Chapter 4.2

Stimulation of the Spinal Cord for the Control of Walking

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This chapter surveys the different control methods developed for spinal cord stimulation to restore walking after neural injury or disease. We start by exploring the networks within the spinal cord that control or modulate walking. Next we introduce the different modes of stimulating the spinal cord: intraspinal microstimulation, epidural spinal cord stimulation, and magnetic spinal cord stimulation. Finally, we delve into the control strategies developed for these spinal cord stimulation methods to generate walking. Many of the control methods were inspired by the locomotor central pattern generator. Others took a more traditional control engineering approach by implementing non-linear control methods such fuzzy logic and sliding mode control. The ultimate goal is to achieve effortless and natural walking that is adaptable and personalized to the user. Although this goal is a few years away from being realized, the integration of engineering, neuroscience, and rehabilitation is certainly the right approach.

1. Introduction

Functional electrical stimulation (FES) is a rehabilitative intervention that activates remaining neural tissue to restore a lost function after injuries of the central nervous system. FES may be a promising approach to restoring function, especially in combination with traditional rehabilitation and pharmacological intervention. In this chapter, we discuss FES approaches that target the spinal cord, as well as the control strategies that have been developed in order to restore walking using these modalities.

2. Natural Spinal Control of Walking

Before we discuss the different control methods used to generate walking by stimulating the spinal cord, we first discuss natural control mechanisms for locomotion that exist within the spinal cord. The spinal cord is not simply a passive cable that carries commands from the brain to the muscles. There are inherent cellular networks within the spinal cord that are capable of generating and modulating locomotor movements. In this section, we will look into the concepts of the central pattern generator, movement primitives, and spinal reflexes, in the context of locomotion control.

2.1. *Central pattern generator*

A locomotion central pattern generator (CPG) is defined as a neural network that is capable of producing coordinated and rhythmic alternation of flexor and extensor motoneurons in the absence of descending drive or afferent input [Guertin, 2009, McCrea and Rybak, 2008]. It resides in the spinal cord, and has been localized in vertebrates such as the lamprey [Grillner, 2006], and is thought to exist in humans as well [Dimitrijevic *et al.*, 1998]. Over the past century, various models of the CPG network have been theorized, stemming from experiments performed most frequently in cats. In this section, we will only highlight a few of the more commonly discussed models, and limit the descriptions to basic overall function. The more complex models for the mammalian CPG have yet to be confirmed, nonetheless, they can be very useful in terms of control. As we shall see in a later section, the concepts and models of CPGs are often incorporated into the control paradigms used in spinal cord stimulation to produce walking.

2.1.1. *Half-centre model*

The half-centre model was proposed by T. Graham Brown in the early 1900s. He demonstrated that basic stepping movements could be produced by the spinal cord in the absence of descending motor control and afferent feedback in spinalized, decerebrate cats [Brown, 1911]. The half-centre model is the most basic description of flexion-extension alternation. In this model, neurons directly activate either flexion or extension motoneurons, and through inhibitory interneurons, suppress the motoneurons of the opposite function (Figure 1a) [Brown, 1914].

Suppose we want activation of extensors for the stance phase in the gait cycle. To achieve this, neurons would have to excite the motoneuron pools of extensor muscles, as well as inhibit the flexor muscles. This reciprocal inhibition is accomplished through two mechanisms: first by inhibiting the flexor motoneuron pools directly, and second, by inhibiting the neurons that directly activate flexor motoneuron pools. Switching from extension to flexion was thought to occur through a fatigue mechanism [Brown, 1914], whereby the drive from the extension neurons would slowly decrease, or fatigue. Once below a threshold, the inhibition of the flexors would cease and the flexors would now be active, and inhibit the extensors. The exact mechanism of alternation has been debated [Miller and Scott, 1977; Guertin, 2009], and still remains to be determined.

The description above discusses the alternation between flexion and extension of a single limb. There is also alternation between the two hind-limbs (assuming we are talking only about bipeds or the hind-limbs of quadrupeds). However, for simplicity, we will only mention the actions of a single-limb CPG.

2.1.2. *Unit burst generators*

The idea behind unit burst generators builds upon the half-centre model. It was developed in an effort to explain why some motoneuron pools were active during both flexion and extension phases of the gait cycle [Rossignol, 1996]. Unit burst generators are separate modules made of oscillators (half-centres) that control subsets of motoneurons, and the modules are coupled together to produce more complex patterns [Grillner, 1981]. In this scheme, each joint has its own module, and the modules communicate through excitatory and inhibitory synapses (Figure 1b). A modification to the single-layer unit burst generator model was later made to separate a rhythm generator network from the units to accommodate observations from experiments called deletions [Lafreniere-Roula and McCrea, 2005; Rybak *et al.,* 2006a]. A rhythm generator behaves much like a clock timer function, and is responsible for the alternation between flexion and extension. This model allows for individual control of the joints as needed, in accordance with a desired rhythm.

2.1.3. *Two-layer model*

Various two-layer models have been proposed by numerous research groups [Jordan, 1991; Koshland and Smith, 1989; Kriellaars *et al.,* 1994; Orsal *et al.,* 1990; Stein and Smith, 1997; Rybak *et al.,* 2006a; Rybak *et al.,* 2006b; McCrea and Rybak, 2007; McCrea and Rybak, 2008]. The difference between these models lies in the number of interneurons and their connections between the layers. In each case, the top layer is the rhythm generator network as described above. The second layer is the pattern formation network, which is responsible for the selection of the motoneuron pools. Burke [2001] had proposed a 3-layer CPG where the third layer includes last-order interneurons before synapsing onto the motoneurons. Rybak and McCrea [2008, 2015] proposed a hierarchical two-layer model. The rhythm generator and pattern formation networks receive inputs from peripheral afferents (Ia and Ib sensory fibers), as well as descending drive from the mesencephalic locomotor region in the brainstem and other cortical areas (Figure 1c). These inputs can modify the timing and/or the pattern of walking, such as changing the speed of locomotion or when walking on ice. The pattern formation network makes connections with a motoneuron level, which consists of Ia inhibitory interneurons and Renshaw cells, in addition to flexor and extensor motoneurons. This local neural network also has afferent feedback mechanisms and is involved in reciprocal and non-reciprocal interactions between the antagonist muscles.

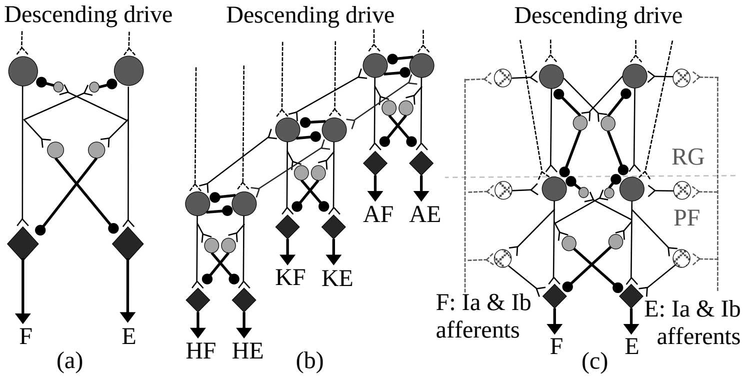

Fig. 1. Models proposed for the central pattern generator. Motoneurons are diamonds; interneurons are gray-scaled circles; neurons receiving sensory input have crisscrosses; excitatory synapses are arrow-like heads; inhibitory synapses are black circles; descending drive is darker hashed lines; sensory input is lighter hashed lines. (a) Half-centre model proposed by Brown [1911, 1914]. The interneurons are responsible for mutual inhibition to produce alternating flexion and extension movements. (b) Unit burst generator proposed by Grillner [1981]. Each joint has its own half-centre. The units for flexion or extension are excitatory with one another, and mutually inhibit the other. (c) Simplified two-layer model proposed by Rybak and McCrea [2008]. The top portion is the rhythm generator (RG) layer responsible for flexion-extension alternation, and the bottom is the pattern formation (PF) network responsible for limb movements to the motoneurons. Both layers receive descending drive and inputs from Ia and Ib sensory afferents.

