform normal walking is important to improve quality of life. After a stroke patients typically exhibit decreased hip and knee flexion, and decreased ankle dorsiflexion during the swing-phase of gait, and decreased knee extension at heel strike (Moore et al. 1993).

To support the production of the swing phase, the nociceptive withdrawal reflex (NWR) may be evoked leading to a synergistic contraction of flexor muscles that result in hip and knee flexion in combination with ankle dorsiflexion. The NWR is typically activated by a painful stimulus, e.g. stepping on a sharp object, and after integrating sensory information from the painful site, postural information, and considering the motor context, it moves the limb away from the stimulus to prevent potential tissue damage (Sherrington 1910).

1.1 <u>Background</u>

To support the rehabilitation of gait, electrical stimulation, that activates motor nerves and thereby produces contraction of the innervated muscles, has been used for several decades (See the review by Lyons et al. (2002). This technique has both pros and cons; a clear advantage is the possibility to control the movement of the legs to great detail, while one of the drawbacks is the inverse recruitment order of motor units as compared to the physiological recruitment order. In a physiological muscle contraction, the recruitment order is in the order of increasing size, but electrical stimulation recruits large motor units before small motor units (inverse recruitment). Inverse recruitment leads to faster muscle fatigue and a poor force gradation (Solomonow 1984). Another drawback of muscle-nerve stimulation is the limited number of muscles that can be activated using surface stimulation. It is possible to activate all the muscles localised superficially, but for deeper muscles i.e. the main hip flexor (iliopsoas), surface stimulation is unsuitable.

As an alternative to muscle-nerve stimulation, spinal reflexes can be used to activate the muscles in a more physiological manner. Stimulation of spinal reflexes has been used for rehabilitation purposes for several decades i.e. stimulation of the peroneal nerve to partly activate the flexion withdrawal reflex and partly stimulate the efferent motor nerve fibers of the tibialis anterior muscle. This method has been successfully used by Liberson et al. (1961), to correct droop-foot by evoking ankle dorsi-flexion. Later, stimulation of the flexion withdrawal reflex has been used in rehabilitation of both spinal cord injured patients (Granat et al. 1992;Granat et al. 1993;Riener et al. 2000), and hemiplegic subjects (Braun et al. 1985;Quintern et al. 2004).

The first extensive description of the flexor reflex was presented by (Sherrington 1910), and since then, the reflex responses have been conceived as stereotyped flexion responses; however, Grimby (1963) observed that the reflex response was dependent on the stimulation site and not only consisted of a flexion of the affected limb. Later, Schouenborg and Kalliomaki (1990) showed that each muscle or synergistic muscle group has a specific reflex receptive field (RRF) and suggested that there was a more refined modular organization of the withdrawal reflex. The hypothesis is that when a painful stimulus evokes a withdrawal reflex the muscles involved in the reflex response are exactly the muscles that remove optimally the affected skin site from the irritating stimulus.

More recent studies on the lower limb nociceptive withdrawal reflex elicited by painful electrical stimulation of the human sole of the foot indicate that a stronger stimulus evokes a stronger withdrawal from the stimulation (Spaich et al. 2005b), and that the reflex response is dependent on the stimulation site (Andersen et al. 1999), frequency (Spaich et al. 2005b) and modulated by posture (Andersen et al. 2003) and the gait cycle (Spaich et al. 2004b;Andersen et al. 2005;Spaich et al. 2006). The variation in withdrawal strategy dependent on the activation paradigm reveals a new property of the withdrawal reflex: controllability. This property may open the opportunity of controlling or guiding a paretic leg through the swing phase of a step and perhaps fine-tuning the resulting movement to the individual needs of each patient.

The reflex response can habituate when a site is stimulated repetitively within a short period of time, which means that the response may gradually disappear. However, it has been found that when the reflex has been habituated by repetitive stimulation it can be dis-habituated (breakdown of the habituation phenomenon resulting in recovery of the reflex movement) by changing the stimulation parameters of the stimulus applied. Dis-habituation can be achieved by changing the stimulation site (Dimitrijevic and Nathan 1971) or by changing the stimulus intensity (Granat et al. 1991). It has also been shown that longer inter-stimulation intervals can reduce habituation (Granat et al. 1993) .

A new therapeutic modality for post-stroke hemiplegic individuals called Functional Electrical Therapy (FET) combines Functional Electrical Stimulation (FES) with task-dependent voluntary exercise. This combined intervention carries potential for promoting recovery of movement in paralyzed extremities. The motivation for this therapeutic modality is based on case reports where patients using FES on a regular basis experienced a significant carry-over effect in function that persisted even when the device was no longer in use (Daly et al. 1996;Taylor et al. 1999;Rushton 2003). The basic idea behind FET is to use a neuroprosthesis in the recovery phase to facilitate functional exercises and the goal is a lasting increase in function. The hypothesis is that due to the plasticity of the brain, extensive use of the affected limbs produces use-dependent cortical reorganization leading to regained motor control of the paralysed limb

Studies in rehabilitation of hand reaching and grasping (Popovic et al. 2003b) have shown that the recovery of acute stroke patients is greatly promoted when using FET. This indicates that FET combined with early rehabilitation is very important in accelerating the recovery of motor function, improving the ability to perform activities of daily living and thereby the quality of life. Thus, it can be hypothesized that reflex-based FET i.e. electrical stimulation of the flexion withdrawal reflex combined with task-dependent voluntary exercise, will result in a faster and higher level of recovery compared to conventional therapy when applied in the sub-acute phase after a cerebrovascular accident.

1.2 Conceptual considerations

The goal of this project is, through basic understanding of the noceceptive withdrawal reflex, to develop a method that allows testing reflex-based FET. The novelty of this project is to apply electrical stimulations under the foot in order to produce targeted cutaneous input to the spinal cord and thereby artificially activate muscles of the lower leg through withdrawal reflex pathways, and to use this in the rehabilitation of hemiplegic gait (Figure 1).

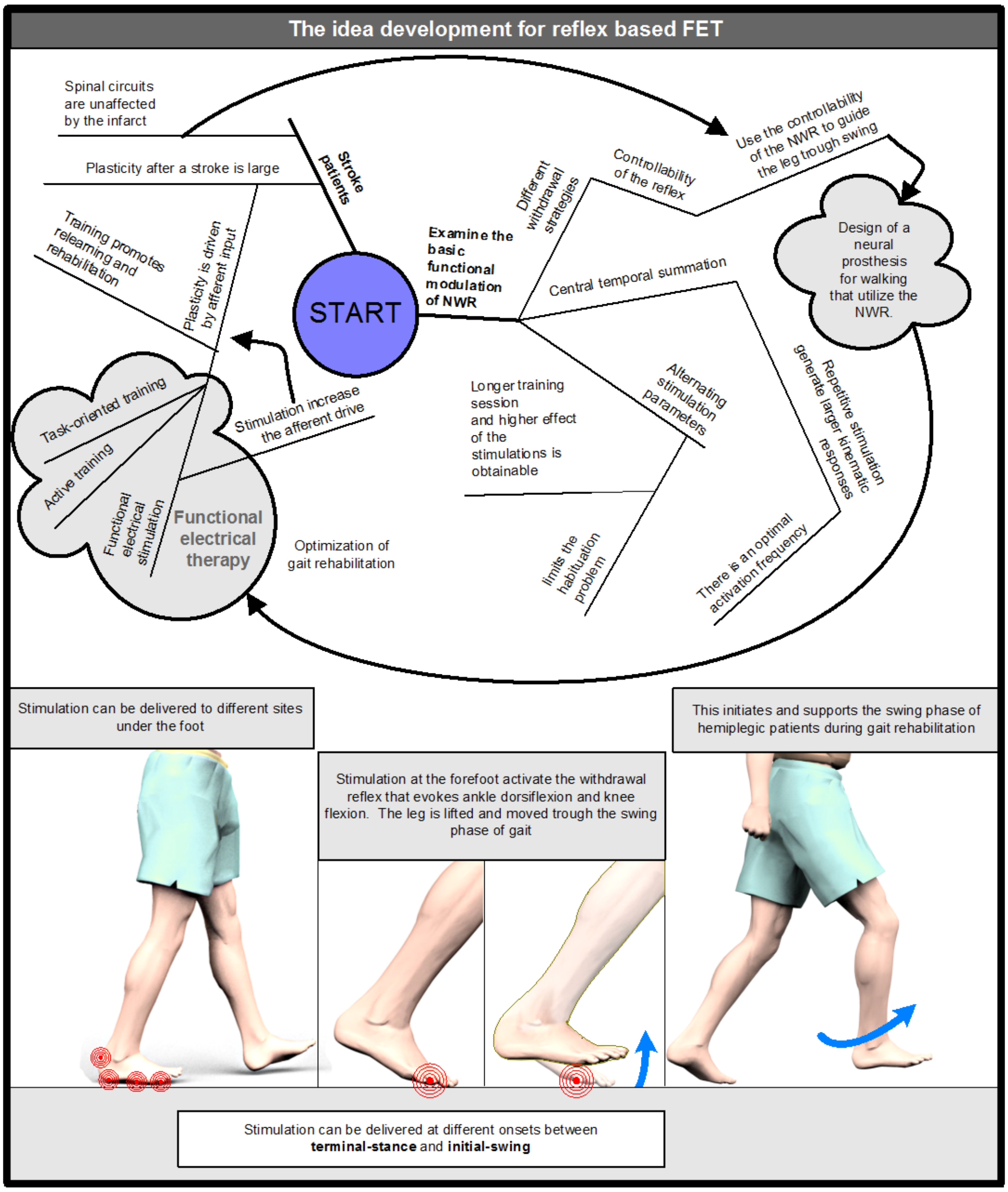

Figure 1: Mind-map and sketch showing the basic ideas behind the work done in this thesis.

The goal is to activate on purpose different withdrawal strategies and thereby generate a controlled movement of the hip, knee, and ankle joints. The electrical stimulation is to be delivered to different sites on the sole of the foot, in different sub-phases of the gait cycle. Thus, the aim is to stimulate at the most appropriate site at the right moment to tailor a desired movement for individual hemiplegic patients. This has the positive side-effect of constantly alternating stimulation parameters, which most likely will reduce the habituation problem (Dimitrijevic and Nathan 1971;Granat et al. 1991). To further reduce the effect of habituation and to give a more efficient reaction, repetitive stimulations with long inter-stimulation intervals (Granat et al. 1993) are used, since the stimulations are delivered during the swing phase and are silent in the stance phase of the gait cycle. To be able to select the optimal stimulation parameters and control the movement of the paretic leg, an automated sensor-driven control system has to be designed. It is hypothesized than an automated sensor-driven closed-loop swing phase controller will prove superior when as compared to an open-loop swing phase controller using pre-programmed fixed stimulation parameters. The automated sensor-driven system has to be based on artificial sensors mounted on the person and has to be feasible to implement in a clinical setting. During the development phase, measurements of joint angles, ground reaction forces, and electromyograms are used to provide a foundation for selecting the optimal sensors.

1.3 PhD project goals

To be able to test reflex-based FET as a therapeutic tool in the gait rehabilitation of sub-acute stroke patients a method for selecting stimulation parameters had to be established and a system for reflex-based gait support had to be developed. ***The hypothesis was that through basic understanding of the NWR it is possible to develop a method that allows testing reflex-based FET.*** Therefore, the overall objective of the PhD project was twofold:

- To increase understanding of the modulation of the reflex and use this to design a control system. The research questions addressed were:
  - *When using repetitive electrical stimulation of the NWR during gait, what inter-stimulation frequency will result in largest kinematic reflex responses?*
  - *Are the known stimulation-site and gait-phase dependencies of the NWR measurable on the joint kinematic responses and the ground reaction forces?*
- Development of an online, real-time, swing phase controller that provided activation of the stroke patient's most affected leg during the swing phase of gait by eliciting the NWR using repetitive distributed electrical stimulation. The research questions addressed were:
  - *Which methods can be used in modelling and control of the hemiplegic gait?*
  - *Which plant feedback is applicable in the sensor-driven control?*
  - *Can a sensor-driven control system support the paretic leg of a hemiplegic patient through the swing phase of gait?*
  - *Do the swing phase controller provide better walking pattern than an open-loop controller using pre-programmed and fixed stimulation parameters?*

1.4 Structure of the thesis

This thesis is organized in two parts. The first part introduces and discusses methodological aspects of this project and presents the general findings of the embedded studies. The last part consists of the three papers containing the experimental work (Referenced as I, II and III).

- Study I:
  - Withdrawal reflex responses evoked by repetitive painful stimulation delivered on the sole of the foot during late stance: site, phase, and frequency modulation. E. G. Spaich, J. Emborg, T. Collet, L. Arendt-Nielsen, and O. K. Andersen, Exp. Brain Res., vol. 194, no. 3, pp. 359-368, Apr.2009. DOI: 10.1007/s00221-009-1705-9
    http://dx.doi.org/10.1007/s00221-009-1705-9
- Study II:
  - Withdrawal reflexes examined during human gait by ground reaction forces: site and gait phase dependency. J. Emborg, E. G. Spaich, and O. K. Andersen, Med Biol Eng Comput 2009;vol. 4, pp 29-39, Jan 2009. DOI: 10.1007/s11517-008-0396-x
    http://dx.doi.org/10.1007/s11517-008-0396-x
- Study III:
  - Design and test of a novel closed-loop system that exploits the nociceptive withdrawal reflex for swing phase support of the hemiparetic gait. J. Emborg, Z. Matjačić, J. D. Bendtsen, E.G. Spaich, I. Cikajlo, N. Goljar, O.K. Andersen. IEEE Transactions on Biomedical Engineering. Accepted for publication December 2010. DOI:10.1109/TBME.2010.2096507
    http://dx.doi.org/10.1109/TBME.2010.2096507

In ***study-I*** the site, phase, and frequency modulation of the NWR elicited during late stance was studied by analyzing joint kinematics and electromyography. In ***study-II***, the site and phase modulation of the NWR was studied during gait by analyzing kinetics and joint kinematics. In ***study-III***, an online, real-time, swing phase controller was designed and tested on hemiplegic subjects, and its performance was compared with a pre-programmed fixed pattern control scheme. An overview of the aspects approached in each study is shown in Figure 2.

