Progress in Biomedical Engineering

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To cite this article before publication: Massimo Sartori *et al* 2021 *Prog. Biomed. Eng.* in press https://doi.org/10.1088/2516-1091/abe3e0

Perspective Article Progress in Biomedical Engineering

Closing the loop between wearable technology and human biology: A new paradigm for steering neuromuscular form and function

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ABSTRACT: Wearable technologies such as bionic limbs, robotic exoskeletons and neuromodulation devices have long been designed with the goal of enhancing human movement. However, current technologies have shown only modest results in healthy individuals and limited clinical impact. A central element hampering progress is that wearable technologies do not interact directly with tissues in the composite neuromuscular system. That is, current wearable systems do not take into account how biological targets (*e.g.,* joints, tendons, muscles, nerves) react to mechanical or electrical stimuli, especially at extreme ends of the spatiotemporal scale (*e.g.,* cell growth over months or years). Here, we outline a framework for 'closing-the-loop' between wearable technology and human biology. We envision a new class of wearable systems that will be classified as "steering devices" rather than "assistive devices" and outline the suggested research roadmap for the next 10-15 years. Wearable systems that *steer*, rather than *assist*, should be capable of delivering coordinated electro-mechanical stimuli to alter, in a controlled way, neuromuscular tissue form and function over time scales ranging from seconds (*e.g.,* a movement cycle) to months (*e.g.,* recovery stage following neuromuscular injuries) and beyond (*e.g.,* across ageing stages). With an emphasis on spinal cord electrical stimulation and exosuits for the lower extremity, we explore developments in three key directions: (1) recording neuromuscular cellular activity from the intact moving human in vivo, (2) predicting tissue function and adaptation in response to electro-mechanical stimuli over time and (3) controlling tissue form and function with enough certainty to induce targeted, positive changes in the future. We discuss how this framework could restore, maintain or augment human movement and set the course for a new era in the development of symbiotic wearable devices. That is, devices designed to directly respond to biological cues to maintain integrity of underlying physiological systems over the lifespan.

1. INTRODUCTION

Preserving the ability to move as we age, or in response to injury, is a key challenge. For decades, scientific effort has aimed at interfacing the human body with robotic restorative technologies such as neuro-modulative devices or exoskeletons, ultimately for enhancing motor capabilities [1]–[3]. Despite advances in surgical procedures, biocompatible implants, and mechatronics, current solutions have had only modest results in healthy [4]–[6] and neurologically impaired individuals [2]. Impact has been hampered by a lack of basic knowledge on how the neuromuscular system responds (in the short-term) and adapts (in the long-term) to device-delivered stimuli, *i.e.* electrical and/or mechanical. Filling this knowledge gap is central for answering a fundamental question at the human-machine interface:

- How should wearable robotic technologies and neuromodulative technologies be controlled to best induce positive restorative changes in users over time?

Recovering from conditions such as muscle paresis, spasticity, or contractures requires profound changes in different parts of the neuromuscular system, *e.g.* at the level of brain plasticity, spinal cord excitability, muscle tone and stiffness [7], [8]. These changes need to be induced and steered gradually over time, to enable an individual's anatomy and motor capacity to undergo structural remodeling. Structural changes in biological tissues are fundamental to the development and physiological integration across organ systems. As we move, our neuromuscular system adapts positively to optimal stimuli. Skeletal muscle, tendon and bone tissues develop, or heal, in response to optimal mechanical strains or loads. Disruptive stimuli, above/below optimal levels can lead to tissue damage/atrophy [9]. A similar analogy holds for the nervous system. Lack of physical training after spinal cord injury or stroke triggers negative neuroplasticity due to loss of appropriate synaptic input to the spinal cord and often results in sensorimotor dysfunction [10].

There currently is no technology that can control stimuli acting on the composite neuromuscular system based on either measured or estimated short-term responses (*e.g.*, within milliseconds) or long-term adaptations (*e.g.*, months to years) in joints, tendons, muscles, and neural circuitries. This is a major element limiting the impact of human-machine interfaces (HMIs) in real-world situations [11].

