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Review Article

A review of methods for achieving upper limb movement following spinal cord injury through hybrid muscle stimulation and robotic assistance

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ABSTRACT

Individuals with tetraplegia, typically attributed to spinal cord injuries (SCI) at the cervical level, experience significant health care costs and loss of independence due to their limited reaching and grasping capabilities. Neuromuscular electrical stimulation (NMES) is a promising intervention to restore arm and hand function because it activates a person's own paralyzed muscles; however, NMES sometimes lacks the accuracy and repeatability necessary to position the limb for functional tasks, and repeated muscle stimulation can lead to fatigue. Robotic devices have the potential to restore function when used as assistive devices to supplement or replace limited or lost function of the upper limb following SCI. Unfortunately, most robotic solutions are bulky or require significant power to operate, limiting their applicability to restore functional independence in a home environment. Combining NMES and robotic support systems into a single hybrid neuroprosthesis is compelling, since the robotic device can supplement the action of the muscles and improve repeatability and accuracy. Research groups have begun to explore applications of movement assistance for individuals with spinal cord injury using these technologies in concert. In this review, we present the state of the art in hybrid NMES-orthotic systems for upper limb movement restoration following spinal cord injury, and suggest areas for emphasis necessary to move the field forward. Currently, NMES-robotic systems use either surface or implanted electrodes to stimulate muscles, with rigid robotic supports holding the limb against gravity, or providing assistance in reaching movements. Usability of such systems outside of the lab or clinic is limited due to the complexity of both the mechanical components, stimulation systems, and human-machine interfaces. Assessment of system and participant performance is not reported in a standardized way. Future directions should address wearability through improvements in component technologies and user interfaces. Further, increased integration of the control action between NMES and robotic subsystems to reanimate the limb should be pursued. Standardized reporting of system performance and expanded clinical assessments of these systems are also needed. All of these advancements are critical to facilitate translation from lab to home.

1. Introduction

There are approximately 291,000 people in the United States living with spinal cord injuries, with approximately 60% with cervical spinal cord injuries leading to tetraplegia (NSCISC, 2019). Injuries at such a high level of the spinal cord create severe arm and hand disabilities, resulting in an inability to complete Activities of Daily Living (ADLs). As a result, 71% of individuals with tetraplegia currently require assistance with ADLs (Collinger et al., 2013a).

Restoration of arm and hand function is a top priority among people with tetraplegia (Anderson, 2004). Regaining the ability to perform these tasks independently will reduce requirements on caregivers and increase opportunities for individuals to return to social participation in their communities, both of which are highly correlated to quality of life (Dijkers, 1997). Furthermore, regaining upper extremity function is a key step towards gainful and rewarding employment. Currently, only 35% of individuals with Spinal Cord Injury (SCI) are employed, and only 12% of individuals return to their pre-SCI jobs (Krause and Anson, 1996; Ottomanelli and Lind, 2009).

Despite the clear and critical need for restoration of arm and hand function following SCI, recovery of such function through rehabilitation is not always achievable. For those with some residual muscle capability, there is evidence that repetitive and intensive practice can induce practice-dependent brain and spinal plasticity, and that exercise

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intensity has a profound effect on sensory-motor recovery (Dietz et al., 2002; Beekhuizen and Field-Fote, 2005). Results from a few pilot studies indicate that the same intensive robotic rehabilitation that has been successful for inducing plasticity and recovery following stroke (Reinkensmeyer et al., 2000; Charles et al., 2005; Blank et al., 2014; Lum et al., 2012) can be effective for SCI (Kadivar et al., 2012; Fitle et al., 2015; Francisco et al., 2017; Yozbatiran and Francisco, 2019). For those *without* residual motor capability, or for those for whom rehabilitation interventions have not been able to restore functional movement, assistive technologies are a more viable option for replacing lost function. Such approaches incorporate mechanical devices that are attached to the limb and have the capability to move the limb or hand, or approaches that electrically stimulate the existing muscles, causing muscle contraction and inducing motion of the upper limb.

Neuromuscular electrical stimulation (NMES) can selectively activate paralyzed muscles – with surface electrodes or with a surgically implanted system for long-term use – to potentially restore these functions. NMES has had some success in restoring grasping to people with C5 and C6 injuries (Kilgore et al., 2008). Restoration of function to people with high tetraplegia (C1–C4) has been much more elusive as coordination of the shoulder, elbow, wrist, and hand is required to restore both reaching and grasping. A major barrier to NMES becoming a more widely-used intervention for functional restoration for reaching and grasping is the prevalence of lower motor neuron damage after spinal cord injury. Lower motor neuron damage leaves some muscles critical to reaching movements – more typically biceps, supraspinatus, and deltoids and less typically pectoralis, triceps, and latissimus dorsi – unresponsive to electrical stimulation (Mulcahey et al., 1999). Lower motor neuron damage can also make muscles critical to wrist and finger movements unresponsive to NMES (Peckham et al., 1976). For many people with spinal cord injuries, NMES alone is not sufficient to restore reaching and grasping movements. Even when muscles are innervated, NMES leads to faster fatigue than voluntarily controlled muscles (Bickel et al., 2011), and precise control of joint movements with NMES is especially challenging due to nonlinearities and electro-mechanical delays in muscle actuation. Due to these difficulties, many NMES systems are controlled using simple methods, such as providing stimulation proportional to a user input or based on a predefined time-varying stimulation profile. These simple techniques work for simple movements, such as opening and closing the hand, but do not produce the accuracy or repeatability required for more complicated movements, such as the coordinated movements required to drink from a glass. See (Lynch and Popovic, 2008) for more details on control strategies for NMES systems.

Actuated robotic systems that actively move the upper limb (supporting, carrying, or physically manipulating the pose of the limb and hand), thereby enabling reaching and grasping, have the potential to support functional movements and restore independence for individuals with severe incomplete SCI or complete injuries that cannot expect recovery through rehabilitation. While end-effector type robots that support the upper limb against gravity can enable some function (see Chang et al. (2019) for a tutorial), these types of devices don't translate well to everyday tasks and environments given their size, bulk, weight, and power requirements. Further, they tend to enable only reaching in a planar workspace, though some systems enable out of plane reaching. These drawbacks inherently limit the utility of end-effector based devices for restoring independence in everyday tasks and environments. In contrast, exoskeleton-based assistive robotic devices (see Gopura et al. (2016) for a survey of exoskeleton robotics) that align with the joints of the upper limb and/or hand prioritize wearability and in turn are appealing to explore for their potential to promote true independence among this population. Either class of robotic system can achieve high accuracy and repeatability by using feedback to regulate the output of the system. Feedback is often provided through some variation of a Proportional Integral Derivative (PID) controller, which sums terms proportional to the derivative of system error, the integral of system error, and the system error itself, to determine the amount of actuation. There are many more complicated controllers used in special circumstances which can adapt to environments, handle uncertainty, or encourage patient engagement. Still, these devices are complex in design, heavy, and require significant power to generate the torques necessary to manipulate the arm and hand through the range of motion necessary to realize activities of daily living.

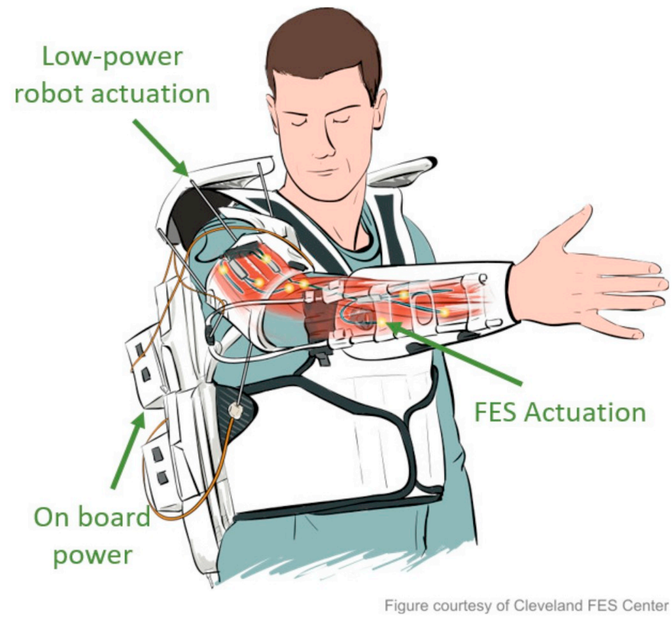

Fig. 1. Concept design for a lightweight and wearable Hybrid FES-Soft Exoskeleton system.

While researchers have made great strides in using NMES to assist individuals with SCI with ADLs, the fundamental limitations still keep this technology from becoming a wide-spread solution to those with motor disabilities. Similarly, the advances made in assistive robotics have not resulted in a general-purpose wearable system that is capable of assisting in ADLs. These limitations have led researchers to look for innovative ways to work around the drawbacks of each individual technology to provide a complete system truly capable of providing general assistance with ADLs. Recent research has aimed to solve this problem by augmenting NMES with assistive orthoses. A concept drawing of a wearable assistive robotic device working with a system for electrical stimulation of the muscles to reanimate the upper limb is illustrated in Fig. 1. Here, full coordination of NMES and robotic support is envisioned, with each working in concert to achieve functional movements and support the user in their ADLs. Integration of robotic and electrical stimulation technologies across a range of levels of cooperation has the potential to selectively reduce the limitations of each individual system; however, this pairing also presents a more complex coordination and control problem of combining these actuation strategies efficiently. To get the most out of a hybrid system, each subsystem must have knowledge of how the other is operating and be able to balance the load based on a collective goal. This creates a full hybrid system architecture where the user provides some functional command, and the hybrid system must supply coordinated output commands for the NMES and robotic subsystems, as shown in Fig. 2. The level of coordination demonstrated by these hybrid systems in the literature ranges from combining NMES with arm splints to maintain desired poses of the limb, to cooperation between NMES and an active orthosis to move the same joint of the upper limb in a coordinated fashion.

