Achieving Neural Compatibility With Human Sensorimotor Control in Prosthetic and Therapeutic Devices

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(Invited Paper)

***Abstract*—Prosthetic and therapeutic devices have been developed to ameliorate the quality of daily living for people with amputation or neurological disorders. However, many of them fall short of functional benefits, and therefore, are frequently rejected by users due to awkward control, or no awareness of interaction during tasks. Traditional wisdom in the design of prosthetic and therapeutic devices may have emphasized the need to provide users with apparatus that replace or assist motor ability. Rather, the notion to achieve neural compatibility with the existing sensorimotor system has not been well recognized. We argue that providing biomimetic control and sensing capacity to prosthetic and therapeutic devices can enhance their neural compatibility, and therefore, can yield greater functionality in performing activities of daily lives, or in rehabilitation training. In this paper, the authors will present a range of neural technologies that may allow implementation of biomimetic sensorimotor control, including natural sensory feedback, neuromuscular like compliant control, natural module of synergy-based control, as well as advanced neural signal processing techniques. Based on the evidence in our research and in literature, we propose that achieving neural compatibility with the existing human sensorimotor system should be the ultimate goal of prosthetic and therapeutic devices.**

***Index Terms*—Neural prosthetics and therapeutics, functional electrical stimulation (FES), sensory feedback, compliant control, EMG.**

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I. Introduction

With great passion, engineers, electrical or mechanical alike have put up their expertise to develop prosthetic or therapeutic devices for people with disabilities (PWD), hoping that these devices will enhance their quality of life. In spite of many successful examples, many other devices, such as myoelectrical prosthetic hand, have not been well received by PWDs, or therapists. The reasons may range from high cost, low effectiveness, but mostly from inadequate functionality and difficulty to control. The wide variety of factors to consider in design, test and manufacture of prosthetic and therapeutic devices have made these devices most time-consuming products to market among medical devices. For example, myoelectrically controlled prosthetic hand has gone through more than a half century of evolution, and is still yet to show an acceptable performance [1]–[3].

Another kind of prosthetic devices is called functional electrical stimulation (FES), which uses a low level of electrical current to activate nerve fibers [4]. This technology is also known as neuromuscular electrical stimulation (NMES) when applied for motor rehabilitation. It was the most exciting development of neurotechnology from neuroscience laboratories in 70's and 80's of last century. FES had been viewed as the most promising means for spinal cord injury patients to regain stance and hand functions [4], [5]. However, FES based devices for therapeutic applications are still not widely accepted by rehabilitation community and medical insurance alike [6]. There has been little consistent evidence from previous studies that FES is effective for upper limb motor recovery after stroke [7]–[20]. Reconciling these findings is difficult, because protocols and patient population are heterogeneous across studies [13], and optimal stimulation parameters are highly individual and influenced by the pathology [21]. It is difficult to differentiate whether improvements are attributable to FES [22] or spontaneous recovery [7].

In the past decades, new neural technologies, such as brain-computer interface and microstimulation of brain and spinal cord, have steadily progressed as promising ways to interact with the nervous system [23]–[27]. Concurrently, system's neurophysiology has made significant stride, consolidating a new concept of modular organization as the principle of multiple muscle control in the sensorimotor system [28]–[30]. Yet, how these innovations in neural technologies and theoretical motor physiology can join hands to help advancing neural prosthetic and therapeutic devices is still staggering.

Increasing evidence has shown that prosthetic or therapeutic devices need to extract from and feed back to the users more accurate neural information, so as to improve functionality, acceptance by the users [31]–[33], and clinical efficacy in therapeutic training [34], [35]. Such efforts are pushing the envelopes of evolution of prosthetic and therapeutic devices. This paper proposes a new concept with regard to the neural coupling between human sensorimotor system and external devices, the neural compatibility, which is referred to as the degree of congruence (or similarity) in the efferent and efferent neural information communicated between the human sensorimotor system and the prosthetic or therapeutic devices as in the intact central and peripheral sensorimotor system. Here we argue that achieving neural compatibility with the existing sensorimotor control system should be an important principle, among others, for designing neural prosthetic and therapeutic devices.

This paper discusses several aspects of neural technologies that can improve neural compatibility for the neural prosthetic or therapeutic devices. First, in Section II, a brief review will be presented on the computational model of neural control of movements that enhances our understanding of functions of human sensorimotor system. In Section III, neural compatible techniques of sensory feedback to provide touch sensation for transradial amputees will be described. Section IV of this paper will discuss a human reflex-like strategy of compliant control for prosthetic hands. An analysis of motor unit firings from high density EMG signals in Section V will further the concept of biomimetic control for prosthetic hands. Finally, we will introduce a recent progress in synergy-based FES that improves motor learning in rehabilitation training for patients post stroke. The paper will close with a summary of neural compatibility for emerging technologies and a perspective for future applications.

II. Human Sensorimotor Control and Models

Understanding how humans make coordinated movements and dexterous manipulations has been a major neuroscience frontier since Sherrington [36], Mayeri *et al.* [37], and Koester *et al.* [38]. Over the past century, accumulating evidence has begun to unveil the perplex of how the complex human body as a mechanical plant with multiple joints and muscles can be controlled by the brain. Add to that complexity is the multiscale nature of neuromuscular system, which gives rise to the fundamental compliant property of the neuromuscular system. In addition, there is the need of the brain for rapid information of motor action and interaction with the environment during motor adaptation or learning, which underlies our ability of motor skill acquisition and rehabilitation. As a consequence, a prosthetic/therapeutic device is interfacing with these properties of the sensorimotor system of patients. If the device emphasizes merely the replication of the ostensible profile of a movement, it may miss the goal to excite the ability of motor relearning, thus, suffering rejection by or no response from the sensorimotor system of the patients. This may explain the high rate of rejection for myoelectrical prosthetic hand [39], and low effectiveness of many therapeutic devices in clinical trials.

However, nature has offered a viable solution to reconcile the multi-target, multi-scale nature in sensorimotor control, that is to divide and share the responsibility among modular components organized in hierarchies, as illustrated in Fig. 1. The sensorimotor system in Fig. 1(B) shows the neuroanatomical structure of the sensorimotor control system, which is organized in a hierarchical order of brain, spinal cord and peripheral system [40]. Somatic voluntary movement is realized through coordinating descending motor signals and sensory feedback in three levels (Fig. 1(A)). The brain designs the task planning based on the external task requirement. The central command is the efferent from the brain to the peripheral system via spinal cord (propriospinal neuron network and spinal regulator). The muscles actuate the joints to generate movements. Simultaneously, the cutaneous receptors and proprioceptors of peripheral system transmit the peripheral information back to the central nervous system (CNS). The spinal cord (propriospinal neuron network and spinal regulator) and brain system may modulate the descending command based on the afferent information to update the voluntary movements.

For the purpose of transcending the performance of therapeutic and assistive devices, it becomes increasingly crucial to leverage the mechanisms of human sensorimotor control [34], [41]–[43]. However, our understanding of voluntary and reflexive control of movement is limited due to lack of detailed neural information, which usually must be obtained via invasive neural recording in human. Fortunately, mammalian experiments have revealed the instrumental elements of sensorimotor control: motor units with patterned recruitment order [44], spinal neural circuitry [45]–[47], spindle transduction [48], [49], muscle force generation with viscoelastic properties [50], [51] and so on. By examining abnormality in features of reflex loop, such as delay and gain, we realize that the spinal reflex system has inherent limitations, such as instability and abnormally high gain [52]–[54]. Its regulatory functions cannot be over emphasized as originally perceived [55]. The real function for the spinal circuits may lie in regulating compliant property of the neuromuscular system, so that adaptive tuning of compliance can be achieved [56].

A minimalist model of human sensorimotor system is expected to characterize a monosynaptic reflex loop, which quantifies spiking neurons [57], [58], spinal circuitry [59], [60], skeletal muscles [61]–[63], proprioceptors [64]–[67], joints with biomechanical properties [68], [69]. The advantage of including spiking neurons instead of rate-based models is to allow for timing-sensitive scenarios such as spike-timing-dependent-plasticity (STDP) [70], which has been shown important in explaining the longitudinal progression of neurological disease [71]. A number of models have been developed for

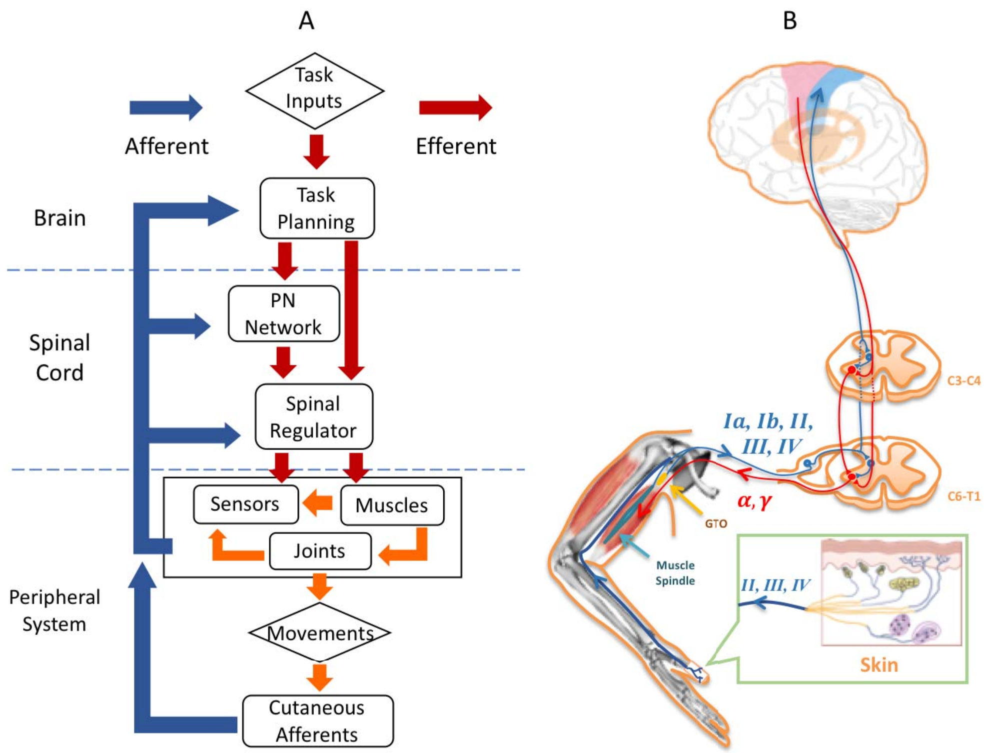

Fig. 1. A model-based view (A) of human sensorimotor control for movements in upper extremity (B). At the brain level, motor commands for accomplishing a task are computed based on inputs through a collection of complex structures, including sensory and motor cortices, basal ganglia, cerebellum, brainstem, etc. The computed motor commands are delegated to the sub-cortical and spinal structures, parts of which pass through a C3-C4 level propriospinal network that screens and distributes the commands, while other parts directly reach the spinal regulator. The spinal regulator executes the descending motor commands via a peripheral system, which is capable of establishing muscle tensions through closed-loop control. Due to the mechanical coupling among muscles, tendons, joints and skeletons, it eventually produces motor consequences of either a movement or a maintained posture; in addition, the sensory consequences are picked up by various receptors and propagated back to the central nervous system in hierarchy. Modified from Lan *et al.* 2017 [83] with permission.

producing realistic EMG waveform [72]–[76], which are not required for model-based control but useful to verify with experimental data [77]. Supra-spinal structures are instrumental for reproducing high-level behaviors such as motor learning or task selection, models exist for supra-spinal structures including the cerebellum [78]; a hierarchical neural-network model for control and learning of voluntary movement [79], [80]; hippocampus [81], cortex [82], etc. Supra-spinal models have yet been extensively tested with those targeting the spinal level. There has not been a comprehensive survey of computational models of sensorimotor system. But a recent research topic in Frontiers of Neuroscience [83], [84] provided a partial review of this field.