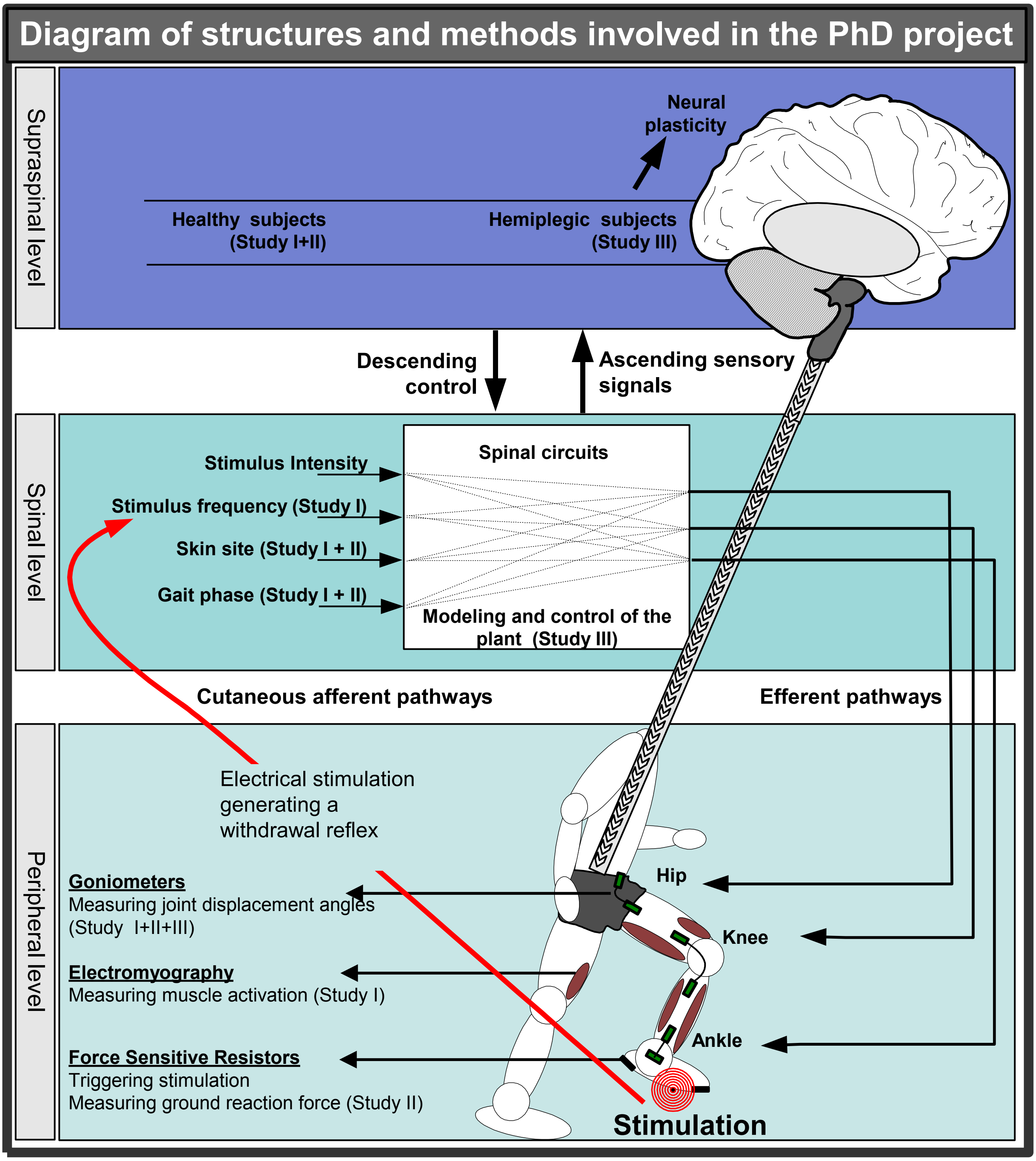

Figure 2: An overview of structures and methods involved in the generation and modulation of the NWR. The aspects approached in each study are indicated.

2. Gait

Gait is an essential element in this project. Therefore, this section contains a brief description of human gait. There are two basic elements that are necessary for any form of bipedal walking: periodic movement of each foot from one position of support to the next one and sufficient ground reaction forces, applied through the feet, to support the body and propel it forward.

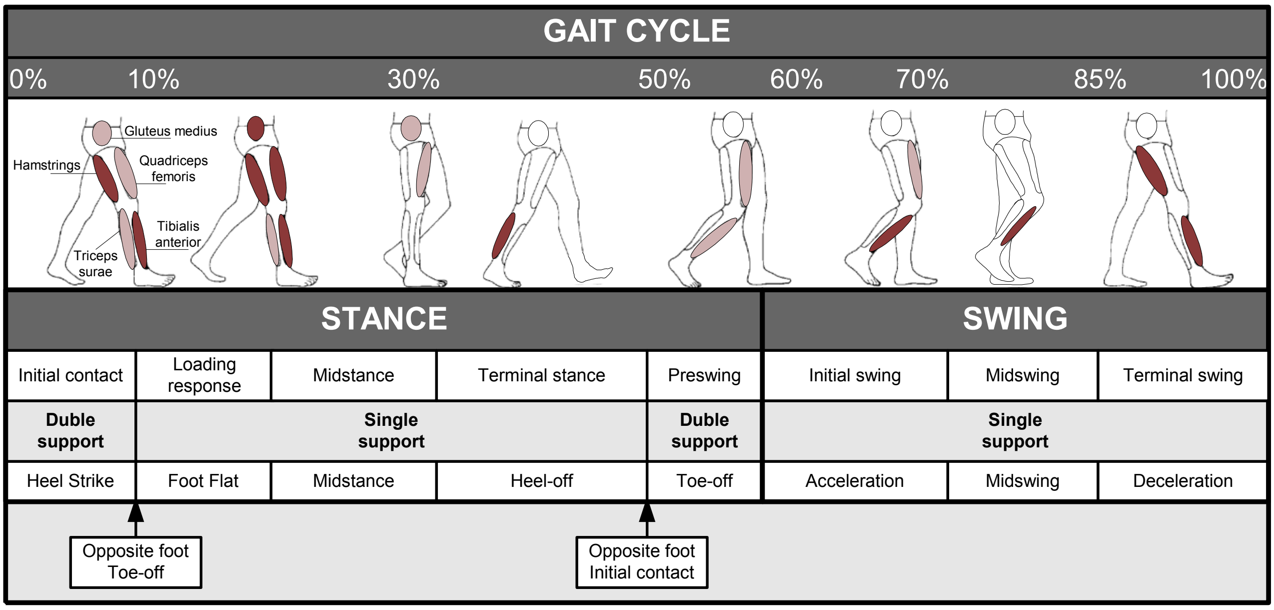

Figure 3: Schematic diagram of the gait cycle indicating the sub-phases of gait and the main muscles involved. Strong coloured muscles indicate high activation while paler colours indicate less activation. Figure is adapted from (Vaughan et al. 1992).

The gait cycle can be divided in two main phases: stance and swing. During the stance phase, the foot is on the ground, whereas in the swing phase, the foot is no longer in contact with the ground, and the leg is swinging forward in preparation for the next heel strike. The stance phase can be further divided into three sub-phases. First double-support, when both feet are in contact with the ground; then, single-limb-stance, when one foot is swinging through and the other is in contact with the ground; then, second double-support, when both feet are in contact with the ground again; and finally contralateral-single-support when the leg is swinging through and the contralateral leg is in contact with the ground. The gait cycle can further be divided into eight sub periods where five are during stance and three during swing, see Figure 3. In all the studies in this thesis, gait detection was performed by means of Force Sensitive Resistors (FSR). Stimulations were triggered in the heel-off/toe-off period based on different delays from the moment of heel-off.

2.1 <u>Pathological gait</u>

Patients who have suffered a CVA often have problems controlling their lower limb, leading to a compromised gait pattern. The most affected leg presents gait kinematics deviating from normal: in the swing-phase, stroke survivors typically exhibit decreased hip flexion, knee flexion, and ankle dorsiflexion and decreased knee extension at heel strike, see Figure 4 (Moseley et al. 1993;Moore et al. 1993). In the stance-phase they typically exhibit decreased hip extension and lateral pelvic displament, increased knee flexion and knee hyperextension

Commonly observed kinematic deviations for hemiplegics								
	STANCE					SWING		
	Heel-on period			Heel-off period				
	Initial contact	Loading response	Midstance	Terminal stance	Preswing	Initial swing	Midswing	Terminal swing
Hip	Decreased lateral pelvic displacement in the stance phase					Decreased peak hip flexion in the swing phase		
Hip				Decreased peak hip extension in late stance				
Knee	Decreased knee flexion or knee hyper-extension in stance					Decreased peak knee flexion in early swing		Decreased knee extension prior to heel strike
Knee	Increased knee flexion in stance							
Ankle					Decreased ankle plantar flexion at toe-off	Decreased ankle dorsiflexion in swing		

Figure 4: Schematic representation of commonly observed kinematic deviations for people with hemipiresis Based on studies from (Moseley et al. 1993;Moore et al. 1993). The blue shaded areas indicate aspects of the gait problems that could be addressed by a swing-phase support system.

3. Stroke and rehabilitation

A stroke is the sudden loss of neurological function caused by an interruption of the blood flow to the brain. Strokes are divided in two types: ischemic stroke (lack of blood supply) and hemorrhagic stroke (due to bleeding in the brain). Ischemic stroke is the most common type, affecting about 80 percent of individuals with stroke (Donnan et al. 2008), and results when a blood clot blocks or impairs blood flow, depriving the brain of essential oxygen and nutrients. Hemorrhagic stroke occurs when blood vessels rupture, causing leakage of blood in or around the brain (Donnan et al. 2008). The term cerebrovascular accident (CVA) covers both types of stroke. Motor deficits due to a stroke are characterized by different degrees of paralysis (hemiplegia/hemiparesis), typically on the body side opposite to the site of the brain lesion. The rehabilitation of gait takes advantage of the capacity of the brain for repair and recovery by focusing on improving practical skills in a real-life environment by practicing task-specific locomotor skills i.e. standing and walking. Neural prosthesis may be used either as temporary devices during the early stages of recovery or as a permanent assistance for stroke-survivors with chronic problems.

3.1 Neural prosthesis and functional electrical stimulation

Functional electrical stimulation (FES) is a technology for restoring body functions through electrical stimulation. FES activates muscles either directly by stimulating efferent nerve fibers or indirectly by activation of reflex pathways. Assistive systems utilizing FES are commonly referred to as neural prosthesis (NP) (Popovic and Thrasher 2004). These are systems for replacing or augmenting a function that is lost or diminished because of an injury or disease of the nervous system. The basic principle for operation of a NP is the activation/stimulation of sensory-motor mechanisms.

The first successful application of a portable NP for walking was presented by (Liberson et al. 1961), that stimulated the common peroneal-nerve to correct drop-foot by evoking ankle dorsi-flexion in individuals with hemiplegia. Liberson's device consisted of a power supply worn in a belt, two surface electrodes positioned to stimulate the common peroneal nerve, and a heel switch. The stimulation was activated whenever the heel switch turned off (no ground contact), and was deactivated when the heel regained ground contact. The stimulation technique includes an efferent component activating the tibialis anterior muscle, and a secondary effect of an afferent component evoking the NWR (Popovic and Thrasher 2004). Other drop-foot stimulators have later emerged using the same approach of peroneal-nerve stimulation. Much of the pioneering work within the field of NP for walking was done by the research group from Ljubljana, Slovenia in the period from 1960 to 1990 and resulted in numerous drop-foot systems of which many of them are commercially available i.e. FEPA-10, MicroFES and IPPO (Acimovic et al. 1987). Other commercially available drop-foot systems are the "Neuro-muscular assist" manufactured by Medtronic Inc, USA (Waters et al. 1975), the ODFS from Salisbury District Hospital, UK (Burridge et al. 1997), the KDC-2000A from Elmetec A/S, Denmark (Pedersen et al. 1986), and the implantable Actigait from Neurodan A/S, Aalborg, Denmark (Haugland et al. 2000).

The first NPs developed in the 1960s and 1970s were hardwired single-channel systems based on surface electrodes. In the late 1970s and in the 1980s, more channels were added with the aim to stimulate muscles controlling all three joints of the most affected leg during both stance and swing, by combining sensory-nerve stimulation with direct motor-nerve stimulation of relevant leg muscles. The general method was to stimulate the quadriceps muscle during stance and the peroneal-nerve during swing (Bajd et al. 1983;Klose et al. 1997;Graupe and Kohn 1998). This stimulation technique

led to the only FDA-approved FES NP (Parastep), that was developed by Sigmedics Inc., Fairborn, Ohio (Graupe and Kohn 1998).
However, most of these multichannel systems suffered from several drawbacks, e.g. difficulties with donning and doffing the system and problems with tolerating surface stimulation that reduced their applicability as take-home devices. In the late 1960s, the first implanted drop-foot system (IDES) was developed by Rancho Los Amigos Medical Centre, University of Southern California and Medtronic Inc,. UAS (Schuck et al. 1973). The implanted systems were a radio-frequency (RF) receiver, a pulse train generator and a bipolar electrode positioned close to the peroneal nerve. An external unit worn on the belt delivered power via an RF coil and received input commands from a wireless foot switch.

From the late 1980s and forward, dual channel implanted peroneal-nerve stimulators, that allowed activation of different fascicles in the peroneal nerve resulting in two-degrees of freedom of foot movement, emerged. ActiGait, developed at the Center for Sensory-Motor Interaction, Aalborg University, Denmark and Neurodan A/S, Aalborg, Denmark is one of those (Haugland et al. 2000). The implanted stimulator uses a four-channel cuff electrode. The signal from a wireless external footswitch is RF-transmitted to an external controller worn at the waist.

A major problem with surface mounted multichannel NPs is that the hip flexors and other deep muscles cannot be stimulated directly. This led to the development of NP that restore standing and walking via intramuscular or implanted electrodes in the 1980s. This approach used individual electrodes for each muscle to be stimulated rather than relying on peroneal-nerve stimulation. One of the NPs with the highest degree of freedom was developed by Kobetic and Marsolais (1994;1997) that included 48 intramuscular electrodes and a 16 channel stimulator. In the 1990s, several groups (Solomonow et al. 1997;Ferguson et al. 1999) developed hybrid systems that combined external orthotics with electrical stimulation of few leg muscles to provide forward propulsion.

3.1.1 Control methods

Although NPs with many degrees of freedom were introduced, the control strategies were often the same: open-loop control where the stimulation was triggered based on gait detection measured by means of artificial sensors i.e. heel switches, tilt-sensors, accelerometers or gyroscopes, or natural sensors i.e. ENG from the sural-nerve that monitor whether there was weight support on the affected foot or not (Haugland and Sinkjaer 1995). Other systems relied on the subject pressing hand-switches embedded in a walker or crutches to trigger a pre-programmed activation profile (Bajd et al. 1983). However, other control strategies for FES have also been investigated i.e. a closed-loop PID control (Crago et al. 1980), stimulation patterns generated by lookup-tables (Buckett et al. 1988), hybrid controllers (Veltink et al. 1992;Ferrarin et al. 2001), hierarchical controllers (Popovic 1993), rule-based controllers (Kostov et al. 1995;Jonic et al. 1999;Popovic et al. 2003a), artificial neural networks (Chang et al. 1997;Sepulveda et al. 1997), fuzzy controllers (Qi et al. 1999) ,adaptive controllers (Davoodi and Andrews 1998;Qi et al. 1999) and sensor-driven controllers (Kojovic et al. 2009).

3.1.2 Functional Electrical Therapy (FET).

Investigation paradigms for rehabilitation of hand reaching and grasping (Popovic et al. 2003b) have shown that recovery is greatly promoted in acute stroke patients when using FET. Similar observations were seen by Quintern et al. (2004) that initiated the swing phase by using electrical stimulation of flexor reflex afferents from the sole of the foot, dorsum of the foot, and lateral to medial aspect of the knee joint during gait retraining. The authors concluded that it enhances the recovery of gait function in patients with hemiparesis after acute stroke. This indicates that FET combined with early rehabilitation is very important in accelerating the recovery of motor function (Sinkjaer and Popovic 2005).