In this review, we discuss the state of the art in hybrid NMES-orthosis systems for restoration of upper limb movement in individuals with spinal cord injury. (We refer the reader to previous reviews of hybrid NMES and robotic systems that have focused on upper limb

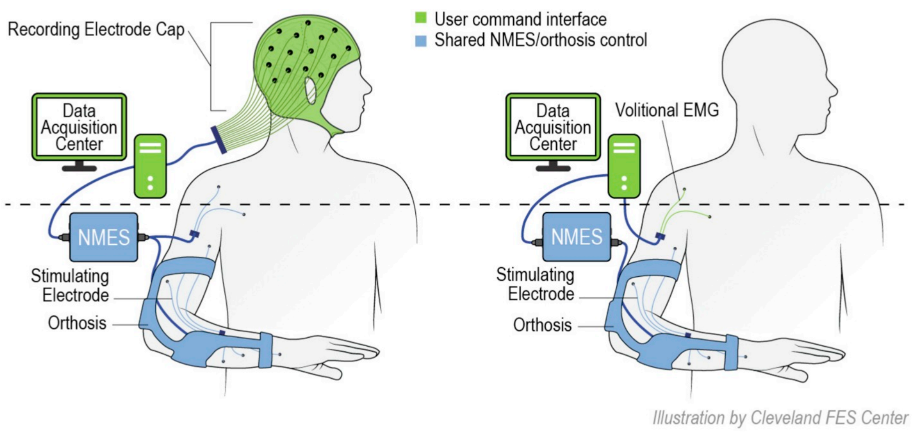

Fig. 2. Two common architectures for hybrid NMES-orthosis systems used to reanimate paralyzed limbs. In each, the sub-systems colored green indicate the method of user intent and command. Sub-systems colored blue indicate the components responsible for generating movement of the limb. (left) Detection of user intent from brain-computer interface, with shared control of NMES and orthosis. (right) Peripheral detection of motor intent via EMG from volitionally controlled muscles, with shared control of NMES and orthosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

stroke rehabilitation (Resquín et al., 2016a, 2016b; Stewart et al., 2017) and restoration of gait after spinal cord injury (Del-Ama et al., 2012).) Throughout this review, we use the terms “restore” and “reanimate” to describe how NMES and robotic systems can support movements in an assistive manner, moving limbs with the aid of the technology. In contrast, we use “recover” and “rehabilitate” to imply that the intervention is therapeutic and thereby intended to enable recovery of function independent of the assistive technology. We identify the application domains where hybrid systems have been developed and evaluated, and highlight the key component technologies that are needed to realize such systems. An intuitive user-command interface is necessary for these systems to support functional independence, so we present a number of approaches that have been reported in the literature. We are particularly interested in how the integration and coordination between NMES and robotic support systems can be realized to advance the field, and as such we highlight the current state of the art in shared control methods for these hybrid systems. Since adoption of this technology depends on usability, both for end-users and clinicians, we discuss both wearability and invasive aspects of NMES-orthosis systems. Finally, we review ways that these systems are evaluated, both from a system performance perspective and in terms of clinical and functional outcomes. The paper concludes with a discussion of possible future research directions that should be pursued to drive the field forward.

2. Methods

We searched Google Scholar for papers to potentially include in this review. To search for articles that included references to the combined use of muscle stimulation and robotic assistance as a therapeutic or assistive intervention for spinal cord injury in the upper limb, we used combinations of key words, one from each of the following four groups:

1. electrical stimulation, FES (functional electrical stimulation), NMES (neuromuscular electrical stimulation)
2. robot, exoskeleton, assistive device, orthosis, arm support
3. spinal, SCI (spinal cord injury)
4. arm, upper limb, upper extremity

We also considered relevant papers referenced in articles found via the Google Scholar search. Each author of this review article read each of the candidate articles found in the initial search, and we reached a consensus on articles to include in this review based on these criteria:

- Electrical stimulation and a robot, exoskeleton, orthosis, or arm support must be used as part of the same intervention.
- The intervention is primarily focused on the upper extremities.
- The intervention is used or intended for use with people with spinal cord injuries.
- The paper must be written in English and have undergone peer review.

We included articles that were early in the development of an intervention but had not yet been used with a specific patient population, but in which the potential to use the intervention for spinal cord injury was mentioned.

3. Results

3.1. Application domains

The vast majority of hybrid NMES-orthosis systems designed for individuals who have suffered severe spinal cord injuries resulting in tetraplegia, or paraplegia with limited upper limb function, seek to restore motor function by animating the paralyzed limbs of these individuals. In these applications, NMES serves to actuate muscles, and orthoses are used to support this action, either by holding the limb against gravity, or by physically acting on the limb to move the joints through desired range of motion. A summary of the application domains that we surveyed is presented in Table 1.

For example, in one study, a single participant with a C1-C2 spinal cord injury used an implanted stimulator with intramuscular electrodes and nerve cuff electrodes that activate muscles in the right arm and shoulder complex, coupled with a passive arm support to act against gravity, to enable reaching movements (Wolf and Schearer, 2018). The iBCI + FES system enabled a single participant with a C4 ASIA A spinal cord injury to command both single joint and coordinated shoulder, elbow, wrist, and hand movements actuated by a powered orthosis (shoulder) and NMES (elbow, wrist, and hand), triggered via an implanted intracortical brain-machine interface (Ajiboye et al., 2017). The system is intended to restore a full range of reaching and grasping functions in persons with high tetraplegia. A similarly conceived system, the TOBI FES + orthosis, uses NMES in combination with an orthosis to achieve functional reaching and grasping in an individual with high tetraplegia (Rohm et al., 2013). Arm supports are often used to hold the limb against gravity or supplement the action of NMES in the proximal muscles of the upper limb. For example, Memberg et al. found it necessary to use a mobile and passive arm support to place the limb in more functional positions or to support the weight of the arm for two individuals with spinal cord injuries at or above the C4 level (Memberg et al., 2014). A different hybrid system was envisioned to allow reach and grasp motions by stimulating grasp with NMES, supporting reaching movements with an active orthosis for the elbow and a passive orthosis to support the forearm, and relying on residual shoulder and scapular movement capability in individuals with cervical level lesions (Varoto et al., 2008).

Table 1
Application and evaluation results for each of the reviewed hybrid systems.

System Name	Main Reference Paper	Population Tested	Intended Population	Calibration Required Every Use?	Intended Environment	Evaluation Techniques	Main Evaluation Results
No name given	Varoto et al., 2008	Cervical (N = 5)	SCI	No	Therapy or every day functional use	Each subsystem validation (independently)	Each subsystem worked independently
TOBI FES + orthosis	Rohm et al., 2013	C4 (N = 1)	SCI	Yes	Every day functional use	Number of successful attempts for tasks	17/26 successes on grasp and release test - Unable to successfully eat pretzel stick (1 success but intervention necessary) - Succeeded 4/10 times with writing task (subject corrected false classification twice) - Successfully ate ice cream cone all 4 times
MUNDUS	Pedrocchi et al., 2013	SCI at C3–7 level, ASIA A to C (N = 3); 2 MS subjects	SCI and MS	Yes	Intended for every day functional use	Commitee ranks task as success, unsuccessful, acceptable. RMSE elbow angle	Mean scores of ~1.6 rated from 0 (unsuccessful) to 2 (fully successful). Most patients either got it (2) or didnt (0)
No name given	Looned et al., 2014	Able-bodied (N = 5)	Neurological Impairment (only validated with healthy, but they mention stroke)	Yes	Therapy or every day functional use	Time it took healthy subjects to complete stages of movements	Between 100 and 160 s to complete a drinking task
IST-12 with mobile arm support	Memberg et al., 2014 Schearer et al., 2015	C4 (N = 2)	SCI	Not necessary but improves performance as muscle strength changes	Every day functional use	Torque and movement with statistics, ability to complete ADL tasks	Sufficent torque to complete ADLs, moment graphs provided in paper. Grasp strength from 11.6 to 25.5 N. ROM Reported as well. ADLs were mostly successful, but subject had trouble acquiring objects.
iBCI + FES	Ajiboye et al., 2017	C4 ASIA A (N = 1)	SCI	Yes	Every day functional use	Time and number of successful attempts in a drinking task	10 trials successful out of 11 and took between ~25 and 45 s
FES + MAHI Exo II	Wolf et al., 2017a, 2017b	Able-bodied (N = 7)	SCI	Yes	Laboratory use	RMS error and torque	Torque was reduced by 74% and RMS tracking error was reduce by 94% using FES with Exo
FES Hand Glove 200	Scott et al., 2018	SCI at C4-C7 level, ASIA A to D (N = 14)	SCI	Not Reported	Therapy	Complications with patients, PROM, AROM, Clinical Outcome Assessments	No significant chages to health or loss of strength in participants. Some improvements to movement in forearm, wrist hands, found as well as improved strength

Some applications of NMES supported with robotic devices are intended to supplement residual capabilities of the user, rather than replace lost function. Ambrosini et al. developed an NMES system that relies on acquisition of EMG signals for intent detection, driving the NMES to support elbow flexion (Ambrosini et al., 2014). Their work specifically targets individuals with neurological impairments (stroke or incomplete spinal cord injury) where some motor function is preserved, and couples the system with a passive elbow brace to support the weight of the limb. The proposed system, which combines NMES support with voluntary drive through the acquisition and amplification of residual EMG activity, does not account for muscle fatigue, and would not be appropriate for individuals with spasticity greater than 2 on the Modified Ashworth scale. The MUNDUS hybrid exoskeleton-NMES system was modular and reconfigurable with active or passive modes depending on user capability (Pedrocchi et al., 2013). The system delivered simultaneous NMES based on EMG activity and robotic arm support to achieve functional movements.

