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Physiologically-based Control Strategies and Functional Electrical Stimulation Paradigms for Restoring Standing and Stepping after Spinal Cord Injury

by

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Abstract

Spinal cord injury (SCI) resulting in paralysis has an enormous impact not only on the health of the individual, but more fundamentally their independence and self-image. Advancements in treatment and rehabilitation can result in an improvement in the quality of life of these individuals. The studies presented in this dissertation were conducted with the goal of developing functional electrical stimulation (FES) techniques and control paradigms for restoring standing and stepping after SCI. The approach taken was to apply physiologically-based control strategies and stimulation paradigms to achieve this goal. Intraspinal microstimulation (ISMS) is an FES technique in which stimulation is applied to the spinal cord through microwires implanted into the ventral horn. This technique taps into some of the physiological characteristics of neuronal recruitment resulting in increased fatigue resistance and more graded force recruitment for ISMS (vs. peripheral FES).

In the first study, continuous trains of supra-motor-threshold ISMS and intramuscular stimulation (IM-S) were used to generate *load-bearing standing*. The duration and stability of standing was improved when using interleaved ISMS, as opposed to non-interleaved IM-S. The addition of a closed-loop controller that used joint angle and hindlimb loading information to minimize the amplitude of the applied stimulation further improved the balance of the ISMS standing.

The second study used a continuous ISMS stimulation protocol similar to that used to generate standing. However, in this study, motor-threshold levels of stimulation acted to excite intrinsic spinal networks involved in generating *locomotor patterns*. The results from this study provide insight into how locomotor networks are distributed within the spinal cord. However, the evoked stepping was characterized by low weight-bearing and propulsive forces making it unsuitable for functional gait.

In the final study, *load-bearing overground locomotion* was generated using several physiologically-based controllers in conjunction with IM-S. Phase transitions governed by intrinsic timing or sensory information alone resulted in unstable gait. A combination of intrinsically-timed and sensory-driven phase transitions demonstrated potential for generating robust overground locomotion.

These studies advanced the development of a physiologically-based FES system for restoring standing and stepping after SCI while also providing insight into the neural control of locomotion.

For Mom and Dad,
the strongest people I know.

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List of Abbreviations

Abbreviation	Definition
2D	two dimensional
3D	three dimensional
AdM	adductor medialis
AFO	ankle, foot orthosis
ALN	adaptive logic networks
ALS	amyotrophic lateral sclerosis
BDNF	brain-derived neurotrophic factor
BCI	brain computer interface
BION^{TM}	BIOnic Neurons
BFa	biceps femoris anterior
BFp	biceps femoris posterior
%BW	percent body weight
CF	caudofemoralis posterior
CL	closed-loop
CNS	central nervous system
CPG	central pattern generator
CWRU/VA	Case Western Reserve University / Veterans Affairs
Cx	cervical segment number x
EDL	extensor digitorum longus
EMG	electromyography
ENG	electroneurography
ETHZ	Eidgenössische Technische Hochschule Zürich
FES	functional electrical stimulation
FDL	flexor digitorum longus
FHL	flexor hallicus longus
FINE	flat interface nerve electrode
FSR	force sensing resistor
i.v.	intravenous
GL (or LG)	lateral gastrocnemius
GlutMax	gluteus maximum
GlutMed	gluteus medialis
GRF	ground reaction force
GUI	graphical user interface
ISMS	intraspinal microstimulation
IM	intramuscular

Abbreviation	Definition
IM-S	intramuscular stimulation
KAFO	knee, ankle, foot orthosis
LARSI	lumbar anterior root stimulation implant
L-DOPA	L-3,4-dihydroxyphenylalanine
LED	light emitting diode
LIFE	longitudinal intra-fascicular electrode
LG (or GL)	lateral gastrocnemius
Lx	lumbar segment number x
MG	medial gastrocnemius
MRI	magnetic resonance imaging
MTP	metatarsasophalangeal
MU	motor unit
NMDA	N-methyl-D-aspartic acid
NT-3	neurotrophin 3
OL-h	open-loop high
OL-l	open-loop low
PID	proportional/intergral/derivative
RF	restus femoris
RGO	reciprocating gait orthosis
ROM	range of motion
SEM	standard error of the mean
SRTa	sartorius anterior
SRTm	sartorius medialis
SCI	spinal cord injury
SMp	semimembranosus anterior
ST	semitendinosus
Sx	sacral segment number x
TA	tibialis anterior
TP	tibialis posterior
Tx	thoracic segment number x
VI	vastus intermedius
VL	vastus lateralis

Chapter 1

Introduction

"In a single rash moment of impatience and stupidity, I had completely ruined my life, and my family's life. I was going to be a burden to everyone, completely dependent on other people for the rest of my days."

- Julie Hill, person with paraplegia (Hill, 2000)

In 1990, at the age of 28, Julie Hill broke her back in a devastating car crash leaving her without control of her lower body. The wife and working mother of two young children was forced to face the fact that her life had been irreversibly changed and that she would never be able to enjoy the freedom that she had previously taken for granted. Julie was not alone in her misfortune. Every year more than 11,000 Americans sustain spinal cord injuries (SCIs) with the majority of injuries occurring in young people like Julie (16-30 years) who are in the prime of their lives (Center, 2005).

These injuries have devastating consequences affecting not only the general health of the individual, but more fundamentally their independence and self-image. The leading causes of death for people with chronic SCIs are bladder and respiratory infections (Kilgore et al., 2001). But due to advances in medical care, a young person with a spinal cord injury can expect to live anywhere from 20 to 50 years post-injury depending on the level and severity of their injury. Advancements in treatment and rehabilitation, including restoring the ability to stand and step, can result in an improvement in the quality of life of these individuals.

Restoring locomotion after injury not only improves independence and self-image but also has the benefit of improving blood flow and bone density resulting in reduced hospitalization. Although the muscles and nerves below the level of the lesion no longer receive descending control signals from the brain and other higher centers, they often remain intact and functional after SCI. Movement can be restored to paralyzed muscles by replacing the descending signals with functional electrical stimulation (FES) applied to the peripheral or central nervous system.

The studies presented in this dissertation were conducted with the goal of developing FES techniques and control paradigms for restoring standing and stepping after SCI. The approach taken was to apply physiological principles of locomotion and to tap into the intrinsic structural organization of the nervous system for the development of this system.

1.1 Neural Control of Movement

In an intact uninjured system, movement is generated through an interaction between the nervous system and the musculoskeletal system. Multijoint movements pose a non-trivial control problem because the biomechanical system has many degrees of freedom and requires complex control signals to generate appropriate muscle activation patterns. While coordinating the activation of agonists and antagonists around each of the joints the controller must compensate for the variable contraction and relaxation times of different muscles, their individual non-linear length-tension properties and take into consideration any contributions to the muscle activation arising from stimulus-evoked reflexes. The relatively simple cyclical movements of the limbs during walking are therefore the product of fine control of muscle activation throughout the cycle. The required activation pattern is also modified to compensate for the presence of external perturbations such as an obstacle blocking the trajectory of the foot during swing or a change in grade of the support surface. Although there is no clear explanation regarding how the nervous system plans and executes precise movements, multiple theories suggest possible mechanisms for the natural control of movement. In the following sections I will discuss some of the theories that have been set forth to explain how the neuromuscular systems solve this control problem.

1.1.1 Central Pattern Generators

Thomas Graham Brown (1911) first proposed that the ability to generate stepping movements is an innate characteristic of neural networks residing within the spinal cord, based on his demonstration that rhythmic stepping could be generated in spinal cats even in the absence of descending cortical control signals and afferent feedback. He described networks within the spinal cord generating alternating flexor and extensor activity comprised of *half-centres*. These spinal networks are now generally referred to as central pattern generators (CPGs). The key feature of a CPG is its ability to generate stable and behaviourally appropriate patterns of oscillatory output even in the absence of descending input or sensory feedback (Grillner, 1981). There are many theoretical models used to describe the structure of the locomotor CPG. These include the ring hypothesis (Shik and Orlovsky, 1976), the three-phasic generator (Gelfand et al., 1988) and the chain of unit burst generators (Grillner, 1981).

One of the more widely accepted models describes the CPG as consisting of two main components; a reciprocally coupled oscillator that generates the basic rhythm and an output motor stage that shapes the rhythm into spatiotemporal signals for the muscles involved in the action (Grillner, 1981; Orlovsky et al., 1999; Lafreniere-Roula and McCrea, 2005). The only input required by the CPG is some form of natural (i.e., supraspinal or sensory) or imposed excitation that initiates the pattern generation. This imposed excitation can be in the form of pharmacological agents such as L-DOPA (Jankowska et al., 1967b,a), clonidine (an α-2 adrenergic agonist) (Forssberg and Grillner, 1973), N-methyl-D-aspartic acid (a glutamate NMDA receptor agonist) (Douglas et al., 1993; Chau et al., 2002) or serotonin (Feraboli-Lohnherr et al., 1999). Electrical stimulation applied either to the spinal cord (Gerasimenko et al., 2003; Magnuson and Trinder, 1997) or to higher centres (Shik and Orlovsky, 1976) can activate locomotor networks in the spinal cord. Disorganized sensory information arising from muscle spindles subjected to tonic muscle vibration has also been shown to evoke alternation in prone subjects (Gurfinkel et al., 1998). Once the CPG is activated, supplementary input arising from supraspinal systems or afferent receptors modulates the generated rhythm and muscle activation patterns (Lafreniere-Roula and

McCrea, 2005).

Brown's idea of centrally generated stepping has been pursued extensively in organisms such as lamprey (Cohen and Wallen, 1980), rats (Kjaerulff and Kiehn, 1996), cats (Grillner and Rossignol, 1978) and primates (Fedirchuk et al., 1998). Although neural networks located in the spinal cord are likely to play an important role in the generation of rhythmic locomotion in many lower organisms, there is no conclusive evidence demonstrating the existence of a locomotor CPG in primates and humans. However, studies demonstrating rhythmic alternation in marmoset monkeys (Fedirchuk et al., 1998), human infants (Lamb and Yang, 2000) and people with incomplete SCI (Dietz et al., 1995; Calancie et al., 1994) suggest that the CPG plays a role in primate locomotion, albeit less substantial than in non-primates.

1.1.2 Movement Primitives

Another theory regarding the role of the spinal cord in generating movements proposes that spinal neural networks code "movement primitives" that constitute the building blocks for more complex behaviours (Saltiel et al., 2001; Mussa-Ivaldi et al., 1994; Lemay et al., 2001; Giszter et al., 1993; Lemay and Grill, 2004). A movement primitive is defined as an indivisible element of motor behaviour that generates a regulated and stable mechanical response (Giszter et al., 1993). Experiments done in frogs (Saltiel et al., 2001; Mussa-Ivaldi et al., 1994; Lemay et al., 2001; Giszter et al., 1993) rats (Tresch and Bizzi, 1999) and cats (Lemay and Grill, 2004) have supported the idea that networks within the intermediate region of the grey matter of the spinal cord are responsible for generating a set of distinct movement primitives. These experiments were conducted by securing the limb of the animal and measuring the force generated at its endpoint while electrical stimulation was applied to the intermediate spinal cord. For a single stimulation site in the cord, the field generated by recording forces at different fixed limb positions sometimes converged to an equilibrium point where joint torques summed to zero. Only a discrete number of typical force fields could be found regardless of where in the intermediate grey matter the stimulation was applied. Each of these force fields was considered a distinct movement primitive.

Further studies indicated that by stimulating multiple sites in the spinal cord new force fields could be generated which were a linear superposition of the fields generated by stimulating each site individually (Mussa-Ivaldi et al., 1994; Tresch and Bizzi, 1999; Lemay et al., 2001). This supported the idea that all movements might be the result of combinations of these basic spinally organized building blocks. The movement primitive theory has also been investigated in human studies where principle component analysis has resulted in the isolation of 5 activation patterns that account for the muscle activity seen during human locomotion (Patla, 1985; Ivanenko et al., 2004).

Although there is evidence to support the movement primitive theory, some researchers question the validity of the assumption that these results are due to a building block organization of neural networks. In one study the hindlimb muscles in cats were peripherally stimulated and the limb was allowed to move freely to its "equilibrium point" (Aoyagi et al., 2004). Combinations of muscle activations resulted in movement vectors that correspond closely to those seen through the stimulation of spinal movement primitives, indicating that these primitives may be a result of muscle properties rather than immutable spinal networks.

1.1.3 Equilibrium Point Control

For any given combination of muscle activation levels the limb will reach a corresponding equilibrium point, or stable position in space, where the sum of all forces acting on the joints is zero. This observation has led to the development of the equilibrium point control theory (Feldman et al., 1998). The theory states that the brain controls movements by planning the "virtual trajectory" consisting of a gradual shift of the equilibrium point from an initial position to the target endpoint (Polit and Bizzi, 1978). Every point along this virtual path will have a corresponding combination of muscle activations resulting in a net torque of zero at each joint (Hogan, 1985). For any point in time the actual limb position will be lagging behind the movement of the virtual trajectory and therefore joint torques will always be present that will act toward moving the limb to the equilibrium point. The actual limb movement will be influenced by external factors such as gravity and other perturbations so increasing limb stiffness through co-activation of antagonistic muscles will result in more accurate tracking. This theory has been used to model single joint movements (Burgess et al., 1995) but cannot easily explain complex movements involving multiple joints. The planning of the virtual trajectory also becomes difficult in the presence of an external field because a complicated virtual trajectory is required in order to generate a movement along a straight path (Gomi and Kawato, 1997).

1.1.4 Feedback Control

The specific contribution of sensory information to the control of movement has been a long debated topic. Sechenov (1865) even suggested that all actions are a result of reflexes arising from sensory stimuli and that voluntary will does not exist. In the late nineteenth century, John Hughlings Jackson introduced the idea that motor activity could be classified over a range from most to least automatic behaviours (Hughlings Jackson, 1884). This classification corresponds with the idea that there is a hierarchical organization of the nervous system where automatic (reflexive) responses are mediated by lower centers such as the brainstem and spinal cord and voluntary movements are controlled by higher centers in the brain. The advantage of such a hierarchical organization is that it releases cognitive centers from the control of background tasks (such as balance and core stability) that are involved in all movements. This means that a volitional task like reaching can be controlled by cortical regions while brainstem and spinal cord circuitry mediate vestibular and stretch reflexes that ensure that an upright posture is maintained throughout the movement.

The question then becomes: where does stepping fit into this hierarchical organization? In the early 1900s Sir Charles Sherrington suggested that stepping movements are generated by a chain of spinal cord mediated reflex responses to afferent feedback (Sherrington, 1910). Sherrington observed that the phase transition from stance to swing depended on the amount of extension at the hip. More recent experiments conducted with spinalized cats stepping on a moving treadmill belt indicated that phase transition was prevented if the leg was blocked from reaching full extension at the end of the stance phase (Grillner and Rossignol, 1978; Pearson et al., 1992). These observations, along with those made in cockroach, lobster and stick insect studies (Pearson and Duysens, 1976; Bassler, 1993; Clarac, 1982), led to the development of a set of *if-then* rules governing the transition from stance to swing in normal walking (Prochazka, 1996). The *if-then* rule listed below uses the state of the ground reaction forces for each leg as well as the hip angle for the ipsilateral leg in order to determine if a stance-to-swing phase transition should occur.

IF	the ipsilateral hip is extended
AND	the ipsilateral limb is unloaded
AND	the contralateral limb is loaded
THEN	initiate swing in the ipsilateral limb
ELSE	prolong the stance phase

The key feature of this set of rules is that it prevents the occurrence of double swing where both limbs are simultaneously unloaded. The force criterion ensures that one leg is always loaded throughout the gait cycle. McVea et al. (2005) also proposed that a threshold value of hip flexion regulated the swing-to-stance phase transition leading to the development of the following *if-then* rule:

IF	the ipsilateral limb is flexed
THEN	initiate stance in the ipsilateral limb

Special rules may also exist to provide reactive responses to perturbations in the gait cycle. For example, the stumble reaction can be described by a simple set of *if-then* statements.

IF	the leg is in the swing phase
AND	an abrupt disruption occurs in the hip angle
THEN	initiate vertical flexion response

The feedback information required to follow these rules is provided by spindle afferents sensing muscle stretch and Golgi tendon organs sensing muscle force. Tendon organs have an additional role in providing positive force feedback during stance which results in a prolongation of the phase duration and reinforcement of extensor activity while the leg is loaded (Whelan et al., 1995; Pearson et al., 1998). The role of proprioceptive feedback becomes apparent in individuals with large fibre sensory neuropathies. These people require intense concentration and visual feedback to walk and perform other directed movements.

Alternatively, voluntary movements may be initiated by the γ-motoneuron system (Marsden et al., 1972; Eldred et al., 1953). All movements would then be a form of continuous stretch reflex response resulting from the activation of γ-motoneurons and corresponding spindle afferent firing. However, this theory is not consistent with the fact that extrafusal muscle activation leads, rather than lags, spindle discharges (Vallbo, 1970).

1.1.5 Feed-forward Control

In contrast to feedback control where sensory information plays a critical role in generating movements, a feed-forward control system can generate movements using predetermined muscle activation patterns. Feed-forward models are based on the ability of the nervous system to predict the expected outcome of a command, and provide an estimate of the current state of the system even in the presence of noisy feedback signals or delays (Kuo, 2002; Wolpert and Miall, 1996). In this control scheme, command signals are generated within the computational centers that selectively activate the motor units required to produce the desired movements. There are various theories regarding the algorithm used to determine the appropriate muscle activation patterns for a given movement.

One theory is that the brain is constantly solving a complex problem of inverse kinematics and dynamics where the desired joint torques and trajectories are used to back compute the required muscle actions (Hollerbach and Flash, 1982). However, the biomechanical system has many degrees of freedom. Generating continuous solutions to such a complicated problem would use a great deal of the computational power of the higher centers, even to perform basic tasks.

Another feed-forward theory uses a neural look-up table to store joint torques for all possible limb configurations, velocities and accelerations (Raibert, 1978). This removes the need to solve the inverse kinematics and dynamics problem by allowing the controller to look up and access the answer quickly. However, a simple limb model with two joint coordinates would require two tables with 100 entries each, and a more complete limb with seven-joint coordinates would require tables with 10^7 entries to represent a full set of inverse solutions for the system (Raibert and Horn, 1978). This large memory requirement limits the use of such a theory when faced with explaining more complex movements involving additional joints.

Wolpert and Miall (1996) proposed instead that the nervous system can construct an internal model of the kinematic and dynamic properties of the body as it interacts with the environment. This allows the controller to incorporate external fields into the initial determination of muscle activation. However, the formulation of an internal model requires information about the success of its output. For example, from experience of repetitive movements in a dynamic field. Once the field is removed the adaptation of the system is evident by the appearance of after-effects in the form of exaggerated movements in a direction opposing the formerly applied field (Shadmehr and Mussa-Ivaldi, 1994). The internal model can be used to generate a set of predicted afferent signals that are then compared to the actual afferent information received during task execution. In this way error correction can be initiated if the predicted and actual feedback signals differ.

Pure feed-forward control is only effective if the controller can precisely determine the muscle activation that corresponds to a planned trajectory. This is not always possible during tasks performed in environments with changing conditions (such as within a train undergoing accelerations and decelerations). A flow of information describing the current state of the limb provides the controller with a means to generate appropriate control signals and maintain the desired motor output.

1.2 A General Overview of Rehabilitation after SCI

Multiple factors must be taken into consideration when designing a treatment strategy for a person with SCI. These factors include the time progression of injury (acute or chronic), the spinal cord segment affected (cervical, thoracic, lumbar or sacral) and the severity of the injury (incomplete or complete). The treatment selected can have a critical impact on the functional recovery of the individual, particularly during the acute phase of SCI.

1.2.1 Neuroprotection

Spinal cord injury is characterized by an interruption in the connections between the cortical control centers generating voluntary commands and the muscles generating the motor output. This interruption is the summed effect of the initial trauma as well as a chain of "secondary injury" processes initiated by the body's physiological response to the injury. The initial injury can be the result of an impact (with or without persistent compression), the application of sheering or stretching forces or a laceration/transection of the cord (Dumont et al., 2001). Immediate traction of the injury site can prevent further mechanical trauma to the spinal tissue. The trauma tends to affect predominantly the grey matter of the spinal cord due to its high vascularization, whereas the damage inflicted to the white matter is progressive. The secondary injury processes following SCI may not stabilize until more than 72 hours after the initial injury. For this reason neuroprotective therapies are critical during the acute phase of SCI. Some studies suggest that a dose of methylprednisolone (a corticosteroid) within 8 hours of the initial injury reduces the inflammatory response, thereby acting as a neuroprotector and improving the neurological outcome (McDonald and Sadowsky, 2002). However, its benefits have been widely debated (Geisler et al., 2002; McDonald and Sadowsky, 2002). Surgical exposure of the spinal cord can also be performed in the acute phase of SCI in cases where there is persistent compression of the cord or bone fragments within the lesion site.

1.2.2 Regeneration

The optimal treatment for SCI would be to repair the damage to the spinal cord and restore functional descending and ascending connections between the brain and the rest of the body. Although it is possible to regenerate peripheral nervous tissue, the central nervous system (CNS) does not provide an environment conducive to axon growth. Factors such as the existence of mechanical barriers (i.e., scar), lack of neurotrophic support and the presence of inhibitory molecules hinder regeneration in the CNS.

Although many efforts have been made to facilitate regeneration within the central nervous system, no consistently effective method has been found. Techniques have included the use of peripheral nerve grafts (David and Aguayo, 1981), Schwann cells (Paino and Bunge, 1991), olfactory ensheathing glial cells (Ramon-Cueto et al., 1998) or stem cells (Stokes and Reier, 1992; McDonald et al., 1999) to fill the lesion site and promote axon growth. Other studies have attempted to improve the growth environment by applying neurotrophic factors such as BDNF and NT-3 (Kobayashi et al., 1997; Schnell et al., 1994) or by neutralizing major inhibitory molecules (such as Nogo-A) (Bregman et al., 1995). Many studies report axonal growth and/or functional recovery in rats but the evaluation techniques are not always appropriate or extensive enough to demonstrate regeneration conclusively (Fouad and Pearson, 2004). Human trials using regeneration techniques in the CNS show mixed results and are not yet considered to be safe (Dobkin et al., 2006).

1.2.3 Training Paradigms and Pharmacological Treatments

People with SCI can benefit from active rehabilitation techniques such as partial body weight support treadmill training (see Harkema (2001) for a review). This technique works to improve balance, weight bearing, and step coordination while progressively removing body support over the duration of the training regime (Wernig and Muller, 1992). Treadmill training is particularly beneficial for people with incomplete injuries where the effects can persist for months or years after completion of the training (Wirz et al., 2001). Attempts to further improve the functional outcome of treadmill training through the administration of phamacological agents (such as the α-2 adrenergic agonist, clonidine) have shown only moderate success (Remy-Neris et al., 1999; Barbeau and Norman, 2003; Dietz et al., 1995).

1.2.4 Functional Electrical Stimulation

Spinal cord injury affects not only the descending tracts carrying control signals, but also the cell bodies of motoneurons within the site of the injury. In order to be a candidate for FES treatment, an individual must have intact motoneurons innervating the muscles involved in the desired function. This requirement is due to the fact that nerve stimulation can activate motor units within muscles at much lower stimulation levels than that required to activate muscle tissue directly. A general introduction to FES can be found in section 2.1

Regular application of FES reduces the conversion of muscle fibres from type I (fatigue resistant) to type II (fast fatigable) that occurs through disuse after SCI (Burnham et al., 1997). People who demonstrate improved muscle strength during two months of FES conditioning exercises are possible candidates for long-term FES treatment (Kralj and Bajd, 2000). There currently exist a wide variety of neuroprosthetic devices that implement FES to restore upper (Prochazka et al., 1997; Peckham et al., 2002) and lower limb function (Weber et al., 2005; Graupe and Kohn, 1998; Popovic et al., 2001) after SCI. A detailed discussion of FES systems for standing and stepping as well as the advantages and limitations of using these systems will be provided in section 2.2.

There has been success using FES in combination with other therapies in order to achieve functional outcomes superior to either method used independently. For example, the addition of FES to a standard treadmill training program improves the outcome of training, possibly by strengthening the connections made by residual descending input (Field-Fote, 2001; Ladouceur and Barbeau, 2000). Functional electrical stimulation has also been used in conjunction with special orthotic braces in order to provide functional standing and stepping (see section 2.2).

1.3 Dissertation Summary and Overview

Developing a system for restoring mobility is a multifaceted task including the interrelated design of a suitable controller and the selection of an appropriate means of generating limb movement. This dissertation addresses these two main components of the system 1) by evaluating the use of different modes of FES as a means of generating functional movements in paralyzed limbs and 2) by designing feedforward- and feedback-based controllers for generating movements appropriate for standing and stepping. An overview is provided in section 2.2 of some of the current systems available for this purpose.

The approach taken in the work presented here was to base the design of the FES system on normal physiology. This was achieved through studies that were designed to evaluate the use of centrally applied FES and control strategies based on some of the physiological principles described previously (section 1.1). A cat model of spinal cord injury was used throughout these studies.

Functional electrical stimulation can activate the nervous system through peripheral or central administration. Peripheral stimulation of nerve and/or muscle can be achieved by using surface or implanted electrodes placed close to the intended target. Existing FES systems commonly use peripheral stimulation techniques that result in non-physiological muscle activation profiles and force recruitment. Some of these methods are discussed briefly in section 2.1. Muscles can also be activated centrally by activating the corresponding motoneurons within the spinal cord in a more physiological manner through a technique called intraspinal microstimulation (ISMS). This technique is described in detail in section 2.3. Briefly, ISMS involves applying stimulation through fine microwires placed within the grey matter of the lumbosacral enlargement where the motoneuronal pools for the muscles of the lower limbs reside. At this point ISMS remains an experimental technique. Several aspects need to be investigated before ISMS can be applied to humans in intra-operative and clinical trials. The studies presented in this dissertation represent a significant step towards this goal. Previously the efficacy of ISMS had only been evaluated in acute experiments (with or without SCI) (Mushahwar and Horch, 1998; Saigal et al., 2004) and chronically in animals with intact spinal cords (Mushahwar et al., 2000). The results of the preliminary chronic stability study presented in section 2.3.2 indicated that ISMS responses remain stable after SCI, suggesting that it is a valid technique to pursue for restoring standing and stepping.

The first hurdle in restoring mobility is maintenance of an upright posture. For this reason a study was conducted to evaluate the ability of ISMS to achieve prolonged load-bearing standing (chapter 3). Intraspinal microstimulation was compared to intramuscular (IM) stimulation, where current was applied peripherally through pairs of wires implanted into the muscle bulk, activating nerve branches near their termination. Open- and closed-loop controllers were also tested for both stimulation paradigms, and evaluated based on the duration and stability of stepping achieved, as well as the current required to maintain an appropriate standing posture.

In the standing study (described above), continuous trains of stimulation pulses applied through ISMS wires at amplitudes greater than motor threshold were shown to generate movements appropriate for standing. However, we also found that sub-threshold level stimulation applied through electrodes placed in more ventromedial regions of the grey matter could evoke alternating movements of the hindlimbs in cats with SCI (chapter 4). Tonic application of ISMS may activate directly or indirectly the locomotor CPG neural circuitry within the spinal cord of the cat. However the in-place stepping achieved using this tonic stimulation protocol was characterized by low levels of weight-bearing and propulsive forces.

Finally, *load-bearing overground locomotion* was generated through the use of physiologically-based control algorithms in conjunction with IM stimulation. In addition to the role of the CPG, a set of *if-then* rules may govern how sensory feedback mediates gait phase transitions (see section 1.1.4). Two control strategies (CPG and sensory rules) were implemented using FES in order to generate overground locomotion (chapter 5).

Chapter 6 provides a general discussion of the results obtained from the studies and the progress made towards the understanding of the physiological principles governing mobility. I evaluate the demonstrated capability of the ISMS and IM stimulation techniques to achieve the functional goals required for this system. Also, I discuss some future work that is required to bring the ISMS technique to clinical realization.

The goal of this dissertation was to develop FES techniques and control paradigms for restoring standing and stepping after SCI by applying knowledge of the physiological system. Physiological control principles (discussed in section 1.1) and ISMS were applied to tap into some of the organizational properties of the nervous system. In the process of doing this we also explored the structure of the locomotor CPG in the spinal cord and inferred the role of sensory- and intrinsically-timed phase transitions during gait.

1.4 Bibliography

Aoyagi, Y., V. Mushahwar, R. B. Stein, and A. Prochazka (2004). The role of neuromuscular properties in determining the end-point of a movement. *IEEE Transactions on Neural Systems & Rehabilitation Engineering. 12*(1), 12–23. [cited at p. 5]

Barbeau, H. and K. E. Norman (2003). The effect of noradrenergic drugs on the recovery of walking after spinal cord injury. *Spinal Cord 41*(3), 137–43. [cited at p. 11]

Bassler, U. (1993). The femur-tibia control system of stick insects–a model system for the study of the neural basis of joint control. *Brain Research Reviews 18*(2), 207–26. [cited at p. 7]

Bregman, B. S., E. Kunkel-Bagden, L. Schnell, H. N. Dai, D. Gao, and M. E. Schwab (1995). Recovery from spinal cord injury mediated by antibodies to neurite growth inhibitors. *Nature 378*(6556), 498–501. [cited at p. 11]

Brown, T. (1911). The intrinsic factors in the act of progression in the mammal. *Proceedings of the Royal Society of London Series B 84*(572), 309–18. [cited at p. 3]

Burgess, P. R., T. A. Cooper, G. L. Gottlieb, and M. L. Latash (1995). The sense of effort and two models of single-joint motor control. *Somatosensory & Motor Research. 12*(3-4), 343–58. [cited at p. 6]

Burnham, R., T. Martin, R. Stein, G. Bell, I. MacLean, and R. Steadward (1997). Skeletal muscle fibre type transformation following spinal cord injury. *Spinal Cord 35*(2), 86–91. [cited at p. 12]

Calancie, B., B. Needham-Shropshire, P. Jacobs, K. Willer, G. Zych, and B. A. Green (1994). Involuntary stepping after chronic spinal cord injury. evidence for a central rhythm generator for locomotion in man. *Brain 117 (Pt 5)*, 1143–59. [cited at p. 4]

Center, N. S. S. (2005). Spinal cord injury: facts and figures at a glance. Technical report, National Spinal Cord Injury Statistical Center. [cited at p. 1]

Chau, C., N. Giroux, H. Barbeau, L. Jordan, and S. Rossignol (2002). Effects of intrathecal glutamatergic drugs on locomotion i. nmda in short-term spinal cats. *Journal of Neurophysiology 88*(6), 3032–45. [cited at p. 3]

Clarac, F. (1982). Decapod crustacean leg coordination during walking. In C. Herreid and C. Fourtner (Eds.), *Locomotion and Energetics in Anthropods*, pp. 31–71. New York: Plenum. [cited at p. 7]

Cohen, A. H. and P. Wallen (1980). The neuronal correlate of locomotion in fish. "fictive swimming" induced in an in vitro preparation of the lamprey spinal cord. *Experimental Brain Research. 41*(1), 11–8. [cited at p. 4]

David, S. and A. J. Aguayo (1981). Axonal elongation into peripheral nervous system "bridges" after central nervous system injury in adult rats. *Science 214*(4523), 931–3. [cited at p. 11]

Dietz, V., G. Colombo, L. Jensen, and L. Baumgartner (1995). Locomotor capacity of spinal cord in paraplegic patients. *Annals of Neurology 37*(5), 574–82. [cited at p. 4, 11]

Dobkin, B. H., A. Curt, and J. Guest (2006). Cellular transplants in china: observational study from the largest human experiment in chronic spinal cord injury. *Neurorehabilitation and Neural Repair 20*(1), 5–13. [cited at p. 11]

Douglas, J. R., B. R. Noga, X. Dai, and L. M. Jordan (1993). The effects of intrathecal administration of excitatory amino acid agonists and antagonists on the initiation of locomotion in the adult cat. *Journal of Neuroscience 13*(3), 990–1000. [cited at p. 3]

Dumont, R. J., D. O. Okonkwo, S. Verma, R. J. Hurlbert, P. T. Boulos, D. B. Ellegala, and A. S. Dumont (2001). Acute spinal cord injury, part i: pathophysiologic mechanisms. *Clinical Neuropharmacology 24*(5), 254–64. [cited at p. 10]

Eldred, E., R. Granit, and P. A. Merton (1953). Supraspinal control of the muscle spindles and its significance. *Journal of Physiology 122*(3), 498–523. [cited at p. 8]

Fedirchuk, B., J. Nielsen, N. Petersen, and H. Hultborn (1998). Pharmacologically evoked fictive motor patterns in the acutely spinalized marmoset monkey (callithrix jacchus). *Experimental Brain Research 122*(3), 351–61. [cited at p. 4]

Feldman, A. G., D. J. Ostry, M. F. Levin, P. L. Gribble, and A. B. Mitnitski (1998). Recent tests of the equilibrium-point hypothesis (lambda model). *Motor Control. 2*(3), 189–205. [cited at p. 5]

Feraboli-Lohnherr, D., J. Y. Barthe, and D. Orsal (1999). Serotonin-induced activation of the network for locomotion in adult spinal rats. *Journal of Neuroscience Research 55*(1), 87–98. [cited at p. 3]

Field-Fote, E. C. (2001). Combined use of body weight support, functional electric stimulation, and treadmill training to improve walking ability in individuals with chronic incomplete spinal cord injury. *Archives of Physical Medicine & Rehabilitation. 82*(6), 818–24. [cited at p. 12]

Forssberg, H. and S. Grillner (1973). The locomotion of the acute spinal cat injected with clonidine i.v. *Brain Research 50*(1), 184–6. [cited at p. 3]

Fouad, K. and K. Pearson (2004). Restoring walking after spinal cord injury. *Progress in Neurobiology 73*(2), 107–126. [cited at p. 11]

Geisler, F. H., W. P. Coleman, E. Benzel, T. Ducker, and R. J. Hurlbert (2002). Spinal cord injury. *Lancet. 360*(9348), 1883–1884. [cited at p. 10]

Gelfand, I., G. N. Orlovsky, and M. L. Shik (1988). Locomotion and scratching in tetrapods. In A. H. Cohen, S. Rossignol, and S. Grillner (Eds.), *Neural Control of Rythmic Movements in Vertebrates*, pp. 167–99. New York: Wiley. [cited at p. 3]

Gerasimenko, Y. P., V. D. Avelev, O. A. Nikitin, and I. A. Lavrov (2003). Initiation of locomotor activity in spinal cats by epidural stimulation of the spinal cord. *Neuroscience & Behavioral Physiology. 33*(3), 247–54. [cited at p. 3]

Giszter, S. F., F. A. Mussa-Ivaldi, and E. Bizzi (1993). Convergent force fields organized in the frog's spinal cord. *Journal of Neuroscience. 13*(2), 467–91. [cited at p. 4]

Gomi, H. and M. Kawato (1997). Human arm stiffness and equilibrium-point trajectory during multi-joint movement. *Biological Cybernetics. 76*(3), 163–71. [cited at p. 6]

Graupe, D. and K. H. Kohn (1998). Functional neuromuscular stimulator for short-distance ambulation by certain thoracic-level spinal-cord-injured paraplegics. *Surgical Neurology. 50*(3), 202–7. [cited at p. 12]

Grillner, S. (1981). Control of locomotion in bipeds, tetrapods and fish. In J. Brookhart and V. Mountcastle (Eds.), *Handbook of Physiology*, Volume 2 of *The Nervous System*, pp. 1179–1236. Baltimore: Waverly Press. [cited at p. 3]

Grillner, S. and S. Rossignol (1978). On the initiation of the swing phase of locomotion in chronic spinal cats. *Brain Research. 146*(2), 269–77. [cited at p. 4, 6]

Gurfinkel, V. S., Y. S. Levik, O. V. Kazennikov, and V. A. Selionov (1998). Locomotor-like movements evoked by leg muscle vibration in humans. *European Journal of Neuroscience. 10*(5), 1608–12. [cited at p. 3]

Harkema, S. J. (2001). Neural plasticity after human spinal cord injury: application of locomotor training to the rehabilitation of walking. *Neuroscientist 7*(5), 455–68. [cited at p. 11]

Hill, J. (2000). *Footprints in the Snow.* London: Macmillan. [cited at p. 1]

Hogan, N. (1985). The mechanics of multi-joint posture and movement control. *Biological Cybernetics 52*(5), 315–31. [cited at p. 5]

Hollerbach, M. J. and T. Flash (1982). Dynamic interactions between limb segments during planar arm movement. *Biol Cybern 44*(1), 67–77. [cited at p. 8]

Hughlings Jackson, J. (1884). On the evolution and dissolution of the nervous system. In *Croonian Lectures 3, 4, and 5 to the Royal Society of London*, Lancet 1:555, pp. 649, 739. [cited at p. 6]

Ivanenko, Y., R. Poppele, and F. Lacquaniti (2004). Five basic muscle activation patterns account for muscle activity during human locomotion. *Journal of Physiology 556(1)*, 267–82. [cited at p. 5]

Jankowska, E., M. G. Jukes, S. Lund, and A. Lundberg (1967a). The effect of dopa on the spinal cord. 5. reciprocal organization of pathways transmitting excitatory action to alpha motoneurones of flexors and extensors. *Acta Physiologica Scandinavica 70*(3), 369–88. [cited at p. 3]

Jankowska, E., M. G. Jukes, S. Lund, and A. Lundberg (1967b). The effect of dopa on the spinal cord. 6. half-centre organization of interneurones transmitting effects from the flexor reflex afferents. *Acta Physiologica Scandinavica 70*(3), 389–402. [cited at p. 3]

Kilgore, K. L., P. H. Peckham, and M. Keith (2001). Advances in upper extremity functional restoration employing neuroprostheses. In J. Chapin and K. Moxon (Eds.), *Neural Prostheses for Restoration of Sensory and Motor Function*, Methods & New Frontiers in Neuroscience Series, pp. 45–74. Washington DC: CRC Press. [cited at p. 1]

Kjaerulff, O. and O. Kiehn (1996). Distribution of networks generating and coordinating locomotor activity in the neonatal rat spinal cord in vitro: a lesion study. *Journal of Neuroscience. 16*(18), 5777–94. [cited at p. 4]

Kobayashi, N. R., D. P. Fan, K. M. Giehl, A. M. Bedard, S. J. Wiegand, and W. Tetzlaff (1997). Bdnf and nt-4/5 prevent atrophy of rat rubrospinal neurons after cervical axotomy, stimulate gap-43 and talpha1-tubulin mrna expression, and promote axonal regeneration. *Journal of Neuroscience 17*(24), 9583–95. [cited at p. 11]

Kralj, A. and T. Bajd (2000). *Functional Electrical Stimulation: Standing and Walking after Spinal Cord Injury.* Boca Raton, Florida: CRC Press, Inc. [cited at p. 12]

Kuo, A. D. (2002). The relative roles of feedforward and feedback in the control of rhythmic movements. *Motor Control 6*(2), 129–45. [cited at p. 8]

Ladouceur, M. and H. Barbeau (2000). Functional electrical stimulation-assisted walking for persons with incomplete spinal injuries: changes in the kinematics and physiological cost of overground walking. *Scandinavian Journal of Rehabilitation Medicine 32*(2), 72–9. [cited at p. 12]

Lafreniere-Roula, M. and D. A. McCrea (2005). Deletions of rhythmic motoneuron activity during fictive locomotion and scratch provide clues to the organization of the mammalian central pattern generator10.1152/jn.00216.2005. *Journal of Neurophysiology 94*(2), 1120–1132. [cited at p. 3]

Lamb, T. and J. F. Yang (2000). Could different directions of infant stepping be controlled by the same locomotor central pattern generator? *Journal of Neurophysiology 83*(5), 2814–24. [cited at p. 4]

Lemay, M. A., J. E. Galagan, N. Hogan, and E. Bizzi (2001). Modulation and vectorial summation of the spinalized frog's hindlimb end-point force produced by intraspinal electrical stimulation of the cord. *IEEE Transactions on Neural Systems & Rehabilitation Engineering. 9*(1), 12–23. [cited at p. 4, 5]

Lemay, M. A. and W. M. Grill (2004). Modularity of motor output evoked by intraspinal microstimulation in cats. *Journal of Neurophysiology. 91*(1), 502–14. [cited at p. 4]

Magnuson, D. S. and T. C. Trinder (1997). Locomotor rhythm evoked by ventrolateral funiculus stimulation in the neonatal rat spinal cord in vitro. *Journal of Neurophysiology. 77*(1), 200–206. [cited at p. 3]

Marsden, C. D., P. A. Merton, and H. B. Morton (1972). Servo action in human voluntary movement. *Nature 238*(5360), 140–3. [cited at p. 8]

McDonald, J. W., X. Z. Liu, Y. Qu, S. Liu, S. K. Mickey, D. Turetsky, D. I. Gottlieb, and D. W. Choi (1999). Transplanted embryonic stem cells survive, differentiate and promote recovery in injured rat spinal cord. *Nature Medicine 5*(12), 1410–2. [cited at p. 11]

McDonald, J. W. and C. Sadowsky (2002). Spinal-cord injury. *Lancet. 359*(9304), 417–25. [cited at p. 10]

McVea, D. A., J. M. Donelan, A. Tachibana, and K. G. Pearson (2005). A role for hip position in initiating the swing-to-stance transition in walking cats. *Journal of Neurophysiology 94*(5), 3497–3508. [cited at p. 7]

Mushahwar, V. K., D. F. Collins, and A. Prochazka (2000). Spinal cord microstimulation generates functional limb movements in chronically implanted cats. *Experimental Neurology. 163*(2), 422–9. [cited at p. 13]

Mushahwar, V. K. and K. W. Horch (1998). Selective activation and graded recruitment of functional muscle groups through spinal cord stimulation. *Annals of the New York Academy of Sciences 860*, 531–5. [cited at p. 13]

Mussa-Ivaldi, F. A., S. F. Giszter, and E. Bizzi (1994). Linear combinations of primitives in vertebrate motor control. *Proceedings of the National Academy of Sciences of the United States of America. 91*(16), 7534–8. [cited at p. 4, 5]

Orlovsky, G., T. Deliagina, and S. Grillner (1999). Walking and running in humans. In *Neuronal Control of Locomotion, Form Mollusc to Man.* Stockholm, Sweden: Oxford University Press. [cited at p. 3]

Paino, C. L. and M. B. Bunge (1991). Induction of axon growth into schwann cell implants grafted into lesioned adult rat spinal cord. *Experimental Neurology 114*(2), 254–7. [cited at p. 11]

Patla, A. E. (1985). Some characteristics of emg patterns during locomotion: implications for the locomotor control process. *J Mot Behav 17*(4), 443–61. 0022-2895 (Print)Journal Article. [cited at p. 5]

Pearson, K. G. and J. Duysens (1976). Function of segmental reflexes in control of stepping in cockroaches and cats. In R. Herman, S. Grillner, P. Stein, and D. G. Stuart (Eds.), *Neural Control of Locomotion*, pp. 519–538. New York: Plenum. [cited at p. 7]

Pearson, K. G., J. E. Misiaszek, and K. Fouad (1998). Enhancement and resetting of locomotor activity by muscle afferents. *Annals of the New York Academy of Sciences. 860*, 203–15. [cited at p. 7]

Pearson, K. G., J. M. Ramirez, and W. Jiang (1992). Entrainment of the locomotor rhythm by group ib afferents from ankle extensor muscles in spinal cats. *Experimental Brain Research 90*(3), 557–66. [cited at p. 6]

Peckham, P. H., K. L. Kilgore, M. W. Keith, A. M. Bryden, N. Bhadra, and F. W. Montague (2002). An advanced neuroprosthesis for restoration of hand and upper arm control using an implantable controller. *Journal of Hand Surgery [American] 27*(2), 265–76. [cited at p. 12]

Polit, A. and E. Bizzi (1978). Processes controlling arm movements in monkeys. *Science. 201*(4362), 1235–7. [cited at p. 5]

Popovic, M. R., A. Curt, T. Keller, and V. Dietz (2001). Functional electrical stimulation for grasping and walking: indications and limitations. *Spinal Cord. 39*(8), 403–12. [cited at p. 12]

Prochazka, A. (1996). Proprioceptive feedback and movement regulation. In L. Rowell and J. Sheperd (Eds.), *Exercise Regulation and Integration of Multiple Systems: Neural Control of Movement Section 12*, pp. 89–127. New York: American Physiological Society. [cited at p. 7]

Prochazka, A., M. Gauthier, M. Wieler, and Z. Kenwell (1997). The bionic glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. *Archives of Physical Medicine and Rehabilitation 78*(6), 608–14. [cited at p. 12]

Raibert, M. and B. Horn (1978). Manipulator control using the configuration space method. *The Industrial Robot 5(2)*(2), 69–73. [cited at p. 9]

Raibert, M. H. (1978). A model for sensorimotor control and learning. *Biological Cybernetics 29*(1), 29–36. [cited at p. 8]

Ramon-Cueto, A., G. W. Plant, J. Avila, and M. B. Bunge (1998). Long-distance axonal regeneration in the transected adult rat spinal cord is promoted by olfactory ensheathing glia transplants. *Journal of Neuroscience 18*(10), 3803–15. [cited at p. 11]

Remy-Neris, O., H. Barbeau, O. Daniel, F. Boiteau, and B. Bussel (1999). Effects of intrathecal clonidine injection on spinal reflexes and human locomotion in incomplete paraplegic subjects. *Experimental Brain Research 129*(3), 433–40. [cited at p. 11]

Saigal, R., C. Renzi, and V. Mushahwar (2004). Intraspinal microstimulation generates functional movements after spinal-cord injury. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 12*(4), 430–440. [cited at p. 13]

Saltiel, P., K. Wyler-Duda, A. D'Avella, M. C. Tresch, and E. Bizzi (2001). Muscle synergies encoded within the spinal cord: evidence from focal intraspinal nmda iontophoresis in the frog. *Journal of Neurophysiology 85*(2), 605–19. [cited at p. 4]

Schnell, L., R. Schneider, R. Kolbeck, Y. A. Barde, and M. E. Schwab (1994). Neurotrophin-3 enhances sprouting of corticospinal tract during development and after adult spinal cord lesion. *Nature 367*(6459), 170–3. [cited at p. 11]

Sechenov, I. (1865). *Refleksy golovonogo mazga.* St. Petersburg. English translation: Gibbons, G (ed) (1965) Reflexes of the Brain, MIT Press, Cambridge. [cited at p. 6]

Shadmehr, R. and F. A. Mussa-Ivaldi (1994). Adaptive representation of dynamics during learning of a motor task. *Journal of Neuroscience. 14*(5 Pt 2), 3208–24. [cited at p. 9]

Sherrington, C. (1910). Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *Journal of Physiology. 40*, 28–121. [cited at p. 6]

Shik, M. L. and G. N. Orlovsky (1976). Neurophysiology of locomotor automatism. *Physiological Reviews 56*(3), 465–501. [cited at p. 3]

Stokes, B. T. and P. J. Reier (1992). Fetal grafts alter chronic behavioral outcome after contusion damage to the adult rat spinal cord. *Experimental Neurology 116*(1), 1–12. [cited at p. 11]

Tresch, M. C. and E. Bizzi (1999). Responses to spinal microstimulation in the chronically spinalized rat and their relationship to spinal systems activated by low threshold cutaneous stimulation. *Experimental Brain Research. 129*(3), 401–16. [cited at p. 4, 5]

Vallbo, A. B. (1970). Discharge patterns in human muscle spindle afferents during isometric voluntary contractions. *Acta Physiologica Scandinavica 80*(4), 552–66. [cited at p. 8]

Weber, D. J., R. B. Stein, K. M. Chan, G. Loeb, F. Richmond, R. Rolf, K. James, and S. L. Chong (2005). Bionic walkaide for correcting foot drop. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 13*(2), 242–6. [cited at p. 12]

Wernig, A. and S. Muller (1992). Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. *Paraplegia 30*(4), 229–38. [cited at p. 11]

Whelan, P. J., G. Hiebert, and K. G. Pearson (1995). Stimulation of the group i extensor afferents prolongs the stance phase in walking cats. *Experimental Brain Research 103*(1), 20–30. [cited at p. 7]

Wirz, M., G. Colombo, and V. Dietz (2001). Long term effects of locomotor training in spinal humans. *Journal of Neurology, Neurosurgery and Psychiatry 71*(1), 93–6. [cited at p. 11]

Wolpert, D. M. and R. C. Miall (1996). Forward models for physiological motor control. *Neural Networks 9*(8), 1265–1279. [cited at p. 8, 9]

Chapter 2

Tapping into the Spinal Cord for Restoring Function After Spinal Cord Injury *

"Our way is not soft grass, it's a mountain path with lots of rocks.