3.1.3 Reflex based neural prosthesis

Despite decades of development, lower extremity NPs have not yet emerged as reliable and widespread aids for the rehabilitation of gait. The technical difficulties involved in improving simple existing neural prosthetic systems have been underestimated. In general, attempts to improve FES by adding more stimulation channels, sensors, and other interfaces have resulted in more cumbersome handling and testing, and a higher failure rate of the system (Riener 1999). This opens up for alternative approaches such as exploring simpler systems i.e. the NWR approach where primarily flexion of the whole leg can be elicited and controlled trough very few surface electrodes.

As an alternative to evoking the NWR by stimulation of the common peroneal-nerve, several groups have used other methods. Lee and Johnston (1976) used stimulation of the sole of the foot, the dorsal surface of the foot, and the lower posterior thigh to evoke a flexion reflex assisting the swing phase of the gait cycle in hemiplegics, and found that stimulation of the sole of the foot evoked similar or higher magnitude reflex responses compared to the dorsal surface of the foot and the lower posterior thigh.

Granat et al. (1992;1993) investigated surface stimulation of the peroneal- and saphenous-nerves to obtain a synergistic flexor response of the hip and knee flexors, as well as the ankle dorsiflexors during the swing phase in spinal cord injured patients. They suggested that the reflex response could be significantly improved by choosing appropriate stimulation parameters and showed that increasing stimulation frequency reduced the latency of the evoked response. They further showed that habituation could be reduced by multiplexing between two sites of stimulation and by applying single high-intensity pulses. The authors used a set of IF-THEN rules to model a higher-level control of phase switching in the step cycle.

Riener et al. (2000) elicited the NWR by applying stimulation 'laterally from the knee joint'. They varied the pulse train duration, the pulse width and the pulse frequency and used a fuzzy logic approach to map inputs to characteristics of the output in form of latency, rise time, duration, and maximal movement in SCI-patients. These measures were fed into a physiological model and joint angles were calculated based on inverse dynamics. They showed good coherence between the simulated and measured model output.

Fuhr et al. (2008), used the NWR in combination with muscle-nerve stimulation in a closed-loop system for walking, standing up, sitting down, and stair climbing. The reflex was elicited by a pair of electrodes placed close to the common peroneal nerve at the medial and lateral side of the condyles.

Other modalities than peroneal-nerve stimulation to activate the NWR with rehabilitation purposes has not been fully investigated. There are for instance problems with the long latency of the mechanical reflex response, and habituation. However, new findings argue for reconsidering using the NWR in rehabilitation of gait:

1. The recent shift from a conception of the NWR as a stereotyped response towards the concept of a modular organised NWR, which gives the possibility of controlling the movement and steer the leg through swing.
2. The promising therapeutic modality of FET permitting NWR stimulations to be applied only in a limited time span as a part of therapy, permitting larger intensities, and the acceptance of a certain degree of discomfort, knowing that stimulation is only applied temporarily.
3. The effect of habituation can be decreased by applying changing stimulation patterns based on closed-loop control.
4. The NWR-method activates several muscles simultaneously and the number of electrodes can herby be reduced compared with techniques based on muscle-nerve stimulation. This will likely reduce the donning/doffing time in the daily therapy.

4. The nociceptive withdrawal reflex – history and main findings

4.1 The basic mechanism

The withdrawal reflex is one of the basic protective mechanisms that exist in almost all living species. The withdrawal reflex is activated by a painful stimulus reaching the skin (for example touching a hot object, stepping on a sharp object), and produces a withdrawal movement that serves to remove the affected skin area from the source of pain (Figure 5). For a comprehensive review of the withdrawal reflex, see Sandrini et al. (2005).

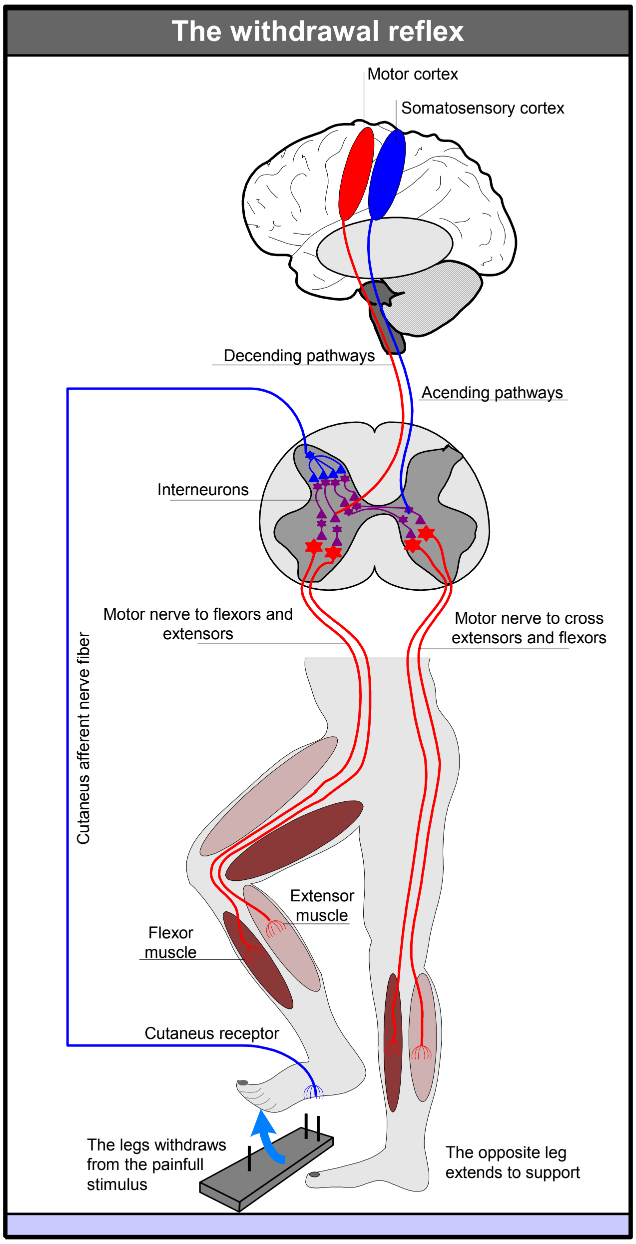

Figure 5: The withdrawal reflex.

The withdrawal motor response is usually the result of the activation of spinal circuits and it persists after complete transection of the spinal cord (Sandrini et al. 2005). This means that the neural circuit responsible for the motor response of this reflex is entirely contained within the spinal cord although it is modulated by control signals emanating from higher centers in the brain.

The idea that the sensory system plays an important role in the regulation of movement was stated in the beginning of the 20th century. Charles Sherrington, who was one of the first scientists to study the reflex in detail, proposed in 1906 that simple reflexes are the basic units for movement. Sherrington conducted animal experiments (frogs, cats and dogs) and observed that after a painful electrical stimulation the animal reacted with an ipsilateral hip, knee, and ankle flexion. He termed this the "nociceptive flexion reflex" (Sherrington 1910). Since these pioneering discoveries, withdrawal reflex responses have been conceived as stereotyped flexion responses in physiology textbooks.

The sensory information responsible for the reflex movements comes from receptors in skin, muscles and joints. These sensors are connected to the spinal circuit by afferent connections through the dorsal horn. The reflex is polysynaptic, and according to the textbook literature on the flexor reflex (Kandel et al. 1991) the sensory signals excite motor neurons that innervate flexor muscles and inhibit those that innervate extensor muscles of the stimulated limb. This is called reciprocal inhibition because the antagonist muscles are activated in the opposite way. Another particularity of the withdrawal reflex is the crossed-extension mechanism. This mechanism has a postural function, and serves to enhance postural support during, e.g. the withdrawal of a foot from a painful stimulation while standing (Figure 5). This is done by exciting the extensors motor neurons and inhibiting the flexor motor neurons of the opposite limb. However, recent findings from studies of the human withdrawal reflex during gait argue against this stereotyped behaviour, in favour of a more refined behaviour (Andersen et al. 2003;Spaich et al. 2004b) .

In the late 50's Eccles and Lundberg (1959) conducted a large amount of studies of the withdrawal reflex in animals, and showed that stimulation of cutaneus afferents, joint afferents, and group-I and group-II muscle afferents tended to produce the same reflex response (excitation of flexors and inhibition of extensors) and may share common interneuron spinal pathways. This convergence led to the term Flexor Reflex Afferents (FRA) to denote different afferent activity that may evoke a flexor reflex.

4.2 <u>Modular organization</u>

The response to stimulation is often a contraction of flexor muscles of the limb. However, the simplicity of the flexor reflex concept was gradually undermined from the 1950s onwards. More and more studies showed that the withdrawal reflex has a high adaptability and could no more be assumed to be a pure flexion reflex. Observations made in the 50's and 60's by Grimby (1963) and Haghbarth (1952) showed a refined reflex movement depending on the stimulation site, since ankle extensor motor neurons were exited from the skin of the heel. In the beginning of the 90's, it became clear that the idea of a stereotyped "flexion reflex" could be challenged. An alternative concept was developed by Schouenborg and colleges (Schouenborg and Kalliomaki 1990;Schouenborg et al. 1992;Levinsson et al. 1999) who suggested that there is a modular organization of the NWR, meaning that stimulation of a particular skin area will activate only the muscles needed for the biomechanically optimal withdrawal of the limb from the stimulus. Thus, the exact movement generated is determined by the location of the stimulus, and could involve flexor as well as extensor muscles acting as the primary movers. During the early 90's they mapped excitatory and inhibitory reflex receptive fields for many hind limb muscles in rats and cats. The main conclusions of this large body of work were (Clarke and Harris 2004):

- Each muscle has a separate excitatory and inhibitory cutaneous reflex receptive field (RRF)
- The contraction of muscles result in the withdrawal of their excitatory RRF from a painful stimuli
- The contraction of muscles results in the movement towards their inhibitory RRFs when a painful stimulus is applied.
- The pattern of inhibitory and excitatory RRFs is maintained by activity in pathways descending from the brain.
- The NWR modules are functionally un-adapted at birth, and the pattern of the RRFs is learned postnatally.

The RRF is however not the only parameter affecting the reflex response. The spinal processing integrates relevant afferent input, descending modulatory signals, descending motor commands, and incorporates the status of the spinal motor systems when determining the withdrawal strategy. Recent studies of reflex modulation of the lower limb nociceptive withdrawal reflex elicited by painful electrical stimulation of the sole of the foot in humans indicate that the intrinsic reflex response is modulated by the stimulation site (Andersen et al. 1999;Andersen et al. 2005;Andersen 2007). For the ankle joint, the reflex response is typically dorsiflexion for mid-distal stimulation sites and plantarflexion for proximal sites (Figure 6). Also, the duration and the force of the muscle contraction depend on the stimulus intensity (Kugelberg et al. 1960;Andersen et al. 2001) and the stimulus pulse frequency (Arendt-Nielsen et al. 2000). The reflexes are also dependent on the position of the body relative to the environment. The response varies for instance between sitting and walking conditions. During withdrawal, the contraction of appropriate muscles is performed in a coordinated fashion in order to move the stimulated limb away from the painful stimuli while maintaining balance (McIlroy et al. 1999;Bent et al. 2001;Andersen et al. 2003).

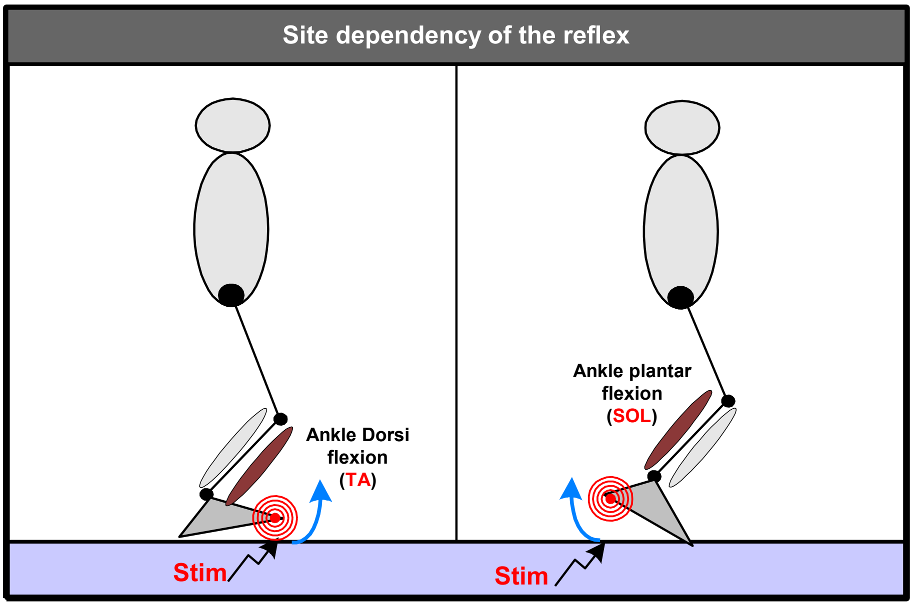

Figure 6: The human lower limb nociceptive withdrawal reflex elicited by painful electrical stimulation of the sole of the foot depends on the stimulation site. If stimulation is applied to the forefoot primarily ankle dorsiflexion and TA activity is evoked. If the stimulation is applied to the heel, it primarily evokes ankle plantarflexion and SOL activity (Andersen et al. 1999).

Further, the withdrawal reflex depends also on the specific motor program e.g. the evoked reflex response was modulated when elicited during a cyclic movement. This is shown for both pedalling and gait (Crenna and Frigo 1984;Brown and Kukulka 1993;Spaich et al. 2004b;Andersen et al. 2005;Spaich et al. 2006). In healthy individuals, withdrawal is primarily accomplished by dorsiflexing the ankle joint when stimulation is delivered during gait near toe-off, while the strategy changes to flexion of the knee and hip joints for stimulations at heel-off (Spaich et al. 2009;Emborg et al. 2009).

4.3 Electrically evoking the nociceptive reflex

Kugelberg et al. (1960) showed that to trigger the NWR, small nociceptive fibers (myelinated nociceptive Aδ fibers/ group III) have to be activated. Later it was shown that also unmyelinated C-fibers mediate NWR reflexes (Andersen et al. 1994;Schomburg et al. 2000). In most human studies, electrical stimuli are used for eliciting the reflex. The use of natural stimuli has never achieved a broad appreciation, mainly because the stimulus intensity needed for eliciting reflexes often causes actual tissue damage and/or gradually changes the properties of the transduction process in the skin following multiple stimuli (Andersen 2007). Electrical stimulation “by-passes” the receptor organ and produces a direct activation of all nerve fibres regardless of their specific receptor type. However, the activation threshold depends on the fibre diameter.

Figure 7: Stimulation electrodes placed at the sole of the foot.

In all three studies (I-III), the nociceptive withdrawal reflex was elicited by transcutaneous electrical stimulation (Noxitest stimulator, Aalborg, Denmark) delivered at different sites on the sole of the foot (Figure 7). The stimulation was delivered through self-adhesive electrodes (2.63 cm^2 surface area, Ag–AgCl, AMBU, Denmark), with a common reference electrode (7x10 cm electrode, Pals, Axelgaard Ltd., USA) placed on the dorsum of the foot. Each stimulus consisted of a constant current pulse burst of five individual 1ms pulses delivered at 200 Hz. Repetitive stimulation was used to obtain larger mechanical responses than what could be achieved with a single stimulus by exploiting the temporal summation property of the reflex (Andersen et al. 1999). Frequencies ranging from 0.1 to 20 Hz have previously been used to elicit the human NWR and it has been shown that higher repetition frequencies result in stronger reflex facilitation, particularly during the early stimulation phase

(Arendt-Nielsen et al. 2000;Bajaj et al. 2005). However, repetition frequencies as low as 2 Hz can produce reflex mediated muscle fused contractions (Arendt-Nielsen et al. 1994).