Still other systems are focused on therapeutic interventions that would take place either in a clinic or in the home, with the goal of recovering function through range of motion exercises combined with electrical stimulation. Research along these lines for individuals with SCI is at a very preliminary stage. One example study reported a robotic glove system, the FES Hand Glove 200, that supports flexion and extension of the hand, providing active movement of the thumb and fingers through range of motion with the robotic system while simultaneously stimulating the corresponding muscles with surface electrodes (Scott et al., 2018). In this case, the inclusion of NMES with robotic therapy may be used to prevent muscle atrophy, maintain or increase functional range of motion, and even strengthen muscles of individuals with incomplete SCI at the cervical level of the spinal cord.

3.2. Component technologies

The two component technologies of the hybrid NMES-orthosis system each present a number of configuration options that should be matched to the desired application scenario. To realize electrical stimulation of muscles, one must consider whether the electrodes are implanted or placed on the skin's surface, the number of electrodes needed to stimulate muscle and achieve desired motion response, and the biphasic stimulation patterns of amplitude, duration, and frequency. The orthosis is specified depending on its desired action (immobilize, stabilize, support against gravity, or actively support movement). Additional considerations are the joints of the upper limb on which the orthosis will act, and in the case of an active orthosis, the actuation method that will be used. Table 2 provides details for the fundamental component technologies used in the papers surveyed for this review article.

Stimulation systems that use surface electrodes range from commercially available systems most often used for therapeutic interventions or to prevent against muscle atrophy, to custom systems that offer more flexibility in choice of number of electrodes and the electrical stimulation patterns. Surface electrodes adhere directly to the skin and can be easily placed on the muscle belly, but it can be challenging to replicate electrode placement for repeat use, leading to performance variability since the electrodes must be located directly over the muscle to be stimulated (see Koutsou et al. (2016) for a review of surface stimulation techniques). Surface electrodes are also not well-suited to stimulation of deeper muscles. As such, surface stimulation methods tend to be best matched to large muscles of the upper limb or for gross tasks such as grasping that engage multiple muscles of the forearm simultaneously. For example, the hybrid NMES-orthosis system in (Rohm et al., 2013) used the Motionstim system (Medel GmbH, Hamburg, Germany) to generate biphasic, constant current impulses for stimulation of grasp, while an orthosis provided stabilization and weight support of the more proximal joints.

Implanted electrodes for NMES can be cuff electrodes that are surgically implanted to surround the nerve that innervates the muscle, epimysial electrodes implanted over a muscle, or intramuscular electrodes placed into the muscle. These systems allow for much more specificity of muscle stimulation, offering greater repeatability than surface electrodes. As an example, the IST-12 with mobile arm support system used two implantable stimulator-telemeters each with 12 stimulating electrodes located intramuscularly in the arm and hand, with additional spiral nerve cuff electrodes to activate proximal arm nerves (Memberg et al., 2014), as shown in Fig. 3. Recent work has shown the potential for selecting multiple individual sensory (Tan et al., 2015) or

Table 2
Configuration and shared control implications for reviewed hybrid systems.

System Name	Main Reference Paper	Patient Interface	Joints supported	Surface or Implanted NMES	Class(es) of orthosis used	Shared Control Strategy
No name given	Varoto et al., 2008	Voice commands	Elbow Hand	Surface	Passive, Active	NMES & active orthosis on separate joints
TOBI FES + orthosis	Rohm et al., 2013	EEG cap BCI	Elbow Hand Finger	Surface	Passive, Semi-Active	NMES & brake on same joint, passive orthosis on separate joint
MUNDUS	Pedrocchi et al., 2013	Volitional control of stimulated muscles, EEG BCI, eye tracking	Shoulder Elbow Hand	Surface	Passive, Semi-Active	NMES & brake on same joints, general passive gravity comp, but configurable
No name given	Looned et al., 2014	EEG headset BCI	Elbow Forearm Hand	Surface	Active	NMES & active orthoses on separate joints
IST-12 with mobile arm support	Memberg et al., 2014 Schearer et al., 2015	Volitional EMG from neck muscles	Shoulder Elbow Forearm Wrist Hand	Implanted	Passive, Active	NMES, passive orthosis and end effector active orthosis on all joints
iBCI + FES	Ajiboye et al., 2017	Intra-cortical BCI	Shoulder Elbow Forearm Wrist Hand	percutaneous implanted	Passive, Active	NMES & active orthosis on separate joints, general passive gravity comp
FES + MAHI Exo II	Wolf et al., 2017a, 2017b	None	Elbow	Surface	Passive, Active	NMES & active orthosis on same joint
FES Hand Glove 200	Scott et al., 2018	None	Hand	Surface	Active	NMES & active orthosis on same joint

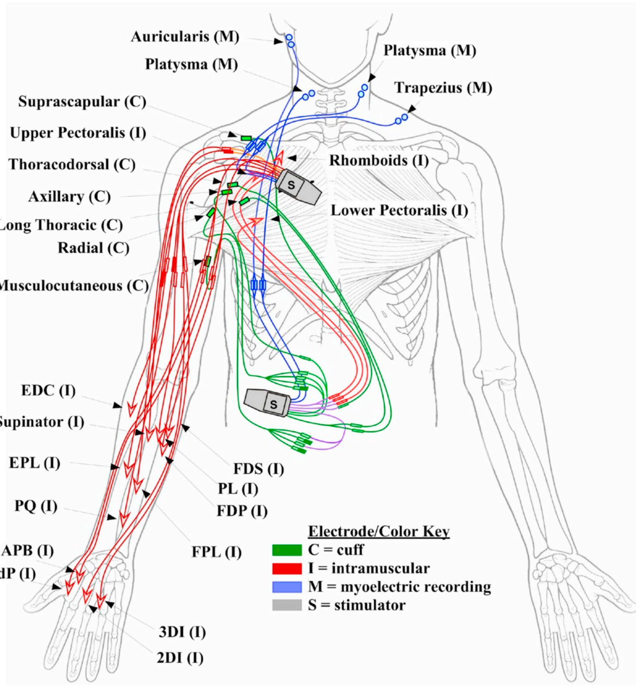

Fig. 3. Example showing several types of implanted electrodes for a multi-joint NMES actuation system (Memberg et al., 2014).

motor responses (Bong et al., 2019) with a single multi-electrode nerve cuff; this could lead to the ability to selectively stimulate multiple muscles with a single nerve cuff, potentially limiting the invasiveness and recovery time associated with implanted systems.

There is a body of evidence that suggests NMES leads to faster muscle fatigue than voluntary activation of muscles (Bickel et al., 2011). Efforts to reduce fatigue when using NMES are ongoing (see Ibitoye et al. (2016) for a recent review). These include techniques for individual muscles like variation of stimulation frequency (Deley et al., 2015) and intensity (Chou et al., 2008), and asynchronous stimulation of multiple electrodes activating the same muscle (Downey et al., 2015). Other strategies aim to balance the effort of redundant actuators such as alternating stimulation of synergistic muscles (Decker et al., 2010), and balancing the contributions of an exoskeleton and FES in controlling knee torques in healthy subjects (Alibeji et al., 2017; del Ama et al., 2014).

Orthotic support devices used in hybrid NMES systems are intended at a minimum to stabilize the limb so that NMES can elicit functional movements. Passive devices such as common arm braces can be used to immobilize or stabilize individual joints, so that NMES systems can stimulate simple grasping actions. Some devices incorporate springs or weights that provide passive gravity compensation, supporting the limb in any configuration without required action by the muscles. For example, one hybrid NMES-orthosis system used surface electrodes for stimulation of the limb to achieve elbow flexion, and used a passive exoskeleton to provide weight support for elbow flexion/extension and two additional degrees of freedom (shoulder rotation in the horizontal plane and shoulder elevation in the sagittal plane) (Ambrosini et al., 2014). When active movement support is desired, robotic devices incorporating motors are used, either in end-effector configurations, where the user grasps or is connected to the device through a handle or forearm splint (Schearer et al., 2016), or in exoskeletal configurations (Elnady et al., 2015; Varoto et al., 2008), where the robotic device envelops the limb and the movable joints of the exoskeleton align with the user's own joints. As the movements supported by the robotic device become more complex and involve multiple joints of the arm, the complexity of the device itself increases, and the weight, bulk, and power requirements are amplified in order to produce the torque necessary to move the limb through functional range of motion in the reachable workspace. Devices that offer this degree of capability are typically custom laboratory prototypes, since commercial robotic arm supports are often focused on support of planar movements at table height.

3.3. *User command interfaces*

A variety of interfaces have been used to allow people with spinal cord injuries to control reaching and grasping movements with hybrid neuroprostheses. We refer to these as "user command interfaces." In some cases, there is no user command interface, and a researcher instead chooses the movement to perform (Schearer et al., 2015; Wolf and Schearer, 2018, 2019; Scott et al., 2018). In cases where users have some volitional control of their arm muscles – typically with incomplete SCI or lower-level cervical SCI – electromyogram (EMG) from volitionally-controlled muscle(s) can trigger the onset or directly control a movement. Brain-computer interfaces have also been explored that allow users with complete high-level cervical SCI to control arm movements by observing electrical activity in the brain. These user command interfaces are illustrated conceptually in Fig. 2.