But it goes upward, forward, toward the sun."

- Ruth Westheimer

Living organisms are intricate systems having thousands of ongoing processes interacting to maintain even the most basic life functions (i.e., energy production and protein synthesis). As the behavioral requirements of the organism increase, the complexity of the nervous system must also increase in order to initiate and coordinate a large variety of movements. For example, the mollusc Clione, which has been studied extensively, has approximately 5,000 neurons organized in 5 pairs of central ganglia. All the functional requirements of the Clione can be regulated by this small nervous system and electrical stimulation applied to specific groups of neurons can evoke stereotypical responses. Although humans possess a much larger repertoire of movements and therefore have significantly more complex nervous systems, levels of functional stereotypical organization remain within the central (brain and spinal cord) and peripheral nervous systems. Knowledge of the neural mechanisms underlying normal movements is an invaluable asset when designing a neuroprosthetic device

*A version of this chapter has been submitted for publication. It is reproduced here with permission. *Neural Engineering: Research, Industry and the Clinical Perspective*, editied by DiLorenzio D. and Bronzino D., CRC Press, 2007 because it enables one to tap into the neural circuitry residing at different levels in order to influence downstream events.

After spinal cord injury the direct connection between the brain and periphery is severed, preventing voluntary control of the muscles below the level of the injury. However, the motoneurons below the lesion often remain viable enabling muscle contractions to be evoked through functional electrical stimulation (FES) applied to the intact nerves. Functional electrical stimulation has achieved a broad range of applications in the field of neural prostheses, where it is used as an interface with the nervous system in order to restore function to muscles and organs after disease or injury.

In this chapter we will provide a brief introduction to FES and existing systems for restoring standing and stepping after spinal cord injury. We will then focus on a technique called intraspinal microstimulation (ISMS) in which electrical stimulation is applied to the spinal cord below the level of the injury in order to activate the neural circuitry normally involved in the control of the lower limbs. By tapping into the nervous system at the level of the spinal cord, we are able to generate movements with some features that are consistent with those seen in intact individuals. An overview of the work currently underway with ISMS will be provided along with specifications required for the future clinical implementation of the system.

2.1 General Introduction to FES

As far back as 2000 BC the Egyptians used electric fish to treat paralysis; their electric discharge activates muscles (Kellaway, 1946). Albert Hyman (1930) experimented with the use of electrical stimulation as a resuscitative technique after cardiac arrest, well before Hodgkin and Huxley (1952) formulated their model of action potential propagation down an axon. Further work on the cardiac system resulted in the development of the cardiac pacemaker (Zoll, 1952; Zoll and Linenthal, 1963) which has become one of the most well known electrical stimulation devices in clinical use today.

Liberson et al. (1961) developed what is credited to be the first clinically-deployed device that stimulates electrically nerves and muscles and restore function to a lower limb.

Their "functional electrotherapy" technique was used to correct footdrop in individuals with hemiparesis. A foot switch detected periods when the foot was off the ground during which time stimulation was applied through surface electrodes placed over the peroneal nerve. A year later the term "functional electrical stimulation" (FES) was coined by Moe and Post and gained wider acceptance than Liberson's "functional electrotherapy" (Moe and Post, 1962).

2.1.1 Surface and Implantable FES Electrodes

Various techniques may be used to deliver functional electrical stimulation to the nervous tissue. Perhaps the least invasive technique is surface stimulation in which electrodes are placed on the surface of the skin over the target nerve or muscle. To function appropriately these electrodes require accurate placement that often translates into a long donning procedure every time the system is utilized. This procedure may be acceptable in systems requiring the activation of a single superficial muscle (e.g., footdrop (Dai et al., 1996)). Surface stimulation has other limitations including the ability to selectively stimulate only superficial muscles. Moreover, movement of the skin over the motor point of the muscle during motion can prevent consistent activation (Popovic, 2004). Poorly adhered electrodes or electrodes that are too small can cause burn injuries at high stimulation amplitudes (Popovic, 2004). Surface stimulation also has higher energy consumption than implanted systems due to the elevated current required when stimulating through the skin.

An alternative to surface stimulation is the use of percutaneous electrodes (Handa et al., 1989; Shimada et al., 1996) that are inserted into the muscle using a hypodermic needle. However, in this case the connecting wires exit the skin at the implantation site, introducing a possible site of infection which requires continuous skin maintenance. The BION^{TM} uses a similar insertion technique but consists of a fully implantable miniature stimulator enclosed completely in a small glass cylinder (Loeb et al., 2006). An external radio frequency coil placed over the implanted device is used to power and control the BION^{TM}. Other fully implanted electrodes include intramuscular, epimysial, nerve-cuff (Naples et al., 1990; Grill and Mortimer, 1996), and flat interface nerve electrodes (FINEs) (Tyler and Durand, 2002), as well as longitudinal intra-fascicular electrodes (LIFEs) (Yoshida and Horch, 1993b). Implanted neuroprostheses often use intramuscular and epimysial electrodes are used often in implanted neuroprostheses where muscle specificity is desired (Sharma et al., 1998). Intramuscular electrodes consist of wires penetrating into the muscle (e.g., percutaneous electrodes), whereas, epimysial electrodes consist of flat meshes or disks that can be stitched to the muscle surface near the motor point (Grandjean and Mortimer, 1986). Cuff electrodes are designed to encircle the target nerve and can be constructed in mono-, bi- or tri-polar configurations. Given that most major nerve trunks are composed of groups of axons (fascicles) innervating various muscles, selective activation muscles with nerve cuff electrodes is often difficult (Prochazka, 1993; Tai and Jiang, 1994; Grill and Mortimer, 1996). In order to activate a single muscle the smallest branch of the nerve must be stimulated near the neuromuscular junction. While nerve cuffs can be implanted directly onto these nerve branches, they may result in nerve damage or mechanical failure if subjected to stresses and strains generated during muscle contractions (Naples et al., 1990). In order to achieve selective muscle activation with cuff electrodes implanted around proximal nerve trunks, cuffs with multiple stimulation sites distributed around the interior surface have been designed. By steering current between the multiple active sites selective fascicles can be activated within the nerve to discriminate between the activation of various muscles (Grill and Mortimer, 1996; Veraart et al., 1993). Alternatively, FINEs can be used where the nerve is reshaped into a flat configuration to separate the fascicles (Tyler and Durand, 2002) and improve the selectivity of activation. The design of LIFEs provides muscle selectivity through the direct implantation of fine microwires into specific nerve fascicles containing axons targeting the desired muscles (Yoshida and Horch, 1993b).

Other electrodes have been developed primarily for single cell intracortical recordings. Electrode arrays such as the Utah and Michigan arrays have multiple electrodes mounted on a single silicon substrate. The Utah array is a 10 x 10 array of electrodes with either a single length or a slanted depth configuration for recording from the cortex and stimulating peripheral nerves, respectively (Nordhausen et al., 1996; Branner et al., 2001). The Michigan array has a planar construction, with each probe having several active sites.

Three dimensional arrays can be constructed from various configurations of these subunits (Hoogerwerf and Wise, 1994).

2.2 Standing and Walking Systems Using FES

People with spinal cord injury have many needs depending on the level and severity of the injury. The highest priority for people with quadriplegia is the restoration of arm and hand function. Improved trunk stability and restoration of bladder, bowel and sexual functions are ranked among the top priorities of people with quadriplegia and paraplegia, followed closely by the desire for restored stepping (Anderson, 2004). Various approaches have been taken in addressing these needs including the use of FES. In this section we review some of the main FES systems currently available for restoring standing and walking after spinal cord injury. The use of ISMS in achieving similar functions will be discussed in section 2.3.

In order to generate standing and stepping movements a combination of muscles must be activated in a coordinated fashion to generate flexion and extension movements across the hip, knee and ankle joints of the legs. Several FES approaches may achieve this including stimulation applied through surface or implanted electrodes. These methods can be used alone or in conjunction with external braces across any, or all of the joints of the leg. No system is complete without an appropriate means of controlling the stimulation. Therefore, a discussion of some of the control strategies currently in use or under development will be provided in the following section.

2.2.1 FES Systems for Restoring Standing

Standing systems must fulfill the functional requirements of generating consistent load bearing force in both legs. One method of achieving this is via knee, ankle, foot orthoses (KAFOs) to maintain the limb in an extended position. Alternatively, limb extension can be achieved through FES of the knee extensor muscles to prevent knee buckling. This stimulation can be provided through surface (Ewins et al., 1988; Bajd et al., 1999; Bijak et al., 2005) or implanted electrodes. An example of an implanted system for restoring standing is the CWRU/VA system (Davis et al., 2001). Eight channels of stimulation are applied though surgically implanted epimysial and intramuscular electrodes targeting the gluteal muscles, semimembranosus, vastus lateralis and lumbar erector spinae. Standing is generated through open-loop application of continuous trains of FES to maintain extension of the lower limbs. Feedback-based control algorithms have also been developed with sensor signals to provide information about the joint angles (Wood et al., 1998) or the load taken by the hands (Donaldson Nde and Yu, 1996; Riener and Fuhr, 1998) in order to modify appropriately the amplitude of stimulation applied to the muscles during standing. Feedback control delays the onset of muscle fatigue by applying the minimal level and duration of stimulation required to maintain functional standing.

2.2.2 FES Systems for Restoring Stepping

Stepping involves the coordinated activation of flexor and extensor muscles in the lower extremities, with full weight-bearing obtained during the stance (extensor) phase and ample foot clearance during swing (flexor phase). Following spinal cord injury, external braces, such as KAFOs, and ankle-foot orthoses (AFOs) have been used alone (Merkel et al., 1984) or in conjunction with the application of FES (Andrews et al., 1989, 1988; Davis et al., 1999; Solomonow et al., 1989) to restore stepping. A reciprocating gait orthosis (RGO) consisting of a set of hip, knee, ankle and foot braces has also been used to provide mechanical coupling between the legs and maintain them in reciprocal phases during stepping in people with limited voluntary control. The use of RGOs in conjunction with FES provides further improvements in stepping (Solomonow et al., 1989; Stein et al., 2005).

The Parastep and ETHZ-Paracare systems are examples of surface FES systems available clinically for restoring stepping (Graupe and Kohn, 1998; Popovic et al., 2001). Both systems use electrodes placed on the skin over the quadriceps, paraspinal (or gluteus) muscles and common peroneal nerve to generate knee extension, hip extension and full limb flexor reflex, respectively. The ETHZ-Paracare stepping system (Popovic et al., 2001) can be controlled with push-buttons for the initiation of swing, or alternatively through feedback signals obtained from foot-switches or gait detection sensors such as accelerometers or goniometers.

A 16-channel version of the CWRU/VA standing system (discussed above) can be implanted targeting extensor and flexor muscles to restore stepping and other leg exercise functions (Sharma et al., 1998). Another more extensive implant is the Praxis FES-22 which consists of one epidural, 8 epineural, 10 cuff and 3 sacral root electrodes. Depending on which muscles are targeted for stimulation, the implant can perform multiple functions including the generation of leg movements for exercise, standing or stepping. Distributed implant systems such as these have been relatively robust but require multiple surgical sites. Damage to the electrodes and lead breakage induced by the movements of the legs during simulation may also occur.

Stimulation applied in the central nervous system provides benefits over peripheral stimulation due to the ability to achieve a localized implant in a region of reduced movement. These benefits were the underlying drive for designing the lumbar anterior root stimulation implant (LARSI) for restoring standing and stepping after spinal cord injury. In this implant, stimulation is applied to the ventral roots exiting the spinal cord in order to evoke lower limb movements (Donaldson et al., 2003). However, this technique has been limited by the fact that each individual anterior root contains many populations of motoneuron axons innervating both agonistic and antagonistic muscles at times generating inappropriate movements. For example, stimulation of a single ventral root evokes knee extension along with hip flexion resulting in movements that are inappropriate for upright standing or stepping. Therefore, the implant has found more success in generating leg movements for cycling.

Several strategies for controlling the amplitude and timing of the electrical stimuli to generate consistent stepping movements have been investigated. The majority of currently available FES systems employ the use of manual push-buttons built in walkers and crutches to initiate the swing phase of each step. Some systems use feedback control in which cyclic joint movements are tracked during the swing and stance phases of the stepping and stimulation is continuously modulated using proportional/integral/derivative (PID) control (Veltink, 1991), or neural networks (Abbas and Triolo, 1997). State control of stepping has also been deployed in systems that use artificial learning to determine an appropriate set of sensor signals to generate appropriately timed transitions between the swing and stance phases (Andrews et al., 1988; Popovic et al., 2003). Alternatively, fuzzy logic can determine gait events during stepping (Skelly and Chizeck, 2001). Popovic et al. (2003) evaluated control strategies for restoring stepping using FES. They found that automatic control of ballistic walking has a lower metabolic cost than either automatic control of slow walking or push-button activated control. However, the volunteers preferred the latter forms due to the ability to coordinate upper and lower limb movements. These findings demonstrate the importance of developing an appropriate control scheme for FES systems.

2.3 Intraspinal Microstimulation

Intraspinal microstimulation is a technique that uses fine microwires to apply stimulation within the ventral horn of the spinal cord below the level of the injury in order to generate functional movements of the legs. The ISMS microwires are implanted in a compact and relatively motion free region of the cord; thus the implant experiences minimal strain during evoked limb movements. The target region for implantation is the lumbosacral enlargement, which is 5 cm-long in humans and contains all the motoneuron pools that innervate the muscles of the lower extremities as well as large proportions of stereotypical neuronal networks involved in the control of leg movements.

2.3.1 Historical Summary of the Use of ISMS

As early as the 1940s, Renshaw used penetration electrodes to stimulate motoneurons in the ventral grey matter of the spinal cord in order to demonstrate the time required for electrical excitation to cross a synapse (Renshaw, 1940). Intraspinal microstimulation has also been used for many years as an electrophysiological technique to demonstrate the reflex circuitry within the cord (Jankowska and Roberts, 1972).

In the late 1960s, Nashold et al. (1971) explored ISMS in animal experiments as a means of restoring micturition after spinal cord injury. A pair of 0.4 mm diameter platinum-iridium wires with deinsulated conical tips was implanted into the spinal cord of cats and dogs, with and without spinal transections. The electrode tips were placed in the intermedio-lateral column to target the micturition centre in the sacral (S1-S3) spinal cord. Starting in the early 1970s, 27 patients in various centres (USA, France, Sweden) were implanted with this spinal stimulation system. The system achieved a 60% success rate for effective bladder voiding but the stimulation was often associated with additional autonomic and motor responses (Nashold et al., 1981). In addition, a sphincterectomy was commonly needed in male patients to allow bladder voiding due to an inability to relax the external urethral sphincter using ISMS. Similar results have been more recently obtained during ISMS experiments in chronically and acutely implanted cats (Grill et al., 1999; McCreery et al., 2004; Tai et al., 2004) and rabbits (Pikov and McCreery, 2004), where high bladder pressures could be achieved, but often in conjunction with little relaxation of the bladder neck and sphincter resulting in incomplete voiding (Prochazka et al., 2003). In both cases the technique was soon abandoned in favour of peripheral stimulation approaches providing similar outcomes (see Gaunt and Prochazka (2006) for a full review of current neuroprostheses for urinary bladder function). Although ISMS has not been efficient in restoring micturition, it shows promising results as a means of restoring lower limb function after spinal cord injury (Pancrazio et al., 2006). In this case, we can tap into the residing circuitry within the lumbosacral enlargement of the spinal cord and activate neuronal networks and pools of motoneurons innervating the muscles of the legs.

2.3.2 Use of ISMS for Inducing Functional Movements of the Limbs

Various forms of spinal cord stimulation can activate the locomotor networks within the spinal cord to investigate their organization. These include surface suction electrodes (Magnuson and Trinder, 1997; Vogelstein et al., 2006) in *in vitro* preparations and epidural electrodes *in vivo* in rats, cats and humans (Dimitrijevic et al., 1998; Herman et al., 2002; Gerasimenko et al., 2003; Minassian et al., 2004).

Intraspinal microstimulation has been used in frogs, rats and cats to investigate the presence of "movement primitives" in the spinal cord (Bizzi et al., 1991; Giszter et al., 1993; Tresch and Bizzi, 1999; Saltiel et al., 2001; Lemay and Grill, 2004). The concept of movement primitives refers to the hypothesized existence of a limited number of immutable neuronal networks that generate distinct movements of the limbs and comprise the building blocks for all movements. However, a comparison of ISMS and peripheral FES responses indicate that these results may be attributable to the mechanical properties of the musculoskeletal system rather than a modular organization at the spinal cord level (Stein et al., 2002; Aoyagi et al., 2004).

Over the past decade we have been developing the use of ISMS as a neuroprosthetic approach for restoring standing and stepping after spinal cord injury. Most of the development to date has been performed in animal models (primarily cats) with plans to conduct intraoperative investigations of ISMS in human volunteers within the next 5 years. Cats have been the animal model of choice due to the size of their spinal cord relative to that of humans. The lumbosacral enlargement in humans is approximately 5 cm long and can be accessed by removing the T12 spinal process whereas in cats this region spans 3 cm and can be accessed by removing the L5 spinal process.

The ISMS implant

The ventral horn of the grey matter in the lumbosacral enlargement contains the cell bodies of all the motoneurons innervating the muscles of the legs. These cells are organized within the cord into pools of motoneurons with each pool innervating a single muscle. The relative locations of the motoneuron pools innervating specific muscles of the leg have been studied extensively in cats and have a consistent spatial organization within the cord (Vanderhorst and Holstege, 1997; Mushahwar and Horch, 2000b) (see figure 2.1). This map is preserved across species, including humans (Sharrard, 1953). Stimulation applied through a single microwire ($< 300\ \mu$A) can directly or indirectly excite the motoneurons in these pools and generate contractions in the muscles they innervate. Electrical stimulation applied through individual electrodes targeting the ventral horn of the grey matter can generate single joint movements as well as whole limb flexion or extension synergies of the hindlimbs (Mushahwar and Horch, 2000a,b). These coordinated multi-joint responses that involve the activation of multiple motoneuron pools, even though the "direct" spread of current within the spinal cord is less than 0.5 mm (Mushahwar and Horch, 1997; Lemay and Grill, 2004; Snow et al., 2006). The possible mechanisms for this will be addressed briefly below.

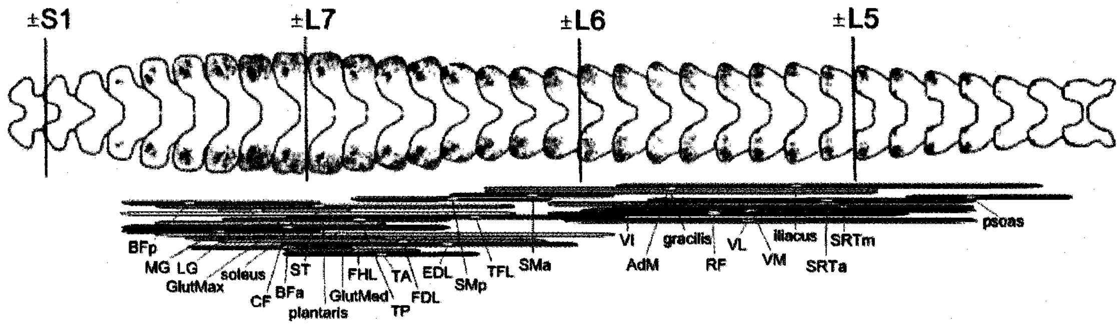

Figure 2.1: *Distribution of motoneuron pools in the lumbosacral enlargement.*

The locations of the motoneuron pools are colour coded on the cross-sections of the grey matter in the top panel. The extent of the pools along the lumbosacral enlargement is indicated by the bars below. Abbreviations (from left to right): BFp - biceps femoris posterior, MG - medial gastrocnemius, LG - lateral gastrocnemius, GlutMax - gluteus maximus, CF - caudofemoralis, BFa - biceps femoris anterior, ST - semitendinosus, GlutMed - gluteus medialis, FHL - flexor hallicus longus, TP - tibialis posterior, TA - tibialis anterior, FDL - flexor digitorum longus, EDL - extensor digitorum longus, SMp - semimembranosus posterior, TFL - tensor fascia latae, SMa - semimembranosus anterior, VI - vastus intermedius, AdM - adductor medialis, RF - rectus femoris, VL - vastus lateralis, VM - vastus medialis, SRTa - sartorius anterior, SRTm - sartorius medialis. Adapted from Mushahwar et al. (2002).

The ISMS implant and fixation techniques are based on a design originally developed for single cell recording from dorsal root ganglia in awake and freely moving cats (Prochazka, 1984). The implant (figure 2.2A) consists of 8 to 24 individual microwires (30 μm diameter, 80%-20% platinum-iridium) arranged into an array and implanted bilaterally spanning a 3 cm-long region of the spinal cord (figure 2.2B). Each platinum-iridium microwire is insulated except for a 30-60 μm tip which is sharpened and inserted through the dorsal surface of the spinal cord. The microwire tips target motoneuron pools in the ventral horn (figure 2.2C) according to their previously mapped organization (Vanderhorst and Holstege, 1997).

ISMS and fatigue resistance

Our results demonstrate that ISMS is characterized by reduced fatigue (Mushahwar and Horch, 1997; Saigal et al., 2004) and a more graded force generation (Mushahwar and Horch, 2000a; Snow et al., 2006) when compared to peripheral modes of stimulation. Electrical stimulation of peripheral nerves activates large fast, fatiguable fibres before smaller fatigue resistant fibres (Mortimer, 1981) leading to rapid muscle fatigue and a steep initial force production. This is a significant concern in situations where a muscle must maintain force

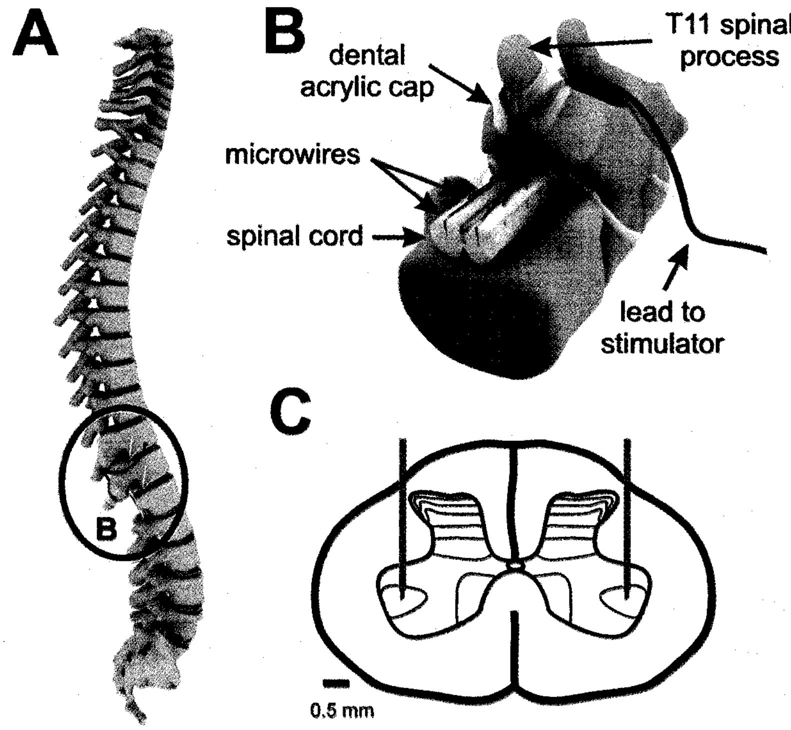

Figure 2.2: *Cartoon illustration of the ISMS implant.*

A laminectomy performed at the T12 vertebral segment in humans will expose the L2-L5 spinal segments (A). The ISMS implant consists of an array of 24 microwires implanted individually through the dorsal surface of the cord (B). The entire array is secured to the T11 process using a dental acrylic cap and a lead travels to the stimulator interface. Motoneurons in the ventral horn of the grey matter are targeted by the microwire tips as indicated in the cross section of the spinal cord (C).

for an extended period of time and may hinder the clinical use of FES. We recently demonstrated, in rats, that ISMS generates a mixed recruitment order of motor units within the activated muscle (Bamford et al., 2005). The fatigue resistance and graded force recruitment seen during ISMS is attributed to the initial recruitment of populations of slow, fatigue-resistant muscle fibres followed at higher stimulation amplitudes by the gradual activation of fast, fatiguable fibres. This sequence of activation resembles the physiological recruitment of motor units. Electrical stimulation (ISMS or peripheral FES), is applied extracellularly and activates axons in a reversed order due to the lower input resistance of the large axons. Peripheral FES activates motor axons directly, leading to the reversed recruitment of motor units. In contrast, ISMS primarily activates motoneurons trans-synaptically which leads to a near normal recruitment of slow to fast motor units. Computer simulations as well as recent experimental studies of ISMS demonstrated that the axons of afferent fibres passing near the microwire tip are excited at a lower stimulus amplitude than the nearby motoneurons (McIntyre and Grill, 2000; Gaunt et al., 2006). This preferential activation of afferent networks by ISMS not only leads to the near normal recruitment of motor units, but is also likely to be the main factor contributing to the spread of excitation to distributed but synergistic motoneuron pools. This could in turn explain the whole-limb coordinated movements elicited by stimulating through single ISMS wires.

Although ISMS provides improved fatigue resistance due to its mixed motor unit recruitment, increased force decay when high stimulation frequencies are used remains prevalent. During a normal contraction motor units are activated in an asynchronous manner which allows fused muscle contraction (tetanus) to be achieved even though the firing frequency of individual fibers (< 20 Hz) is well below that required for fused muscle contraction (> 40 Hz). However, electrical stimulation results in the simultaneous phase-locked activation of a large population of motor units (Mushahwar and Horch, 1997). Trains of stimulation at the fusion frequency are therefore required to generate a tetanic contraction of the muscle when the motor units are activated synchronously. This in turn causes an increased rate of fatigue and onset of muscle pain due to an increased production of metabolic byproducts and a reduction in the amount of time available to remove these waste materials between fibre contractions (Prochazka, 1993).

Multiple techniques have been developed to reduce the rate of fatigue during FES by activating different sets of motoneurons to perform a common function. These techniques include interleaving or rotating stimulation sites (Rack and Westbury, 1969; Yoshida and Horch, 1993a), and performing postural switching. Interleaved stimulation more closely mimics the asynchronous firing of motor units seen in the natural activation of muscle in which low-frequency, non-overlapping stimuli are applied to different sub-populations of fibres in a single muscle. This has been demonstrated using ISMS by implanting several microwires into a single target motoneuron pool. By alternating the stimuli through two or more electrodes the frequency of stimulation applied through each electrode is only a fraction of the muscle fusion frequency. In this way, multiple populations of motor units can be activated asynchronously at sub-tetanic frequencies with the result being a summed smooth contraction (Mushahwar and Horch, 1997). This approach has also been demonstrated using LIFEs (Yoshida and Horch, 1993a) as well as the Utah slant electrode array (McDonnall et al., 2004).

Rotating stimulation utilizes a strategy similar to that of interleaving. During interleaving the stimulus is applied in alternation through multiple electrodes, each at sub-fusion frequency, whereas, during stimulus rotation a train of 40-50 Hz stimulation is applied through a single electrode for a set duration before switching to the next stimulation site. The stimulation continues to be rotated between electrodes in this fashion, providing the motor units activated by the first electrode adequate time to recover from fatigue. Rotating stimulation was demonstrated using a nerve cuff with multiple active sites, each recruiting different populations of motor units within the same nerve (Grill and Mortimer, 1996). This has also been applied in FES phrenic pacemakers for restoring breathing in people with high tetraplegia (Thoma et al., 1987).

Another solution to fatigue is the use of a technique called postural switching where different muscles can be activated to achieve the same overall functional outcome. This technique is generally used in standing during which the weight of the individual can be shifted in such a way that the activation of postural muscles is periodically rotated, thus reducing the rate of fatigue (Krajl et al., 1986). Postural shifting can be applied to both ISMS and peripheral stimulation systems in order to further extend the duration of functional contraction.

ISMS implant stability

Special considerations have been taken to ensure that minimal damage is induced during the implantation of ISMS microwires and as a result of the continued presence of the implant. The material and diameter of the microwires used in the ISMS implant developed in our laboratory were selected based on the requirements that the microwires; (1) have sufficient stiffness to penetrate the cord yet cause minimal tissue displacement during implantation, (2) remain mechanically stable yet free to move ("float") with the tissue, (3) are electrochemically inert, and (4) can apply stimulation pulses that activate nervous tissue while remaining within the safety constraints of the interface. Histological techniques were used to evaluate the extent of the damage caused when ISMS microwires were chronically implanted in the spinal cord (Prochazka et al., 2001). Figure 2.3 shows a 6 μm-thick section of spinal tissue showing the track of a microwire that had been implanted for 6 months. Only mild gliosis was seen around the shaft (fig 2.3A) and microwire tip (fig 2.3B). Furthermore, the absence of lymphocytes and macrophages indicated that no chronic inflammation occurred. These results demonstrate the advantage of designing a flexible implant in which each individual wire can "float" in the cord during the small translation, rotation and compression of the spinal cord caused by postural movements. In contrast, systems constructed from single solid substrates may be less mechanically compatible with the cord and may cause increased tissue inflammation (Woodford et al., 1996; Biran et al., 2005; Polikov et al., 2005).

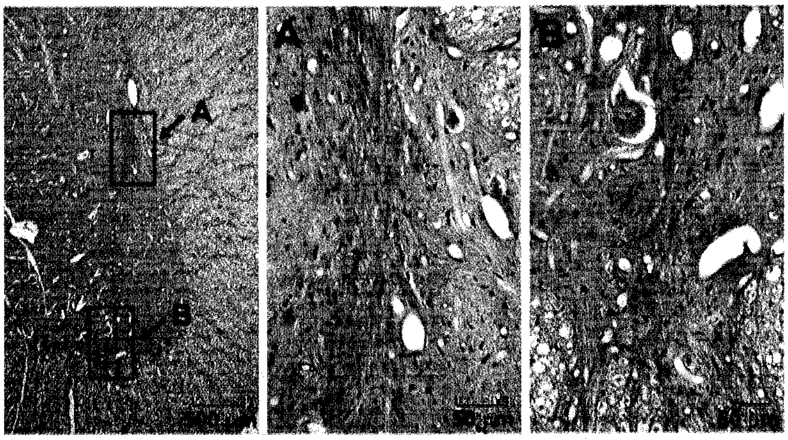

Figure 2.3: *Histological evaluation of spinal cord tissue around a microwire implanted for 6 months.*

All panels show a 6 μm-thick cross-section of spinal cord tissue. The panel of the left shows the track generated by the implanted microwire. No lymphocytes or macrophages were found around the shaft (A) or tip (B) of the microwire. This indicates the absence of chronic inflammation over the 6 month period of the implant. Reproduced from Prochazka et al. (2001).

The maximum current that can safely be applied through an electrode is based on the amount of charge that can be injected into nervous tissue (McCreery et al., 1990) as well as the electrochemical processes that occur at the electrode tip (Mortimer, 1981). Duty cycle, charge per phase, charge density and stimulation frequency are all factors that can influence the extent of tissue damage when stimulation is applied to the central nervous system

(McCreery et al., 2004). In chronic implants stimulation limits and pulse shapes (mono- vs. bi-phasic) must be selected to prevent the initiation of electrochemical reactions that can compromise the integrity of the electrode (through corrosion or deposition) and produce byproducts that cause fluctuations in the pH that may damage the tissue surrounding the electrode tip (Mortimer, 1981). The maximum safe stimulation amplitude for the platinum-iridium wires used by our lab is 300 μA applied in bi-phasic charge balanced pulses with a 200 μs initial cathodic phase. These values were determined based on the surface area of the microwire tip and the acceptable charge density to maintain electrochemical stability (0.3 to 0.45 $\mu C/m^2$ for platinum materials) (Mortimer, 1981). The values are also within the safe range of electrical stimulation applied to the central nervous system (Agnew et al., 1990).

The long term efficacy of the ISMS implant was examined previously in intact (Mushahwar et al., 2000) and more recently in spinal cord injured cats. Three animals with complete spinal transections were implanted chronically with arrays of 24 platinum-iridium microwires targeting the motoneuron pools in the lumbosacral enlargement (L5-S1). Two animals were implanted 4-5 weeks after receiving a spinal cord transection at T11. Both of these implants failed before the end of the 6 month study due to mechanical failures at the spinal cord and connector levels. These failures were considered when designing future implants and will be discussed in greater detail in later sections. The third animal received an ISMS implant and a complete transection of the spinal cord at the T11 level during a single surgical session. The implant remained functional for the duration of the 6 month experiment. Figures 2.4 and 2.5 summarize results obtained from periodic measurements of the electrode impedances, motor thresholds and motor responses conducted throughout the 6 month period of implantation. We found that there were only small variations in the resistances of the microwires (fig 2.4A) indicating that there was little physical change (corrosion or deposition) at the electrode tip. The small decrease in electrode impedance may suggest that the polyimide insulation around the microwire tips was degrading but there is no evidence to support this at this time and the effect is not substantial. Further evaluation must be conducted if these materials are to be used in future studies. The motor threshold of individual microwires (fig 2.4B) increased by an average of 2 fold over the course of the 6 month implant. However, the average motor threshold of all microwires increased from 76 to 83 μA indicating that the absolute change in threshold (as opposed to relative to the initial threshold value recorded) was small. These increases are within the expected range and indicate a minor gliosis associated with the implant. No indication of chronic inflammation was observed.

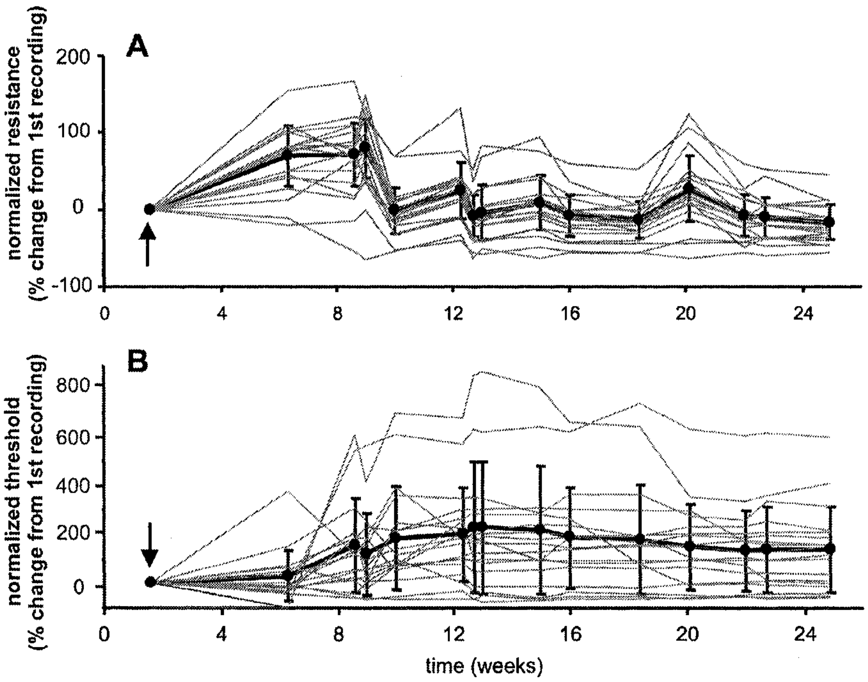

Figure 2.4: *Microwire resistances and motor thresholds measured periodically throughout a 6 month ISMS implant in a cat with spinal cord injury.*

The animal received a complete spinal transection at the T11 level and an ISMS implant during a single surgical session. Resistances and motor threshold values were normalized to the first recording (arrow) taken 10 days after surgery (each thin line represents one microwire) and the mean values (thick black line) are plotted with standard deviation bars. Microwire resistances varied only slightly over the duration of the implant indicating an absence of significant microwire corrosion, material deposition or insulation breakdown (A). The motor thresholds increased by 2 fold from start to termination of the experiment (B). This is consistent with the expected encapsulation around the microwire tip.

The motor responses evoked through stimulation of single electrodes changed over the first 8-10 weeks after implantation and simultaneous spinal transection. Early responses were more often characterized by flexion movements around the hip, knee, ankle and toe joints. This time period corresponds to the expected duration of spinal shock during which flexor hyperreflexia is prominent. After this initial phase a spectrum of responses similar to those seen in an intact animal was achieved and the characteristics of the responses obtained from each microwire became increasingly consistent between recording sessions (i.e., stable responses). Figure 2.5 shows examples of the time course of motor responses evoked when stimulation was applied through 4 individual microwires. The data obtained from this animal provides further support for the stability of the ISMS implant in terms of both its physical integrity and functional responses. The changes in responses may be avoided in clinical application by excluding patients in the acute phase of spinal cord injury and selecting patients who have stable chronic injuries.

