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Intelligent Control of a Spinal Prosthesis to Restore Walking After Neural Injury: Recent Work and Future Possibilities

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This review focuses on the development of intelligent, intuitive control strategies for restoring walking using an innovative spinal neural prosthesis called intraspinal microstimulation (ISMS). These control strategies are inspired by the control of walking by the nervous system and are aimed at mimicking the natural functionality of locomotor-related sensorimotor systems. The work to date demonstrates how biologically inspired control strategies, some including machine learning methods, can be used to augment remaining function in models of complete and partial paralysis developed in anesthetized cats. This review highlights the advantages of learning predictions to produce automatically adaptive control of over-ground walking. This review also speculates on the possible future applications of similar machine learning algorithms for challenging walking tasks including navigating obstacles and traversing difficult terrain. Finally, this review explores the potential for plasticity and motor recovery with long-term use of such intelligent control systems and neural interfaces.

Keywords: Machine learning; predictive and adaptive control; neural prosthesis; reinforcement learning; walking.

1. Introduction

Neural prostheses are prosthetic devices that interface with the nervous system for recording or stimulation purposes. The goal of a neural prosthesis is to restore or augment a function that is impaired after neural injury or disease. Examples of neural prostheses include deep brain stimulators for reducing tremors in Parkinson's disease [1], cochlear implants for restoring hearing in the profoundly deaf [2, 3], retinal prostheses for restoring vision to the blind [4, 5], spinal cord stimulators for restoring walking after spinal cord injury (SCI) [6–8], and other methods of functional electrical stimulation (FES) such as those that target the peripheral and vagus nerves [9–11].

With respect to rehabilitation and motor recovery, neural prostheses have demonstrated success with restoring functions such as grasping [12, 13], trunk control [14], standing [15–17], and even walking [18–23]. Regaining the ability to walk is of high importance for improving quality of life for people with paraplegia, with a majority of paraplegic individuals ranking the recovery

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of walking as a first or second priority [24]. However, many neural interface devices to restore walking operate with an open-loop control strategy [25–28]. This means that the stimulation delivered to restore the impaired function is controlled using pre-set patterns and does not adapt to the user's needs. Feedback from muscle activity or push-buttons are sometimes used to trigger the timing of the stimulation; however, an adaptive component is not present [20,29–31].

To improve the interaction of a neural interface user with the device to perform functional tasks of daily living, more intuitive control strategies are needed. Better device interaction that is more seamless to control could also lead to better device use and acceptance through increased independence of the user. To achieve better user–device interaction, there needs to be a method for representing the user's intentions and have these intentions preemptively produce a control decision. Machine learning methods have the ability to make predictions about sensor signals and numerical outputs that may be useful to control walking. Machine learning may hold the key to improved human-device interaction and may facilitate more intuitive, predictive, and adaptive use of neural prostheses, and further improve the lives of people with neural injury or disease. This review will highlight neural prostheses developed for restoring walking and describe various machine learning methods that have been used in people and in animal models to control walking. This review will also touch on what is needed to translate these methods to use in people with an SCI and how restoring walking using intelligent control strategies and a spinal prosthesis could improve residual function.

2. Spinal Cord Implants for Restoring Walking After Neural Injury

The spinal cord houses locomotor networks and motoneurons that can generate and modulate movements such as walking [32,33]. These networks and motoneurons below the level of an SCI remain intact after injury [34] and can be targeted by neural interfaces to restore function. Two primary implantable approaches have been developed to improve lost function after SCI: epidural spinal cord stimulation (eSCS) and intraspinal microstimulation (ISMS).

eSCS consists of electrodes implanted extradurally over the dorsal surface of the spinal cord [35–37]. eSCS is hypothesized to increase the excitability of the spinal cord through activation of primary afferents [38]. eSCS was originally developed for the treatment of chronic pain [39] and is now a widely used neuromodulation technique [40,41]. Combined eSCS and intense rehabilitation training in people with chronic SCI has demonstrated the recovery of voluntary functions such as walking. Early studies combined eSCS with body-weight supported treadmill training (BWSTT) in people with incomplete SCI, resulting in enhanced muscle activity and walking ability [42–44]. Participants in one study underwent 80 locomotor sessions without eSCS, followed by combined eSCS and stand and step training. At the end of training, three of the four participants could oscillate their legs between flexion and extension and stand with minimal assistance [6, 45]. Recently, three independent studies reported assistive over-ground walking in participants with motor complete [18, 19] and incomplete [23] SCIs after several months of extensive rehabilitation combined with eSCS. These results suggest that eSCS assists spinal cord plasticity by increasing the excitability of the spinal cord, making rehabilitation more effective.

An alternative spinal cord implant is ISMS, which uses fine microwires (30–50 μm in diameter) to target the ventral horn of the lumbosacral enlargement [46, 47] (Fig. 1). The electrode tips primarily target lamina IX, where the motoneuronal pools innervating the muscles of the lower limbs reside [47–49]. Although the electrode tips are placed very close to the motoneuron pools, ISMS, like other methods of microstimulation, activates both nearby axons and motoneurons [50]. However, due to afferent, propriospinal, and other interneuron activation, the motoneurons are largely recruited indirectly [51–54]. This is supported by the fatigue-resistance and near-normal recruitment properties of ISMS [51], where ISMS produces large, yet graded, increases in force [46, 55], even after a complete SCI [56]. Fatigue resistance is essential for a neural prosthesis because it allows for reasonably long distances of weight-bearing walking that enables ambulation in the community.

Targeting the ventral horn, single-joint movements as well as multi-joint synergies can be evoked in the hind-limbs using very low levels of stimulation current

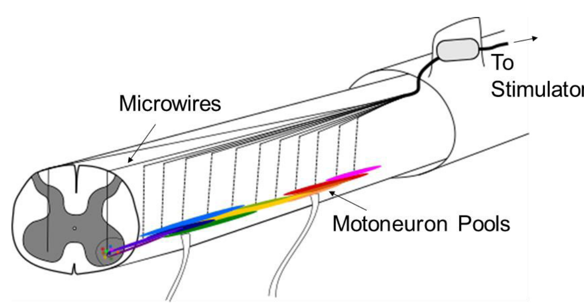

Fig. 1. Depiction of an intraspinal microstimulation (ISMS) implant. Microwires target the lamina IX (outlined) of the ventral horn of the lumbosacral enlargement containing motoneuron pools. The motoneuron pools for various muscles are represented by the colored strips along the enlargement. Stimulation through each wire elicits graded and selective movements in the hind-limbs.

($\leq 100\,\mu$A) through a single electrode [47, 49, 56, 57]. By implanting several electrodes along the lumbosacral enlargement, various movements can be generated and coordinated to produce a walking cycle. The implant region is only 3 cm long in cats [47, 58] and 5 cm long in humans [59, 60]. The number of electrodes required to produce the walking cycle can be as few as four [56]; however, more electrodes provide the advantage of redundancy in evoked responses and higher selectivity [8, 56]. ISMS in the lumbosacral enlargement has been used to produce weight-bearing standing [61] and over-ground walking in anesthetized cats [8, 62], as well as weight-bearing stepping in cats with a complete SCI [56]. To test the fatigue resistance of ISMS, a recent study showed that functional over-ground walking can be achieved in anesthetized cats for ~ 470 m, on average [8]. ISMS for walking has only been tested in animals, but ISMS has been used in people for restoring bladder function [63, 64]. Development of ISMS for human use for walking is currently underway [65]. ISMS has also been implanted into the cervical enlargement to produce reaching and grasping movements in rats and monkeys [66–70], as well as to activate diaphragm and intercostal muscles in rats for breathing [71, 72].