In the present work the stimulus was repeated four times at a fixed frequency. In Study-I, frequencies of 15 and 30 Hz were used to find the optimal frequency for eliciting large kinematic reflex responses during the swing phase. In Study-II and Study-III, a frequency of 15Hz was used based on the conclusions of Study-I. The stimulation intensities at the individual electrode sites were normalized to the pain threshold. Hence, the stimulus intensity was calculated as the pain threshold detected at each electrode site multiplied by a constant factor common to all sites. The pain threshold for a single stimulus was determined with the volunteers in sitting position, using a staircase method consisting of a series of increasing and decreasing stimuli. The sites of stimulation were chosen to evoke different withdrawal strategies, based on the following considerations:

1. Mid-forefoot:
    - Stimulation of this site has previously been shown to result in ankle dorsiflexion and large knee flexion (Andersen et al. 1999;Spaich et al. 2004b;Spaich et al. 2006).
2. Arc of the foot:
    - Stimulation of this site has previously been shown to result in large knee and hip flexion and large ankle dorsiflexion (Spaich et al. 2004b).
3. Heel:
    - Stimulation of this site has previously been shown to result in ankle plantarflexion (Andersen et al. 1999;Spaich et al. 2004b;Spaich et al. 2006).
4. Posterior side of the heel:
    - This site was included since it was hypothesized that stimulations of the posterior side of the heel would evoke forward propulsion of the leg and also evoke knee extension during swing.

Sites 1-3 were used in all studies; in ***study-II*** and ***study-III,*** site 4 was included as well.

In applications in which the goal is to facilitate the initiation of the swing phase of the hemiparetic leg (Quintern et al. 2003) the late stance and early swing phases are the target intervals to deliver electrical stimulations. This is due to the latency between stimulation onset and the mechanical response of the reflex, which is approximately 140ms, and the duration of the mechanical response, that lasts up to 360ms after the stimulation onset (Crenna and Frigo 1984;Spaich et al. 2006). Therefore, to ensure that the kinematic reflex response will occur within the current step, stimuli were delivered between heel-off and toe-off. Previous studies have indicated that the withdrawal strategy depends on the stimulation onset during the gait cycle (Duysens et al. 1992); thus, different stimulus onsets may be crucial for a rehabilitation system intending to exploit the differences in withdrawal strategy. Therefore, multiple onsets between heel-off and toe-off were tested.

4.4 <u>Habituation of the NWR</u>

The mechanical NWR response can habituate when a site is stimulated repetitively, which means that after several stimulations the response gradually disappears. This is the major disadvantage when using the flexion reflex to produce movement. According to Andrews et al. (1990), repetitive stimulation of the peroneal or saphenous nerve in SCI patients can eliminate the reflex evoked hip flexion after a number of stimuli. . However, it has been found that when the reflex has been habituated by repetitive stimulation it can be dis-habituated either by stimulating a second site or changing stimulation parameters. Dimitrijevic and Nathan (1971) reported that stimulation of sites 3-4 cm away from a habituated stimulation site still evoke a full response. Related findings were reported by Carstens and Wilson (1993) who examined transfer of habituation in rats by testing tail flick by noxious radiant thermal stimulation. They observed that a habituated response at one site did not transfer to a site 0.75cm from the habituated site. Dimitrijevic et al. (1972) found that habituation is mainly seen for low intensity stimuli at short, regular inter-stimulus intervals. Varying the stimulus intensity might have a dis-habituating effect itself as demonstrated by Granat et al. (1991), who stimulated the common peroneal nerve in spinal cord injured patients and observed that a high intensity stimulation burst dis-habituated the reflex response. Similar findings were done by Carstens and Wilson (1993) when examining rat tail reflexes. They observed that a tail pinch (high intensity stimulation) at another site could dis-habituate the reflex response.

5. Quantifying the reflex response

For quantification of the reflex response analysis of joint kinematics were used. Further, in ***study-I,*** analysis of electromyography (EMG) was also used and in ***study-II***, kinetic analysis of ground reaction forces was performed. Several methods are available to measure the kinematic and kinetic responses e.g. 3D motion analysis systems and force plate systems. Neither of these quantification methods are however feasible to implement in a clinical rehabilitation system that must have a short donning/doffing time, user friendliness, robust design, and be independent of having specialized laboratory surroundings available. Therefore, quantification methods that are portable, affordable, and practical to use in a clinical setting were favoured.

5.1 EMG response

For quantifying the EMG response different approaches have been used by different authors. The difference in mean amplitude of the envelope of the EMG was used by Crenna and Frigo (1984) and the difference between the root mean square (RMS) of post- and pre-stimulation EMG was used by Andersen et al. (1995). Normally, the response is analyzed in a time window between 50-300ms after the stimulation onset (Crenna and Frigo 1984;Meinck et al. 1985;Spaich et al. 2004a;Spaich et al. 2005a;Spaich et al. 2006).

EMG was only evaluated in ***study-I.*** The RMS-method was used in order to be able to compare results with previous findings where the topography of the reflex receptive fields was assessed (Andersen et al. 1995;Sonnenborg et al. 2000;Andersen et al. 2005;Spaich et al. 2005a). However, due to the nature of the repetitive stimulation used in this project the EMG responses were contaminated with stimulation artefacts throughout the stimulation period (15Hz corresponds to a total stimulation time of 221ms and 30Hz corresponds to 121ms) and results based on analysis performed in this period would be misleading. Therefore, an alternative method was used where the EMG response was analyzed in a window starting 50ms after the onset of the last stimulus in the train, and lasting 250ms.

EMG from tibialis anterior, soleus, vastus lateralis, and biceps femoris of the ipsilateral leg, and soleus and vastus lateralis of the contralateral leg were recorded. Primarily superficial mono-articular muscles were chosen since it is easier to relate their response to the observed kinematic responses. There are no superficial mono-articular flexors of the knee thus a bi-articular muscle was chosen for the knee (biceps femoris). The reflex responses were assessed as the difference between the root mean square (RMS) of post- and pre-stimulation EMG normalized to the average EMG recorded during unperturbed control steps.

5.2 Kinematic measures

To monitor the kinematic responses three goniometers (type SG150 and SG110/A, Biometrics Ltd, Gwent, U.K.) were mounted on the lateral side of the ankle, knee, and hip joints. The reflex kinematic responses were determined as the angle change between the post-stimulation goniogram and the corresponding goniogram recorded in an unperturbed step and were quantified by the peak-change.

The analysis time window used to quantify the kinematic response varied across the studies. In ***study-I***, the period from heel-off to heel-on was used to quantify the "pure" reflex response and subsequent changes in the ongoing gait pattern in the current swing-phase. The same approach was used for the online system in s***tudy-III,*** where the entire heel-off phase was used by the real-time Model Reference Adaptive Control (MRAC) controller to select appropriate stimulation parameters.

However, when evaluating the system' performance, a time window, according to the individual subjects training aims, was used. This could be either the first, mid or last 50% of the heel-off period. In ***study-II*** the "pure" kinematic reflex response was quantified regardless of subsequent changes in the ongoing gait pattern in an interval ranging from 125 to 360 ms post-stimulation. This interval is in accordance with Spaich et al. (2006) and was chosen to be able to compare the findings from with previous findings on joint kinematics.

5.3 Kinetic measures

To examine whether changes in ground reaction forces could be used for reflex quantification during gait, ***Study-II*** examined the capability of forces measured at anatomical landmarks to characterize changes in the ground reaction forces due to electrically evoked reflexes. Further it was investigated if the force measures were able to detect reflex modulation associated with stimulation at different skin sites and different gait phases. In-shoe systems do not have the limitation of single-strike measurements (as those provided by a force plate). Several consecutive footsteps can be measured, permitting analysis of the circumstances leading up to, and following, a particular footstep. Forces recorded at anatomical landmarks have previously been used for characterizing weight shifts (Warabi et al. 2004) and gait changes (Kiriyama et al. 2004) in healthy volunteers as well as hemiplegic subjects (Kobayashi et al. 2006).

An approach based on FSRs was selected due to its low cost and ease of implementation and despite its relatively poor accuracy (FSR: LuSense, PS3, Standard 174, area 2.48 cm^2, thickness 0.2 mm, measurement range 2.5-500 N, Hysteresis: 20%, Repeatability: +/-5% Repeatability for loads below 20% of max: 35-90%). The vertical ground reaction force was recorded at four anatomically distinct landmarks under each foot. Both the individual signals and the summed vertical forces were analyzed and the force response was quantified by calculating the peak force change (PFC) between the unperturbed control steps and the post stimulation steps. The analysis was performed in five time windows determined by the type of gait support e.g. single/double support..

6. Control schemes for a reflex-based neural prosthesis for walking

6.1 Modelling the neuromuscular plant

The human lower limbs can be conceived as a multiple-link, unstable, inverted pendulum (Riener 1999). Movements are driven by a large number of muscle groups, that can be grouped in hip, knee and ankle flexors and extensors, some of them are bi-articular while other are mono-articular. Traditional attempts to model and control the *neuromuscular plant* encompasses the sub-part from muscle activation profiles to induced movement, i.e. the *musculoskeletal-system;* however, in this thesis the *spinal-circuits* from afferent stimulation to muscle activation are also added (Figure 8).

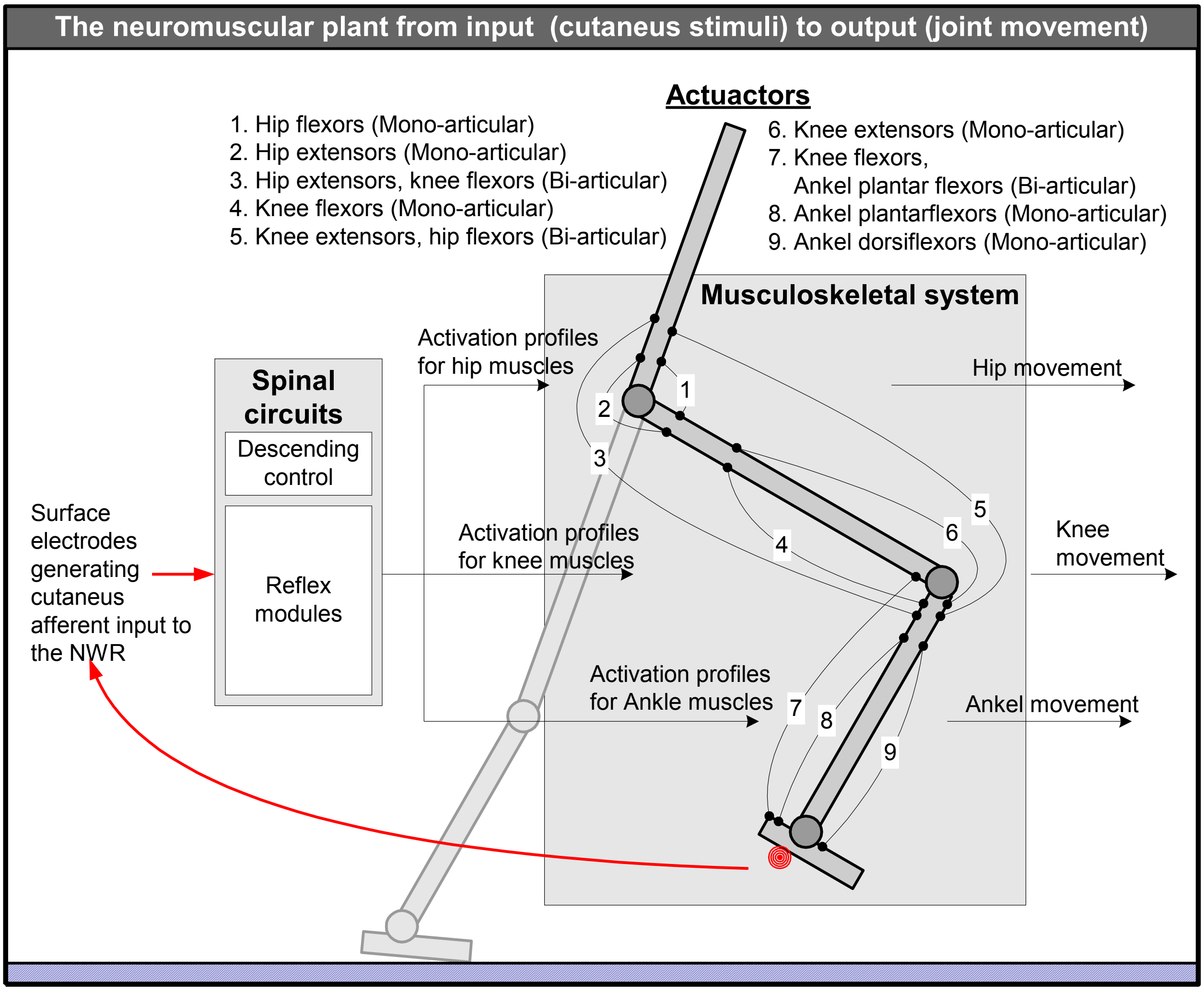

Figure 8: Modelling the neuromuscular plant

6.1.1 Physiological based modelling

Physiological-based modelling of the *musculoskeletal-system* has been very well described in the literature (Riener 1999) and despite of its complexity, several accurate models based on either forward dynamics or inverse dynamics have been used to provide insight into internal muscle dynamics, segmental dynamics, multi joint coordination, optimization of muscular force output during FES, etc. Unfortunately, the mechanical characteristics of the NWR have not yet been studied in detail, making thus physiological-based modelling of the *spinal-circuits* involved in the reflex response very complex. Only very few investigators have described detailed modelling or control of the lower limb NWR, for instance, Riener et al. (2000) used a fuzzy logic approach to map inputs to output in terms of latency, rise time, duration and maximal movement. These measures were fed into a physiological model and joint angles were calculated based on inverse dynamics. Kim et al. (2006) modelled the moment induced by the flexion withdrawal reflex due to stimulations at the arch of the foot in SCI-patients resting in a supine position, and attempted to optimize stimulation parameters for restoring swing. Furthermore, a two dimensional dynamic model using a linear regression model was used to optimize amplitude, frequency, and burst duration of the stimuli. An assumption in their approach was that muscle activation was equal to the applied stimulation profile.