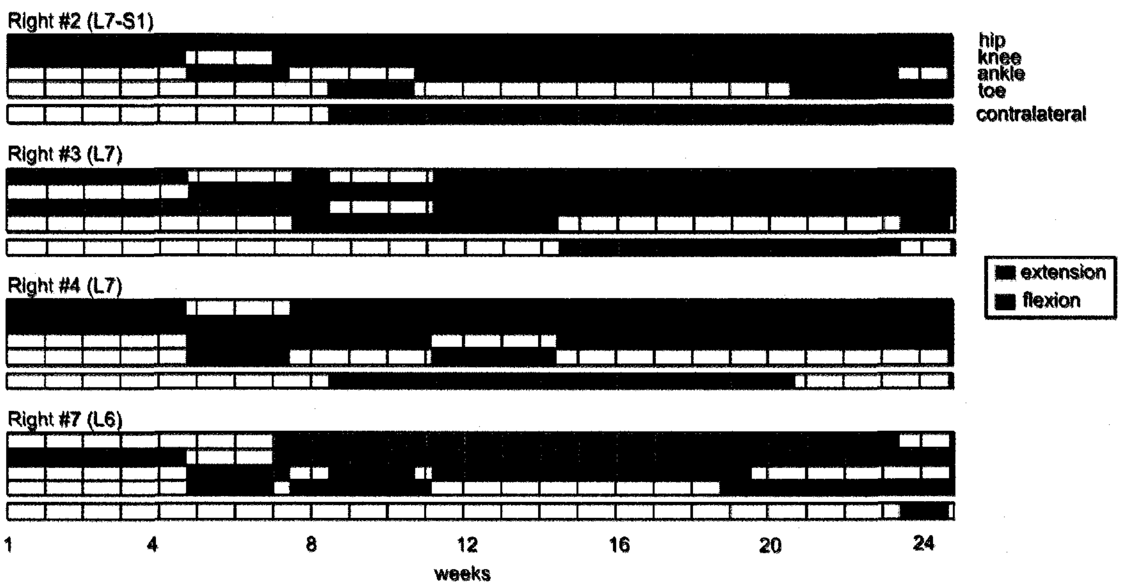

Figure 2.5: *Motor responses evoked by stimulation applied through single microwires.* Each band represents the time course of changes to the motor responses over the duration of a 6 month implant in a cat that received a complete spinal cord injury on the same day as the implant. Each large band represents the responses of a single microwire. The horizontal subdivisions indicate the movement seen across each joint in the ipsilateral leg and the general reponse in the contralateral leg (flexion - blue, extension -red, no response - white). Flexor responses were dominant for the first 8-10 weeks after which time some responses switched to extension. After the 10 week point the responses became increasingly stable. The flexor-dominated responses over the first 8 weeks are presumably due to spinal shock and excessive hyper-reflexia soon after spinal cord injury.

Restoring standing and stepping

The fatigue resistant properties of ISMS make it particularly attractive for restoring standing after spinal cord injury, where prolonged stimulation is required to maintain a stable upright posture. Intraspinal microstimulation applied in an interleaved manner through 8 microwires implanted bilaterally in the spinal cord resulted in prolonged standing in cats.

The duration and quality of standing achieved using intramuscular stimulation and ISMS were compared and the results indicate that ISMS is capable of increasing the duration of standing achieved in comparison to peripheral FES (e.g., fig 2.6). The addition of feedback rules which were used to modify the amplitude of stimulation based on the angles of the knee and ankle, and loading in the limbs was found to further improve the duration of standing using both stimulation techniques. Up to 32 minutes of stable standing was achieved using feedback-based control of ISMS (versus 4.5 min for intramuscular stimulation) indicating that feedback control of ISMS could provide a substantial benefit in a neuroprosthetic device designed for restoring standing after spinal cord injury (Lau et al., 2006, 2007).

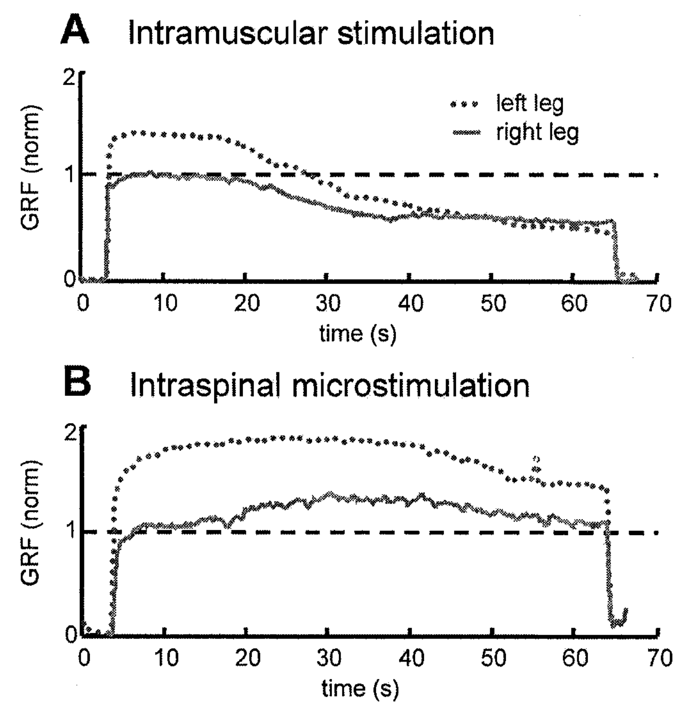

Figure 2.6: *Comparison of standing generated using intramuscular stimulation and ISMS.* Examples from two cats that were made to stand by applying constant levels of stimulation for 1 min. Stimulation was applied either through intramuscular electrodes implanted in the quadriceps and gastrocnemius muscles (A), or intraspinal microwires targeting extensor motoneuron pools (B). The vertical ground reaction force (GRF) recorded using intramuscular stimulation decayed much more rapidly than that obtained using ISMS. Ground reaction forces have been normalized to the minimum force criteria for functional standing (12.5% body weight per hindlimb, equivalent to 4.8 N in A and 4.0 N in B) indicated by the horizontal dashed line.

In addition to standing, the use of ISMS for restoring stepping has been explored. We define functional stepping as rhythmic alternations of the hindlimbs that provide full load-bearing support for the hind quarters of the animal during stance and ample foot clearance during swing. Functional overground locomotion has the additional requirement to generate substantial propulsive forces for the forward progression of the animal.

The ISMS implant initially proposed for restoring lower limb function consisted of 4 rows of 48 electrodes (192 in total) implanted into each side of the spinal cord (Mushahwar and Horch, 1997). The objective of this design was to ensure full selectivity and complete activation of all motoneurons within a pool with minimal current spread from the electrode tip. However, more recent studies have demonstrated that due to the activation of networks in the spinal cord, stimulation applied through a single electrode can generate full limb extensor or flexor synergies appropriate for the stance and swing phases of stepping, respectively. This means that weight-supported locomotor-like stepping patterns can be generated by applying phasic stimulation through as few as 4 different electrodes eliciting flexion and extension responses in the left and right legs (Saigal et al., 2004; Mushahwar et al., 2002).

The fact that ISMS activates networks of neurons within the spinal cord has other interesting implications. We have found that 40 or 50 Hz trains of low-level (amplitude $\leq$ motor threshold) tonic stimulation can evoke in-place alternating stepping movements of the hindlimbs when applied through groups of microwires implanted in the intermediate and ventral areas of the spinal cord (Guevremont et al., 2006). Stimulation probably acts to excite intrinsic locomotor networks residing in the lumbosacral spinal cord (Brown, 1911; Cazalets et al., 1995; Kjaerulff and Kiehn, 1996). Figure 2.7 indicates the regions of the cord that generated various movements when stimulation was applied through single microwires. Microwires placed in the intermediate and medio-ventral areas (laminae VII and VIII) of the spinal cord were found to be most potent in eliciting alternating movements, and stimulation of the ventral horn (lamina IX) evoked single joint or whole-limb flexor or extensor synergies depending on the rostro-caudal location of the microwire tip. In contrast, stimulation applied to the dorsal horn primarily evoked flexion movements and sensory responses (i.e., paw shake or limb withdrawal) in intact awake animals (Mushahwar et al., 2002) due to activation of sensory fibres with ascending connections. Intraspinal microstimulation in intermediate and medio-ventral areas was most potent in generating stepping movements suggesting that neurons in these regions play a role in rhythmogenesis during fictive locomotion (Kjaerulff and Kiehn, 1996; Noga et al., 1995; Tscherter et al., 2001).

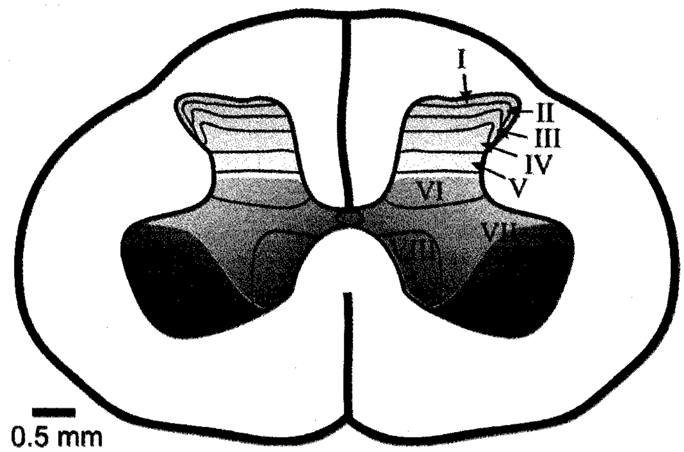

Figure 2.7: *Microwire tip locations within the lumbosacral spinal cord of cats.* Stimulation applied through microwire tips in the dorsal horns of the grey matter (laminae I-VI) generated primarily flexion responses (yellow). Ventrally placed tips could evoke single joint movements or full limb flexion or extension synergies depending on the specific target within the cord (purple). Stimulation of the intermediate and medio-ventral areas (red) often evoked unilateral or bilaterally alternating stepping movements of the hindlimbs.

While tonic stimulation was capable of producing rhythmic alternation of the hindlimbs, the evoked stepping-like movements were not fully load bearing and therefore did not meet the requirements of functional stepping stated above. In order to increase the level of load bearing, supra-threshold amplitudes of stimulation were phasically applied through alternating groups of microwires evoking flexion and extension movements (Saigal et al., 2004). Series of 140 steps were achieved with predetermined patterns of stimulation corresponding to a travel distance of approximately 200 m in human locomotion. A high degree of fatigue resistance was seen over series of steps as indicated by low levels of force decay and kinematic stability (i.e., consistent joint movements) throughout the stepping sequences (fig 2.8). Closed-loop control of stepping was also achieved using hip angle and limb loading (ground reaction force) to determine the appropriate timing for transitions from stance (extension) to swing (flexion). These control algorithms were further developed using intramuscular FES to achieve overground locomotion (Guevremont et al., 2006), and will be applied to ISMS in future studies.

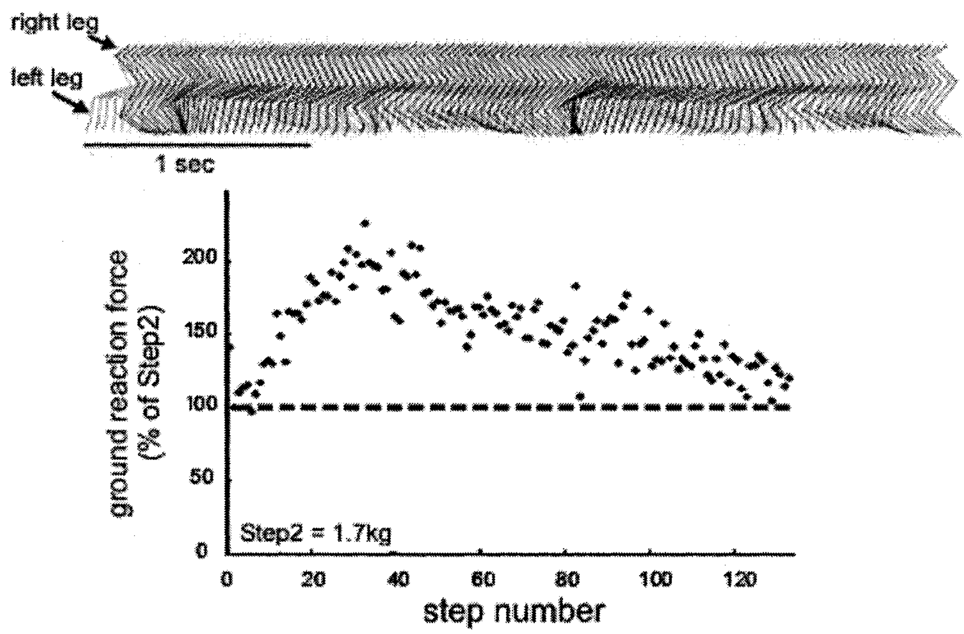

Figure 2.8: *In-place stepping evoked using phasic ISMS.*

The stick figures were reconstructed from video taken of the left (grey) and right (black) legs. The graph plots the ground reaction force (vertical loading) generated during a series of more than 120 steps. The force has been normalized to the load bearing of the second step which corresponded to 45-50% of the full weight of the animal (indicated by the horizontal dashed line). The number of steps taken by this animal would correspond to approximately 200 m travelled by an average North American man (modified from Saigal et al. (2004)).

In summary, we have shown that ISMS in the ventral horn of the spinal cord produces single joint movements and coordinated multi-joint synergies. It recruits motor units in a near-normal physiological order, which contributes to the increased fatigue resistant seen in ISMS-evoked responses. By tapping into the existing neuronal networks controlling leg movements, ISMS can produce prolonged durations of weight-bearing standing by stimulating through as few as 4 microwires within the lumbosacral enlargement. Similarly, stimulating through as few as 4 microwires in each side of the spinal cord can produce bilateral stepping of the paralyzed hindlimbs. The responses evoked by ISMS appear to be stable over time (following some initial variability after SCI, figure 2.5) and the implantation procedure induces minimal tissue damage (figure 2.3). Based on these findings, we believe that ISMS can be a viable neuroprosthetic approach for restoring leg function after spinal cord injury.

2.4 Requirements for Clinical Implementation of ISMS

2.4.1 Current Techniques for ISMS

The ISMS implant currently being used in our lab consists of 24 microwires arranged into a bilateral array. The microwires are implanted individually into the target motoneuron pools in the L5-S1 segments and the whole array is affixed to the L4 spinal process using cyanoacrylate and a dental acrylic cap. Figure 2.9A shows a cartoon illustration of the implanted end of the ISMS system. The array is constructed from 24 microwires each deinsulated (30-60 μm) and sharpened at the tip (10-15°) before being bent to the appropriate depth to penetrate from the dorsal surface of the cord into the targeted motoneuron pool (dimension a). The microwires are then organized into two columns spanning the length of the lumbosacral enlargement (dimension b). The microwires are bundled and are drawn through a length of silastic tubing so that each electrode and its lead remain as one continuous wire. The ends of the tubing are sealed, with the array protruding in one direction and the connector, mounted on the animal's head, soldered to the leads at the other end. Finally the array is bent (dimension c) so that the tube can be fixed to the spinal process with the wires running along the surface of the spinal cord. Figure 2.9B shows the implant after each of the individual wires has been implanted into the spinal cord. The wires lie along the dorsal surface of the cord and penetrate (direction into the page) to reach the motoneuron pools. Figure 2.9C shows the fixation technique to secure the implant to the L4 spinal process. The spinal cord is covered with a layer of plastic thin film before the surgical wound is closed (fig 2.9B).

There are advantages and disadvantages with this implantation and fixation technique. One of the main advantages is that each microwire is implanted individually so the responses can be optimized by evaluating the responses during the implantation procedure. However, this comes at the cost of having a long and tedious surgery requiring extensive knowledge of spinal anatomy in order to adjust appropriately the microwire placement based on the response evoked. Although each wire is placed individually the range of vertical and longitudinal targets along the cord is limited by the preset bend and single active site at each

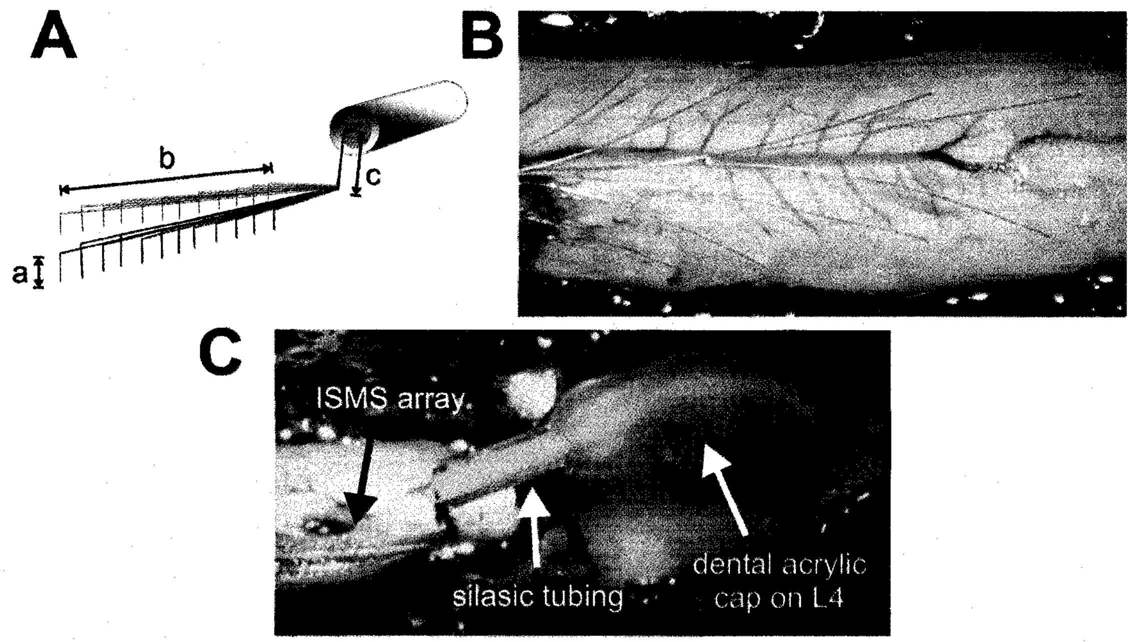

Figure 2.9: *Implantation and fixation of the ISMS microwires.*

The implant consists of 24 individual microwires arranged into a bilateral array (A). Each microwire is cut and bent to target a motoneuron pool at a particular depth (dimension a) and longitudinal distance (dimension b) along the lumbosacral spinal cord. The array is bent at the point where it protrudes from the silastic tube so that the tube can be fixed to the L4 spinal process while allowing the array to lie flush with the surface of the cord (dimension c). Upon implantation, the wires lie along the dorsal surface of the cord and penetrate (into the page) to reach the ventral horn (B). An example of the fixation technique is shown in (C). This implant failed due to the long extension of the silastic tubing from the bone which was deflected during closure of the surgical wound and resulted in the dislodgement of the wires from the cord.

tip (dimension a), and the longitudinal spacing (dimension b) of the array which are determined during array construction. The wires must lie flat yet not taut to remain securely in place in order to minimize the tissue damage that can be evoked by the mismatch of mechanical properties of the microwires and the spinal cord tissue.

The array shown in figure 2.9C was implanted into an intact cat and is an example of an implant that failed as a result of the protrusion of the silastic tubing from the dental acrylic fixation cap on L4. Although the implant generated appropriate responses during surgery no post operative responses could be elicited and the animal suffered from motor deficits in its hindlegs. Postmortem analysis indicated that the region of silastic tubing extending beyond the edge of the remaining L4 vertebra was displaced during the closing of the incision. This caused pressure to be applied to the surface and the microwires to pull out of the cord. Generally, the first 24 hours are critical in determining the success of the implant. During this time initial processes of connective tissue formation (film formation) take place around the implant which secure it in place and only minimal movement of the animal can be tolerated safely during this period.

2.4.2 Design Specifications for a Clinical ISMS System

The key features for the development of an ISMS implant for clinical use are 1) movement towards a more standardized electrode array and implantation technique, and 2) use of electrode arrays that are tailored to the specific dimensions of the lumbosacral spinal cord of each recipient. Our current implantation technique requires specialized skill in handling the microwires and extensive knowledge of spinal cord anatomy. Furthermore, to date, the microwire arrays have been constructed based on the average dimensions of the spinal cord, determined from large numbers of animals used during various procedures performed in our laboratory, rather than the specific dimensions of each recipient. In this section we will discuss some of the developments that are required for the clinical use of ISMS.

Pre- and post-operative imaging

In the future, pre-surgical magnetic resonance imaging (MRI) of the lumbosacral enlargement will be utilized to obtain a more accurate representation of the dimensions of the spinal cord of each subject (e.g., fig 2.10). Although this does not provide an indication of the functional organization of the particular motoneuron pools, imaging the cord prior to surgery guides the tailoring of the implant to the specific animal or human recipient.

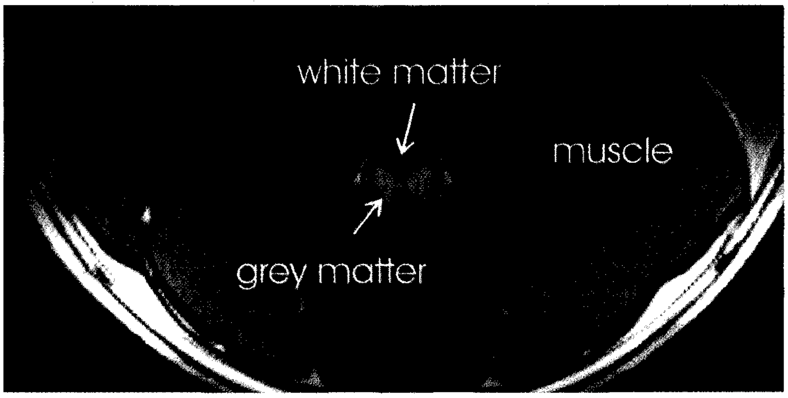

Figure 2.10: *Magnetic resonance image (MRI) of the spinal cord of a cat.*
The white and grey matter can be distinguished using this technique (0.35 mm in-plane and 4 mm though plane resolution).

Another consideration is the ability to image the ISMS implant *in vivo*, allowing us to determine changes in its position over time. Therefore, future ISMS designs should be composed of MRI-compatible, non-magnetic materials such as platinum-iridium (e.g., fig 2.11). The development of improved MRI techniques will result in increased image resolution and therefore more accurate measurements. This imaging technique could also significantly improve the surgical procedure if used intra-operatively for microwire implantation, similar to its use for the implantation of deep brain stimulation devices (Gibson et al., 2003; De Salles et al., 2004).

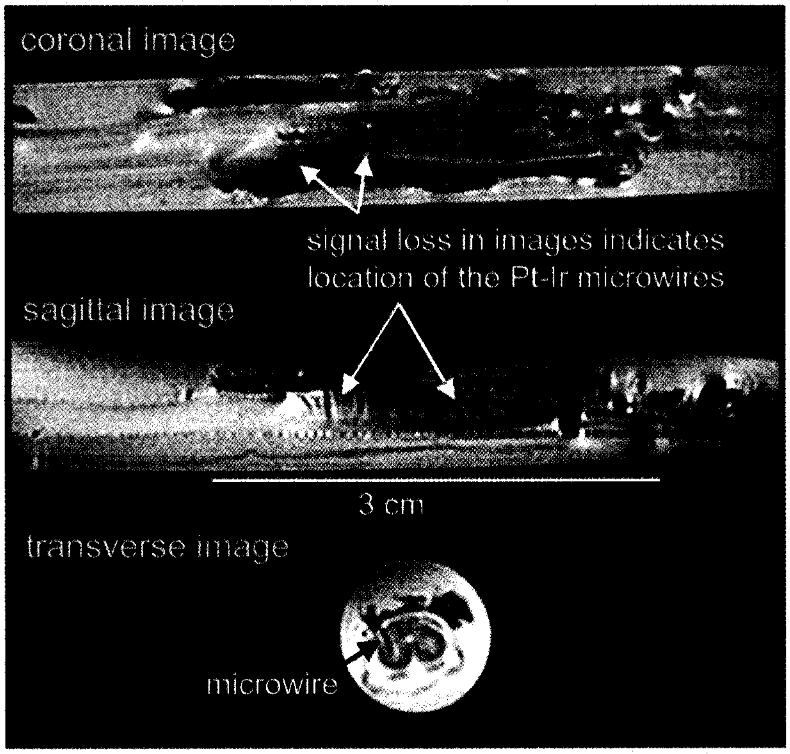

Figure 2.11: *MRI of ex-vivo spinal tissue with an implanted ISMS array.*

The spinal cord of a cat implanted with an ISMS array was extracted post mortem and imaged using MRI. The microwires appear as dark regions (signal voids) in the images. The figure shows a coronal (from the dorsal surface), a sagittal and a transverse view (0.39 mm in-plane and 1.6 mm though plane resolution).

Electrode array

The ultimate ISMS array would consist of at least two rows of electrodes implanted bilaterally into the spinal cord and spanning longitudinally the lumbosacral enlargement. In addition to this each shaft would have more than one active site allowing the depth of the stimulated region to be selected once the array is implanted. These criteria can be met either by using a custom tailored array designed based on previous knowledge of the dimensions of the cord (from pre-operative images), or alternatively, through the use of an implant consisting of several small, flexible, prefabricated arrays. The stiffness of the implanted device is critical due to the small, but present, motion of the cord during postural movements. Although this shift is minimal when compared to the displacement of the actual joints and muscle tissue, the cord does undergo translation, rotation and compression.

The ISMS array currently being used in our lab is fabricated from individual microwires with exposed tips that have been constructed into a single array with pre-determined dimensions (see above). This design allows the individual wires to be virtually mechanically independent from one another and to move freely in concert with the spinal cord. However, its construction limits the target locations that can be reached. Future versions of the implant will make use of multiple contact sites along the penetrating electrode shaft. This would improve motoneuronal recruitment by stimulating through a single active site or by interleaving the stimuli between multiple sites on the same shaft. We experimented with the use of cylindrical lithography for fabricating stimulating electrodes with 4 active sites along each shaft (fig 2.12A) (Snow et al., 2006a,b) and obtained a 100% yield in appropriate targeting of the motoneuron pools of interest. Further developments to reduce the electrode diameter (currently 85 μm) and stiffness and connection of lead wires are needed. Another technique involves the use of planar lithography where multiple stimulation sites can be placed on a flexible polyimide substrate which is inserted into the tissue using a silicon shuttle which is then removed leaving the highly flexible device in place (fig 2.12B). By controlling the surface area, thus the impedance of each site, we could record or stimulate through different active sites using a single implanted device.

Insertion and stabilization techniques

To become a widely available FES technique, future designs of the ISMS system should include simple electrode insertion and fixation methods that can be used to provide highly reproducible results. For this reason we suggest the design of an array that provides a

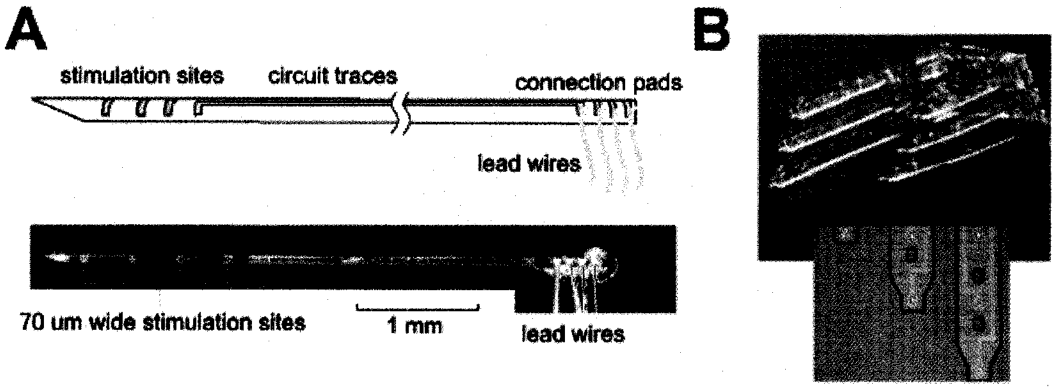

Figure 2.12: *Alternative designs for ISMS electrodes.*

An electrode constructed using cylindrical lithography technology (A). The shaft is 85 μm and has insulated traces running to 4 distinct stimulation sites from lead wires bonded to connection pads at the non-implanted end of the shaft. (Modified from figures 1 and 3 (Snow et al., 2006b)). First generation polymer intra-cortical probe (courtesy of Dr. Daryl Kipke, University of Michigan) that can be modified to stimulate spinal tissue (B). Multiple electrode sites are laid-out on a thin-film polyimide planar substrate which can be folded into a 3D array. Insertion is performed using a stiff silicone shuttle which is then removed leaving only the highly flexible array in the spinal tissue.

modular approach to the implantation. Groups of 4-6 electrodes on a flexible substrate (fig 2.12B) could be fabricated in bilateral or unilateral strips to match the dimensions of the individual (based on spinal cord images). The surgeon could then implant several groups of these into the cord based on segmental landmarks and test the responses using intra-operative stimulation. Another possibility is the use of image guided implantation to provide more specific targeting of the substrate shafts within the ventral horn of the grey matter.

The use of cats as the animal model for the development of ISMS provides some additional challenges that may not be encountered in humans. For one, the human spinal cord is larger and is surrounded by a significantly stronger dura mater. This means that additional stability could be provided to the implant if modular sections of it are secured to the dura mater instead of relying solely on the attachment to the spinal process. A loop of wire near the implant would provide the required strain relief before being secured to the bone and traveling to the implanted stimulator.

Electronics interface

The current state-of-the-art technology for FES systems makes use of implanted stimulators that are powered and programmed through inductive coupling, which eliminates the need for percutaneous connections. A receiving (or transmitting) coil is implanted under the skin typically below the clavicle (for deep brain stimulation) or below the last rib (for bladder and lower extremity FES systems). A transmitting (or receiving) coil can then be placed over the skin to communicate control signals to the implanted device. The clinical implementation of the ISMS technique could utilize similar technology.

The cabling from the implanted stimulator to the spinal array needs to be carefully designed so as to reduce bulk. The possibility of having 24 wires each with 3-4 active sites means that nearly 100 channels of communication are needed. One possible design is to use 10 μm wires in a highly flexible ribbon cable. Alternatively the signals picked-up by the implanted receiver could be multiplexed and transmitted in series to a de-multiplexing and stimulating stage closer to the implant that would translate the serial signals into meaningful stimulation pulses through each of the active electrode sites.

Stimulator

The studies conducted for restoring standing and stepping using ISMS suggest that a minimum of 4 channels are required (Saigal et al., 2004; Mushahwar et al., 2002). Increasing the number of available channels improves the possible repertoire of movements that can be generated and allows interleaving techniques to be used to provide additional fatigue resistance. It also allows for necessary redundancy in the system. For this reason the stimulator should have the capability of generating at least 16 independent channels of stimulation. Currently available implantable stimulators (e.g., Davis et al. (1987); Kljajic et al. (1992); Bijak et al. (2001)) will be adopted.

The control system should be user friendly while remaining highly flexible. Independently programmable signals are required for each of the stimulation channels which can be set by a therapist based on the motor thresholds and range of movements evoked by stimulation applied through each electrode. In addition, the control unit should have input for a number of feedback signals which can be used to determine the appropriate stimulation parameters during standing and stepping sequences.

2.5 Future Directions

Several future developments of the ISMS system can be envisioned. The use of a biomimetic interface instead of 3D electrode structures or microwires would provide a seamless interaction with the spinal cord. Integration of neuromorphic electronic chips such as the silicon central pattern generator (Lewis et al., 2003) to control the timing and amplitude of stimulation would further enhance the quality and metabolic efficiency of functional leg movements produced by ISMS.

Perception of movements evoked by ISMS would be a valuable addition to the system. Continuous awareness of the position of the limbs, foot placement and loading would provide a higher level of interaction between the implant and the user. It would also increase the user's confidence in utilizing the ISMS system and improve their adaptability to it. Finally, the incorporation of cortical control of ISMS (Mushahwar et al., 2006) would grant the user a volitionally-driven system that mimics, to a large extent, the natural control of movements.

Intraspinal microstimulation can also be used in combination with other interventions such as regeneration, neuro-pharmacology and body weight supported treadmill training, for restoring function after spinal cord injury. The effect of ISMS before and after the application of neuromodulatory drugs (e.g., the $\alpha2$ noradrenergic receptor agonist, clonidine) in cats with spinal cord injury has been investigated in order to evaluate the functional benefits borne by the combination of these two approaches (Barthelemy et al., 2006; Guevremont et al., 2006). The evoked movements were enhanced and sites that produced only flexor-dominated responses prior to the delivery of the drug were capable of eliciting coordinated weight-bearing stepping after its administration. The use of ISMS can also be deployed for the restoration of arm movements in individuals with cervical-level injuries. This exciting extension of the applicability of ISMS is currently in its early stages of investigation (Moritz et al., 2007).

2.6 Conclusion

In this chapter we discussed the strengths and current weaknesses involved in utilizing the ISMS technique for restoring lower limb function after spinal cord injury. The main advantages of the technique include not only the localization of the implant in a 5 cm region of the lumbosacral spinal cord, but also its ability to activate neural circuitry in a more physiological manner than peripheral systems. This leads to the generation of synergistic movements and the recruitment of muscle fibres in a near-normal order. We have investigated the use of ISMS for restoring standing and stepping and although there are technical improvements that need to be made to the design of the implant, the benefits provide evidence of the potential efficacy of ISMS. Our results indicate that with the future developments suggested here, ISMS may be able to translate into a successful, clinically implemented FES technique.

2.7 Bibliography

Abbas, J. and R. Triolo (1997). Experimental evaluation of an adaptive feedforward controller for use in functional neuromuscular stimulation systems. *IEEE Transactions on Rehabilitation Engineering 5*(1), 12–22. [cited at p. 31]

Agnew, W., D. McCreery, T. G. Yuen, and L. Bullara (1990). Effects of prolonged electrical stimulation of the central nervous system. In W. Agnew and D. McCreery (Eds.), *Neural Prostheses: Fundamental Studies*, pp. 226–251. N.J.: Prentice Hall. [cited at p. 40]

Anderson, K. (2004). Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma 21*(10), 1371–83. [cited at p. 29]

Andrews, B. J., R. Barnett, G. F. Phillips, and C. A. Kirkwood (1989). Rule-based control of a hybrid fes orthosis for assisting paraplegic locomotion. *Automedica 11*, 175–199. [cited at p. 30]

Andrews, B. J., R. H. Baxendale, R. Barnett, G. F. Phillips, T. Yamazaki, J. P. Paul, and

P. A. Freeman (1988). Hybrid fes orthosis incorporating closed loop control and sensory feedback. *Journal of Biomedical Engineering. 10*(2), 189–95. [cited at p. 30, 32]

Aoyagi, Y., V. Mushahwar, R. B. Stein, and A. Prochazka (2004). The role of neuromuscular properties in determining the end-point of a movement. *IEEE Transactions on Neural Systems & Rehabilitation Engineering. 12*(1), 12–23. [cited at p. 5, 34]

Bajd, T., A. Kralj, M. Stefancic, and N. Lavrac (1999). Use of functional electrical stimulation in the lower extremities of incomplete spinal cord injured patients. *Artificial Organs. 23*(5), 403–9. [cited at p. 29]

Bamford, J. A., C. T. Putman, and V. K. Mushahwar (2005). Intraspinal microstimulation preferentially recruits fatigue-resistant muscle fibres and generates gradual force in rat. *Journal of Physiology (London) 569*(3), 873–884. [cited at p. 36]

Barthelemy, D., H. Leblond, J. Provencher, and S. Rossignol (2006). Non-locomotor and locomotor hindlimb responses evoked by electrical microstimulation of the lumbar cord in spinalized cats. *Journal of Neurophysiology.* [cited at p. 54]

Bijak, M., W. Mayr, W. Girsch, H. Lanmuller, E. Unger, H. Stohr, H. Thoma, and J. Plenk, H. (2001). Functional and biological test of a 20 channel implantable stimulator in sheep in view of functional electrical stimulation walking for spinal cord injured persons. *Artificial Organs 25*(6), 467–74. [cited at p. 53]

Bijak, M., M. Rakos, C. Hofer, W. Mayr, M. Strohhofer, D. Raschka, and H. Kern (2005). Stimulation parameter optimization for fes supported standing up and walking in sci patients. *Artificial Organs 29*(3), 220–3. [cited at p. 29]

Biran, R., D. C. Martin, and P. A. Tresco (2005). Neuronal cell loss accompanies the brain tissue response to chronically implanted silicon microelectrode arrays. *Experimental Neurology 195*(1), 115–26. [cited at p. 39]

Bizzi, E., F. A. Mussa-Ivaldi, and S. Giszter (1991). Computations underlying the execution of movement: a biological perspective. *Science 253*(5017), 287–91. [cited at p. 33]

Branner, A., R. B. Stein, and R. A. Normann (2001). Selective stimulation of cat sciatic nerve using an array of varying-length microelectrodes. *Journal of Neurophysiology 85*(4), 1585–94. [cited at p. 28]

Brown, T. (1911). The intrinsic factors in the act of progression in the mammal. *Proceedings of the Royal Society of London Series B 84*(572), 309–18. [cited at p. 3, 44]

Cazalets, J. R., M. Borde, and F. Clarac (1995). Localization and organization of the central pattern generator for hindlimb locomotion in newborn rat. *Journal of Neuroscience. 15*(7 Pt 1), 4943–51. [cited at p. 44]

Dai, R., R. Stein, B. Andrews, K. James, and M. Wieler (1996). Application of tilt sensors in functional electrical stimulation. *IEEE Transactions on Rehabilitation Engineering 4*(2), 63–72. [cited at p. 27]

Davis, R., R. Eckhouse, J. F. Patrick, and A. Delehanty (1987). Computerized 22-channel stimulator for limb movement. *Applied Neurophysiology 50*(1-6), 444–8. [cited at p. 53]

Davis, R., T. Houdayer, B. Andrews, and A. Barriskill (1999). Paraplegia: prolonged standing using closed-loop functional electrical stimulation and andrews ankle-foot orthosis. *Artificial Organs 23*(5), 418–20. [cited at p. 30]

Davis, R., J. Patrick, and A. Barriskill (2001). Development of functional electrical stimulators utilizing cochlear implant technology. *Medical Engineering & Physics 23*(1), 61–68. [cited at p. 29]

De Salles, A. A., L. Frighetto, E. Behnke, S. Sinha, L. Tseng, R. Torres, M. Lee, C. Cabatan-Awang, and R. Frysinger (2004). Functional neurosurgery in the mri environment. *Minim Invasive Neurosurg 47*(5), 284–9. [cited at p. 50]

Dimitrijevic, M. R., Y. Gerasimenko, and M. M. Pinter (1998). Evidence for a spinal central pattern generator in humans. *Annals of the New York Academy of Sciences 860*(1), 360–376. [cited at p. 33]

Donaldson, N., D. Rushton, T. A. Perkins, D. E. Wood, N. J., and A. Krabbendam (2003). Recruitment by motor nerve root stimulators: significance for implant design. *Medical Engineering and Physics 25*, 527–537. [cited at p. 31]

Donaldson Nde, N. and C.-N. Yu (1996). Fes standing: control by handle reactions of leg muscle stimulation (chrelms). *IEEE Transactions on Rehabilitation Engineering. 4*(4), 280–284. [cited at p. 30]

Ewins, D. J., P. N. Taylor, S. E. Crook, R. T. Lipczynski, and I. D. Swain (1988). Practical low cost stand/sit system for mid-thoracic paraplegics. *Journal of Biomedical Engineering 10*(2), 184–8. [cited at p. 29]

Gaunt, R. A. and A. Prochazka (2006). Control of urinary bladder function with devices: successes and failures. *Progress in Brain Research 152*, 163–94. [cited at p. 33]

Gaunt, R. A., A. Prochazka, V. K. Mushahwar, L. Guevremont, and P. H. Ellaway (2006). Intraspinal microstimulation excites multisegmental sensory afferents at lower stimulus levels than local alpha-motoneuron responses. *Journal of Neurophysiology 96*(6), 2995–3005. [cited at p. 37]

Gerasimenko, Y. P., V. D. Avelev, O. A. Nikitin, and I. A. Lavrov (2003). Initiation of locomotor activity in spinal cats by epidural stimulation of the spinal cord. *Neuroscience & Behavioral Physiology. 33*(3), 247–54. [cited at p. 3, 33]

Gibson, V., J. Peifer, M. Gandy, S. Robertson, and K. Mewes (2003). 3d visualization methods to guide surgery for parkinson's disease. *Studies in Health Technology and Informatics 94*, 86–92. [cited at p. 50]

Giszter, S. F., F. A. Mussa-Ivaldi, and E. Bizzi (1993). Convergent force fields organized in the frog's spinal cord. *Journal of Neuroscience. 13*(2), 467–91. [cited at p. 4, 33]

Grandjean, P. A. and J. T. Mortimer (1986). Recruitment properties of monopolar and bipolar epimysial electrodes. *Annals of Biomedical Engineering 14*(1), 53–66. [cited at p. 28]

Graupe, D. and K. H. Kohn (1998). Functional neuromuscular stimulator for short-distance ambulation by certain thoracic-level spinal-cord-injured paraplegics. *Surgical Neurology. 50*(3), 202–7. [cited at p. 12, 30]

Grill, W. M., J. and J. T. Mortimer (1996). Quantification of recruitment properties of multiple contact cuff electrodes. *IEEE Transactions on Rehabilitation Engineering. 4*(2), 49–62. [cited at p. 27, 28, 38]

Grill, W. M., N. Bhadra, and B. Wang (1999). Bladder and urethral pressures evoked by microstimulation of the sacral spinal cord in cats. *Brain Research 836*(1-2), 19–30. [cited at p. 33]

Guevremont, L., J. Norton, and V. Mushahwar (2006). Open- and closed-loop control strategies for restoring overground locomotion using fes. In *11th Annual Conference of the International FES Society*, Zao, Japan, pp. 23–25. [cited at p. 45]

Guevremont, L., C. Renzi, J. Norton, J. Kowalczewski, R. Saigal, and V. Mushahwar (2006). Locomotor-related networks in the lumbosacral enlargement of the adult spinal cat: Activation through intraspinal microstimulation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 14*(3), 266–272. [cited at p. 44, 54]

Handa, Y., N. Hoshimiya, Y. Iguchi, and T. Oda (1989). Development of percutaneous intramuscular electrode for multichannel fes system. *IEEE Trans Biomed Eng 36*(7), 705–10. [cited at p. 27]

Herman, R., J. He, S. D'Luzansky, W. Willis, and S. Dilli (2002). Spinal cord stimulation facilitates functional walking in a chronic, incomplete spinal cord injured. *Spinal Cord. 40*(2), 65–8. [cited at p. 33]

Hodgkin, A. L. and A. F. Huxley (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol 117*(4), 500–44. 0022-3751 (Print)Journal Article. [cited at p. 26]

Hoogerwerf, A. C. and K. D. Wise (1994). A three-dimensional microelectrode array for chronic neural recording. *IEEE Transactions on Biomedical Engineering 41*(12), 1136–46. [cited at p. 29]

Hyman, A. S. (1930). Resuscitationof the stopped heart by intracardiac therapy. *Archives of Internal Medicine 46*, 553–568. [cited at p. 26]

Jankowska, E. and W. J. Roberts (1972). An electrophysiological demonstration of the axonal projections of single spinal interneurones in the cat. *Journal of Physiology 222*(3), 597–622. [cited at p. 32]

Kellaway, P. (1946). The part played by electric fish in the early history of bioelectricity and electrotherapy. *Bulletin of the History of Medicine 20*, 112–137. [cited at p. 26]

Kjaerulff, O. and O. Kiehn (1996). Distribution of networks generating and coordinating locomotor activity in the neonatal rat spinal cord in vitro: a lesion study. *Journal of Neuroscience. 16*(18), 5777–94. [cited at p. 4, 44, 45]

Kljajic, M., M. Malezic, R. Acimovic, E. Vavken, U. Stanic, B. Pangrsic, and J. Rozman (1992). Gait evaluation in hemiparetic patients using subcutaneous peroneal electrical stimulation. *Scandinavian Journal of Rehabilitation Medicine 24*(3), 121–6. [cited at p. 53]

Krajl, A., T. Bajd, R. Turk, and H. Benko (1986). Posture switching for prolonging functional electrical stimulation standing in paraplegic patients. *Paraplegia. 24*(4), 221–230. [cited at p. 38]