ISMS produces strong and selective movements immediately and may reduce the rehabilitative burden on users. Due to the selective nature of ISMS, the activation of the electrodes must be coordinated using a control strategy. However, as with all neural prostheses, the control method needs to be intuitive and intelligent to ensure seamless interaction between the user and the device. These control strategies need to utilize and augment remaining function and deliver stimulation to compensate for the deficits caused by the injury or disease. Since eSCS has less specific activation of muscles due to current spread in the cerebrospinal fluid [73], development of control strategies for this neural interface has not been explored beyond flexor and extensor activation [23, 38]. The current review focuses on control strategies developed for ISMS and FES to restore walking, with emphasis on those using predictive and machine learning methods. A comprehensive review of more traditional control strategies for FES and ISMS can be found in Ref. [74].

3. Feline Model of SCI

Cats have a long history as an animal model for locomotion studies [75, 76]. Inducing complete and incomplete SCIs in cats is very common in the literature and is frequently done to study spinal circuitry for locomotion such as the central pattern generator (CPG) [77–81]. When developing control strategies to restore walking after an SCI, it is important to consider the physiological changes to the spinal cord and muscles and balance these considerations with the question at hand. For example, after a chronic SCI, there is muscle atrophy, muscle fibers type changes from fatigue resistant to fatigable, and bone density loss [82–85]. Even with changes in muscle fiber types after chronic complete SCI, ISMS was able to demonstrate fatigue-resistant graded increases in force [56]. Interestingly, chronic stimulation using ISMS in completely spinalized rats showed a fast-to-slow twitch transformation in the limb that received stimulation compared to the unstimulated limb [86]. Similar results have been demonstrated in long-term training using FES [87, 88].

An awake cat with a chronic SCI would provide the most realistic environment for determining performance of control strategies for restoring walking. Control strategies for a complete SCI require all movements of the hind-limbs to be produced by the implant. Chronic ISMS implants in awake cats have been performed previously [49]; however, acute implants are preferred for testing novel control strategies in order to ensure the best possible functionality of the implant. Acute implants are not sterile; therefore, the cat must be under anesthesia for the duration of the experiment. Alternatively, a decerebration, which entails the removal of brain regions responsible for cognition and pain, could be performed to allow the removal of anesthesia [89]. Decerebrations after chronic complete SCI have been used as a model to study locomotor networks and the control of stepping using ISMS [53, 56]. A pre-mammillary decerebration could be performed, which allows for the pain-free removal of anesthetics and analgesics without extensor rigidity that occurs with other decerebration models [89, 90]. Decerebration procedures require further surgery in addition to a chronic SCI and implant procedure. To purely assess the performance of a control system in vivo, it is most ethical to first perform proof-of-concept testing in anesthetized cats prior to testing in SCI cats. Testing the development of lower limb control strategies using ISMS in anesthetized cats has also been demonstrated by other groups [91, 92]. Furthermore, early testing of ISMS control of upper limb functions was tested in anesthetized monkeys [69] prior to testing in awake animals with temporary drug-induced paralysis [70].

An approximate model for a complete SCI is an anesthetized cat supported by a sling, since all the movements of the hind-limbs will still be made by the implant. For modeling an incomplete SCI, it becomes more challenging to replicate the voluntary control that would remain. A first approach to developing and testing control strategies in a model of incomplete SCI is replicating the functional deficits that would result from a hemisection SCI, as demonstrated in the work described below. A cat with a hemisection SCI would have voluntary control of one hind-limb (intact limb), with motor

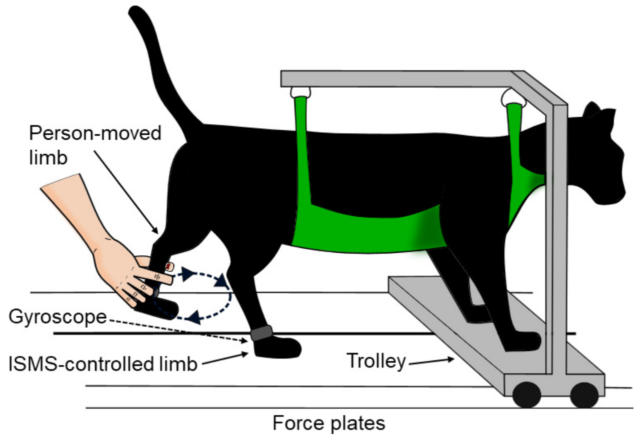

Fig. 2. Experimental setup for a model of hemisection SCI in an anesthetized cat. One hind-limb was transitioned through the walking cycle by a person manually moving the limb (representing the intact limb that would be under voluntary control). The other hind-limb was transitioned through the walking cycle using ISMS (representing the affected or paralyzed limb). A sling suspended from a trolley supported the trunk, forelimbs, and head of the anesthetized cat. The ISMS-controlled limb produced walking movements that pushed the cat and trolley forward during the walking trials.

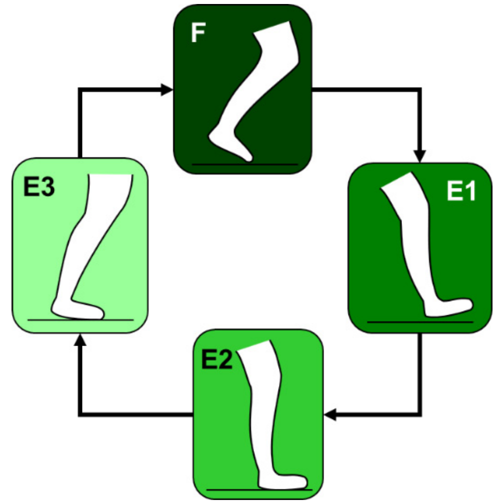

Fig. 3. Walking cycle of one limb divided into four phases of the walking cycle. F = toe-off to early swing; E1 = late swing to heel strike; E2 = heel strike to mid-stance; E3 = mid-stance to toe-off.

deficits in the other hind-limb (affected limb). Under anesthesia, paralysis of the "affected limb" is replicated by the anesthesia; the voluntary or residual function of the "intact limb" can be simulated by moving that limb through the phases of the walking cycle manually by a person (Fig. 2) [93, 94]. Therefore, the intentions of the person moving the limb simulate the intentions of the animal if it were awake. These movements can be recorded using sensors and used to control ISMS to produce movements in the "affected limb". However, prior to translation to humans, chronic testing of the control strategies should be performed in cats with chronic SCIs, both complete and incomplete.

4. Biologically Inspired Control Strategies

4.1. *The walking cycle*

The walking cycle can be divided into four phases consisting of flexion (F) and extension (E): F (toe-off to early swing), E1 (late swing to heel strike), E2 (heel strike to mid-stance), and E3 (mid-stance to toe-off) (Fig. 3) [95–97]. The swing phase is comprised of F and E1 and the stance phase includes E2 and E3. Typically, the stance phase accounts for 60% of the walking cycle. As the walking speed increases, the proportion of time spent in the stance phase decreases [98, 99]. Generally, when one limb is in the stance phase, the other is in the swing phase, with a brief period of double limb support for stability. Natural walking, specifically the transition from stance to swing, can be described by a finite state IF-THEN rule, which uses sensory information from the periphery to initiate the transition [100–102]:

IF in stance AND limb is loaded
THEN transition to swing

Limb loading information is provided by Golgi tendon organs. Unloading of the ankle extensor muscles along with hip extension (indicated by type Ia muscle spindles) is necessary for the transition from stance to swing [103–106]. Body-worn sensors can provide similar information as peripheral sensory organs and can be used as feedback signals for a control strategy. Specifically, limb loading can be measured using force-sensitive resistors or capacitive sensors placed in show insoles; gyroscopes can provide information regarding limb position and velocity; goniometers can inform on joint angle; and accelerometers can be used to indicate body or shank tilting.