In this context, the current state of the art includes restorative technologies that are controlled in open-loop with respect to biological tissues. Lower-limb exoskeletons are still predominantly controlled via pre-defined joint trajectories or torque profiles that are prescribed based on pre-assumed body positions across the gait cycle [4] or optimized online to minimize walking metabolic energy [5], [12]. The shape and timing of these profiles is determined 'externally', *i.e.*, not based on estimates of internal body neuromuscular function. Although biological tissue function (*e.g.*, skeletal muscles) contributes to the metabolic cost of walking, measurements of metabolic energy use do not offer the temporal or spatial

resolution required for the precise closed-loop control of the dynamics of targeted individual skeletal muscles. Therefore, even if the exoskeleton assistance would provide a metabolic advantage, it is unknown how the neuromuscular system would re-model, *e.g.,* would muscle-tendon mass or stiffness change in the long term? Would these changes be linked to a biomechanical benefit or to tissue maladaptation? Similarly, spinal cord electrical stimulation technologies operate in open-loop with parameters empirically tuned and with no real-time corrective feedback at the level of motor neuron cellular activity [13]. Restorative technologies controlled without considering the resulting neuromuscular responses hamper translation of personalized rehabilitation and assistive robots for movement enhancement. The ability to incorporate cellular- and tissue-level analyses into closed-loop control schemes could lead to a new class of wearable technologies capable of shaping dynamic function and adaptation of the human neuromuscular system at a level not considered before.

Here, we propose and discuss a new framework for the design and application of external wearable systems that interact based on feedback from the human neuromuscular system, thereby 'closing-the-loop' between wearable technology and human biology (**Fig. 1**). The focus is on lower extremity technologies for neurological impairment including stroke and spinal cord injury. With an emphasis on spinal cord electrical stimulation and exoskeletons, we present developments in three key directions: (1) interfacing with cells in the spino-muscular system, (2) estimating function and adaptation in the spino-muscular system in response to electro-mechanical stimuli and (3) steering the spino-muscular system function and adaptation overtime by continuously adjusting stimulus delivery online.

Within this framework, we envision the birth of a new class of wearable robotic systems to be developed within the next 10-15 years. These will be classified as "steering systems". Wearable robots that *steer*, rather than *assist*, will deliver coordinated electro-mechanical stimuli to alter, in a controlled way, neuromuscular form and function across recovery or ageing stages (**Fig. 1**).

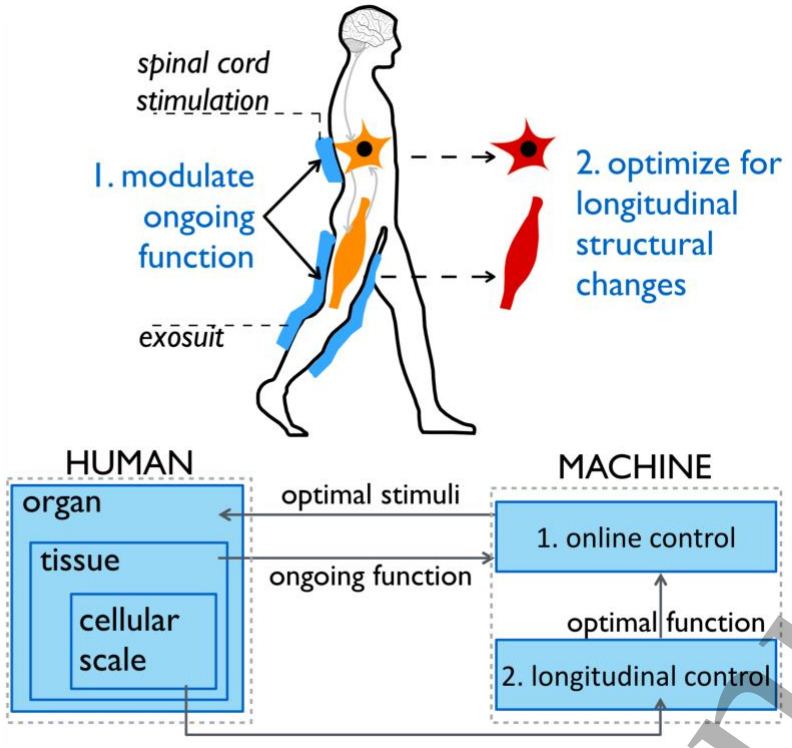

Figure 1. A conceptual framework for the closed-loop control of wearable robotic systems to steer neuromuscular tissue structure and function over time. A multi-system and multiscale human-machine interface (HMI) architecture to enable controlling spinal cord stimulation and exosuit technologies based on the activity of the underlying neuro-muscular system. Integrating novel bio-sensing techniques (**Fig. 2, Section 2**) with novel multi-scale data-model fusion formulations (**Fig. 3, Section 3**) into novel closed-loop control schemes (**Fig. 4, Section 4**) could help deliver electrical stimuli and mechanical loads to the neuro-muscular system that best enhance motor function and optimize for structural changes across short-to-long time scales.