2.2. *Movement primitives*

Movement primitives can be thought of as the building blocks, or modules, of motor behaviors [Bizzi *et al.*, 1991; Giszter *et al.*, 1993; Giszter, 2015a]. It is thought that more complex movements are generated by combining movement primitives that lie in the intermediate gray matter of the lumbar spinal cord (lamina

VII) [Bizzi *et al.,* 1991; Giszter *et al.,* 1993; Bizzi *et al.,* 2002; Bizzi *et al.,* 2008; Giszter, 2015a]. Early experiments used intraspinal stimulation in decerebrate or spinalized frogs [Bizzi *et al.,* 1991; Giszter *et al.,* 1993]. The motor responses from the stimulation were characterized as force fields that converged to an equilibrium point [Giszter *et al.,* 1993; Bizzi *et al.,* 2008]. Moreover, the force fields were almost identical to the behaviors elicited from mechanical cutaneous stimulation [Tresch *et al.,* 1999]. Chemical stimulation by applying focal NMDA iontophoresis into the spinal cord revealed seven different muscle synergies [Saltiel *et al.,* 2001]. When pairs of sites were simultaneously electrically stimulated, the response was a vectorial summation of the responses seen in the two individual sites [Mussa-Ivaldi *et al.,* 1994; Lemay *et al.,* 2001]. These experiments led to the hypothesis that in the spinal cord lies circuitry that defines certain motor behaviors, or movement primitives, that can be summated to make more complex motor patterns [Bizzi *et al.,* 1991; Mussa-Ivaldi *et al.,* 1994]. Recordings of neurons in the frog spinal cord revealed that cutaneous and intermediate zone neurons are related to premotor drive [Hart and Giszter, 2010].

It has been shown; however, that there are some inconsistencies with the movements generated by stimulating in the intermediate gray matter. For example, if the limb is placed in a particular location in space and stimulation is applied, the movement generated is different from the movement produced if the limb was initially placed in a different starting location [Bizzi *et al.,* 1991]. It has also been reported that increasing the stimulation amplitude (>12µA) changes the response generated [Giszter *et al.,* 1993; Lemay *et al.,* 2001; Stein *et al.,* 2002; Mushahwar *et al.,* 2004a; Aoyagi *et al.,* 2004], possibly due to current spread in the tissue to other nearby networks. In chronically spinalized rats, the majority of responses moved the limb towards the body [Tresch and Bizzi, 1999]. Frequently after cessation of the stimulation, the movements continued, sometimes changing magnitude or direction [Tresch and Bizzi, 1999; Lemay and Grill, 2004; Lemay *et al.,* 2009]. A study by Mushahwar and colleagues [2004a] tested the movement primitives hypothesis in cats under varying conditions of descending drive: anesthetized, decerebrate, and spinalized. They noted that under anesthesia the movements generated were similar to those generated by the nearby motoneuron pools. Additionally, acute decerebration and spinalization drastically changed the evoked responses, particularly the direction of the movements. There is also a lack of vectorial summation of responses in the decerebrate cat [Lemay *et al.,* 2009]. Instead of producing a response that is a combination of the two sites stimulated, the response generated was the same as one or the other of the sties.

For a neural prosthesis, electrically-evoked responses have to be consistent and predictable, not only for reliability but also for safety and acceptability of the device. Stimulation in the intermediate gray matter may be a good tool for investigating spinal mechanisms and circuitry, but may not be suitable for a neural prosthesis. However, combining intermediate spinal cord stimulation with other methods of spinal cord stimulation that are more rhythmic (like a CPG) could be used for generating basic gait patterns [Giszter, 2015b]. The notion of movement primitives and hierarchical activation may also be a useful control technique that could be adopted by a neuroprosthesis [Overduin *et al.*, 2015].

2.3. *Spinal reflexes*

Spinal reflexes can play a role in the modification of locomotion. Their influence is state-dependent, meaning that the reaction produced by the reflex can be different for the different phases of the gait cycle. First, we will describe each spinal reflex, and follow with their relevance to locomotion.

2.3.1. *The stretch reflex*

The stretch reflex, also known as the myotatic reflex, is a monosynaptic spinal reflex [Saladin, 2015; Purves *et al.*, 2012; Burke and Pierrot-Deseilligny, 2012]. Its purpose is to regulate muscle length. When a muscle is stretched, such as when a person is holding an object, the intrafusal muscle fibers are also stretched, activating type Ia muscle spindle afferents. These afferents travel to the spinal cord, where they make direct excitatory synapses onto the α-motoneurons of the same (homonymous) muscle. The Ia afferents also make a polysynaptic connection to the α -motoneurons of the antagonist muscles via reciprocal inhibition. The result is a contraction of the stretched muscle, and relaxation of the antagonist muscle.

2.3.2. *The Golgi tendon reflex*

The Golgi tendon reflex serves the purpose of protecting the muscles from extreme loads that could cause damage or tearing of the muscle fibers [Saladin, 2015; Purves *et al.*, 2012; Burke and Pierrot-Deseilligny, 2012]. Its actions are the reverse of the stretch reflex. When a muscle contracts, such as when a load is applied, the tendons in series with the muscle experience tensile force, which is detected by Golgi tendon organs. The Ib afferents from the Golgi tendon organs travel to the spinal cord where they synapse onto Ib inhibitory interneurons, that then synapse onto the homonymous muscles' α-motoneurons, ultimately inhibiting the muscles. The afferents also cause indirect excitation of the antagonist muscles' α-motoneurons. This mechanism is useful when the muscle is generating extremely large forces, such as when a person is lifting an exceptionally heavy object, as it inhibits the muscle before serious damage can be done. It is interesting to note that during instances of smaller levels of loading, the Golgi tendon reflex helps maintain constant muscle force by counteracting small changes in tension.

2.3.3. *Flexor-withdrawal reflex*

The flexor-withdrawal reflex is a polysynaptic reflex that is activated in response to a painful stimulus [Saladin, 2015; Purves *et al.,* 2012; Burke and Pierrot-Deseilligny, 2012]. Imagine what happens when you unexpectedly touch a hot surface. Your first reaction is to quickly pull your arm away from the surface. This reaction is due to the flexor-withdrawal reflex, which causes activation of the flexor muscles, and reciprocal inhibition of the extensor muscles. It is yet another protective reflex, since by traversing directly through spinal pathways, it can cause a fast escape from the painful stimulus. It is shortly after this reflex response that you experience the pain associated with the stimulus, as this requires the stimulus to travel via longer, cortical pathways.

2.3.4. *Flexion-crossed extension reflex*

The flexion-crossed extension reflex is an expansion of the above described flexor-withdrawal stimulus. In reaction to a painful stimulus, such as stepping on a sharp object, the flexor-withdrawal reflex is triggered in that leg. Specifically, the ipsilateral flexor muscles are activated, and the extensor muscles are inhibited [Saladin, 2015; Purves *et al.,* 2012; Burke and Pierrot-Deseilligny, 2012]. This reaction is paired with the opposite activation pattern in the contralateral leg, where the extensor muscles are activated, and the flexor muscles are inhibited. Hence the name flexion-crossed extension reflex. The end result is the limb that has experienced the painful stimulus is retracted from said stimulus, and postural support is maintained by transitioning the body's weight onto the contralateral limb that is extended.

2.3.5. *Reflexes and locomotion*

Sherrington proposed in that spinal reflexes were responsible for producing gait [Sherrington, 1910]. Specifically, he suggested that proprioceptive stimuli are responsible for an alternating reflex composed of flexion and extension, and that alternation is achieved through a refractory period of the responses. He believed that the flexion phase was equivalent to the nociceptive-induced flexor withdrawal response and the contralateral limb's extension phase equivalent to the crossed-extension part of the reflex. However, stronger evidence supporting the existence of inherent spinal circuitry for locomotion led to the pursuit of the CPG [Lundberg, 1960; Jankowska, 1965; Grillner, 1985].

There is evidence for spinal reflexes playing important roles during locomotion, either to facilitate loading and posture during certain states, or to provide a corrective response to perturbations during locomotion. For instance, the stretch reflex has been shown to assist weight-bearing during the stance phase of gait in cats [Akazawa *et al.*, 1982] and humans [Capaday and Stein, 1986]. Ib afferents from the Golgi tendon organs have been shown to reverse their role of inhibition to excitation during locomotion in the cat [Pearson and Collins, 1993] and humans [Stephens and Yang, 1996], suggesting that the Ib afferents in extensor muscles largely contribute to weight support and postural responses during stance [Zehr and Stein, 1999]. Moreover, the Golgi tendon organ reflex can regulate and modify the timing and rhythm of the step cycle [Pearson, 1995]. Electrical stimulation of Ib afferents in a decerebrate cat's extensor nerves resulted in a prolonged stance phase during treadmill locomotion [Whelan *et al.,* 1995].