Computational modeling has paved a different but systematic way for translating the functions of human sensorimotor control. The unique value of modeling is that it provides a deductive approach of explaining the sufficiency (rather than necessity) of sensorimotor principles for production of movement behavior, e.g., a spinal-like regulator with classical circuitry was shown capable of accomplishing a range of movement tasks [85], a network with spiking neurons has the same capability to approximate arbitrary continuous functions as does an artificial neural network [86], a system implemented monosynaptic spinal loop with spiking neurons could replicate realistic reflex in robotic and cadaveric fingers [87], etc. Computational modeling also provides a tool to consolidate the ever-mounting experimental data to generate a more holistic understanding of motor control, to test hypotheses or to generate new hypotheses regarding the principles of sensorimotor control. Computational systemic models can form a basis on which new data from experimental mapping of neural circuits, or neural modeling, can be configured into new models [88], [89].

One purpose of computational modeling is to guide the design of prosthetic or therapeutic devices that possess human-like capability of moving that is compatible with the nervous system [83], [84], [90]. As eloquently put in Carr and Shepherd [91], "Rehabilitation, for patients, is fundamentally a process of relearning how to move to carry out their needs successfully". Therefore, incorporating learning effects of plastic changes into models provides a new, promising tool for the understanding of disease progression [71] and closed-loop control of therapeutic devices [92].

III. Neural Technologies for Sensory Feedback

The sensorimotor system (Fig. 1) is composed of efferent and afferent bi-directional neural information pathways [40]. Motor intent is carried in the descending volley of impulse from the brain to the effectors (muscles). While the motor action is monitored by a large set of proprioceptors and skin receptors, and the sensory information is sent back from peripheral body locations to the brain via the ascending pathway. The sensorimotor system relies on the integrity of efferent and afferent information to perform motor tasks effectively and to complete motor learning. The latter is fundamental to human's ability to adapt to changes in environments, and to relearn sensorimotor functions after injury through rehabilitation [93], [94].

Interruption of sensory flow in any part of the ascending pathway below the brain will lead to loss of somatosensation, such as in spinal cord injury or amputation. The importance of providing sensory information back to the human brain from prosthetic and therapeutic devices has been well recognized in recent years [95]–[97]. However, implementation of sensory feedback to human brain has proven to be challenging [98]. This is due not only to limitations in neural interface technologies, but also to constraints on the appropriate ways of providing sensory feedback to the brain.

In general, when designing a sensory feedback method, three attributes are usually considered, which are homology of sensation, somatotopic location in the body, and stability and longevity of neural information [99]. The first and second attributes are closely related to the issue of neural compatibility raised here. For effective motor relearning in rehabilitation, the brain needs to receive sensory information that is consistent to normal motor control. If the sensory information provided is incomplete, or inconsistent in homology of sensation and somatotopic locations as that of original limbs, the brain may not adapt to the incongruity in neural information, and may fail to perform motor relearning with the device [1], [2], [100]–[103]. This would be exhibited as difficulties to improve motor functions in the part of patients using the devices, or as unwillingness to accept the devices in performing routine daily activities, resulting in rejecting, e.g., myoelectrically controlled prosthetic hands.

The third attributes may be achieved with various neural technologies. With rapid advancement of neural engineering in recent decades, a number of neural interface technologies have emerged as promising means to communicate sensory information to the brain of amputees and patients with spinal cord injury [104]–[106]. Intracortical microstimulation (ICMS) within the hand area of primary somatosensory cortex (SI) has been used to restore sensory perception for patients with spinal cord injury [24], [25], [107]. One study demonstrated that the tactile percepts evoked by ICMS delivered through Utah electrode arrays were naturalistic in sensations and followed the somatotopic organization [24]. A recent study reported that both the cutaneous and proprioceptive sensations in human were elicited by ICMS with microelectrode arrays implanted in SI [25]. ICMS could, therefore, be an effective technique for sensory feedback, as long as the interface between array and neural tissue remains safe and stable over time.

Microstimulation of peripheral nerve is another invasive way to induce discriminable sensations. Stimulation through longitudinal intrafascicular electrodes (LIFEs) implanted in the peripheral nerve stumps can produce discriminable sensations of touch, joint movement and position referred to the amputees' lost hand [102], [108]. It has been demonstrated that stimulus enter into the median nerve and ulnar nerve of an amputee through implanted transversal intrafascicular multichannel electrodes (TIMEs) restored touch sensation and the evoked hand sensation is used to achieve bidirectional control of a hand prosthesis [109]. However, the hand area evoked by LIFEs and TIMEs is limited because of the implanted location of electrodes. Subjects with previous transradial amputations can perceive spatially distinct and stable sensory percepts with Utah slant electrode arrays (USEAs) implanted in median or ulnar nerve [110], [111]. Although USEAs provide high-density somatotopic locations of the lost hand, it needs to establish a long-term stability with electrodes penetrating the nerve fascicles. The flat intrafascicular nerve electrodes (FINEs) are non-penetrating multi-contact cuff electrode arrays and they can induce highly localized sensations by stimulating subunits of the nerve [112]. The studies have been extended to take-home trials that took place more than 3 years post-implant [32].

The vibrotactile and electrotactile represent the general non-invasive techniques to provide sensory feedback applying on the skin surface. Vibrating feedback matches the modality of vibration sensation of normal skin. Transcutaneous electrical nerve stimulation (TENS) can elicit a volley of sensory afferents and induce multiple modalities of sensation [113]–[115]. In general, the vibrotactile or electrotactile was used as a substitute for sensory feedback because of lack in locational specification corresponding to the lost hand.

It remains to clarify how adequate is the sensory information afforded by these methods of neural technologies for the amputees or patients with spinal cord injury to relearn to operate prosthetic devices effectively. So far, tests in amputees indicate that even limited substitutional sensory cues can enhance the performance of prosthetic hands [116], [117]. With an awareness of touching or grasping, amputees felt greater embodiment of the prosthetic hands [32].

Evoked tactile sensation (ETS) is a unique phenomenon found in the stump skin of many trans-radial amputees [113], [118]. Stimulating specific skin areas in the stump of amputees by either mechanical or electrical stimuli can elicit the feeling of the palm, lost fingers and even digits by the amputees. ETS with TENS could be used to restore naturalistic sensations of the fingers of the lost hand with a rich variety of sensory modalities [113], [119]. This technique has the potential to establish a safe neural interface with long-term stability for conveying sensory information of the prosthetic hand to the brain of amputees [120], [121].

These different approaches will be judged ultimately by the outcome of their functional benefits. Since many approaches are still in their developmental stage, it is not clear yet which one would yield higher functionality. However, in terms of implementation, non-invasive approach may be preferred if neural pathway permits. In the case of spinal cord injury, communication between central and peripheral sensorimotor system hardly exists, and invasive approaches appear necessary.

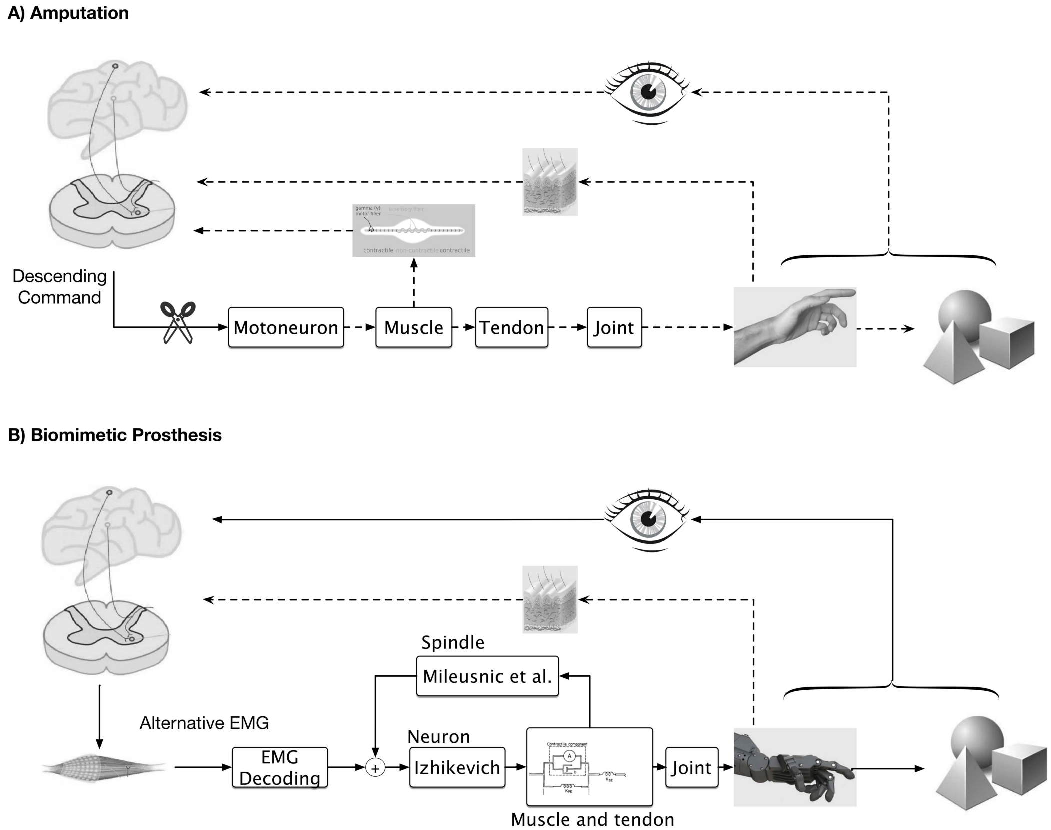

Fig. 2. (A) Illustration that when the biological pathways of neuromuscular control in an able-bodied individual are cut off due to amputation. (B) biomimetic controller aims to graft EMG from an alternative muscle, decode its latent information as a proxy of descending motor command, and emulate the subsequent physiological components to produce human-like interactions between hand and object.