Lau, B., L. Guevremont, and V. Mushahwar (2006). Control strategies for restoring standing with intramuscular and intraspinal stimulation. In *11th Annual Conference of the International Functional Electrical Stimulation Society*, Zao, Japan. [cited at p. 43]

Lau, B., L. Guevremont, and V. K. Mushahwar (2007). Open- and closed-loop control strategies for restoring standing using intramuscular and intraspinal stimulation. *IEEE Trans Neural Syst Rehabil Eng In Press.* [cited at p. 43]

Lemay, M. A. and W. M. Grill (2004). Modularity of motor output evoked by intraspinal microstimulation in cats. *Journal of Neurophysiology. 91*(1), 502–14. [cited at p. 4, 33, 34]

Lewis, M. A., R. Etienne-Cummings, M. J. Hartmann, Z. R. Xu, and A. H. Cohen (2003). An in silico central pattern generator: silicon oscillator, coupling, entrainment, and physical computation. *Biological Cybernetics 88*(2), 137–151. [cited at p. 54]

Liberson, W., H. Holmquest, D. Scot, and H. Dow (1961). Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. *Archives of Physical Medicine and Rehabilitation.* (42), 101–105. [cited at p. 26]

Loeb, G. E., F. J. Richmond, and L. L. Baker (2006). The bion devices: injectable interfaces with peripheral nerves and muscles. *Neurosurgery Focus 20*(5), E2. [cited at p. 27]

Magnuson, D. S. and T. C. Trinder (1997). Locomotor rhythm evoked by ventrolateral funiculus stimulation in the neonatal rat spinal cord in vitro. *Journal of Neurophysiology. 77*(1), 200–206. [cited at p. 3, 33]

McCreery, D., V. Pikov, A. Lossinsky, L. Bullara, and W. Agnew (2004). Arrays for chronic functional microstimulation of the lumbosacral spinal cord. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 12*(2), 195–207. [cited at p. 33, 40]

McCreery, D. B., W. F. Agnew, T. G. Yuen, and L. Bullara (1990). Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. *IEEE Transactions on Biomedical Engineering 37*(10), 996–1001. [cited at p. 39]

McDonnall, D., G. A. Clark, and R. A. Normann (2004). Selective motor unit recruitment via intrafascicular multielectrode stimulation. *Canadian Journal of Physiology and Pharmacology 82*(8-9), 599–609. Journal Article. [cited at p. 38]

McIntyre, C. C. and W. M. Grill (2000). Selective microstimulation of central nervous system neurons. *Ann Biomed Eng 28*(3), 219–33. [cited at p. 37]

Merkel, K. D., N. E. Miller, P. R. Westbrook, and J. L. Merritt (1984). Energy expenditure of paraplegic patients standing and walking with two knee-ankle-foot orthoses. *Archives of Physical Medicine and Rehabilitation 65*(3), 121–4. [cited at p. 30]

Minassian, K., B. Jilge, F. Rattay, M. M. Pinter, H. Binder, F. Gerstenbrand, and M. R. Dimitrijevic (2004). Stepping-like movements in humans with complete spinal cord injury induced by epidural stimulation of the lumbar cord: electromyographic study of compound muscle action potentials. *Spinal Cord 42*(7), 401–16. [cited at p. 33]

Moe, J. H. and H. W. Post (1962). Functional electrical stimulation for ambulation in hemiplegia. *J Lancet 82*, 285–8. [cited at p. 27]

Moritz, C. T., T. H. Lucas, S. I. Perlmutter, and E. E. Fetz (2007). Forelimb movements and muscle responses evoked by microstimulation of cervical spinal cord in sedated monkeys. *Journal of Neurophysiology 97*(1), 110–20. Journal ArticleResearch Support, N.I.H., ExtramuralResearch Support, Non-U.S. Gov't. [cited at p. 54]

Mortimer, J. (1981). Motor prostheses. In B. V.B. (Ed.), *American Handbook of Physiology II, Section 1 Motor Control*, pp. 155–187. Baltimore: Williams and Williams. [cited at p. 35, 39, 40]

Mushahwar, V. K., D. F. Collins, and A. Prochazka (2000). Spinal cord microstimulation generates functional limb movements in chronically implanted cats. *Experimental Neurology. 163*(2), 422–9. [cited at p. 13, 40]

Mushahwar, V. K., D. M. Gillard, M. J. Gauthier, and A. Prochazka (2002). Intraspinal micro stimulation generates locomotor-like and feedback-controlled movements. *IEEE Transactions on Neural Systems & Rehabilitation Engineering 10*(1), 68–81. [cited at p. 35, 44, 53]

Mushahwar, V. K., L. Guevremont, and R. Saigal (2006). Could cortical signals control intraspinal stimulators? a theoretical evaluation. *IEEE Transactions on Neural Systems & Rehabilitation Engineering 14*(2), 198–201. [cited at p. 54]

Mushahwar, V. K. and K. W. Horch (1997). Proposed specifications for a lumbar spinal cord electrode array for control of lower extremities in paraplegia. *IEEE Transactions on Rehabilitation Engineering. 5*(3), 237–43. [cited at p. 34, 35, 37, 38, 44]

Mushahwar, V. K. and K. W. Horch (2000a). Muscle recruitment through electrical stimulation of the lumbo-sacral spinal cord. *IEEE Transactions on Rehabilitation Engineering. 8*(1), 22–9. [cited at p. 34, 35]

Mushahwar, V. K. and K. W. Horch (2000b). Selective activation of muscle groups in the feline hindlimb through electrical microstimulation of the ventral lumbo-sacral spinal cord. *IEEE Transactions on Rehabilitation Engineering. 8*(1), 11–21. [cited at p. 34]

Naples, G., J. T. Mortimer, and T. G. Yuen (1990). Overview of peripheral nerve electrode design and implantation. In W. Agnew and D. McCreery (Eds.), *Neural Prostheses: Fundamental Studies*, pp. 108–145. N.J.: Prentice Hall. [cited at p. 27, 28]

Nashold, B. S., J., H. Friedman, and S. Boyarsky (1971). Electrical activation of micturition by spinal cord stimulation. *Journal of Surgery Research 11*(3), 144–7. [cited at p. 32]

Nashold, B. S., J., H. Friedman, and J. Grimes (1981). Electrical stimulation of the conus medullaris to control the bladder in the paraplegic patient. a 10-year review. *Applied Neurophysiology 44*(4), 225–32. [cited at p. 33]

Noga, B., P. Fortier, D. Kriellaars, X. Dai, G. Detillieux, and L. Jordan (1995). Field potential mapping of neurons in the lumbar spinal cord activated following stimulation of the mesencephalic locomotor region. *Journal of Neuroscience 15*(3), 2203–2217. [cited at p. 45]

Nordhausen, C. T., E. M. Maynard, and R. A. Normann (1996). Single unit recording capabilities of a 100 microelectrode array. *Brain Research 726*(1-2), 129–40. [cited at p. 28]

Pancrazio, J., D. Chen, B. Fertig, R. Miller, E. Oliver, G. Peng, N. Shinowara, M. Weinrich, and N. Kleitman (2006). Toward neurotechnology innovation: Report from the 2005 neural interfaces workshop. an nih-sponsored event. *Neuromodulation 9*(1), 1–7. [cited at p. 33]

Pikov, V. and D. McCreery (2004). Mapping of spinal cord circuits controlling the bladder and external urethral sphincter functions in the rabbit. *Neurourology and Urodynamics 23*(2), 172–179. [cited at p. 33]

Polikov, V. S., P. A. Tresco, and W. M. Reichert (2005). Response of brain tissue to chronically implanted neural electrodes. *Journal of Neuroscience Methods 148*(1), 1–18. [cited at p. 39]

Popovic, D. (2004). Neural prostheses for movement restoration. In J. Moore and G. Zouridakis (Eds.), *Biomedical Technology and Devices Handbook*, pp. 1–47. London: CRC Press. [cited at p. 27]

Popovic, D., M. Radulovic, L. Schwirtlich, and N. Jaukovic (2003). Automatic vs hand-controlled walking of paraplegics. *Medical Engineering & Physics. 25*(1), 63–73. [cited at p. 32]

Popovic, M. R., A. Curt, T. Keller, and V. Dietz (2001). Functional electrical stimulation for grasping and walking: indications and limitations. *Spinal Cord. 39*(8), 403–12. [cited at p. 12, 30]

Prochazka, A. (1993). Comparison of natural and artificial control of movement. *IEEE Transactions on Rehabilitation Engineering. 1*(1), 7–17. [cited at p. 28, 37]

Prochazka, A., V. Mushahwar, J. Downie, S. Shefchyk, and R. A. Gaunt (2003). Functional microstimulation of the lumbosacral spinal cord: Quarterly report #5. Technical report, NIH-NINDS contract N01-NS-2-2342. [cited at p. 33]

Prochazka, A., V. K. Mushahwar, and D. B. McCreery (2001). Neural prostheses. *Journal of Physiology 533*(Pt 1), 99–109. Review. [cited at p. 39]

Rack, P. M. and D. R. Westbury (1969). The effects of length and stimulus rate on tension in the isometric cat soleus muscle. *Journal of Physiology 204*(2), 443–60. [cited at p. 37]

Renshaw, B. (1940). Activity in the simplest spinal reflex pathway. *Journal of Neuophysiology 3*, 373–87. [cited at p. 32]

Riener, R. and T. Fuhr (1998). Patient-driven control of fes-supported standing up: a simulation study. *IEEE Transactions on Rehabilitation Engineering.* *6*(2), 113–124. [cited at p. 30]

Saigal, R., C. Renzi, and V. Mushahwar (2004). Intraspinal microstimulation generates functional movements after spinal-cord injury. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* *12*(4), 430–440. [cited at p. 13, 35, 44, 45, 46, 53]

Saltiel, P., K. Wyler-Duda, A. D'Avella, M. C. Tresch, and E. Bizzi (2001). Muscle synergies encoded within the spinal cord: evidence from focal intraspinal nmda iontophoresis in the frog. *Journal of Neurophysiology* *85*(2), 605–19. [cited at p. 4, 33]

Sharma, M., E. B. Marsolais, G. Polando, R. J. Triolo, J. Davis, J. A., N. Bhadra, and J. P. Uhlir (1998). Implantation of a 16-channel functional electrical stimulation walking system. *Clinical Orthopaedics & Related Research* *347*, 236–42. [cited at p. 28, 31]

Sharrard, W. J. (1953). Correlation between changes in the spinal cord and muscle paralysis in poliomyelitis; a preliminary report. *Proceedings of the Royal Society of Medicine* *46*(5), 346–9. [cited at p. 34]

Shimada, Y., K. Sato, H. Kagaya, N. Konishi, S. Miyamoto, and T. Matsunaga (1996). Clinical use of percutaneous intramuscular electrodes for functional electrical stimulation. *Archives of Physical Medicine and Rehabilitation* *77*(10), 1014–8. [cited at p. 27]

Skelly, M. M. and H. J. Chizeck (2001). Real-time gait event detection for paraplegic fes walking. *IEEE Transactions on Neural Systems & Rehabilitation Engineering.* *9*(1), 59–68. [cited at p. 32]

Snow, S., K. W. Horch, and V. K. Mushahwar (2006). Intraspinal microstimulation using cylindrical multielectrodes. *IEEE Transactions on Biomedical Engineering* *53*(2), 311–9. [cited at p. 34, 35, 51]

Snow, S., S. C. Jacobsen, D. L. Wells, and K. W. Horch (2006). Microfabricated cylindrical multielectrodes for neural stimulation. *IEEE Transactions on Biomedical Engineering 53*(2), 320–6. [cited at p. 51]

Solomonow, M., R. Baratta, S. Hirokawa, N. Rightor, W. Walker, P. Beaudette, H. Shoji, and R. D'Ambrosia (1989). The rgo generation ii: muscle stimulation powered orthosis as a practical walking system for thoracic paraplegics. *Orthopedics. 12*(10), 1309–15. [cited at p. 30]

Stein, R. B., Y. Aoyagi, V. K. Mushahwar, and A. Prochazka (2002). Limb movements generated by stimulating muscle, nerve and spinal cord. *Archives Italiennes de Biologie. 140*(4), 273–81. [cited at p. 34]

Stein, R. B., F. Hayday, S. L. Chong, A. K. Thompson, R. Rolf, K. B. James, and G. Bell (2005). Speed and efficiency in walking and wheeling with novel stimulation and bracing systems after spinal cord injury: a case study. *Neuromodulation 8*, 264–271. [cited at p. 30]

Tai, C., A. M. Booth, W. C. de Groat, and J. R. Roppolo (2004). Bladder and urethral sphincter responses evoked by microstimulation of s2 sacral spinal cord in spinal cord intact and chronic spinal cord injured cats. *Experimental Neurology 190*(1), 171–83. [cited at p. 33]

Tai, C. and D. Jiang (1994). Selective stimulation of smaller fibers in a compound nerve trunk with single cathode by rectangular current pulses. *IEEE Transactions on Biomedical Engineering. 41*(3), 286–91. [cited at p. 28]

Thoma, H., H. Gerner, J. Holle, P. Kluger, W. Mayr, B. Meister, G. Schwanda, and H. Stohr (1987). The phrenic pacemaker. substitution of paralyzed functions in tetraplegia. *ASAIO Transactions 33*(3), 472–9. [cited at p. 38]

Tresch, M. C. and E. Bizzi (1999). Responses to spinal microstimulation in the chronically spinalized rat and their relationship to spinal systems activated by low threshold cutaneous stimulation. *Experimental Brain Research. 129*(3), 401–16. [cited at p. 4, 5, 4, 5, 33]

Tscherter, A., M. O. Heuschkel, P. Renaud, and J. Streit (2001). Spatiotemporal characterization of rhythmic activity in rat spinal cord slice cultures. *European Journal of Neuroscience 14*(2), 179–190. [cited at p. 45]

Tyler, D. and D. Durand (2002). Functionally selective peripheral nerve stimulation with a flat interface nerve electrode. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 10*(4), 294–303. [cited at p. 27, 28]

Vanderhorst, V. G. and G. Holstege (1997). Organization of lumbosacral motoneuronal cell groups innervating hindlimb, pelvic floor, and axial muscles in the cat. *Journal of Comparative Neurology. 382*(1), 46–76. [cited at p. 34, 35]

Veltink, P. (1991). Control of fes-induced cyclical movements of the lower leg. *Medical and Biological Engineering and Computing 29*(6), NS8–NS12. [cited at p. 31]

Veraart, C., W. Grill, and J. Mortimer (1993). Selective control of muscle activation with a multipolar nerve cuff electrode. *IEEE Transactions on Biomedical Engineering 40*(7), 640–653. [cited at p. 28]

Vogelstein, R. J., R. Etienne-Cummings, N. V. Thakor, and A. H. Cohen (2006). Phase-dependent effects of spinal cord stimulation on locomotor activity. *IEEE Transactions on Neural Systems & Rehabilitation Engineering 14*(3), 257–65. [cited at p. 33]

Wood, D., V. Harper, F. Barr, P. Taylor, G. Phillips, and D. Ewins (1998). Experience in using knee angles as part of a closed-loop algorithm to control fes-assisted paraplegic standing. In *6th Vienna International Workshop on Functional Electrostimulation*, pp. 137–140. [cited at p. 30]

Woodford, B. J., R. R. Carter, D. McCreery, L. A. Bullara, and W. F. Agnew (1996). Histopathologic and physiologic effects of chronic implantation of microelectrodes in sacral spinal cord of the cat. *Journal of Neuropathology & Experimental Neurology 55*(9), 982–91. [cited at p. 39]

Yoshida, K. and K. Horch (1993b). Selective stimulation of peripheral nerve fibers using dual intrafascicular electrodes. *IEEE Transactions on Biomedical Engineering 40*, 492–494. [cited at p. 28]

Zoll, P. M. (1952). Resuscitation of the heart in ventricular standstill by external electric stimulation. *New England Journal of Medicine 247*(20), 768–71. [cited at p. 26]

Zoll, P. M. and A. J. Linenthal (1963). External and internal electric cardiac pacemakers. *Circulation 28*, 455–66. [cited at p. 26]

Chapter 3

Strategies for Generating Prolonged Functional Standing Using Intramuscular Stimulation or Intraspinal Microstimulation *

"The ultimate measure of a man is not where he stands in moments of comfort and convenience, but where he stands at times of challenge and controversy."

- Dr. Martin Luther King, Jr.

3.1 Introduction

Spinal cord injury (SCI) is a devastating neurological trauma that has an enormous impact on the quality of daily life of the affected individual. One approach to improving the quality of life for people with SCI is to develop a system to restore standing using functional electrical stimulation (FES). The use of FES has been shown to play a role in strengthening muscles, improving bone density and reducing spasticity and contractures in people with SCI (Stefanovska et al., 1989; Bajd et al., 1985; Belanger et al., 2000). Upright posture has the physiological benefits of improving the functioning of internal organs and increasing blood pressure (Belanger et al., 2000; Guest et al., 1997). It also has the psychological advantage of allowing people who use wheelchairs to interact at eye-level with their peers

*A version of this chapter has been published. ©2007 IEEE. Reprinted, with permission, from: **Lau B., **Guevremont L., Mushahwar V.K., Generating Prolonged Functional Standing Using Intramuscular Stimulation or Intraspinal Microstimulation, *IEEE Transactions on Neural Systems and Rehabilitation Engineering* (E-Pub ahead of print, March 2007, **co-first authors) and to perform tasks in areas otherwise inaccessible from a seated position. For these reasons much work has been done to develop a stable FES system for restoring standing in people with paraplegia and low-level quadriplegia.

Current strategies for restoring standing in individuals with SCI most often involve the open-loop control of electrical stimulation which is applied peripherally to the nerves or motor point of the extensor muscles in the legs. Predetermined stimulation levels are applied using surface electrodes (Wieler et al., 1999), or through implanted systems (Sharma et al., 1998). These methods have achieved some success; however, residual problems remain, such as unpredictable and non-linear force recruitment of the muscles as well as rapid fatigue of evoked responses. These issues have partially been addressed by designing more sophisticated controllers that use feedback signals to provide information about the kinematics and kinetics of standing in order to determine appropriate stimulation levels and reduce the incidents of unnecessary over-stimulation of muscles (Donaldson Nde and Yu, 1996; Veltink and Donaldson, 1998; Davis et al., 2001; Wood et al., 1998).

Intraspinal microstimulation (ISMS) is a novel FES technique that, through the activation of motoneurons within the spinal cord, is able to generate more fatigue-resistant muscle contractions than conventional peripheral FES techniques such as intramuscular stimulation (IM-S). Muscle contractions with ISMS are generated by applying low levels of electrical stimulation (1-300 μA) through an array of microwires (30 μm in diameter) implanted within the ventral horn of the grey matter in the lumbosacral region of the spinal cord. This region is relatively motion-free, and is protected by the spinal column, but most importantly it contains the cell bodies of the majority of motoneurons innervating the muscles of the lower limbs. By stimulating in this region of the spinal cord we are able to elicit a large set of muscle responses ranging from single joint movements to full limb flexion or extension synergies (Mushahwar et al., 2002).

The purpose of this study was to develop a FES system that uses closed-loop control of ISMS in order to generate functional standing. Ground reaction forces (GRFs) and knee and ankle joint angles were used as feedback signals for the controller. Threshold-based rules were used to modulate the stimulation amplitude applied to the knee and ankle extensor muscles in order to maintain a standing posture with minimal muscle activation. Our results demonstrated that the combination of the fatigue-resistant properties of ISMS and the amplitude modulation of stimulation during closed-loop control provides prolonged periods of balanced standing posture. These results were compared to open- and closed-loop strategies similar to those currently in use with IM-S.

3.2 Methods

Seven spinally-intact adult cats (2 females, 5 males) weighing between 2.9-4.5 kg were used in the study. All experimental procedures were approved by the University of Alberta Animal Welfare Committee. Anesthesia was temporarily induced through the inhalation of isoflurane (2-3% isofluorane in carbogen) and an intravenous (i.v.) catheter was inserted for use in administering sodium pentobarbitol (Somnotol) throughout the remainder of the experiment (25 mg/kg induction; maintenance 1:10 saline dilutions of the anesthetic). At the end of the experiment the animals recovered in a heated kennel. A total of 13 experimental sessions were performed using either IM-S (9 experiments) or ISMS (4 experiments) paradigms. During these experiments, individual trials were conducted to test the open-loop (14 trials) and closed-loop (17 trials) control strategies.

3.2.1 Intramuscular Electrode Implantation

Nine experiments were conducted in a total of 6 cats (3 animals were used in two experimental sessions) using IM-S. The cats were implanted with sterilized IM electrodes while under isoflurane anesthesia before their transfer to i.v. Somnotol for the remainder of the experiment. The IM electrodes (9 strand stainless steel Cooner wire, insulated except for 3-4 mm tips) were implanted percutaneously near the motor point of the knee extensor (vastus lateralis) and ankle extensor (gastrocnemius lateralis) muscles of each leg. Wires were not implanted in the hip extensors since they provided a backwards, rather than downwards, trajectory leading to slippage of the hindlimb. At the end of the experiment the wires were removed and the animal recovered in a heated kennel.

Two dual-channel constant current stimulators (EMS-6500, Electrostim Medical Services, Inc., Tampa, FL) generated and delivered trains of IM-S (biphasic charge balanced, 0.1-20 mA, 200 μs depolarizing pulse, 50 pulses/s) as dictated by the control program.

3.2.2 Intraspinal Microstimulation Array Implantation

Four animals were implanted with ISMS arrays consisting of 12 microwire electrodes (30 μm diameter, stainless steel, insulated except for 30-60 μm exposed tips). The wires were bilaterally implanted in segments L5-L7 of the spinal cord of adult cats under sodium pentobarbital anesthesia. The microwire tips were placed in the ventral horn (lamina IX) within the spinal cord and targeted 2 regions generating strong knee extension and whole limb extensor movements. Independent knee extensor and whole limb extensor movements of the left and right hindlimbs were evoked by ISMS through microwires implanted bilaterally in the cord using techniques described in detail elsewhere (Mushahwar et al., 2000). The muscle activity evoked during stimulation through individual microwires or combinations of wires was evaluated qualitatively through palpation and visual inspection. Activation of specific muscles within a synergy was not quantified due to the need to minimize trauma to the legs (i.e., avoid implantation of electromyography and nerve cuff electrodes for quantification). Two animals received chronic implants during surgeries performed under aseptic conditions after which they recovered for 10 days before conducting stimulation experiments. The other 2 animals in this group were used in terminal experiments where data collection was performed immediately following the implantation of the ISMS array. At the end of these experiments the animals were sacrificed by i.v. administration of euthanyl (100 mg/kg).

A custom made 16-channel constant current stimulator was used to deliver low levels of electrical current through the microwires in order to evoke the desired motor responses. Fused muscle contractions were achieved by applying trains of interleaved pulses (1-300 μA, biphasic charge balanced, 200 μs depolarizing pulse, 400 μs balancing pulse, 25 pulses/s) through pairs of microwires which generated similar movements (e.g., knee extension) when stimulated independently. Two pairs of interleaved stimulation channels were used in each side of the spinal cord to elicit ipsilateral knee extension and whole limb extensor movements, resulting in a total of 8 stimulation channels.

3.2.3 Experimental Setup

The anesthetized cat was transferred to a partial body support sling (figure 3.1A). Reflective markers were placed on the iliac crest, the hip, knee, ankle and metatarsophalangeal (MTP) joints and the tip of the third toe so that limb positions and joint angles could be determined offline from video recordings. Both sides of the animal were filmed using two JVC digital video cameras (30 frames/s) placed orthogonally at a distance of approximately 1 m from the animal. This significantly reduced the distortion in the limb segments due to parallax effects. A calibration grid was placed in the field of view in order to perform frame-by-frame scaling of the video data.

The hindlimbs of the animal were placed on parallel force plates allowing GRF information to be recorded independently for the left and right legs. The force plates were calibrated at the beginning of each experiment using a 1 kg-weight. Joint angles were obtained through four biaxial accelerometers (Analog Devices ADXL213) that were secured firmly along the limb axis above and below the ankle joint on the tibial and foot segments, respectively, of each hindlimb. The initial angles of the knee and ankle during passive, partially supported standing were measured with a protractor before each stimulation trial. These angles were used by the controller to shift the accelerometer voltage values to the appropriate range. Since the accelerometers were aligned along a limb axis, the angle of each accelerometer represented the angle of that limb segment in space. The accelerometers provided measures of the projection of gravity onto their x- and y-axes which were then used in trigonometric equations to determine the angle of the limb relative to horizontal. The ankle angle was approximated by summing the angles of the foot and tibial segments of the limb as calculated from the accelerometers. The knee angle was approximated by doubling the angle of the tibial limb segment and correcting with an offset.

The ankle and knee angles measured from the video data and calculated from the accelerometer signals are shown in figure 3.1B. A high correlation is seen between the two methods indicating that accelerometers can be used to obtain a real-time approximation of

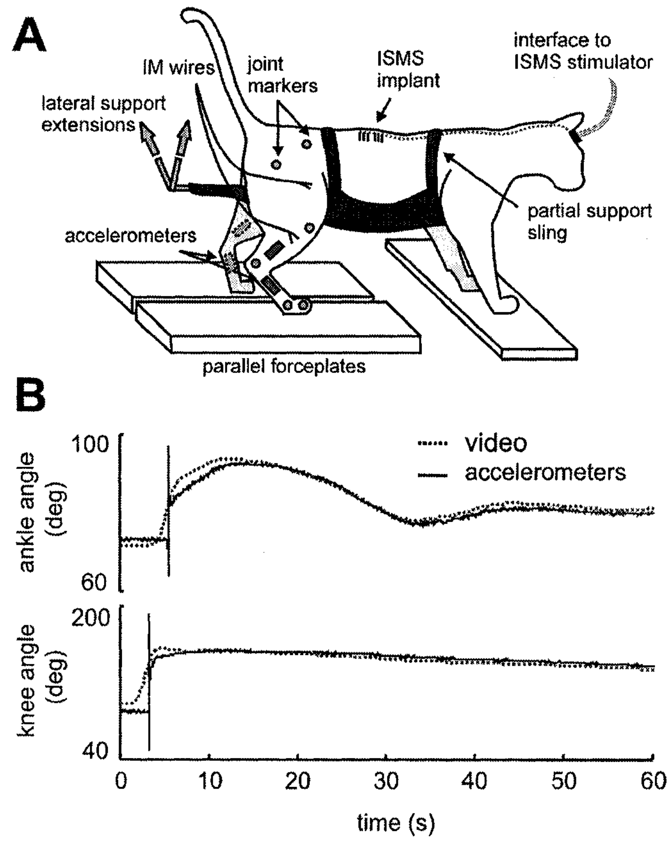

Figure 3.1: *Experimental set-up and methods.*

(A) Schematic of setup used for animal suspension and stimulation. The weight of the animal is partially supported by a body harness. The hindlimbs are placed on two parallel force plates for GRF recordings, and dual-axis accelerometers are attached securely above and below the ankle joints of both hindlimbs for real-time knee and ankle joint angle measurements. Joint markers are attached for offline kinematic analysis. (B) Ankle and knee angles calculated from the video (dotted) and approximated from the accelerometer signals (solid). The strong correlation indicates that the accelerometers provide a good real-time estimation of the limb kinematics. The accelerometer signals contain high frequency acceleration profiles (spikes) at the onset of standing due to the abrupt change in posture.

the ankle and knee angles for closed-loop control.

3.2.4 Controller Design

The open-loop and closed-loop controllers were implemented in Visual C++. The program was executed on a desktop PC which was interfaced with the IM-S or ISMS constant current stimulators via a digital-to-analog (NI-6723) board. Feedback signals from the accelerometers (8 channels) and force plates (2 channels) were sampled at 500 samples/s by an analog-to-digital (NI-6033) board before being smoothed in the control software by applying a 150 ms sliding window average.

During open-loop control pre-determined stimulation levels were applied to activate extensor muscles of the leg using IM-S or ISMS. The stimulation level eliciting the first visible contraction (motor threshold), and the stimulation level required for achieving the desired response were determined at the beginning of each trial by visual inspection. These values, along with the rate of increase of stimulation amplitude from the threshold to desired level (default increment of 0.75 mA/pulse) were set using a graphical user interface (GUI) to the control program. At the initiation of each standing trial, the amplitude of stimulation applied to each muscle was increased automatically by the controller from motor threshold to the specified desired level and maintained for the duration of each open-loop trial.

The closed-loop controller used joint angles and GRFs to detect collapse of each limb and to modulate appropriately the amplitude of the stimulation required for standing. Independent control decisions for the left and right legs were made based on comparisons between the joint angle and GRF signals and the threshold values selected to represent the kinematics and kinetics associated with stable standing. The closed-loop controller used a GRF level corresponding to 12.5% of the total body weight per hind leg as the target GRF during standing. Upper and lower thresholds for the acceptable range of GRFs were set at 1 N from this level. The use of 12.5% of the total body weight as the target was based on GRF levels seen during preliminary open-loop FES standing trials when the cat's hind quarters were observed to lift completely out of the support sling. Unloading of the sling occurred at a summed left and right GRF value equivalent to 25% of the total body weight of the animal, indicating that this level of force was sufficient for achieving load-bearing standing in our setup. A force transducer placed inline with the rear tether of the support sling during preliminary trials indicated no vertical load at this point (data not shown). During these trials, when the hindlimbs of the animal began to collapse the force transducer registered increased loading of the rear tether of the support sling with corresponding reduction in the GRFs at the force plates. Reduction in vertical GRF was then used as a measure of reduction in the percentage of body weight that the animal was supporting with its own limbs (as opposed to support provided by the sling). The transducer was removed during actual trials so that dual tether points could be used to provide some lateral stability (fig

3.1A). The decay in force in a trial was presumed to be due to muscle fatigue because after a period of recovery, the same force levels could be elicited with the same stimulus amplitudes both in the intramuscular and intraspinal stimulation trials.

Target values specifying the minimum acceptable ankle and knee angles for each leg were selected based on signals obtained during an open-loop trial conducted during the same experiment. The upper and lower threshold limits to the range of acceptable joint angles were set to $\pm$ 5° from the target value.

Joint angles and GRF signals were initially acquired by the control program for 0.5 s before the onset of stimulation in order to obtain baseline values from the force plates and accelerometers to correct for drifts in the signals between trials. The following closed-loop control rules were designed such that the stimulation of the knee extensor was modulated in order to maintain both the GRF and knee joint angle for that limb within the predetermined threshold ranges.

IF	ipsilateral GRF $>$ upper threshold
	OR ipsilateral knee angle $>$ upper threshold
THEN	decrease ipsilateral knee extensor stimulation
ELSE IF	ipsilateral GRF $<$ lower threshold
	OR ipsilateral knee angle $<$ lower threshold
THEN	increase ipsilateral knee extensor stimulation
ELSE	maintain ipsilateral knee extensor stimulation at current level

Similarily, stimulation of the ankle extensor muscle was modulated in order to maintain the ankle angle within the threshold range for that joint.

IF	ipsilateral ankle angle $>$ upper threshold
THEN	decrease ipsilateral ankle extensor stimulation
ELSE IF	ipsilateral ankle angle $<$ lower threshold
THEN	increase ipsilateral ankle extensor stimulation
ELSE	maintain ipsilateral ankle extensor stimulation at current level

Since the knee extensor stimulation was based both on GRF and knee joint angle, priority was given to decisions based on GRF levels in cases when the two responses contradicted (i.e., if the knee was extended beyond the acceptable range and the GRF was low the extensor stimulation would continue to be increased to generate more GRF).

Balance of the GRF of each hindlimb was achieved by setting the desired force range to be the same for both legs. During closed-loop control the amplitude of stimulation was updated every 600 ms using increments specified in the GUI for each channel. Default increments of 0.25 mA and 10 μA were used for closed-loop control of IM-S and ISMS, respectively. Three stimulation trials were typically conducted during each experimental session. The first trial consisted of 60 s of open-loop control using the IM-S or ISMS amplitudes previously selected by visual inspection. The data recorded during this initial trial (OL-l) were used to select appropriate threshold levels of the feedback signals for closed-loop control. The remaining two trials were conducted using: 1) the closed loop controller (CL) with initial stimulation amplitudes similar to those used in the first trial, and 2) the open-loop controller using high stimulation levels (OL-h) comparable to those reached at the end of closed-loop control. The OL-h trial was designed to provide a better comparison between the standing achieved using open- and closed-loop control by selecting elevated stimulation levels in order to preempt muscle fatigue (Kobetic et al., 1999). The initial objective of this study was to demonstrate that standing could be achieved for a duration of 15 min. For this reason, during OL-h trials stimulation was terminated after 15 min. However, CL trials were allowed to continue until either the GRF provided by the two hindlimbs was insufficient for load bearing, or the standing posture (the balance of knee and ankle joint angles) could no longer be maintained. The animals were given i.v. injections of dextrose and were allowed to rest for 30 min after the OL-l trial and at least 1 hr between each subsequent trial. The CL and OL-h trials were not performed in the same sequence in all animals to minimize order effects on the overall results of the study.

3.2.5 Data Acquisition and Analysis

The raw accelerometer and force signals as well as the stimulation control signals generated by the controller were acquired at a rate of 2083 samples/s using CED Power 1401 analog-to-digital board and Spike2 data acquisition software (Cambridge Electronic Design, Ltd., Cambridge, UK). Data analysis was completed using custom written routines for Matlab V7.0 (The MathWorks Inc., Natick, MA, US).

The video recordings were digitized and the x-y coordinates of each of the joint markers were extracted using a custom software package (MotionTracker2D) written in Matlab by Dr. Douglas Weber (University of Pittsburgh, Pittsburgh, PA, USA). The motion of both hindlimbs was reconstructed using the coordinates of the markers as well as the measured lengths of the limb segments. Each frame was calibrated in the x and y axes to correct for skew introduced by the camera angle. The resulting values were used to reconstruct stick figures from which ankle and knee joint angles were extracted. A flashing light emitting diode (LED) located within the video field of view of the cameras was used to synchronize the kinematic and kinetic data.

For analysis and representation, the left and right GRFs were normalized to the lower limit of the acceptable force range for each leg (12.5% full body weight - 1 N). The duration of standing achieved was determined by comparing the sum of the left and right GRFs to a summed threshold value (25% full body weight - 2 N). The period of time after which the animal was unable to maintain the GRFs above this threshold level was determined to be the duration of standing. This was done in order to differentiate between the actual collapse of standing and postural shifts during which the weight of the animal was dynamically transferred from one limb to the other while still maintaining total load-bearing forces.

The rate of force decay was calculated for each leg as the difference between the GRF achieved during the first 10 s of the trial and the GRF maintained by that leg at the end of standing. This change in force was expressed in terms of the percent of the total body weight of the animal divided by the duration of standing (%BW/min). An indication of the amount of current required to generate standing was determined by summing the instantaneous current applied through all electrodes over the course of standing and dividing by the duration of standing achieved. Variance in the forces achieved in the left and right legs during each trial was calculated for all data points (n) as the squared difference between the recorded GRF and the threshold value ($(\text{force - threshold})^2/\text{n}$). The balance between the two legs was calculated as the average percent difference in loading throughout the trial. For the force calculations, the raw signal (2083 sample/s) was down-sampled by a factor of 2 and filtered at 30 Hz.

3.3 Results

A total of 9 IM-S and 4 ISMS experiments were conducted for this study. The criteria used to define functional standing were: 1) to have balanced loading of each leg, and 2) to maintain a prolonged standing posture. Some degree of standing was achieved using open- and closed-loop control in all of the IM-S experiments and 3 of the 4 ISMS experiments. Movements were elicited in all ISMS experiments by applying 25 Hz interleaved stimulation through pairs of microwires, whereas in IM-S experiments 50 Hz non-interleaved stimulation was applied through single electrodes. In one of the four animals implanted with ISMS arrays, the prefabricated wires were too short and could not reach the target locations within the ventral horn. For this reason, sufficient extensor force for standing could not be generated while applying safe levels of stimulation (<350 μA) through the microwires implanted in this animal. Results from this animal were not included in the analysis.

3.3.1 Initial Open-loop Control Trials

At the onset of each trial, visual inspection was used to select stimulation levels resulting in the balanced posture of the cat. However, unbalanced loading of each leg was typically seen during open-loop standing trials regardless of the stimulation method used (IM-S or ISMS). The data shown in figure 3.2 are taken from two OL-l trials and are representative of left and right GRF imbalances observed in all OL-l and OL-h trials. Standing was typically maintained for the full duration of each OL-l trial due to the 60 s limit imposed by the experimental protocol. However, the force profiles achieved using IM-S and ISMS had strikingly different features, primarily in the rate of decay of the GRFs. Intramuscular stimulation trials were characterized by a rapid decay in GRF at a rate of 26.77 ± 19.29 %BW/min (mean $\pm$ standard deviation) whereas ISMS demonstrated a net potentiation of GRFs over the first 60 s of stimulation (increases in GRF by 3.57 ± 7.52 %BW/min).

During OL-1 trials, less than 7% of the current required during IM-S standing (11.11 $\pm$ 3.69 mA) was needed for standing with ISMS (0.80 $\pm$ 0.14 mA). Standing using ISMS was achieved by stimulating through 6 (in one animal) or 8 (in two animals) microwires implanted bilaterally in the spinal cord.

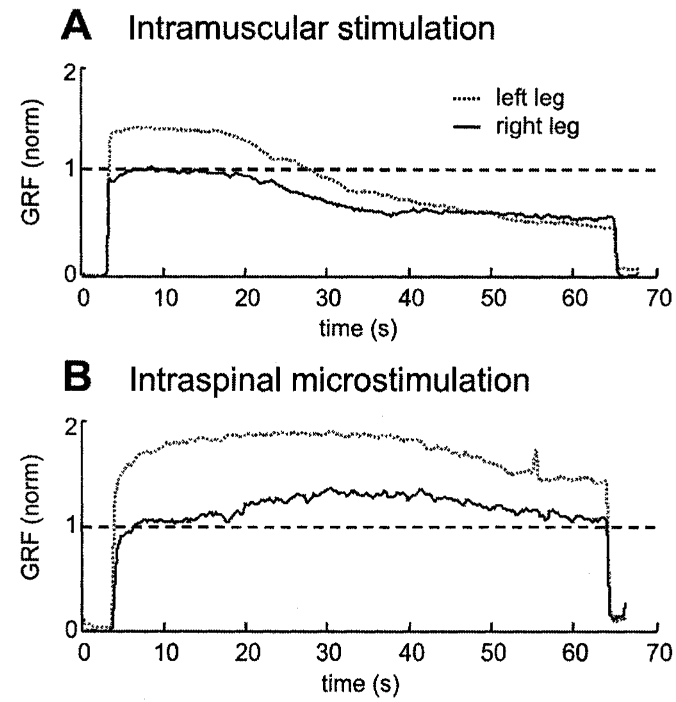

Figure 3.2: *Ground reaction forces during open-loop control.*

Examples of ground reaction forces for the left (grey) and right (black) hindlimbs during 2 OL-1 trials using (A) non-interleaved IM-S and (B) interleaved ISMS. Stimulation levels for these trials were selected by visual inspection and resulted in imbalanced forces in the two legs. Ground reaction forces were normalized to the minimum force criteria for functional standing (12.5% body weight per hindlimb, equivalent to 4.8 N in A and 4.0 N in B) indicated by the horizontal dashed line.

3.3.2 Intramuscular Stimulation vs. Intraspinal Microstimulation

A more detailed comparison of standing achieved using non-interleaved IM-S and interleaved ISMS was performed based on results from OL-h and CL standing trials.

Open-loop control

Figure 3.3 shows data from OL-h trials conducted using IM-S (A) and ISMS (B). The groups of 4 stick figures at the top of the figure indicate the kinematics of the left and right legs of the animal immediately prior to the onset of stimulation, within the first 30 s of stimulation, within the last 30 s of stimulation, and immediately after the termination of stimulation. Also shown are the full sequences of stick figures representing the posture of the cat at 10 s and 30 s time intervals throughout the IM-S and ISMS trials, respectively. Non-interleaved intramuscular stimulation was characterized by a rapid decay in the GRF (normalized, first trace) and joint angles (bottom two traces), whereas, interleaved ISMS resulted in GRF and joint angles which typically remained stable after an initial period of potentiation. The duration of standing achieved during the IM-S trial is indicated by the arrow on the x-axis at 1.83 min. The ISMS trial was terminated before the collapse of standing due to a 15 min time-limit imposed by the experimental protocol. The rates of force decay for these IM-S (27.08 %BW/min) and ISMS trials (0.47 %BW/min) are representative of all OL-h trials conducted using the two stimulation techniques (summary data provided below).

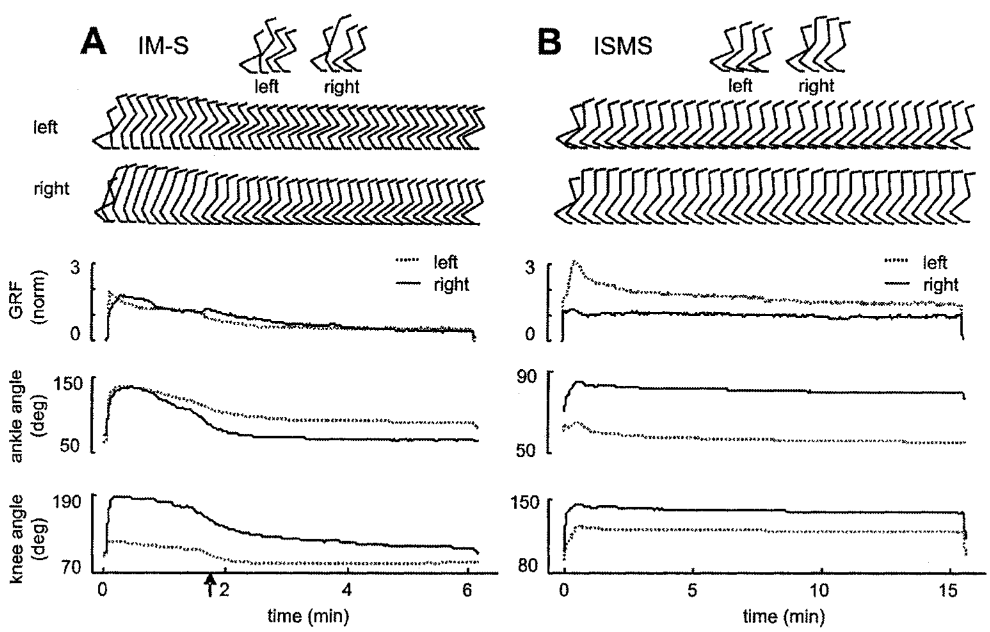

Figure 3.3: *Open-loop control of IM-S and ISMS.*

Data from OL-h trials conducted using non-interleaved IM-S (A) and interleaved ISMS (B). The groups of 4 stick figures in the top row indicate the kinematics of the left and right hindlimbs of the animal immediately prior to the onset of stimulation, within the first 30 s of stimulation, within the last 30 s of stimulation, and immediately after the termination of stimulation. The sequences of stick figures in the 2nd and 3rd rows show the hindlimb kinematics at 10 s and 30 s intervals throughout the IM-S and ISMS trials, respectively. The normalized GRF (first trace) and joint angle signals (bottom two traces) show a rapid decay in the muscle responses during IM-S, but remain stable after an initial period of potentiation during ISMS. Note that the time scales are different in A and B.