Forssberg [1979] was the first to assess the functional role of cutaneous reflexes during locomotion by combining kinematics and neural responses. He electrically and mechanically stimulated the dorsum of a cat's paw during the swing phase of locomotion, and observed a stumbling corrective response, where the perturbed limb continued past the obstacle in order to maintain stability. Prochazka [1978] and Wand [1980] demonstrated that the origin of the response is cutaneous afferents. This response was also elicited in people by stimulating the superficial peroneal nerve [Zehr *et al.,* 1997; van Wezel *et al.*, 1997]. Zehr and colleagues [1997, 1998] went further to investigate the role of cutaneous reflexes on locomotion by electrically stimulating various nerves in order to activate cutaneous afferents of the foot in humans. They found that during the stance to swing transition, tibial nerve stimulation elicited a withdrawal response, which allowed for the continuance of the intended swing phase. However, during late swing, the same stimulus generated a placing response, ensuring stability during the weight-transfer. During early swing, stimulation of the superficial peroneal nerve generated a stumble corrective response characterized by knee flexion, as if the limb was clearing an obstacle that made contact with the dorsum of the foot. Stimulation of the sural nerve has different effects for the swing and stance phases of gait. During swing, a withdrawal of the foot occurs through knee flexion and ankle dorsiflexion for an avoidance movement, whereas during stance the withdrawal is characterized by hip and knee flexion and ankle dorsiflexion, transferring the body weight to the unperturbed limb.

Reflexes during locomotion seem to make necessary adjustments to ensure stability, and may elicit different reactions for different phases of the gait cycle. From this we can say that reflexive reactions during locomotion are state-dependent. Reflexes are capable of optimizing reactions in a state-dependent manner, a fact that could be useful when designing a controller to restore walking using spinal cord stimulation.

3. Spinal Cord Stimulation

Spinal cord stimulation is a type of FES, and can be achieved through several different modalities, varying in their targets and location with respect to the spinal cord. Specifically, spinal cord stimulation can be achieved by placing electrodes intraspinally or epidurally, or more recently, using magnetic stimulation over the lower back (Figure 2). Each modality functions through different mechanisms, hence the control methods for each differs. We will first discuss intraspinal microstimulation, followed by epidural electrical stimulation, and finally, magnetic spinal cord stimulation.

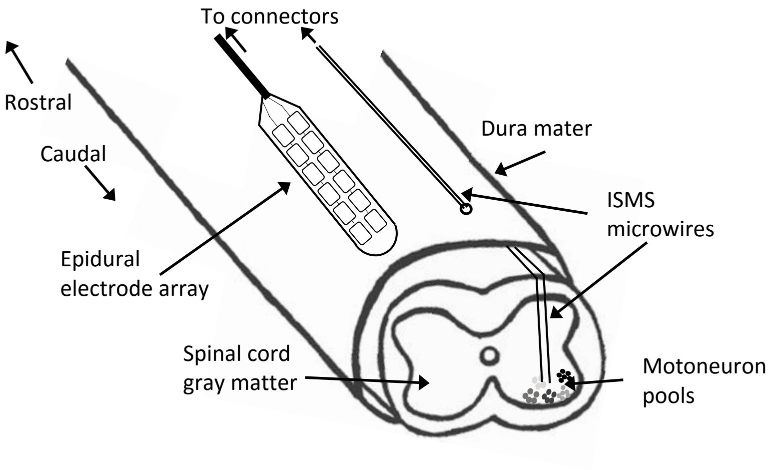

Fig. 2. Cross-section of the lumbosacral enlargement of the spinal cord. An epidural electrode array lies on the dorsal surface of the dura mater. The electrodes are the rectangular pads on the paddle. Intraspinal microwires (50µm) penetrate the spinal cord and target lamina IX of the gray matter, where the motoneuron pools are in close proximity (gray-colored dots). Anatomy and stimulation devices are not to scale.

3.1. *Intraspinal microstimulation*

Intraspinal microstimulation (ISMS) originated as a research tool to study spinal networks. Renshaw [1940] stimulated in the spinal cord to measure the synaptic delay in reflex pathways. Later, mapping experiments were performed to investigate the connections between interneurons mediating reciprocal inhibition [Jankowska and Roberts, 1972]. ISMS in cats showed that motoneurons can be activated directly if the tip of the electrode was adjacent to the initial segment of the motoneuron axon, or the soma itself [Gustafsson and Jankowska, 1976]. As previously described, ISMS was used by Bizzi [1991], Giszter [1993], and colleagues to study the organization of spinal circuitry in the intermediate gray matter of bull frogs. More recently, ISMS in the ventral horn of the spinal cord gray matter has been explored as a possible intervention to restore walking after injury or disease. ISMS has been tested in various animal models, including but not limited to rats, cats, pigs, and monkeys. The majority of work investigating the use of ISMS to produce walking has been tested in cat and rat models.

3.1.1. *Mechanism of intraspinal microstimulation*

ISMS can selectively generate movements in muscles of the hind limbs necessary for walking [Mushahwar and Horch, 2000a] using very small current (less than 150 µA) [Mushahwar *et al.,* 1998; Saigal *et al.,* 2004; Holinski *et al.,* 2011]. Selective activation of muscle groups is possible because the electrodes are implanted into lamina IX of the ventral horn of the lumbosacral enlargement in the spinal cord (Figure 2). Motoneuron pools for the lower limb muscles are in lamina IX. Despite the close proximity to the motoneuron pools, ISMS likely activates them indirectly through networks of afferent projections, propriospinal, and other interneuronal pathways [Mushahwar *et al.,* 2003; Bamford *et al.,* 2005; Gaunt *et al.,* 2006; Mushahwar *et al.,* 2007]. Through these networks, ISMS can selectively produce movements in individual muscles or multi-joint synergies with a single electrode [Mushahwar *et al.,* 1998; Mushahwar *et al.,* 2000b; Saigal *et al.,* 2004; Holinski *et al.,* 2011].

3.1.2. *Advantages of intraspinal microstimulation*

By producing large forces, FES to date has provided the most promising restoration of movements after neural injury or disease. FES can also improve bone and muscle health [Belanger *et al.,* 2000], reduce spasticity [Braun *et al.,* 1985; Stefanovska *et al.,* 1988; Stefanovska *et al.,* 1989; Mirbagheri *et al.,* 2002, Elbasiouny *et al.,* 2010], increase circulatory function, and restore functions including respiration [Talonen *et al.,* 1983], bladder evacuation [Brindley, 1977; Brindley *et al.,* 1982; Tanagho *et al.,* 1989; McCreery *et al.,* 2004], standing [Bajd *et al.,* 1981; Triolo *et al.,* 2012], and even walking [Vodovnik *et al.,* 1981; Marsolais and Kobetic, 1983; Waters *et al.,* 1985; Strojnik *et al.,* 1987; Kobetic *et al.,* 1999; Kuzelicki *et al.,* 2002; Guiraud *et al.,* 2006; Hardin 2 *et al.,* 007; Dutta *et al.,* 2007].

There are three main advantages of ISMS over peripheral FES systems: The ISMS implant is distant from moving muscles; the ISMS implant is small, and contained within a localized region; and ISMS preferentially recruits fatigue-resistant muscle fibers. Details of these advantages are as follows.

The ISMS implant is distant from moving muscles [Mushahwar and Horch, 1993]. Peripheral FES systems involve activating peripheral nerve axons by stimulating through surface or implanted electrodes. The electrodes can target nerves at the nerve trunk, motor point, or at the muscle belly. An example of a surface peripheral FES system is the Parastep (Sigmedics, Inc., Northfield, IL, USA) [Chaplin, 1996], which is the only FDA approved walking FES system, and is primarily targeted to individuals with a complete spinal cord injury (SCI). The Parastep activates knee and hip extensors for the stance phase, and peroneal nerves to induce the flexor withdrawal reflex for the swing phase. Peripheral FES systems that use implanted electrodes were developed for use in people with both complete [Kobetic *et al.,*1999; Guiraud *et al.,* 2006] and incomplete [Hardin *et al.,* 2007; Dutta *et al.,* 2007] SCIs. Each system uses between 8 and 16 channels, distributed throughout the legs and trunk muscles for stability. Results demonstrated standing times between 3-40 minutes [Davis *et al.,* 2001] and walking up to 100 m [Guiraud *et al.,* 2006] and 300 m [Hardin *et al.,* 2007] for complete and incomplete SCI, respectively. Dutta and colleagues [2007] added surface electromyographic (EMG) recordings as feedback signals to trigger the stimulation to restore walking. However, a study done by the Triolo group [2012] involving 15 subjects found that their system was used primarily for exercise.