IV. Compliant Motor Control With Real-Time Computing

More challenges arise when using prosthetic devices to interact with real-world objects that are deformable or crispy, in which the prosthetic hand should differentiate the stiffness or brittleness of the object as the human hand does. Therefore, it is expected to adapt its behavior commensurate with object compliance. Core to fulfilling this goal is to mimic how compliant control is accomplished by humans. In able-bodied individuals (shown as Fig. 2A), nuances of an object are perceived through an interplay among visual, tactile, and proprioceptive information; In amputees (shown as Fig. 2A after amputation), tactile and proprioceptive feedback are compromised at their stumps, leaving visual feedback as an indirect information source to calculate grasp forces. If proprio-sensor signals on prosthetic hands can be engineered into biomimetic forms such as spike trains, it may be possible to emulate the flow of proprioceptive information at spinal-level control, which can be further utilized in a biomimetic control strategy (Fig. 2B). This is a fundamentally alternative approach than many control strategies for robotics.

Prosthetic hands are expected to restore the hand function of amputee, which relies primarily on the premises that the prosthesis would: 1) reproduce the same motor consequences for accomplishing a task, and 2) reproduce the same sensory outcomes for inducing changes through cortical plasticity or motor learning in the human brain. Both demand that the prosthetic hand should faithfully execute the descending motor command, which is achieved in able-bodied subjects through the machinery of neurons, muscles, tendons, joints, proprioceptors, cutaneous receptors, etc. In specific, the descending commands must pass through a series of physiological structures before the commands eventually materialize in the environment. It follows that if the informational dynamics can be modeled and simulated in real-time, this would create an artificial controller capable of reproducing human-like interactions between the hand and the object. Previous work has demonstrated the capability of simulated monosynaptic reflex for replication of human-like movements in health and disease [60], [87]. This "virtual reflex" model implements spiking neurons, muscle spindles, synapses, skeletal muscles, and monosynaptic spinal circuitry. Models in the form of differential equations (e.g., spindle) are computationally expensive and generally difficult to run in real-time [67], [122], making it difficult to be integrated in the closed-loop control of prosthetic hand.

The need for real-time simulation of the models brings up another challenge. Numerical solution of differential equation calls for large volumes of floating-point calculations within reasonably short time. All the more so when the application requires real-time performance, such as controlling a prosthetic hand. The heavy burden of numerical calculation is less likely to be lifted by pure algorithmic improvements, but rather frequently offloaded to hardware-in-the-loop. Along this path, general purpose hardware such as GPU (graphics processing unit) has demonstrated its value far beyond its original rationale of graphics rendering, for demonstrations look only to mounting reports on training of deep artificial neural networks [123], token evaluation for cryptocurrency [124], etc. It follows that general-purpose hardware may also prove useful in sensorimotor simulation [67], [125]. At the other end of the spectrum is fully-customized hardware such as FPGA (field programmable gate array). Cost is inevitably high by custom design of arithmetic circuits, which transfers into scalability, flexibility in data transferring, and generally higher evaluation speed.

Scientists started creating artificial neurons and neural networks using electronic circuits since 1940s [126]. Models of neuron dynamics [57], [127] soon emerged to be simulated on digital computers. Since the 1980s, special- purpose hardware with Very Large Scale Integrated-circuit (VLSI) technology started to benefit from some of the key insights in neural computation, including spike representation of information, asynchrony among neurons, and self-improvements via plasticity [128]–[131]. This category of designs, termed “neuromorphic” hardware, has been successful in understanding mechanisms of memory [132], visual representation [133], and recently cognitive function [82]. For sensorimotor function, the neuromorphic approach should not only describe neurons, but also the physiological environment (muscles, proprioceptors, peripheral nerves, skeletal system) that the neurons interact with, such that the emulated nervous system could reproduce the human-like movement behavior.

V. High Density EMG Analysis for Prosthetic Control

Deciphering motor information from sEMG signals seem to have encountered a bottleneck due to the intrinsic limitations of sEMG compositions [3]. The sEMG signal is the spatial and temporal summation of hundreds of MU action potentials (MUAPs) arisen from the neural inputs [134], [135]. Although the sEMG signal can partly reflect the high-level cortical control of the muscle contraction, the underlying neural information can still be masked due to the interference from the MUAPs, such as the cancellation of MUAP waveforms [136], [137] and the cross-talk among multiple muscle groups [138]. Moreover, EMG signal can be distorted by external factors, such as motion artifacts (De Luca *et al.* 2010), or during the conductive process from muscle to skin surface [139], etc. These uncertainties may undermine the achievement of neural compatibility in efferent information to the prosthetic device.

In contrast, with the development of flexible high-density (HD) sensor techniques, a neural interface was proposed to address the issues of traditional global sEMG-based approach [140]. The novel interface is based on the truly neural information—discharge events of motoneuron—via the decomposition of HD EMG recordings. The decomposed motoneuron discharge events at the population level can precisely reflect the physiological mechanism of motor control, providing the natural coding of movements at the spinal cord level [140], [141]. The decoded neural drive information is represented as a binary motor unit spike train (MUST), and then processed to translate user’s intent into the commands of prosthetic control. The use of MUST can overcome most disadvantages of traditional control methods caused by the MUAP interference or external noise. Therefore, the novel HD-based technique has been considered as a breakthrough of the development of the prosthetic control.

To acquire the neural information, the HD EMG signals need to be deconvoluted into individual MUSTs using blind source separation (BSS) algorithms. To date, only fast independent component analysis (FastICA) [142] and convolution kernel compensation (CKC) [143] have been systematically validated on both simulated and experimental data [143]–[145]. The details of the decomposition algorithms were described in [143], [144].

Fig. 3 shows an example of decomposition of 160 (8 rows $\times 20$ columns) EMG channels and prediction of the joint movements during individual finger extension. The details about the experimental data collection were described in [146]. Briefly, the subject was required to extend the designated finger every 2 seconds with a 1-s rest interval. During the movement, the HD EMG signals of the extensor digitorum communis muscle were recorded using EMG_USB2+ system (OT Bioelettronica, Torino, Italy), and the corresponding finger joint angles were tracked with an 8-camera Optitrack system (Natural Point Inc, Corvallis, OR). Individual MUSTs were decomposed using FastICA-based algorithm and then pooled into one composite spike train (CST). The discharge frequency of the CST with a smoothing window $\leq$ 200 ms was calculated for the input of estimation. The model between the discharge rate of CST and the joint angle was calibrated using the quadratic regression. A testing trial was used to estimate the joint angle. The discharge of the CST shows a higher R2 value with the measured finger kinematics, compared with the classic EMG-envelope-based method.

The results of recent studies have established the findings that the HD-based interface is a promising approach for the prosthetic control [141], [147], [148]. One study mapped the novel interface into the control commands of upper-limb prostheses on the amputees following targeted muscle reinnervation [141]. The study reported that the HD-based approach showed a higher pattern recognition accuracy than the traditional sEMG-based approach. Another study used the HD-based approach to estimate individual finger joint torques on a stroke survivor [148], and reported that the root-mean-square errors of novel methods were much smaller than the classic method.

Despite the bright prospects, the novel interface is still far from the clinical applications [149]. All HD-based studies are currently based on the offline analysis. The computation time of EMG decomposition is a challenge for the online prosthetic control. Although the EMG decomposition algorithm has been implemented online, the results of user’s real-time control could still be different from the offline outcomes [150]. Second, current related studies used the regression method

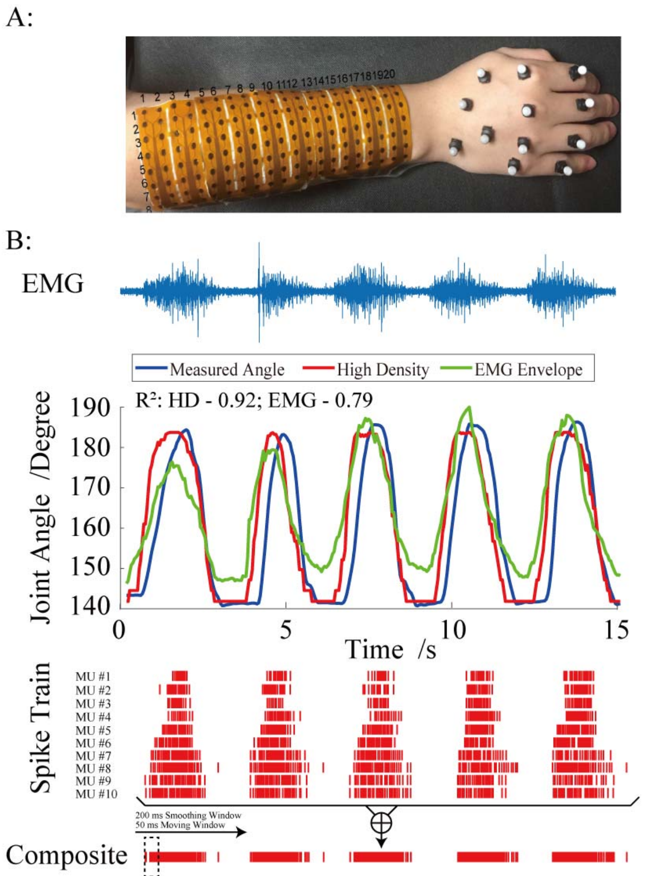

Fig. 3. An example of time series plots of joint angle estimation under individual finger movement. A: Experimental set-up. The grid of 8 $\times$20 high-density (HD) electrodes recorded the EMG signals. The optical markers recorded the joint angle movement. B: The illustration of EMG decomposition and joint angle estimation. One channel EMG was plotted, and the decomposed motor unit (MU) spike trains were shown. The estimate of the novel HD-based approach was shown in red, and the estimate of traditional EMG-envelope-based approach was shown in green as the reference. The measured angle was plotted in blue. This example indicates that the deconvoluted signals of HD EMG recordings from forearm muscles (e.g., extensor digitorum communis, flexor digitorum superficialis and profundus muscles, etc.) could be a promising interface for the control of prosthetic hand.

calibrated within one force level, but only tested on the same force effort. The question is if the novel methods can be calibrated on one condition, but tested across different conditions. The challenge of solving this issue is that the decomposed MU pool for each force level is not linearly correlated with the force level [147]. Since the normalization cannot be performed practically in each condition, future work should realize a generalized calibration across different conditions.

VI. Intelligent Control Strategies for Neural Therapeutics

Therapeutic devices for neurorehabilitation can assist posture maintenance, joint excursion, muscle activation and other crucial aspects in rehabilitation training. Therapeutic devices could guide a patient to correct the disrupted motor control toward its normal pattern [151], or to promote novel compensatory strategies [152]. In this way, therapeutic devices evolve under a unique set of principles different from those of prosthetic devices. To name a few, a therapeutic device is expected to switch flexibly between assistance and resistance, as both patterns may enhance motor learning [153], which is not usually performed in neural prosthesis. Another difference is that therapeutic devices usually monitor user performance at much longer time intervals compared to that of neural prosthesis. One primary reason is that motor re-learning takes place in therapeutics at longer time scales (hours and days), in comparison to the millisecond-level fine motor control in prosthesis.