2. INTERFACING WITH THE SPINO-MUSCULAR SYSTEM

Although neural activity associated with the control of movement can be recorded from the brain, the spinal cord is the *locus* of afferent somatosensory and efferent motor inputs [14]. Therefore, recording and interpreting events in the composite spino-muscular system, is central for understanding motor control [15], [16]. Focusing on spinal cord neural activity is central not only for injuries of spinal origin but also for injuries of cortical origin [14], [17]. Positive spinal cord neuroplasticity has been shown to promote brain neuroplasticity in both spinal cord injury and post-stroke subjects [14]. In this section we present an approach for recording spinal and muscular cell activity in the intact, moving human *in vivo*.

2.1. Recording neural cell activity associated to the control of movement

We propose to use muscles as a biological interface with the spinal cord [18], [19]. The activity of spinal neural cells can be inferred in a clinically viable way (*e.g.* non-invasively) by means of soft electronic skins, which are bi-dimensional grids containing tens of electrodes closely located with one another, *e.g.* < 5 mm inter-electrode distance. These grids can be placed in the correspondence of a muscle on the skin surface and enable recording high-density electromyograms (HD-EMGs); weak electrical signals generated by hundreds of muscle fibres simultaneously (**Fig. 2A**).

Because muscle fibres are directly innervated by α-motor neurons in the spinal cord's ventral horn, HD-EMGs carry neural information in the form of an interferent signal. Given the safe synaptic connection between α-motor neuron and innervated muscle fibres, there is a one-to-one relationship

between motor neuron action potentials and those elicited in innervated muscle fibres [20]. Therefore, each motor neuron action potential is transduced into a compound muscle fibre action potential that carries the same neural code. Using advanced signal processing techniques such as deconvolution-based blind source separation, it is possible to decompose the interferent HD-EMG into the contribution of underlying α-motor neurons that are active in the control of the muscle [18], [19]. This provides access to trains of motor neuron discharges, the same feature that invasive direct nerve interfacing would extract with implanted electrodes (**Fig. 2A**) [19].

This process relies on the development of a mathematical model of the EMG mixing process. This may be expressed as the convolution between finite impulse response filter and delta functions, where the finite impulse response filter represents muscle fiber action potential and delta function the innervating alpha motor neuron spike events [21]. The objective is to unmix the neural spike events from the recorded HD-EMG signals. **Fig. 2B** shows an example of how HD-EMGs recorded from the soleus muscle can be decomposed to reveal underlying motor neuron spike trains during an isometric contraction [18]. Section 5 discusses the challenges to be tackled to enable decomposition algorithms to be valid across muscle dynamic contraction types, *i.e.*, isometric, concentric and eccentric.

The authors recently used HD-EMG recordings from five ankle muscles using more than 250 recording sites and demonstrated how multi-muscle spatial sampling and deconvolution of high-density fiber electrical activity can be used to decode accurate α-motor neuron discharges across five lumbosacral segments in the human spinal cord [18], [22]. This is an important step that will enable understanding of how hundreds of α-motor neurons interact with each other's for the control of multi-muscle contraction *in vivo*. Decoded motor neuron information could be directly used to generate high-fidelity estimates of how different lumbosacral segments in the spinal cord are activated for the control of the ankle joint, a key feature that could help understand how impairment alters spinal cord neuromechanics and how external intervention may restore normative physiological function. This approach was recently employed to infer how synaptic input to α-motor neurons is altered in response to trans-spinal electrical stimulation in a group of incomplete spinal cord injury patients [23].

HD-EMG and related signal processing can also be used to understand how the central nervous system (CNS) modulates neuromechanical delays, a factor that is central to understanding closed-loop motor control strategies in humans [24]. The neuromechanical delay is the latency between motor neuron discharges and the generation of mechanical force in muscle-tendon units. HD-EMG studies have revealed that neuromechanical delays are modulated by the CNS as a function of the rate of muscle force generation, where recruitment of fast *versus* slow motor units drives a decrease *versus* increase of ongoing neuromechanical delays, respectively. Similar techniques were used to understand how α-

motor neurons receive synaptic input not only from muscular and spinal levels but also from supraspinal levels [25], [26].