Surface peripheral FES systems require much effort donning and doffing the electrodes, while implanted systems are susceptible to lead breakage and dislodgement or shifting from the implant site due to the contractions of the muscles surrounding them [Kilgore *et al.,* 2003]. However, an intraspinal implant, which is contained in the spinal cord, is not susceptible to dislodgement or lead breakage because it is distant from contracting muscles and moving joints [Mushahwar *et al.,* 2000b]. There is the possibility of some shifting of the electrode locations due to extreme trunk movements and the relative motion between the spinal cord and the fixation point on the vertebral body; however, this possibility can be avoided by using strain-relief mechanisms such as coiling of the lead wires

[Toossi *et al.*, 2016]. Thus, the possibility of ISMS electrodes being removed or broken due to physiological movements is substantially less than for peripheral FES systems.

The ISMS implant is small, and contained within a localized region of the spinal cord. The lumbar enlargement in cats is only 3 cm long, and 5 cm in humans. Therefore, the implant itself need only be 3-5 cm long in addition to a small connector that fixes the implant to a spinous process just rostral to the lumbosacral enlargement [Saigal *et al.*, 2004]. The number of implanted electrodes required to produce walking movements can be as few as four [Saigal *et al.*, 2004]; however, it is advantageous to implant more electrodes to achieve redundancy in responses, higher selectivity [Holinski *et al.*, 2011], and to deliver the stimulation in an interleaved manner [Mushahwar and Horch, 1997; Lau *et al.*, 2007; Bamford *et al.*, 2010; Bamford *et al.*, 2011a]. Interleaved stimulation entails stimulating through two electrodes targeting the same function at half of the desired frequency such that the combined frequency will be the desired frequency. For example, suppose there are two electrodes that target the quadriceps muscles to produce knee extension. Instead of stimulating through both electrodes at 50Hz, one could stimulate through each electrode at 25Hz, alternating between the two electrodes for a combined frequency of 50Hz. This has the advantage of recruiting different motor units at a lower frequency, thereby reducing fatigue of the muscles.

The entire ISMS system is implantable. Specifically, implantable wireless stimulators have been developed that can be fixed onto the same spinous process that the electrode lead wires are adhered to [Troyk *et al.*, 2012; Grahn *et al.*, 2015]. They communicate and receive power via radio frequency to an external coil that lies on the surface of the skin over the implant area. Additionally, ISMS control strategies have been successfully implemented on an implantable microchip [Mazurek *et al.*, 2010] that was used *in vivo* to produce walking [Mazurek *et al.*, 2016].

ISMS preferentially recruits fatigue-resistant muscle fibers. ISMS has been shown to activate motor units in a near-normal recruitment order [Bamford *et al.*, 2005] to produce graded responses [Saigal *et al.*, 2004], largely due being located within the central nervous system and through trans-synaptic activation of motor units [Gaunt *et al.*, 2006, Mushahwar *et al.*, 2003]. Particularly at higher stimulation amplitudes, ISMS activates fatigue-resistant motor units [Bamford *et al.*, 2005], adhering to Henneman’s size principle [Henneman *et al.*, 1965]. Because ISMS recruits motor units in a near-natural physiological order, it is capable of gradually generating force in the muscles as stimulation amplitude is increased. Force recruitment curves demonstrated that peripheral FES at the femoral nerve had a slope that was 4.9 times steeper than that obtained from ISMS targeting the quadriceps motoneuron pool [Bamford *et al.,* 2005].

Despite the tremendous outcomes of peripheral FES systems, people who use them experience rapid fatigue of their muscles and plateaus in strength [Kobetic *et al.,* 1999; Maffiuletti, 2010; Gregory and Bickel, 2005]; thus limiting the use of these systems to exercise tools [Triolo *et al.*, 2012]. The fatigue in the stimulated muscles is due to an unnatural recruitment order of motor units [Trimble and Enoka, 1991; Maffiuletti, 2010; Doucet *et al.,* 2012; Gregory *et al.,* 2012;] that has been characterized as disorderly and synchronous with limited spatial-activation and favoring of fast fatigable motor units [Bickel *et al.*, 2011; Maffiuletti, 2010; Gregory and Bickel, 2005]. The functional consequences of fatigue can be seen by comparing standing times and distances walked using FES versus ISMS. For example, an 8-channel implanted peripheral FES system to produce standing in spinal cord injured subjects [Davis *et al.,* 2001] achieved a range of 3-40 minutes of standing. In a cat model, ISMS produced an average of 20 minutes and up to 40 minutes of standing [Lau *et al.,* 2007]. Note that the people had an assistive device available to unload some weight onto their upper body. Walking after complete and incomplete SCI using an FES system in people has accomplished up to 100 m [Guiraud *et al.,* 2006] and 300 m [Hardin *et al.,* 2007], respectively. Conversely, ISMS produced nearly a kilometer of walking in a cat model [Holinski *et al.,* 2016]. For a person, this could mean walking to the grocery store and back. However, ISMS is limited by only having been tested in an animal model, yet the potential extrapolation from the accomplishments in the animal model to humans could mean an increase in functional capabilities for longer distances.

3.1.3. *Stability of an intraspinal implant*

With any implanted neuroprosthesis, it is imperative to consider the tissue’s response to the implant, as well as to the delivery of electrical stimulation. The body has a natural tendency to reject foreign bodies, such as electrodes, largely due to mechanical mis-match between the tissue and the electrode [Bamford *et al.,* 2016]. The central nervous system reacts to a foreign body through an inflammatory response [Grill *et al.,* 2009]. Acutely, capillaries and extracellular matrix are damaged from the mechanical insertion of the electrode [Polikov *et al.,* 2005; Grill *et al.,* 2009], and microglia are activated and surround the electrode [McConnell *et al.,* 2007; Grill *et al.,* 2009]. Chronically, astrocytes encapsulate the electrode [Szarowski *et al.,* 2003; Grill *et al.,* 2009], ultimately increasing the impedance of the electrode-tissue interface [Turner *et al.,* 1999; Grill *et al.,* 2009]. There is also some migration of neurons away from the electrode implantation site

[Biran *et al.*, 2005, 2007]. This remains a challenge for any implanted device, and investigations are underway by many groups to reduce or inhibit the tissue's inflammatory response [for a review see Grill *et al.*, 2009].

However, up to 70 months after implanting deep brain stimulation electrodes, only mild gliosis along the track was observed [Haberler *et al.*, 2000], demonstrating that ongoing electrical stimulation in the nervous tissue did not induce an ongoing inflammatory response. Rats with a complete SCI received ISMS for 4 hours per day for 30 days developed a glial scar in the electrode tracks, and no decrease in neuron density near the electrode [Bamford *et al.*, 2010]. Furthermore, cats that had an ISMS implant for 6 months and stimulation 2-3 times per week had no lasting inflammation around the tracks, and no damage to nearby motoneurons [Prochazka *et al.*, 2001]. The small inflammatory response seen after an ISMS implant could be due to the small diameter of the electrodes, the current injected is within safe limits [McCreery *et al.*, 1990; McCreery *et al.*, 2004], and the electrodes are free-floating, as compared to tethered electrodes which can cause an increased tissue response [Biran *et al.*, 2007; Bamford and Mushahwar, 2011b; Bamford *et al.*, 2016].

Implant stability can also be indicated by the functional consistency of responses with a chronic implant, and after a SCI. Functional consistency refers to the movements produced by stimulating through individual electrodes, consistent force recruitment, and stabilization of the stimulation threshold. The movements produced by ISMS have been shown to be relatively consistent throughout a 6-month implantation period, where at least 67% (average of 80%) of the electrodes maintained the same responses [Mushahwar *et al.*, 2000b] in intact awake cats. Thirty days following the implant, ISMS was still able to produce forces in a graded manner [Bamford *et al.*, 2010]. Shortly after implantation of the electrodes, the stimulation threshold has been shown to either increase (in cats) [Mushahwar *et al.*, 2000b] or decrease (in rats) [Bamford *et al.*, 2010]. Although this seems contradictory, it is hypothesized that these differences are due to the different stimulation protocols performed in each study [Bamford and Mushahwar, 2011b]. Whether the stimulation threshold increased or decreased after the implantation, responses steadied over time [Mushahwar *et al.*, 2000b], and the stimulation amplitudes required to produced functional movements were always within safe limits [McCreery *et al.*, 1990; McCreery *et al.*, 2004]. A cat with a chronic SCI and an ISMS implant maintained stimulation threshold throughout a 6-month period, and following the spinal shock, demonstrated consistent stimulation-evoked movements [Mushahwar *et al.*, 2004b].