The stimulation amplitudes applied during OL-h trials using IM-S often resulted in hyperextension of the knee and ankle joints. This occasionally resulted in the hip joint being elevated above the iliac crest. As the stimulated muscles fatigued, the animal's posture adopted a more normal stance with the hip inline or below the iliac crest. This behavior was limited to the use of IM-S and was not seen when using ISMS.

Closed-loop control

During each CL trial, periods of stable standing were achieved by selecting appropriate GRF and joint angle threshold ranges based on the levels recorded during an initial OL-I trial. Three different standing postures were achieved using closed-loop control of IM-S: hyper-extended standing, standing with oscillations, and stable standing with postural shifts. Hyper-extended standing was due to the high priority given to maintaining GRF levels resulting in an uncompensated hyper-extension of the knee joint. Standing with oscillations occurred when an excessively large stimulation increment was used during amplitude modulation. Selecting an appropriate stimulation increment was difficult due to the sharp force recruitment profile and hysteresis properties of the muscles. This resulted in a large amount of variability in the response generated for small changes in the stimulation amplitude. Increments of 0.75 mA applied every 600 ms typically resulted in oscillations (data not shown), whereas, 0.25 mA increments provided smoother responses during closed-loop control. Stable standing with postural shifts was a desirable result of closed-loop control. A postural shift was characterized by a decrease in GRF in one limb with a corresponding increase in GRF of the other limb. This introduced some unevenness in the GRF and joint angles allowing stimulation levels to be decreased in some muscles and increased in others. During a postural shift the total force exerted by both hindlimbs was maintained within the threshold range; thus, load-bearing standing was preserved. Although ISMS typically generated stable GRFs, postural shifts were achieved in several IM-S trials through the corrective responses of the closed-loop controller.

Figure 3.4 shows data taken from one trial in which an 8.50 min period of standing was achieved using closed-loop control of IM-S. The stick figures and plots shown have the same format as those in figure 3.3 but are separated for the left and right legs and include an additional trace indicating the level of stimulation applied through each IM-S electrode (ankle extensor - dashed; knee extensor - solid). The upper and lower limits of the threshold ranges for GRF and joint angles are indicated by the horizontal dotted lines. Throughout this trial the stimulation of the knee extensor was increased in both legs in order to maintain the GRF and knee angle within the acceptable ranges. Several periods of ankle hyper-extension occurred as a result of the steep force recruitment curve of the ankle extensor muscle, and the differential muscle fatigue of the knee and ankle extensor muscles. In this example, as the stimulation to the left ankle extensor muscle (gastrocnenius lateralis) was increased to maintain the ankle joint angle within the acceptable range, there was a sharp increase in the force generated by this muscle, causing the ankle joint to hyper-extend. This was coupled shortly after with a flexion of the left knee as the knee extensor muscle fatigued, allowing the knee flexor component of gastrocnemius lateralis to dominate the knee movement. The controller responded by decreasing the stimulation to the ankle extensor which resulted in the ankle joint angle returning to within the acceptable range. Coupling of knee flexion with ankle hyper-extension was not seen unless the knee extensor was fatigued. In the absence of fatigue, the knee extensor force was typically sufficient to maintain knee extension in the presence of the flexor component of gastocnemius lateralis (e.g., right ankle and knee joint extension at 4 min). The kinematics of these movements were well captured in the sequence of stick figures, showing data taken at 15 s intervals throughout the trial. This trial was terminated when the left and right knee stimulation amplitudes reached the maximum safe stimulation level (20 mA) and it was apparent that no further modulation of knee angle or GRF could be achieved.

Figure 3.5 shows data taken from one trial where a 28.33 min period of standing was achieved using closed-loop control of ISMS. The plots are formatted the same as those in figure 4 except for the stimulation amplitude traces which have been divided into the two channels providing ankle extension and the two generating knee extension for the left and right legs. The sequence of stick figures at the top right of the figure represent kinematic data taken at 60 s intervals throughout the duration of standing. The GRF and joint angles achieved using ISMS were very stable and required only minor changes in the amplitude of the stimulation applied in order to maintain the standing posture. The amplitude of

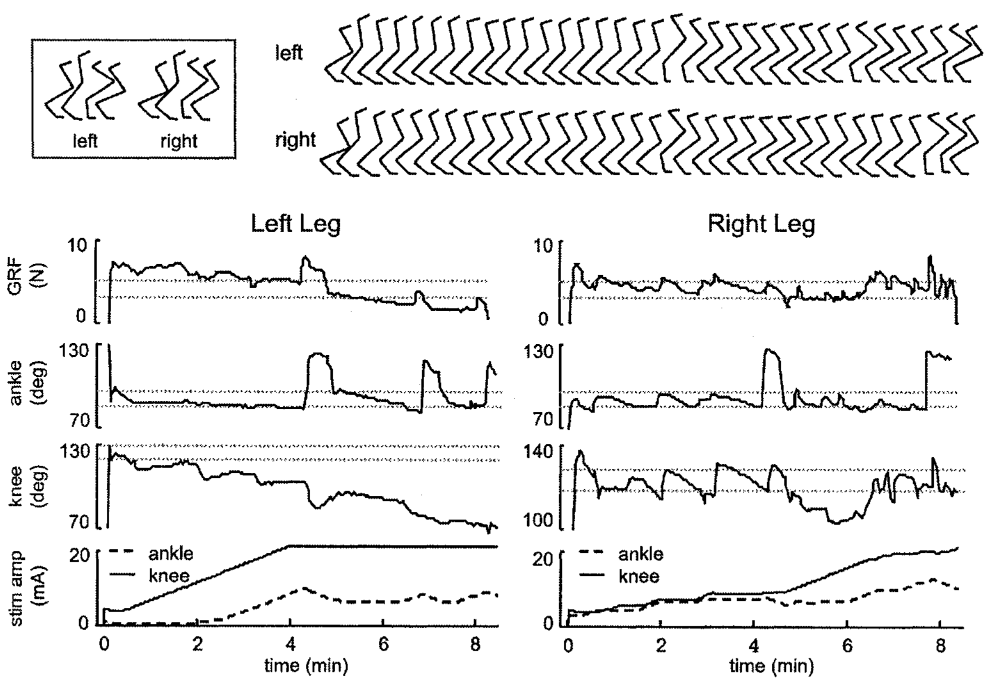

Figure 3.4: *Closed-loop control of IM-S.*

The GRFs, joint angles and stimulation amplitudes for the left (left column) and right (right column) hindlimbs during one CL trial using IM-S. The groups of 4 stick figures (box, top left) indicate the kinematics of the left and right hindlimbs of the animal immediately prior to the onset of stimulation, within the first 30 s of stimulation, within the last 30 s of stimulation, and immediately after the termination of stimulation. The sequences of stick figures (top right) show the kinematics of the hindlimbs at 10 s intervals throughout the 8.50 min-long IM-S trial. The upper and lower limits of acceptable GRF and joint angle ranges are indicated by the horizontal dotted lines. Throughout this trial the amplitude of stimulation to the knee (solid) and ankle (dashed) extensors was modulated in both legs in order to maintain the GRF and angle signals within the acceptable ranges. This sequence shows an example of the effect of steep muscle force recruitment and differential muscle fatigue causing the ankle to hyper extend and the knee angle to collapse.

stimulation to the ankle extensors was decreased and maintained at the minimum level in both legs, and the amplitude of stimulation to the left knee extensor stimulation was increased slightly as the GRF decayed below the minimum acceptable range. Periods of knee collapse and ankle hyper-extension were not encountered in any of the trials with ISMS.

Summary

The GRF data for all standing trials conducted in this study are shown in figure 3.6. Intramuscular stimulation trials using OL-h and CL control are shown in A and B, and ISMS trials using OL-h and CL control are shown in C and D. Each thin grey line represents the GRF from a single trial normalized to the lower bound of the acceptable force range

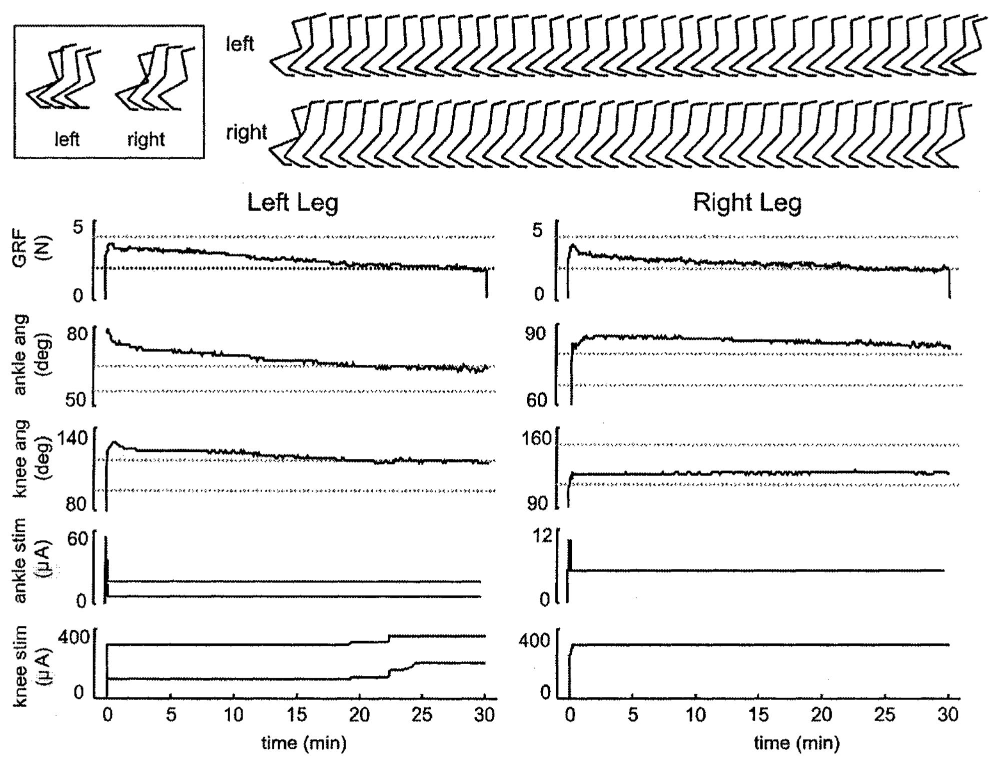

Figure 3.5: *Closed-loop control of ISMS.*

The GRFs, joint angles and stimulation amplitudes for left (left column) and right (right column) hindlimbs during one CL trial using ISMS. The groups of 4 stick figures (box, top left) indicate the kinematics of the left and right hindlimbs of the animal immediately prior to the onset of stimulation, within the first 30 s of stimulation, within the last 30 s of stimulation, and immediately after the termination of stimulation. The sequences of stick figures (top right) show the kinematics of the hindlimbs at 60 s intervals throughout the 28.33 min-long ISMS trial. The upper and lower limits of the GRF and joint angle acceptable ranges are indicated by the horizontal dotted lines. The amplitude of stimulation applied to the ankle extensor muscles remained stable for the majority of the trial. Increased stimulation was applied to the left knee extensor at 19 min due to a progressive reduction in the GRF.

for standing (indicated by the horizontal line at 1). The time at which each thin trace falls and remains below this critical level is determined to be the time of failure of standing for that trial. The thick black line in each plot represents the average of all of the GRF data calculated up to the duration of the shortest trial in each group.

The most striking difference between trials conducted using non-interleaved IM-S (A and B) and interleaved ISMS (C and D) is the rate of decay of the forces. Intramuscular stimulation is characterized by rapid muscle fatigue while ISMS is able to elicit prolonged and stable force generation. Using open-loop control of ISMS, in two separate trials, 15 min-long periods of standing were achieved before the stimulation was terminated at the time-limit imposed by the experimental protocol. One trial was conducted in the ISMS

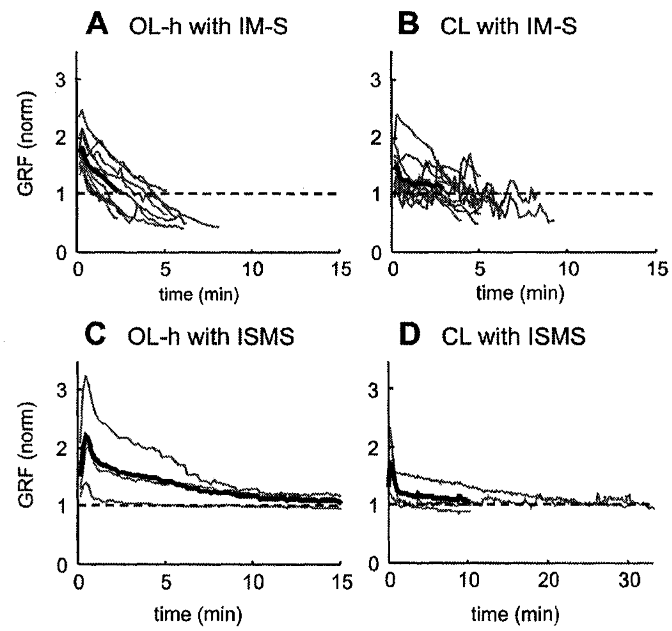

Figure 3.6: *Ground reaction forces.*

The GRFs recorded during all standing trials. Data from non-interleaved IM-S trials using OL-h and CL control are shown in A and B, and data from interleaved ISMS trials using OL-h and CL control are shown in C and D. Each thin grey line represents the GRF from a single trial normalized to the lower bound of the acceptable force range for standing (indicated by dashed line at 1). The dark line is the average of all trials taken until the termination of the shortest trial. The GRFs during IM-S trials decayed rapidly to the threshold level, while ISMS generated more fatigue resistant muscle responses. Closed-loop control resulted in an extension of the time before the IM-S evoked standing fell below threshold. Note that the time scale is different in D.

implanted animal in which sufficient forces could not be generated within safe stimulation levels. The GRF data for this trial is not shown and was excluded from the average for this group. Although the force generated in this animal was not strong enough to achieve prolonged load-bearing standing, the force decayed at a rate similar to those seen during other ISMS trials. Three closed-loop trials were conducted using ISMS. One failed quickly because an insufficient rest period (1 hr) was given between trials during the experimental session. The two prolonged CL trial using interleaved ISMS (28.33 and 32.00 min-long) were conducted after allowing 2-3 hrs rest between trials and resulted in standing that was more than 3 times longer than the best CL trial using non-interleaved IM-S (8.50 min).

Figure 3.7 provides a summary of the duration of standing (A), rate of force decay (B), average injected current (C), variance in force from threshold (D), and balance between the left and right legs (E) during all OL-h and CL trials using non-interleaved IM-S (dark bars) and interleaved ISMS (white bars). Student's t-tests ($P < 0.05$) were performed comparing control strategies (*), stimulation paradigms (**) and CL IM-S and OL-h ISMS (***). The ISMS trials conducted using the OL-h controller required an average current of 1.24 mA in order to generate 12.11 min of load-bearing standing. Intraspinal microstimulation used much less current than required during IM-S ($\sim$2.2%) and could achieve prolonged standing in most cases. The rate of decay of GRF during the ISMS OL-h trials was 1.65 $\pm$ 1.03 %BW/min, indicating a significantly slower rate of fatigue than that seen using IM-S (30.65 $\pm$ 16.70 %BW/min). In all cases ISMS resulted in significantly less variance in the forces during standing. The balance of the loading between the hind legs was significantly improved when using CL control of ISMS and IM-S.

The results of the trials conducted using various modes of stimulation indicate that interleaved ISMS is able to generate prolonged, stable, fatigue-resistant standing when compared to non-interleaved IM-S.

3.3.3 Open-loop vs. Closed-loop Control

The OL-h and CL control paradigms were compared based on the duration of load-bearing standing achieved, the rate of force decay, and the average injected current. In figure 6A and B it can be seen that the forces during OL-h trials using IM-S decay below the acceptable GRF level sooner and at a faster rate than during CL trials. The summary results shown in figure 3.7 demonstrate that for standing evoked by IM-S (black bars), the duration of standing achieved was prolonged significantly (Student's t-test, $P < 0.05$) when using CL control (4.24 $\pm$ 2.35 min) as opposed to OL-h control (2.60 $\pm$ 1.47 min). This increase in duration of IM-S evoked standing when using CL vs. OL-h control was coupled with a significant (Student's t-test, $P < 0.05$) decrease in the rate of force decay (7.64 $\pm$ 11.31 vs. 30.65 $\pm$ 16.70 %BW/min, respectively) and average injected current (44.54 $\pm$ 12.07 vs. 55.11 $\pm$ 11.59 mA, respectively).

Summary data from ISMS trials conducted using OL-h or CL control paradigms are shown in figure 3.7 (white bars). The duration of standing during ISMS trials conducted using the OL-h and CL controllers cannot be readily compared due to the fact that all OL-h trials were terminated after 15 min, even in cases when the forces had not yet decayed below

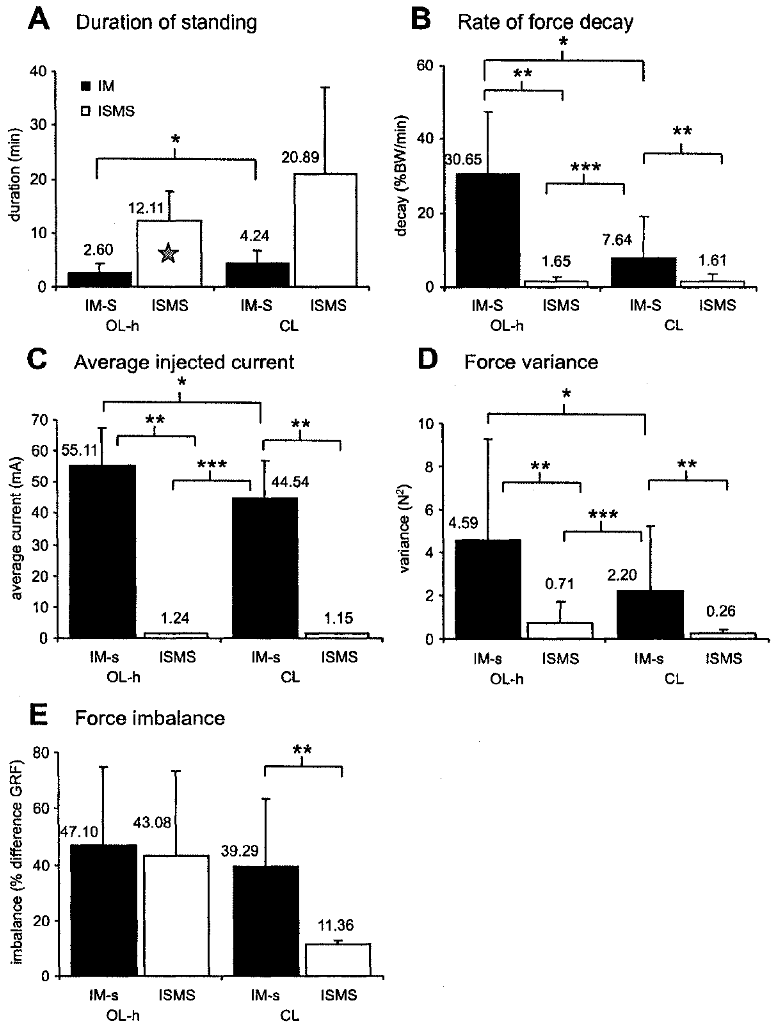

Figure 3.7: *Summary of results.*

A summary of the duration of standing achieved (A), the rate of fatigue of the muscle in terms of the decay in GRF produced (B), the average amount of current delivered to the hindlimbs per minute (C), the variance of left and right force from the GRF threshold in Newtons (D), and the imbalance between the left and right legs as a percent of limb loading (E) for all non-interleaved IM-S (dark bars) and interleaved ISMS (white bars) trials. The number of trials conducted using IM-S with CL and OL-h are 13 and 10, respectively. Three trials were conducted using ISMS with both CL and OL-h. Error bars indicated one standard deviation and significant differences (Student's t-test, $P < 0.05$) between control strategies (*), stimulation paradigms (**) and CL IM-S and OL-h ISMS (***). The ISMS duration of standing for the OL-h group was limited to 15 min in the experimental protocol. This group is marked with a star ($\star$) in A and was not included in the statistical comparison for duration of standing.

threshold. Although significance was not reached (due to the small sample size for ISMS) there is an apparent decrease in force variance and imbalance in the hindlimbs when using closed-loop control.

3.4 Discussion

Postural control of standing in the intact neuromuscular system provides 3 main functions: 1) full weight support of the body, 2) balance of the body over the base of support, and 3) stabilization of the body during movements (Rothwell, 1995). The first two functions are critical for maintaining quiet standing and the third becomes important primarily during functional reaching tasks or in the presence of external perturbations. The requirements used in this study to define successful standing were: 1) balanced loading of each leg, and 2) maintenance of a prolonged standing posture. Since perturbations could not be easily applied in our experimental setup, we cannot comment on the extent of the stabilizing support system that would be needed. These criteria were used to evaluate the relative effectiveness of the different stimulation paradigms (IM-S and ISMS), and control strategies (open- and closed-loop) implemented in this study. An anaesthetized cat model was used to resemble in part conditions of complete spinal cord injury in which descending input and long loop reflexes are disrupted. The same model was used in all trials so that valid comparisons could be made between stimulation paradigms and control strategies.

3.4.1 Stimulation Paradigms

Two different stimulation paradigms were tested: non-interleaved IM-S and interleaved ISMS. Intramuscular stimulation is a well established technique that can be implemented easily and consistently with open surgery. It also corresponds to the peripheral mode of muscle activation most widely employed in existing clinical and experimental systems for restoring functional standing. In these systems, small numbers of FES channels (typically 1-4 per leg) are used to activate large muscles (e.g., quadriceps and gluteus) to generate standing force. The IM-S approach taken here is comparable in that we stimulated the major extensors of the cat's hindlimbs. Peripheral FES is typically characterized by the reversed recruitment order of motor units (MUs) (Mortimer, 1990) leading to two consequences: 1) steep force recruitment with small increments in stimulation current, and 2) rapid decay in force due to fatigue. The strong muscle twitches generated by the MUs with lower FES thresholds result in large increases in the force generated for small increments in stimulation amplitude at levels just above motor threshold. At higher stimulation amplitudes, large stimulation increments are required to achieve small changes in the muscle force produced. A hysteresis effect also occurs, resulting in a difference between the recruitment and derecruitment profiles of the muscle. The non-linearity and hysteresis of the force recruitment curve make it difficult to generate graded muscle responses using peripherally applied FES.

Due to the preferential activation of fast MUs during peripherally applied FES, high stimulation frequencies ($\geq$20 Hz) must be utilized in order to achieve strong, fused muscle contractions. Whereas, in physiologically activated muscle, MUs typically fire asynchronously at 10-15 Hz during normal movements (Rothwell, 1995). The high stimulation frequencies required during FES result in an increase in the rate of muscle fatigue possibly through failure of the contractile mechanism of the muscle fibre (Rothwell, 1995). This rate of fatigue can be reduced by using interleaved stimulation applied to synergistic MUs in order to generate fused contractions at lower stimulation frequencies. Interleaving requires the ability to activate multiple groups of MUs within the same muscle. This can be achieved using various FES devices including intraspinal arrays (Mushahwar et al., 2002; Pikov and McCreery, 2004), multi-site cuff electrodes (Veraart et al., 1993; Tyler and Durand, 2002), or intra-fascicular electrodes (Yoshida and Horch, 1993; McDonnall et al., 2004). Another method is to use stimulation rotation, where groups of MUs are stimulated at high frequency for a short duration of time before a different group is activated (Lanmuller et al., 1999). Alternatively, surface FES can be used to activate synergistic muscles in a cyclic pattern (Krajl et al., 1986).

The fact that the fast fatigable MUs are recruited first also means that the initial level of force generated cannot be maintained for the prolonged periods of time required for functional standing. A more physiological MU recruitment order can be achieved using peripheral FES by applying various techniques including novel stimulation waveforms (Fang and Mortimer, 1991), multi-site flat interface nerve electrodes (FINEs) (Tyler and Durand, 2002), or longitudinal intrafascicular electrodes (LIFEs) (Yoshida and Horch, 1993) to activate selectively axons within a nerve. An alternative method is to apply stimulation to the ventral horn of the spinal cord in order to activate indirectly populations of motoneurons residing there. Direct extracellular activation of spinal motoneurons results in reversed recruitment similar to that seen with peripheral FES. However, the abundance of interneurons and fibres in passage in the ventral horn of the spinal cord means that these cells are most likely activated first, resulting in the recruitment of motoneurons in their normal physiological order through trans-synaptic pathways (Bamford et al., 2005; Gaunt et al., 2006). Fibres in passage (e.g., propriospinal neurons) may also be activated in the white matter adjacent to lamina IX plays a role. This physiological recruitment order explains in part the ability of ISMS to generate more graded and fatigue resistant muscle responses (Mushahwar and Horch, 1997) when compared to peripheral nerve stimulation.

The graded and fatigue resistant contractions generated using ISMS improved the stability of the responses seen during closed-loop control of standing. During closed-loop modulation of stimulation levels, instability occurred when using IM-S due to the steep force recruitment curve, and the differential rates of fatigue between the gastrocnemius lateralis and vastus lateralis muscles. In order to compensate for extreme muscle responses with IM-S, the closed-loop controller was designed with an interface allowing the user to select small stimulation increments for each channel individually. The use of small increments resulted in a closed-loop IM-S system which was responsive and stable at low stimulation levels but responded more slowly when operating at high stimulation levels (due to the decreased slope of the force recruitment curve). Open-loop control did not depend heavily on the ability to generate precision changes in muscle force once the initial stimulation levels had been selected but did occasionally demonstrate imbalances in ankle and knee joint angles during IM-S due to the differential rates of fatigue of the two extensor muscles. Imbalances in the ankle and knee joint angles were not seen in any of the trials with ISMS. It is possible that during ISMS the same spinal circuitry involved in the physiological recruitment order of motoneurons also provides a more natural balance of the muscle activation during synergistic extensor movements (Wilmink and Nichols, 2003). This would avoid the differential fatigue of various muscle groups and thereby prevent imbalances of the knee and ankle joints.

An additional advantage of ISMS is the ability to implant multiple stimulating microwires into a single target region within the spinal cord, meaning that multiple control channels can be used to generate a single movement without increasing the complexity of the system. In this study, interleaved patterns of stimulation were applied through pairs of microwires activating different MUs within a common muscle. This allowed the stimulation frequency to be reduced from 50 pulses/s for a single channel to 25 pulses/s interleaved between two channels. The reduced stimulation frequency is likely to have significantly contributed to the prolonged muscle force generated during ISMS-evoked standing by allowing the additional recovery time for the MUs between stimulation pulses (Mushahwar and Horch, 1997).

The total current needed by ISMS was significantly lower than that required for IM-S (figure 3.7C). This factor is of particular value when designing a clinical system in which the lower power requirements can result in extended battery life.

The ISMS technique is currently under development and further work is needed to achieve more accurate and stable targeting of motoneuron pools within the spinal cord. Nonetheless, the ISMS results presented here demonstrate the feasibility of this technique and the potential benefits of its use in systems for restoring standing.

3.4.2 Control Strategies

Clinical and experimental FES systems that use a wide range of control strategies for restoring standing after SCI are currently in existence. The control of standing can be achieved through continuous or state control approaches. Systems that use continuous control make stimulation decisions based on the instantaneous sensor signals as well as the rate of signal changes and cumulative error. With the careful selection of parameters, the use of continuous control in non-biological systems can result in improved tracking speed and reduced errors. However, the use of continuous control in physiological systems is difficult to implement and requires time-consuming parameter tuning (Wood et al., 1998). This is primarily due to the fact that the input/output function of muscle is non-linear and changes continuously as the muscle fatigues. For this reason, we chose to implement a state controller that modulated the amplitude of stimulation based on a limited number of system states defined by threshold values for GRFs and knee and ankle joint angles.

The human standing system can be modeled as an unstable inverted pendulum (Loram et al., 2001). In this model the ankle acts as the base pivot point above which the weight of the body is supported on a single rigid leg segment. Stability can be achieved by locking the knee and stiffening the ankle joint to maintain the center of mass over the base of support provided by the foot. The cat model used in this study does not conform to the inverted pendulum model due to the differences in standing posture between quadrupeds and bipeds. Cats stand on their toes with bent knees (digitigrade posture), whereas, humans stand with the entire sole of the foot on the ground and a straight supporting limb (plantigrade posture). The state-driven closed-loop controller described here was designed for the digitigrade posture assumed by cats and was meant to provide a comparison between the standing achieved by using open- and closed-loop control of various stimulation methods. Although the differences in biomechanics between cats and humans prevents the direct translation of our control rules, our use of joint angles and reaction forces is consistent with experimentally and clinically implemented FES systems for restoring standing in people with SCI.

Classical methods for restoring standing in individuals with paraplegia include the use of extensive knee-ankle-foot orthoses to provide a rigid support over which the centre of mass could be balanced using the voluntary control of the upper body and external supports. The most common approach for achieving standing with FES is to stimulate the quadriceps muscle in order to counteract the collapse of the knee and to maintain the joint in a locked position. The duration of standing achieved using FES can be prolonged through the use of hybrid techniques such as the combination of ankle-foot orthoses (providing ankle stiffness) and FES applied to the quadriceps muscle (providing a rigid supporting limb) (Davis et al., 1999). The ankle-foot othosis would replace the use of ankle joint feedback signals in our animal model and allow a single channel of stimulation per leg to generate the limb extension forces. Due to the fact that no additional GRF can be generated in humans once the knee is in the locked position, the force balancing feature of our controller would require additional muscles to be stimulated (such as the leg adductor/abductors) or the upper body to be used to provide balance voluntarily. In our quadruped model there was no anterior/posterior instability. However, these fore/aft movements have been addressed in other systems for human standing by using sensory feedback for voluntary correction of sway (Andrews et al., 1988) or by providing variable stimulation to the ankle muscles to generate appropriate joint stiffness (Hunt et al., 2001). Functional electrical stimulation systems can be designed to provide additional stability of the pelvis and lower back, allowing the user to remove a hand from the support when performing functional tasks (Triolo et al., 1993).

The accelerometer configuration used to measure the ankle joint angles of the cats was based on work done by Veltink and Franken (Veltink et al., 1996) in measuring knee angles in able-bodied humans. They found that a differential configuration consisting of accelerometers placed above and below the joint gave the earliest detection of slowly occurring flexion of the knee, whereas, configurations with both accelerometers placed on the thigh segment resulted in the earliest detection of rapid unlocking of the knee (Veltink et al., 1996). Due to the natural bent knee posture of the cat during standing, knee locking/unlocking did not occur during our experiments. Changes in posture were characterized by relatively slow movements making the cross joint accelerometer configuration appropriate for our study. We found that the accelerometers used in our system required calibration before the initiation of each trial in order to obtain the baseline angle from which variations could be calculated. For this reason, and because the success of closed-loop standing is heavily dependent on the quality of the feedback signal, future clinical implementation of our control system would require developments to the software interpretation of the accelerometer signals for measuring joint angles. Although standing posture was achieved in this study using open-loop control, the results did not consistently meet the functional standing requirement of balanced loading of each leg. Selection of stimulation amplitudes based on visual inspection was shown to be an ineffective method of balancing posture, as demonstrated by the large disparity between the GRF of each hindlimb during the OL-1 stimulation trials shown in figure 3.2. The closed-loop controller was able to correct for these imbalances by increasing or decreasing the stimulation levels of the knee extensor muscle if the GRF fell below or rose above the acceptable force threshold range. The GRF level set for full load bearing of the hindlimbs was equivalent to the force required to support 25% of the total weight of the animal. In a normal unsupported standing cat, the hindlimbs support on average 46% of the total body weight (Macpherson, 1988). The critical level for weight support used in this study was lower due to the increased head and body support provided by the sling. During closed-loop control we used a range of GRFs corresponding to 12.5% of full body weight $\pm$ 1 N in each leg, which allowed postural shifts to occur while still maintaining full load bearing and a good balance between the two legs. Postural shifts provided variability in the muscle activation during closed-loop control and were seen in some of the IM-S trials in this study. In the future this feature may be extended to ISMS by programming shifts in the threshold GRF levels for the two legs.

In agreement with previous reports, our results indicate that closed-loop control of IM-S is capable of generating significantly longer durations of standing than when using open-loop control. Our closed-loop controller was more effective in maintaining force since it applied the minimum level of stimulation needed to generate sufficient muscle contractions and avoid premature muscle fatigue. Prolonged standing through open-loop control required the initial selection of excessive stimulation amplitudes in order to preempt muscle fatigue. This strategy is implemented in open-loop systems in which a strong quadriceps contraction ensures that the knee remains locked, preventing an inadvertent collapse of the standing posture. The use of interleaved ISMS, even when used with a simple open-loop controller, resulted in a prolongation of the duration of standing achieved when compared to non-interleaved IM-S. The addition of feedback rules during ISMS resulted in standing with balanced loading of the two legs. Although the duration of standing achieved for open- and closed-loop control of ISMS could not be compared statistically, the IM-S results suggest that closed-loop control could extend the duration of standing achieved with ISMS.

3.4.3 Concluding Remarks

In this study we have demonstrated further evidence that closed-loop control of FES-evoked standing results in prolonged periods of balanced, load-bearing posture when compared to open-loop control. Threshold-based rules were implemented with GRF and joint angle feedback signals in order to minimize the stimulation applied to the ankle and knee extensor muscles while maintaining standing posture. The use of interleaved ISMS resulted in a further increase in the duration of standing achieved due to the improved fatigue resistance of the evoked muscle contractions. Taken collectively, the results of this study suggest that prolonged periods of load-bearing standing can be achieved by using closed-loop control in conjunction with interleaved ISMS.

3.5 Bibliography

Andrews, B. J., R. H. Baxendale, R. Barnett, G. F. Phillips, T. Yamazaki, J. P. Paul, and P. A. Freeman (1988). Hybrid fes orthosis incorporating closed loop control and sensory feedback. *Journal of Biomedical Engineering. 10*(2), 189–95. [cited at p. 30, 32, 30, 32, 94]

Bajd, T., M. Gregoric, L. Vodovnik, and H. Benko (1985). Electrical stimulation in treating spasticity resulting from spinal cord injury. *Archives of Physical Medicine and Rehabilitation 66*, 515–516. [cited at p. 69]

Bamford, J. A., C. T. Putman, and V. K. Mushahwar (2005). Intraspinal microstimulation preferentially recruits fatigue-resistant muscle fibres and generates gradual force in rat. *Journal of Physiology (London) 569*(3), 873–884. [cited at p. 36, 91]

Belanger, M., R. B. Stein, G. D. Wheeler, T. Gordon, and B. Leduc (2000). Electrical stimulation: Can it increase muscle strength and reverse osteopenia in spinal cord injured individuals? *Archives of Physical Medicine and Rehabilitation 81*(8), 1090–1098. [cited at p. 69]

Davis, R., T. Houdayer, B. Andrews, and A. Barriskill (1999). Paraplegia: prolonged standing using closed-loop functional electrical stimulation and andrews ankle-foot orthosis. *Artificial Organs 23*(5), 418–20. [cited at p. 30, 93]

Davis, R., J. Patrick, and A. Barriskill (2001). Development of functional electrical stimulators utilizing cochlear implant technology. *Medical Engineering & Physics 23*(1), 61–68. [cited at p. 29, 70]

Donaldson Nde, N. and C.-N. Yu (1996). Fes standing: control by handle reactions of leg muscle stimulation (chrelms). *IEEE Transactions on Rehabilitation Engineering. 4*(4), 280–284. [cited at p. 30, 70]

Fang, Z. and J. T. Mortimer (1991). Selective activation of small motor axons by quasitrapezoidal current pulses. *IEEE Transactions on Biomedical Engineering 38*(2), 168–174. [cited at p. 90]

Gaunt, R. A., A. Prochazka, V. K. Mushahwar, L. Guevremont, and P. H. Ellaway (2006). Intraspinal microstimulation excites multisegmental sensory afferents at lower stimulus levels than local alpha-motoneuron responses. *J Neurophysiol 96*(6), 2995–3005. [cited at p. 37, 91]

Guest, R. S., K. J. Klose, B. M. Needham-Shropshire, and P. L. Jacobs (1997). Evaluation of a training program for persons with sci paraplegia using the parastep(r)1 ambulation system: Part 4. effect on physical self-concept and depression,. *Archives of Physical Medicine and Rehabilitation 78*(8), 804–807. [cited at p. 69]

Hunt, K. J., H. Gollee, and R. P. Jaime (2001). Control of paraplegic ankle joint stiffness using fes while standing. *Medical Engineering & Physics. 23*(8), 541–55. [cited at p. 94]

Kobetic, R., R. J. Triolo, J. P. Uhlir, C. Bieri, M. Wibowo, G. Polando, E. B. Marsolais, J. Davis, J. A., and K. A. Ferguson (1999). Implanted functional electrical stimulation system for mobility in paraplegia: a follow-up case report. *IEEE Transactions on Rehabilitation Engineering 7*(4), 390–8. [cited at p. 77]

Krajl, A., T. Bajd, R. Turk, and H. Benko (1986). Posture switching for prolonging functional electrical stimulation standing in paraplegic patients. *Paraplegia. 24*(4), 221–230. [cited at p. 38, 90]

Lanmuller, H., S. Sauermann, E. Unger, G. Schnetz, W. Mayr, M. Bijak, D. Rafolt, and W. Girsch (1999). Battery-powered implantable nerve stimulator for chronic activation of two skeletal muscles using multichannel techniques. *Artificial Organs 23*(5), 399–402. [cited at p. 90]

Loram, I. D., S. M. Kelly, and M. Lakie (2001). Human balancing of an inverted pendulum: is sway size controlled by ankle impedance? *Journal of Physiology. 532*(Pt 3), 879–91. [cited at p. 93]

Macpherson, J. M. (1988). Strategies that simplify the control of quadrupedal stance. i. forces at the ground. *J Neurophysiol 60*(1), 204–217. [cited at p. 95]

McDonnall, D., G. Clark, and R. Normann (2004). Interleaved, multisite electrical stimulation of cat sciatic nerve produces fatigue-resistant, ripple-free motor responses. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 12*(2), 208–215. [cited at p. 90]

Mortimer, J. T. (1990). Electrical excitation of nerve. In W. F. Agnew and D. B. McCreery (Eds.), *Neural Prostheses. Fundamental Studies.*, pp. 67–83. Englewood Cliffs, NJ: Prentice Hall. [cited at p. 89]

Mushahwar, V. K., D. F. Collins, and A. Prochazka (2000). Spinal cord microstimulation generates functional limb movements in chronically implanted cats. *Experimental Neurology. 163*(2), 422–9. [cited at p. 13, 40, 72]

Mushahwar, V. K., D. M. Gillard, M. J. Gauthier, and A. Prochazka (2002). Intraspinal micro stimulation generates locomotor-like and feedback-controlled movements. *IEEE Transactions on Neural Systems & Rehabilitation Engineering. 10*(1), 68–81. [cited at p. 35, 44, 53, 35, 44, 53, 70, 90]

Mushahwar, V. K. and K. W. Horch (1997). Proposed specifications for a lumbar spinal cord electrode array for control of lower extremities in paraplegia. *IEEE Transactions on Rehabilitation Engineering. 5*(3), 237–43. [cited at p. 34, 35, 37, 38, 44, 34, 35, 37, 38, 44, 91, 92]

Pikov, V. and D. McCreery (2004). Mapping of spinal cord circuits controlling the bladder and external urethral sphincter functions in the rabbit. *Neurourology and Urodynamics 23*(2), 172–179. [cited at p. 33, 90]

Rothwell, J. C. (1995). *Control of Human Voluntary Movement* (2 ed.). London: Croom Helm. [cited at p. 89, 90]

Sharma, M., E. B. Marsolais, G. Polando, R. J. Triolo, J. Davis, J. A., N. Bhadra, and J. P. Uhlir (1998). Implantation of a 16-channel functional electrical stimulation walking system. *Clinical Orthopaedics & Related Research 347*, 236–42. [cited at p. 28, 31, 28, 31, 70]

Stefanovska, A., L. Vodovnik, N. Gros, S. Rebersek, and R. Acimovic-Janezic (1989). Fes and spasticity. *IEEE Transactions on Biomedical Engineering 36*(7), 738–745. [cited at p. 69]

Triolo, R., B. Reilley, W. Freedman, and R. Betz (1993). Development and standardization of a clinical evaluation of standing function: the functional standing test. *IEEE Transactions on Rehabilitation Engineering 1*(1), 18–25. [cited at p. 94]

Tyler, D. and D. Durand (2002). Functionally selective peripheral nerve stimulation with a flat interface nerve electrode. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 10*(4), 294–303. [cited at p. 27, 28, 27, 28, 90]

Veltink, P., W. de Vries, H. Hermans, G. Baardman, M. Ijzerman, S. Heinze, A. Nene, G. Zilvold, and H. Boom (1996). A comprehensive fes control system for mobility restoration in paraplegics. In A. Pedotti, M. Ferrarin, J. Quintern, and R. Riener (Eds.), *Neuroprosthetics From Basic Research to Clinical Applications*, pp. 163–168. Springer. [cited at p. 94]

Veltink, P. and N. Donaldson (1998). A perspective on the control of fes-supported standing. *IEEE Transactions on Rehabilitation Engineering 6*(2), 109–112. [cited at p. 70]

Veraart, C., W. Grill, and J. Mortimer (1993). Selective control of muscle activation with a multipolar nerve cuff electrode. *IEEE Transactions on Biomedical Engineering 40*(7), 640–653. [cited at p. 28, 90]

Wieler, M., R. B. Stein, M. Ladouceur, M. Whittaker, A. W. Smith, S. Naaman, H. Barbeau, J. Bugaresti, and E. Aimone (1999). Multicenter evaluation of electrical stimulation systems for walking,. *Archives of Physical Medicine and Rehabilitation 80*(5), 495–500. [cited at p. 70]

Wilmink, R. J. and T. R. Nichols (2003). Distribution of heterogenic reflexes among the quadriceps and triceps surae muscles of the cat hind limb. *Journal of Neurophysiology 90*(4), 2310–24. [cited at p. 91]

Wood, D., V. Harper, F. Barr, P. Taylor, G. Phillips, and D. Ewins (1998). Experience in using knee angles as part of a closed-loop algorithm to control fes-assisted paraplegic standing. In *6th Vienna International Workshop on Functional Electrostimulation*, pp. 137–140. [cited at p. 30, 70, 92]

Yoshida, K. and K. Horch (1993). Reduced fatigue in electrically stimulated muscle using dual channel intrafascicular electrodes with interleaved stimulation. *Annals of Biomedical Engineering 21*, 709–714. [cited at p. 37, 38, 37, 38, 90]

Chapter 4

Locomotor-Related Networks in the Lumbosacral Enlargement of the Adult Spinal Cat: Activation through Intraspinal Microstimulation *

"He who joyfully marches to music rank and file... has been given a large brain by mistake, since for him the spinal cord would surely suffice."