4.2. *Central Pattern Generator*

In the absence of sensory input, walking can be produced using a pre-determined sequence of movements generated by a CPG. The locomotor CPG is a neural network in the spinal cord that is capable of producing coordinated alternation of flexors and extensors [107, 108]. A prominent model of the CPG has two hierarchical layers [108]. The top layer is the rhythm generator network and is responsible for the basic timing of alternation between flexion and extension. The second layer comprises the pattern formation network which drives the motoneuronal pools and selects the appropriate networks to produce movement synergies involving the coordinated contractions of multiple muscles.

The locomotor CPG itself is a feedforward (open loop) control system capable of producing coordinated motor outputs in the absence of descending or sensory input [107, 108]. The timing, duration, and magnitude of the flexor/extensor oscillations produced by the CPG are modulated by either descending drive mediated through the brainstem, or in response to sensory information from proprioceptive and cutaneous afferents such as the IF-THEN rule described above (closed loop). The most critical sensory information modifying the rhythm produced by the CPG is limb loading and limb position [33, 109, 110]. Concepts derived from the neural control of walking have served as inspiration for control systems developed for ISMS and other interventions to restore walking.

4.3. *Control strategies inspired by natural walking*

A biologically inspired controller for restoring walking was developed using intramuscular stimulation (IMS) [111, 112] and later tested using ISMS [8, 62, 113] in anesthetized cats. The controller consisted of a feedforward state machine for producing intrinsically timed walking phases (similar to the rhythm generating network of the CPG). The pattern formation network was mimicked by the selection of functions produced by stimulating through each implanted microwire, which were used to construct synergies for each phase of the walking cycle. Feedback from sensors including force plates, gyroscopes, and accelerometers, signaling the amount of loading and position of the limbs in space, was used to modify the feedforward pattern (IF-THEN rules). Using ISMS and the combined CPG, IF-THEN control strategy, weight-bearing, and propulsive over-ground walking were achievable for long distances (~ 470 m on average) [8]. Although most studies employed external sensors for feedback control, one study used feedback from dorsal root ganglia (DRG) recordings to adapt unilateral stepping [62]. The DRG contain the cell bodies of the sensory neurons. Using recordings from the DRG as feedback control signals closely mimic natural feedback mechanisms, allowing for a more autonomous neural prosthesis for restoring walking. CPG-inspired control strategies are not unique to ISMS. CPG-based control strategies have been implemented in FES, exoskeletons, robots, and prostheses and have been reviewed elsewhere [114].

The aforementioned controllers were successful in producing walking in anesthetized cats that represent a model of complete SCI, where there is no representation for residual voluntary function and only the stimulation provided by ISMS is responsible for producing the movements of the hind-limbs. For restoring walking after an incomplete SCI, it is imperative for the neural prosthesis to adapt to and augment the remaining function to facilitate cooperation with the user's intentions. Anticipatory and predictive adaptation of the control strategies can be achieved through machine learning methods, which may reduce the tuning burden of the devices and allow for a personalized neural prosthesis.

5. Machine Learning Strategies to Augment Walking

5.1. *Machine learning methods*

5.1.1. *Supervised learning*

Supervised learning uses pre-labeled data to generate generalizations between paired inputs and outputs [115,116]. The inputs are features that represent or describe the data, and the outputs are often numerical values or classification labels. The training phase uses the labeled inputs and outputs to generalize between them using a function or algorithm. The training phase often uses a cross-validation method, such as 10-fold cross-validation. Once a function has produced a generalization for the training data, new data are presented for testing. The function uses the inputs of the testing data and the generalization formed during training to produce a prediction for the output. The predicted output is compared to the actual output to determine the testing accuracy. Good performance on testing and training data sets indicate that the function sufficiently generalized on the training data to make effective predictions on novel data. Ideally, the generalizations from training are broad enough to perform well with new data without overfitting to the training data. Supervised learning is useful when inputs can be labeled with the desired output for training and predicting. During walking, examples of events or values that can be labeled for learning include step initiation, phase of the walking cycle, and even gait speed, as outlined in the works below.

5.1.2. *Reinforcement learning*

Traditional reinforcement learning is an area of machine learning that focuses on achieving a goal by maximizing future reward [117]. Typically, a learning agent interacts with its environment by taking actions according to a defined policy. The environment supplies the agent with state information about the environment as well as the value of the reward corresponding to the current state. The goal of the learning agent is to maximize the long-term reward. The current value of future rewards is referred to as the value function and is estimated according to a discounting factor, γ, the step size or learning rate, α, and of course, the reward received at a given state. The estimates for future reward are used to update the policy, thus the learning agent uses experience to drive its actions. How the agent estimates future rewards depends on which algorithm is used.

A popular reinforcement learning algorithm is temporal difference (TD) learning, which uses previously obtained estimates of the value function to generate new estimates [117–119]. By estimating the value function using other estimates (bootstrapping), TD learning performs much faster than other reinforcement learning methods [119]. To learn estimates of the value function for more than one time-step ahead, a method called eligibility traces is used. An eligibility trace is a temporary record of which states were recently visited by the learning agent, where recency is represented by the factor $\gamma\lambda$, where γ is the discounting factor and λ is the trace decay parameter [117]. TD learning with an eligibility trace is referred to as TD(λ) [118].

Reinforcement learning methods can also be used to estimate the future values of any arbitrary signal of interest [120]. The arbitrary signals are referred to as cumulants, which are estimated, or predicted, using general value functions. Instead of maximizing future reward, the goal is to accumulate and summarize the future values of the cumulants. The discount factor γ from traditional reinforcement learning is now referred to as the termination signal, which now defines events of interest in the cumulant signal that is desirable to predict within a certain time-frame [121].

One major piece of the reinforcement learning puzzle is how to best represent the state, which in real-world applications is often composed of sensor signals, to the learning algorithm. Sensor signals are complex with a wide range of possible values. Each sensor adds a dimension to the state space. To reduce computational load, it is advantageous to represent the high-dimensional state space of the sensor values using a function approximation method [117]. Function approximation methods convert the high-dimensional combination of sensor values into a binary vector, called the feature vector. In linear function approximation, the binary feature vector is multiplied by a weight vector to get the predicted (general) value function. The weight vector is updated and learned through interactions with the environment. This review will focus on the function approximation that was used in the work reviewed below, selective Kanerva coding [122]. Selective Kanerva coding can easily handle the addition of sensor signals without significantly impacting performance or computational demand. For a description of other function approximation methods, such as the commonly used tile coding, see Ref. [117]. For a comparison of the performance of tile coding versus selective Kanerva coding, see Ref. [122].