3.3.1. *Electromyogram from volitionally controlled muscles*

The MUNDUS system offers volitional-muscle EMG as one of three different user command interfaces depending on the capability of each potential user (Pedrocchi et al., 2013). For people who can produce some volitional shoulder and elbow movement, surface EMG signals from deltoids and biceps initiate NMES of the same muscles to trigger a ramp up or ramp down of electrical stimulation to actively control movements with gravity support from an exoskeleton (Ambrosini et al., 2012, 2014).

The IST-12 uses implanted EMG from volitionally-controlled neck muscles to either select the current mode of operation (eg. pronation/supination, wrist flexion/extension, shoulder elevation/depression), or to provide proportional control of pre-programmed stimulation patterns for single and multiple joint movements (Memberg et al., 2014). The user has no control over the gravity support orthosis, which is entirely passive.

3.3.2. *Brain-machine interfaces*

Electroencephalography is a non-surgical technique that uses measurements of brain activity from electrodes, typically placed on the scalp, called electroencephalograms (EEG). Researchers use machine learning techniques to decode EEG signals to determine a user's intent.

A wearable powered orthosis and NMES are controlled by signals collected by an EEG headset in (Looned et al., 2014). A drinking task was divided into 11 stages, and the onset of each stage is triggered by the user imagining the movement and the EEG classifier identifying the desired movement, regardless of whether it was with the orthosis or NMES. Each stage was stopped by a user jaw clench which is again classified by the EEG decoder.

For users without volitional control of deltoid or biceps muscles, the MUNDUS system uses EEG to select from a discrete set of targets or "GO" and "STOP" commands displayed on a screen, while a low-level controller determines the amount of electrical stimulation and orthosis actuation (Pedrocchi et al., 2013). MUNDUS leverages radio-frequency identification to identify the coordinates of specific items – for example, a cup – to reach for and grasp.

The TOBI FES + orthosis system uses an EEG-based brain-machine interface and a shoulder motion sensor to command arm movements (Rohm et al., 2013). The EEG signals are decoded to allow the user to specify three modes of use of the hybrid system: 1) pause, 2) control elbow flexion/extension, 3) control hand open/close. In modes 2 and 3, the shoulder position sensor allows the user to actively modulate predefined muscle stimulation patterns to change elbow extension/flexion and hand open/close. The user command interface did not control the orthosis which provided gravity compensation for the elbow and wrist stabilization.

Surgically-implanted intracortical electrode arrays are more invasive but potentially offer more flexible control than EEG. A brain-machine interface with intracortical electrode arrays has been used by one research group to control shoulder, elbow, and hand movements (Ajiboye et al., 2017). Two 96-channel microelectrode arrays (Blackrock Microsystems, Salt Lake City, Utah) were surgically implanted on the participant's motor cortex. The participant's cortical signals were decoded into desired velocities of each joint, and the mobile arm support (shoulder) and predefined muscle stimulation patterns (elbow and hand) produced the desired movements.

3.3.3. Other interfaces

An additional option of the MUNDUS system (Pedrocchi et al., 2013) is to use an eye tracking system to make the same selections as in the Brain-Machine Interface option (selecting targets or “GO” and “STOP” commands displayed on a screen).

Voice commands act as the user command interface for a system that uses electrical stimulation for palmar and lateral grasping aided by a glove instrumented with force sensors along with a powered orthosis for elbow flexion/extension and forearm support (Varoto et al., 2008). The voice commands allow the user to start, stop, increase, and decrease muscle stimulation level for grasping patterns. In this system, the user also gets feedback on grip strength from force sensors that is displayed visually by LEDs (more LEDs lit for larger forces) or audibly by the frequency of a buzzer. The authors do not explicitly state how the elbow flexion/extension orthosis is controlled by the user.

3.4. Shared control methodology

Hybrid NMES-orthosis systems are envisioned to share the job of reanimating paralyzed limbs. The degree of sharing varies in the papers reviewed here, and is often determined by the class of orthosis that is integrated with NMES (passive, semi-active, or active). This section first outlines how NMES and robotic actuation are distributed to control the limb, then explains how each subsystem is independently controlled in state of the art hybrid NMES-robotic systems.

3.4.1. Distribution of actuation

In many implementations of hybrid NMES-robotic systems, the action of NMES and the robotic support are applied to independent tasks. This is often the case for passive orthoses that simply immobilize, stabilize, or support a joint against gravity, so that the action of NMES is more repeatable and reliable. For example, the iBCI + FES system (Ajiboye et al., 2017) and IST-12 with mobile arm support system (Memberg et al., 2014) both provided gravity support for the arm as subjects performed NMES-assisted motions of the various joints of the upper limb. In a similar approach, passive wrist orthoses were used to maintain a desirable wrist pose while performing grasping movements, such as in (Varoto et al., 2008) and (Rupp et al., 2013). Because these orthoses provide passive support against gravity, the hybrid system is calibrated with the arm support in place, negating the need for additional coordination between orthosis and NMES sub-systems at the time of operation.

Semi-active orthoses use brakes to hold the limb in place, reducing the necessary torques that must be generated by NMES to produce desired joint movements. For example, the iBCI + FES (Ajiboye et al., 2017) provided a brake on the elbow, and the MUNDUS (Pedrocchi et al., 2013) provided a brake for both the elbow and the shoulder. In these examples, the brake supports movement of a joint that is also actuated by NMES. This sharing of action allows the brake to hold the limb in position once the target position is achieved with NMES, enabling the muscles to relax and preventing fatigue. These systems alternate between NMES action and brake action in a coordinated fashion.

Active orthoses are able to move the joints of the upper limb through functional range of motion. As such, these systems can be used in a more integrated fashion to complement NMES, either implementing NMES and orthosis on different joints to achieve desired whole arm reaching and grasping, or sharing control between the two actuation strategies on the same joint. For example, several groups have activated grasping with NMES, while using an active orthosis to generate movements of the proximal joints of the upper limb (Varoto et al., 2008; Looned et al., 2014). Ajiboye et al. actuated grasping, wrist, and elbow movements with NMES, while providing humerus abduction/adduction with an active orthosis (Ajiboye et al., 2017). In each of these cases, a high-level control system coordinated the transition of active movements using rules to govern transitions. In each phase, either NMES or the orthosis was actively moving the limb, depending on the particular phase of motion. More recent work has strived to integrate the action of NMES and active orthoses simultaneously. For example, one group designed the shared control system between NMES and a robotic arm support to realize coordinated reaching movements across multiple joints actuated at the same time (Schearer et al., 2015). This system coordinated shared control by calculating the required torques for a movement, and optimizing the distribution of torque to favor NMES actuation over the robot. In another example, Wolf et al. simultaneously actuated the elbow with NMES and a robotic exoskeleton by combining the actions of the two subsystems, shown in Fig. 4, that were tuned independently (Wolf et al., 2017a, 2017b).

3.4.2. Control of subsystems

NMES and robotic systems execute low-level commands – amount of muscle stimulation (Fig. 5) or robot torque generation – in response to high-level intent – typically start/stop or proportional changes in movement commands – specified via a user interface described in Section 3.3.

In many cases low-level NMES commands are specified explicitly by the research team. To produce a motion, researchers start with an initial muscle stimulation pattern and then iteratively update the pattern until it produces the desired movement as in (Rupp et al., 2012). A more sophisticated variant is to use a computer simulation of the arm's musculoskeletal dynamics, define a desired movement, use an inverse dynamics solver to find the corresponding muscle activations (Blana et al., 2013), apply stimulation to achieve these activations on a real human participant, and then manually fine-tune the muscle stimulation to correct errors in movement due to differences between the computer model and the real person (Memberg et al., 2014).

Another approach is to use feedback control to adjust NMES commands in response to the arm's position as sensed by an orthosis that aids in the movement. A simple way to do this is to ramp up the stimulation level until a desired joint position is reached (Pedrocchi et al., 2013). A more sophisitcated feedback controller assumes a dynamic model of the joint to be moved and then uses pole placement to achieve a desired dynamic response when controlled by NMES (Pedrocchi et al., 2013).

More recent efforts have focused on selecting NMES commands automatically based on person-specific models. One approach is to learn a model of the arm's inverse dynamics – the shoulder and elbow torques required to achieve a specified arm motion – from motion capture data gathered while a robot applies a measured force to move a person's arm (Schearer et al., 2014). Using a similar data-driven model of the muscles' ability to produce torques during NMES (Schearer et al., 2016), NMES commands can be automatically chosen by minimizing the sum of squared muscle activations (or some other objective) that produce the torques required by the arm's inverse dynamics (Schearer et al., 2015). Alternatively, similar models can be combined with predefined muscle synergies to automatically choose NMES commands (Razavian et al., 2018).