2.2. Recording muscular cell activity associated to the control of movement

In addition to using HD-EMGs to extract the neural input to a given muscle it is also possible to non-invasively monitor the resulting functional output from muscles at different spatial scales. B-mode ultrasonography (USG) has become the standard approach used to image muscle fascicles during dynamic contractions in both healthy and impaired individuals [27], [28]. Recently, USG was employed to study how bi-lateral ankle exoskeletons influence muscle mechanics during human locomotion, establishing a path toward closed-loop control of wearable robotics based on measured muscle dynamics [29], [30]. Automated image processing of B-mode images [31]–[33] is also accelerating toward the possibility for real-time tracking of muscle length and shape changes *in vivo* [34], [35]. Developments in machine learning have enabled automated measurements of muscle architectural properties as well as fascicle length and pennation angle during dynamic contractions [36]–[38]. Recent advances in microscopy have enabled direct muscle imaging at the sub-cellular scale, *i.e.*, imaging of individual sarcomere lengths and contractility in striated muscles across the human body, without surgery or anesthesia [39]–[41]. However, sarcomere-level analysis of muscle function is yet to be translated into fully portable and clinically viable solutions. Other measurement and signal processing techniques including shear wave elastography [42] to measure muscle stiffness, speckle-tracking to extract tendinous tissue strain from ultrasound radio frequency signals [43] and most recently, tensiometry to measure tendon stress are also unlocking the possibility to non-invasively measure muscle-tendon forces *in vivo* [44], [45].

The possibility of combining HD-EMG techniques (Section 2.1) with clinically viable muscle imaging techniques (*e.g.*, B-mode USG, Section 2.2) and neuromuscular modelling (Section 3), has the potential to unlock a window into broader spinal neural mechanisms and their influence on mechanical force generation. For example, leveraging these simultaneous input-output recordings could give insight into how the nervous system controls muscle force generation in a quantal manner by successively recruiting motor units of increasing size as well as how these processes are altered by aging, training or injury. Overall, the combination of HD-EMG, USG and data-driven modelling may provide a generic paradigm to decode mechanical function from different sources of neural information (**Figs 1-2**); *e.g.*, muscle surface or indwelling electrodes, nerve intrafascicular electrodes [46], epimysial devices [47].