Selective Kanerva coding represents a high-dimensional state space using a fixed number of points distributed randomly in nth dimensional space [122, 123]. These points are referred to as prototypes. In selective Kanerva coding, the current state (according to the sensor signals) is indicated in the state space. The c closest prototypes to the current state, according to their Euclidean distance, are activated, or set equal to one. All other prototypes are set equal to zero. The list of prototypes (now either one or zero) forms the binary feature vector, where only prototypes near the current state are used during learning. The feature vector, along with the weight vector learned using an algorithm such as TD(λ), is used to form general value functions, or predictions, of sensor signals.

5.1.3. *Pavlovian control*

As indicated by the name, Pavlovian control utilizes Pavlovian conditioning to produce a control output [124]. Specifically, learned predictions are used to produce a fixed control output. Pavlovian conditioning in psychology consists of a sensory stimulus (conditioned stimulus) preceding a different sensory stimulus (unconditioned stimulus) to elicit a fixed, automatic response after a training period [125, 126]. In machine learning, predictions can be formulated from available sensor data (using TD(λ) learning of general value functions) and used to trigger a pre-defined output, or response (such as ISMS output).

Using machine learning-derived predictions to produce a fixed control output is a relatively new concept in machine learning and, in the context of rehabilitation, has been primarily applied to controlling a prosthetic arm. Specifically, general value functions were used to predict switching events that determined which joint of a prosthetic arm was to be controlled by electromyography (EMG) signals [127–131]. In these studies, the joint switching events were the unconditioned stimulus, the new joint to actuate was the response, and the conditioning stimulus was the prediction of switching event determined by the general value functions of the servo motors for each joint. Both the conditioned and unconditioned stimuli normally elicit the stimulation response; however, because the prediction precedes the sensor signal, it is less susceptible to variability in the sensor recordings and users. Therefore, learning predictions online during a task could be useful to control walking using a neural interface.

5.2. *Detection and prediction of phases of the walking cycle*

The primary focus of this review is to highlight machine learning for the control of walking. However, some research has focused on the detection or prediction of the phases of the walking cycle but not the control aspects and is worth summarized as they can provide valuable components to an adaptive control strategy.

The phases of the walking cycle can be detected using a variety of methods and sensors. Reference [132] used accelerometers and ground reaction forces from able-bodied subjects to detect the phases of the walking cycle with an accuracy of 91% using supervised learning. One group used force-sensitive resistors inside shoes to indicate limb loading and unloading, as well as angular velocity to estimate foot inclination relative to the ground [97]. Using these signals, the four phases of the walking cycle were detected 99% of the time in both unimpaired and impaired subjects. They also tested the algorithm's ability to detect the phases of the walking cycle while walking on irregular surfaces, navigating small obstacles, and while walking up and down stairs, achieving 96% detection accuracy in impaired subjects. Alternatively, kinematic data can be used to identify the phase of the walking cycle [133]. Switched linear dynamical systems modeled joint kinematics of neurologically intact people walking on a treadmill. During testing, the model grouped the phases of the walking cycle according to kinematic similarity. Offline, the model was able to label the correct phase of the walking cycle with 84% precision. Surface EMG activity of neurologically intact exoskeleton users was used to correctly classify the phases of the walking cycle with 80.4% accuracy using supervised learning [134]. While a classification accuracy greater than 80% seems reasonable, when the context is the control of walking in people with SCI or other impairments, there is no room for such frequent mistakes.

5.3. *Machine learning control of FES*

Supervised learning has been implemented to varying extents to produce leg movements in people using FES. However, most of the work did not focus on predicting or controlling the entire walking cycle. For example, supervised methods have been used to track joint angles during FES-induced muscle contractions [135, 136]. Several groups used supervised learning to predict an FES user's intention to step, normally triggered by a push button, to initiate open-loop control of stimulation for walking [31, 137–140].

Reference [141] created a simulation of an able-bodied person whose walking was restricted by an ankle–foot orthosis, knee braces, and a walker. He then used the simulation to model muscle activations and movements of the limb segments. The simulation was used to train supervised learning algorithms to control hip and knee flexion and extension using FES. This algorithm was tested in one subject with a complete SCI. Reference [142] later reported testing in a person with a complete SCI. However, the algorithm required multiple updates to accommodate changes in the subject's walking patterns. The need for retraining highlights two limitations with supervised learning for the control of walking. First, the walking algorithms here were trained on data from an intact person, which does not accurately reflect the walking of a person with an SCI, despite their efforts at approximating this using orthoses, braces, and a walker. Second, without retraining, supervised learning itself is not adaptable unless feedback is incorporated into the algorithm, such as with recurrent neural networks [116]. However, supervised learning still has utility in the control of neural prostheses, as outlined below.

5.4. *Machine learning control of ISMS*

5.4.1. *Hemisection SCI model for developing control strategies*

Anesthetized cats were used to test novel control strategies developed for ISMS in a hemisection SCI model, which is a model of unilateral paralysis [93, 94]. As described above, the functional consequences of a hemisection SCI were mimicked by a person moving one hind-limb through the walking cycle (Fig. 2). This limb is referred to as the person-moved limb (PML) and represents the limb that would normally be intact after a hemisection SCI. The other hind-limb, representing the would-be paralyzed limb, was moved using stimulation in the spinal cord through a unilaterally placed ISMS implant (stimulation-controlled limb (SCL)). Since the cat was anesthetized, it was suspended in a sling (Fig. 2). All forward movements of the trolley were caused by the muscle contractions in the hind-limb controlled by the ISMS implant. The general goal of the control strategies was to provide stimulation such that the SCL was in the opposite phase of the walking cycle compared to the PML. Opposite phases were F–E2 and E1–E3 (Fig. 3). The control strategies used information from two types of sensors: force plates underneath the walking platform (left and right ground reaction forces) and gyroscopes on the tarsals of both hind-limbs (left and right angular velocity).

5.4.2. *Supervised learning for speed adaptation*

People walk differently, with their own style and pace of walking. Moreover, people with motor impairments experience a variety of deficits and recover at different rates. One consideration for an adaptive control strategy is to allow users to walk at a self-selected pace. This requires the control strategy to consistently perform at varying speeds of walking. Therefore, speed-adaptable control strategies were developed and tested in anesthetized cats over a split-belt treadmill [93].

Rule-based control was used to produce alternating stepping in a model of unilateral paralysis. Thresholds were placed on the ground reaction force (loading) and

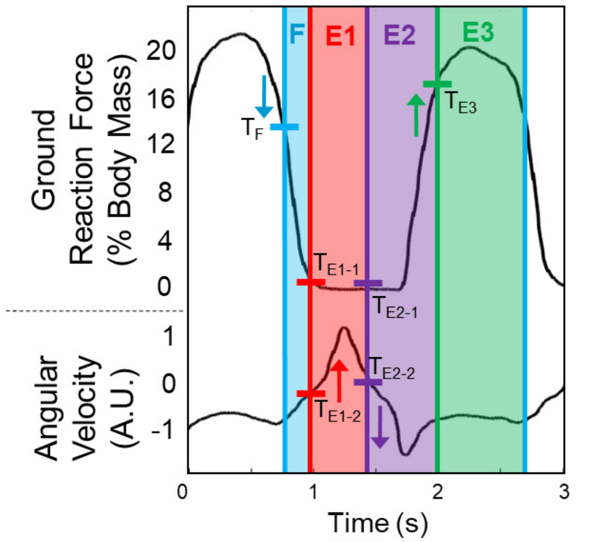

Fig. 4. Rule-based control of walking. Thresholds were placed on ground reaction force and angular velocity recorded from the person-moved limb (PML) during treadmill stepping. If the threshold for a phase was reached and the slope of the sensor signal was in the direction indicated by the arrow, stimulation through intraspinal microstimulation was triggered to transition the stimulation-controlled limb (SCL) to the opposite phase of the walking cycle as the PML.