For the most part, research articles on hybrid NMES/robotic systems refer to NMES inputs in terms of percent stimulation, activation level,

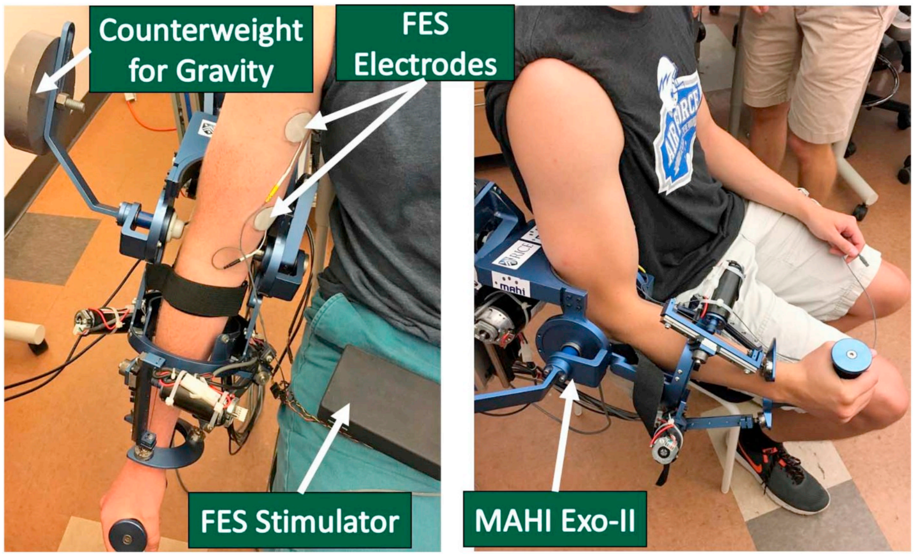

Fig. 4. Hybrid surface FES-Exoskeleton system for moving the elbow joint (Wolf et al., 2017a, 2017b).

or some similar term representing the amount of electrical stimulation that is delivered. Little detail is presented on the low-level specifics of the stimulation wave forms, frequencies, amplitudes, pulse durations, and other features that produce "percent stimulation" or some similar measure. We refer the reader to a comprehensive review of considerations for selecting these various low-level electrical stimulation parameters (Doucet et al., 2012).

Robotic support devices that interact with users are often controlled with some variant of position control (e.g. PID control introduced in Section 1), creating a mass-spring-damper relationship between the actual position and the desired position or trajectory as specified by user intent (Carignan et al., 2009; Kousidou et al., 2007; Staubli et al., 2009; Tsai et al., 2010). For robots that have well-known properties, this enables researchers to reliably and accurately follow intended trajectories without putting the patient in harm's way. It is also common to combine this control approach with feedforward actuation to offset

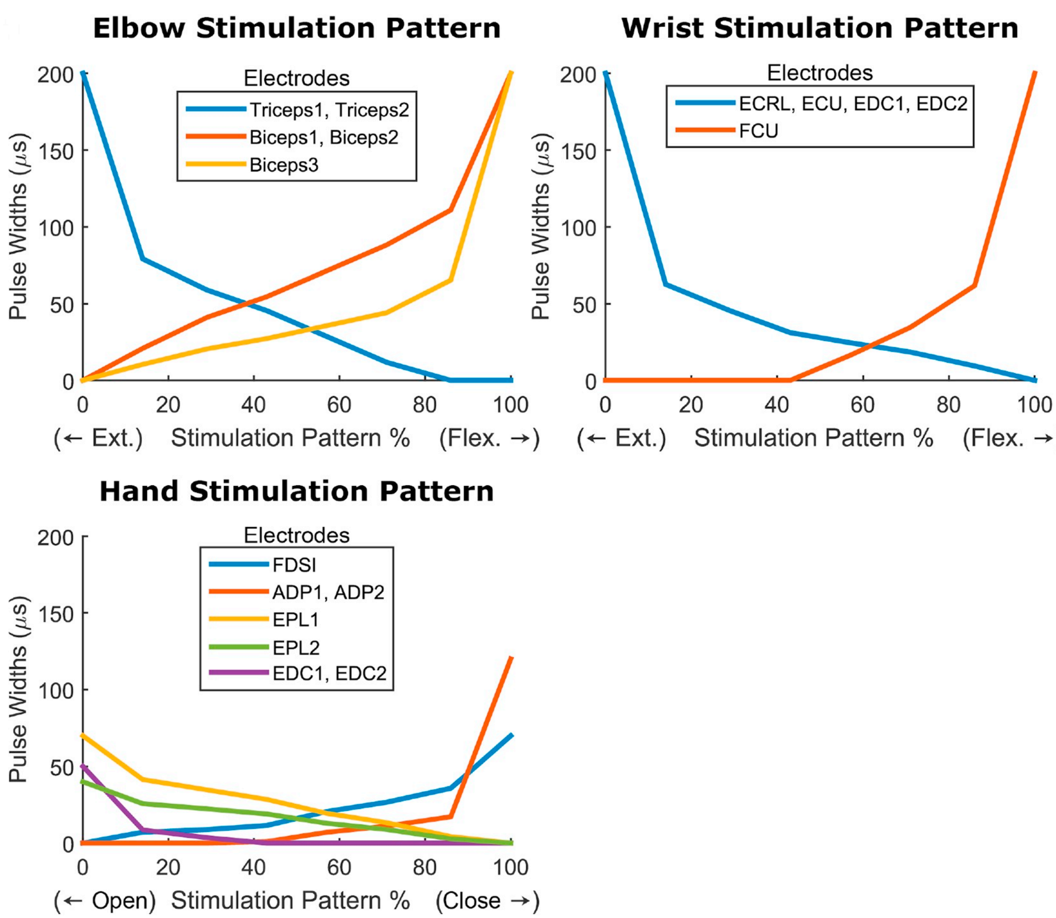

Fig. 5. FES Profiles for several joints, actuated by multiple muscles each, shown as a percent of stimulation pattern (Ajiboye et al., 2017).

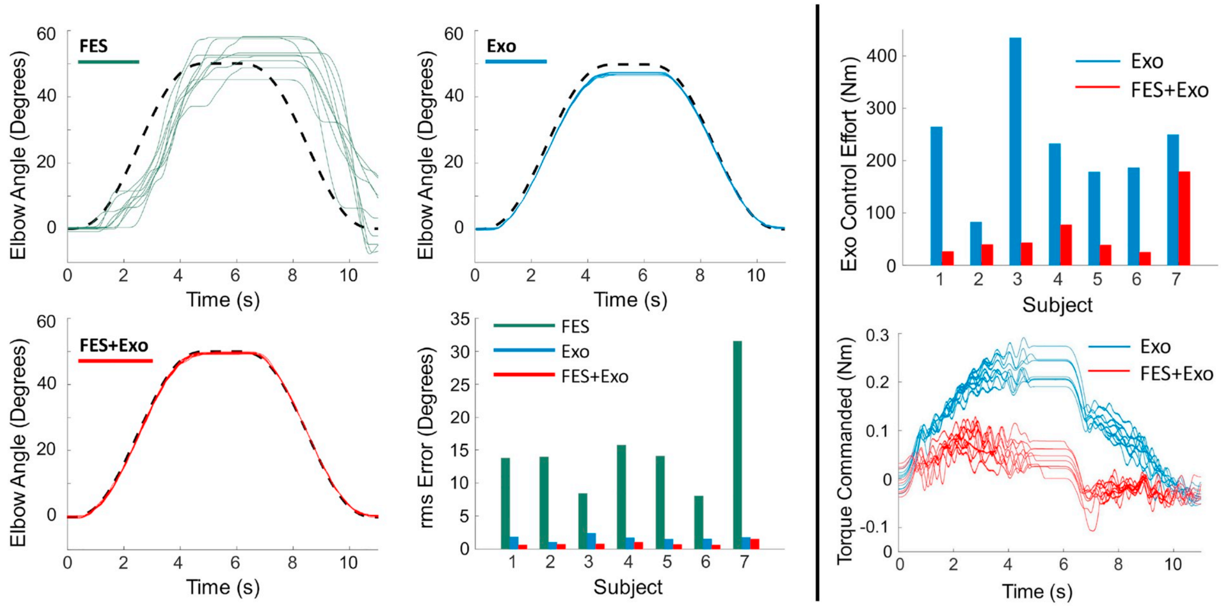

Fig. 6. Position (left) and torque (right) data for subjects moving elbow through a predefined trajectory (Wolf et al., 2017a, 2017b).

undesired gravity and friction effects (Proietti et al., 2015; Wolbrecht et al., 2008), which can be increasingly important when trying to assist someone with decreased functional ability. Only one paper from our review reported specifics of their robot control implementation (using PD control for the robot (Wolf et al., 2017a, 2017b) to track a trajectory). The remainder did not report on the control methodology for the robotic systems, though they most likely used some sort of a PID control scheme, as it is easy to understand and tune, and works well with most robotic systems, even with disturbances.

Neuromusculoskeletal modeling is being used in some applications of assistive or rehabilitation robots to improve the control of the robotic device. For example, one group has gathered EMG signals from users as activations in a Hill-type muscle model, and related the resulting neuromusculoskeletal torques from the model to joints torques of an exoskeleton, providing control based on a user's continuous intent rather than based on a predefined profile (Durandau et al., 2019).

3.5. Usability

The eventual acceptance of hybrid NMES and robotic systems depends largely on the balance between the functional ability gained from using a system and the expense of time, effort, and money required to use the system. Here we discuss time and effort required to don, doff, set up, and calibrate these systems.

3.5.1. Donning and doffing

Systems with surgically implanted recording electrodes for determining user intent and NMES electrodes for activating the muscles – the IST-12 (Memberg et al., 2014) and the iBCI + FES systems (Ajiboye et al., 2017) – require months for surgical preparation and rehabilitation before they can be used. They sometimes require multiple surgeries – two surgeries in (Memberg et al., 2014) and three surgeries in (Ajiboye et al., 2017) – to install different components depending on the functions targeted for restoration. After this initial installation period, these systems require very little time – typically less than one minute – for donning and doffing orthoses that provide support or further actuation.