Taken together, chronic ISMS implants are safe, and can produce consistent responses throughout the implantation period, even after a SCI [Bamford *et al.*, 2016]. Although this technique is more invasive as it requires a laminectomy over the implant region, spinal surgery not uncommon following a SCI [Fehlings and Perrin, 2006].

3.2. *Epidural spinal cord stimulation*

Epidural spinal cord stimulation (SCS) entails delivering electrical pulses to the dorsal surface of the spinal cord through electrodes that are implanted exterior to the dura mater (Figure 2). It was originally developed for the treatment of chronic pain [Shealy *et al.*, 1967], and is now a widely used clinical neuromodulation tool to treat pain [Raslan *et al.*, 2007; Tator *et al.*, 2012]. It has also been explored as a possible treatment for spasticity [Richardson and McLone, 1978; Barolat, 1988; Barolat *et al.*, 1988; Pinter *et al.*, 2000; Dekopov *et al.*, 2015], with variable results [Barolat *et al.*, 1988].

3.2.1. *Investigations in animal models and humans*

A study by Iwahara and colleagues [1992] demonstrated that epidural SCS in the decerebrate cat could elicit locomotion over a moving treadmill. Specifically, stimulation over the cervical enlargement elicited stepping in all four limbs, and stimulation of the lumbosacral enlargement elicited stepping in the hindlimbs only. Locomotor activity over a moving treadmill in the chronically spinalized cat was demonstrated using epidural SCS between the L4 and L5 spinal segments [Gerasimenko *et al.*, 2002; Gerasimenko *et al.*, 2003]. In spinalized rats, rhythmic activity could be elicited, but typically only in a single limb for a short duration of time (<10 s), and required at least 5% of body weight support [Ichiyama *et al.*, 2005]. After an acute SCI only weak rhythmic movements that were not weight-bearing were generated in cats [Musienko *et al.*, 2007]. Similar results were seen in the acute spinalized rat [Lavrov *et al.*, 2006], where stepping could only be achieved 3 weeks after the injury, and improved up to 6 weeks post-injury.

Dimitrijevic and colleagues [1998] demonstrated that epidural SCS over the lumbar enlargement could generate rhythmic flexion and extension muscle activity in individuals with a chronic complete SCI in the prone position. Similar results were repeated using epidural SCS in other subjects with a chronic incomplete SCI during partial body-weight bearing therapy [Herman *et al.*, 2002; Huang *et al.*, 2006], as well as in subjects with a chronic complete SCI in the prone position [Gerasimenko *et al.*, 2002] and during manually-assisted treadmill stepping [Minassian *et al.*, 2005; Minassian *et al.*, 2007].

Recently, studies in human subjects with a motor complete SCI have shown remarkable results where, after training with epidural SCS, some voluntary function returns. A subject with an injury classified as AISA-B (motor complete, sensory incomplete) underwent 7 months of stand training in combination with epidural SCS [Harkema *et al.*, 2011]. At the end of the 7-month period, the subject was able to stand with minimal assistance for at least 4 minutes, and had recovered the ability to perform some toe extension, and ankle and hip flexion. This led to follow-up studies with additional participants (1 ASIA B, 2 ASIA A) [Angeli *et al.*,2014; Rejc *et al.*, 2015]. All participants underwent at least 80 locomotor training sessions before receiving an implant, then underwent standing followed by step training with epidural SCS after receiving the implant [Angeli *et al.*, 2014]. By the end of training, 3 out of 4 subjects were able to oscillate their leg between flexion and extension, and modulate the force produced during leg movement (one individual could not perform these tasks due to severe clonus). All subjects achieved full weight-bearing with minimal assistance [Rejc *et al.*, 2015]. Interestingly, the ASIA A subjects required less assistance for standing than the ASIA B participants (holding onto horizontal bars for balance versus elastic bands attached to a frame for assistance with hip extension). Stimulation parameters required for standing ranged from 25-60 Hz at 1-9 V, depending on the participant. Each participant's stimulation settings were non-transferrable to other participants.

3.2.2. *Epidural spinal cord stimulation combined with pharmacological activation*

Recent studies in completely spinalized rats have demonstrated that training combined with epidural SCS and pharmacological agents such as amine agonists can restore weight-bearing stepping over a treadmill in the presence of stimulation [Courtine *et al.*, 2009; Musienko *et al.*, 2012]. Rats with staggered hemisection SCIs that were trained using a transition from treadmill stepping to intentional over-ground stepping in addition to the electrical and chemical stimulation regained full weight-bearing bipedal locomotion after 5 to 6 weeks [van den Brand *et al.*, 2012]. Furthermore, an additional 2 to 3 weeks of training, the rats were able to avoid obstacles and climb stairs in the presence of stimulation.

3.2.3. *Mechanism of epidural spinal cord stimulation*

The precise mechanisms of epidural SCS have yet to be elucidated; however, many theories have been proposed, primarily based on the concept that the stimulation increases the excitability of the spinal cord. Many studies agree that epidural SCS could be activating intrinsic spinal networks, such as a CPG for locomotion

[Dimitrijevic *et al.,* 1998; Iwahara *et al.,* 1992; Gerasimenko *et al.,* 2002; Gerasimenko *et al.,* 2003; Huang *et al.,* 2006; Minassian *et al.,*2007; Courtine *et al.,* 2009] or for standing [Rejc *et al.,* 2015]. It has also been proposed that the stimulation enhances the response of spinal networks to sensory input associated with weight-bearing [Ichiyama *et al.,* 2005], especially proprioceptive feedback [Minassian *et al.*, 2007; Musienko *et al.*, 2012] to control stepping-like patterns. Lavrov [2006] suggested that after an acute SCI, epidural SCS assisted with the return of spinal reflexes, and only then could stepping be initiated. It is also possible that the increased spinal excitability in combination with training reactivates spared neural networks and enhances plasticity [Herman *et al.*, 2002; Harkema *et al.,* 2011]. In fact, remodeling of corticospinal projections and the formation of intraspinal and supraspinal relays that detoured an injury were identified after a dual hemisection SCI and volitional effort-based training [van den Brand *et al.*, 2012]. These are promising results in the field of spinal cord regeneration and rehabilitation; however, this method of spinal cord stimulation offers little capacity for selectivity and control of spinal circuits needed to achieve weight-bearing over-ground locomotion.

3.3. *Magnetic spinal cord stimulation*

Recently, a non-invasive approach to stimulating the spinal cord to produce walking has emerged. Magnetic stimulation over the lumbar vertebrae, in combination with surface electrical stimulation of the sural nerve, has been shown to produce walking movements in healthy subjects [Sasada *et al.,* 2014]. EMG activity recorded from either the posterior deltoid during arm swing or the first dorsal interosseous during hand grip were used to control the frequency of the magnetic pulses delivered to the spinal cord as well as the frequency and amplitude of the sural nerve stimulation. The participants showed variation in the optimal stimulation site over the vertebrae: T12-L1, L1-L2, or over L2-L3. The reason for individual differences is unknown at this time, and is of interest since these subjects had an intact nervous system. The authors speculate that it may be due to differences in the subjects' posture or gait strategy.

The mechanism of magnetic spinal cord stimulation has yet to be elucidated; however, the authors propose that it likely activates spinal circuits in addition to non-selective activation of afferents in the dorsal roots through eddy currents. Specifically, they believe that large diameter propriospinal and cutaneous afferents are activated and drive the locomotor CPG. Stimulating the sural nerve activates the flexor-crossed extension reflex to enhance the walking movements.

4. Control of Walking using Spinal Cord Stimulation

This section describes the control methods that have been used to produce locomotor movements by stimulating the spinal cord. Also included are the control methods that were developed and tested using other stimulation modalities, such as surface or intramuscular stimulation (IMS), but were either intended to be used or led up to the control strategies for spinal cord stimulation. Some of the control strategies employed do not comply with traditional engineering control methods. Rather, they are physiologically-inspired, attempting to mimic the function of the CPG. We will start with the simplest control strategies, and work our way to more complex approaches.

4.1. *Feed-forward control*

Feed-forward control entails delivering stimulation in a pre-timed pattern with preset amplitudes to produce the desired movements. This is much like the concept of the CPG without sensory feedback, where there is an inherent timing mechanism that drives a pattern of movements of the limbs.