6.1.2 Properties for the neuromuscular plant

It is known that the reflex response depends on stimulation site, intensity, frequency, posture, and the gait cycle. In ***study-I***, the optimal frequency when applying repetitive stimulation was found to be 15Hz. The input to the system is therefore a stimulus parameterized by a combination of two categorical variables (*Site* and *Phase*) and one continuous variable (*Intensity*), and the outputs are the trajectories for kinematics of hip($\mathcal{T}_{HIP}$), knee($\mathcal{T}_{KNEE}$) and ankle($\mathcal{T}_{\mathrm{ANKLE}}$) joints (Figure 9). The use of trajectories, rather than parameterized dynamical input-output models, is stressed by the use of the symbol $\mathcal{T}$. The categorical variables evoke different withdrawal strategies, while the continuous variable is a scaling-factor mainly affecting the amplitude of the reflex response. The plant can therefore be characterized as a Multiple Input Multiple Output (MIMO) dynamical system. The output is coupled, since the posture of i.e. the hip joint affects the withdrawal strategies for the knee and ankle joint. The system is highly time variant, stochastic, and nonlinear since the reflex response is influenced by habituation, descending commands, and voluntary contributions to the movement. Additionally, there are significant latencies in the system. Furthermore, neither model structure nor parameter values are known. Effects such as structural changes in the nervous system induced by the CVA and gradual improvement in walking performance may affect the output and further complicate the modelling and control task. This means that most normal modelling tools such as Linear Time Invariant (LTI) tools, transfer functions, step response analysis, and state space modelling cannot be used. In addition, it should be considered that the model should be executable in real time and contain a restricted number of parameters that are easy to identify for each specific subject.

6.1.3 Choice of modelling approach

When choosing a modelling method, different approaches could be used to compensate for the nonlinear behaviour of the plant, like for instance black-box modelling. Black-box models can be derived from simple statistical models or by measuring and mapping input-output data via e.g. artificial neural networks and fuzzy logic approaches. They can be built without extensive and detailed knowledge of the plant. Black-box modelling does, on the other hand, not contribute to an understanding of the system whose behaviour they predict. The musculoskeletal system and the spinal reflex systems were grouped and treated as one black-box system and a relative simple, but nonlinear black-box model was designed and subsequently used for the design of an adaptive real time controller.

The key modelling challenge in the present case was to model the continuous response of the three joint trajectories based on one single stimulus parameterized by a combination of two categorical variables and one continuous variable (Figure 9).

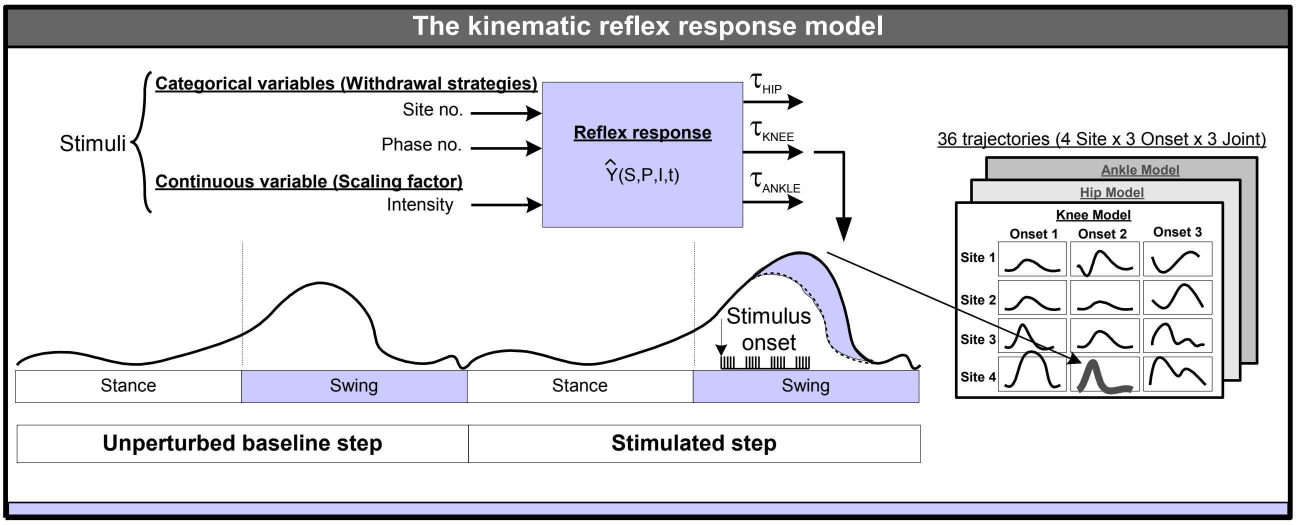

Figure 9: The key modelling problem was to model continuous trajectories based on one stimulus parameterized by two categorical variables and one continuous variable.

6.2 Model Reference adaptive control

The requirement for the controller was that it had to be able to always follow the same reference trajectory, by keeping the controller in tune as the behaviour of the neuromuscular-plant vary (a model-follower behaviour). The reference signal was the training aim for the patient, optimally, the gait pattern of a healthy able-bodied subject. The Model Reference Adaptive Control (MRAC) framework was originally proposed to solve a problem in which the specifications are given in terms of a reference model that tells how the process output ideally should respond to the command signal (Landau 1974;Astrom and Wittenmark 1989). This is also referred to as the model-following problem. Further, the framework accounts for the nonlinear and stochastical behaviour of the controlled plant and the technique suggests a method coping with unknown disturbances. Attempts to use MRAC in muscle-nerve stimulations have previously been reported: Hatwell et al. (1991) used MRAC to control FES induced movement of the knee joint of paraplegics. Allin and Inbar (1986) used a MRAC-system in a FES application for elbow and wrist movement and found that the MRAC-system was superior to the performance of a fixed parameter controller. However, no references to the use of MRAC to control reflex based FES have been found in the literature.

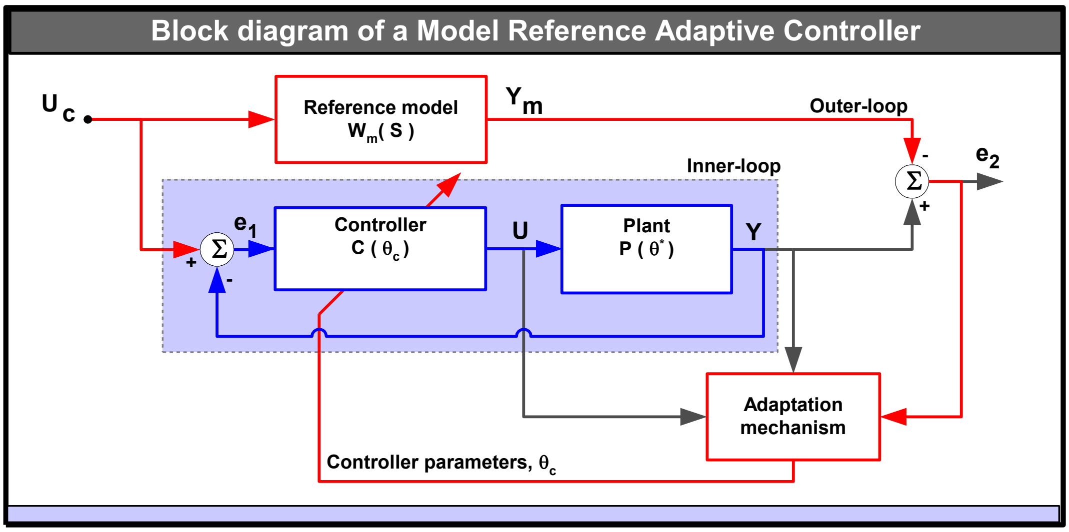

Figure 10: Model reference Adaptive Controller

A block diagram of the basic MRAC principle is shown in Figure 10. The system can be considered as consisting of two loops, an inner- and an outer-loop (Figure 10). The inner loop is a normal feedback loop consisting of a controller, $C(\theta_c)$ and the plant, $P(\theta^*)$. The outer loop consists of the reference model, Y_m and the adaptation mechanism that adjusts the dynamics of the inner loop by changing the controller parameters (θ_c). The general idea is to create a closed-loop system independent of the plant parameters and where the desired behaviour of the closed-loop is defined by a reference model. The outer loop adapts the controller parameters (θ_c) in order to minimize the tracking error *($e_2 = Y - Y_m$)* between the desired response (Y_m) and the plant output (Y). Here the key challenge is to determine the feedback control-law that changes the structure and dynamics of the closed-loop and results in a stable system which brings the tracking error to zero.

A fundamental idea of the initial MRAC method is a parameter adjustment scheme called the sensitivity method or the MIT-rule (Developed at the Instrumentation laboratory at Massachusetts Institute of Technology (MIT) in the 1950es). This builds upon an assumption that the dynamics of the inner loop is much faster than the dynamics of the outer loop. The sensitivity method is used to design the control-law so that the estimated controller parameters (θ_c) are adjusted in a direction that minimizes a certain performance function. It is assumed that the partial derivative of the performance function with respect to the estimated parameters (sensitivity function) is constant. This further permits to define an adjustment rule for the controller parameters. The control-law is driven by the sensitivity function multiplied by the tracking error (e_2). If the sensitivity function can be generated on-line, then, the adaptive law is implementable. Further, the method requires knowledge of both model structure and parameters of the plant. The lack of stability of the MIT rule gave rise to the development of alternative design solutions for the control-law based for instance on stability design e.g. Lyapunovs theorem, a gradient method, and a least squares methods based on estimation-error-cost-criteria. However, all those methods are based on parametric approaches and therefore unfeasible for the present control problem. Thus, a modified MRAC-scheme had to be developed. Furthermore, an alternative way of finding the best parameters for the controller also had to be developed.

In ***Study-III*** a novel, modified rule-based MRAC method was introduced, in which Moving Average (MA) models of entire kinematic trajectories in the heel-off phase were recursively derived from input-output data for the three joint angles (hip, knee, and ankle) and embedded in the inner loop of the MRAC design (Figure 10). Based on this model, the controller continuously compared the deviation in relation to a target trajectory. The controller minimized the tracking error between the reflex response and the baseline gait pattern. The controller then estimated all outcome possibilities and conducted a numeric search among them, choosing the combination of stimulation parameters that resulted in the lowest tracking error; the embedded plant model forced thereby the adaptive controller to change the stimulation parameters, if needed. The performance of this system was compared with an open-loop pre-programmed Fixed Pattern of Stimulation Controller (FPS), (see setup in Figure 11). When designing the MRAC-system, it was chosen to fix the intensity at one level and develop a method for controlling the categorical variables. The categorical variables (*Site* and *Phase*) evoke different withdrawal strategies, while the continuous variable (*Intensity*) is a scaling-factor mainly affecting the amplitude of the reflex response (Figure 9). To make the performance of the two systems comparable, it was vital to keep identical intensities.

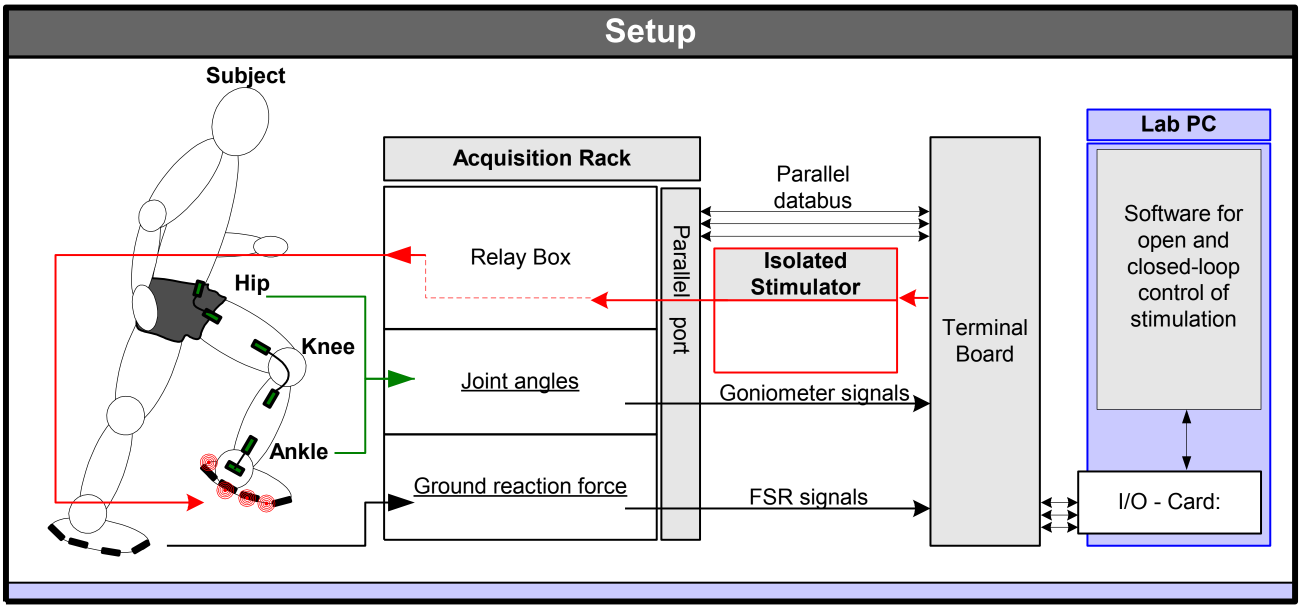

Figure 11: Moderately painful electrical stimulations evoked afferent input to spinal circuits, which respond with activation of the muscle groups controlling the stimulated limb (and interacting with the entire locomotion pattern). This withdraws the affected site from the stimulus by activating muscles controlling the hip, knee and ankle joints depending on the stimulation parameters. The subject was instrumented with goniometers and force sensitive resistors. Stimulations were only enabled in the swing phase and were delivered to 4 locations of the sole of the foot at 3 different time points between heel-off and toe-off.

7. Results and discussion

This thesis has focused on investigating the modulation of the nociceptive withdrawal reflex and to utilize this knowledge in the design of a gait rehabilitation system for hemiparetic people.

7.1 Stimulation site modulation

The findings across the three studies regarding the stimulation site- and stimulation onset dependencies of the kinematic responses are illustrated in Figure 12. The ankle joint exhibited substantial site modulation whereas the hip joint did not display any site modulation and the knee joint exhibited a minor degree of site modulation.

For the ankle joint, stimulations delivered at the most distal sites (forefoot, arc of the foot) evoked significantly higher degree of dorsiflexion after push-off than that evoked by the more proximal sites (heel and the posterior side of the heel). This was in line with previous observations (Spaich et al. 2004b). In ***study-I,*** stimulations at the heel resulted both in lowest plantar flexion-reduction before push-off and least dorsiflexion-increase after push-off. However, in ***study-II*** stimulations at the posterior side of the heel resulted in ankle plantar flexion, suggesting a strategy where withdrawal is accomplished by lifting the heel and plantarflexing the forefoot.

Previous studies investigating the modulation of the NWR during gait in humans have not found evidence for site modulation of the kinematic response of the knee joint. Neither of the present studies showed significant stimulation site modulation for the knee joint; however, observations of a trend towards site modulation for the late onsets was observed. This is in line with (Schouenborg and Kalliomaki 1990) that found that extensors could work as the primary movers if their RRF was activated, which also would enable stimulus site modulation for the knee joint reflex trajectory. In ***study-III***, it was observed that for the hemiplegic subjects with need for extra knee extension in terminal stance, stimulations controlled by the MRAC-system were primarily delivered to the heel area (posterior side of the heel and under the heel) near toe off (Figure 12). However, in that study no direct analysis of site and phase modulation across all subject were conducted, and therefore there is no statistical evidence for that observation. Findings from both ***study-I*** and ***study-II*** however support the finding of site modulation for the knees. In ***study-I***, onsets near heel-off exhibited a tendency for smaller knee flexion responses for stimulations delivered to the heel area. In ***study-II***, the two distal sites (forefoot and arc of the foot) exhibited values of knee flexion responses around zero and tending to negative (extension). A possible explanation for this observation could be the interaction with the stimulation onset, since this may be more influential on the kinematic reflex response at the knee than the stimulation site. Both findings from ***study-I*** and ***study-II*** indicated that for stimulations near toe-off, withdrawal was primarily accomplished by ankle dorsiflexion, while the strategy for stimulations at heel-off was flexion of the knee and hip joint. In ***study-III,*** it was observed that for hemiplegic subjects with primary need for knee support, stimulations were commonly delivered to the distal sites near toe-off.