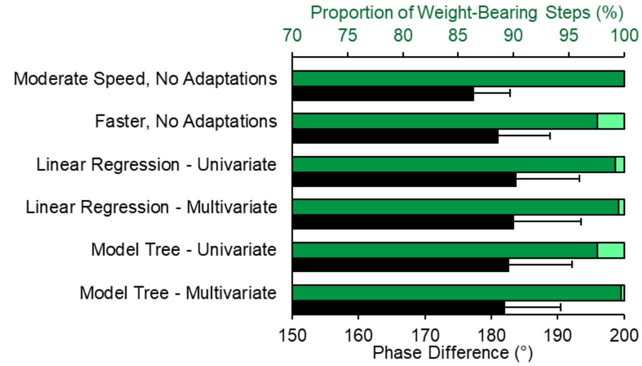

Fig. 5. Alternation (phase difference, $\text{target} = 180^\circ$) and weight-bearing (target: 100%) performance for stepping trials at a moderate speed and faster speeds with and without speed adaptation using supervised learning. Faster steps had reduced weight-bearing ($p = 0.002$). Weight-bearing was restored in three of the four supervised learning speed adaptation methods ($p < 0.04$).

angular velocity (limb position) produced by the PML (Fig. 4). If the sensor values crossed the threshold, the SCL was transitioned to the next phase of the walking cycle (Fig. 3). This approach is similar to the one proposed by Pappas *et al.* [97], described above; however, the thresholds for rule-based control applied by Dalrymple *et al.* [93] were selected to anticipate the transition to the next phase of walking, rather than simply detect it. The treadmill belt ipsilateral to the PML was adjusted to different speeds, while the belt ipsilateral to the SCL remained stationary. Three different people took turns to move the PML through the phases of forward walking. Using the ground reaction force and the angular velocity from the PML, the thresholds were used to anticipate the next phase of the walking cycle and initiated stimulation in the spinal cord to transition the SCL to the opposite phase of the walking cycle. The feedback for the rule-based control phases-by-phase transitions through the walking cycle was too slow, necessitating a different control strategy for faster steps only. If the step was fast step, then the phases of the walking cycle were transitioned using a feedforward control strategy. However, in order to adapt the control strategy according to walking speed, it first needs to be known beforehand if the step is going to be fast. Therefore, the speed of the step produced by the PML was predicted using supervised learning.

Four different supervised learning algorithms were trained using previous experimental walking data: univariate linear regression, multivariate linear regression, univariate model tree, and multivariate model tree. The supervised learning algorithms used either the total time spent in F, E1, and E2 (univariate) to predict the total step period (analog of stepping speed), or the individual times spent in F, E1, and E2 (multivariate). Testing of these trained algorithms on new data occurred during successive walking experiments using ISMS in the same hemisection SCI model.

Hind-limb alternation was defined by the difference between the mid-way time of limb loading between the two hind-limbs, converted into the degrees of a circle, where the onset of loading of the PML indicated the points 0° and 360° [93]. The target alternation is 180° indicating that the limbs were alternating successfully. Stepping at a moderate speed (treadmill belt $\text{speed} = 0.17\text{–}0.2\,\text{m/s}$) resulted in hind-limb alternation of 177° ($\pm 5.6^\circ$) (Fig. 5). Furthermore, all steps were weight-bearing, as the sum of force produced by each limb exceeded the weight-bearing threshold for the setup (12.5% of body weight for each limb [61]).

When the treadmill belt speed was increased ($0.26\text{–}0.42\,\text{m/s}$), 2.4% of the steps were no longer weight-bearing ($p = 0.002$), indicating that if the anesthetized cat was not suspended in the sling, it would have fallen. This was largely due to the lagging of the movements produced by the SCL, leaving a gap between the unloading of the PML and the loading of the SCL. By implementing a speed-adaptive control strategy using supervised learning to predict the speed of stepping, alternation and weight-bearing were achieved at faster stepping speeds. Overall, all speed-prediction methods except the univariate model tree were able to restore weight-bearing to nearly 100% of the steps while maintaining alternation (Fig. 5). The multivariate model tree algorithm was the most accurate, had the fewest number of steps that lost weight-bearing (1/399), and had an alternation value closest to $180^\circ (182^\circ \pm 9.0^\circ)$. Therefore, supervised learning methods were successful at predicting the speed of walking, leading to successful alternation and weight-bearing stepping in a model of partial paralysis at varying speeds.

These speed-adaptive control strategies were the first demonstration of machine learning to augment residual function, as represented by the person moving the "intact" limb, using a neural prosthesis. These control strategies demonstrate that safe and alternating stepping can be achieved at different speeds by employing simple supervised learning algorithms that operate in real time during stepping. They were generalizable to different people walking the PML over several experiments. These speed-adaptive anticipatory corrections to the control strategy were inspired by the role of the cerebellum during walking [143, 144]. Additionally, the external sensors used in this work relay signals relevant to walking that are similar to natural sensors such as the Golgi tendon organs (force) and stretch (position and speed) receptors [104, 145]. Through automatic speed adaptation, these control strategies are the first step toward a personalized neural prosthesis.

5.4.3. *Pavlovian control for personalized walking*

A limitation of currently available walking systems is that they employ an open-loop control strategy where the transitions between the phases of the walking cycle are pre-determined and not adapted. This open-loop strategy is dictated to the user, forcing them to comply with their device instead of the user and device cooperating to achieve a single goal: walking [25–28]. Generally, making predictions while performing a task is extremely useful. The central nervous system is continually processing sensory information from cutaneous receptors and proprioceptors, as well as from vestibular and visual regions in order to navigate the surroundings [146–148]. Predictions can be an expectation of sensory input; if the expectation is not met, an error between the predicted and actual outcomes results. The cerebellum is capable of making short-term predictions during walking and can make corrections to the gait pattern [149]. Reinforcement learning can be used to learn predictions of sensor signals, such as those recorded during walking. The predictions of various signals can then be used for control, such as for controlling a neural prosthesis, using Pavlovian control. As described above, when Pavlovian control is used to control a neural prosthesis, a prediction (conditioned stimulus) is learned for a sensor signal (unconditioned stimulus) to initiate a fixed stimulation response (ISMS).

Pavlovian control was used to achieve adaptable overground walking in a model of hemisection SCI [94]. Specifically, selective Kanerva coding was used to represent the sensor values [122] to the learning algorithm, true online TD learning. True online TD learning is similar to TD(λ) but with added terms to the eligibility trace and weight update equations to increase the precision with negligible increase in computational cost [119]. True online TD learning was used to learn predictions for three walking-relevant sensor signals from the PML during over-ground walking: ground reaction force, angular velocity, and unloading (defined as the weight-bearing threshold minus the ground reaction force) [94, 123].

Thresholds were placed on the predictions of the signals and used to initiate the SCL to the next phase of the walking cycle (Fig. 6). Four different people took turns to move the PML through the walking cycle: each of whom produced vastly different walking patterns in terms of temporal patterns and the magnitude of the movements and forces generated. The threshold settings for Pavlovian control were not modified between people or between experiments. Pavlovian control was compared to traditional rule-based control, which used thresholds on the raw sensor data as opposed to learning predictions (Fig. 4). Rule-based control is the same algorithm that was used in the previously described study without supervised learning for speed adaptability [93]. In Pavlovian control, a back-up reaction occurred if the predictions did not initiate a change of phase of the walking cycle. This was executed using rule-based control and was analogous to the unconditioned response in Pavlovian conditioning.