The simplest way to implement feed-forward control is to alternate between flexion and extension movements, which act as the swing and stance phases, respectively [Mushahwar *et al.*, 2002; Saigal *et al.*, 2004; Guevremont *et al.*, 2007]. This alternation between flexion and extension can be thought of as the half-centre model of the CPG described above. This control strategy has been accomplished using IMS in cats [Guevremont *et al.*, 2007] as well as using ISMS with as little as 2 electrodes per side of the spinal cord in intact cats [Mushahwar *et al.*, 2002] and 4 electrodes per side in spinalized cats [Saigal *et al.*, 2004]. The time spent in swing and stance for a single limb is 60% and 40% of the gait cycle, respectively [Saigal *et al.*, 2004; Halbertsma, 1983; Guevremont *et al.*, 2007]. Using this simple control method with very few electrodes, full weight bearing (ground reaction forces equivalent to 1.6 kg [Saigal *et al.*, 2004] and 3.71 kg [Mushahwar *et al.*, 2002]) and ample foot clearance (4.8 cm [Mushahwar *et al.*, 2002]) were achieved using ISMS. However, during IMS, maximum forces produced only reached 10-12% of the animals' body weight [Guevremont *et al.*, 2007], which is insufficient for weight-bearing. Reasons for insufficient force include slipping and fatigue.

Another method of feed-forward control involves dividing the walking cycle for cats into 4 phases: F, E1, E2, and E3 [Engberg and Lundberg, 1969; Goslow *et al.*, 1973], which correspond to lift off to early swing, late swing to touch down, touch down to mid-stance, and mid-stance to push-off, respectively [Yang and

Winter, 1985], and constitute 20%, 20%, 20%, and 40% of the step cycle, respectively (Figure 3).

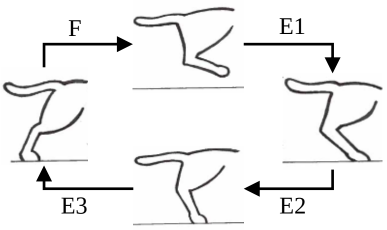

Fig. 3. The phases of the cat gait cycle with the proportion of time spent in each phase. Phases F (20%), E1 (20%), E2 (20%), and E3 (40%) correspond to lift off to early swing, late swing to touch down, touch down to mid-stance, and mid-stance to push-off, respectively.

Breaking down the gait cycle in this way is similar to the two-level CPG model, where there is still an inherent timing mechanism but the pattern of movements is separately produced. Each phase of the gait cycle can be produced separately by stimulating through a combination of ISMS electrodes, depending on their function. For example, E1 includes hip flexion, knee extension, and dorsiflexion, and can be accomplished by simultaneously stimulating through the electrodes that individually perform these movements. Once each phase is put together, they can be concatenated in a cyclical manner to produce a gait cycle.

However, this is only half of the story. Each limb needs to traverse the gait cycle, and the limbs need to alternate with each other while maintaining limb loading during weight transfer. Combining the 4 phases for each limb to achieve successful alternation of the limbs is accomplished by creating 8 states [Holinski *et al.*, 2011; Mazurek *et al.*, 2012; Holinski *et al.*, 2016] (Figure 4). As shown in the figure, the proportion of time spent in each phase for an individual limb is maintained, with more time spent in the stance phases. Using ISMS [Holinski *et al.*, 2011], 5 of 12 walking trials were successful, as defined by traversing 55% of the walkway (2.5 m). The average sum of the ground reaction forces achieved were equivalent to 10.2% of the cat's body weight, attributed to peak forces that were sufficient for body weight support but periods of very little (4.1%) ground reaction force during weight transfer between the limbs. When this control strategy was implemented using IMS [Mazurek *et al.*, 2012], 49% of the steps taken had sufficient body weight support (>12.5% body weight) and a step length less than 20 cm. The authors noted regions of hyperextension during the push-off phase. Since this is a feed-forward controller, it is not possible to make adaptations to the stimulation output to correct this. As we will see later section, adding sensory feedback can correct for hyperextension in real-time.

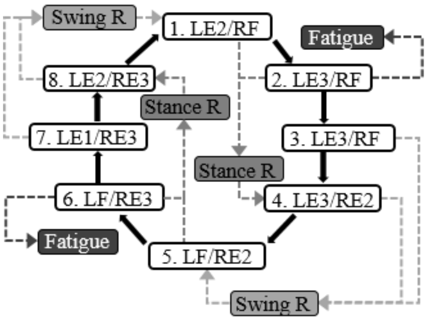

Fig. 4. The states of the gait cycle for the combined feed-forward and feedback controller. Feed-forward states are numbered in the white boxes. The phases shown are F: early swing, E1: late swing, E2: mid-stance, and E3: propulsion. Feedback can trigger safety rules that modify the timing of the state transitions: fatigue compensation rule (dark gray box-Fatigue), swing-to-stance rule (medium gray box-Stance R), and stance-to-swing rule (light gray box-Swing R).

4.2. *Feedback control*

A disadvantage of a feed-forward control system is that it is unable to respond to perturbations or changes within the system. Feedback from sensors allows for such modifications to the output. Different control strategies developed for ISMS have allocated different roles for sensory feedback. In this section, we will outline the pure sensory-based controller. By sensory-based, we mean that the transitions between the states of the step cycle only occur when particular sensory signals cross a threshold. Guevremont and colleagues [2007] implemented two IF-THEN rules to accomplish state transitions in cats using information from force plates and accelerometers:

Stance-to-swing transition:

IF	ipsilateral limb is extended
AND	ipsilateral limb is unloaded
AND	contralateral limb is loaded
THEN	initiate swing in ipsilateral limb

Swing-to-stance transition:

IF	ipsilateral limb is flexed
THEN	initiate stance in ipsilateral limb

Criteria to indicate a successful walking trial included the ability to traverse 75% of the distance of the walkway, which was 3 m long, while maintaining appropriate range of motion and paw traction. Out of 157 trials using the sensory-driven controller, only 18 (11.5%) were successful. Reasons for failure included slips and misses that resulted in the paw losing traction with the walkway, doubleunloaded stance where both limbs were fully extended behind the animal, standing, stepping in place (no forward progression), and poor limb movements. This controller was highly sensitive to parameter selection, especially since sensor thresholds were used to control state transitions. It is interesting to note that the intrinsically-timed controller only had a 15.5% success rate (15/97 successful trials), largely due to slips and misses, in-place stepping, and poor limb movements.

In another study, a neuromorphic silicon chip was developed to mimic the function of the half-center CPG [Vogelstein *et al.,* 2008]. It utilized four silicon neurons: one each for the left extensor, the left flexor, the right extensor, and the right flexor. Sensory inputs conveying information about the cats' hip angle and limb loading were relayed to the CPG network, and were used to initiate transitions between the swing and stance states. Many of the trials in these experiments failed due to the same reasons described above [Guevremont *et al.*, 2007]. The authors also reported that the walking differed from normal walking. Specifically, the swing-stance ratio was much smaller than in normal walking, and because there were only flexion and extension states, the timing of the onset of different muscles was different from normal walking. Nonetheless, the stimulation was still able to propel the animal across the walkway. In the next section, we shall see that supplementing the intrinsically-timed feed-forward controller with sensory feedback results in more robust walking.

4.3. *Combined feed-forward and feedback control*

Mammals are constantly processing sensory information to accommodate their gait. Moreover, the CPG, which by itself is a feed-forward system, integrates sensory information from proprioceptive and cutaneous afferents, as well as descending information from visual centers and the cerebellum, to adjust the timing and pattern of walking. Therefore, it is logical to replicate physiological control mechanisms to control walking using ISMS. Guevremont and colleagues [2007] proposed and tested this concept initially using IMS, and it was further developed and tested in simulation [Mazurek *et al.*, 2010] as well as using both IMS [Mazurek *et al.*, 2012] and ISMS [Holinski *et al.*, 2011; Holinski *et al.*, 2013; Holinski *et al.,* 2016] in cats. Each controller implemented a feed-forward control by generating intrinsically-timed walking. Feedback signals from force plates, gyroscopes, and accelerometers were then used to monitor the walking using various IF-THEN rules that interrupt and modify the feed-forward control. These rules are outlined below, and include rules that both adjust the transition times between the phases of the step cycle, as well as adapt the stimulation output to ensure sufficient weight-bearing.