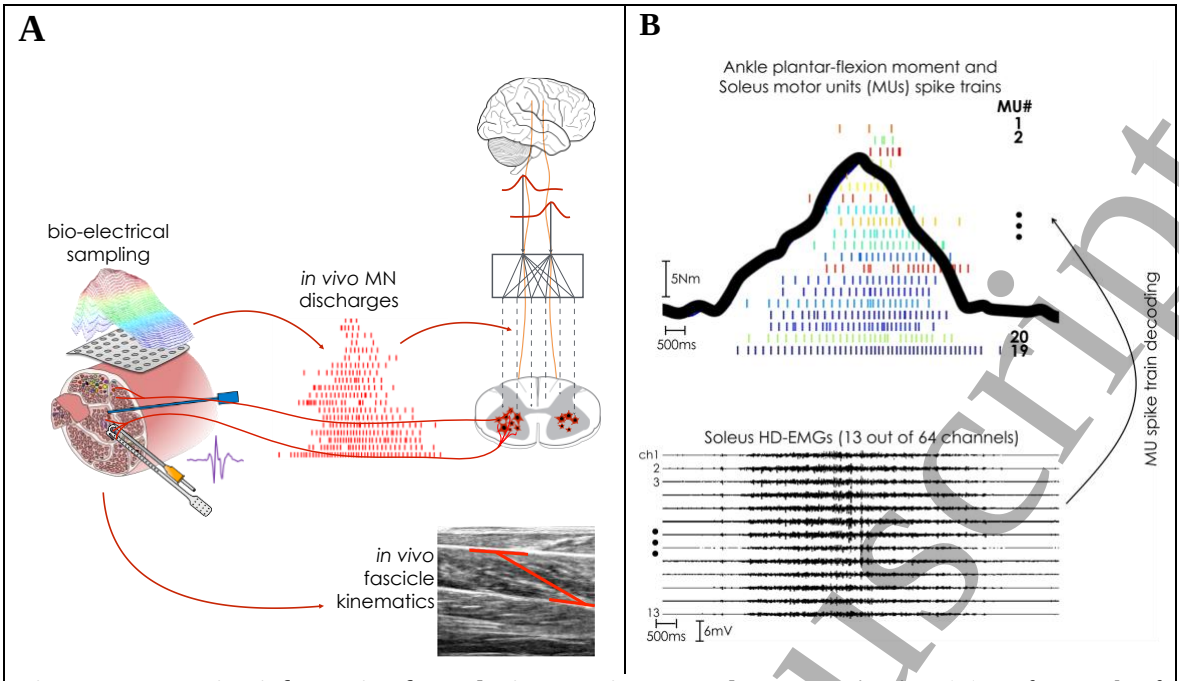

Figure 2. Extracting information from the intact spino-muscular system *in vivo*. (A) Surface grids of closely located electrodes in combination with intramuscular fine wire electrodes can be used to record high-density electromyograms (HD-EMG). Given the safe synaptic connection between α-motor neuron in the spinal cord and innervated muscle fibers (*i.e.*, motor units, or MUs), there is a one-to-one relationship between motor neuron and innervated fibers' electrical activity. From these recordings, deconvolution-based blind source separation can be used to extract the contribution of the α-motor neuron active in the control of a given muscle. In addition, ultrasonography (USG) can be used concurrently to measure the kinematics of muscle fascicles in response to neural discharges. From these images, fully or semi-automated algorithms can be used to measure length and pennation angle of a given muscle. In combination, these signals provide comprehensive *in vivo* recordings of individual muscle neuro-mechanical function. **(B)** The interferent electromyogram can be separated into its central and peripheral components. High-density electromyograms (HD-EMGs) visualized for 13 out of 64 channels located in the middle column of a 13 × 5 electrode grid. This exemplary signal is recorded from the soleus muscle during a 30% maximal voluntary contraction performed with the ankle joint at neutral position. Experimental ankle plantar-dorsi flexion moment (continuous curve) is depicted synchronously with soleus HD-EMG and the decoded α-motor neuron discharge events (spike trains).

3. PREDICTING SPINO-MUSCULAR FUNCTION AND ADAPTATION

Neuromuscular models that can be driven in real-time by recordings of a user's neuromuscular cellular activity will be critical for implementing devices that can operate in closed-loop feedback with biological variables that are difficult to measure (*e.g.*, individual muscle force or stiffness). These models should predict how an individual user's neuromuscular system reacts and adapts to device-delivered electro-mechanical stimuli to the body (**Fig. 3**). In the remainder of this Section we propose a framework for the development of data-driven models of neuromuscular function (Section 3.1) and adaptation (Section 3.2).

3.1. Data-driven models of neuromuscular function

Recordings of *in vivo* motor neuron discharges and muscle fascicle kinematics (Section 2) [18], [19] can be used to drive an *in silico* framework that hosts numerical models of spinal neural networks and the musculoskeletal system, **Fig. 3A** [48].

3.1.1. Numerical models of the musculoskeletal system

The musculoskeletal modelling framework we propose comprises six main components inspired by the authors' previous work [49]–[57]. *The neural activation component:* converts incoming motor neuron discharges into resulting twitch responses triggered in the innervated muscle fibers using a critically damped, linear, second-order, differential system [58], expressed in a discrete form using a time history-dependent, infinite impulsive response filter [59]. The resulting signal is further processed via a nonlinear transfer function to compute the resulting neural activation, reflecting the ensemble dynamics of all electro-chemical transformations triggered at the muscle fiber level by the motor neuron discharges [11].

The musculotendon kinematics component: synthetizes subject-specific musculoskeletal geometry models into a set of muscle-specific multidimensional cubic B-splines [52]. Each B-spline computes musculotendon length and moment arms as a function of input joint angles [52].

The musculotendon dynamics component: uses HD-EMG-derived neural activation (Section 2.1) and USG-derived fascicle kinematics recordings (*i.e.*, estimates of instantaneous length and contraction velocity, Section 2.2) to drive a Hill-type muscle model and compute viscoelastic force in the muscle fibers, as well as strain and force in the series-elastic tendon [49], [50]. The static properties of muscle fibers are modelled using parallel force-length passive and activation-dependent curves [59]. The dynamic properties of fibers are modelled using an activation-dependent force-velocity curve. The tendon properties are modelled using a force-strain function with non-linear toe region [60].