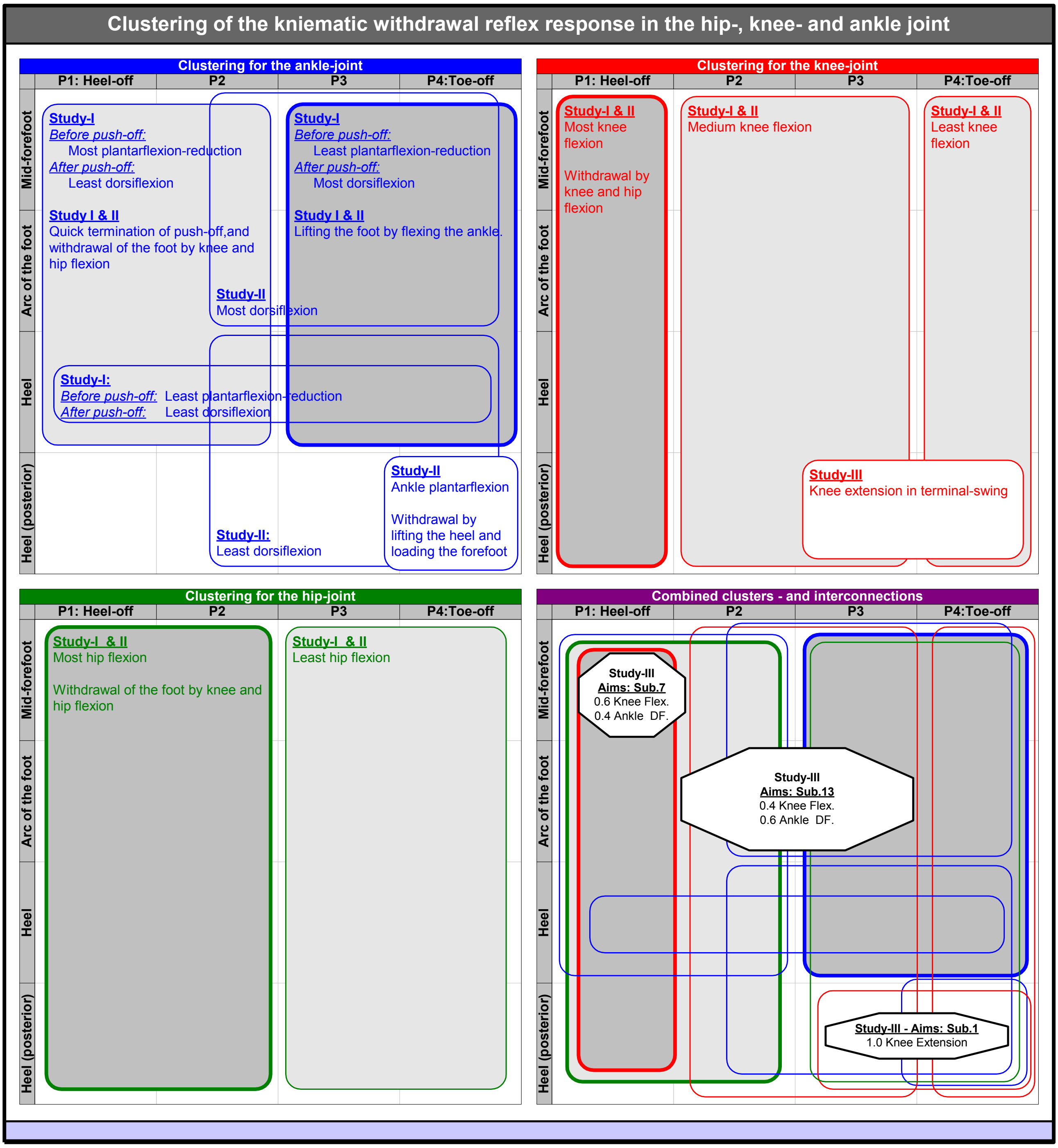

Figure 12: Illustration of the input-space (Stimulation sites, and onsets), and the output-space (frames) depicting clusters with similar output. Each of the three first squares (upper-left, upper-right and lower-left) indicates withdrawal dependencies of the individual joints. The dark shaded frames indicate strong reactions whereas lighter shaded frames indicate weak responses. The lower-right square indicates the interconnections between the joints. Here all shaded frames indicate strong reactions. Notice that there are no overlap between strong reaction for the ankle with strong reactions for knee and hip. Further the octagons indicate examples of how the MRAC-system applied its majority of stimulations for three of the subjects from ***study-III.*** The numbers indicate the weight factor for the specific joint.

7.2 Gait phase modulation

The gait phase modulation of the NWR is the result of the integration of sensory inputs and descending information with locomotor control patterns at the spinal level. In ***study-II***, the kinematic responses were analyzed in the typical analysis window from 140 to 360ms post stimulation. However, the GRF were analyzed in 5 subsequent sub-phases from first-double-support to third-double- support i.e. a whole gait cycle for the ipsilateral leg. The results presented evidence for functional reflex modulation in all analyzed sub-phases suggesting that integration of sensory and descending information with locomotor patterns has a major impact on the gait pattern. The main findings from ***study-I*** and ***study-III*** also indicate that the reflex response exhibited a strong dependency of the stimulation onset, and this factor dominated the reflex response. For the ankle joint stimulations near toe-off evoked decreased ankle plantarflexion before the moment of peak plantarflexion (i.e. push-off) and increased ankle dorsiflexion after push-off (Figure 12). If the stimulation was delivered at the heel area, withdrawal was accomplished by lifting the heel and loading the forefoot. Stimulations near heel-off typically resulted in least dorsiflexion flexion, and withdrawal was obtained by a quick termination of push-off and flexion of hip and knee joints. For the hip and knee joint most flexion was evoked by stimulations near heel-off, while stimulations near toe-off evoked least flexion.

7.3 A new tool for control of walking for hemiplegic individuals

Considering that the reflex-gain is largest for the muscles supporting the ankle joint near toe-off, and largest for the knee and hip joints near heel-off, and that there exist complicated interactions between the modulations (Figure 12), it is clear that for rehabilitation purposes, a control algorithm prioritizing reflex behaviour between the joints is vital for success.

The results from ***study-III*** indicate that the closed-loop MRAC-system was superior to the open-loop FPS-system. This may partly be due to its embedded possibility to select the appropriate stimulation patterns according to a training aim, and due to its adaptive nature that may limit the habituation problem.

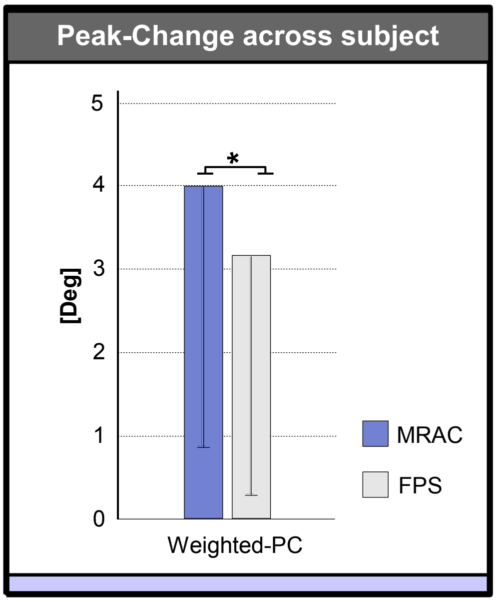

Figure 13: Overall across-subject performance for the two controllers. The bars indicate *weighted Peak-Change* combined for all joints and weighted according to a weight factor. The error bars indicates ±two standard deviations (95%) and the * indicates a significant difference.

To discuss some of the mechanisms of the MRAC-system, a few cases from ***study-III*** are presented in this paragraph. Sub#7 needed support for knee-flexion and ankle dorsiflexion, sub#1 needed extra knee extension and sub#13 needed support for ankle dorsiflexion and knee-flexion. In Figure 12, it is illustrated how the MRAC-system applied the majority of stimulations for those subjects. For sub#7, the preferred stimulation pattern was delivered to the fore-foot at heel-off, which is in line with the findings from ***study-I*** and ***study-II***. However, since the aim for largest knee flexion and largest ankle dorsiflexion was incompatible, the MRAC system used the weight-factors to reach a compromise. For sub#1, stimulations were preferably delivered to the posterior side of the heel near toe-off and for Sub#13, the preferred stimulation pattern was the arc of the foot at the onset between heel-off and toe-off.

The MRAC-system did not adapt its internal parameters in a classical way, but adapted the patterns of the output trajectories for the three joints by means of MA-models. The controller then compared the deviation from a target trajectory and conducted a numeric search among the estimated tracking errors and chose the combination of stimulation parameters that presumably would result in the lowest error.

The MRAC-system depended on the controller-target which was the training-aim set with advice from a physiotherapist and that was used to generate a target trajectory for each joint i.e. both amplitude and temporal characteristics had to be set for the entire heel-off phase. This was not a trivial task, since it required consideration to both normal healthy gait patterns, the hemiplegic's unperturbed gait-pattern, and an estimate of what was a realistic aim for the individual person. Further, a weighting factor that determined the priority between each joint was needed for the MRAC system to conduct a sensible compromise. To what degree variation in the weight factors might affect the performance of the MRAC-system was not thoroughly investigated in this work; setting both trajectory aims and weights require clinical experience in the rehabilitation field and ar time consuming.

Another issue that may require attention in a future system is the influence of limited range of motion for the individual joints. In normal gait, the range of motion of the knee joint is significantly larger than the range of motion of the hip and ankle joints during gait. This may cause an unbalanced relation between the tracking errors for the three joints.

7.4 <u>Future work</u>

In the process of designing and testing the system for reflex-based FET , some issues for future work emerged:

- Incorporation of variable stimulation intensity. This could be beneficial to change the magnitude of the reflex response as well as in case the reflex starts to habituate, since varying the stimulus intensity might also help to dis-habituate the reflex.
- A robust gait detection method has to be developed; the present use of FSR signals caused problems with detection of false-positive, footswitch signals for several of the hemiplegic subjects since there were many steps with forefoot-landings and minimal ground-clearance.
- For a future system to be successful in clinical practice the use of goniometers is not feasible, due to lack of robustness and long and tedious donning and doffing. Therefore, more work is needed on alternative sensors e.g. FRSs, accelerometers, gyroscopes or combinations of them must be implemented.

- The process of setting the individual controller targets and weight factors may be investigated and a standardized way of setting both amplitude and temporal characteristics has to be developed.
- When the adaptive plant model in the MRAC updated the baseline model, non-stereotyped steps had a larger impact since they were used directly without any pre-processing. In future work, this may be circumvented by applying a moving-average filter to the baseline model in order to reduce the impact of non-stereotyped steps.
- Investigate the effect differences in range of motion of the joints has on the relation between the tracking errors for the three joints.

7.5 Conclusions

7.5.1 Answer to the research questions

Initially, a set of research questions was posed. In this section they are answered consecutively:

7.5.1.1 What inter-stimulation frequency results in largest kinematic reflex responses?

This question was addressed in ***study-I***. Here, the modulation of the lower limb NWR elicited during late stance by a stimulus train with frequencies of 15 and 30 Hz was investigated. The kinematic responses were frequency dependent with maximum responses evoked by stimulation at 15Hz.

7.5.1.2 Are the known site and phase dependencies of the NWR measurable on ground reaction forces?

This question was addressed in ***study-II.*** Peak force changes were measured by FSRs attached to the big toe, distal to the 1st and 4th metatarsophalangeal joints, and the medial process of the calcaneus on both feet. Force changes were assessed in five gait sub-phases. Both the peak force change and the kinematic response were site- and phase modulated. The stimulation led to increased ipsilateral unloading (10±1N) and contralateral loading (12±1N), which depended on the stimulation site and phase. A remarkable observation was the behaviour of the ipsilateral big toe (hallux), which was consistently loaded while the rest of the ipsilateral foot was unloaded following the stimulations. Functionally, this implies that the hallux flexed to initiate push-off. The highest degree of plantar flexion (manifested by additional loading of 23±10N, range: 8-44N) was seen in the second double support phase following the stimulation. Furthermore, mechanical changes in the kinetic pattern were not only detected by the force signals immediately after the stimulus onset in both legs, but also in the subsequent 3rd double support phase. Site and phase modulation of the reflex were observed in the force signals from all selected anatomical landmarks.

7.5.1.3 Which methods can be used in modelling and control of hemiplegic gait?

This question was addressed in ***study-III.*** Modelling and control of the neuro-muscular plant are complicated because knowledge about the neural pathways involved in the activation of the kinematic response is not complete, so a precise parametric model could not be established. Instead, a rule-based Model Reference Adaptive Control system (MRAC) was designed and tested with an embedded adaptive plant model for estimation of the trajectories of the entire swing phase for combinations of two categorical variables: stimulation site and stimulation onset within the gait cycle. Based on the unperturbed gait and withdrawal strategies of the individual subject, control targets for the hip, knee, and ankle joints were identified and based on weight factors defined for each of the joints, the weighted squared error to a pre-set target trajectory was used to select the optimal stimulation configuration. The controller chose different stimulation parameters during the MRAC regime in order to improve the gait pattern by approaching the desired controller target. This utilizes differences in withdrawal strategy dependent on the stimulation site and timing. Furthermore, as a second effect, it may have maintained a large response by minimizing the effect of habituation by alternating stimulation parameters. This method has, to the authors' knowledge, not been reported in the literature before.

7.5.1.4 Which plant feedback is applicable?

In ***study-II,*** the applicability of using ground reaction forces measured by FSRs at anatomical landmarks under the foot as plant feedback was investigated. A strong coherence between goniometer observations and FSR observations indicate that both technologies were capable of detecting differences in withdrawal strategies depending on the stimulation onset and site. Considering the individual FSRs ability to detect differences in withdrawal strategy, the highest level of information was obtained from the FSRs placed on the the ipsilateral calcaneous, the first metatarsophalangeal joint, and the contralateral first metatarsophalangeal joint, suggesting that positioning of FSRs on these locations would be optimal. However, when designing the sensor-driven controller (***study-III***), it was realized that to be able to set sensible controller targets (training-aims) the available knowledge about healthy and pathological GRFs is insufficient. Therefore, a solution based on goniometers was chosen. However, for a future system to be successful in clinical practice this solution is not feasible, due to lack of robustness and long and tedious donning and doffing. Therefore, more work is needed on the characterization of reflex responses by force measurements or the joint kinematics have to be estimated based on e.g. FRSs, accelerometers, or gyroscopes.

7.5.1.5 Can a sensor-driven control system support the paretic leg through the swing phase?

This question was addressed in ***study-III***. Overall, both the MRAC-system and the FPS-system resulted in a more functional gait compared to no-stimulation with a weighted Peak Change in joint kinematics of 4.0±1.6 degrees (Mean ± St.dev) and 3.1±1.4 degrees, respectively. Hence, evidence was found that a sensor-driven control system can support the paretic leg through the swing phase.