Ground Reaction Force Rule: [Guevremont *et al.,* 2007]

IF stance leg becomes unloaded
THEN terminate swing in contralateral leg

Rolling Rule: [Guevremont *et al.,* 2007]

IF forward progression stops
THEN position each leg under body, stand, and push until start moving forward again

Safety Rule: [Holinski *et al.,* 2011]

IF insufficient load bearing
THEN hold leg in stance while other leg cycles through gait cycle until regain loading

Swing/Swing-to-Stance Rule: [Mazurek *et al.,* 2010; Holinski *et al.,* 2011; Mazurek *et al.,* 2012; Holinski *et al.,* 2016]

IF hip is flexed forward beyond threshold
THEN transition limb to stance (E1 to E2)

Slip/Stance-to-Swing Rule: [Mazurek *et al.,* 2010; Holinski *et al.,* 2011; Mazurek *et al.,* 2012; Holinski *et al.,* 2016]

IF hip hyperextends
THEN transition limb to swing (E3 to F)

Fatigue Compensation: [Holinski *et al.,* 2011; Mazurek *et al.,* 2012; Holinski *et al.,* 2016]

IF force in propulsion is reduced
THEN increase stimulation amplitude next stance phase

A visual representation of the combined feed-forward and feedback control featuring some of the more widely used rules described above is shown in Figure 4. As the control strategies evolved, the rules became more fine-tuned for use in an ISMS neuroprosthesis. Although they are not often triggered, it is imperative to ensure safety and full weight bearing while maintaining efficiency of the walking.

Earlier we said that the rules used feedback from various external sensors; however, there is an exception. Holinski and colleagues [2013] used feedback recorded from an implant in the dorsal root ganglia (DRG) at the L6 and L7 spinal levels to adapt ISMS-controlled unilateral stepping. A training phase consisted of matching information from external sensors to recorded neural afferent data from the DRG. The testing phase entailed interpreting the spikes from the DRG neurons as predictions for external sensor signals on-line in real-time. They found that the gyroscope could be predicted most accurately from the neural data, achieving a variance accounted for of 73±8%. In terms of successful rule triggering, the prediction of force yielded the highest number of successful activations (96.3%). This study demonstrates that an adaptable control system for ISMS to produce walking can be fully implanted (i.e., no need for external sensors on limbs).

4.4. *Volitional feedback control*

To control magnetic spinal cord stimulation, subjects used voluntary contractions of upper body muscles to adjust the frequency of the cord stimulation and the frequency and amplitude of stimulation to the sural nerve [Sasada *et al.*, 2014]. Healthy subjects were positioned on their side with the legs suspended. The EMG-controlled stimulation produced alternating EMG activity in the hip flexor and extensor muscles and walking-like movements that could be enhanced by adding stimulation of the sural nerve. Interestingly, continuous magnetic stimulation failed to produce walking movements in 8 of the 10 subjects. Three subjects were also held upright in a partial body weight support walking frame. At 47% body weight support, the subjects moved forward using walking-like movements. This study demonstrated that magnetic stimulation of the spinal cord could be controlled volitionally using EMG activity from any residual muscle. However, there are a few technological advances needed before this can be implemented as a take-home system, such as miniaturization of the magnetic coil. This could also be used as a rehabilitation tool after neural injury or disease.

4.5. *Non-linear control*

Fuzzy logic control and sliding mode control have been tested to restore movements using ISMS. First we will give an overview of fuzzy logic and sliding mode control methods, followed by how they were used and adapted to generate limb movements.

4.5.1. *Introduction to fuzzy logic control*

Fuzzy logic is a method of using values ranging between 0 and 1 as logical probabilities, depicting the inexact way of the world, making it closer to human thinking. In the context of control, fuzzy logic can incorporate expert knowledge [Lee, 1990; Kovacic and Bodgan, 2006]. There are four main components to fuzzy logic control: fuzzification, fuzzy rules, implication, and defuzzification [Roshani and Erfanian, 2013b]. Fuzzification entails modifying the inputs by converting them from a numerical value into a linguistic value by association with a membership function so that they can be interpreted in the rule base. The fuzzy rules are a set of IF-THEN rules, and this is where the prior knowledge is stored. Fuzzy implication uses an inference engine to decide which rules are currently relevant and what the input should be. Defuzzification converts the fuzzy decisions to control actions.

4.5.2. *Fuzzy logic control and intraspinal microstimulation*

Fuzzy logic control has been used to control the ankle joint using ISMS in a rat model, with separate fuzzy controllers for dorsiflexion and plantarflexion [Roshani and Erfanian, 2013a,b] aimed to track a target trajectory. Each controller controlled two electrodes, for a total of four electrodes controlling ankle movements measured by a motion tracking system. The average root mean square (RMS) tracking error using fuzzy logic control was 6.3º [Roshani and Erfanian, 2013a], with trajectory convergence in less than 1 s. The authors noted a 200 ms time delay in the neuromusckuloskeletal response to the stimulation in the spinal cord. To improve the transient response of the controller, a lag compensator was incorporated into the fuzzy logic control system [Roshani and Erfanian, 2013b], resulting in an average RMS error of 6.4º.

4.5.3. *Introduction to sliding mode control*

Sliding mode control (SMC) is a non-linear control method known for its accuracy, robustness to uncertainty, perturbation rejection, and simple implementation [Utkin, 2009]. The goal of the control system is to track a desired trajectory or target by driving the system states onto a surface in the state space, known as the sliding surface [Vecchio, 2008]. Once the states reach the sliding surface, SMC forces the states to stay within a boundary along the sliding surface. Two steps are required to design a sliding mode controller: design of a sliding surface and selection of a control law that forces the system to track a desired state [Utkin 1977; Vecchio, 2008]. The sliding surface depends on the tracking error along with some of its derivatives. The function defining the sliding surface is driven to zero, and in doing so should give rise to a stable differential equation. The sliding manifold is often in the form:

$$s = e^{(k)} + \sum_{i=0}^{k-1} c_i e^{(i)} \tag{1}$$

where k denotes the number of derivatives to be included, and should be $k = r$-1, where r is the relative degrees of freedom of the input and output and c_i are positive constants. By steering s to zero, the error and its derivatives disappear in the exponential [Kobravi and Erfanian, 2012].

The next step is to select a control law that forces the state trajectory to the sliding surface and keep it in the vicinity of that surface by switching. For first-order SMC, the control is defined as:

$$u = -\kappa \cdot sgn(s) \tag{2}$$

where κ is the controller gain, and *sgn* is the sign function. The gain of the switching control must be sufficiently large in order to reject any uncertainties or perturbations in the system. However, this results in high-frequency switching across the surface. This phenomenon of oscillating about the surface is known as chattering [Ajoudani and Erfanian, 2007; Vecchio, 2008; Shtessel *et al.*, 2014] (Figure 5). It is undesirable because it causes excitation of the unmodeled high-frequency control components, which can lead to poor system performance or instability. One possible solution to solve the chattering problem is to replace the discontinuous *sgn* function with an approximation such as the continuous *sat* (saturation) or *tanh* (hyperbolic tangent) functions [Vecchio, 2008]. Unfortunately, these approximations can prevent the system from reaching convergence [Ajoudani and Erfanian, 2007, Kobravi and Erfanian, 2009].

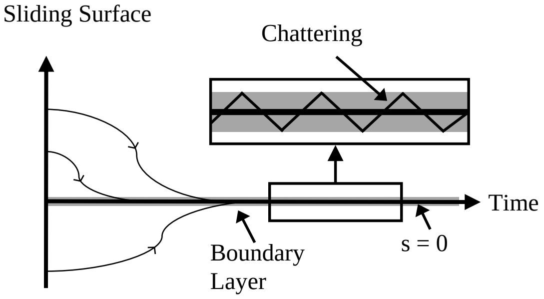

Fig. 5. The sliding surface s converges to zero from multiple initial conditions. Chattering is seen within the boundary layer.

4.5.4. *Sliding mode control and surface electrical stimulation*

Initial control strategies utilizing SMC were tested using surface electrical stimulation over leg muscles at the level of a single joint [Ajoudani and Erfanian, 2007; Kobravi and Erfanian, 2009; Nekoukar and Erfanian, 2010] for standing [Kobravi and Erfanian, 2012] and to produce walking [Nekoukar and Erfanian, 2012]. Only later was it tested using ISMS [Asadi and Erfanian, 2012; Asadi, 2014] and epidural SCS [Khazaei and Erfanian, 2016] stimulation.