Rule-based control required manual tuning of the thresholds for each of the four people that moved the PML through the walking cycle because each individual had their own style of walking. Additionally, individuals often walked differently over time, which reflects the variability that is seen in individuals with neural injury or disease.

When predictions were learned with no prior experience, i.e. learning parameters were initialized to zero, learning of the sensor signals occurred very quickly. Prediction-initiated phase transitions through the walking cycle occurred within one step in 84.1% of the walking trials (trips across the walkway), up to a maximum of four steps before all transitions were initiated by predictions only. Therefore, back-up reactions were seldom needed after four steps because the learning of predictions occurred quickly and accurately. As learning continued across walking trials, the learned predictions became more accurate and initiated transitions between the phases of the walking cycle for 95.6% of the steps taken (Fig. 7). Furthermore, the walking was alternating (alternation $= 180.8^\circ \pm 5.5^\circ$) and successfully propelled the cat across the walkway. The forward propulsion was solely produced by the SCL as the cats were anesthetized.

One of the most important findings from this work was that the thresholds for the predictions did not require retuning for different people walking the PML nor

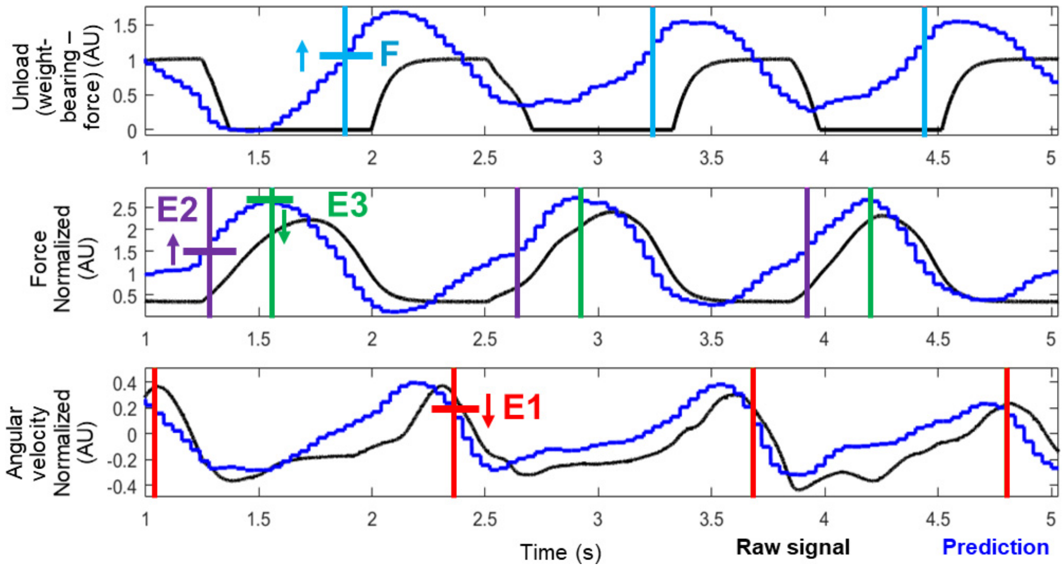

Fig. 6. Example of Pavlovian control. Thresholds (horizontal solid) were placed on the learned predictions (blue) of signals of interest (black) from the person-moved limb (PML) recorded during walking. The arrows indicate the direction of the slope of the prediction needed when crossing the threshold. When the prediction crossed the threshold with a certain slope direction, the stimulation-controlled limb (SCL) was transitioned to the next phase of the walking cycle. Note that the predictions are down sampled compared to the raw data. The solid vertical lines indicate that the prediction crossing the threshold, as opposed to a back-up reaction, was what initiated the SCL to transition to the next phase successfully (F = toe-off to early swing; E1 = late swing to heel strike; E2 = heel strike to mid-stance; E3 = mid-stance to toe-off).

for the different implanted animals. In fact, walking trials with learning parameters carrying over between different people and animal experiments were repeated to test the transferability of the thresholds. To add further perturbations, unspecified mistakes were made during walking trials. These mistakes occurred at the discretion of the person walking the PML and ranged from elongating different phases to slipping and tripping motions. A prediction-initiated transition occurred immediately following 94.4% of the mistakes.

Reinforcement learning of predictions of walking-relevant sensor signals occurred rapidly online during over-ground walking, making it ideal for applications in neural prostheses. Predictions are more reliable for

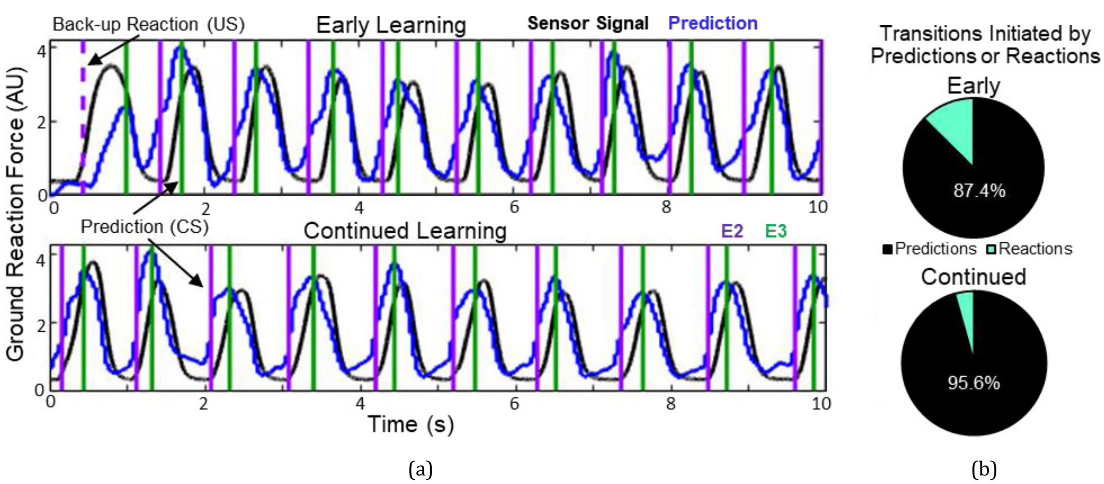

Fig. 7. Predictions initiated transitions between the phases of the walking cycle quickly after learning began and improved as learning continued during walking. (a) Examples of raw and predicted ground reaction force signal from early learning trials (learning started from zero) and continued learning trials (learning continued beyond one walking trial). Transitions for mid-stance (E2) and push-off (E3) indicated by a prediction (solid vertical line) or back-up reaction (dashed vertical line) to trigger the stimulation-controlled limb (SCL) to the opposite phase of the walking cycle (F = early swing, E1 = late swing, respectively). Note: the predictions are down sampled compared to the raw data. (b) Proportion of steps initiated by predictions or reactions for walking trials with early learning or continued learning.

control applications because they are not largely affected by sudden changes in the raw data. However, the online learning was able to adapt to lasting changes as seen when a different subject was walking. Since there was no need for retuning of the thresholds, Pavlovian control demonstrated the ability to automatically adapt to each subject, creating a personalized control system for ISMS. This included different walking styles produced by the people walking the PML, as well as throughout several animal experiments with varying responses produced by the implants (in this work, both are considered users of the neural prosthesis). The automatic adaptability suggests that Pavlovian control could withstand day-to-day changes within a single user, as well as carrying over and adapting to other users without the need for retuning of control thresholds. Pavlovian control, along with ISMS, could be the answer to restoring walking in people with partial paralysis and improve their overall independence and health and should be pursued in future studies in chronic experiments in animals with an SCI.