7.5.1.6 Do the closed-loop swing-phase-controller prove superior to the open-loop?

In ***study-III,*** the Peak Change of the kinematic response was analyzed in a time window adjusted to the training aim (controller-target) of the individual hemiplegic subjects. A performance index was calculated based on a weighted sum of Peak Changes for the individual joints. The weights were individually set for each subject depending on their need for support. The results indicate that in 5 out of 11 trials, both control schemes supported the hemiparetic gait equally well; the MRAC-system was better for 5 out of 11 subjects, while the FPS-system was better for one subject. The controllers were equally good at providing knee support. For hip support, the FPS-system was optimal while for ankle support the MRAC-system was best. This suggests that most hemiparetic subjects may benefit from withdrawal reflex based support during gait training, which likely will facilitate the rehabilitation of gait by supporting the voluntary movement. Overall, the MRAC-system proved superior, which suggests that it might be able to adapt better to the varying needs presented during a lengthy rehabilitation therapy.

7.6 Overall conclusions

The goal of this thesis was to develop a method that allowed testing of reflex-based FET through basic understanding of the NWR. The reflex response to repetitive painful electrical stimuli of different skin sites on the sole of the foot in varies different phases of the gait cycle was investigated. The results demonstrate stimulation site and stimulation onset modulation that are detectable by kinematic and kinetic recordings, and muscle activity. The results further indicate that the kinematic responses were stimulation frequency dependent. For stimulations near toe-off, withdrawal was primarily accomplished by ankle dorsiflexion, while the strategy for stimulations at heel-off was flexion of the knee and hip joints. Stimulation delivered to the distal stimulation sites evoked a distinct ankle dorsiflexion, whereas stimulation delivered to proximal sites evoked significantly less dorsiflexion. Overall increased ipsilateral unloading and contralateral loading were the kinetic response. In contrast, the hallux of the ipsilateral leg was consistently loaded while the rest of the ipsilateral foot was unloaded following the stimulations, thus facilitating push-off. A rule-based Model Reference Adaptive Controller (MRAC) was designed for improving gait in hemiparetic patients by supporting the production of the swing phase using electrical stimulations to evoke the nociceptive withdrawal reflex. The performance of the MRAC-system was compared to an open-loop pre-programmed Fixed Pattern of Stimulation Controller (FPS). Overall the MRAC-system proved superior which suggests that the MRAC system might be able to adapt better to the varying needs presented during the lengthy rehabilitation therapy. Furthermore, it suggests that most hemiparetic subjects may benefit from reflex-based support during gait training, which likely will facilitate the rehabilitation of gait by supporting the voluntary effort to establish a functional gait pattern.

8. References

Acimovic R, Gros N, Malezic M, Strojnik P, Kljajic M, Stanic U, Simic V. Comparative study of the functionality of the second generation of peroneal stimulators. Steele, Richard D. and Gerrey, William. (Washington, DC, USA), 621-623. 1987. San Jose, CA, USA, RESNA-Assoc for the Advancement of Rehabilitation Technology. RESNA '87, Meet the Challenge, Proc of the 10th Annu Conf on Rehabil Technol. 19-6-1987.
Ref Type: Conference Proceeding

Allin J, Inbar GF. FNS control schemes for the upper limb. IEEE Trans Biomed Eng 1986;33:818-828.

Andersen OK. Studies of the organization of the human nociceptive withdrawal reflex. Focus on sensory convergence and stimulation site dependency. Acta Physiol (Oxf) 2007;189 Suppl 654:1-35.

Andersen OK, Jensen LM, Brennum J, Arendt-Nielsen L. Evidence for central summation of C and A delta nociceptive activity in man. Pain 1994;59:273-280.

Andersen OK, Jensen LM, Brennum J, Arendt-Nielsen L. Modulation of the human nociceptive reflex by cyclic movements. Eur J Appl Physiol Occup Physiol 1995;70:311-321.

Andersen OK, Sonnenborg F, Matjacic Z, Arendt-Nielsen L. Foot-sole reflex receptive fields for human withdrawal reflexes in symmetrical standing position. Exp Brain Res 2003;152:434-443.

Andersen OK, Sonnenborg FA, Arendt-Nielsen L. Modular organization of human leg withdrawal reflexes elicited by electrical stimulation of the foot sole. Muscle Nerve 1999;22:1520-1530.

Andersen OK, Sonnenborg FA, Arendt-Nielsen L. Reflex receptive fields for human withdrawal reflexes elicited by non-painful and painful electrical stimulation of the foot sole. Clin Neurophysiol 2001;112:641-649.

Andersen OK, Spaich EG, Madeleine P, Arendt-Nielsen L. Gradual enlargement of human withdrawal reflex receptive fields following repetitive painful stimulation. Brain Res 2005;1042:194-204.

Andrews BJ, Baxendale RH, Granat MH, Nicol DJ. Flexion withdrawal reflexes in spinal cord-injured man. J Physiol 1990;429:50.

Arendt-Nielsen L, Brennum J, Sindrup S, Bak P. Electrophysiological and psychophysical quantification of temporal summation in the human nociceptive system. Eur J Appl Physiol Occup Physiol 1994;68:266-273.

Arendt-Nielsen L, Sonnenborg FA, Andersen OK. Facilitation of the withdrawal reflex by repeated transcutaneous electrical stimulation: an experimental study on central integration in humans. Eur J Appl Physiol 2000;81:165-173.

Astrom KJ, Wittenmark B. Adaptive Control Addison-Wesley, 1989.

Bajaj P, rendt-Nielsen L, Andersen OK. Facilitation and inhibition of withdrawal reflexes following repetitive stimulation: electro- and psychophysiological evidence for activation of noxious inhibitory controls in humans. Eur J Pain 2005;9:25-31.

Bajd T, Kralj A, Turk R, Benko H, Sega J. The use of a four-channel electrical stimulator as an ambulatory aid for paraplegic patients. Phys Ther 1983;63:1116-1120.

Bent LR, Potvin JR, Brooke JD, McIlroy WE. Medio-lateral balance adjustments preceding reflexive limb withdrawal are modified by postural demands. Brain Res 2001;914:100-105.

Braun Z, Mizrahi J, Najenson T, Graupe D. Activation of paraplegic patients by functional electrical stimulation: training and biomechanical evaluation. Scand J Rehabil Med Suppl 1985;12:93-101.

Brown DA, Kukulka CG. Human flexor reflex modulation during cycling. J Neurophysiol 1993;69:1212-1224.

Buckett JR, Peckham PH, Thrope GB, Braswell SD, Keith MW. A flexible, portable system for neuromuscular stimulation in the paralyzed upper extremity. IEEE TRANS BIOMED ENG 1988;35:897-904.

Burridge J, Taylor P, Hagan S, Swain I. Experience of clinical use of the Odstock dropped foot stimulator. Artif Organs 1997;21:254-260.

Carstens E, Wilson C. Rat tail flick reflex: magnitude measurement of stimulus-response function, suppression by morphine and habituation. J Neurophysiol 1993;70:630-639.

Chang GC, Luh JJ, Liao GD, Lai JS, Cheng CK, Kuo BL, Kuo TS. A neuro-control system for the knee joint position control with quadriceps stimulation. IEEE Trans Rehabil Eng 1997;5:2-11.

Clarke RW, Harris J. The organization of motor responses to noxious stimuli. Brain Res Brain Res Rev 2004;46:163-172.

Crago PE, Mortimer JT, Peckham PH. Closed-loop control of force during electrical stimulation of muscle. IEEE Trans Biomed Eng 1980;27:306-312.

Crenna P, Frigo C. Evidence of phase-dependent nociceptive reflexes during locomotion in man. Experimental Neurology 1984;85:336-345.

Daly JJ, Marsolais EB, Mendell LM, Rymer WZ, Stefanovska A. Therapeutic neural effects of electrical stimulation. Rehabilitation Engineering, IEEE Transactions on 1996;4:218-230.

Davoodi R, Andrews BJ. Computer simulation of FES standing up in paraplegia: A self-adaptive fuzzy controller with reinforcement learning. IEEE Trans Rehabil Eng 1998;6:151-161.

Dimitrijevic MR, Faganel J, Gregoric M, Nathan PW, Trontelj JK. Habituation: effects of regular and stochastic stimulation. J Neurol Neurosurg Psychiatry 1972;35:234-242.

Dimitrijevic MR, Nathan PW. Studies of spasticity in man. 5. Dishabituation of the flexion reflex in spinal man. Brain 1971;94:77-90.

Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet 2008;371:1612-1623.

Duysens J, Tax AA, Trippel M, Dietz V. Phase-dependent reversal of reflexly induced movements during human gait. Exp Brain Res 1992;90:404-414.

Eccles RM, Lundberg A. Supraspinal control of interneurones mediating spinal reflexes. J Physiol 1959;147:565-584.

Emborg J, Spaich EG, Andersen OK. Withdrawal reflexes examined during human gait by ground reaction forces: site and gait phase dependency. Med Biol Eng Comput 2009;47:29-39.

Ferguson KA, Polando G, Kobetic R, Triolo RJ, Marsolais EB. Walking with a hybrid orthosis system. Spinal Cord 1999;37:800-804.

Ferrarin M, Palazzo F, Riener R, Quintern J. Model-based control of FES-induced single joint movements. IEEE Trans Neural Syst Rehabil Eng 2001;9:245-257.

Fuhr T, Quintern J, Riener R, Schmidt G. Walking with WALK! A cooperative, patient-driven neuroprosthetic system 1. IEEE Eng Med Biol Mag 2008;27:38-48.

Granat M, Keating JF, Smith AC, Delargy M, Andrews BJ. The use of functional electrical stimulation to assist gait in patients with incomplete spinal cord injury. Disabil Rehabil 1992;14:93-97.

Granat MH, Heller BW, Nicol DJ, Baxendale RH, Andrews BJ. Improving limb flexion in FES gait using the flexion withdrawal response for the spinal cord injured person. J Biomed Eng 1993;15:51-56.

Granat MH, Nicol DJ, Baxendale RH, Andrews BJ. Dishabituation of the flexion reflex in spinal cord-injured man and its application in the restoration of gait. Brain Res 1991;559:344-346.

Graupe D, Kohn KH. Functional neuromuscular stimulator for short-distance ambulation by certain thoracic-level spinal-cord-injured paraplegics. Surgical Neurology 1998;50:202-207.

Grimby L. Normal plantar response: integration of flexor and extensor reflex components. J Neurol Neurosurg Psychiatry 1963;26:39-50.

Haghbarth KE. Excitatory and inhibitory skin areas for flexor and extensor motoneurons. Acta Physiol Scand Suppl 1952;26:1-58.

Hatwell MS, Oderkerk BJ, Sacher CA, Inbar GF. The development of a model reference adaptive controller to control the knee joint of paraplegics. IEEE Trans Autom Control 1991;36:683-691.

Haugland M, Childs C, Ladouceur M, Haase J, Sinkjaer T. An implantable foot drop stimulator. Proc 5th Ann IFEES Conf 2000;59-62.

Haugland MK, Sinkjaer T. Cutaneous whole nerve recordings used for correction of footdrop in hemiplegic man. IEEE Trans Rehabil Eng 1995;3:307-317.

http:, hjernesagen.dk. Statistiske oplysninger om blodprop eller blødning i hjernen - apopleksi. http://hjernesagen.dk/baggrundsviden/statistiske-oplysninger/statistiske-oplysninger-om-blodprop-eller-blodning-i-hjernen-apopleksi/ . 1-6-2009. 1-6-2007.
Ref Type: Internet Communication

Jonic S, Jankovic T, Gajic V, Popovic D. Three machine learning techniques for automatic determination of rules to control locomotion. IEEE TRANS BIOMED ENG 1999;46:300-310.

Kandel ER, Schwartz JH, Jessel TM. Principles of Neural Science New York: Elsevier, 1991.

Kim Y, Schmit BD, Youm Y. Stimulation parameter optimization for functional electrical stimulation assisted gait in human spinal cord injury using response surface methodology. Clinical Biomechanics 2006;21:485-494.

Kiriyama K, Warabi T, Kato M, Yoshida T, Kobayashi N. Progression of human body sway during successive walking studied by recording sole-floor reaction forces
6. Neurosci Lett 2004;359:130-132.

Klose KJ, Jacobs PL, Broton JG, Guest RS, Needham-Shropshire BM, Lebwohl N, Nash MS, Green BA. Evaluation of a training program for persons with SCI paraplegia using the Parastep®1 ambulation system: Part 1. Ambulation performance and anthropometric measures. Archives of Physical Medicine and Rehabilitation 1997;78:789-793.

Kobayashi N, Warabi T, Kato M, Kiriyama K, Yoshida T, Chiba S. Posterior-anterior body weight shift during stance period studied by measuring sole-floor reaction forces during healthy and hemiplegic human walking
1. Neurosci Lett 2006;399:141-146.

Kobetic R, Triolo RJ, Marsolais EB. Muscle selection and walking performance of multichannel FES systems for ambulation in paraplegia. IEEE Trans Rehabil Eng 1997;5:23-29.

Kobetic R, Marsolais EB. Synthesis of paraplegic gait with multichannel functional neuromuscular stimulation. IEEE Trans Rehabil Eng 1994;2:66-79.

Kojovic J, Djuric-Jovicic M, Dosen S, Popovic MB, Popovic DB. Sensor-driven four-channel stimulation of paretic leg: functional electrical walking therapy. J Neurosci Methods 2009;181:100-105.

Kostov A, Andrews BJ, Popovic DB, Stein RB, Armstrong WW. Machine learning in control of functional electrical stimulation systems for locomotion. IEEE TRANS BIOMED ENG 1995;42:541-551.

Kugelberg E, Eklund K, Grimby L. An electromyographic study of the nociceptive reflexes of the lower limb. Mechanism of the plantar responses. Brain 1960;83:394-410.

Landau ID. Survey of Model Reference Adaptive Techniques - Theory and Applications. Automatica 1974;10:353-379.

Lee KH, Johnston R. Electrically induced flexion reflex in gait training of hemiplegic patients: induction of the reflex. Arch Phys Med Rehabil 1976;57:311-314.

Levinsson A, Garwicz M, Schouenborg J. Sensorimotor transformation in cat nociceptive withdrawal reflex system. Eur J Neurosci 1999;11:4327-4332.

Liberson WT, Holmquest HJ, Scot D, Dow M. Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. Arch Phys Med Rehabil 1961;42:101-105.

Lyons GM, Sinkjaer T, Burridge JH, Wilcox DJ. A review of portable FES-based neural orthoses for the correction of drop foot. IEEE Trans Neural Syst Rehabil Eng 2002;10:260-279.

McIlroy WE, Bent LR, Potvin JR, Brooke JD, Maki BE. Preparatory balance adjustments precede withdrawal response to noxious stimulation in standing humans. Neurosci Lett 1999;267:197-200.

Meinck HM, Kuster S, Benecke R, Conrad B. The flexor reflex--influence of stimulus parameters on the reflex response. Electroencephalogr Clin Neurophysiol 1985;61:287-298.

Moore S, Schurr K, Wales A, Moseley A, Herbert R. Observation and analysis of hemiplegic gait: Swing phase. AUST J PHYSIOTHER 1993;39:271-278.

Moseley A, Wales A, Herbert R, Schurr K, Moore S. Observation and analysis of hemiplegic gait: Stance phase. AUST J PHYSIOTHER 1993;39:259-267.