The don and doff time for wearable systems – ranging from less than one minute to over one hour – depends largely on the complexity of the system. The MUNDUS system (Pedrocchi et al., 2013), which is intended for everyday functional use, has an adjustable orthosis that attaches to a person's wheelchair and electrodes for intent recognition and NMES. The multi-module version of MUNDUS for people with high tetraplegia can be donned in 35 to 45 min. A simpler version of MUNDUS for people with lower-level cervical injuries requires only 6 to 15 min to don. The TOBI system (Rohm et al., 2013) which is similar in complexity to the multi-module MUNDUS system, requires more than an hour to align an orthosis and position sensor and to install an EEG cap. Systems that use NMES electrodes only for hand movement and an orthosis for support or actuation of other joints (Looned et al., 2014; Scott et al., 2018) can sometimes be donned in less than a minute.

3.5.2. Setup and calibration

The time for setup and calibration depends both on the complexity

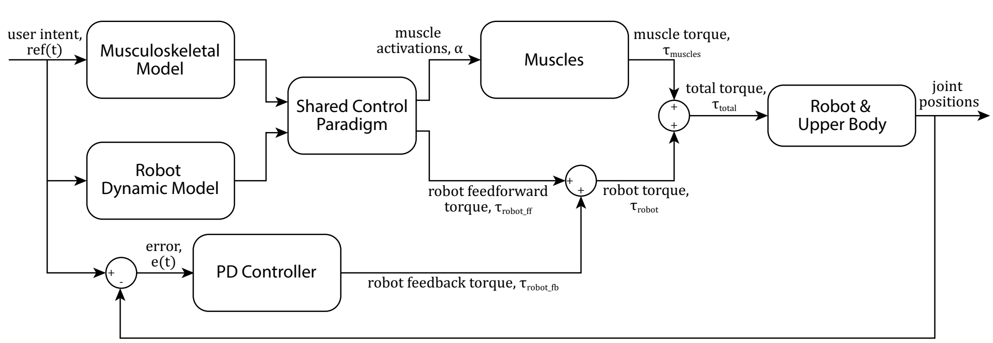

Fig. 7. Diagram showing a potential control scheme for sharing torque between NMES and an orthosis.

of the system and whether is is implanted or wearable.

Systems using brain-machine interfaces require significant daily calibration, even if they are implanted, as signals recorded from the brain signifying the same intent are not constant over time. The MUNDUS system with an EEG cap (Pedrocchi et al., 2013) requires a 20-min calibration. Although daily calibration is necessary, calibration time for other systems using brain-machine interfaces is not reported (Ajiboye et al., 2017; Looned et al., 2014; Rohm et al., 2013). Simpler interfaces with voice commands (Varoto et al., 2008) do not require calibration.

NMES systems also require calibration although calibration time is not typically reported. NMES systems with surface electrodes (Pedrocchi et al., 2013; Varoto et al., 2008; Looned et al., 2014; Rohm et al., 2013) typically require an expert to select current amplitudes and pulse widths to maximize muscle contraction that to some extent need to be recalibrated each time an electrode is removed and replaced during a later session. The time for this process is proportional to the number of electrodes used. Implanted NMES systems (Memberg et al., 2014; Ajiboye et al., 2017) require some calibration as muscle response may change over time, but electrode placement is for the most part fixed.

3.6. Engineering and clinical evaluation

For each of the hybrid systems, the research group must decide on a way to verify the capabilities of their system. The majority of systems in this review focus on identifying success based on participant-centric outcomes, assessing a participant's capabilities to perform a functional task using the proposed system. Other groups identified system-centric results related to the performance of the hybrid system itself, independent of the end user. In these cases, papers tend to report on the resultant motions or torques that the hybrid system was able to generate. In this section, we present a summary of these evaluation methods, grouped as such.

3.6.1. Participant-centric assessments

There are various ways that success has been recorded for participant-centric assessments. The most basic metric used to validate hybrid systems in these cases was the number of successful attempts in performing a proposed functional task. These assessments were reported for systems intended to assist movement. Groups either reported success as a binary result, with subjects either completing a functional task or not (Rohm et al., 2013; Ajiboye et al., 2017), or used a three-category scoring system, where a group of experts declared an attempt as unsuccessful, acceptable, or successful (Pedrocchi et al., 2013). Other groups reported the time it took subjects to complete a functional task, or subtasks as a part of a single functional task (Ajiboye et al., 2017; Looned et al., 2014). Functional tasks used for participant-centric assessments mostly focused on capabilities in ADLs, such as eating (Rohm et al., 2013; Memberg et al., 2014), drinking (Looned et al., 2014; Ajiboye et al., 2017; Pedrocchi et al., 2013), and grasping (Pedrocchi et al., 2013) tasks.

In cases where the NMES-orthosis system is intended to serve as a rehabilitation aid, typical clinical assessments are reported. For example, Scott et al. focused on rehabilitation rather than assistance and reported results based on changes in validated functional outcome measures after treatments (Scott et al., 2018). The metrics reported include portions of the Stroke Impairment Assessment Set, the Simple Test for Evaluating Hand Function, Active and Passive Range of Motion, Modified Ashworth scale, and Functional Independent Measure metrics. A summary of participant-centric assessment outcomes for the systems reviewed in this paper are included in Table 1.

3.6.2. System-centric assessments

The most common reporting metric for system-centric assessment is RMS position error, a means of reporting the accuracy with which the NMES-orthosis system can achieve a desired movement, either throughout the movement (along the path) (Wolf et al., 2017a, 2017b), or at the final target location (Pedrocchi et al., 2013; Wolf and Schearer, 2018). Torque measurements are also provided throughout movements by some groups (Wolf et al., 2017a, 2017b; Memberg et al., 2014). An example of system-centric position and torque results are shown in Fig. 6.

4. Discussion

In recent years, there has been increased interest in applying NMES in combination with robotic devices to reanimate paralyzed limbs after spinal cord injury. The motivation for such work is strong - rising health care costs and the need for constant care to perform the necessary activities of daily living mean that if technology can restore basic reaching and grasping function to an individual, they can enjoy an increase in independence and a decrease in dependence on full-time care. Despite these strong motivating principles, restoration of functional reaching and grasping, demonstrated across a significant population of motor-impaired individuals in a robust fashion, remains a lofty goal. Still, important foundations have been laid, as highlighted in this review.

We have seen, as of late, hybrid NMES-orthotic systems applied to a broader range of impairments, and expanded use for therapy in addition to movement support and assistance. Still, most of the research papers reviewed here feature case studies or case series that report feasibility of NMES combined with robotics for rehabilitation, or document modest success at achieving reaching or grasping function in individuals with SCI. Further work is needed to more robustly demonstrate the potential of hybrid NMES-orthosis systems.

Despite significant engineering advances in recent years, component technologies often suffer from the so-called Goldilocks Principle, with readily available commercial devices failing to offer the tunability needed to achieve useful movement across a broad range of individuals, and custom hardware requiring significant technical expertise to implement and operate in a repeatable and reliable manner. Ideal scenarios of hybrid NMES-orthosis systems envision the user interface to respond intuitively to the end-user's intent; however, due to complexities with system integration, novel interface methods that capture human intent have been limited, falling short of the goal of true integration of man and machine, and introducing additional feasibility challenges through the added complexity of sub-system integration. To date, hybrid NMES-orthosis systems divide up the tasks of reach and grasp such that true sharing of limb movement control is not fully realized. Researchers are just beginning to explore the potential benefit of seamless integration of muscle stimulation and orthotic support. As most of the reported systems are laboratory prototypes with limited clinical feasibility testing, much opportunity lies in improving usability of these systems, both from a wearability standpoint and an operational one, so that the technology can translate beyond the lab to the clinic and even the home. Finally, evaluation of these hybrid systems is inconsistently carried out and reported, highlighting the need for better standardization in system evaluation and metrics that capture both the performance of the hybrid system and the functional gains realized by study participants.

In this section, we discuss the current state-of-the-art from each of these topical perspectives, and propose future research directions and necessary next steps to move the field of hybrid NMES-orthosis systems for upper limb movement support forward.

4.1. Application domains

The case for hybrid NMES-orthosis systems to support and potentially restore upper limb movement capability following neurological injury is clear, but research advancements are in their infancy. We presented three objectives across a spectrum of movement impairment severity: using NMES-orthosis systems to replace lost function, to support reduced function, or to restore function through therapeutic interventions. While this review has focused on NMES-orthosis systems for individuals with spinal cord injury, researchers have applied these systems to other impairments, including rehabilitation of the upper limb following stroke (see, for example, the review by Resquín et al. (2016a, 2016b)). Because of the relatively small number of research groups exploring NMES-orthosis systems for individuals with SCI, this review has focused on promising preliminary outcomes, and recommends areas of focus for ongoing research. The sparse amount of literature means that it is difficult to draw general conclusions on the suitability of NMES-orthotic systems for a given level of injury or severity of impairment. Another challenge in assessing the current state of the art more broadly is that groups tend to focus on specific tasks (reaching alone, or grasping alone) rather than full functional restoration of the upper limb. The most advanced sub-field is the restoration of reaching (supported by passive or powered orthoses) and grasping (supported by NMES) in individuals with implanted electrodes, though due to the limited number of individuals with implanted NMES systems and the complexity of sub-system integration, research along these lines is not easily replicated.