5.4.4. *Machine learning for selection of stimulation parameters*

The work described above detailed machine learning approaches to controlling the timing of the transitions between the phases of the walking cycle. The stimulus amplitude and electrode channels were manually selected upon setup by a human experimenter. This can be a tedious process that becomes more complicated with additional implanted electrodes, varying responses elicited between subjects implanted, and with the variable nature of SCI. An automated approach to stimulation parameter selection would greatly improve the translatability of ISMS to humans with SCI. Machine learning could also be used to select the appropriate stimulation channel and parameters for a given desired functional response. Reinforcement learning for stimulation parameter selection was demonstrated using eSCS in spinalized rats [150]. The goal of the algorithm was to locate the optimal electrode for eliciting the strongest EMG response in the tibialis anterior. Specifically, the algorithm selected stimuli (delivered at a constant amplitude) and received a reward signal comprising the EMG activity of the tibialis anterior muscle. Electrode selection far away from the target region was limited using a Gaussian process-batch upper confidence bound, which limited exploration by incorporating prior knowledge of anatomy. EMG processing for constructing the reward signal required 2–3 min, followed by 5 s of execution time of the algorithm to learn and select the next channel. Despite this long execution time, reinforcement learning was faster than a human expert at locating the best electrode location. Therefore, this reinforcement learning approach is feasible for selecting stimulation parameters and could even extend to selecting stimulation amplitude, but a different approach such as supervised learning or Pavlovian control is better for predicting and initiating transitions between phases of the walking cycle.

6. Translation to People with SCI

The control strategies reviewed here were tested in anesthetized cats with an intact spinal cord. The anesthetized model does not reflect the physiological changes that occur after an SCI, including muscle atrophy, conversion of muscle fibers to be more fatigable, bone density loss, and spasticity [82–85, 151]. However, it is a feasible model of SCI for proof-of-concept testing of control methods. Future work should test these control methods in chronically injured awake or decerebrate animals which would more accurately capture the intentions of the animal rather than rely on an approximation by a person moving the limb. Evidence to date reports that ISMS can produce graded, fatigue-resistant forces sufficient for weight-bearing after an SCI [56], as well as counteract the changes in muscle fiber types from fast-fatigable to slow fatigue-resistant [86]. Spasticity may interfere with the desired movements and create noisy or unreliable sensor values. Additional sensors such as EMG or accelerometers could be used to predict spasticity during walking, such as with the supervised learning methods described above, and facilitate an adaptation to the control strategy or a safety mechanism to cease walking.

For any method to restore walking after SCI, whether it be a neural prosthesis, a powered orthosis, or even exercise-based interventions such as BWSTT, a pre-training period is necessitated to prepare the body for the intervention [6, 19, 152]. For example, FES is used to induce muscle hypertrophy and reverse the changes in muscle fiber types [87] as well as increase bone mineral density in order to prevent bone breaks [153]. Tilt tables and stand training are used to train the body to be upright to avoid rapid decreases in blood pressure and to increase bone density [154]. Pre-implant training can also include FES and BWSTT to improve muscle and bone strength [152, 155]. Translating ISMS to use in humans with an SCI would also require a training program prior to implant.

For controlling ISMS, users would need to be instrumented with sensors. Gyroscopes are small and can be placed on the shoe for wireless communication to the controller. Ground reaction forces can be recorded using insoles made of force-sensitive resistors or capacitive sensors and are commercially available. As demonstrated in the control strategies described above, angular velocity (gyroscopes) and ground reaction forces (insoles) provide adequate information to predict the phases of the walking cycle and gait speed. This is relevant to complete SCIs and a hemisection SCI (Brown–Sequard syndrome in humans), which have more stereotypic functional deficits compared to other SCIs such as bilateral incomplete SCIs. Although Brown–Sequard syndrome is rare [156, 157], the control strategies can also be extended to other cases of hemiplegia including stroke and traumatic brain injury. For translation to people with bilateral incomplete SCIs, additional sensors are likely required to better capture the intentions of the user. EMG sensors (either external or implanted) can be used to record residual muscle activity. A control method such as Pavlovian control using selective Kanerva coding for state representation can easily accommodate additional sensors to learn many simultaneous predictions [122]. Surface EMG to indicate movement intention was successful at reducing the resistance felt by an exoskeleton user by reducing the time lag between the intention to step and the initiation of a step [158]. Surface EMG has also been used in people with an incomplete SCI and implanted FES electrodes to indicate the user's intention to step and initiated open-loop control of FES for walking [29]. Fully implantable sensor systems to control ISMS are possible using intramuscular EMG electrodes [159] and DRG recordings [160]. DRG recordings from penetrating electrodes have been used to adapt stepping produced by ISMS in cats [62]. Recently, single- and multi-unit activity were recorded epineurally from cat DRG, demonstrating the detection of primary and secondary muscle spindles, as well as cutaneous afferents during passive movements of the hind-limb [160]. Epineural DRG recordings could be realized in humans using DRG stimulating electrodes and surgical procedures, which are common practice for the neuromodulation of pain [161].

Ongoing research may also lead to volitional intentions for walking to be detected from the pre-motor or motor cortices of the brain using noninvasive methods such as electroencephalography (EEG) or invasive methods such as electrocorticography (ECoG) and intracortical recordings. EEG-based control of walking has been explored in exoskeletons [162]. One study by Ref. [163] describes a training program that included EEG to control the start and stop of a lower limb exoskeleton in people with chronic SCI. They demonstrated that after a year of training, all subjects had improved sensation and volitional control of muscles below the SCI as well as improvements in walking ability. Reference [164] reported that ECoG is better suited to interpret walking duration and speed rather than limb trajectory, which may also be suitable for indicating the intention to step. Intracortical arrays in the pre-motor cortex of monkeys have been used to control grasping elicited by cervical ISMS [70]. Intracortical arrays in the motor cortex have been used to control flexor and extensor activation by eSCS in hemisected monkeys stepping on a treadmill [38]. Therefore, cortically derived signals for the intention to walk are not only possible but includes several options for neural prosthesis developers and users.

7. Complex Locomotor Tasks Using Machine Learning

Intelligent control of neural prostheses likely requires a suite of machine learning algorithms, just as the central nervous system has several structures and networks contributing to the execution of different motor tasks. Level, over-ground walking is a relatively simple task as it is rhythmic and nondemanding. However, when the task becomes more difficult, such as with faster walking, a different control strategy had to be employed. Supervised learning was appropriate for the task of speed prediction and enabled the change of control strategy according to the stepping speed [93]. Using supervised learning for initiating a change in control strategy could also be applied to other locomotor-related tasks including switching between walking, running, stair climbing, slopes, stand-to-sit transfers, etc. To this end, Ref. [165] used supervised learning to classify EMG activity above the SCI lesion to indicate an FES user's intention to stand, sit, or step left or right. The intention classifier was then used to initiate open-loop control of FES using the Parastep system (Sigmedics, Inc., Northfield, IL, USA). Surface EMG activity from the lower limbs of intact individuals using an exoskeleton was used to successfully classify different walking environments (level, stair ascent and descent, and ramp ascent and descent) with 96.1% accuracy [134]. A similar approach was used to classify the same walking environments using surface EMG of intact individuals and amputees, achieving a classification accuracy of 97.9% in amputees [166]. Control of an exoskeleton or prosthesis using the walking environment classification has yet to be tested; however, the classification results suggest that similar methods could be developed and extended to other interventions including neural prostheses.