The engineering challenges in the control of neural therapeutics using functional electrical stimulation (FES) for post-stroke rehabilitation are at least three folds: first, almost every device requires an optimal scheme to produce a pattern of stimuli that maximize motor re-learning; second, the stimulation pattern must be accompanied by a formulae to adjust its parameters and training dosage along during rehabilitation training; third, special attention must be given to patient compliance, therapist experience, and the overall ease-of-use in clinical environment [154], [155].

The foremost challenge for therapeutic devices is how to evoke positive responses of the brain that will maximize the motor relearning during training [156]. Critical to this is a systematic approach that produces stimuli to either facilitates or impedes the movement. By carefully directing the facilitation or impedance, it would adjust the sensory afferents essential for motor relearning. Toward this end, *muscle synergy* provides a useful principle for neuromuscular electrical stimulation as a human-compatible strategy. Muscle synergies are patterns identified from electromyogram, which are hypothesized to coordinate the spatial [157], [158], temporal [159], [160] or spatiotemporal [30], [161] activation patterns of multiple muscles. Despite an ongoing debate [29] that muscle synergy may reflect biomechanical constraints instead of originating from a neural basis [162], growing evidence has demonstrated the spinal provenance [163]–[165] and cortical relevance [166], [167] of muscle synergy.

In clinical applications, muscle synergy has been successfully used for the evaluation of deficits for stroke patients [168]–[170]. In the case of therapeutic devices, such as functional electrical stimulation, muscle synergy provides a theoretical foundation, which solves the critical issue of formulating multiple channels of FES patterns to drive multiple muscles acting at a multiple joint limb [34], [35]. In addition, muscle synergy can be helpful to drive the development of robot-assisted therapy aiming at complex human-machine-environment interactions (reviewed in [171], [172]). Examples include the integration of musculoskeletal models in EMG-force mapping [173], and selection of muscles in multi-channel myoelectric controls [171].

Fig. 4 below illustrates an intelligent paradigm using synergy-based FES for upper-limb training post-stroke. As can be seen, muscle synergies were first extracted when a healthy subject performed the training task, and the synergies were subsequently included in the calculation of FES envelope and timing for intervention. During each trial, FES-elicited muscle activation was superimposed to the residual movement of the patient, which produced a combined movement to be

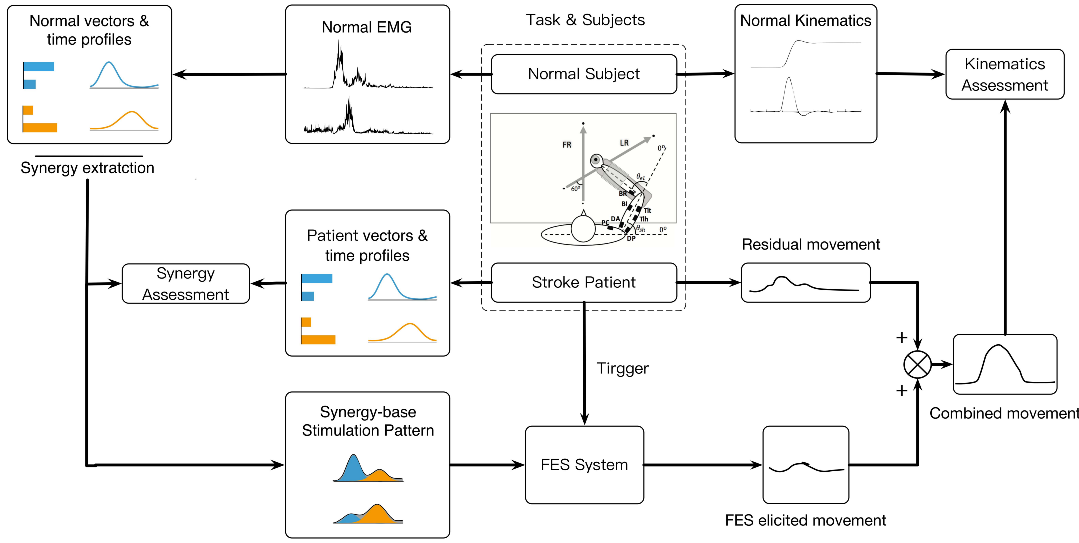

Fig. 4. Paradigm of synergy-based therapeutic FES for post-stroke upper extremity training and assessment. Muscle synergies are extracted from normal movements as the baseline for FES pattern and assessing motor abilities in patients. The FES-elicited movement assists the residual movement from the patient post stroke, resulting in a combined movement with kinematics closer to normal movements. In the intelligent synergy-based FES system, the combined movement can be immediately compared to its normal counterpart with kinematic. The comparison can guide parameter adjustment in the next trial of movement. This figure is modified from Niu *et al.* 2019 [34] with permission.

compared with assessments. With this paradigm, a pilot study showed increased movement velocity and Fugl-Myer scores with a short intervention of 5 days [34]. One explanation is that FES-elicited activation of muscle is similar to that of normal muscle activation, thus resulting in a sensory feedback that is compatible in context with the normal motor program.

In order to maximize the neural compatibility with human sensorimotor control in therapeutic devices, the stimulation should be delivered to match the residual voluntary movements in proper timing as well. Given the fact that the intention of movement should always precedes the movement per se, the therapeutic stimuli should be well controlled to follow the movement initiation. The solution to this may be to trigger the stimulation once the intention of execution has been detected—either via a brain-computer interface (BCI), or EMG, or kinematics, or kinetics. At least two principles of motor learning were reflected in EMG-triggered FES: repetition and sensorimotor integration [174]. The efficacy of EMG-triggered FES in stroke [175], [176] largely echoes the consensus that motor learning provides a basis for stroke rehabilitation [177], [178]. One explanation is that when synchronizing the stimuli with residual movement, the processing algorithm bears higher burden with peripheral neural signals, such as EMG, than using cortical signals such as EEG. Without sacrificing the ease-of-use, a therapeutic device should welcome all sources of information for maximizing its ability to stay compatible with the timing of residual movement.

The second challenge lies in parameter adjustment. Parameters are to a training protocol what ingredients are to a prescription of medication. Equally challenging is the rate at which the parameter should be adjusted. It has been proven that adjusting the amount of training along with the progress is the critical factor to delay or revert degenerative motor disorders [179]. Besides finding the optimal rate empirically through experimentation, another promising approach is to predict the rate of learning or plastic change using computational models [71], [90], and match the rate of parameter adjustment according to progress in training.

To confront the third challenge in therapeutic technology, considerable efforts are required to optimize the hardware/software in order to maximize patient engagement. Gamification and immersive virtual reality have been introduced into rehabilitation training [180]. Although the clinical advantage has yet to be demonstrated, these technologies may increase the attention level of patients. In addition, new technologies have been developed to better assist therapists to increase their productivity, for instance, the motion tracking [181], and the Internet [182], and the robotics [183].

VII. Summary

This paper presents several ways for prosthetic or therapeutic devices to sub-serve the human sensorimotor system to accomplish or to re-acquire motor functions. We explain that the external devices interfacing with human subjects must be compatible with their sensorimotor system not only in functional structures, but also in neural information content understandable by each other. Emerging neurotechnologies supply ways to communicate between the human and machine. However, the information communicated between the human sensorimotor system and the device must be compatible to match the roles in motor tasks. Neural compatibility is referred to as the notion that the efferent motor and afferent sensory information of the sensorimotor system must be interpretable in a way as in normal motor control. There are two aspects in achieving neural compatibility: 1) the external devices should execute the motor intention of the sensorimotor system as faithfully as possible, including extracting motor intentions as accurately as possible from the efferent signals and producing normal-like motor behaviors; 2) the external device should also return sensory consequence of motor actions through proprio-sensors or proprioceptors to the sensorimotor system as consistent as possible to that perceived in normal motor actions. By so doing, neutral compatible information may facilitate the sensorimotor system for motor learning or re-learning with the devices in repeated training. In such a way, the external device may be re-embodied or adapted more readily by the sensorimotor system as if it is the original part of the body. Recent evidence in sensory feedback for prosthetic hands and synergy-based FES training suggests that the more enriched in neural informational compatibility, the better the performance by the external device. Based on a large body of evidence in literature and in our research, we propose here that a general principle for the design of prosthetic or therapeutic devices (mechanical or electronic) is to achieve neural compatibility in the efferent and afferent communication interacting with the human sensorimotor system.

A general guide to achieve neural compatibility is to mimic the functions of sensorimotor system. The ways to enrich neural compatibility may be different in prosthetic and therapeutic devices. For prosthetic devices, replacing lost functions may require re-establishing interrupted efferent and afferent neural pathways through novel neural interface technologies, such as brain-computer interface (BCI), or non-invasive evoked tactile sensation, or high-density EMG. For therapeutic devices, existing neural pathways may be utilized to provide more compatible afferent neural information by driving the devices with novel strategies. In either case, compatibility in neural information promotes greater motor learning or re-learning, so that the human sensorimotor system may accept the external devices for permanent use (prosthetics) or as an aid for functional recovery (therapeutics).

References

[1] E. Biddiss and T. Chau, "Upper-limb prosthetics: Critical factors in device abandonment," *Amer. J. Phys. Med. Rehabil.*, vol. 86, no. 12, pp. 977–987, Dec. 2007.

[2] F. Cordella *et al.*, "Literature review on needs of upper limb prosthesis users," *Front. Neurosci.*, vol. 10, no. 209, pp. 1–14, 2016.

[3] D. Farina *et al.*, "The extraction of neural information from the surface EMG for the control of upper-limb prostheses: Emerging avenues and challenges," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 22, no. 4, pp. 797–809, Jul. 2014.

[4] P. H. Peckham and J. S. Knutson, "Functional electrical stimulation for neuromuscular applications," *Annu. Rev. Biomed. Eng.*, vol. 7, no. 1, pp. 327–360, 2005.

[5] M. R. Popovic, T. Keller, I. P. I. Papas, V. Dietz, and M. Morari, "Surface-stimulation technology for grasping and walking neuroprostheses," *IEEE Eng. Med. Biol. Mag.*, vol. 20, no. 1, pp. 82–93, Jan./Feb. 2001.

[6] P. R. Bosch, J. E. Harris, and K. Wing, "Review of therapeutic electrical stimulation for dorsiflexion assist and orthotic substitution from the american congress of rehabilitation medicine stroke movement interventions subcommittee," *Archives Phys. Med. Rehabil.*, vol. 95, no. 2, pp. 390–396, Feb. 2014.