Pedersen E, Petersen T, Hansen CA, Klemar B. [Clinical experience with a new footdrop stimulator]. Ugeskr Laeger 1986;148:1272-1275.

Pedersen PM, Olsen TS. Rehabilitering af patienter med apopleksi. Ugeskr Læger 2007; 2007;40:3398-3400.

Popovic D, Radulovic M, Schwirtlich L, Jaukovic N. Automatic vs hand-controlled walking of paraplegics. Medical Engineering and Physics 2003a;25:63-73.

Popovic DB. Finite state model of locomotion for functional electrical stimulation systems. Progress in Brain Research 1993;97:397-407.

Popovic MB, Popovic DB, Sinkjaer T, Stefanovic A, Schwirtlich L. Clinical evaluation of Functional Electrical Therapy in acute hemiplegic subjects. J Rehabil Res Dev 2003b;40:443-453.

Popovic MR, Thrasher TA. Neuroprostheses. Encyclopedia of Biomaterials and Biomedical Engineering 2004;1056-1065.

Qi H, Tyler DJ, Durand DM. Neurofuzzy adaptive controlling of selective stimulation for FES: A case study. IEEE Trans Rehabil Eng 1999;7:183-192.

Quintern J, Bisle G, Hartmann E. Controlled clinical study of stimulation of flexor reflex afferents for gait rehabilitation in patients with hemiplegia. Gantchev N et al (eds) From basic motor control to functional recovery III , 240-246. 2003. St. Kliment Ohridski University Press.
Ref Type: Conference Proceeding

Quintern J, Krewer C, Bisle G, Husemann B, Heller S. Enhancement of Gait Retraining by Electrical Stimulation of Flexor Reflex Afferents in Acute Stroke Patients: A Randomized, Controlled Clinical Study. 9th Annual Conference of the International FES Society September 2004 - Bournemouth, UK 2004.

Riener R. Model-based development of neuroprosthesis for paraplegic patients. Philos Trans R Soc Lond B Biol Sci 1999;354:877-894.

Riener R, Fuhr T, Antico D, Quintern J. Modelling and control of the flexion withdrawal reflex for gait neuroprosthesis. In: Sinkjær T, Popovic D, Struijk JJ (eds) Proceedings for the 5th annual conference of the international functional electrical stimulation society Aalborg 2000;421-424.

Rushton DN. Functional Electrical Stimulation and rehabilitation--an hypothesis. Medical Engineering & Physics 2003;25:75-78.

Sandrini G, Serrao M, Rossi P, Romaniello A, Cruccu G, Willer JC. The lower limb flexion reflex in humans. Prog Neurobiol 2005;77:353-395.

Schomburg ED, Steffens H, Mense S. Contribution of TTX-resistant C-fibres and Adelta-fibres to nociceptive flexor-reflex and non-flexor-reflex pathways in cats. Neurosci Res 2000;37:277-287.

Schouenborg J, Holmberg H, Weng HR. Functional organization of the nociceptive withdrawal reflexes. II. Changes of excitability and receptive fields after spinalization in the rat. Exp Brain Res 1992;90:469-478.

Schouenborg J, Kalliomaki J. Functional organization of the nociceptive withdrawal reflexes. I. Activation of hindlimb muscles in the rat. Exp Brain Res 1990;83:67-78.

Schuck E, Friedman H, Wilemon W, McNeal D. Developing clinical devices for hemiplegic stroke patients. Adv External Control of Human Extremities 1973;535-546.

Sepulveda F, Granat MH, Cliquet A, Jr. Two artificial neural systems for generation of gait swing by means of neuromuscular electrical stimulation. Med Eng Phys 1997;19:21-28.

Sherrington CS. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. J Physiol 1910;40:28-121.

Sinkjaer T, Popovic DB. Trends in the Rehabilitation of Hemiplegic Subjects. Journal of Automatic Control 2005;15:1-10.

Solomonow M. External control of the neuromuscular system. IEEE Trans Biomed Eng 1984;31:752-763.

Solomonow M, Aguilar E, Reisin E, Baratta RV, Best R, Coetzee T, D'Ambrosia R. Reciprocating gait orthosis powered with electrical muscle stimulation (RGO II). Part I: Performance evaluation of 70 paraplegic patients. Orthopedics 1997;20:315-324.

Sonnenborg FA, Andersen OK, Arendt-Nielsen L. Modular organization of excitatory and inhibitory reflex receptive fields elicited by electrical stimulation of the foot sole in man. Clin Neurophysiol 2000;111:2160-2169.

Spaich EG, Andersen OK, Arendt-Nielsen L. Tibialis Anterior and Soleus Withdrawal Reflexes Elicited by Electrical Stimulation of the Sole of the Foot during Gait. Neuromodulation 2004a;7:126-132.

Spaich EG, Arendt-Nielsen L, Andersen OK. Modulation of lower limb withdrawal reflexes during gait: a topographical study. J Neurophysiol 2004b;91:258-266.

Spaich EG, Arendt-Nielsen L, Andersen OK. Repetitive painful stimulation produces an expansion of withdrawal reflex receptive fields in humans. Artif Organs 2005a;29:224-228.

Spaich EG, Collet T, Arendt-Nielsen L, Andersen OK. Repetitive painful stimulation evokes site, phase, and frequency modulated responses during the swing phase of the gait cycle : pre-liminary results. In: Gantchev,N , (ed) From Basic Motor Control to Functional Recovery IV Sofia: Marin Drinov Academic Publishing House 2005b;136-140.

Spaich EG, Emborg J, Collet T, Arendt-Nielsen L, Andersen OK. Withdrawal reflex responses evoked by repetitive painful stimulation delivered on the sole of the foot during late stance: site, phase, and frequency modulation. Exp Brain Res 2009;194:359-368.

Spaich EG, Hinge HH, Arendt-Nielsen L, Andersen OK. Modulation of the withdrawal reflex during hemiplegic gait: effect of stimulation site and gait phase. Clin Neurophysiol 2006;117:2482-2495.

Taylor PN, Burridge JH, Dunkerley AL, Wood DE, Norton JA, Singleton C, Swain ID. Clinical use of the Odstock dropped foot stimulator: Its effect on the speed and effort of walking. Archives of Physical Medicine and Rehabilitation 1999;80:1577-1583.

Vaughan CL, Davis BL, O'Conner JC. Dynamics of human gait 1992.

Veltink PH, Chizeck HJ, Crago PE, El-Bialy A. Nonlinear joint angle control for artificially stimulated muscle. IEEE TRANS BIOMED ENG 1992;39:368-380.

Warabi T, Kato M, Kiriyama K, Yoshida T, Kobayashi N. Analysis of human locomotion by recording sole-floor reaction forces from anatomically discrete points
24. Neurosci Res 2004;50:419-426.

Waters RL, McNeal D, Perry J. Experimental correction of footdrop by electrical stimulation of the peroneal nerve. J Bone Joint Surg Am 1975;57:1047-1054.

9. English summery

A new therapeutic modality for post-stroke hemiplegic individuals called Functional Electrical Therapy (FET) combines Functional Electrical Stimulation (FES) with task-dependent voluntary exercise. This combined intervention carries potential for promoting recovery of movement in paralyzed extremities. We proposed a reflex-based FET approach (electrical stimulation of the flexion withdrawal reflex combined with task-dependent voluntary exercise) where primarily flexion of the entire leg can be evoked and controlled through few surface stimulation electrodes. The goal of this thesis was via improved understanding of the nociceptive withdrawal reflex during gait, to develop a method that allows testing reflex-based FET. The reflex response to repetitive painful electrical stimuli of different skin sites on the sole of the foot in different phases of the gait cycle was investigated. A fixed stimulus train at frequencies of 15 and 30 Hz was investigated. The results indicated that the kinematic responses were frequency dependent with maximum responses evoked by stimulation at 15Hz. The results further demonstrate that for stimulation near toe-off, withdrawal was primarily accomplished by ankle dorsiflexion, while the strategy for stimulations at heel-off was flexion of the knee and hip joints. Stimulation delivered to the distal stimulation sites evoked a distinct ankle dorsiflexion, whereas stimulation delivered to proximal sites evoked significantly less dorsiflexion. Further, the reflex response depended strongly on the stimulation onset within the gait cycle, and this factor dominated the reflex response. Quantification of the reflex responses by ground reaction forces recorded by means of force sensing resistors (FSR) was investigated. Furthermore, it was also investigated if the reflex site and phase dependencies can be detected from FSR signals. Overall a strong coherence between goniometers and FSR recordings was found. Painful stimulations led to increased ipsilateral unloading and contralateral loading, which were dependent on stimulation site and phase. In contrast, the hallux of the ipsilateral foot was consistently loaded while the rest of the ipsilateral foot was unloaded following the stimulations, thus, facilitating push-off. Modelling and control methods for the neuromuscular plant (from stimulation of afferents to induced movement) were investigated. However, due to the limited knowledge about the spinal reflex systems involved in the mechanical reflex response, a precise parametric model could not be established. Instead, an adaptive plant model for estimation of the trajectories of the entire swing phase for combinations of two categorical variables (stimulation site and onset) was developed based on a moving average approach. However, during the controller design process it was realized that the information from current FSR technology was insufficient for controlling the desired targets for the individual gait performance. Therefore, a solution based on goniometers was chosen. A novel closed-loop system for improving gait in hemiparetic patients by supporting the production of the swing phase using electrical stimulations evoking the nociceptive withdrawal reflex was designed. A rule-based Model Reference Adaptive Controller (MRAC) was designed to select the best stimulation parameters. Withdrawal reflexes were evoked by choosing between a set of twelve combinations of four stimulation electrode locations on the foot and three different stimulation onset times between heel-off and toe-off. The performance of the MRAC-system was compared to an open-loop pre-programmed Fixed Pattern of Stimulation controller (FPS). Overall, both the MRAC-system and the FPS-system resulted in a more functional gait compared to no-stimulation. Both controllers showed the largest improvement in the knee joint trajectory. For hip support, the FPS-system was superior, while for ankle support the MRAC-system performed best. Overall the MRAC-system proved superior and most likely this system will be able to adapt better to the varying needs during a single rehabilitation session and more importantly during lengthy rehabilitation therapy. Furthermore, it suggests that most hemiparetic subjects may benefit from reflex-based support during gait training, which likely will facilitate the rehabilitation of gait by supporting the voluntary effort to establish a functional gait pattern.

10. Danish summery / Dansk sammenfatning

En ny terapeutisk metode til rehabilitering af patienter med apoplexi der kaldes Funktionel Elektrisk Terapi (FET), kombinerer Functional Electrical Stimulation (FES) med opgave-specifik frivillig træning. Denne kombinerede intervention indebærer mulighed for at fremme patienternes egen mulighed for igen at kunne bevæge de lammede ekstremiteter. I denne afhandling foreslås en refleks-baseret FET tilgang, dvs. elektrisk stimulering af afværgerefleksen kombineret med opgave-specifik frivillig træning, hvor primært fleksion af hele benet kan opnås og kontrolleres via nogle få overflade stimulations elektroder. Målet med denne afhandling var via en bedre forståelse af mekanismerne i den nociceptive afværgerefleks under gang, at udvikle en metode, der giver mulighed for afprøvning refleks-baserede FET. Refleks reaktionen som følge af gentagne smertefulde elektriske stimulation af forskellig hud steder på fodsålen i forskellige faser af gang cyklus blev undersøgt. Et fast stimulations puls-tog blev undersøgt ved frekvenser på 15 og 30 Hz. Resultaterne viste, at de kinematiske reaktioner var frekvens afhængige, og at de maksimale reaktioner blev fremkaldt ved stimulation med 15Hz. Resultaterne demonstrerer endvidere, at for stimulation omkring toe-off, var afværge strategien først og fremmest ankel dorsiflexion, mens strategien for stimulering omkring heel-off var fleksion af knæ-og hofteled. Stimulationer der blev leveret til distale stimulations steder fremkaldte en særskilt ankel dorsiflexion, mens stimulationer leveret til proksimale steder vakte betydeligt mindre dorsiflexion. Endvidere afhang refleks reaktionen i høj grad hvornår i gang cyklus der blev stimuleret, og resultaterne tyder på at denne faktor dominerede refleks reaktionen. Kvantificering af refleks reaktioner via reaktionskraften mellem jord og fod blev undersøgt ved hjælp af kraft følsomme modstande (FSR). Endvidere blev det undersøgt, om refleks reaktionens sted og fase afhængigheder kunne spores på FSR signalerne. Overordnet blev der set en stærk sammenhæng mellem optagelser fra goniometers og FSR. De smertefulde stimulationer førte til en øget ipsilateral aflastning og øget kontralaterale belastning af foden. Disse var afhængige af både stimulations sted og tidspunkt. Mens resten af den ipsilateral fod blev aflastet som følge af stimulation, blev den ipsilateral storetå derimod konsekvent yderligere belastet som følge af stimulationerne, hvorved push-off faciliteres. Gennem arbejdet med design af kontrolleren blev det konstateret, at den tilgængelige viden om FSR teknologien var utilstrækkelig til at disse kunne bruges til at sætte trænings mål for den individuelle patient Det er derfor i stedet valgt at baserer løsningen goniometer målinger. Metoder til modellering og automatisk kontrol af det neuro-muskulære-system, (Dvs. fra stimulering af afferente nerver til induceret bevægelser) blev undersøgt. En præcis parameterisk model kunne dog ikke opstilles, grundet den begrænsede viden om de spinale refleks-systemer, der er involveret i den mekaniske refleks reaktion. I stedet blev der udviklet en adaptiv system model, der estimerede trajektorier af hele sving-fasen for alle kombinationer af to de kategoriske variable (stimulations sted og fase). Metoden var baseret på en moving-average teknik. Der blev designet et nyskabende lukket-sløjfe kredsløb. Systemet skal forbedre gangfunktionen hos patienter med apoplexi, ved at støtte produktionen af sving-fasen, sådan at den frivillige bevægelse suppleres med elektriske aktiverede afværgereflekser. Kontrolleren, en regel-baseret Model Reference Adaptiv kontroller (MRAC) var designet til at vælge de bedste stimulations parametre. Afværgereflekser var fremkaldt ved at vælge mellem tolv parameter kombinationer (fire elektrode positioner og tre forskellige stimulations tidspunkter mellem heel-off og toe-off). MRAC-systemets ydeevne blev sammenlignet med en åben-sløjfe kontroller med et forprogrammeret fast mønster af stimulationer (FPS). Overordnet resulterede både MRAC-systemet og FPS-systemet i et mere funktionelt gangmønster sammenlignet med når der ikke blev stimuleret. Begge kontrollere viste den største forbedring i for knæleddets bevægelser. FPS-systemet var overlegent til at yde hofte støtte, mens MRAC-systemet var bedst til at yde ankel støtte. Samlet set var MRAC-systemet overlegent og dette system vil sandsynligvis også være i stand til bedre at tilpasse sig de varierende behov i løbet af en enkelt rehabilitering session og endnu vigtigere i løbet af langvarig rehabiliterings terapi. Endvidere tyder det på, at de fleste apoplexi patienter kan drage fordel af refleks-baseret støtte i gang træningen, hvilket sandsynligvis facilitere rehabilitering af gangfunktionen ved at støtte den frivillige indsats for at etablere et funktionelt gangmønster.