- Albert Einstein

4.1 Introduction

In 1911, Brown demonstrated that the spinal cord of mammals is capable of generating rhythmic locomotor patterns in the absence of both descending and afferent input (Brown, 1911). Later experiments reaffirmed the existence of locomotor-related neural networks within the lumbar spinal cord, and these networks are now commonly referred to as central pattern generators (Orlovsky et al., 1999; Grillner, 1985). Experiments aimed at localizing the most active or "leading" elements of the locomotor networks have been conducted in in vitro preparations of the neonatal spinal cord of rats (Cazalets et al., 1995; Kjaerulff

*A version of this chapter has been published. ©2006 IEEE. Reprinted, with permission, from: Guevremont L., Renzi C.G., Norton J.A., Kowalczewski J., Saigal R., Mushahwar V.K., Locomotor-Related Networks in the Lumbosacral Enlargement of the Adult Spinal Cat: Activation through Intraspinal Microstimulation, *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 2006, Sept;14(3): 266-272 and Kiehn, 1996; Cowley and Schmidt, 1997; Kremer and Lev-Tov, 1997) and in vivo in adult cats (Orlovsky et al., 1999; Deliagina et al., 1983; Marcoux and Rossignol, 2000). These studies utilized techniques such as serial sectioning and application of pharmacological agents. The findings resulted in the formation of two contrasting views: 1) the "leading" elements of the locomotor networks are localized within the more rostral segments of the lumbar cord (L1-L2 in rats and L3-L4 in cats) (Cazalets et al., 1995; Marcoux and Rossignol, 2000), or 2) the locomotor networks extend more caudally, but their capacity to generate rhythmic alternation decreases significantly in the most caudal lumbar segments (L4-L5 in rats and L6-S1 in cats) (Kjaerulff and Kiehn, 1996; Cowley and Schmidt, 1997). Results from the latter studies also suggest that rhythm generation originates in the medioventral regions of the grey matter (laminae VII and VIII) (Kjaerulff and Kiehn, 1996; Noga et al., 1995). Although the above studies primarily made use of pharmacological activation of neural circuitry, tonic electrical stimulation of the ventrolateral funiculus results in locomotor-like activity in the neonatal *in vitro* rat preparation (Magnuson and Trinder, 1997).

In this study, we used constant amplitude (tonic) low-level intraspinal microstimulation (ISMS) through adjacently-located microwires in the ventral horn to generate stepping-like patterns in the hindlimbs of adult, spinal cord-injured cats. The primary goal of the study was to investigate the ability of tonic ISMS to elicit rhythmic locomotor patterns when applied to the ventral horn of the spinal cord of the adult cat. Secondary to this goal, we evaluated the quality of stepping generated when stimulation was applied to various lumbosacral spinal segments. Our results suggest that tonic ISMS is capable of eliciting stepping patterns. Furthermore, ISMS applied to the caudal regions (L7-S1) of the lumbosacral enlargement is more effective in inducing load-bearing, organized stepping-like movements in the hindlimbs than similar stimulation applied to more rostral segments (L3-L6). Intraspinal microstimulation could be a useful new technique for examining the nature and distribution of spinal locomotor-related networks. However, further investigations are required in order to better understand the mechanisms of ISMS action and its effective spread in the spinal cord.

4.2 Methods

Five adult cats (4 male, 1 female, 2.5 - 5.5 kg) were used in this study. All experimental procedures were approved by the University of Alberta Animal Welfare Committee. Each cat received a complete spinal transection at T11 (techniques described elsewhere (Saigal et al., 2004)). Cats 1-4 were allowed to recover for 2-6 weeks before the terminal experiments. During the same surgical procedure, cat 5 also received a second lesion between L4/L5 and was allowed to recover for 8 months before the terminal experiment. During each terminal experiment, microwires were implanted into the lumbosacral enlargement of the spinal cord and data were acquired.

4.2.1 Experimental Setup

Microwires were prepared using techniques described elsewhere (Mushahwar et al., 2000; Mushahwar and Prochazka, 2000) . Briefly, arrays of microwires were fashioned using 30 μm stainless steel wire (California Fine Wire, Grover Beach, California, USA) with 30-60 μm deinsulated and sharpened tips. The wires were spaced 2 mm apart and bent to 90°, 2.5 - 3.2 mm from the tip. These depths corresponded to the intermediate and ventral areas of the spinal cord (Rexed laminae VII to IX).

The experimental setup used in this study is the same as that previously described (Saigal et al., 2004). Under isoflurane anesthesia, each cat received a laminectomy and the microwires were implanted into the cord along the rostral-caudal axis of the lumbosacral enlargement (L3/L4 to S1 spinal segments; L6 to S1 in cat 5). Electromyographic (EMG) electrodes were implanted in the main hip, knee and ankle flexor and extensor muscles of each leg. The cats were then decerebrated intercollicularly and anesthesia was discontinued. One hour after decerebration, the cats were transferred to a body support harness suspended over a split-belt treadmill with two embedded force plates.

4.2.2 Intraspinal Microstimulation Protocol

Stimulus pulses (biphasic, charge-balanced, <100 μA, 200 μs, 40 or 50 pulses/sec) were delivered in 1s trains through each microwire individually and stimulus thresholds (minimal stimulus level evoking a detectable muscle response) were noted. Combinations of up to 8 adjacent (bilateral) microwires were then chosen and trains of threshold-level stimuli were delivered through them simultaneously for 10-40 s. This stimulation duration provided adequate time for the movements to develop and allowed for their sustainability to be assessed. Kinematic, kinetic and EMG data were recorded to quantify evoked hindlimb movements. The majority of ISMS trials were conducted with the treadmill belts OFF. The belts were only turned on (0.1-0.4 m/s) in order to determine if ISMS-induced stepping is modulated by afferent input (see Results).

4.2.3 Data Acquisition and Analysis

The EMG and kinetic (ground reaction force, GRF) data were recorded using CED Power 1401 A/D board and Signal 1.92 data acquisition software (Cambridge Electronic Design, Ltd., Cambridge, UK). The EMG records were band-pass filtered at 30-1000 Hz, amplified 500x and sampled at a frequency of 4000 Hz.

To assess the kinematics of hindlimb movements, reflective markers were placed on the iliac crest, and third toe as well as the hip, knee, ankle and metatarsophalangeal joints of the cats. The hindlimbs were filmed at 30 or 120 frames per second using 2 JVC digital video cameras positioned orthogonally to the sagittal plane on both sides of the cat. A stationary grid (10 x 10 cm) was used to determine the pixel / mm ratio of the video frame and correct for out-of-plane distortions. Data analysis was completed using custom written routines for Matlab v6.5 (The MathWorks Inc., Natick, MA, US). The video was digitized and stick figures of the hindlimbs were reconstructed using MotionTracker2D (Dr. Douglas Weber, University of Pittsburg, Pittsburgh, PA, USA). Stepping movements were observed to occur primarily in the sagittal plane allowing the representation of the 3D movements onto a 2D plane for the purpose of stick figure reconstructions. The force signals were low-pass filtered (7 Hz) and a threshold-based algorithm was used to detect when the limb was unloaded (swing phase) and when it was loaded (stance phase).

Circular statistical analysis of rectified, low-pass filtered (4 Hz) EMG data was used to verify the phasic organization of flexor and extensor muscle activity during ISMS-induced stepping. Time of onset of EMG bursts were detected using a threshold-based algorithm described elsewhere (Yakovenko et al., 2005).

4.2.4 Determining Location of Microwire Sites in the Spinal Cord

Upon completion of the experiments, the animals were deeply anesthetized with sodium pentobarbital and perfused through the heart with a 4% formaldehyde fixative solution. The region of the spinal cord with implanted microwires was removed, carefully sliced along the plane of the microwires, and the locations of the microwire tips were identified.

4.3 Results

4.3.1 Generation of Hindlimb Alternation by Threshold Level Tonic Stimulation

The observation that tonic ISMS in the ventral horn can generate locomotor-like stepping of the hindlimbs in chronically spinalized adult cats was first made in cat 1. This was seen during 1 s-long threshold-level stimuli delivered through a microwire implanted in the ventral region of the S1 spinal segment (data not shown). This finding was then investigated more rigorously in cats 2-5.

In cats 2-4, alternation of the hindlimbs was elicited by delivering threshold-level tonic stimulation through groups of ISMS microwires implanted in the lumbosacral enlargement of the spinal cord. The mean ISMS threshold level for all microwires across these three animals was 32 ± 2.4 μA (mean $\pm$ standard error of the mean).

Figure 4.1A summarizes the microwire tip locations for cats 2-4, superimposed on one lumbosacral hemisection. The tip locations have been color-coded to represent the limb movements elicited when stimulating for 1 s through each of the microwires individually (with stimulus amplitudes ranging from 2-4x threshold). The elicited movements were broadly divided into ipsilateral flexion (grey), ipsilateral extension (white), and ipsilateral, contralateral or bilateral stepping (black). Stepping consisted of alternating flexion/extension movements with interlimb coordination. These stepping movements ranged from air-stepping to partial weight support and were elicited by stimulating in laminae VII, VIII or IX. Figure 4.1B summarizes the responses elicited through individual wires as a function of rostral-caudal location in the cord. The 110 microwires implanted across the 3 cats were evenly distributed between the L3-L6 region (51%) and the L7-S1 region (49%). Of the electrodes located in the rostral and caudal regions, 17.9% and 35.2%, respectively, generated alternating movements when suprathreshold stimulation was applied.

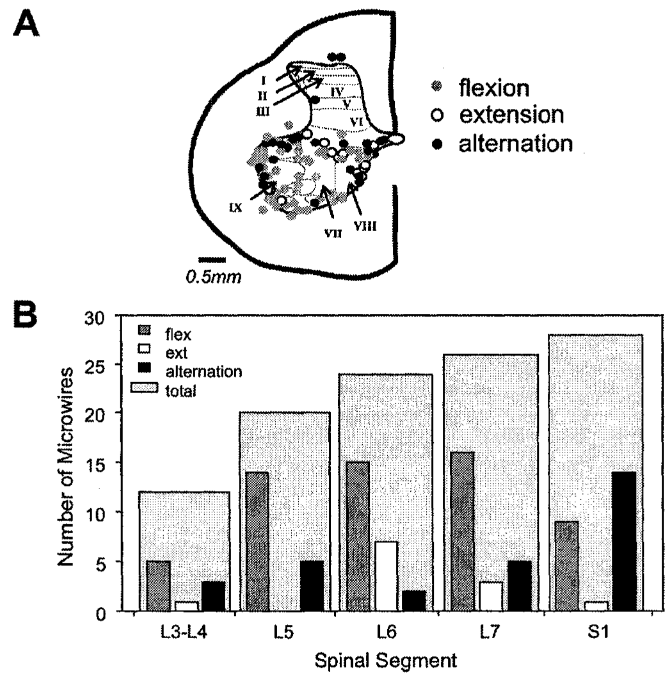

Figure 4.1: *ISMS microwire implant.*

(A) Summary of all microwire tip locations superpositioned on a single hemisection of the cord. Locations are color-coded for response seen when stimulus was delivered through each microwire for a duration of 1s. Movements were characterized as flexion (grey), extension (white) or ipsilateral, contralateral, or bilateral alternating movements (black). The locations inducing alternation are located primarily in laminae VII and VIII. (B) Distribution of microwires and elicited movements as a function of spinal segment. Large bars indicate total number of wires implanted in each segment. Small bars indicate the number of microwires eliciting each of the movements classified in A.

Figure 4.2 shows examples of sustained bilateral locomotor-like stepping generated in cats 2-4 by stimulating at threshold levels through groups of 4-6 microwires implanted in the ventral grey matter of spinal segments L7-S1. These data were obtained with the treadmill belts OFF. Figure 4.2A shows the activity recorded during 5 seconds preceding the application of ISMS in cat 2. Stepping data obtained during tonic ISMS stimulation of cats 2-4 are shown in figure 4.2B-D. The stick figures represent frame-by-frame reconstructions of the limb kinematics recorded during the 2 s period marked by the vertical dotted lines. Also shown are the joint angles of the hip, knee, and ankle, bilateral GRFs and normalized, raw EMG data for selected extensor and flexor muscles in both legs. The tip locations of the microwires used in each trial are indicated in the spinal cross sections at the bottom of the figure. Excessive rotations of the hind limbs were not seen in any of the cats allowing for the use of 2D kinematic analysis. The responses seen in cat 2 were characterized by large fore/aft stepping movements of the legs, whereas cats 3 and 4 demonstrated primarily up/down alternation with increased levels of GRF. The average joint excursions for the hip, knee and ankle in cat 2 were 22°, 18° and 24° respectively and represented 78%, 56% and 67% of normal ranges of motion (28°, 32°, 36°) seen in intact cats walking at slow to medium speeds (Rossignol et al., 1996). Ground reaction forces during stepping sequences recorded across all cats ranged from 0N (air stepping) to 6N (51% of full load bearing of the hind quarters in our set up). As is typical after spinal cord injury, bursts of EMG activity were dominated by rapid oscillations (clonus) in all cases. However, neither the clonus (~12 Hz) nor the stepping-like bursting pattern (i.e., step frequency ~1 Hz) was time-locked to the stimulus frequency (40-50 Hz). Cat 5 (the animal with a second lesion between L4/L5) responded to threshold-level tonic ISMS primarily with a combination of bilateral hip extension and knee flexion (backwards and upwards movement of the legs). This animal was highly spastic throughout the experiment and did not demonstrate organized alternation.

Figure 4.3 summarizes the phase relationships between bursting activity in the EMG data obtained during the same stepping sequences represented in figure 4.2B-D. The bursting EMG activity of the muscle shown in the first column was used as the phase reference for each cat (shown in rows A-C). Each point on a circular plot represents the phase shift of a burst detected in the EMG data relative to the EMG burst in the reference muscle. For example, the first three plots in C illustrate that ankle extensor activity is in-phase with contralateral flexors and out-of-phase with contralateral extensors. The number of bursts detected in each muscle (N) ranged from 11 in cat 3 (10 s stimulation), to 33 in cat 2 (40 s stimulation). The mean angle and its dispersion are illustrated by the direction and length of solid arrow for each plot, and the angular standard deviation (s, a statistical measure of dispersion) is indicated. The out-of-phase bursting seen between ipsilateral antagonists and contralateral agonists, and in-phase bursting seen between ipsilateral agonists is consistent

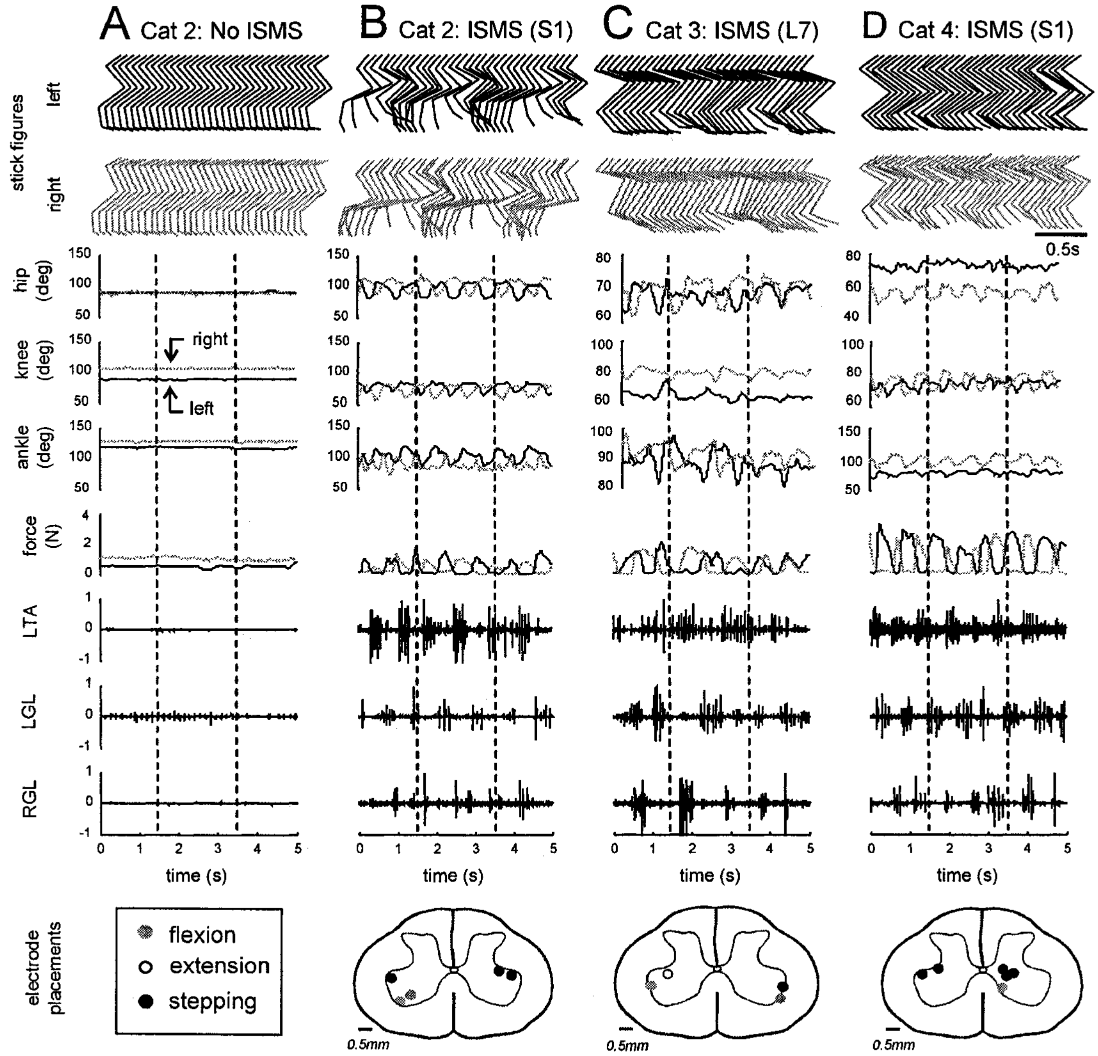

Figure 4.2: *Stepping-like movements induced by tonic ISMS in the absence of other stimuli.*

Kinematic, kinetic and select EMG (left tibialis anterior - LTA, and left/right gastrocnemius lateralis - LGL/RGL) activity are shown for: (A) activity before ISMS in cat 2 and (B-D) activity during ISMS applied to L7-S1 regions of the spinal cord in cats 2-4. The average threshold amplitude for microwires in these examples was 25.6 ± 6.0 μA (mean standard error of the mean). Stimulus frequency was 40 Hz for cats 2, and 50 Hz for cats 3 and 4. The stick figures were reconstructed from video and represent steps taken in the interval between the two vertical dotted lines shown in each data set.(A) Prior to ISMS, no joint angle or GRF modulation occurred, and only clonic muscle activity could be seen. (B) During tonic ISMS, cat 2 exhibited stepping patterns represented by regular joint excursions and ground reaction force alternations. (C, D) Alternation in cats 3 and 4 was characterized by smaller ranges of movement but increased rhythmic loading of the legs. In all cases, reciprocal EMG activity was visible in ipsilateral flexors and extensors and contralateral pairs of antagonist muscles. Vertical scale shown on left. Black traces - left leg, grey traces - right leg.

with alternating gait patterns.

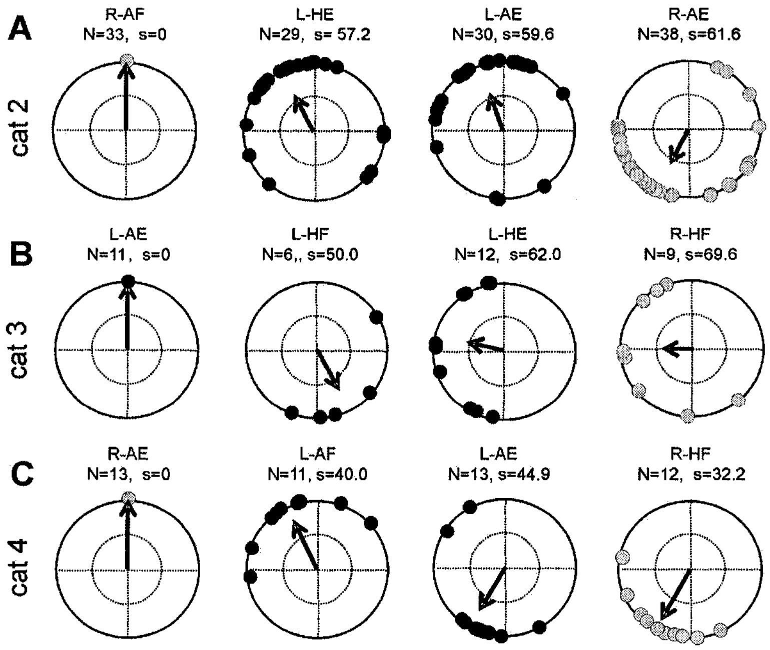

Figure 4.3: *Phase relationships between ipsilateral and contralateral flexor and extensor muscles.*

Results from circular statistics indicate in-phase EMG activity between ipsilateral agonists and contralateral antagonists. Out-of-phase activity is seen between contralateral agonists. Rows A-C represent data obtained from stepping sequences in cats 2-4. Each point on the polar plots represents a burst in the EMG data and its phase shift with respect to the bursts detected in the reference muscle indicated in the first column. The direction of the arrow indicates the average angle and its length represents the dispersion of the data. Plot labels indicate: left or right (L or R) hip extension (HE), hip flexion (HF), ankle extension (AE), ankle flexion (AF), number of bursts detected (N), and angular standard deviation (s).

4.3.2 Effect of Afferent Input on the Rhythm Elicited by ISMS

We also investigated the interaction of ISMS with sensory activation of spinal locomotor networks. The effect of afferent input on the ISMS evoked-stepping was examined in cats 3 and 4 by turning the treadmill belts on at various speeds during ISMS-evoked alternation (figure 4.4). Data points in figure 4.4 represent the duration of stance and swing phases for steps taken at different treadmill speeds with and without ISMS (circles and triangles, respectively). In both cases, as the treadmill speed increased the step frequency also increased, which was primarily achieved through a shortening of the stance phase with little change in the swing phase. These examples demonstrate that the locomotor-like stepping generated by the application of tonic, low-level ISMS can be modulated by afferent input in a manner similar to that seen during normal stepping (Halbertsma, 1983). This indicates that ISMS allows natural step cycle modulation to occur and does not block the transmission of afferent input to the spinal cord.

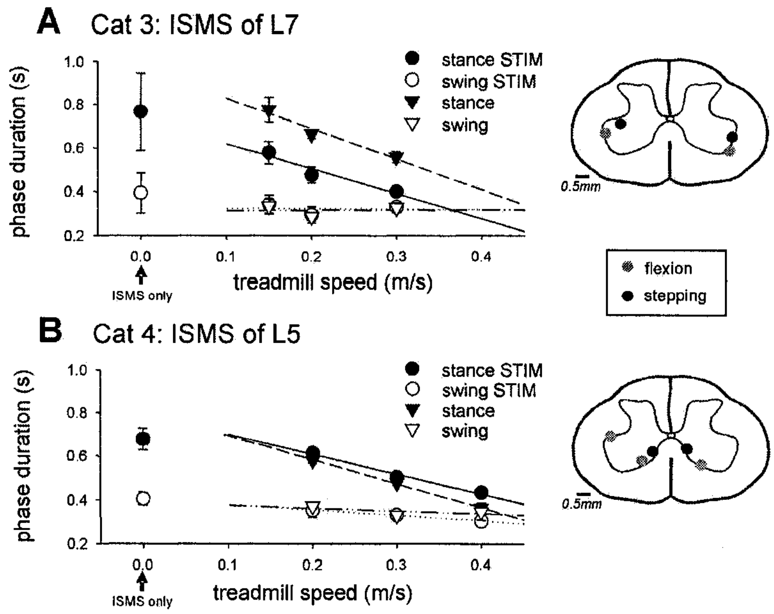

Figure 4.4: *Modulation of ISMS-generated stepping by afferent input.*

Shown are examples of the effect of afferent input on the swing and stance durations of caudal ISMS-induced stepping. A and B show for cats 3 and 4, respectively, the swing (open) and stance (filled) durations (mean standard error of the mean) during stepping with (circles) and without (triangles) ISMS and while the treadmill was OFF and ON. In the absence of electrical stimulation, sensory-induced stepping showed a decrease in stance duration and little change in swing duration as treadmill speed increased. Similar changes to the phase duration occurred to ISMS-induced stepping indicating that ISMS did not block the transmission of afferent input to the spinal cord nor did it lock the cord in a set state.

4.4 Discussion

In this study, we demonstrated the capacity of low-level tonic ISMS in the ventral horn to induce alternating, locomotor-like stepping in the hindlimbs of spinal cord-injured cats. The results suggest that microwires implanted in the caudal lumbosacral segments (L7-S1) are more effective in activating the locomotor-related neuronal spinal networks than those implanted in the rostral segments (L3-L6).

Tonic stimulation of laminae VII and VIII within the ventral horn generated organized stepping of the hindlimbs in the adult cat (figure 4.1) which is in agreement with previous studies (Kjaerulff and Kiehn, 1996; Noga et al., 1995; Tscherter et al., 2001). In this study, stimulation of lamina IX also generated stepping-like movements. Tonic ISMS of laminae VII-IX may have activated local elements of the locomotor networks. It may also have indirectly activated elements of the ventral lateral funiculus suggested to be involved in locomotor stepping (Magnuson and Trinder, 1997; Shik, 1997).

4.5 Proposed Mechanisms of Action of Intraspinal Microstimulation

The relative capacity of tonic ISMS to induce locomotor-like stepping when applied to various lumbosacral segments suggests that either 1) ISMS is specifically activating oscillating locomotor-related networks residing within the region of stimulation (local effect) or 2) ISMS is activating distal locomotor-related elements through fibers-in-passage (non-local effect). The effectiveness of ISMS in the latter would depend on the specific connectivity of the stimulated segment and the neural elements along the rostral-caudal axis of the lumbosacral cord.

Grillner (1985) suggested that the locomotor CPG consists of chains of coupled oscillators distributed along the rostocaudal axis of the cord. At the stimulation levels used in this study the direct current spread would be less than 0.5 mm from the microwire tip (Mushahwar and Horch, 1997). This direct current may activate local locomotor oscillators at the site of stimulation which in turn recruit the full orchestration of locomotor-related networks within the lumbosacral cord. However, remote networks (e.g., the hypothesized "leading" regions in L3-L4) may be activated via projections of neurons stimulated by the locally applied ISMS. These projections could originate from multiple sources such as the firing of afferent endings in the ventral horn, and propriospinal interneurons with axons extending along the lumbosacral cord.

The role of activating afferent endings was investigated in a separate study (Mushahwar et al., 2003). We found that the threshold for evoking activity in dorsal rootlets when applying ISMS in the ventral horn was lower than that for direct activation of motoneurons (indicated by short-latency EMG activity). However, the antidromic activity caused by ISMS was observed in dorsal rootlets located 3 mm rostral and caudal from the ISMS microwire. Therefore, although the afferent backfiring may have amplified the local effect of ISMS, the stimulus applied to the L7-S1 segments in the current study probably did not spread to the L3-L4 segments located 20-30 mm away. In humans, localized activation of primary spindle afferents (through tendon vibration of leg muscles at 30-50 Hz) generates bilateral stepping of the legs (Gurfinkel et al., 1998). The finding that caudal segments are more efficient in inducing stepping with tonic ISMS may be due to the greater density of afferent fibers in these segments than in the L3-L4 segments. This could result in a more intense input to local oscillating networks through the activation of primary afferent fibers in the caudal regions.

Caudal ISMS-evoked stepping may be the result of the activation of sacral perineal afferents. Activation of these afferents through manual perineal stimulation is commonly used to induce adult cats and rats to step after complete transection of the spinal cord. However, due to the typically more caudal distribution of these sacral sensory inputs in the spinal cord (middle of S1 to S3) (Jankowska et al., 2000; Ueyama et al., 1984) we believe that stimulation of sacral afferents alone, cannot fully explain the ISMS-evoked stepping patterns observed.

Propriospinal neurons play a significant role in locomotion (Grillner, 1985; Shik, 1997; Jordan and Schmidt, 2002). Activation of propriospinal neurons through ISMS of L7-S1 segments could in fact result in the activation of the L3-L4 segments through rostrally projecting axons. The observation that caudal ISMS could not induce organized alternation when the L3-L4 spinal segments were disconnected (cat 5) supports the idea that these rostral segments have a significant role in locomotion. Also, the effect of caudal ISMS is probably not strictly local, but activates neuronal circuitry spanning the lumbosacral cord.

The quality of stepping elicited may also be influenced not only by the connectivity or oscillatory properties of the given segment but also by the contribution of its local motoneuronal activation. Stepping responses evoked by tonic stimulation applied at the L3-L4 level were flexion dominated (less load bearing). This may reflect the fact that this region of the cord is heavily populated with flexor motorneuron pools whose direct activation by ISMS could bias the resulting stepping pattern towards flexion. Similarly, the extensor motorneuron pools in the more caudal segments could contribute to the load bearing capability seen when stimulating these segments.

Epidural stimulation of the spinal cord has been shown to induce locomotor-like stepping in rats (Ichiyama et al., 2005), cats (Iwahara et al., 1991; Gerasimenko et al., 2003) and humans (Gerasimenko et al., 2002) after complete spinal cord injury. Although epidural stimulation produces load bearing stepping in rats (Ichiyama et al., 2005), epidural stimulation in the absence of pharmacological agents characteristically generates non-weight bearing air-stepping in cats and humans (Iwahara et al., 1991; Gerasimenko et al., 2003, 2002). The evoked stepping through tonic ISMS differs from epidural stimulation in two ways: 1) the cats in our study demonstrated partial weight-bearing during stepping (up to 51% of full load of the hind quarters) without the application of drugs, and 2) ISMS was most effective in generating alternating movements when applied to laminae VII and VIII, regions known to be involved in the initiation and maintenance of rhythmic locomotor movements (Kjaerulff and Kiehn, 1996; Noga et al., 1995). Moreover, stimulation applied deep within the ventral horn of the grey matter results in the activation of more locomotor-specific afferent modalities such as primary Ia afferents. It also avoids the activation of myelinated axons residing in more dorsal laminae (i.e., Iδ pain fibers) (Feirabend et al., 2002), thus reduces the possible contribution of flexor withdrawal behaviors which may play a role in generating non-weight bearing stepping responses (Iwahara et al., 1991; Gerasimenko et al., 2003, 2002).

4.6 Conclusion

The results of this study suggest that tonic ISMS of the ventral horn of the grey matter can activate intrinsic locomotor related networks within the lumbosacral cord. Possible mechanisms include direct activation of local oscillating networks within the spinal cord by the focally applied electrical stimulus or indirect activation of non-local segments of the network by afferent backfiring or propriospinal activation. Further studies will indicate if ISMS can selectively activate regions of the cord allowing it to be used for investigating the function and distribution of locomotor networks within the spinal cord.

4.7 Bibliography

Brown, T. (1911). The intrinsic factors in the act of progression in the mammal. *Proceedings of the Royal Society of London Series B 84*(572), 309–18. [cited at p. 3, 44, 101]

Cazalets, J. R., M. Borde, and F. Clarac (1995). Localization and organization of the central pattern generator for hindlimb locomotion in newborn rat. *Journal of Neuroscience. 15*(7 Pt 1), 4943–51. [cited at p. 44, 101, 102]

Cowley, K. C. and B. J. Schmidt (1997). Regional distribution of the locomotor pattern-generating network in the neonatal rat spinal cord. *Journal of Neurophysiology 77*(1), 247–259. [cited at p. 102]

Deliagina, T. G., G. N. Orlovsky, and G. A. Pavlova (1983). The capacity for generation of rhythmic oscillations is distributed in the lumbosacral spinal cord of the cat. *Experimental Brain Research. 53*(1), 81–90. [cited at p. 102]

Feirabend, H. K. P., H. Choufoer, S. Ploeger, J. Holsheimer, and J. D. van Gool (2002). Morphometry of human superficial dorsal and dorsolateral column fibres: significance to spinal cord stimulation. *Brain 125*(5), 1137–1149. [cited at p. 113]

Gerasimenko, Y. P., V. D. Avelev, O. A. Nikitin, and I. A. Lavrov (2003). Initiation of locomotor activity in spinal cats by epidural stimulation of the spinal cord. *Neuroscience & Behavioral Physiology. 33*(3), 247–54. [cited at p. 3, 33, 113]

Gerasimenko, Y. P., A. N. Makarovskii, and O. A. Nikitin (2002). Control of locomotor activity in humans and animals in the absence of supraspinal influences. *Neuroscience and Behavioral Physiology 32*(4), 417–423. [cited at p. 113]

Grillner, S. (1985). Neurobiological bases of rhythmic motor acts in vertebrates. *Science 228*(4696), 143–9. [cited at p. 101, 111, 112]

Gurfinkel, V. S., Y. S. Levik, O. V. Kazennikov, and V. A. Selionov (1998). Locomotor-like movements evoked by leg muscle vibration in humans. *European Journal of Neuroscience. 10*(5), 1608–12. [cited at p. 3, 112]

Halbertsma, J. M. (1983). The stride cycle of the cat: the modelling of locomotion by computerized analysis of automatic recordings. *Acta Physiologica Scandinavica. Supplementum. 521*, 1–75. [cited at p. 110]

Ichiyama, R., Y. Gerasimenko, H. Zhong, R. Roy, and V. Edgerton (2005). Hindlimb stepping movements in complete spinal rats induced by epidural spinal cord stimulation. *Neuroscience Letters 383*(3), 339–344. [cited at p. 113]

Iwahara, T., Y. Atsuta, E. Garcia-Rill, and R. D. Skinner (1991). Spinal cord stimulation-induced locomotion in the adult cat. *Brain Research Bulletin 28*, 99–105. [cited at p. 113]

Jankowska, E., E. Bichler, and I. Hammar (2000). Areas of operation of interneurons mediating presynaptic inhibition in sacral spinal segments. *Experimental Brain Research 133*(3), 402–406. [cited at p. 112]

Jordan, L. M. and B. J. Schmidt (2002). Propriospinal neurons involved in the control of locomotion: potential targets for repair strategies? *Progress in Brain Research 137*, 125–39. [cited at p. 112]

Kjaerulff, O. and O. Kiehn (1996). Distribution of networks generating and coordinating locomotor activity in the neonatal rat spinal cord in vitro: a lesion study. *Journal of Neuroscience. 16*(18), 5777–94. [cited at p. 4, 44, 45, 44, 45, 101, 102, 110, 113]

Kremer, E. and A. Lev-Tov (1997). Localization of the spinal network associated with generation of hindlimb locomotion in the neonatal rat and organization of its transverse coupling system. *Journal of Neurophysiology. 77*(3), 1155–70. [cited at p. 102]

Magnuson, D. S. and T. C. Trinder (1997). Locomotor rhythm evoked by ventrolateral funiculus stimulation in the neonatal rat spinal cord in vitro. *Journal of Neurophysiology. 77*(1), 200–206. [cited at p. 3, 33, 102, 111]

Marcoux, J. and S. Rossignol (2000). Initiating or blocking locomotion in spinal cats by applying noradrenergic drugs to restricted lumbar spinal segments. *Journal of Neuroscience 20*(22), 8577–8585. [cited at p. 102]

Mushahwar, V. and A. Prochazka (2000). Spinal cord microstimulation: Long-term stability of implanted wires and evoked responses. In *5th Annual IFESS Meeting, Aalborg, Denmark.* [cited at p. 103]

Mushahwar, V., A. Prochazka, P. Ellaway, L. Guevremont, and R. Gaunt (2003). Microstimulation in cns excites axons well before neuronal cell bodies. In *Society for Neuroscience Abstracts*, pp. 33: 276.6. [cited at p. 111]

Mushahwar, V. K., D. F. Collins, and A. Prochazka (2000). Spinal cord microstimulation generates functional limb movements in chronically implanted cats. *Experimental Neurology. 163*(2), 422–9. [cited at p. 13, 40, 72, 103]

Mushahwar, V. K. and K. W. Horch (1997). Proposed specifications for a lumbar spinal cord electrode array for control of lower extremities in paraplegia. *IEEE Transactions on Rehabilitation Engineering. 5*(3), 237–43. [cited at p. 34, 35, 37, 38, 44, 34, 35, 37, 38, 44, 91, 92, 91, 92, 111]

Noga, B., P. Fortier, D. Kriellaars, X. Dai, G. Detillieux, and L. Jordan (1995). Field potential mapping of neurons in the lumbar spinal cord activated following stimulation of the mesencephalic locomotor region. *Journal of Neuroscience 15*(3), 2203–2217. [cited at p. 45, 102, 110, 113]

Orlovsky, G., T. Deliagina, and S. Grillner (1999). Walking and running in humans. In *Neuronal Control of Locomotion, Form Mollusc to Man.* Stockholm, Sweden: Oxford University Press. [cited at p. 3, 101, 102]

Rossignol, S., C. Chau, E. Brustein, M. Belanger, H. Barbeau, and T. Drew (1996). Locomotor capacities after complete and partial lesions of the spinal cord. *Acta Neurobiologiae Experimentalis 56*(1), 449–63. [cited at p. 107]

Saigal, R., C. Renzi, and V. Mushahwar (2004). Intraspinal microstimulation generates functional movements after spinal-cord injury. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 12*(4), 430–440. [cited at p. 13, 35, 44, 45, 46, 53, 35, 44, 45, 46, 53, 103]

Shik, M. (1997). Recognizing propriospinal and reticulospinal systems of initiation of stepping. *Motor Control 1*, 310–313. [cited at p. 111, 112]

Tscherter, A., M. O. Heuschkel, P. Renaud, and J. Streit (2001). Spatiotemporal characterization of rhythmic activity in rat spinal cord slice cultures. *European Journal of Neuroscience 14*(2), 179–190. [cited at p. 45, 110]

Ueyama, T., N. Mizuno, S. Nomura, A. Konishi, K. Itoh, and H. Arakawa (1984). Central distribution of afferent and efferent components of the pudendal nerve in cat. *J Comp Neurol 222*(1), 38–46. [cited at p. 112]

Yakovenko, S., D. A. McCrea, K. Stecina, and A. Prochazka (2005). Control of locomotor cycle durations. *Journal of Neurophysiology 94*(2), 1057–1065. [cited at p. 105]

Chapter 5

A Physiologically-based Controller for Generating Overground Locomotion using Functional Electrical Stimulation *

"The longest journey begins with a single step."

- Lao Tsu, Tao Te Ching

5.1 Introduction

Stepping in physiological systems is controlled both through signals descending from supraspinal systems, as well as through circuitry residing within the lumbosacral spinal cord. Sherrington (1910) suggested that locomotion is the result of a chain of reflexes. In 1911, Brown demonstrated that the spinal cord of adult cats is capable of generating rhythmic locomotor outputs in the absence of descending drive or sensory input (Brown, 1911). Later experiments have supported the existence of locomotor-related neural circuitry within the spinal cord, now commonly referred to as the locomotor central pattern generator (CPG) (Grillner, 1985; Orlovsky et al., 1999). Although the CPG is capable of generating a rhythmic output when activated by a tonic input in the form of electrical stimulation (Dimitrijevic et al., 1998; Guevremont et al., 2006; Magnuson and Trinder, 1997; Shik, 1997) or application

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of pharmacological agents (Cazalets et al., 1995; Cowley and Schmidt, 1997; Kjaerulff and Kiehn, 1996; Rossignol et al., 2001), it is modulated by afferent feedback. Limb position (Grillner and Rossignol, 1978) and force (Duysens and Pearson, 1980) influence the timing and duration of flexor (swing) and extensor (stance) activation during stepping (Norton et al., 2005). The goal of the current study was to evaluate the capacity of externally implemented controllers mimicking these physiological systems in restoring locomotion after neurological damage, such as a spinal cord injury.

Functional electrical stimulation (FES) is used as an interface with the nervous system to restore function to muscles and organs after disease or injury. The technique is effective after spinal cord injury since the motoneurons below the level of the lesion remain intact and form a viable connection with the muscles they innervate. Electrical stimuli applied to intact nerves or muscles can then generate functional contractions of targeted muscles. The clinical use of electrical stimulation dates back to the early 1960s as a method for restoring lower (Liberson et al., 1961) and upper limb (Long, 1963) function after stroke or spinal cord injury. Currently available systems for restoring stepping require the user to initiate each step through the use of manual push buttons. In addition to being less desirable to the user, these hand controlled systems have a higher metabolic cost than more automated controllers (Popovic et al., 2003). The ultimate system would be able to generate stable and reliable stepping in a manner similar to the way normal locomotion is controlled, using a combination of subconscious mechanisms with intermittent conscious effort.

Previous studies conducted in our laboratory have demonstrated that intraspinal microstimulation can generate in-place stepping in cats with spinal cord injury (Saigal et al., 2004). This was first achieved by applying predetermined phasic sequences of stimulation through groups of microwires generating reciprocal flexion and extension movements of the hindlimbs. Sensory-driven stepping was also achieved using a physiologically-based *if-then* rule to govern the transitions between stance and swing (Prochazka, 1996; Saigal et al., 2004).

In the present study we focused on investigating the capacity of two controllers to generate overground locomotion through the independent use of intrinsically-timed (CPG) or sensory-driven phase transitions. Although the role of the CPG in human locomotion is unclear (Dimitrijevic et al., 1998), the intrinsic rhythmicity and ability to modulate output in response to external conditions makes the CPG an attractive model for the design of an FES control system. Our observations suggest that although both controllers were capable of generating overground locomotion, neither provided consistent load-bearing stepping. In addition, the intrinsically-timed controller suffered from an inability to respond to changing internal and external conditions (i.e., fatigue and friction) and the sensory-driven controller exhibited high sensitivity to the selection of the initial parameters. For these reasons we suggest that a "combined controller" which uses sensory signals to modify an intrinsic rhythm may significantly improve the robustness of stepping. The combined controller may offer a more physiological representation of the neural control of overground locomotion by providing a balance between the roles of the CPG and sensory input. A controller was implemented in two experimental sessions to test the advantages of this combined approach.

5.2 Methods

Eight spinally-intact adult male cats weighing between 3.5-5.0 kg were used in the study. All experimental procedures were approved by the University of Alberta Animal Welfare Committee. The cats were anesthetized for the duration of each recording session and intramuscular (IM) electrodes were implanted percutaneously into 6 major extensor and flexor muscles of each of the hindlimbs. At the end of the experiment the electrodes were removed and the animals recovered in a heated kennel. A total of 14 recording sessions were performed for this study (5 animals were tested more than once).

5.2.1 Animal Preparation and Intramuscular Electrode Implantation

Anesthesia was temporarily induced through the inhalation of isoflurane (2-3% isofluorane in carbogen) and an intravenous catheter was inserted for administering sodium pentobarbital throughout the remainder of the experiment (0.25 mg/kg induction; maintenance 1:10 saline dilutions of the anesthetic). Sterilized IM electrodes were implanted bilaterally in 6 muscles that act to flex or extend the joints of the hindlimb. The implanted muscles were:

sartorius anterior (hip flexor), semimembranosus anterior (hip extensor), biceps femoris posterior (knee flexor), vastus lateralis (knee extensor), tibialis anterior (ankle flexor) and gastrocnemius lateralis (ankle extensor). Intramuscular electrodes (9 strand stainless steel Cooner wire, insulated except for 3-4 mm tips) were implanted near the motor point of the desired muscle according to the technique described by Basmajian and DeLuca (1985).