Future work should explore the application of NMES-orthotic systems across a more diverse subject pool (expand the level of injury, or the degree of impairment) so that it is evident how best to match the technology to the desired functional outcomes. Additionally, the utility of surface versus implanted NMES systems for these same expanded populations should be explored, since end users may not be able or willing to undergo the surgical procedures required for implanted electrodes. These types of studies would improve the ability of researchers to make more informed choices regarding the application of hybrid NMES-orthotic systems to particular impairment profiles and desired functional outcomes.

4.2. Component technologies

The vast majority of hybrid NMES-orthosis systems use surface electrodes to achieve muscle stimulation, given their widespread availability. Surface electrodes and the accompanying electrical stimulation systems that are used to generate the stimulation signals are commercially available, but commercial systems offer limited user flexibility over the various stimulation pattern options. As a result, some groups have developed custom stimulation hardware, enabling users to tailor the stimulation to the desired use case and subject capabilities. Custom stimulation systems are also able to support closed-loop control implementation, where the stimulation patterns can be adapted automatically and in real-time in response to changing motion objectives, muscle fatigue, or other circumstances. Customized hardware often requires that the user have a high level of expertise and knowledge about the electrodes, placement, and stimulation patterns necessary to achieve desired movements. Further, custom stimulation systems have the potential to inhibit rapid advancement of the field, since duplication of results by multiple groups is not achievable without clear dissemination of the makeup and configuration details of the particular system reported in any one article. Implanted electrodes offer greater specificity and repeatability of muscle stimulation due to their precise location on the muscle body or directly on the nerve that generates muscle contraction, at the cost of a surgical procedure.

Future research directions for NMES systems might address these current tradeoffs by improving the tunability of custom stimulation systems, or providing open source resources for developers who want to duplicate custom systems. Electrodes that can provide the stimulation specificity of implantable systems without the need for invasive procedures would also advance the field.

To physically support movement of the limb when using NMES, orthoses are fitted to the individual. When the objective is to immobilize or stabilize a joint, standard off the shelf orthoses are sufficient to realize this aim. Active movement support necessitates more complex and powered orthoses, robotic support devices, or exoskeletons. Often such hardware is not commercially available, or if commercially available, the devices offer little in the way of customization. Therefore, like with the custom NMES systems, custom active robotic support systems have been developed to enable active support with a device that is uniquely suited to the individual and desired use case scenario. These customized robotic systems require greater expertise to operate, are often relegated to the laboratory setting since hardware lacks robustness, and limit large scale advancement since each research group has their own customized system configuration.

Current robotic support systems for the upper limb also tend to be rigid and interfere with the natural reaching motion intended by the FES system, leading to larger trajectory errors for the FES controller to correct and more additional required work by the muscles themselves (Kobravi and Erfanian, 2009; Ajiboye et al., 2017; Memberg et al., 2014; Pedrocchi et al., 2013). The ability to integrate external actuation in a more wearable, compliant exoskeleton is critical to successful useful movements in home environments. As has been shown for the lower limb (Asbeck et al., 2015), a soft exosuit imposes fewer constraints to the smooth, natural joint motion than does its rigid counterpart, but the torque contributions of fully soft exosuits are likely not sufficient to achieve full reanimation of the limb since FES will induce muscle fatigue, and the robotic system will have to fully support movements as the muscles recover. Advancements in actuation technologies have ushered in novel compliant and wearable robotic device designs for the upper limb that offer sufficient torque output to support FES in reanimating the limb using remotely located actuators and Bowden cable transmissions (see Rose and O'Malley (2019) and Kadivar et al. (2017) for examples). Development of soft exosuits for the proximal joints of the upper extremities is only just beginning, and very few clinical trials have been conducted with individuals with motor impairments (Kadivar et al., 2017) (shoulder and elbow), (Dinh et al., 2017) (elbow only). Research along these lines should continue, as the approaches seem promising. Advancements in these robotic component technologies that are lightweight with less bulk, yet with sufficient torque output capabilities to reanimate the limbs, would move us closer to translating these technologies from the lab to the home, and would enhance functional independence in these individuals, thereby decreasing the need for full-time caregivers.

4.3. User command interfaces

Each of the user interfaces discussed has practical limitations. Volitional EMG is best when the spinal cord injury is incomplete. In this case NMES or a powered orthosis can amplify the weak but still existing natural signal to activate a muscle below the injury. With complete spinal cord injuries this direct amplification is not possible, and volitional proximal muscles can be used to control NMES or an orthosis of a distal joint (e.g. using deltoid EMG to control elbow movements). As the spinal cord injury gets higher, fewer volitional muscles are available to control a greater number of paralyzed joints.

Brain-machine interfaces are an alternative for people with complete and/or high spinal cord injuries. There is an inherent trade off between invasiveness and the control flexibility of an interface. Non-invasive EEG is typically used only to start and stop a movement or switch between modes of operation, whereas an invasive intracortical interface can potentially offer continuous control of multiple joints. Brain-machine interfaces currently require regular daily calibration but research into robust and adaptive decoding methods offers a bright prospect for less-frequent calibration (Lotte et al., 2018; Azab et al., 2018).

It is unclear at this point how a user interface might allow a person to control NMES and an orthosis simultaneously or whether this ability is even desired. In the reviewed research, user interfaces typically only actively control either NMES or an orthosis. One exception is the work in (Ajiboye et al., 2017) in which an intracortical BCI controls both

NMES and a powered othosis, but the modes of actuation occur for separate degrees of freedom. As the field moves forward, it will be necessary to continue to explore novel methods for detecting movement intent that don't require residual muscle activation or EMG. Additionally, the ideal user command interface should adapt to changing neural signals, either due to normal day-to-day variability or to changing user capabilities, reducing the need for constant recalibration. Further, as we see more coordination between the NMES and robotic sub-systems, it would be ideal if the user interface might allow a user to determine the gross actuation of a joint, with the distribution of actuation between NMES and orthosis determined by a predefined algorithm.

4.4. Shared control methodology

The majority of hybrid NMES-orthosis systems reviewed here take the task of reanimating the limb and use a divide and conquer approach. In other words, systems use NMES to reanimate some movements of the upper limb, and rely on an orthosis to stabilize, support, or actuate other motions.

As an independent actuation technique, powered orthoses have the advantage of generating movements with high accuracy and repeatability, but with the disadvantage of requiring large actuators and accompanying power requirements to generate the torques necessary to move the limb through its range of motion. NMES can provide actuation with very little power requirement or mechanical footprint. However, it is an open research challenge to produce precise and repeatable motion and force output with NMES, and fatigue and denervation cause NMES to be ineffective for some muscles and/or people.

A largely unexplored yet promising implementation of hybrid NMES-orthosis systems uses these actuation approaches on the same joints of the upper limb, and triggers their action simultaneously. This technique aims to combine the advantages of each of the independent use cases, while reducing the inherent limitations. For example, NMES can be used to generate torques for gross movements of the upper limb, and the active orthosis can use its onboard sensors to refine the motions to achieve precise positioning for functional tasks. Further, the active orthosis can be used to compensate for NMES when muscle fatigue sets in after repeated stimulation. By using these actuation techniques in concert together, we envision that the torque and power requirements of the active orthosis would be offset by the contributions of NMES, enabling more lightweight powered orthoses to be used, such as the concept shown in Fig. 1, and ushering in the potential for deployment of hybrid NMES-orthosis systems outside of the typical clinical environment.

An illustration of this control framework that coordinates the action of NMES and robotic support is shown in Fig. 7. A version of this framework has already been demonstrated in practice to control arm movements with FES aided by an end-effector robot (Schearer et al., 2015). This coordinated control concept has been explored further for lower-limb devices than for upper limb devices. A recent article describes a general framework for controlling a hybrid NMES-robot system for lower limb rehabilitation and tests the strategy in computer simulation (Romero-Sánchez et al., 2019). In this framework, an inverse dynamics model determines joint torques to be produced by the combined actuation of NMES and a robot, an optimization problem is solved to distribute the torque between the robot and muscles, another optimization problem is solved to determine the contributions of individual muscles, and each muscle's activation dynamics are inverted to choose stimulation commands.

Limited practical demonstrations of this general hybrid strategy, mostly for lower extremity hybrid systems, have explored two key challenges to implementation: 1) the need to predict the response of muscles to NMES and 2) the need to choose an appropriate objective by which to determine sharing of the load between each muscle and each robot actuator. One example of this approach is presented in Bao et al. (2019), where a recurrent neural network is used to identify muscle dynamics and a feedforward neural network is used to allocate effort between muscles and electric motors for a hybrid system to control a single joint of a healthy participant. Another method is to use the idea of dynamic postural synergies to choose between muscles and electric motors as in (Alibeji et al., 2018).

A promising approach for controlling hybrid neuroporstheses is the use of real-time neuro-musculoskeletal simulations (see Pizzolato et al. (2019) for a brief review). These real-time models can be tailored to specific people to predict movements evoked by muscle and robotic actuators and to experiment with different strategies to balance NMES and robotic actuators. Although this tailoring can be facilitated by sensing joint moments with a robot, they often require EMG data from a user, hence they are referred to as EMG-driven models. The use of EMG-driven models (Durandau et al., 2019; Sartori et al., 2016) may be less useful for people with complete spinal cord injuries who have weak or non-existent EMG signals from paralyzed muscles. However, reflexive (spastic) and even voluntary muscle activation exists in incomplete spinal cord injuries, which is where EMG-driven NMES modeling may be of use. Furthermore, NMES is reflected in EMG, so EMG-driven NMES modeling can be used to predict the NMES generated torque.