The joint interaction dynamics component: transfer of musculotendon forces to the skeletal joint level using musculotendon moment arms.

3.1.2. Numerical models of spinal neural networks

Modelling muscle proprioceptors: Numerical models of muscle spindles can be created and placed in parallel to muscle fibers (Section 3.1.1), receiving commands from gamma motor neurons [61]–[63]. Numerical models of Golgi tendon organs can be placed in series with elastic tendon models (Section 3.1.1). Proprioceptive feedback to spinal neurons can be modelled via Ia, II and Ib axons mediating fundamental pathways associated with standing/gait, *e.g.* monosynaptic Ia excitations, di-synaptic Ib inhibition, di-synaptic II excitation, reciprocal inhibition from antagonist Ia afferents [64].

Modelling spinal neural networks: Models can be created that capture the integration of signals formed by combinations of alpha motor neurons and inter-neurons including inputs from musculoskeletal afferents and supraspinal drive. Motor neuron types (S-, FR-, FF-type) can be modelled as two-

compartment conductance-based neuron models, with one compartment for the soma and one compartment for one dendrite and with motor axons represented as simple spike conductors transferring one spike from soma to end-plate with a given delay dictated by conduction velocity and distance [65]. Inter neurons can be modelled with a single compartment [66]. In this context, the distribution of motor neuron type can be inferred via HD-EMG decomposition techniques, *e.g.* by extracting motor unit properties that can be related to motor neuron types including fiber diameter and contraction speed [67].

3.1.3. Driving models of neuromuscular function

The *in silico* framework proposed in Section 3.1.2 can be controlled so that synthetic inter-neurons, α-motor neurons and sensory fibers fire to reproduce *in vivo* recordings of discharges extracted from HD-EMG as described in Section 2. This validation step would give confidence that simulations are neuro-mechanically consistent with *in silico* spinal cord and musculoskeletal structures interacting to reproduce an individual's *in vivo* neuro-muscular function.

The approach we propose is in contrast to available methods that solve for individual muscle contributions to joint actuation according to *a priori*-defined optimization criteria (*e.g.*, minimize squared muscle activation sum, cost of transport) [68]–[70] or muscle and spinal reflex rules, *i.e.* stretch reflex, positive force feedback, reciprocal inhibition [71]. Although current theoretical models provide a valuable starting point for the computational investigation of motor function, they cannot capture subject-specific signatures of *in vivo* neuromuscular function [72], [73], and thus are limited when extrapolating to novel conditions. Even though one model can be tuned to reproduce experimental outputs (*i.e.*, muscle activity) in one instance [74], synergies between muscles [75], or even between motor units [15], are highly variable across motor tasks [76], [77], pathology [78], and directly influenced by assistive devices [79].

The feasibility of the approach we propose is supported by recent results. Along with colleagues we have developed physiologically correct computational models of the human musculoskeletal system driven by EMG-derived excitations [49], [51], [52] and by low-dimensional sets of excitation primitives [80], rather than pre-defined mathematical rules. This approach avoided *a priori* assumptions on muscle neural recruitment strategies [49] and allowed us to extrapolate across conditions, *e.g.* motor tasks, training, impairment levels [81]. This concept was generalized to estimate torques about multiple degrees of freedom and to satisfy multiple mechanical constraints including multi-joint moments [49], [82], compressive loads [83], [84] and dynamic joint stiffness [85], a central component for understanding mechanical function in redundant musculoskeletal systems. Current developments are now linking *in vivo* α-motor neuron cellular discharges decoded from electrophysiological recordings with subject-specific musculoskeletal models, **Figs, 2-3** [18]. This is a paradigm shift from current

formulations that are driven by global EMGs, where underlying motor neuron behavior is hidden within the EMG envelope failing to reveal the neuro-muscular processes of human movement [18].

3.2. Data-driven models of neuromuscular adaptation

Wearable systems interacting with the human body can only become pervasive if they take into account the variable nature of the human body. By a simplified example, the same neural command to a muscle would yield different force profiles (*i.e.*, function) depending on the muscle form. (*e.g.*, changes in muscle cross-sectional area or tendon compliance post-impairment or post-training [20]). In this context, multi-scale musculoskeletal modelling would have great potential to reveal the interplay between form and function with unexplored opportunities for personalizing wearable robots to the structural features of individual users [86].