5.2.2 Experimental Setup and Data Acquisition

Following the implantation of IM wires the animal was transferred to a partial body support sling suspended from a sliding trolley (figure 5.1A). The trolley was placed on a track system allowing it to move with variable friction along the length of a 2.5 m custom built walkway. The walkway consisted of two 3-axis parallel force plates. The hindlimbs of the animal were placed on individual force plates allowing independent left and right force signals to be recorded along the entire length of the walkway during the stepping sequences. Accelerometers were secured firmly between the ankle and metatarsal phalangeal (MTP) joint of each hindlimb to provide a voltage signal representing the relative flexion or extension of the limb. Kinematic tracking markers were placed on the right side of the cat to indicate the iliac crest, and the hip, knee, ankle and MTP joints. Due to the movement of the skin over the knee joint during locomotion the knee joint marker could not be used to indicate the correct joint location. Therefore, limb segment lengths were recorded and triangulation algorithms were used to provide a better estimate of the position of the knee joint.

The raw accelerometer and force signals as well as the stimulation control signals generated by the controller were sampled at 2000 or 4000 samples/s using CED Power 1401 analog-to-digital board and Spike2 data acquisition software (Cambridge Electronic Design, Ltd., Cambridge, UK). The entire length of the walkway was filmed from the right side using a high speed JVC digital video camera (120 frames/s) placed orthogonally to the midpoint at a distance of approximately 4 m. This significantly reduced the distortion in the limb segments due to parallax effects. A calibration grid was also attached to the trolley in order to perform frame-by-frame scaling of the video data. A light emitting diode

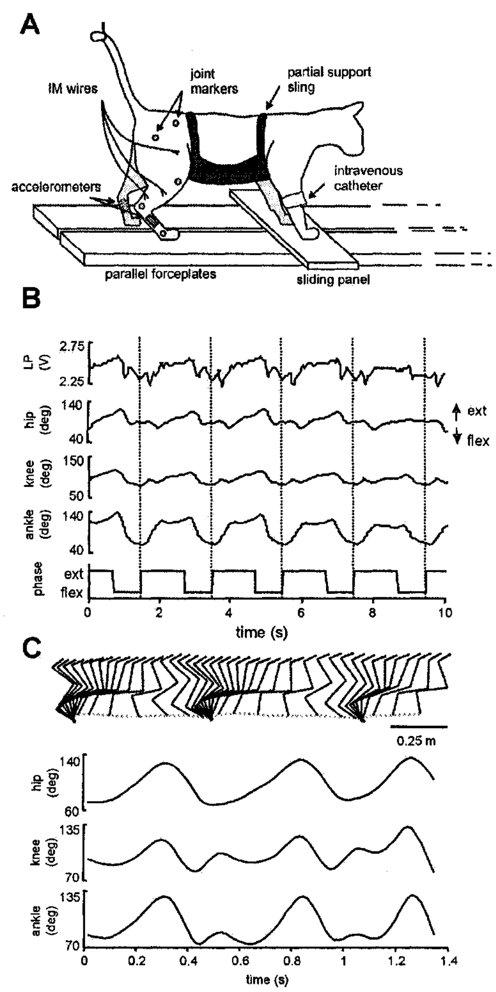

Figure 5.1: *Experimental setup.*

Schematic of setup used for animal suspension and IM stimulation (A). The weight of the animal is partially supported by a body harness. A sling placed under the chin of the animal (not shown) is used to support the head and maintain an open airway throughout the recording session. The cat is positioned with its forelimbs on a sliding platform which is slightly elevated over two parallel force plates for GRF recordings. Accelerometers are attached securely between the ankle and MTP joints for limb position (LP) recordings. Joint markers are attached for kinematic analysis. A comparison of accelerometer signals and joint angles derived from video data (B). Data from an intact cat during overground locomotion (C). Stick figures and joint angles are reconstructed from video data. Each stick figure represents the data at 2 s intervals.

(LED) was used to synchronize the kinematic and kinetic data.

5.2.3 Intramuscular Stimulation Protocol

Six dual-channel constant current stimulators (EMS-6500, Electrostim Medical Services, Inc., Tampa, FL) were used to apply patterned trains of stimulation (biphasic charge balanced, 0.1-20 mA, 200 μs depolarizing pulse, 50 pulses/s) to activate flexor and extensor muscles in sequences which would generate coordinated stepping movements.

At the onset of each experiment the stimulation amplitude for motor threshold (level eliciting first visible muscle contraction) was determined as well as the stimulation amplitude required to generate the desired response. This was done using 1 s-trains of stimulation applied to each individual muscle. After the stimulation amplitudes for individual muscles were obtained, synergies (groups of flexor or extensor muscles) were tested in order to generate functional movements of the whole limb with proportional changes in the joint angles throughout the action. Stimulation amplitudes were adjusted to evoke qualitatively balanced responses in the left and right legs. The adjusted stimulation amplitudes generating the desired muscle responses were recorded and used during the initial stepping trial as the plateau values for the stimulation envelopes. Further adjustments were made to these values from trial to trial based on observations made during the stepping sequences or by retesting the responses using 1 s-long stimulation trains applied to individual or synergistic muscles. This was done in order to achieve a combination of muscle activation levels that generated bilaterally balanced functional gait. This balance was subject to change due to factors such as the level of muscle fatigue and the amount of walkway friction at the onset of each stepping trial. This high dependence on initial parameter selection is consistent with results seen in 2D (Yakovenko et al., 2004) and 3D (Ekeberg and Pearson, 2005) models of feline locomotion.

5.2.4 The Control System

We designed three controllers that reflected some of the principles thought to govern locomotion in physiological systems; one that behaved like an intrinsically-timed CPG, another that was a fully sensory-driven state controller, and a third that was a combination of intrinsically-timed and sensory-driven control. Each controller used a different method for determining the timing and duration of the gait phases. However, a single output algorithm was used to translate these phases into stimulation waveforms based on predetermined stimulation levels. The controllers were tested during 14 recording sessions.

The intrinsically-timed controller generated consistent patterns of flexion and extension based entirely on intrinsic timing in a manner similar to the output of an isolated CPG. The gait cycle of a cat can be divided into one flexion (F) and three extension (E1, E2, and E3) phases (Engberg and Lundberg 1969). A basic gait cycle consisting of a swing (hip, knee and ankle flexion - F) phase and a stance (hip, knee and ankle extension - E3) phase was implemented in all experiments. After preliminary tests using various phase durations, including those described by Halbertsma Halbertsma (1983), we used a 2 s gait cycle and set the stance and swing phase durations to 60% and 40%, respectively. Delayed retraction (hip extension) was added to this cycle so that the propulsive extension of the hip was only initiated once the load bearing extension of the knee and ankle was well established. In the final recording sessions we also added a short burst of stimulation to the knee flexor at the onset of swing to prevent toe drag (two sessions), and an increase in knee extensor stimulation during retraction to maintain ground contact (one session). All stimulation envelopes were trapezoidal in shape, consisting of three segments; 1) a ramp segment where the stimulation increased from motor threshold to the previously selected desired value, 2) a constant stimulation segment where the desired amplitude was maintained for the duration of the phase, and 3) a ramp segment where the stimulation amplitude returned from the desired level to motor threshold before the stimulation terminated. Step period, percent of the phase spent in stance and swing, timing of the retraction phase and duration of the ramp segments were set on the computer via a user interface to the control program. We did not experiment with different gait speeds using the intrinsically-timed controller. However, this could be accomplished by changing the step period and adjusting the timing of the various gait phases as well as the stimulation amplitudes in order to achieve functional responses within a new phase duration. Figure 5.2A shows a conceptual illustration of a half-center CPG model which would generate continuous and rhythmic flexion and extension output patterns similar to those generated by our controller. Also shown is a schematic representation of stimulation envelopes achieved using the previously determined amplitudes with the intrinisically-timed controller. Functional overground locomotion was first demonstrated in each cat using this controller prior to testing the other controllers. The activation profiles for the last step (to the right of the vertical dashed line, fig. 5.2A) represent envelopes of EMG data during overground locomotion in awake, intact cats, as collated from multiple sources by Yakovenko et al. (2002).

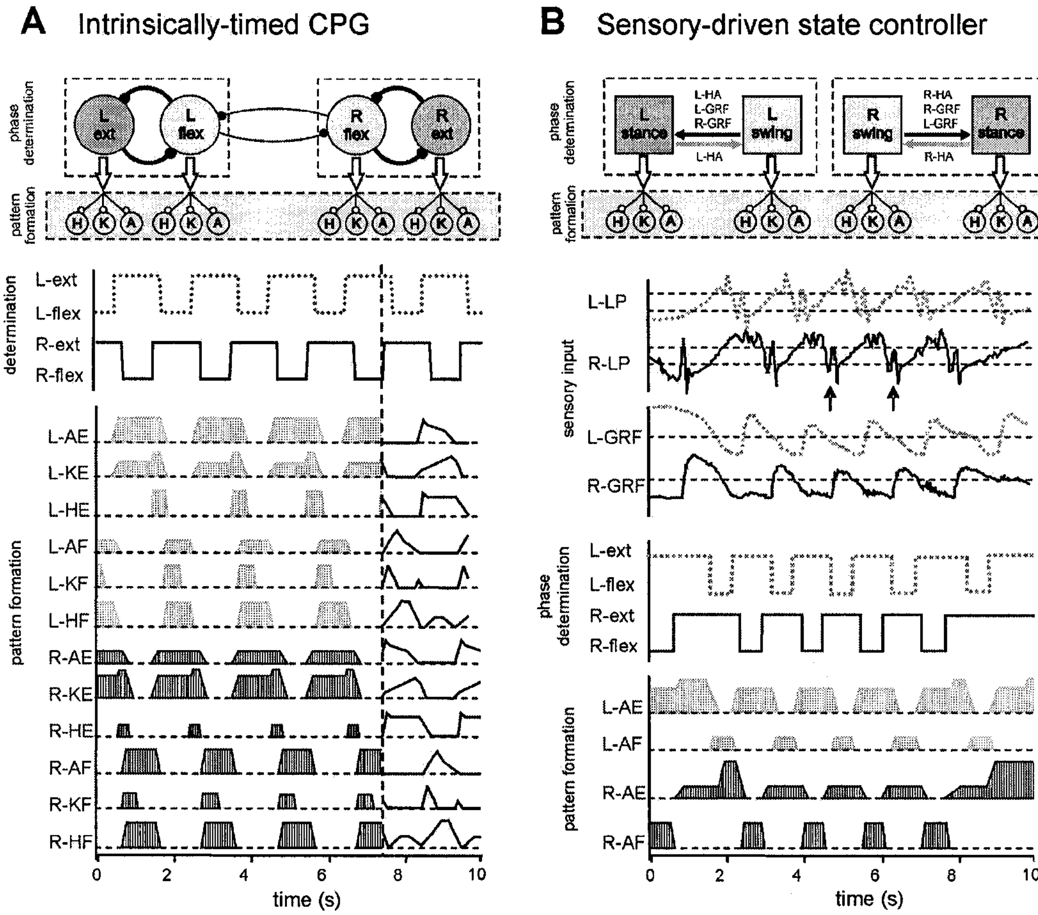

Figure 5.2: *Controller design and operation.*

A schematic representation of the controller as well as output signals from the phase determination and pattern formation stages are shown for the intrinsically-timed CPG controller (A) and the sensory-driven state controller (B). The figure at the top is a conceptual illustration of a system which would generate output patterns similar to those of the two controllers developed for this study. Outputs from the phase determination stage illustrate flexor (low) and extensor (high) signals for the left (dotted) and right (solid) legs. The schematic representation of the output traces shown for the pattern formation stage indicate stimulation patterns applied to ankle (A), knee (K) and hip (H), flexor (F) and extensor (E) muscles in the left (L) and right (R) legs. Note that the increases in KE stimulation in A are a pre-programmed feature implemented to maintain paw contact during retraction, whereas, the increases to AE in B are dynamically generated by the controller in order to overcome variable walkway friction. Sensory input signals from the accelerometers (limb positions) and forceplates (GRFs) are also included for the sensory driven controller. The arrows in the R-LP plot indicate acceleration profiles generated at foot contact. The horizontal dotted lines represent thresholds for limb extension, flexion and loading.

The sensory-driven controller relied entirely on feedback signals in order to time the switching between flexion and extension activity. Signals representing hip angle and ground reaction force (GRF) were used because they play significant roles in governing phase transitions in physiological systems (Duysens and Pearson, 1980; Grillner and Rossignol, 1978;

McVea et al., 2005; Norton et al., 2005). The role of these signals during gait can be described by a set of *if-then* rules (Prochazka, 1996) which we implemented using finite state control (fig. 5.2B). The following rules were used to govern the swing-to-stance and stance-to-swing phase transitions:

Stance-to-swing transitions:
IF the ipsilateral limb is extended
AND the ipsilateral limb is unloaded
AND the contralateral limb is loaded
THEN initiate swing in the ipsilateral limb

Swing-to-stance transitions:
IF the ipsilateral limb is flexed
THEN initiate stance in the ipsilateral limb

Although these rules allowed the left and right limbs to switch independently, they prevented the occurrence of a state of double swing and allowed a period of double stance during which both limbs were in the loaded phase of the gait cycle. The rule governing swing-to-stance allowed for early termination of swing if the stance leg became unloaded. This was done in order to avoid periods of no body support throughout the stepping sequences. Modulation of the stimulation amplitude applied to the knee extensor was also implemented such that if the phase transition rules were not met within a set period of time, the controller would increase the stimulation amplitude until either a maximum safe value was reached (20 mA), or the *if-then* rules were met. This feature enabled the animals to overcome walkway resistance in situations where the selected desired stimulation levels did not result in the generation of sufficient muscle force. The states of limb extension/flexion and limb loading/unloading during stepping were determined using threshold based measurements of signals from the accelerometers and force plates, respectively. Due to the movement of skin over the femur it is difficult to measure hip angle directly in cats. Therefore, accelerometers secured to each foot of the animal were used to provide an estimate of the overall condition of flexion or extension of the limbs. The validity of this estimation is demonstrated by the examples of raw accelerometer signals and joint angles derived from video data shown in figure 5.1B. The joint angle data taken from FES evoked stepping can also be compared to the data shown in figure 5.1C which were obtained during overground locomotion in an awake, intact cat. Thresholds were selected based on the ranges of limb position and GRF signals obtained during intrinsically-timed CPG trials achieved during the same recording session. The thresholds were typically set at 20% less than the maximum accelerometer signal for limb extension, 20% greater than the minimum accelerometer signal for limb flexion, and 50-75% of the average vertical force signals for limb loading. In order to reduce the number of false state transitions resulting from large movement generated acceleration profiles during stepping (arrows in fig. 5.2B), the limb position sensor signal was required to remain past the extension or flexion threshold for 100 ms before the state condition was met. Figure 5.2B uses sample feedback signals to illustrate the thresholds and resulting phase signals. Sensory-driven stepping often terminated in a state of double unloaded extension in which both hindlimbs were extended behind the base of support of the cat.

A combined controller was implemented and tested in the final recording session with the objective of preventing the occurrence of double unloaded extension. This controller implemented the beneficial stability of the intrinsically-timed system along with the state-dependent decision making capacity of the sensory-driven system. The underlying switching was provided by an intrinsically-timed CPG pattern which could be overridden based on two sensory rules whose purpose was to ensure limb loading at all times. The *if-then* rules for this controller were designed with the objective of preventing the occurrence of double unloaded extension. The rules were:

GRF rule:
IF the stance leg becomes unloaded
THEN terminate swing in the contralateral leg

Rolling rule:
IF the forward progression stops
THEN take a step with each leg to a position under the body.
Extend limbs until the trolley starts to roll again.

An additional sensor (servo potentiometer) was added to the setup which provided a saw tooth displacement signal profile as the trolley rolled. When the unloaded condition of the GRF rule was met, the intrinsic timer was interrupted and reset to the point of termination of contralateral swing. When the rolling rule was invoked the intrinsic timer was paused in double stance and resumed only when the trolley movement was sensed.

All of the controllers were implemented in software (programmed in the high level computer language of C). The program was executed on a desktop computer which was interfaced to the stimulators through a National Instruments (NI) digital-to-analog card. Feedback signals from the accelerometers and force plates were digitized at 500 samples/s by an NI analog-to-digital card and smoothed by applying a 140 ms sliding window average.

5.2.5 Data Analysis

Data analysis was completed using custom written routines for Matlab V7.0 (The MathWorks Inc., Natick, MA, US).

Kinematics

The video recordings were digitized and the x-y coordinates of each of the joint markers were extracted using a custom software package (MotionTracker2D) written in Matlab by Dr. Douglas Weber (University of Pittsburgh, Pittsburgh, PA, USA). The motion of the right hindlimb was reconstructed using the coordinates of the markers as well as the measured lengths of the limb segments. The position of the knee joint was determined using triangulation methods due to movement of the skin over the joint during locomotion. Each frame was calibrated in the x and y axes to correct for skew introduced by the camera angle. The resulting values were used to reconstruct stick figures from which limb trajectories and joint excursions were extracted.

Kinetics

Vertical GRFs recorded during the evoked locomotion were used to quantify the functional value of stepping achieved. Force measurements were low-pass filtered (cutoff frequency 8 Hz) before analysis. Steps were divided into stance and swing phases based on output signals from the controller and mean vertical force was calculated for each individual step. Each stepping trial was initiated with a short period of double stance during which the animal typically lifted its hindquarters out of the support sling. The peak vertical force generated during this period of "forceful standing" was determined for each animal. Due to the forceful nature of this movement this peak GRF value was assumed to be an overestimation of the weight of the hindquarters. Trials conducted in human volunteers performing sit-to-stand movements indicated that the weight of the individual (obtained during quiet standing) represents 85% of the peak force generated during the transition (data not shown). Therefore, 85% of the peak vertical force recorded during the initial period of forceful standing in the animals was used as an approximation of the GRF required for full hindlimb loading.

5.3 Results

The two main criteria used to define functional overground locomotion were: 1) the ability to generate forward propulsive movement, and 2) the ability to ensure a period of double limb support where the weight of the animal is transferred from one limb to the other. Achieving stable stepping was not a simple task due to a heavy dependence on the stimulation parameters selected. Reasons to abort a trial included: little or no forward progression (i.e., in-place stepping), excessive paw slippage (to the back or side), and poor paw placement (too far forward relative to the hip or on the dorsal surface). A trial was continued as long as the overall functionality of the stepping was not compromised by the aforementioned errors. A total of 264 trials were recorded over the first 12 experimental sessions included in this study. Fifteen of the 97 intrinsically-timed trials (15.5%) and 18 of the 157 sensory-driven trials (11.5%) were considered to be successful based on the quality of the steps taken (appropriate range of movement, and paw traction), the distance traveled along the walkway ($> 75\%$ of the full length), and the state in which the animal stopped (in-place stepping or stable standing). Traveling the full length of the walkway was not a necessary requirement for a stepping sequence to be deemed successful. As long as the trial terminated in an acceptable state (in-place stepping or stable standing), successful trials could include trials where the animal traveled $> 75\%$ of the length of the walkway before forward progression was hindered due to muscle fatigue or walkway resistance. An average of 8 unsuccessful trials was attempted in each recording session before the first successful intrinsically-timed stepping sequence was achieved. After the initial successful trial it was often possible to achieve several additional successful sequences with only minor changes being made to the stimulation amplitudes in order to compensate for muscle fatigue. Figure 5.3A summarizes the reasons for terminating all trials conducted during this study. Some trials have been included in more than one category if a combination of factors contributed to termination. Intrinsically-timed trials were most often terminated due to an excessive number of paw slips or walkway misses caused by excessive limb movements, or in a state of in-place stepping resulting from insubstantial force generation. The most common state of termination during sensory-driven control was double unloaded extension. This state was considered to be a failure mode which was a consequence of the high rolling resistance of the trolley. Double unloaded extension occurred primarily when the amount of force generated during the stance phase of a single leg was insufficient to push the trolley forward resulting in a two legged push during double stance and a movement of the animal past the base of support provided by the limbs. The data shown in figure 5.3B represent the total number of steps taken by the left and right legs during the successful intrinsically-timed and sensory-driven stepping sequences. The loading profiles were analyzed for these sequences, and steps during which the force was maintained until the contralateral leg became loaded were considered to be "good." Using this approach it becomes apparent that in this setup a controller based on intrinsic timing is more capable of generating consistent load bearing stepping than one based entirely on sensory signals.

5.3.1 Intrinsically-timed CPG Controller

The locomotion achieved using a predetermined gait pattern generated by the intrinsically-timed controller was characterized by rhythmic and consistent movements. Control parameters such as gait cycle duration, stance and swing phase durations, and stimulation amplitudes were selected at the onset of each trial and were invariable after the initiation of stepping. All stepping trials were conducted with a step cycle of 2 s with 60% (65% in one

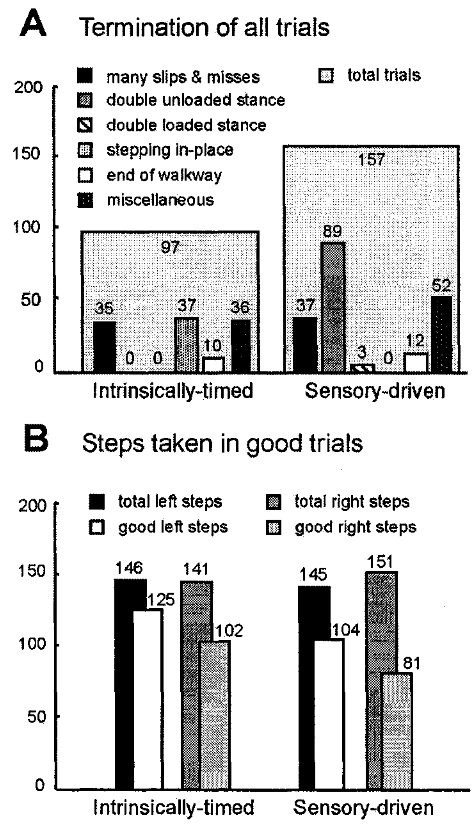

Figure 5.3: *Summary of all attempted trials.*

(A) Summary of the reasons for terminating each of the trials attempted using the intrinsically-timed and sensory-driven controllers. The large box indicates the total number of trials attempted for each mode. Each small bar represents a possible reason for terminating a trial. Each trial can be included in more than one of the following categories if multiple factors contributed to its termination: 1) many slips and misses resulting in loss of traction causing the leg to move backwards or off the side of the walkway; 2) double unloaded stance with both legs fully extended behind the animal (outside the base of support); 3) double loaded stance (i.e., functional standing); 4) stepping in-place consisting of alternating movements without forward progression; 5) reaching the end of walkway; 6) miscellaneous factors including poor limb movement, plantar paw placement, etc. (B) The total number of steps and the number of "good" steps taken during all successful intrinsically-timed and sensory-driven trials. Trials were considered to be successful if the occurrence of errors did not deter from the overall quality of the walking and the animal was able to travel a significant distance along the walkway. A step was "good" if the GRF force did not decay completely before the other leg became loaded.

animal) of the duration spent in stance. The timing of hip retraction was delayed from the initiation of stance by either 0 ms (hip extension occurs with knee and ankle extension), 200 ms, 300 ms, 400 ms, or coincided with the initiation of contralateral stance (i.e., during double stance). The delay was selected in order to complement the forward and downward force generated by the knee extensor. The duration of the flexor burst at the onset of swing was typically 300-400 ms in duration (37-50% of swing), allowing the toe to clear the surface while the leg was being swung forward by the ankle and hip flexors.

Figure 5.4 shows two 10 s clips taken from successful intrinsically-timed trials in two different animals (refer to figure 1C for comparison with normal cat locomotion). The sequences of stick figures were reconstructed from kinematic data recorded during each of the full 10 s segments shown. Also shown are the calculated angles for the hip, knee and ankle joints as well as filtered accelerometer and GRF signals. The phase determination signals in the bottom trace represent the stance (high) and swing (low) phase signals generated by the controller for the left (dotted) and right (solid) legs. The data displayed in figure 5.4A represent the final 10 s of a 17.5 s trial during which the animal took 9 steps with each leg and traveled a total distance of 1.95 m. The maximal range of motion of the hip, knee and ankle joints were 38°, 35°, and 50°, respectively, and represented 1.4x, 1.1x, and 1.4x of the ranges typically seen (28°, 32°, 36°) in intact cats walking at slow to medium speeds (Rossignol et al. 1996). Left and right hindlimb vertical GRFs were 4.43 ± 1.25N and 5.48 ± 0.47 N (mean ± std), respectively. These values represented approximately 10% and 12% of the total weight of the cat (3.68 kg) or 37% and 46% of the estimated force required for full hindlimb loading (11.9 N). The overlap between the force traces for the left and right legs indicate periods of double limb loading. This is a desired characteristic of functional stepping. This trial was terminated when the animal was no longer able to progress forward due to walkway friction and muscle fatigue. A characteristic of intrinsically-timed control was that even after the forward progression stopped, the animal continued to step in-place (arrow) until the stimulation was terminated at the end of the trial. Figure 5.4B shows 10 s of data from the middle of an intrinsically-timed trial which was deemed to be successful even though it was punctuated by slips of the right hindlimb. The total trial time was 27.5 s during which the animal took 13 steps with each leg and traveled a total distance of 2.5 m. Slips can be seen in the backward and upward trajectory of the MTP joint on the stick figures (as indicated by the direction of the arrow) and also as rapid increases in the limb angles at the end of the extension phase. The maximal range of motion of the hip, knee and ankle joints was 55°, 70°, and 90°, respectively, and represented 1.8x, 2.2x, and 2.5x the typical joint ranges. Left and right hindlimb vertical GRFs were 8.51 ± 2.24 N and 5.26 ± 1.10 N (mean ± std), respectively. These values represented approximately 24% and 15%

of the total weight of the cat (4.64 kg) or 67% and 41% of the estimated force required for full hindlimb loading (12.7 N). This trial was terminated when the animal reached the end of the walkway.

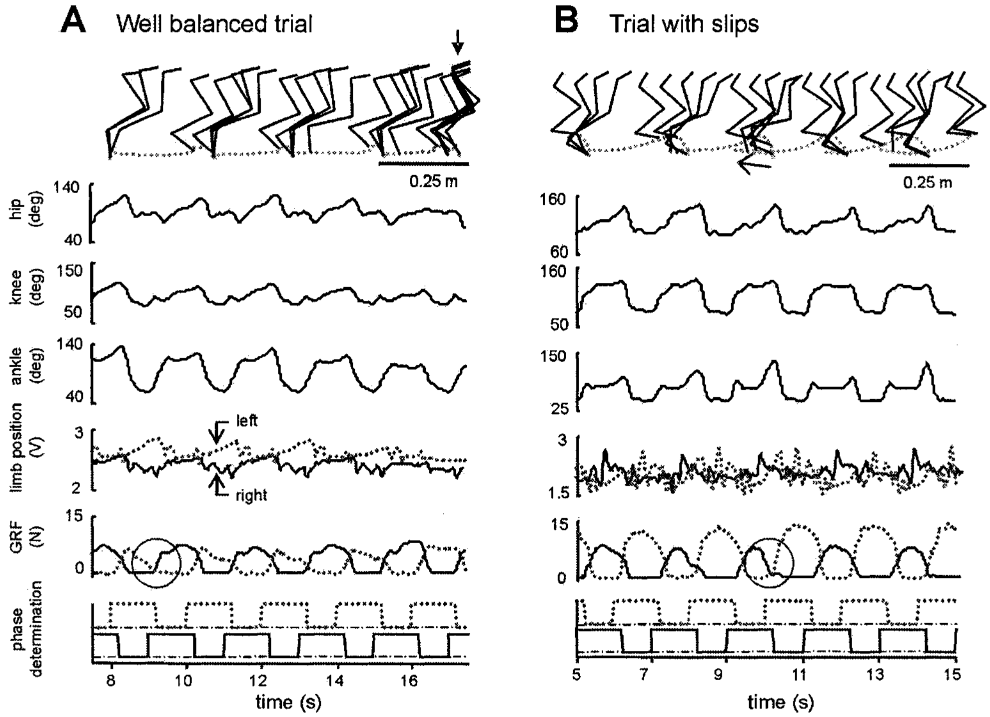

Figure 5.4: *Intrinsically-timed control.*

Examples of steps taken from successful trials using the intrinsically-timed CPG controller. Kinematic and kinetic data and output signals from the phase determination stage of the controller are shown for a series of well balanced steps terminating in in-place stepping (A) and a series of step punctuated by slips (B). The trial shown in A terminated with in-place stepping (arrow) when the animal reached the end of the walkway. The trial shown in B was deemed to be successful because the animal was able to traverse the entire length of the walkway even though there were moments when the paw lost traction and slid backwards along the walkway (indicated by the arrow in the stick figures). Both trials have examples of double unloading (circles in GRF traces).

Even in successful steps such as the ones shown in figure 5.4A, it was common to observe moments of insignificant loading in either leg due to a rapid decay of vertical force in the supporting limb (circle in A). This was often the result of an increase in propulsive force at the termination of stance causing the animal to move too far forward over the base of support provided by the limb. A similar decay in vertical GRF was seen during slips when the limb lost traction and was extended behind the body (circle in B). Attempts were made to reduce the occurrence of these errors by increasing the knee extensor (vastus lateralis) and reducing the hip extensor (semimembranosus anterior) stimulation in order to keep the paw firmly on the ground while still achieving the propulsive force required for forward progression.

5.3.2 Sensory-driven State Controller

We found that the stimulation amplitudes for successful intrinsically-timed stepping had to be established in order to generate appropriate sensory-driven phase transitions. Each sensory-driven sequence was initiated with 1 intrinsically-timed step. This placed the hindlimbs of the cat in an "acceptable" state of ipsilateral extension and unloading, and contralateral loading (*if-then* conditions required for stance-to-swing transitions) prior to the onset of sensory-driven switching. Poor parameter selection resulted in the "unacceptable" state of double unloaded extension and an inability to switch to the swing phase of the gait cycle due to the unmet criteria of limb loading. Figure 5.5 shows two examples of sensory-driven stepping obtained during a single recording session in one animal. The traces have the same format as those shown in figure 5.4 for intrinsically-timed control with the exception of the phase determination signals, where the greyed regions during stance (high signal) represent periods during which the extensor stimulation amplitude was increased. This increase was triggered by a prolonged stance phase and resulted in an improvement in the ability of the animal to push the trolley in the presence of walkway resistance and muscle fatigue. The arrow at the bottom of the traces in A indicates the transition from intrinsically-timed control (initiation steps) to sensory-driven control. The black dashed lines on the GRF and limb position traces indicate the threshold levels selected to represent limb extension (> 2.4 V, 135°), flexion (< 2.0 V, 100°), and loading (> 4.4 N) for the right leg. Similar values were selected for the left leg (> 2.7 V, < 2.6 V and > 4.4 N, respectively) but are not illustrated here. The data shown in A represent a complete 25 s trial during which the animal took 9 steps and traveled a total distance of 2.4 m. The initial step was taken using intrinsically-timed parameters (2 s gait cycle, 60% stance, 6.3 ± 3.7 mA) with each of the following steps occurring when the *if-then* conditions for phase transitions were met. The cycle duration increased visibly as the animal progressed until it reached the end of the walkway and maintained double loaded stance (standing). The stick figures illustrate only the last 10 s of these data starting at the point indicated by the arrow at the top of the traces. The sequence shown in B represents a trial which was terminated in double unloaded extension. Note that the force profiles of the two legs decay simultaneously (circle in B) resulting in a state that does not meet any of the conditions for the initiation of swing. This is an unrecoverable and highly undesirable state in this system. This type of error was the most common mode of failure for sensory-driven stepping (fig. 5.3) and represents a potentially dangerous situation in a clinical setting.

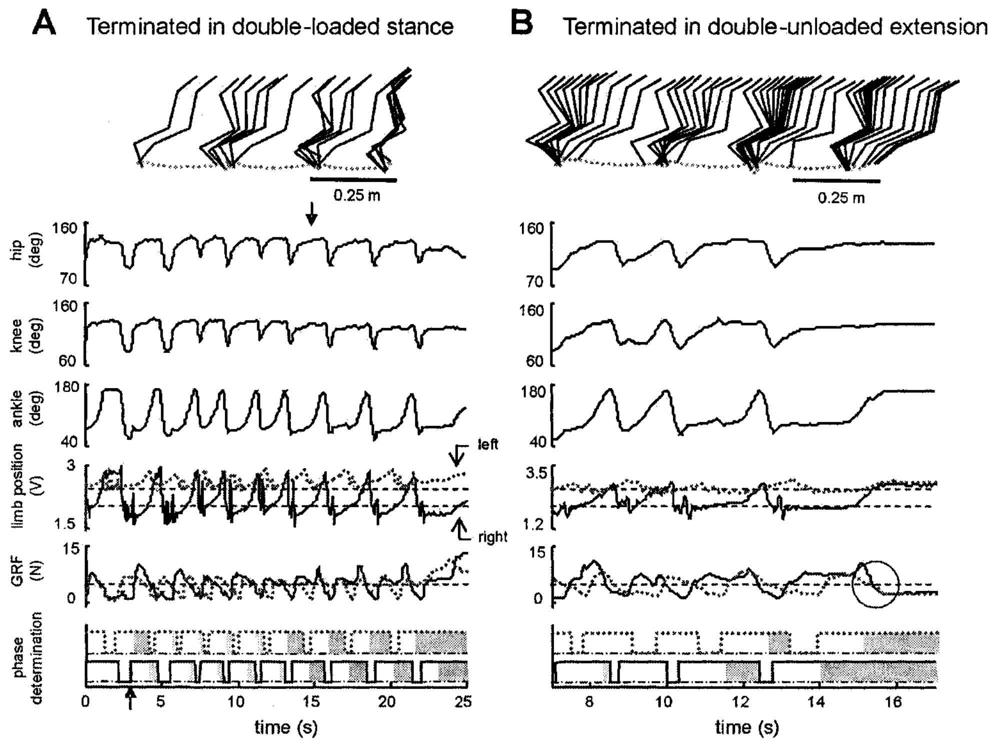

Figure 5.5: *Sensory-driven control.*

Examples of steps taken from successful trials using the sensory-driven state controller. Kinematic and kinetic data and output signals from the phase determination stage of the controller are shown for a series of steps terminating in the stable state of double loaded standing (A) and in the failure state of double unloaded extension (B). Threshold levels for limb flexion, extension and loading are indicated by the horizontal dashed lines. The stick figures shown in A represent the last 10 s of the data starting at the time indicated by the arrow at the top of the hip angle trace. The arrow at the bottom of the phase determination trace indicates the transition point from intrinsically-timed (initiation steps) to sensory-driven control. Note that the failure state in B is caused when both the left and right GRF signals decay simultaneously (circled in the GRF trace) resulting in a state which can not be overcome by the state controller. Grey regions in the phase determination signals in A and B indicate periods where the stimulation levels to the extensor muscles are increasing due to the detection of a prolonged extensor phase by the controller.

5.3.3 Combined Controller

The difficulty in generating robust overground stepping using strictly intrinsically-timed or sensory-driven control led us to design a controller that implemented both intrinsically-timed and sensory-driven phase transitions. Two recording sessions were conducted using this controller in order to demonstrate the advantages of a combined design. The underlying phase switching was provided by an intrinsically-timed pattern which could be overridden based on two sensory rules that were designed to prevent the occurrence of double-unloaded extension. A conceptual representation of this controller is illustrated in figure 5.6A. Figure 5.6B shows a 40 s data clip taken from a 90 s-long trial using the combined controller. The stick figures shown in B are reconstructed frame-by-frame from kinematic data. The threshold level indicated by the dashed line on the GRF trace shown in B was used by the GRF rule to terminate swing in the case where loading decayed in the stance leg. The rolling rule was implemented using the displacement signal (dashed) shown in the first row of traces. The displacement signal is shown in conjunction with the trigger signal (solid) that was generated by the controller to indicate that the trolley was rolling (low) or stationary (high). In this trial, the forward progression of the trolley was blocked by the experimenter (at the point indicated by the arrow in the stickfigures) in order to test the functionality of the rolling rule. Note that, in B, after the trolley became stationary the legs took an additional step before halting in double loaded stance. This is a stable termination point. At this point assistance was provided in the form of a small push applied to the trolley in order for forward progression to be resumed. The controller responded to the movement of the trolley by reinitiating the intrinsically-timed stimulation patterns. This resulted in the commencement of a new series of steps during which the GRF rule was evoked to correct for moments of unloading.

5.4 Discussion

The goal of this study was to evaluate the ability of physiologically-based controllers to generate overground stepping, through the application of FES, in a manner similar to the subconscious control seen during normal locomotion (i.e., with minimal user intervention).

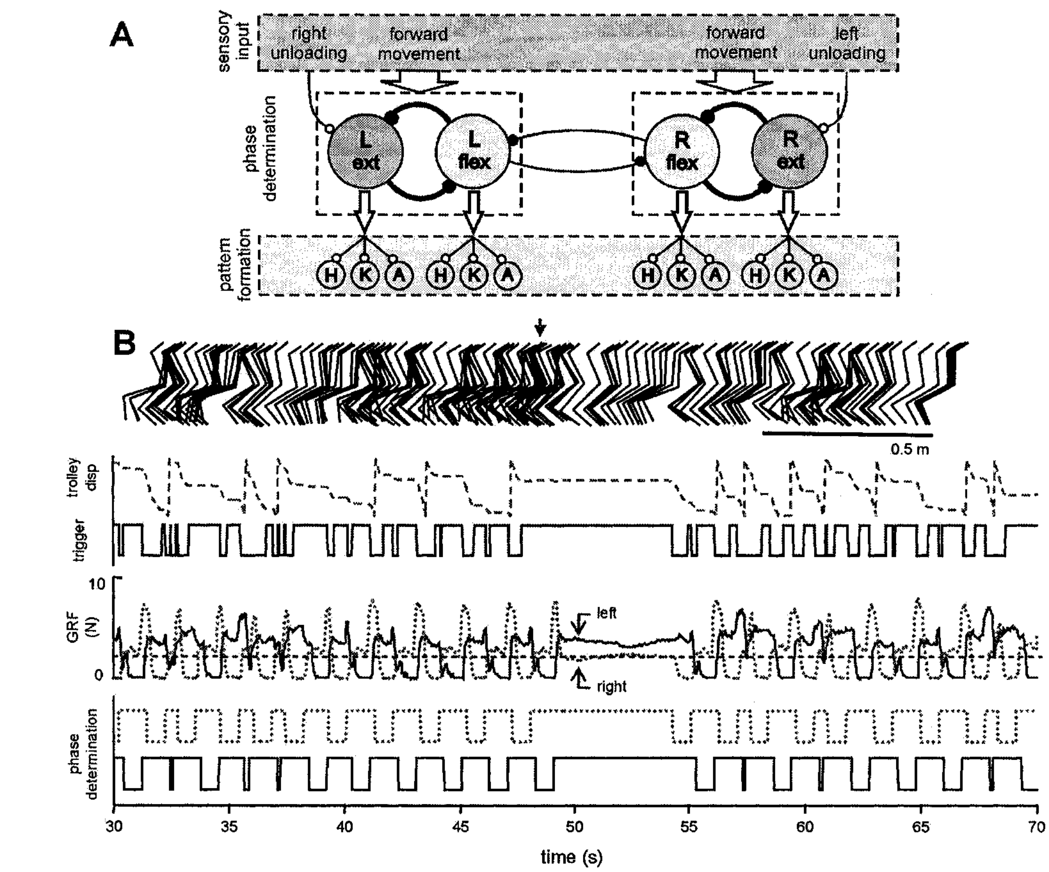

Figure 5.6: *Combined control.*

(A) A Schematic representation of the combined controller. The combined controller consists of the structure of the intrinsically-timed CPG, as illustrated by the reciprocal half centre models, with the addition of sensory inputs providing information about the current state of the system. The intrinsic rhythm generator receives tonic drive (is turned on) during forward movement indicated by a displacement signal. The extension half-centre is excited (resulting in a switch to stance) when the contralateral leg is unloaded as indicated by the GRF signal. (B) A 40 s-long clip illustrating sensory input signals and phase determination output signals taken from a 90 s trial using the combined controller. A threshold level (dashed line) was applied to the GRF signals and was used to reset the intrinsically-timed pattern to extension if the contralateral leg became unloaded. The displacement of the trolley was determined from a saw-tooth voltage signal (provided by a servo potentiometer) which was modulated as the platform rolled. When the trolley was stopped the potentiometer signal remained constant and the trigger signal was switched to the high state. If the trigger remained high for an extended duration, the controller responded by placing both limbs in stance until the trolley resumed motion

5.4.1 Controller Structure and Behaviour

Three controllers were designed following some of the basic principles thought to govern locomotion in physiological systems. Two controllers were tested thoroughly over a series of 12 recording sessions: an intrinsically-timed controller in which phase switching was based on predetermined patterns, and a sensory-driven controller in which switching was based on feedback signals. A third controller, consisting of a combination of these two approaches, was implemented in two sessions to demonstrate the advantages of the combined control.

The controllers were designed using a hierarchical structure of 3 concurrently running processes which: 1) determined appropriate phase transitions, 2) formed stimulation output patterns, and 3) processed sensory inputs. In the intrinsically-timed controller shown in figure 5.2A, the phase determination process generated rhythmic switching signals which were then used by the stimulation output process to generate appropriate stimulation waveforms for each muscle. This structure corresponds to a hierarchical model for the spinal control of locomotion consisting of separate rhythm generation and pattern formation layers. The hierarchical model was proposed based on observations of CPG driven activity obtained during fictive locomotion in adult cats. In these conditions, the underlying rhythm was uninterrupted even in the presence of spontaneous deletions of flexor or extensor bursts in the respective nerves (Kriellaars et al., 1994; Lafreniere-Roula and McCrea, 2005), suggesting that the input to motoneurons is generated independently from the oscillating circuitry. The presence of resetting and non-resetting deletions during fictive locomotion indicates that sensory signals can access both the rhythm generation and pattern formation layers of the CPG, respectively (Lafreniere-Roula and McCrea, 2005). This hierarchal structure was used in the present controllers because it allowed the timing of the gait phases (either through intrinsically-timed or sensory-driven algorithms) to be controlled without knowledge of the actual stimulation profiles. Critical points in the gait cycle (such as the onset of stance, swing, and retraction) were dictated by the rhythm generation layer, which were then translated into appropriate stimulation profiles by the pattern formation layer.

Pattern formation

The patterns used at the onset of the study consisted of basic trapezoidal activation profiles with all extensors active during stance and all flexors during swing. Several modifications were subsequently made to the stimulation pattern produced by the controller in order to improve the quality of the generated gait. Comparisons of the stimulation envelopes produced by the controller to EMG patterns recorded in cats during locomotion (Yakovenko et al., 2002) indicated striking resemblances (i.e., increasing knee extensor activation during swing, and bursting knee flexion at the onset of swing). Interestingly, this evolution towards "normal" activation profiles occurred entirely through efforts to improve the quality of gait with the comparison to EMG data only occurring after all data had been obtained. This indicates the importance of appropriate activation profiles in the quality of overground stepping achieved. It also illustrates that it is possible to generate overground stepping through the activation of only a subset of the many muscles normally active during locomotion.