Much work is still needed in hybrid neuroprostheses to identify effective control strategies to share the action of reanimating the upper limb between these two actuation strategies. In lower limb systems, researchers have exploited the periodic nature of walking to estimate muscle fatigue after each gait cycle and update FES and robotic control commands for hybrid systems (del Ama et al., 2014; Ha et al., 2016). Upper extremity movements are typically not periodic and involve many biarticular muscles. It is not clear how data from one reaching movement might help predict muscle response during another movement and how to update muscle models simultaneously when an exoskeleton applies fewer torques than there are muscles. In addition, we must continue to explore optimization goals, deciding whether to optimize for reduced muscle fatigue, reduced external power requirements, or improved precision of upper limb movements, among other possible objectives.

4.5. Usability

The most notable distinction in usability we make in this review is between wearable devices and implanted devices. Implantable NMES systems for arm and hand function have been commercially available for decades with the Freehand System receiving FDA approval in 1987 (Keith et al., 1989). While there is substantial risk in any surgery and the utility of devices is not guaranteed, implantable NMES systems can be robust and often last for many years. Alternative actuation methods include spinal stimulation, which has been implemented with implantable systems for decades (North et al., 1991) and optical stimulation (Zhao, 2017), for which implantable devices are in their infancy. Implantable myoelectric user interfaces have existed for many years for control of prostheses and NMES (Weir et al., 2003), but brain-machine interfaces have only more recently been successfully implanted for controlling arm movements (Collinger et al., 2013a). Cortical electrodes can also be implanted, but their development is at an early stage. Implantable systems offer very targeted actuation allowing for more precise control and everyday usability not available in external systems. However, they also incur risks, time, effort in rehabilitation, and money inherent with surgical interventions.

Wearable systems lack the risk and expense of a surgical intervention and are potentially available to many more users than implanted systems. As the amount of assistance required increases, powered orthoses require heavier, more powerful, and more numerous actuators, making these systems less useful for activities of daily living. Further, wearable systems that provide significant function require a great amount of expert time to position and calibrate NMES electrodes, user interface sensors, and orthoses, making them impractical for daily use in functional activities. There is great potential for engineering advances that make don/doff and calibration require less time and expert input, making wearable systems more useful on a daily basis.

One potential avenue for reducing the need for expert input is developing intelligent NMES control strategies that adapt to inconsistent electrode or sensor placement and to the daily changes in muscles' response to electrical stimulation. These include iterative learning control, where stimulation commands adjust over time during repetitive motions (Freeman et al., 2009), and reinforcement learning, where stimulation is updated based on success or failure in achieving some objective (Jagodnik et al., 2017). These strategies and other intelligent adaptive strategies have seen tremendous recent progress in robotics. Future research should focus on translation of these strategies to NMES control, which has been slow due to additional physical and practical complexity of controlling arm movements with NMES.

Even with adaptive strategies, placement of electrodes on the surface of the skin and determination of current amplitude and pulse width ranges for individual muscles on a day-to-day basis is a practical challenge for non-implanted NMES systems. Electrodes may not provide sufficient activation if not near a muscle's motor point, and poorly placed electrodes may spill current to adjacent muscles making independent muscle stimulation difficult and control more complex. Advances addressing this problem include probing for motor points with an electrode “pen” (Gobbo et al., 2014) using large arrays of electrodes and using pattern recognition to determine which electrode combinations evoke the largest independent responses (Bouton et al., 2016), and wearable electrode sleeves which are typically designed to include sensors such as EMGs (Gonçalves et al., 2018), but have also been used for stimulation (Hara, 2010). Future research directions should focus on translating these technological advancements to hybrid NMES-robotic systems.

Advances in robot actuation and design increasingly are focusing on improving wearability through adjustable components that fit snugly to the body, as in Kadivar et al. (2017) and Rose and O'Malley (2019), which both use ratcheting cabling and lacing systems that allow for an adjustable, personalized fit even for those with reduced dexterity. These systems also use remotely located actuators to reduce the weight borne by the wearer while still offering sufficient torque to reanimate the limbs. These approaches still suffer from difficulty in donning and doffing the robotic exosuit due to the complex routing of the transmission cables, and pose difficult control challenges due to the frictional losses in the cable transmission systems. Another challenge to wearability of the robotic device is power. Power must be supplied to these actuators either with remotely located batteries or through some tethered power supply, limiting mobility and independence. Therefore, continued investigation into novel device and transmission design is necessary to improve wearability, while also considering ease of donning and doffing the robotic exosuit. These advances will help to support the translation of hybrid NMES robotic systems out of the research lab and clinic and into the home.

This review does not report on user preferences. The balance between the amount of function that a device provides and the amount of risk, time, and cost a person incurs to use a device is largely dependent on the individual's specific preferences and severity of injury. For instance, a person with a complete C4 injury might be more open to a brain surgery to implant a brain-computer interface or a long don/doff time than a person with a less disabling injury. Keep in mind that spinal cord injury is inherently heterogeneous even at the same injury level and ASIA classification, and individual people with similar injuries might have different tolerance for difficulty of use or goals for functional recovery. We refer the reader to two prominent surveys on user preferences in people with spinal cord injuries (Anderson, 2004; Collinger et al., 2013b).

4.6. Engineering and clinical evaluation

There is a wide variety of metrics used for evaluating the usefulness and effectiveness of the proposed hybrid systems. These generally fall under two categories - one that focuses on the patient-centric outcomes observed by the performance of tasks by the end user, and the other focused on the system-centric performance of the hybrid NMES-orthosis system, independent of the end-user. Due to wide variability in these evaluation techniques, it is generally difficult to compare performance across hybrid NMES-orthosis systems. Therefore, there is a need for unified metrics in evaluating these systems to identify the state of the field and where it should move in the future.

The authors recommend a phased evaluation approach based on the stage of development and implementation of the proposed system. In early phases of development, it is most appropriate to evaluate systems according to quantitative system-centric metrics, especially when evaluation is primarily performed with healthy subjects. In this stage, it is useful to identify how well the hybrid systems are able to complete general movements they are asked to perform, irrespective of the injury that may add confounding factors. Such performance measures include torque, and position error throughout movements, with the inclusion of statistical measures to give a sense of repeatability. Smoothness can also be a useful metric to report on the quality of resultant movement, especially given the potential for competing actions of the two types of actuation technologies. Many of the reported systems also use some sort of intent detection, where the accuracy and repeatability should be reported, as it plays an important part in the success of the system (see the review by Losey et al. (2018)). Gathering data before assessments with impaired subjects allows for an evaluation of how impairment may influence the performance of these hybrid systems.

As hybrid systems become more refined, and after evaluation of subcomponents and system-level operation as suggested above, it is then appropriate to evaluate performance with respect to how they can assist impaired populations in achieving functional movement and task completion. These patient-centered evaluations may use standard Clinical Outcome Assessments (COA) to evaluate the ability of patients who suffer from upper-limb impairment due to SCI (Jones et al., 2018). However, we acknowledge that there is not consensus regarding preferred clinical assessments to report outcomes. Some COAs that the authors would recommend as relevant for the purpose of assessing functional capabilities include Spinal Cord Independence Measure version III (SCIM III), Capabilities of UE Function Test (CUE-T), and Spinal Cord Injury-Functional Index (SCI-FI). Each of these assessments identify some aspect of functional capabilities of the upper extremities, with SCIM III focusing on general independence levels in ADLs, CUE-T focusing on more specific functional abilities, and SCI-FI measuring self-care and fine motor abilities, assessed by the patient themselves. We recommend that future research assess COAs based on the design and intended application area of the hybrid system.

5. Conclusions

Individuals with spinal cord injury and resulting upper limb impairment would benefit from technological interventions that restore their reaching and grasping capabilities, since their dependence on caregivers would decrease. Neuromuscular electrical stimulation can be used to generate movements from the individual's own muscles, and when combined with orthotic arm supports, either passive or active, can elicit reaching and grasping capabilities in a functional workspace. Hybrid NMES-orthotic systems have been demonstrated in a number of small scale clinical trials and feasibility studies. In this review, we have identified the state of the art in hybrid NMES-orthosis systems for restoration of upper limb movement in individuals with spinal cord injury. These systems show great promise for restoring independence in individuals with spinal cord injury. Through our discussion of relevant application domains, component technologies, human-machine interface approaches, shared control techniques, usability, and common evaluation methods, we have identified future research directions needed to advance the field.

Clinical demonstrations of hybrid systems are limited and should be pursued more extensively. Advancements in NMES component technologies are needed to improve tunability and specificity of stimulation without need for invasive electrodes. Advancements in robotic component technologies are needed to reduce size, bulk, and weight of robotic support systems. The interface between human and hybrid NMES-robotic systems should detect user intent in an intuitive and unobtrusive way, and adapt to changing neural signals. The performance of the NMES-robotic system as a whole will be enhanced when the control of each subsystem is truly integrated to optimize the performance of each, for example trading actuation from stimulation to robotic support to allow muscles to recover from fatigue due to repeated stimulation. Usability of these hybrid systems remains a challenge, and future research should aim to improve donning and doffing of the stimulation subsystem in a way that still guarantees repeatable and robust performance, along with a focus on wearability of both the stimulation and robotic subsystems. Finally, evaluation of these systems needs to consider both the performance of the engineered system, and the functional performance of the user assisted by the hybrid NMES-robotic system, using standardized methods and assessment tools. We are confident that the full potential of these technologies will be realized when they are truly integrated to leverage the strengths of each component technology, and when consistent evaluation methods are employed and reported.

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