Prediction, rather than detection, of different walking environments or other types of locomotor tasks could be achieved using general value functions and Pavlovian control. Additional sensors can be used to provide more context of the environment for to learn predictions quickly and accurately online during walking. One could imagine using cameras or infrared lasers on, for example, a pair of glasses worn by the user, to provide valuable information for navigating difficult walking terrain such as avoiding obstacles, turning, or walking on uneven ground. With more information about the environment, further development of control rules with Pavlovian control could expand the utility of a neural prosthesis to several tasks related to everyday life. Furthermore, predictions could also be learned to provide enhanced stability, such as predicting fatigue, loss of balance, or excessive use of the upper body for support using information from EMG activity, tilt sensors, or the forces applied to a walking aid. These ideas can be implemented in other complex tasks as well, including reaching and grasping or driving a vehicle, to increase the utility and adaptability of prostheses and improve the lives of people living with neural injury or disease.

With inspiration from the nervous system itself, many of the machine learning and control concepts strive to replicate the complex and effective functionality of biological learning and motor systems. It is a natural expansion to use these biologically inspired algorithms in rehabilitation to restore and augment function after neural injury or disease. Supervised learning and Pavlovian control allow expert knowledge to be incorporated into the design of the controller. Much is known about walking and how to achieve walking safely and efficiently. Incorporating this knowledge into a control strategy to restore walking merges the knowledge of the designer with the automatic adaptability of machine learning. Machine learning methods such as unsupervised learning or true reinforcement learning control could be dangerous when used to control a neural interface user as these methods require exploration and testing to find an optimal solution [117]. For example, restricting the exploration of reinforcement learning control to known safe control states or electrode configurations confines the learning ability of algorithm, which conflicts with the foundation of reinforcement learning control. Additionally, exploration can be time consuming as it requires hundreds to thousands of repetitions of a state being visited by the learning agent. Pavlovian control is not burdened by the need for exploration as reinforcement learning is responsible for predicting the sensor signals, but the control decision is determined by those predictions crossing a threshold. This greatly simplifies the control strategy and enables fast translation and operation with a neural interface [94] or prosthetic arm [127, 128].

8. Long-Term Learning and Potential for Lasting Functional Improvements

Under Pavlovian control, as learning continued across many walking trials, the predictions of the sensor signals became more accurate [94]. The repetition of concurrent sensor signals with similar temporal patterns reinforced the learned predictions as walking continued. More precise predictions lead to more accurate control decisions for more reliable transitions between the phases of the walking cycle during walking. Long-term ISMS under Pavlovian control could promote functional recovery and spinal cord plasticity through several mechanisms. ISMS produces walking by evoking muscle contractions and moving the limbs. These limb movements activate sensory fibers including Golgi tendon organs and cutaneous afferents during loading and muscle spindles during movements about the joints [167] which interact with spinal interneurons and motoneurons [168]. Using ISMS for walking is a form of locomotor training, which has been shown to improve locomotor ability in people with SCI by inducing activity-dependent plasticity in the spinal cord [169–173]. Epidural and transcutaneous SCS can improve mobility after SCI [7, 18, 19, 23, 42, 174]. Empirical evidence and computer simulations suggest that the electrical stimulation of the dorsal roots modulates and enhances muscle activity during locomotion through activation of motoneurons in the spinal cord [175–177]. Furthermore, it is likely that the sensory afferents activated during walking can selectively enhance the activity of motoneuron pools that are relevant to the movement, further increasing their activation [178–180].

Intentions and volitional control play a large role in the recovery of locomotion and can enhance the effects of locomotor training. With respect to epidural and transcutaneous SCS, stimulation is thought to bring the motor pathways closer to threshold, facilitating spared but weak volitional commands to evoke movements [181–184]. After several weeks of eSCS combined with descending volitional commands and excitatory neurotransmitters, dual hemisected rats regained full weight-bearing bipedal locomotion and were able to later avoid obstacles and climb stairs with the use of eSCS [184]. The functional recovery induced extensive remodeling in the spinal cord, including intraspinal relays of corticospinal and brainstem projections across the injury site. Stimulation-facilitated functional recovery has also reported in rats with a cervical contusion SCI that received ISMS for restoring forelimb function [66, 185]. Specifically, rats with a chronic SCI that received ISMS at threshold for movements in the forelimb for 7 h per day, 5 days per week, for 12 weeks demonstrated superior elbow extension, opening of the digits, and reaching success without stimulation compared to rats that did not receive stimulation [66]. In another study, ISMS was synchronized with volitional motor commands recorded from the EMG activity of the impaired forelimb to support the movement made by the rat during reaching and grasping training [185]. Rats that received intention-triggered ISMS for 5 days per week for 13 weeks had a greater reaching performance than rats that received open-loop stimulation or physical retraining alone. The improved reaching ability was maintained and did not reduce after 3 weeks without stimulation. Although not demonstrated histologically, the improved reaching success of the rats when tested without stimulation suggest extensive remodeling occurred during stimulation-supported training and does not require the presence of stimulation to perform the movements.

FES of the peripheral nerves has shown to have lasting improvements in walking after SCI in rodents [186] and people and is reviewed in Refs. [9, 187]. Cellular changes resulting from increased neural activity, such as with using ISMS, including neuronal survival, differentiation, axonal growth, synaptogenesis, and dendrite stability, are reviewed by Ref. [188]. Spinal network plasticity can also be facilitated by pharmacological approaches such as chondroitinase ABC, Nogo antibody, nerve growth factor (NGF), neurotrophin-3 (NT3), or brain-derived neurotrophic factor (BDNF), as reviewed by Ref. [189]. Lasting functional changes after an SCI likely requires a combination of pharmacological intervention, electrical stimulation, and intention-driven rehabilitation.

Although yet to be determined experimentally, related work supports the hypothesis that ISMS in the lumbosacral spinal cord can improve walking function over time. Additionally, predictive and adaptive control strategies such as Pavlovian control could further improve function after SCI by (i) providing contextual sensory information to the spinal cord during walking through the evoked limb movements; (ii) delivering accurately timed stimulation with respect to the walking cycle and the user's intentions as determined by external sensors; and (iii) adapting to the user's changes in residual function over time.

9. Summary/Conclusion

ISMS is an effective neural interface that has been shown to restore over-ground walking in models of complete and partial paralysis [8, 94]. The control strategies developed for ISMS are inspired by natural motor control mechanisms throughout the nervous system. Recent work has implemented various machine learning algorithms for speed adaptation and prediction-based control in a model of partial paralysis [83, 94]. These machine learning algorithms were able to augment residual function, as modeled by a person-moved limb of an anesthetized cat, to produce safe and alternating walking that allowed multiple people to walk the limb at a self-selected pace and with varying walking styles. Similar control strategies may be readily implemented in other neural interfaces, prostheses, and powered orthoses for walking and other locomotor tasks. Predictive control strategies allow for automatic adaptation that could enhance the recovery of users through long-term use. Much needs to be explored in the utility of machine learning algorithms and neural interfaces, but the possibilities are numerous.

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