SMC was chosen as a suitable control method for controlling electrical stimulation of muscle because stimulated muscle is non-linear and is subject to fatigue and other time-varying properties [Ajoudani and Erfanian, 2007]. A neuroprosthesis needs to be reliable and stable with the changing conditions of the muscle. Control of the knee-joint angle was achieved by stimulating over the quadriceps muscles. In order to decrease chattering caused by the large controller gain, the authors sought to decrease the gain by decreasing the system uncertainty using an accurate model of the system. They proposed three modules to model the knee joint dynamics. The first module uses prior knowledge to represent the passive knee-joint dynamics. The second module represents the active component of the muscle dynamics. Finally, the third module represents the unmodeled dynamics. The uncertainties were modeled using a neural network, whose parameters were adjusted using gradient descent. Furthermore, they utilized a single-neuron controller instead of a saturation function to reduce chattering. By combining the outputs from the sliding mode controller and the neural controller, control of the knee joint was successful. This control method was tested in intact subjects and subjects with a complete SCI. Using a goniometer to feed-back the knee joint angle, they reported accurate tracking and reduced chattering in all subjects. Furthermore, the controller compensated for fatigue by adapting the stimulation output as needed.

Other variations of SMC were used to control the ankle joint angle by switching between stimulating the tibialis anterior and the soleus and gastrocnemius muscles [Kobravi and Erfanian, 2009; Nekoukar and Erfanian, 2010]. To reduce chattering, both approaches used adaptive robust control to change the boundary around the sliding surface. The system uncertainties were modeled and tuned online based on Lyapunov stability analysis using measurements from input signals. Fuzzy logic was used to approximate the unknown non-linear functions used in the SMC. Kobravi and Erfanian [2009] took a decentralized approach by using two different controllers for flexion and extension movements in order to reach a joint angle target. This approach was proposed because in order to coordinate several muscles in a task such as walking, the complexity of the control may be reduced by implementing a set of individual controllers. The interactions between the sub-controllers are simply taken as external disturbances to each isolated controller. This approach was tested in intact and paraplegic subjects. Tracking convergence was achieved after approximately 2 s. For a range of motion of 42°, the average RMS errors for over 90 trials for intact and paraplegic subjects were 3.2° and 3.4°, respectively. Nekoukar and Erfanian [2010] did not use a decentralized control scheme, rather they used adaptive terminal SMC to adjust the ankle angle, which is known to achieve stability with a faster convergence rate. This system was tested in two paraplegic subjects. Tracking convergence was achieved after about 2s, with a RMS of 1.3°. Chattering was eliminated using this control strategy. Both strategies were able to track the ankle joint angle target in the presence of fatigue as well as external disturbances applied to the foot, maintaining an RMS error of less than 8° in both cases.

The decentralized adaptive controller developed by Kobravi and Erfanian [2009] was used to control ankle joint movement in paraplegic subjects during quiet standing using surface stimulation [Kobravi and Erfanian, 2012]. The goal of this work was to replicate the ankle strategy used to maintain posture in intact individuals, thereby eliminating the need for the paraplegic subjects to hold on to an assistive device and freeing their arms for other tasks. The subjects were placed in a body brace to lock the joints above the ankles, and were suspended in a harness system for safety. The body's inclination angle was measured by placing a motion tracking sensor over the 3rd lumbar vertebrae, and was used as a feedback signal for the controller. Centre of pressure was also measured and used as for stability analysis. During independent quiet standing, the controller rapidly switched stimulation between ankle flexors and extensors to correct for body sway, maintaining a safe centre of pressure. An average RMS error of less than 2° for inclination angle and 10° for centre of pressure were maintained even with external disturbances induced by subjects lifting weights forward and backward during standing. Fatigue was, again, compensated for. After a few trials, subjects were able to stand for about 10 minutes before falling.

As seen with approaches such as the Parastep [Chaplin, 1996] and the implanted IMS walking systems [Triolo *et al.*, 2012] discussed above, users rely on their upper body for support and fatigue quickly. This motivated the development of new closed-loop control strategies for controlling the legs during walker-assisted FES [Nekoukar and Erfanian, 2012], whereby the walking pattern follows a target trajectory to minimize the effort exerted on the upper body. A decentralized approach was used with two modules. Module 1 adjusted hip flexion and extension and knee extension using three controllers: one to control the joint angle trajectories, one to minimize the effort exerted by the upper body using a measure of handle reaction force, and the third to regulate the stimulation amplitude using fuzzy logic. The first two controllers used adaptive terminal SMC as described above for fast convergence and reduced chattering. Module 2 produced dorsiflexion or plantarflexion using two fuzzy logic controllers to modulate stimulation pulse width and amplitude. A walking reference for trunk, hip, knee, and ankle trajectories were obtained from a healthy male subject that walked slowly with the walker. The controllers were tested in complete SCI subjects. Surface electrodes were placed over the quadriceps, gluteus maximus/minimus, soleus and gastrocnemius, and iliacus muscles as well as over the common peroneal nerve. Feedback measurements included trunk, hip, knee, and ankle joint angles, ground reaction force, and handle reaction force for a single hand. Trajectory matching was aimed to be within one standard deviation of the reference joint angles. For all three subjects, the average RMS tracking errors for the hip, knee, and ankle joints were less than 7°. During swing there was ample foot clearance. The subjects only exerted an average of 12.05% of their body weight on the walker for stability, and could walk at approximately 0.55 m/s (the target speed).

4.5.5. *Sliding mode control and spinal cord stimulation*

Control of knee and ankle joints using ISMS in rats was realized using a combination of approaches discussed above [Asadi and Erfanian, 2012]. Specifically, the system uncertainties of the system were obtained online using an adaptive law based on Lyapunov stability theory with fuzzy logic approximation of the non-linear plant functions. Chattering was further reduced using a neural sliding mode controller. The ISMS implant targeted knee and ankle flexors and extensors. Joint targeting was accomplished individually and coincidentally. Multi-joint control was accomplished using decentralized controllers; however, the authors noted that there was an interaction between the responses at the joints when more than one motoneuron pool was targeted as compared to individual responses. Nonetheless, the trajectory tracking for each joint during multi-site stimulation was robust, attaining average RMS errors of 1.8° and 2.8° for knee and ankle joints, respectively. Furthermore, longer trials of 7 min demonstrated robustness of the tracking to fatigue by adjusting the stimulation amplitudes accordingly (average RMS error = 1.9°). This controller was further tested using ISMS in the intermediate spinal cord of the rat to target movement primitives [Asadi, 2014]. Although RMS error was not reported in this study, the tracking was not as accurate as with ISMS in the ventral horn of the gray matter.

SMC-based controllers have been shown to be extremely accurate in tracking joint trajectories using surface stimulation, ISMS, and epidural SCS. They are also robust to external disturbances as well as to muscle fatigue. However, this control method requires that a target trajectory to be known and available. This could be difficult to implement clinically since each individual would need a reference from a person that is of similar height and weight. Additionally, the users would need to have goniometers and possibly other sensors placed on their legs to provide feedback to the controllers.

4.6. *Intraspinal microstimulation in the cervical enlargement*

Although this chapter discusses the use of ISMS to control walking, this technique is now being investigated in the cervical enlargement to restore reaching and grasping after a SCI in both rat [Kasten *et al.,* 2013; Sunshine *et al.,* 2013] and non-human primate models [Moritz *et al.,* 2007; Zimmerman *et al.,* 2011; Zimmerman and Jackson, 2014]. Zimmerman and Jackson [2014] induced hand paralysis by injecting a temporary paralytic muscimol in the primary motor cortex, and used signals from an implant located in the ventral pre-motor area to control the rate of stimulation delivered to the spinal cord to achieve a grasping task. In some cases, the muscimol did not fully paralyze the hand muscles, mimicking an incomplete SCI. In those cases, residual voluntary muscle activity was used to control the stimulation. Kasten and colleagues [2013] demonstrated that cervical ISMS improved motor function, with benefits lasting beyond the stimulation trial. Cervical ISMS after incomplete SCI may promote long-term recovery of function, possibly attributed to axonal growth and elongation regulated by neural activity, synaptogenesis, and dendrite stability [Mondello *et al.,* 2014].

5. Conclusion

Various stimulation modalities targeting the spinal cord have been utilized. The modalities differ in both stimulation technique (magnetic or electrical) and target (surface, epidural, intraspinal). Many control methods have been proposed, ranging from simple open loop systems, feedback control, central pattern generator-inspired control, to non-linear control methods such as fuzzy logic and sliding mode control. All of these studies have the same goal: to target the spinal cord’s remaining circuitry in order to restore walking after neural injury or disease. The control methods being developed for these stimulation modalities are all moving towards adaptability, personalization, and miniaturization, with great strides.

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