[7] R. D. Wilson *et al.*, "Upper-limb recovery after stroke: A randomized controlled trial comparing EMG-triggered, cyclic, and sensory electrical stimulation," *Neurorehabil. Neural Repair*, vol. 30, no. 10, pp. 978–987, Nov. 2016.

[8] S. Dorsch, L. Ada, and C. G. Canning, "EMG-triggered electrical stimulation is a feasible intervention to apply to multiple arm muscles in people early after stroke, but does not improve strength and activity more than usual therapy: A randomized feasibility trial," *Clin. Rehabil.*, vol. 28, no. 5, pp. 482–490, May 2014.

[9] H. Kim, G. Lee, and C. Song, "Effect of functional electrical stimulation with mirror therapy on upper extremity motor function in poststroke patients," *J. Stroke Cerebrovascular Diseases*, vol. 23, no. 4, pp. 655–661, Apr. 2014.

[10] S. Carda *et al.*, "Electrically assisted movement therapy in chronic stroke patients with severe upper limb paresis: A pilot, single-blind, randomized crossover study," *Archives Phys. Med. Rehabil.*, vol. 98, no. 8, pp. 1628–1635, Aug. 2017.

[11] Y. Y. Jang, T. H. Kim, and B. H. Lee, "Effects of brain–computer interface-controlled functional electrical stimulation training on shoulder subluxation for patients with stroke: A randomized controlled trial: BCI-controlled FES improved shoulder subluxation in stroke survivors," *Occup. Ther. Int.*, vol. 23, no. 2, pp. 175–185, Jun. 2016.

[12] T. Kim, S. Kim, and B. Lee, "Effects of action observational training plus brain–computer interface-based functional electrical stimulation on paretic arm motor recovery in patient with stroke: A randomized controlled trial," *Occup. Ther. Int.*, vol. 23, no. 1, pp. 39–47, Mar. 2016.

[13] J. Knutson, J. Chae, and D. Gunzler, "Contralaterally controlled FES for chronic upper limb hemiplegia: Single site RCT," *Archives Phys. Med. Rehabil.*, vol. 96, no. 10, p. e4, Oct. 2015.

[14] S. Koyama *et al.*, "NMES with rTMS for moderate to severe dysfunction after stroke," *NeuroRehabilitation*, vol. 35, no. 3, pp. 363–368, 2014.

[15] Y. Y. Lee, K. C. Lin, H. J. Cheng, C. Y. Wu, Y. W. Hsieh, and C. K. Chen, "Effects of combining robot-assisted therapy with neuromuscular electrical stimulation on motor impairment, motor and daily function, and quality of life in patients with chronic stroke: A double-blinded randomized controlled trial," *J. Neuroeng. Rehabil.*, vol. 12, no. 1, p. 96, Dec. 2015.

[16] S.-F. Liu, C.-L. Gao, W.-J. Wang, C.-S. Yu, X.-P. Wang, and J.-L. Wu, "Effects of motor imagery combined with functional electrical stimulation on upper limb motor function of patients with acute ischemic stroke," *Chin. J. Contemporary Neurol. Neurosurgery*, vol. 15, no. 3, pp. 209–213, Mar. 2015.

[17] W. Rong *et al.*, "A neuromuscular electrical stimulation (NMES) and robot hybrid system for multi-joint coordinated upper limb rehabilitation after stroke," *J. Neuroeng. Rehabil.*, vol. 14, no. 1, p. 34, Dec. 2017.

[18] V. Sattler *et al.*, "Anodal tDCS combined with radial nerve stimulation promotes hand motor recovery in the acute phase after ischemic stroke," *Neurorehabil. Neural Repair*, vol. 29, no. 8, pp. 743–754, Sep. 2015.

[19] T. Schick *et al.*, "Synergy effects of combined multichannel EMG-triggered electrical stimulation and mirror therapy in subacute stroke patients with severe or very severe arm/hand paresis," *Restorative Neurol. Neurosci.*, vol. 35, no. 3, pp. 319–332, Jun. 2017.

[20] A. Tosun *et al.*, "Effects of low-frequency repetitive transcranial magnetic stimulation and neuromuscular electrical stimulation on upper extremity motor recovery in the early period after stroke: A preliminary study," *Topics Stroke Rehabil.*, vol. 24, no. 5, pp. 361–367, Jul. 2017.

[21] F. Quandt and F. C. Hummel, "The influence of functional electrical stimulation on hand motor recovery in stroke patients: A review," *Exp. Trans. Stroke Med.*, vol. 6, no. 1, p. 9, Dec. 2014.

[22] A. Biasiucci *et al.*, "Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke," *Nat. Commun.*, vol. 9, no. 1, p. 2421, Dec. 2018.

[23] T. Aflalo *et al.*, "Decoding motor imagery from the posterior parietal cortex of a tetraplegic human," *Science*, vol. 348, no. 6237, pp. 906–910, May 2015.

[24] S. N. Flesher *et al.*, "Intracortical microstimulation of human somatosensory cortex," *Sci. Transl. Med.*, vol. 8, no. 361, Oct. 2016, Art. no. 361ra141.

[25] M. A. Salas *et al.*, "Proprioceptive and cutaneous sensations in humans elicited by intracortical microstimulation," *Elife*, vol. 7, Apr. 2018, Art. no. e32904.

[26] D. J. Weber *et al.*, "Limb-state information encoded by peripheral and central somatosensory neurons: Implications for an afferent interface," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 19, no. 5, pp. 501–513, Oct. 2011.

[27] T. M. Bruns, J. B. Wagenaar, M. J. Bauman, R. A. Gaunt, and D. J. Weber, "Real-time control of hind limb functional electrical stimulation using feedback from dorsal root ganglia recordings," *J. Neural Eng.*, vol. 10, no. 2, Apr. 2013, Art. no. 026020.

[28] E. Bizzi, V. C. K. Cheung, A. d'Avella, P. Saltiel, and M. Tresch, "Combining modules for movement," *Brain Res. Rev.*, vol. 57, no. 1, pp. 125–133, Jan. 2008.

[29] E. Bizzi and V. C. K. Cheung, "The neural origin of muscle synergies," *Front. Comput. Neurosci.*, vol. 7, p. 51, Apr. 2013.

[30] I. Delis, S. Panzeri, T. Pozzo, and B. Berret, "A unifying model of concurrent spatial and temporal modularity in muscle activity," *J. Neurophysiol.*, vol. 111, no. 3, pp. 675–693, Feb. 2014.

[31] F. Clemente *et al.*, "Intraneural sensory feedback restores grip force control and motor coordination while using a prosthetic hand," *J. Neural Eng.*, vol. 16, no. 2, Feb. 2019, Art. no. 026034.

[32] E. L. Graczyk, A. Gill, D. J. Tyler, and L. J. Resnik, "The benefits of sensation on the experience of a hand: A qualitative case series," *PLoS ONE*, vol. 14, no. 1, Jan. 2019, Art. no. e0211469.

[33] M. A. Schweisfurth, M. Markovic, S. Dosen, F. Teich, B. Graimann, and D. Farina, "Electrotactile EMG feedback improves the control of prosthesis grasping force," *J. Neural Eng.*, vol. 13, no. 5, 2016, Art. no. 056010.

[34] C. M. Niu *et al.*, "Synergy-based FES for post-stroke rehabilitation of upper-limb motor functions," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 27, no. 2, pp. 256–264, Feb. 2019.

[35] S. Ferrante *et al.*, "A personalized multi-channel FES controller based on muscle synergies to support gait rehabilitation after stroke," *Front. Neurosci.*, vol. 10, p. 425, Sep. 2016.

[36] C. S. Sherrington, "Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing," *J. Physiol.*, vol. 40, nos. 1–2, pp. 28–121, Apr. 1910.

[37] E. Mayeri, J. Koester, I. Kupfermann, G. Liebeswar, and E. R. Kandel, "Neural control of circulation in Aplysia. I. Motoneurons," *J. Neurophysiol.*, vol. 37, no. 3, pp. 458–475, May 1974.

[38] J. Koester, E. Mayeri, G. Liebeswar, and E. R. Kandel, "Neural control of circulation in Aplysia. II. Interneurons," *J. Neurophysiol.*, vol. 37, no. 3, pp. 476–496, May 1974.

[39] K. Østlie, I. M. Lesjø, R. J. Franklin, B. Garfelt, O. H. Skjeldal, and P. Magnus, "Prosthesis rejection in acquired major upper-limb amputees: A population-based survey," *Disability Rehabil. Assistive Technol.*, vol. 7, no. 4, pp. 294–303, Jul. 2012.

[40] A. Shumway-Cook and M. Woollacott, *Motor Control: Translating Research Into Clinical Practice*, 5th ed. Philadelphia, PA, USA: Wolters Kluwer, 2017.

[41] L. M. Zitella *et al.*, "Subject-specific computational modeling of DBS in the PPTg area," *Front. Comput. Neurosci.*, vol. 9, p. 93, Jul. 2015.

[42] N. Wenger *et al.*, "Spatiotemporal neuromodulation therapies engaging muscle synergies improve motor control after spinal cord injury," *Nat. Med*, vol. 22, no. 2, pp. 138–145, Feb. 2016.

[43] J. L. Pons, R. Raya, and J. González, Eds., *Emerging Therapies in Neurorehabilitation II* (Biosystems & Biorobotics), vol. 10. Cham, Switzerland: Springer Int., 2016.

[44] E. Henneman, "Relation between size of neurons and their susceptibility to discharge," *Science*, vol. 126, no. 3287, pp. 1345–1347, Dec. 1957.

[45] E. Pierrot-Deseilligny and D. Burke, *The Circuitry of the Human Spinal Cord: Its Role in Motor Control and Movement Disorders*. New York, NY, USA: Cambridge Univ. Press, 2005.

[46] B. Alstermark, T. Isa, L.-G. Pettersson, and S. Sasaki, "The C3–C4 propriospinal system in the cat and monkey: A spinal pre-motoneuronal centre for voluntary motor control," *Acta Physiologica*, vol. 189, no. 2, pp. 123–140, Feb. 2007.

[47] B. Alstermark and T. Isa, "Circuits for skilled reaching and grasping," *Annu. Rev. Neurosci.*, vol. 35, pp. 559–578, Jul. 2012.

[48] P. B. C. Matthews, "Muscle spindles and their motor control," *Physiol. Rev.*, vol. 44, pp. 219–288, Apr. 1964.

[49] I. A. Boyd, "The isolated mammalian muscle spindle," *Trends Neurosci.*, vol. 3, no. 11, pp. 258–265, Nov. 1980.

[50] P. M. H. Rack and D. R. Westbury, "The short range stiffness of active mammalian muscle and its effect on mechanical properties," *J. Physiol.*, vol. 240, no. 2, pp. 331–350, 1974.

[51] P. M. Rack and D. R. Westbury, "Elastic properties of the cat soleus tendon and their functional importance," *J. Physiol.*, vol. 347, no. 1, pp. 479–495, 1984.