Rhythm generation and sensory integration

The behaviour of the intrinsically-timed controller was similar to that of a reciprocally-coupled half-center as proposed by Brown (Brown, 1911, 1914) and illustrated in figure 5.2A. The controller generated a periodic pattern of flexor and extensor activity in the absence of input signals. The sensory-driven controller more closely resembled the theory proposed by Sherrington in which stepping is generated solely through a chain of reflexes (Sherrington, 1910). The controller had no intrinsic rhythmicity, and the switching between flexor and extensor activity was completely dependent on sensory feedback signals. The feedback signals were also used by the controller to modulate the stimulation pattern (e.g., increase stimulation to the knee extensor when a prolonged stance phase was detected).

Signals representing limb position and GRF were selected for the sensory-driven controller due to their roles in timing gait transitions in insects (Bassler and Buschges, 1998; Pearson and Duysens, 1976), cats (McVea et al., 2005; Grillner and Rossignol, 1978; Norton et al., 2005; Pearson, 1995; Whelan et al., 1995) and human infants (Pang and Yang, 2000). Experiments conducted in cats indicated that information about hip angle and limb loading is derived from muscle spindles in hip flexors (Hiebert et al., 1996) and Golgi tendon organs in ankle extensors (Pearson et al., 1998; Whelan et al., 1995), respectively. Both hip angle and GRF play important roles in regulating stepping, as shown in cats with complete spinal cord injury and selective deafferentations (Norton et al., 2005). Cutaneous sensory input also has a modulatory effect on the gait pattern (Bouyer and Rossignol, 2003a,b). This input represents loading information that is provided through pathways other than those involving the Golgi tendon organs. In order to simplify the design of our controllers we removed the redundancy of the cutaneous input that is normally present in natural systems.

In the present study, the sensory signals were interfaced with both the rhythm generation (for phase transitions) and the pattern formation (for stimulation amplitude modulation) layers of the controller. Feedback to the pattern formation layer acted to reinforce the pattern rather than generate deletions as seen during fictive locomotion. The deletion of an extensor phase without a compensatory action would result in a loss of loading in our animal and was therefore not desirable.

Although neither the intrinsically-timed nor the sensory-driven phase transitions consistently produced functional locomotion, we found that the intrinsically-timed stepping was typically more robust than the sensory-driven stepping. This reinforces the idea that sensory information may actually decrease the stability of a system by adding signal noise (Kuo, 2002) as well as requiring additional control parameters. However, the intrinsically-timed controller was unable to respond to changes in the state of stepping caused by loss of traction, variable walkway resistance or muscle fatigue. For these reasons we proposed the use of a third controller consisting of an underlying rhythm that could be reset or modified as indicated by sensory feedback signals. The combined controller (figure 5.6A) was constructed from the phase determination and pattern formation stages of the intrinsically-timed controller, with the addition of a sensory input stage which acted to modify the switching of the flexion and extension half-centres. Two recording sessions were conducted in order to demonstrate the concept of a combined controller and the results indicate its potential in providing a versatile foundation for generating robust stepping. The sensory rules used in this session were designed specifically to prevent periods of insignificant limb loading by influencing the rhythm generation layer.

The design of a combined controller is not limited to the two sensory rules implemented in this study and its performance could potentially be improved by designing additional sensory rules which also modulate the pattern formation layer. The rules implemented in this study were selected in order to prevent the critical modes of failure seen in our model. Rules specific to bipedal gait could be selected and implemented clinically. These rules could provide features such as stimulation amplitude modulation in the presence of muscle fatigue and phase duration modulation either to induce or to respond to changes in forward velocity. Buttons or switches allowing direct user intervention can also be implemented with the combined controller to address situations where more specific control is required (such as going up or down stairs). These mechanisms would reflect the natural ability to provide conscious control of gait in challenging conditions.

5.4.2 Parameter Selection

We found that the proper selection of stimulation parameters was critical for achieving successful stepping sequences. Despite the thought that feedback control should allow the system to adjust to small imbalances, parameter selection was particularly critical when using the sensory-driven controller. This could be due to the fact that the sensory signals were used strictly to generate phase transitions. In physiological systems reinforcing/inhibitory reflex pathways probably play a role in adjusting the muscle activation levels in response to the specific needs at any point throughout the gait cycle (Pearson and Duysens, 1976). These reflexes act to increase the force output during stance and limit the amplitude of the movement during swing. Implementing such feedback loops into our controller may have widened the range of acceptable starting parameters for successful stepping sequences. However, they would have also had the effect of introducing additional parameters (such as acceptable sensor signal ranges and thresholds) which may have ultimately required additional tuning for functional operation. In addition, the use of IM stimulation of a select number of muscles limits the spectrum of movements that can be generated. The differences in recruitment characteristics resulting from muscle properties and IM electrode placement make synergistic movements particularly difficult to generate due to the requirement for the balanced contributions of various muscles over a range of stimulation levels. The combined controller had the benefit of using a simple interpretation of sensor signals in order to produce only the necessary changes to an underlying rhythm. Control algorithms using hip angle and GRF feedback signals have also been implemented in 2D (Yakovenko et al., 2004) and 3D (Ekeberg and Pearson, 2005) computer models of cat hindlimb locomotion.

Results from the 2D model indicated that the use of state dependent control rules similar to the ones implemented in our sensory-driven controller, increased the range of parameters suitable for stable locomotion and enabled the model to step at different velocities. Our sensory-driven controller probably suffered from reduced stability due to the complexity of the *in-vivo* system. Additional variability was introduced by sensor noise, as well as by muscle fatigue and recruitment properties. Unlike the computer simulations, two consecutive trials performed in our *in-vivo* system would not generate identical results. For this reason we did not perform a detailed analysis of the stable parameter space in our system.

The 3D cat model developed by Ekeberg and Pearson (2005) was used to examine the relative roles of hip angle and GRF information in the appropriate initiation of stance-to-swing phase transitions during overground locomotion. They implemented a state controller similar to the one used in our sensory-driven system. Initially, hip angle and GRF were combined linearly to determine phase transitions (i.e., low force would initiate flexion at less extension, while high force would require more extension). They then removed the contribution of hip angle or GRF from the controller and observed the effect on the quality of stepping achieved. Coordinated stepping could be generated when GRF was used alone but hip angle alone resulted in decoupled gait. This supports the idea that the point in the gait cycle where weight is transferred from one limb to the other is critical and must be carefully regulated, as is done through the use of our *if-then* rules. Even though both models (Ekeberg and Pearson, 2005; Yakovenko et al., 2004) were able to generate stable locomotion, they both suffered from high sensitivity to parameter selection. However, a simple pendulum model of rhythmic limb movements demonstrated that a combination of feedforward (intrinsically-timed) and feedback (sensory-driven) control can provide improved stability (Kuo, 2002).

Although the goal of our study was not to reproduce the aforementioned models, our findings in an *in-vivo* system extend some of the results achieved in the computer simulations by incorporating real muscle properties. We found that in the *in-vivo* system, the balance of muscle activation through FES becomes increasingly difficult to achieve as a result of the non-linear responses to stimulation during individual movements (due to the order of muscle fibre recruitment, and hysteresis) and between consecutive steps and trials (due to muscle fatigue). This is a property that is not necessarily present in computer models, where the same set of initial conditions can be replicated and parameters tuned using optimizing algorithms. The use of stimulation applied at 50 pulses/s may also add to the instability of the responses due to the extended plateau region of the length-tension relationship of near tetanized muscle, and the sharp decay in force that occurs at short muscle lengths. The generation of locomotion in an intact physiological system is a complex task in which threshold levels and feedback signals are used dynamically to regulate phase transitions and muscle activation levels. Our efforts in achieving stable locomotion using strictly intrinsically-timed or sensory-driven phase transitions leads us to propose that a combined controller, consisting of a balance of these two components, may provide the most robust locomotion while still providing a fair representation of the physiological control of locomotion. As a corollary, the presence of "threshold levels" of supraspinal and sensory inputs in individuals with incomplete spinal cord injury has recently been suggested as a necessary factor for translating the benefits of body weight supported treadmill locomotor training to functional gains in overground ambulation (Dobkin et al. 2006).

5.4.3 Clinical Implications

Electrical stimulation to restore movement can be controlled through either open- or closed-loop control. Comparatively simple systems that aid in restoring gait such as foot-drop stimulators use closed-loop control with stimulation being driven by signals such as leg angle (Dai et al., 1996) or foot contact (Burridge et al., 1997) derived automatically during the step cycle. More complicated systems that require several channels of stimulation to restore stepping in users with complete motor paralysis typically operate under open-loop control in which users initiate each step, or part of a step, through manual push buttons.

The primary benefit of the controllers implemented in this study is that each is able to produce functional outputs without the conscious intervention of the user. The output patterns are either generated in a predetermined manner, driven by feedback signals as the movements progressed, or preferably by a combination of the two.

Other groups have developed control strategies for restoring walking after spinal cord injury. A dual level (pattern generator/pattern shaper) adaptive feedforward controller which can track cyclic knee torques during knee flexion and extension movements while sitting has been developed (Abbas and Triolo, 1997; Abbas and Chizeck, 1995). This controller used cycle-to-cycle corrections to make appropriate modifications to the stimulation applied during the subsequent cycles. The adaptive feedforward system was expected to compensate for slow changes in muscle properties and the addition of a feedback loop would allow the controller to respond rapidly to mechanical perturbations. Riess and Abbas (2001) demonstrated that angle feedback signals can be used by the feedforward controller to track cyclic movements during muscle fatigue. The sensitivity of our system to the selection of stimulation amplitudes suggests that the addition of cycle-to-cycle feedforward correction may improve the gait by changing the stimulation levels in order to maintain consistent movements over multiple steps.

If-then rule based state controllers have been used in other systems to restore mobility. In one system, signals from goniometers, accelerometers and load sensors on crutches were used to determine the current position of the user (seated or standing), their intention to move (stand or step), and make discrete state transitions throughout the movement (Veltnik et al., 1996). A feedback controller which used *if-then* sensory rules determined from machine learning algorithms was implemented in a subject with complete paraplegia and yielded good overground stepping (Fisekovic and Popovic, 2001). In contrast to these systems, our sensory-driven controller is based on physiological *if-then* rules for locomotion. We started with a fundamental set of *if-then* rules and a simple output activation pattern and added features as required in order to improve the quality of stepping achieved. By taking this bottom up approach we have been able to examine the roles of the control rules and activation patterns in generating stable gait.

Our sensory-driven controller uses limb position and GRF feedback signals with *if-then* rules to generate appropriate phase transitions. Accelerometers have already been used on humans to measure effectively knee joint angles during standing (Veltink and Franken, 1996) or tilt of the shank during stepping (Dai et al., 1996). These results suggest that the direct measurement of hip angle using accelerometers secured to the thigh will be feasible in a clinical setting. We used force plates to obtain GRF information since they generate signals that are simple to interpret and have a large signal to noise ratio. For clinical implementation, force sensing resistors (FSRs) placed in the sole of the shoe can be used to provide information about the distribution of pressure under the foot. These sensors have been used to detect events in the gait cycle during walking (Skelly and Chizeck, 2001). Pressure related sensory signals can also be obtained through an implanted cuff placed on the sural nerve to record electroneurographic (ENG) signals carried by cutaneous sensory nerve fibres originating from the lateral sole of the foot. Small ENG signals (5-10 μA) can be recorded in the presence of stimulation evoked muscle activity (10-100 mV) by using a tripolar recording cuff and simple data processing methods (Haugland and Hoffer, 1994). These nerve signals can then be used by a state controller to determine gait events during FES walking (Strange and Hoffer, 1999). Adaptive logic networks (ALNs) can be used to interpret these signals even when walking on various surfaces or while wearing different footwear (Hansen et al., 2004).

A study conducted to evaluate 4 different modes of FES stepping (hand control and automatic control of slow walking, near-normal walking, and near ballistic walking) indicated that the metabolic cost and physiological cost index of hand controlled phase transitions was higher when compared to more automated forms of control (Popovic et al., 2003). Although ballistic walking was shown to have the lowest cost, 5 of the 6 subjects selected the automatic control of slow walking to be their preferred mode due to the need to coordinate upper and lower limb movements during stepping. The control system was designed using a 3D model of walking which implemented neural networks to generate predetermined stimulation patterns that activated muscles in sequences corresponding to the desired gait. A system such as this one could be used in conjunction with our combined controller in order to generate appropriate intrinsically-timed muscle activation sequences (as determined by the model and neural network) which could then be modified by sensory signals. These feedback signals could improve the ability of the user to coordinate upper and lower limb movements by ensuring that the stepping remains within the individual's base of support.

Push buttons could also be provided allowing the user to intervene actively in cases where the intrinsic pattern is not suitable for the desired task. The ultimate combined control system would achieve a balance between the low metabolic costs of a fully automated system and the increased biomechanical stability experienced by users of manually controlled systems. The use of a more fatigue resistant stimulation paradigm such as intraspinal microstimulation might result in further improvements to the quality of stepping achieved (Saigal et al. 2004).

5.4.4 Concluding Comments

In this study we have demonstrated that although FES evoked overground locomotion can be generated using either intrinsically-timed or sensory-driven controllers, the stepping achieved lacks the robustness and load bearing qualities characteristic of functional locomotion. We demonstrated that intrinsically-timed stepping is less susceptible to failure due to poor initial parameter selection but that sensory-driven stepping has the advantage of being able to adapt to changes in walkway friction or muscle properties during the stepping sequence. A combined controller that has an underlying rhythmic output which can be modified by sensory signals would best resemble the rhythmic output of a locomotor CPG in a physiological system. A combined control system such as this one may provide a means for restoring robust and functional overground locomotion for people with spinal cord injury.

5.5 Bibliography

Abbas, J. and H. Chizeck (1995). Neural network control of functional neuromuscular stimulation systems: computer simulation studies. *IEEE Transactions on Biomedical Engineering 42*(11), 1117–1127. [cited at p. 144]

Abbas, J. and R. Triolo (1997). Experimental evaluation of an adaptive feedforward controller for use in functional neuromuscular stimulation systems. *IEEE Transactions on Rehabilitation Engineering 5*(1), 12–22. [cited at p. 31, 144]

Basmajian, J. and C. DeLuca (1985). *Muscles Alive. Their Functions Revealed by Electromyography.* Baltimore, MD: Williams and Wilkins. [cited at p. 121]

Bassler, U. and A. Buschges (1998). Pattern generation for stick insect walking movements–multisensory control of a locomotor program. *Brain Research Reviews 27*(1), 65–88. [cited at p. 139]

Bouyer, L. J. and S. Rossignol (2003a). Contribution of cutaneous inputs from the hindpaw to the control of locomotion. i. intact cats. *Journal of Neurophysiology 90*(6), 3625–39. [cited at p. 139]

Bouyer, L. J. and S. Rossignol (2003b). Contribution of cutaneous inputs from the hindpaw to the control of locomotion. ii. spinal cats. *Journal of Neurophysiology 90*(6), 3640–53. [cited at p. 139]

Brown, T. (1911). The intrinsic factors in the act of progression in the mammal. *Proceedings of the Royal Society of London Series B 84*(572), 309–18. [cited at p. 3, 44, 101, 118, 139]

Brown, T. G. (1914). On the nature of the fundamental activity of the nervous centers; together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system. *Journal of Physiology (London) 48*, 18–46. [cited at p. 139]

Burridge, J., D. N. Taylor, S. Hagan, D. Wood, and I. Swain (1997). The effects of common peroneal stimulation on the effort and speed of walking: a randomized controlled trial with chronic hemiplegic patients. *Clinical Rehabilitation 11*, 201–210. [cited at p. 143]

Cazalets, J. R., M. Borde, and F. Clarac (1995). Localization and organization of the central pattern generator for hindlimb locomotion in newborn rat. *Journal of Neuroscience. 15*(7 Pt 1), 4943–51. [cited at p. 44, 101, 102, 101, 102, 119]

Cowley, K. C. and B. J. Schmidt (1997). Regional distribution of the locomotor pattern-generating network in the neonatal rat spinal cord. *Journal of Neurophysiology 77*(1), 247–259. [cited at p. 102, 119]

Dai, R., R. Stein, B. Andrews, K. James, and M. Wieler (1996). Application of tilt sensors in functional electrical stimulation. *IEEE Transactions on Rehabilitation Engineering 4*(2), 63–72. [cited at p. 27, 143, 144]

Dimitrijevic, M. R., Y. Gerasimenko, and M. M. Pinter (1998). Evidence for a spinal central pattern generator in humans. *Annals of the New York Academy of Sciences 860*(1), 360–376. [cited at p. 33, 118, 120]

Duysens, J. and K. G. Pearson (1980). Inhibition of flexor burst generation by loading ankle extensor muscles in walking cats. *Brain Research 187*(2), 321–332. [cited at p. 119, 125]

Ekeberg, O. and K. Pearson (2005). Computer simulation of stepping in the hind legs of the cat: An examination of mechanisms regulating the stance-to-swing transition. *Journal of Neurophysiology. 94*(6), 4256–4268. [cited at p. 123, 141, 142]

Fisekovic, N. and D. B. Popovic (2001). New controller for functional electrical stimulation systems. *Medical Engineering & Physics. 23*(6), 391–9. [cited at p. 144]

Grillner, S. (1985). Neurobiological bases of rhythmic motor acts in vertebrates. *Science 228*(4696), 143–9. [cited at p. 101, 111, 112, 101, 111, 112, 118]

Grillner, S. and S. Rossignol (1978). On the initiation of the swing phase of locomotion in chronic spinal cats. *Brain Research. 146*(2), 269–77. [cited at p. 4, 6, 4, 6, 119, 125, 139]

Guevremont, L., C. Renzi, J. Norton, J. Kowalczewski, R. Saigal, and V. Mushahwar (2006). Locomotor-related networks in the lumbosacral enlargement of the adult spinal cat: Activation through intraspinal microstimulation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 14*(3), 266–272. [cited at p. 44, 54, 44, 54, 118]

Halbertsma, J. M. (1983). The stride cycle of the cat: the modelling of locomotion by computerized analysis of automatic recordings. *Acta Physiologica Scandinavica. Supplementum. 521*, 1–75. [cited at p. 110, 124]

Hansen, M., M. Haugland, and T. Sinkjaer (2004). Evaluating robustness of gait event detection based on machine learning and natural sensors. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 12*(1), 81–88. [cited at p. 145]

Haugland, M. and J. Hoffer (1994). Artifact-free sensory nerve signals obtained from cuff electrodes during functional electrical stimulation of nearby muscles. *IEEE Transactions on Rehabilitation Engineering 2*(1), 37–40. [cited at p. 145]

Hiebert, G., P. Whelan, A. Prochazka, and K. G. Pearson (1996). Contribution of hind limb flexor muscle afferents to the timing of phase transitions in the cat step cycle. *Journal of Neurophysiology. 75*(3), 1126–1137. [cited at p. 139]

Kjaerulff, O. and O. Kiehn (1996). Distribution of networks generating and coordinating locomotor activity in the neonatal rat spinal cord in vitro: a lesion study. *Journal of Neuroscience. 16*(18), 5777–94. [cited at p. 4, 44, 45, 44, 45, 101, 102, 110, 113, 101, 102, 110, 113, 119]

Kriellaars, D. J., R. M. Brownstone, B. R. Noga, and L. M. Jordan (1994). Mechanical entrainment of fictive locomotion in the decerebrate cat. *Journal of Neurophysiology 71*(6), 2074–2086. [cited at p. 138]

Kuo, A. D. (2002). The relative roles of feedforward and feedback in the control of rhythmic movements. *Motor Control 6*(2), 129–45. 1087-1640 (Print)Journal ArticleResearch Support, Non-U.S. Gov'tResearch Support, U.S. Gov't, Non-P.H.S.Research Support, U.S. Gov't, P.H.S. [cited at p. 8, 140, 142]

Lafreniere-Roula, M. and D. A. McCrea (2005). Deletions of rhythmic motoneuron activity during fictive locomotion and scratch provide clues to the organization of the mammalian central pattern generator. *Journal of Neurophysiology 94*(2), 1120–1132. [cited at p. 3, 138]

Liberson, W., H. Holmquest, D. Scot, and H. Dow (1961). Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. *Archives of Physical Medicine and Rehabilitation* (42), 101–105. [cited at p. 26, 119]

Long, C., n. (1963). An electrophysiologic splint for the hand. *Archives of Physical Medicine and Rehabilitation 44*, 499–503. [cited at p. 119]

Magnuson, D. S. and T. C. Trinder (1997). Locomotor rhythm evoked by ventrolateral funiculus stimulation in the neonatal rat spinal cord in vitro. *Journal of Neurophysiology. 77*(1), 200–206. [cited at p. 3, 33, 102, 111, 102, 111, 118]

McVea, D. A., J. M. Donelan, A. Tachibana, and K. G. Pearson (2005). A role for hip position in initiating the swing-to-stance transition in walking cats. *Journal of Neurophysiology 94*(5), 3497–3508. [cited at p. 7, 125, 139]

Norton, J., L. Guevremont, and V. Mushahwar (2005). Significance of sensory input for stepping inchronically spinalized cats. In *Society for Neuroscience Abstracts*, Volume 630.5, Washington, DC. [cited at p. 119, 126, 139]

Orlovsky, G., T. Deliagina, and S. Grillner (1999). Walking and running in humans. In *Neuronal Control of Locomotion, Form Mollusc to Man.* Stockholm, Sweden: Oxford University Press. [cited at p. 3, 101, 102, 101, 102, 118]

Pang, M. Y. and J. F. Yang (2000). The initiation of the swing phase in human infant stepping: importance of hip position and leg loading. *Journal of Physiology. 528*(Pt 2), 389–404. [cited at p. 139]

Pearson, K. G. (1995). Proprioceptive regulation of locomotion. *Current Opinion in Neurobiology 5*(6), 786–791. [cited at p. 139]

Pearson, K. G. and J. Duysens (1976). Function of segmental reflexes in control of stepping in cockroaches and cats. In R. Herman, S. Grillner, P. Stein, and D. G. Stuart (Eds.), *Neural Control of Locomotion*, pp. 519–538. New York: Plenum. [cited at p. 7, 139, 141]

Pearson, K. G., J. E. Misiaszek, and K. Fouad (1998). Enhancement and resetting of locomotor activity by muscle afferents. *Annals of the New York Academy of Sciences. 860*, 203–15. [cited at p. 7, 139]

Popovic, D., M. Radulovic, L. Schwirtlich, and N. Jaukovic (2003). Automatic vs hand-controlled walking of paraplegics. *Medical Engineering & Physics. 25*(1), 63–73. [cited at p. 32, 119, 145]

Prochazka, A. (1996). Proprioceptive feedback and movement regulation. In L. Rowell and J. Sheperd (Eds.), *Exercise Regulation and Integration of Multiple Systems: Neural Control of Movement Section 12*, pp. 89–127. New York: American Physiological Society. [cited at p. 7, 119, 126]

Riess, J. and J. Abbas (2001). Adaptive control of cyclic movements as muscles fatigue using functional neuromuscular stimulation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 9*(3), 326–330. [cited at p. 144]

Rossignol, S., N. Giroux, C. Chau, J. Marcoux, E. Brustein, and T. A. Reader (2001). Pharmacological aids to locomotor training after spinal injury in the cat. *Journal of Physiology (London) 533*(1), 65–74. [cited at p. 119]

Saigal, R., C. Renzi, and V. Mushahwar (2004). Intraspinal microstimulation generates functional movements after spinal-cord injury. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 12*(4), 430–440. [cited at p. 13, 35, 44, 45, 46, 53, 35, 44, 45, 46, 53, 103, 119]

Sherrington, C. (1910). Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *Journal of Physiology. 40*, 28–121. [cited at p. 6, 118, 139]

Shik, M. (1997). Recognizing propriospinal and reticulospinal systems of initiation of stepping. *Motor Control 1*, 310–313. [cited at p. 111, 112, 111, 112, 118]

Skelly, M. M. and H. J. Chizeck (2001). Real-time gait event detection for paraplegic fes walking. *IEEE Transactions on Neural Systems & Rehabilitation Engineering. 9*(1), 59–68. [cited at p. 32, 145]

Strange, K. D. and J. A. Hoffer (1999). Gait phase information provided by sensory nerve activity during walking: applicability as state controller feedback for fes. *IEEE Transactions on Biomedical Engineering. 46*(7), 797–809. [cited at p. 145]

Veltink, P. and H. Franken (1996). Detection of knee unlock during stance by accelerometry. *IEEE Transactions on Rehabilitation Engineering. 4*(4), 395–402. [cited at p. 144]

Veltnik, P., W. de Vries, H. Hermans, G. Baardman, M. Ijzerman, S. Heinze, A. Nene, G. Zilvold, and H. Boom (1996). A comprehensive fes control system for mobility restoration in paraplegics. In A. Pedotti, M. Ferrarin, J. Quintern, and R. Riener (Eds.), *Neuroprosthetics From BasicResearch to Clinical Applications*, pp. 163–168. Springer. [cited at p. 144]

Whelan, P. J., G. Hiebert, and K. G. Pearson (1995). Stimulation of the group i extensor afferents prolongs the stance phase in walking cats. *Experimental Brain Research 103*(1), 20–30. [cited at p. 7, 139]

Yakovenko, S., V. Gritsenko, and A. Prochazka (2004). Contribution of stretch reflexes to locomotor control: a modeling study. *Biological Cybernetics 90*(2), 146–155. [cited at p. 123, 141, 142]

Yakovenko, S., V. Mushahwar, V. VanderHorst, G. Holstege, and A. Prochazka (2002). Spatiotemporal activation of lumbosacral motoneurons in the locomotor step cycle. *Journal of Neurophysiology. 87*(3), 1542–53. [cited at p. 125, 138]

Chapter 6

General Discussion

"Now if I don't stand, step or cycle, it's because I don't want to, not because I can't."

- Julie Hill, person with paraplegia (Hill, 2000)

6.1 Discussion

Designing a system for restoring mobility after SCI requires a multidisiplinary approach encompassing aspects of medical science and engineering. This involves the development of a method for generating limb movements and a control system for restoring the desired function. The studies presented in this dissertation address these two components of the system 1) by evaluating the use of different modes of FES as a means of artificially evoking functional movements and 2) by designing feed-forward and feedback controllers to coordinate these movements in a manner appropriate for standing and stepping.

Functional electrical stimulation systems for restoring standing and stepping after SCI currently exist (see section 2.2 for a review). However, the approach taken in the studies presented in this dissertation was to apply physiological principles and biological features to the design of the FES system. By taking this approach we were also able to investigate the structure of the locomotor CPG and infer its role in generating overground locomotion. Throughout this dissertation, a large focus was placed on the development of intraspinal microstimulation (ISMS) as a technique for restoring mobility after spinal cord injury (SCI). Although ISMS has many beneficial features (section 2.3.2) the rate of success of ISMS is currently limited by the hardware and implantation procedure. Significant engineering issues need to be addressed before we can continue to evaluate the long-term utility of the technique after SCI (section 2.4). By evaluating the efficacy of ISMS to generate prolonged standing, a function relevant to people with SCI, we have demonstrated that it is worth pursuing these technical developments. Continuous trains of ISMS were also able to activate intrinsic networks within the spinal cord to generate locomotor-like patterns in the hindlimbs of cats with SCI, however, this strategy may not be appropriate for clinical implementation due to the low levels of force generated. For this reason alternative control strategies were designed for generating load-bearing overground locomotion, and evaluated with intramuscular stimulation. These control algorithms can be implemented with any mode of FES and will be tested using ISMS once some of the engineering issues have been addressed.

Intraspinal microstimulation is a technique that allows stimulation to be applied within the central nervous system to generate functional movements. Low levels of stimulation passed through microwires implanted into the lumbosacral enlargement have been shown to evoke single joint movements and multi-joint flexion and extension synergies in the lower limbs. By targeting specific motoneuronal pools within the grey matter of the cord specific leg movements can be evoked. These movements can then be used to restore function after damage to the upper motoneuron (i.e., SCI or stroke). It is worth noting that ISMS may not be equally suitable for restoring a wide variety of functions after SCI. For example, ISMS has not been effective in restoring bladder function. This may be due to differences in the neural organization of the micturition circuitry, the requirement for strong inhibition of the external sphincter and the involvement of autonomic processes in the control of micturition.

The FES systems currently available for restoring standing and stepping often use classical peripheral FES techniques such as surface stimulation, epimysial and/or intramuscular electrodes to generate movements (refer to section 2.1 for an overview). These techniques are characterized by fast fatiguing contractions and steep force recruitment curves resulting from the reversed order of muscle fibre activation. Recent studies have indicated that ISMS has an advantage over peripheral techniques by recruiting muscle fibres in a more physiological order (Bamford et al., 2005). This results in the ability of ISMS to generate graded force profiles (Snow et al., 2006; Mushahwar and Horch, 2000) appropriate for the control of fine movements.

Another advantage of ISMS is the fact that a broad range of movements can be evoked by implanting an array of microwires within a small region of the spinal cord (approximately 5 cm-long in humans). In addition to the fact that a diversity of responses can be evoked, a redundancy of stimulation points can be implanted within a single motoneuron pool without significantly increasing the complexity and distribution of the surgical procedure. This allows fatigue reduction paradigms, such as interleaving or stimulation rotation, to be implemented. Although ISMS is currently in the experimental phase, the results to date (summarized in section 2.3) provide promise for its future development into a clinically viable technique for restoring function after SCI.

Although ISMS can be used to produce stepping rhythms by appropriate patterning of independent ISMS-evoked movements of the limbs (Saigal et al., 2004; Mushahwar et al., 2002), true functional actions such as load-bearing standing and overground locomotion had not been demonstrated. The study included in chapter 3 of this dissertation evaluated the relative capacity of interleaved ISMS and non-interleaved IM stimulation to generate prolonged weight-bearing standing. As mentioned above, ISMS lends itself easily to the use of fatigue prevention stimulation paradigms, such as interleaving. Interleaved stimulation patterns can be applied through IM electrodes, however, this is not common practice in clinical systems and was not implemented in our study. Reducing the stimulation frequency could have also acted to prolong the duration of standing achieved in the IM trials and provided a more balanced evaluation of the ISMS and IM stimulation techniques. Our study demonstrates that the fatigue resistant properties of ISMS, enhanced by the use of interleaved stimulation protocols, results in a more consistent standing posture than when non-interleaved IM stimulation is applied. The two stimulation paradigms were also tested using open-loop and closed-loop control algorithms in order to achieve prolonged standing by minimizing the applied stimulation. These results indicate that closed-loop control can prolong the duration of standing, particularly during IM stimulation.

As mentioned above, ISMS has been demonstrated to recruit muscle fibres in a more physiological order than peripheral stimulation. This feature of ISMS indicates that its mechanisms of action may include an indirect activation of motoneurons through trans-synaptic pathways. The preferential excitation of afferent projections (Gaunt et al., 2006) or interneurons within the vicinity of the stimulating electrode may explain the responses evoked by ISMS. These neurons may then synapse onto large distributions of motoneurons within the target pool as well as pools corresponding to synergistic muscles. The motoneurons within all of these pools are in turn recruited according to the size principle (Henneman et al., 1974). The ability of ISMS to activate networks of neurons can be used to explain the results achieved in the study described in chapter 4 of this dissertation. In this study, low levels of continuous ISMS (motor threshold, 40 or 50 Hz) applied through groups of microwires implanted in the lumbosacral region could evoke stepping-like patterns in the hindlimbs of cats with SCI. This finding is interesting because continuous trains of stimulation were used both in the standing study (chapter 3) and the tonic stimulation study (chapter 4). Differences in the stimulation frequency and amplitude applied through microwires placed in similar locations within the spinal cord resulted in significant differences in the evoked responses (load bearing standing vs. locomotor-like alternation). These results indicate that a shift in the dominant activation effect of ISMS occurs depending on the stimulation parameters used (i.e., with increased stimulation amplitude) (Gaunt et al., 2006).

Although low levels of tonic ISMS appear to activate innate locomotor networks within the spinal cord, the evoked movements were characterized by low weight bearing and in-place stepping. Therefore, this stimulation protocol is not suitable for clinical implementation where load-bearing and propulsive forces are important features of functional mobility. The findings described in this study may however provide some insight into the organization of the locomotor CPG in the spinal cord. It has been commonly thought that the locomotor CPG has its leading areas in the more rostral regions of the spinal cord (Cazalets et al., 1995; Marcoux and Rossignol, 2000). However, ISMS was more effective in activating the locomotor CPG when applied through microwires implanted in the caudal (L7-S1) segments of the spinal cord, supporting the idea that the locomotor rhythm generator may be distributed (Dai et al., 2005; Kjaerulff and Kiehn, 1996). The mechanisms of ISMS are not fully understood, but it is possible that ISMS excites a combination of afferent endings and propriospinal interneurons that in turn recruit elements of the locomotor CPG in areas rostral to the stimulation site (Gaunt et al., 2006).

The final study included in this dissertation (chapter 5) evaluated the use of several different physiologically-based control paradigms for restoring *overground* locomotion after SCI. In contrast to the ISMS protocols described above, phasic FES was applied in patterns through intramuscular electrodes implanted in the main hip, knee and ankle, flexor and extensor muscles of the hindlimbs. The rationale for using IM stimulation during this experiment was to allow us to proceed with the development of a control system in parallel with other projects focusing on technical issues involved in improving the success rate of the ISMS implant. The current limitations of ISMS, and their proposed solutions were discussed in section 2.4 of this dissertation and include difficulties in targeting the specific motoneuron pools and securing the array safely and stably to a spinous process. The use of ISMS is expected to improve the quality of gait achieved using phasic stimulation. The graded force recruitment associated with ISMS could act to prevent ballistic extensor movements (obtained using IM stimulation) that were often associated with a loss of traction.

By coordinating the phasic pattern of IM stimulation appropriately we were able to generate load-bearing, propulsive locomotion. The two primary controllers were designed to mimic the roles of the CPG and sensory information during the neural control of gait. The CPG controller generated phase transitions based entirely on a predetermined timing pattern, whereas the sensory-driven controller used only information describing the current position and loading of the hindlimb to initiate transitions. The study was designed to test the hypothesis that the sensory-driven controller would generate more stable gait due to the ability to adapt to external conditions. However, our results indicate that a combination of intrinsically-timed transitions and sensory-information may provide the ultimate solution for achieving robust overground locomotion.

6.2 Future Directions

The studies included in this dissertation were conducted in order to examine the use of FES in restoring locomotion. In particular ISMS was explored as a means of improving on some of the current limitations of classical peripheral stimulation techniques. However, ISMS remains an experimental technique that must undergo some significant engineering developments before chronic functional testing can be resumed. These improvements are discussed in some detail in sections 2.4 and 2.5 of this dissertation and funding is currently being sought by the Mushahwar laboratory to initiate these projects. In addition, developments to the controllers for overground stepping will be made and tested in humans with various FES systems.

6.2.1 Critical Evaluation prior to Clinical Implementation

There are several criteria that must be met before ISMS can become a clinical technique for restoring standing and stepping in people with SCI. Experiments must be conducted to demonstrate that: 1) the ISMS implant and the long-term delivery of stimuli do not cause excessive damage to the spinal cord tissue, 2) the evoked responses remain stable and functional for long periods of time in animal models of SCI, 3) a high success rate can be achieved in an animal model in terms of microwire yield, function and stability and 4) ISMS can evoke a spectrum of functional responses during intra-operative trials in human subjects.

The issue of spinal tissue health will be addressed by chronic experiments (30 day implants) currently being conducted in our lab in rats with SCI. These experiments examine the effects of repetitive stimulation paradigms on the composition of the stimulated muscles and the health of the spinal tissue surrounding stimulating and non-stimulating microwires. In order for ISMS to be clinically viable, spinal cord tissue health must be maintained.

The long-term stability and functionality of ISMS in cats with SCI (preliminary data shown in section 2.3.2) must be evaluated once some of the technical developments to the ISMS system (discussed in chapter 2) have been implemented. These 6 month to 1 year-long chronic experiments are critical in evaluating the stability and functionality of ISMS-evoked responses after SCI. The suitability of ISMS for restoring standing and stepping in people with SCI will be contingent on its ability to consistently generate a functional spectrum of flexion and load-bearing extension movements throughout these chronic experiments.

A high success rate in microwire yield, function and stability needs to be established in an animal model prior to implanting full ISMS systems in human volunteers with SCI. These rates of success should be comparable to those achieved with established implants such as deep brain stimulators (Volkmann, 2004).

Intra-operative evaluations of ISMS should be performed in human patients that are already receiving laminectomies as part of other surgical procedures. These trials will provide information about the practical aspects of implementing this technique in human subjects, such as array design, insertion techniques, and fixation strategies as well as its ability to generate functional movements. Histological evaluations after chronic ISMS experiments indicate that the fine microwires cause minimal damage to the surrounding spinal cord tissue (Prochazka et al., 2001), and suggest that acute testing in human subjects will not result in adverse effects. The histological data obtained from rat experiments (discussed above) will also be considered before attempting acute implants in human subjects.

After these criteria have been met, the next step would be to initiate clinical trials where people with SCI are implanted with ISMS arrays with the goal of restoring standing and stepping. These implants could be used in conjunction with other rehabilitation approaches (i.e., treadmill training and/or application of pharmacological agents) to improve the ultimate functional outcome.

6.3 Concluding Comments

The field of neural prostheses and interfaces is in an exciting stage of development. With the current improvements in engineering and medical sciences we can now interface electronic systems with the spinal cord and the brain. Of particular interest is the advancements made to the development of brain-computer interfaces (BCIs) which enable otherwise incapacitated individuals to control external devices through the use of volitionally controlled signals (Birbaumer et al., 1999; Kennedy et al., 2004; Muller-Putz et al., 2005). Using signal processing algorithms two independent control signals can be extracted from electroencephalogram (EEG) electrodes placed on the surface of the scalp (Wolpaw and McFarland, 1994) to control the movements of a computer cursor in a 2D environment. Monkeys (Taylor et al., 2002) and humans (Hochberg et al., 2006) have been implanted with cortical recording electrodes for control of computer cursors and other electronic devices. The ISMS technique should benefit from the developments in BCI systems, by allowing a user to control a standing and stepping FES system by thought processes (Mushahwar et al., 2006). It was not too long ago that we could only dream about the possibility of "bridging the gap" created by a lesion in the spinal cord. However, the current developments being made to neural recording and processing algorithms, and central stimulation techniques such as ISMS indicate that perhaps this goal is not as far fetched as it may have once seemed.

6.4 Bibliography

Bamford, J. A., C. T. Putman, and V. K. Mushahwar (2005). Intraspinal microstimulation preferentially recruits fatigue-resistant muscle fibres and generates gradual force in rat. *Journal of Physiology (London) 569*(3), 873–884. [cited at p. 36, 91, 154]

Birbaumer, N., N. Ghanayim, T. Hinterberger, I. Iversen, B. Kotchoubey, A. Kubler, J. Perelmouter, E. Taub, and H. Flor (1999). A spelling device for the paralysed. *Nature 398*(6725), 297–298. [cited at p. 159]

Cazalets, J. R., M. Borde, and F. Clarac (1995). Localization and organization of the central pattern generator for hindlimb locomotion in newborn rat. *Journal of Neuroscience. 15*(7 Pt 1), 4943–51. [cited at p. 44, 101, 102, 101, 102, 119, 156]

Dai, X., B. R. Noga, J. R. Douglas, and L. M. Jordan (2005). Localization of spinal neurons activated during locomotion using the c-fos immunohistochemical method. *Journal of Neurophysiology 93*(6), 3442–52. [cited at p. 157]

Gaunt, R. A., A. Prochazka, V. K. Mushahwar, L. Guevremont, and P. H. Ellaway (2006). Intraspinal microstimulation excites multisegmental sensory afferents at lower stimulus levels than local alpha-motoneuron responses. *Journal of Neurophysiology 96*(6), 2995–3005. [cited at p. 37, 91, 156, 157]

Henneman, E., H. P. Clamann, J. D. Gillies, and R. D. Skinner (1974). Rank order of motoneurons within a pool: law of combination. *Journal of Neurophysiology. 37*(6), 1338–49. [cited at p. 156]

Hill, J. (2000). *Footprints in the Snow.* London: Macmillan. [cited at p. 1, 153]

Hochberg, L. R., M. D. Serruya, G. M. Friehs, J. A. Mukand, M. Saleh, A. H. Caplan, A. Branner, D. Chen, R. D. Penn, and J. P. Donoghue (2006). Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature 442*(7099), 164–71. [cited at p. 160]

Kennedy, P., M. Kirby, M. Moore, B. King, and A. Mallory (2004). Computer control using human intracortical local field potentials. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 12*(3), 339–344. [cited at p. 159]

Kjaerulff, O. and O. Kiehn (1996). Distribution of networks generating and coordinating locomotor activity in the neonatal rat spinal cord in vitro: a lesion study. *Journal of Neuroscience 16*(18), 5777–94. [cited at p. 4, 44, 45, 44, 45, 101, 102, 110, 113, 101, 102, 110, 113, 119, 157]

Marcoux, J. and S. Rossignol (2000). Initiating or blocking locomotion in spinal cats by applying noradrenergic drugs to restricted lumbar spinal segments. *Journal of Neuroscience 20*(22), 8577–8585. [cited at p. 102, 156]

Muller-Putz, G. R., R. Scherer, G. Pfurtscheller, and R. Rupp (2005). Eeg-based neuroprosthesis control: A step towards clinical practice. *Neuroscience Letters 382*(1-2), 169–174. [cited at p. 159]

Mushahwar, V. K., D. M. Gillard, M. J. Gauthier, and A. Prochazka (2002). Intraspinal micro stimulation generates locomotor-like and feedback-controlled movements. *IEEE*

Transactions on Neural Systems & Rehabilitation Engineering 10(1), 68–81. [cited at p. 35, 44, 53, 35, 44, 53, 70, 90, 70, 90, 155]

Mushahwar, V. K., L. Guevremont, and R. Saigal (2006). Could cortical signals control intraspinal stimulators? a theoretical evaluation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 14*(2), 198–201. [cited at p. 54, 160]

Mushahwar, V. K. and K. W. Horch (2000). Muscle recruitment through electrical stimulation of the lumbo-sacral spinal cord. *IEEE Transactions on Rehabilitation Engineering. 8*(1), 22–9. [cited at p. 34, 35, 34, 35, 155]

Prochazka, A., V. K. Mushahwar, and D. B. McCreery (2001). Neural prostheses. *Journal of Physiology. 533*(Pt 1), 99–109. [cited at p. 39, 159]

Saigal, R., C. Renzi, and V. Mushahwar (2004). Intraspinal microstimulation generates functional movements after spinal-cord injury. *IEEE Transactions on Neural Systems and Rehabilitation Engineering 12*(4), 430–440. [cited at p. 13, 35, 44, 45, 46, 53, 35, 44, 45, 46, 53, 103, 119, 155]

Snow, S., K. W. Horch, and V. K. Mushahwar (2006). Intraspinal microstimulation using cylindrical multielectrodes. *IEEE Transactions on Biomedical Engineering 53*(2), 311–9. [cited at p. 34, 35, 34, 35, 155]

Taylor, D. M., S. I. H. Tillery, and A. B. Schwartz (2002). Direct cortical control of 3d neuroprosthetic devices. *Science 296*(5574), 1829–1832. [cited at p. 160]

Volkmann, J. (2004). Deep brain stimulation for the treatment of parkinson's disease. *J Clin Neurophysiol 21*(1), 6–17. [cited at p. 159]

Wolpaw, J. R. and D. J. McFarland (1994). Multichannel eeg-based brain-computer communication. *Electroencephalography and Clinical Neurophysiology 90*(6), 444–449. [cited at p. 160]