[52] W. Z. Rymer and Z. Hasan, "Prolonged time course for vibratory suppression of stretch reflex in the decerebrate cat," *Exp. Brain Res.*, vol. 44, no. 1, pp. 101–112, Sep. 1981.

[53] J. M. Hidler and W. Z. Rymer, "A simulation study of reflex instability in spasticity: Origins of clonus," *IEEE Trans. Rehabil. Eng.*, vol. 7, no. 3, pp. 327–340, Sep. 1999.

[54] J. van Doornik, S. Kukke, and T. D. Sanger, "Hypertonia in childhood secondary dystonia due to cerebral palsy is associated with reflex muscle activation," *Movement Disorders Official J. Movement Disorder Soc.*, vol. 24, no. 7, pp. 965–971, May 2009.

[55] R. B. Stein, "Peripheral control of movement," *Physiol. Rev.*, vol. 54, no. 1, pp. 215–243, Jan. 1974.

[56] J. C. Houk, W. Z. Rymer, and P. E. Crago, "Dependence of dynamic response of spindle receptors on muscle length and velocity," *J. Neurophysiol.*, vol. 46, no. 1, pp. 143–166, Jul. 1981.

[57] A. L. Hodgkin and A. F. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," *J. Physiol.*, vol. 117, no. 4, pp. 500–544, Aug. 1952.

[58] E. M. Izhikevich, "Simple model of spiking neurons," *IEEE Trans. Neural Netw.*, vol. 14, no. 6, pp. 1569–1572, Nov. 2003.

[59] M. Hao, X. He, Q. Xiao, B. Alstermark, and N. Lan, "Corticomuscular transmission of tremor signals by propriospinal neurons in Parkinson's disease," *PLoS ONE*, vol. 8, no. 11, 2013, Art. no. e79829.

[60] S. Li *et al.*, "Coordinated alpha and gamma control of muscles and spindles in movement and posture," *Front. Comput. Neurosci.*, vol. 9, p. 122, Oct. 2015.

[61] F. E. Zajac, "Muscle and tendon: Properties, models, scaling, and application to biomechanics and motor control," *Critical Rev. Biomed. Eng.*, vol. 17, no. 4, pp. 359–411, 1989.

[62] A. A. Biewener, J. M. Wakeling, S. S. Lee, and A. S. Arnold, "Validation of hill-type muscle models in relation to neuromuscular recruitment and force-velocity properties: Predicting patterns of *in vivo* muscle force," *Integr. Comp. Biol.*, vol. 54, no. 6, pp. 1072–1083, Jun. 2014.

[63] M. B. Shapiro and R. V. Kenyon, "Control variables in mechanical muscle models: A mini-review and a new model," *Motor Control*, vol. 4, no. 3, pp. 329–349, Jul. 2000.

[64] M. P. Mileusnic, I. E. Brown, N. Lan, and G. E. Loeb, "Mathematical models of proprioceptors. I. Control and transduction in the muscle spindle," *J. Neurophysiol.*, vol. 96, no. 4, pp. 1772–1788, Oct. 2006.

[65] M. P. Mileusnic and G. E. Loeb, "Mathematical models of proprioceptors. II. Structure and function of the Golgi tendon organ," *J. Neurophysiol.*, vol. 96, no. 4, pp. 1789–1802, Oct. 2006.

[66] N. Lan and X. He, "Fusimotor control of spindle sensitivity regulates central and peripheral coding of joint angles," *Front. Comput. Neurosci.*, vol. 6, p. 66, Aug. 2012.

[67] C. M. Niu, S. K. Nandyala, and T. D. Sanger, "Emulated muscle spindle and spiking afferents validates VLSI neuromorphic hardware as a testbed for sensorimotor function and disease," *Front. Comput. Neurosci.*, vol. 8, p. 141, Dec. 2014.

[68] E. J. Cheng, I. E. Brown, and G. E. Loeb, "Virtual muscle: A computational approach to understanding the effects of muscle properties on motor control," *J. Neurosci. Methods*, vol. 101, no. 2, pp. 117–130, Sep. 2000.

[69] D. Song, N. Lan, G. E. Loeb, and J. Gordon, "Model-based sensorimotor integration for multi-joint control: Development of a virtual arm model," *Ann. Biomed. Eng.*, vol. 36, no. 6, pp. 1033–1048, Jun. 2008.

[70] G.-Q. Bi and M.-M. Poo, "Synaptic modifications in cultured hippocampal neurons: Dependence on spike timing, synaptic strength, and postsynaptic cell type," *J. Neurosci. Official J. Soc. Neurosci.*, vol. 18, no. 24, pp. 10464–10472, Dec. 1998.

[71] W. J. Sohn, C. M. Niu, and T. D. Sanger, "A neuromorphic model of motor overflow in focal hand dystonia due to correlated sensory input," *J. Neural Eng.*, vol. 13, no. 5, Oct. 2016, Art. no. 055001.

[72] A. J. Fuglevand, D. A. Winter, and A. E. Patla, "Models of recruitment and rate coding organization in motor-unit pools," *J. Neurophysiol.*, vol. 70, no. 6, pp. 2470–2488, Dec. 1993.

[73] D. Farina, A. Crosetti, and R. Merletti, "A model for the generation of synthetic intramuscular EMG signals to test decomposition algorithms," *IEEE Trans. Biomed. Eng.*, vol. 48, no. 1, pp. 66–77, Jan. 2001.

[74] P. Rosenfalck, "Intra- and extracellular potential fields of active nerve and muscle fibres. A physico-mathematical analysis of different models," *Acta Physiologica Scandinavica. Supplementum*, vol. 321, pp. 1–168, Jan. 1969.

[75] M. M. Lowery, N. S. Stoykov, J. P. A. Dewald, and T. A. Kuiken, "Volume conduction in an anatomically based surface EMG model," *IEEE Trans. Biomed. Eng.*, vol. 51, no. 12, pp. 2138–2147, Dec. 2004.

[76] D. Farina, R. Colombo, R. Merletti, and H. B. Olsen, "Evaluation of intra-muscular EMG signal decomposition algorithms," *J. Electromyography Kinesiol.*, vol. 11, no. 3, pp. 175–187, Jun. 2001.

[77] K. Jalaleddini *et al.*, "Neuromorphic meets neuromechanics, part II: The role of fusimotor drive," *J. Neural Eng.*, vol. 14, no. 2, 2017, Art. no. 025002.

[78] D. V. Buonomano and M. D. Mauk, "Neural network model of the cerebellum: Temporal discrimination and the timing of motor responses," *Neural Comput.*, vol. 6, no. 1, pp. 38–55, Jan. 1994.

[79] B. E. McKay and R. W. Turner, "Physiological and morphological development of the rat cerebellar Purkinje cell," *J. Physiol.*, vol. 567, no. 3, pp. 829–850, 2005.

[80] R. Hogri, S. A. Bamford, A. H. Taub, A. Magal, P. D. Giudice, and M. Mintz, "A neuro-inspired model-based closed-loop neuroprosthesis for the substitution of a cerebellar learning function in anesthetized rats," *Sci. Rep.*, vol. 5, p. 8451, Feb. 2015.

[81] D. Song, R. H. M. Chan, V. Z. Marmarelis, R. E. Hampson, S. A. Deadwyler, and T. W. Berger, "Nonlinear dynamic modeling of spike train transformations for hippocampal-cortical prostheses," *IEEE Trans. Biomed. Eng.*, vol. 54, no. 6, pp. 1053–1066, Jun. 2007.

[82] C. Eliasmith *et al.*, "A large-scale model of the functioning brain," *Science*, vol. 338, no. 6111, pp. 1202–1205, Nov. 2012.

[83] N. Lan, V. C. K. Cheung, and S. C. Gandevia, *Neural and Computational Modeling of Movement Control*. Lausanne, Switzerland: Frontiers Media SA, 2017.

[84] N. Lan, V. C. K. Cheung, and S. C. Gandevia, "Editorial: Neural and computational modeling of movement control," *Front. Comput. Neurosci.*, vol. 10, p. 90, Aug. 2016.

[85] G. Raphael, G. A. Tsianos, and G. E. Loeb, "Spinal-like regulator facilitates control of a two-degree-of-freedom wrist," *J. Neurosci. Official J. Soc. Neurosci.*, vol. 30, no. 28, pp. 9431–9444, Jul. 2010.

[86] T. D. Sanger, "Probability density methods for smooth function approximation and learning in populations of tuned spiking neurons," *Neural Comput.*, vol. 10, no. 6, pp. 1567–1586, Aug. 1998.

[87] C. M. Niu, K. Jalaleddini, W. J. Sohn, J. Rocamora, T. D. Sanger, and F. J. Valero-Cuevas, "Neuromorphic meets neuromechanics, part I: The methodology and implementation," *J. Neural Eng.*, vol. 14, no. 2, Apr. 2017, Art. no. 025001.

[88] F. Baldissera, H. Hultborn, and M. Illert, "Integration in spinal neuronal systems," in *Comprehensive Physiology*, Amer. Physiol. Soc., Jan. 2011.

[89] A. Prochazka and P. Ellaway, "Sensory systems in the control of movement," in *Comprehensive Physiology*, Amer. Physiol. Soc., Oct. 2012.

[90] D. J. Reinkensmeyer *et al.*, "Computational neurorehabilitation: Modeling plasticity and learning to predict recovery," *J. Neuroeng. Rehabil.*, vol. 13, no. 1, p. 42, Dec. 2016.

[91] J. Carr and R. B. Shepherd, *A Motor Relearning Programme for Stroke*, 2nd ed. Rockville, MD, USA: Butterworth-Heinemann, 1987.

[92] V. S. Huang and J. W. Krakauer, "Robotic neurorehabilitation: A computational motor learning perspective," *J. Neuroeng. Rehabil.*, vol. 6, no. 1, p. 5, Dec. 2009.

[93] C. Darian-Smith, "Somatosensory plasticity," in *Encyclopedia of Neuroscience*, L. R. Squire, Ed. Oxford, U.K.: Academic, 2009, pp. 99–110.

[94] J. A. Kleim, "Neural plasticity and neurorehabilitation: Teaching the new brain old tricks," *J. Commun. Disorders*, vol. 44, no. 5, pp. 521–528, Sep./Oct. 2011.

[95] D. S. Childress, "Closed-loop control in prosthetic systems: Historical perspective," *Ann. Biomed. Eng.*, vol. 8, nos. 4–6, pp. 293–303, Jul. 1980.

[96] C. L. Van Doren, R. R. Riso, and K. Milchus, "Sensory feedback for enhancing upper extremity neuromuscular prostheses," *Neurorehabil. Neural Repair*, vol. 5, nos. 1–2, pp. 63–74, Jan. 1991.

[97] C. Antfolk, M. D'Alonzo, B. Rosén, G. Lundborg, F. Sebelius, and C. Cipriani, "Sensory feedback in upper limb prosthetics," *Expert Rev. Med. Devices*, vol. 10, no. 1, pp. 45–54, Jan. 2013.

[98] X. Navarro, T. B. Krueger, N. Lago, S. Micera, T. Stieglitz, and P. Dario, "A critical review of interfaces with the peripheral nervous system for the control of neuroprostheses and hybrid bionic systems," *J. Peripheral Nervous Syst.*, vol. 10, no. 3, pp. 229–258, Sep. 2005.

[99] J. S. Schofield, K. R. Evans, J. P. Carey, and J. S. Hebert, "Applications of sensory feedback in motorized upper extremity prosthesis: A review," *Expert Rev. Med. Devices*, vol. 11, no. 5, pp. 499–511, Sep. 2014.

[100] C. Church, C. Price, A. D. Pandyan, S. Huntley, R. Curless, and H. Rodgers, "Randomized controlled trial to evaluate the effect of surface neuromuscular electrical stimulation to the shoulder after acute stroke," *Stroke*, vol. 37, no. 12, pp. 2995–3001, Dec. 2006.

[101] W. S. Harwin, J. L. Patton, and V. R. Edgerton, "Challenges and opportunities for robot-mediated neurorehabilitation," *Proc. IEEE*, vol. 94, no. 9, pp. 1717–1726, Sep. 2006.

[102] G. S. Dhillon and K. W. Horch, "Direct neural sensory feedback and control of a prosthetic arm," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 13, no. 4, pp. 468–472, Dec. 2005.

[103] S. Mangold, C. Schuster, T. Keller, A. Zimmermann-Schlatter, and T. Ettlin, "Motor training of upper extremity with functional electrical stimulation in early stroke rehabilitation," *Neurorehabil. Neural Repair*, vol. 23, no. 2, pp. 184–190, Feb. 2009.

[104] S. V. Hiremath *et al.*, "Human perception of electrical stimulation on the surface of somatosensory cortex," *PLoS ONE*, vol. 12, no. 5, May 2017, Art. no. e0176020.

[105] A. B. Schwartz, X. T. Cui, D. J. Weber, and D. W. Moran, "Brain-controlled interfaces: Movement restoration with neural prosthetics," *Neuron*, vol. 52, no. 1, pp. 205–220, Oct. 2006.

[106] H. Charkhkar, C. E. Shell, P. D. Marasco, G. J. Pinault, D. J. Tyler, and R. J. Triolo, "High-density peripheral nerve cuffs restore natural sensation to individuals with lower-limb amputations," *J. Neural Eng.*, vol. 15, no. 5, Jun. 2018, Art. no. 056002.

[107] V. de Lafuente, "Regaining the senses of touch and movement," *Elife*, vol. 7, Apr. 2018, Art. no. e36137.

[108] G. S. Dhillon, S. M. Lawrence, D. T. Hutchinson, and K. W. Horch, "Residual function in peripheral nerve stumps of amputees: Implications for neural control of artificial limbs," *J. Hand Surgery*, vol. 29, no. 4, pp. 605–615, Jul. 2004.

[109] S. Raspopovic *et al.*, "Restoring natural sensory feedback in real-time bidirectional hand prostheses," *Sci. Transl. Med.*, vol. 6, no. 222, Feb. 2014, Art. no. 222ra19.

[110] T. S. Davis *et al.*, "Restoring motor control and sensory feedback in people with upper extremity amputations using arrays of 96 microelectrodes implanted in the median and ulnar nerves," *J. Neural Eng.*, vol. 13, no. 3, Mar. 2016, Art. no. 036001.

[111] D. M. Page *et al.*, "Motor control and sensory feedback enhance prosthesis embodiment and reduce phantom pain after long-term hand amputation," *Front. Human Neurosci.*, vol. 12, p. 352, Sep. 2018.

[112] D. W. Tan, M. A. Schiefer, M. W. Keith, J. R. Anderson, J. Tyler, and D. J. Tyler, "A neural interface provides long-term stable natural touch perception," *Sci. Transl. Med.*, vol. 6, no. 257, Oct. 2014, Art. no. 257ra138.

[113] G. Chai, X. Sui, S. Li, L. He, and N. Lan, "Characterization of evoked tactile sensation in forearm amputees with transcutaneous electrical nerve stimulation," *J. Neural Eng.*, vol. 12, no. 6, Dec. 2015, Art. no. 066002.

[114] A. Y. J. Szeto and R. R. Riso, "Sensory feedback using electrical stimulation," in *Rehabilitation Engineering*, R. V. Smith and J. H. Leslie, Jr., Eds. Boca Raton, FL, USA: CRC Press, 1990.

[115] A. Y. J. Szeto and F. A. Saunders, "Electrocutaneous stimulation for sensory communication in rehabilitation engineering," *IEEE Trans. Biomed. Eng.*, vol. BME-29, no. 4, pp. 300–308, Apr. 1982.

[116] M. Isaković *et al.*, "Electrotactile feedback improves performance and facilitates learning in the routine grasping task," *Eur. J. Transl. Myol.*, vol. 26, no. 3, p. 6069, Jun. 2016.

[117] F. Clemente, M. D'Alonzo, M. Controzzi, B. B. Edin, and C. Cipriani, "Non-invasive, temporally discrete feedback of object contact and release improves grasp control of closed-loop myoelectric transradial prostheses," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 24, no. 12, pp. 1314–1322, Dec. 2016.

[118] A. Björkman, U. Wijk, C. Antfolk, I. Björkman-Burtscher, and B. Rosén, "Sensory qualities of the phantom hand map in the residual forearm of amputees," *J. Rehabil. Med.*, vol. 48, no. 4, pp. 365–370, Apr. 2016.

[119] X. X. Liu, G. H. Chai, H. E. Qu, and N. Lan, "A sensory feedback system for prosthetic hand based on evoked tactile sensation," in *Proc. 37th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. (EMBC)*, Aug. 2015, pp. 2493–2496.

[120] X. D. Liu, M. Z. Hao, C. Y. Cao, C. M. Niu, and N. Lan, "Somatosensory cortex activation during electrical stimulation of projected finger map on the stump skin of forearm amputee," presented at the IEEE Life Sci. Conf. (LSC), 2017, pp. 316–319.

[121] P. Y. Yin, M. Z. Hao, X. D. Liu, C. Y. Cao, C. M. Niu, and N. Lan, "Neural correlation between evoked tactile sensation and central activities in the somatosensory cortex," in *Proc. IEEE 40th Annu. Int. Conf. Eng. Med. Biol. Soc. (EMBC)*, 2018, pp. 2296–2299.

[122] B. Bäuml and G. Hirzinger, "When hard realtime matters: Software for complex mechatronic systems," *Robot. Auton. Syst.*, vol. 56, no. 1, pp. 5–13, Jan. 2008.

[123] A. Krizhevsky, I. Sutskever, and G. E. Hinton, "ImageNet classification with deep convolutional neural networks," in *Proc. Adv. Neural Inf. Process. Syst. 25*, 2012, pp. 1097–1105.

[124] K. J. O'Dwyer and D. Malone, "Bitcoin mining and its energy footprint," in *Proc. ISSC/CIICT*, Jan. 2014, pp. 280–285.

[125] M. Peniak, A. Morse, C. Larcombe, S. Ramirez-Contla, and A. Cangelosi, "Aquila: An open-source GPU-accelerated toolkit for cognitive and neuro-robotics research," in *Proc. Int. Joint Conf. Neural Netw.*, 2011, pp. 1753–1760.

[126] W. S. McCulloch and W. Pitts, "A logical calculus of the ideas immanent in nervous activity," *Bull. Math. Biophys.*, vol. 5, no. 4, pp. 115–133, Dec. 1943.

[127] F. Rosenblatt, "The perceptron: A probabilistic model for information storage and organization in the brain," *Psychol. Rev.*, vol. 65, no. 6, pp. 386–408, 1958.

[128] C. Mead, *Analog VLSI and Neural Systems*. Boston, MA, USA: Addison Wesley, 1989.

[129] R. Serrano-Gotarredona *et al.*, "CAVIAR: A 45k neuron, 5M synapse, 12G connects/s AER hardware sensory-processing-learning-actuating system for high-speed visual object recognition and tracking," *IEEE Trans. Neural Netw.*, vol. 20, no. 9, pp. 1417–1438, Sep. 2009.

[130] G. Indiveri *et al.*, "Neuromorphic silicon neuron circuits," *Front. Neurosci.*, vol. 5, p. 73, May 2011.

[131] E. Neftci, S. Das, B. Pedroni, K. Kreutz-Delgado, and G. Cauwenberghs, "Event-driven contrastive divergence for spiking neuromorphic systems," *Frontiers Neurosci.*, vol. 7, no. 272, 2013.

[132] E. Chicca *et al.*, "A VLSI recurrent network of integrate-and-fire neurons connected by plastic synapses with long-term memory," *IEEE Trans. Neural Netw.*, vol. 14, no. 5, pp. 1297–1307, Sep. 2003.

[133] P. Lichtsteiner, C. Posch, and T. Delbruck, "A 128×128 120 dB 15 μs latency asynchronous temporal contrast vision sensor," *IEEE J. Solid-State Circuits*, vol. 43, no. 2, pp. 566–576, Feb. 2008.

[134] R. S. LeFever and C. J. De Luca, "A procedure for decomposing the myoelectric signal into its constituent action potentials—Part I: Technique, theory, and implementation," *IEEE Trans. Biomed. Eng.*, vol. BME-29, no. 3, pp. 149–157, Mar. 1982.

[135] R. S. LeFever and C. J. De Luca, "A procedure for decomposing the myoelectric signal into its constituent action potentials—Part II: Execution and test for accuracy," *IEEE Trans. Biomed. Eng.*, vol. BME-29, no. 3, pp. 158–164, Mar. 1982.

[136] D. Farina, R. Merletti, and R. M. Enoka, "The extraction of neural strategies from the surface EMG," *J. Appl. Physiol.*, vol. 96, no. 4, pp. 1486–1495, 2004.

[137] K. G. Keenan, D. Farina, K. S. Maluf, R. Merletti, and R. M. Enoka, "Influence of amplitude cancellation on the simulated surface electromyogram," *J. Appl. Physiol.*, vol. 98, no. 1, pp. 120–131, 2005.

[138] C. J. De Luca and R. Merletti, "Surface myoelectric signal cross-talk among muscles of the leg," *Electroencephalography Clin. Neurophysiol.*, vol. 69, no. 6, pp. 568–575, 1988.

[139] D. Farina, L. Mesin, S. Martina, and R. Merletti, "A surface EMG generation model with multilayer cylindrical description of the volume conductor," *IEEE Trans. Biomed. Eng.*, vol. 51, no. 3, pp. 415–426, Mar. 2004.

[140] D. Farina, A. Holobar, R. Merletti, and R. M. Enoka, "Decoding the neural drive to muscles from the surface electromyogram," *Clin. Neurophysiol.*, vol. 121, no. 10, pp. 1616–1623, 2010.

[141] D. Farina *et al.*, "Man/machine interface based on the discharge timings of spinal motor neurons after targeted muscle reinnervation," *Nat. Biomed. Eng.*, vol. 1, p. 25, Feb. 2017.

[142] A. Hyvärinen and E. Oja, "Independent component analysis: Algorithms and applications," *Neural Netw.*, vol. 13, nos. 4–5, pp. 411–430, 2000.

[143] A. Holobar and D. Zazula, "Multichannel blind source separation using convolution kernel compensation," *IEEE Trans. Signal Process.*, vol. 55, no. 9, pp. 4487–4496, Sep. 2007.

[144] M. Chen and P. Zhou, "A novel framework based on FastICA for high density surface EMG decomposition," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 24, no. 1, pp. 117–127, Jan. 2016.

[145] F. Negro, S. Muceli, A. M. Castronovo, A. Holobar, and D. Farina, "Multi-channel intramuscular and surface EMG decomposition by convolutive blind source separation," *J. Neural Eng.*, vol. 13, no. 2, 2016, Art. no. 26027.

[146] C. Dai and X. Hu, "Finger joint angle estimation based on motoneuron discharge activities," *IEEE J. Biomed. Health Inform.*, to be published.

[147] C. Dai, Y. Cao, and X. Hu, "Prediction of individual finger forces based on decoded motoneuron activities," *Ann. Biomed. Eng.*, vol. 47, no. 6, pp. 1357–1368, 2019.

[148] C. Dai, Y. Zheng, and X. Hu, "Estimation of muscle force based on neural drive in a hemispheric stroke survivor," *Front. Neurol.*, vol. 9, p. 187, Mar. 2018.

[149] N. Jiang, S. Dosen, K.-R. Muller, and D. Farina, "Myoelectric control of artificial limbs—Is there a need to change focus?" *IEEE Signal Process. Mag.*, vol. 29, no. 5, pp. 150–152, Sep. 2012.

[150] V. Glaser, A. Holobar, and D. Zazula, "Real-time motor unit identification from high-density surface EMG," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 21, no. 6, pp. 949–958, Nov. 2013.

[151] L. R. Sheffler and J. Chae, "Neuromuscular electrical stimulation in neurorehabilitation," *Muscle Nerve*, vol. 35, no. 5, pp. 562–590, 2007.

[152] P. Langhorne, J. Bernhardt, and G. Kwakkel, "Stroke rehabilitation," *Lancet*, vol. 377, no. 9778, pp. 1693–1702, May 2011.

[153] Y. Ren, H.-S. Park, and L.-Q. Zhang, "Developing a whole-arm exoskeleton robot with hand opening and closing mechanism for upper limb stroke rehabilitation," in *Proc. IEEE Int. Conf. Rehabil. Robot.*, 2009, pp. 761–765.

[154] E. P. Cherniack, "Not just fun and games: Applications of virtual reality in the identification and rehabilitation of cognitive disorders of the elderly," *Disabil. Rehabil. Assist. Technol.*, vol. 6, no. 4, pp. 283–289, Jul. 2011.

[155] T. A. Thrasher, V. Zivanovic, W. McIlroy, and M. R. Popovic, "Rehabilitation of reaching and grasping function in severe hemiplegic patients using functional electrical stimulation therapy," *Neurorehabil. Neural Repair*, vol. 22, no. 6, pp. 706–714, Nov. 2008.

[156] E. Raffin and F. C. Hummel, "Restoring motor functions after stroke: Multiple approaches and opportunities," *Neuroscientist*, vol. 24, no. 4, pp. 400–416, 2018.

[157] M. C. Tresch, P. Saltiel, and E. Bizzi, "The construction of movement by the spinal cord," *Nat. Neurosci.*, vol. 2, no. 2, pp. 162–167, Feb. 1999.

[158] P. Saltiel, K. Wyler-Duda, A. D'Avella, M. C. Tresch, and E. Bizzi, "Muscle synergies encoded within the spinal cord: Evidence from focal intraspinal NMDA iontophoresis in the frog," *J. Neurophysiol.*, vol. 85, no. 2, pp. 605–619, Feb. 2001.

[159] Y. P. Ivanenko, R. E. Poppele, and F. Lacquaniti, "Five basic muscle activation patterns account for muscle activity during human locomotion: Basic muscle activation patterns," *J. Physiol.*, vol. 556, no. 1, pp. 267–282, Apr. 2004.

[160] N. Dominici *et al.*, "Locomotor primitives in newborn babies and their development," *Science*, vol. 334, no. 6058, pp. 997–999, Nov. 2011.

[161] A. d'Avella, P. Saltiel, and E. Bizzi, "Combinations of muscle synergies in the construction of a natural motor behavior," *Nat. Neurosci.*, vol. 6, no. 3, pp. 300–308, Mar. 2003.

[162] J. J. Kutch and F. J. Valero-Cuevas, "Challenges and new approaches to proving the existence of muscle synergies of neural origin," *PLOS Comput. Biol.*, vol. 8, no. 5, 2012, Art. no. e1002434.

[163] T. Takei, J. Confais, S. Tomatsu, T. Oya, and K. Seki, "Neural basis for hand muscle synergies in the primate spinal cord," *Proc. Nat. Acad. Sci. USA*, vol. 114, no. 32, pp. 8643–8648, Aug. 2017.

[164] P. Saltiel, K. Wyler-Duda, A. d'Avella, R. J. Ajemian, and E. Bizzi, "Localization and connectivity in spinal interneuronal networks: The adduction–caudal extension–flexion rhythm in the frog," *J. Neurophysiol.*, vol. 94, no. 3, pp. 2120–2138, Sep. 2005.

[165] Q. Yang, D. Logan, and S. F. Giszter, "Motor primitives are determined in early development and are then robustly conserved into adulthood," *Proc. Nat. Acad. Sci. USA*, vol. 116, no. 24, pp. 12025–12034, Jun. 2019.

[166] S. A. Overduin, A. d'Avella, J. M. Carmena, and E. Bizzi, "Microstimulation activates a handful of muscle synergies," *Neuron*, vol. 76, no. 6, pp. 1071–1077, Dec. 2012.

[167] S. L. A. Huffmaster, G. M. Van Acker, C. W. Luchies, and P. D. Cheney, "Muscle synergies obtained from comprehensive mapping of the primary motor cortex forelimb representation using high-frequency, long-duration ICMS," *J. Neurophysiol.*, vol. 118, no. 1, pp. 455–470, Jul. 2017.

[168] V. C. K. Cheung *et al.*, "Muscle synergy patterns as physiological markers of motor cortical damage," *Proc. Nat. Acad. Sci. USA*, vol. 109, no. 36, pp. 14652–14656, Sep. 2012.

[169] P. Tropea, V. Monaco, M. Coscia, F. Posteraro, and S. Micera, "Effects of early and intensive neuro-rehabilitative treatment on muscle synergies in acute post-stroke patients: A pilot study," *J. Neuroeng. Rehabil.*, vol. 10, no. 1, p. 103, 2013.

[170] D. J. Clark, L. H. Ting, F. E. Zajac, R. R. Neptune, and S. A. Kautz, "Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke," *J. Neurophysiol.*, vol. 103, no. 2, pp. 844–857, Feb. 2010.

[171] D. Torricelli *et al.*, "Muscle synergies in clinical practice: Theoretical and practical implications," in *Emerging Therapies in Neurorehabilitation II* (Biosystems & Biorobotics), vol. 10, J. L. Pons, R. Raya, and J. González, Eds. Cham, Switzerland: Springer Int., 2016, pp. 251–272.

[172] M. Coscia, P. Tropea, V. Monaco, and S. Micera, "Muscle synergies approach and perspective on application to robot-assisted rehabilitation," in *Rehabilitation Robotics*. San Diego, CA, USA: Elsevier, 2018, pp. 319–331.

[173] D. J. Berger, R. Gentner, T. Edmunds, D. K. Pai, and A. d'Avella, "Differences in adaptation rates after virtual surgeries provide direct evidence for modularity," *J. Neurosci.*, vol. 33, no. 30, pp. 12384–12394, Jul. 2013.

[174] J. W. Krakauer, "Motor learning: Its relevance to stroke recovery and neurorehabilitation," *Current Opin. Neurol.*, vol. 19, no. 1, pp. 84–90, Feb. 2006.

[175] D. A. E. Bolton, J. H. Cauraugh, and H. A. Hausenblas, "Electromyogram-triggered neuromuscular stimulation and stroke motor recovery of arm/hand functions: A meta-analysis," *J. Neurol. Sci.*, vol. 223, no. 2, pp. 121–127, Aug. 2004.

[176] K. Monte-Silva, D. Piscitelli, N. Norouzi-Gheidari, M. A. P. Batalla, P. Archambault, and M. F. Levin, "Electromyogram-related neuromuscular electrical stimulation for restoring wrist and hand movement in poststroke hemiplegia: A systematic review and meta-analysis," *Neurorehabil. Neural Repair*, vol. 33, no. 2, pp. 96–111, Feb. 2019.

[177] L. M. Carey, *Stroke Rehabilitation: Insights From Neuroscience and Imaging*. New York, NY, USA: Oxford Univ. Press, 2017.

[178] J. H. Carr and R. B. Shepherd, Eds., *Movement Science: Foundations for Physical Therapy in Rehabilitation*. 2nd ed. Gaithersburg, MD, USA: Aspen, 2000.

[179] D. M. Corcos *et al.*, "A two-year randomized controlled trial of progressive resistance exercise for Parkinson's disease," *Movement Disord.*, vol. 28, no. 9, pp. 1230–1240, 2013.

[180] S. Subramanian, L. A. Knaut, C. Beaudoin, B. J. McFadyen, A. G. Feldman, and M. F. Levin, "Virtual reality environments for post-stroke arm rehabilitation," *J. Neuroeng. Rehabil.*, vol. 4, no. 1, p. 20, Jun. 2007.

[181] B. Lange *et al.*, "Towards pervasive physical rehabilitation using Microsoft Kinect," in *Proc. 6th Int. Conf. Pervasive Comput. Technol. Healthcare (PervasiveHealth) Workshops*, 2012, pp. 159–162.

[182] S. James, J. Ziviani, R. S. Ware, and R. N. Boyd, "Randomized controlled trial of Web-based multimodal therapy for unilateral cerebral palsy to improve occupational performance," *Develop. Med. Child Neurol.*, vol. 57, no. 6, pp. 530–538, 2015.

[183] P. Lam *et al.*, "A haptic-robotic platform for upper-limb reaching stroke therapy: Preliminary design and evaluation results," *J. Neuroeng. Rehabil.*, vol. 5, no. 1, p. 15, May 2008.