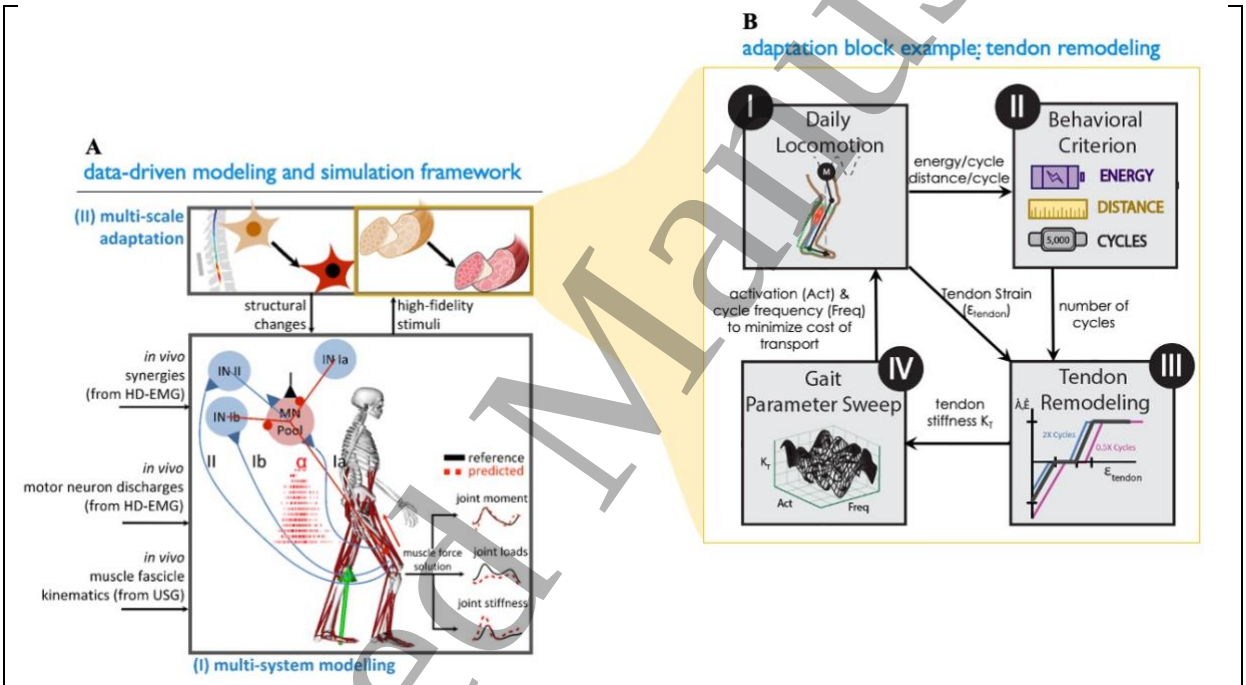

Figure 3. Multi-system and multi-scale data-driven modeling and simulation. (A) We record neuromuscular activity *in vivo* via high-density surface/intramuscular electromyography (HD-EMG) and ultrasonography (USG). We establish neuromuscular models that track *in vivo* data and estimate a larger spectrum of neuromuscular mechanisms than is possible via signal-based techniques alone (panel I). This creates neuro-mechanically consistent estimates of neural discharges and muscle forces, which provide high-fidelity stimuli to drive multi-scale models of neuromuscular structural adaptation (panel II). **(B)** A concrete example of (A). Simulating long-term tendon adaptation to gait-induced mechanical stimuli. A simplified neuro-mechanical simulation of human locomotion (panel I) is used to generate estimates of energy consumed per muscle-tendon unit and distance travelled over a day of walking under different behavioral criteria (*e.g.*, when constraining cumulative energy used, distance travelled, or number of gait cycles, panel II). Using tendon strain (ε_{Tendon}) per cycle and the number of walking cycles per day as inputs, a tendon remodeling algorithm (panel III), can predict changes in tendon tissue stiffness (K_T) per day. Finally, the new resulting tendon structure can be used to generate a new neuromuscular model that will walk with updated muscle activation and cycle frequency (panel IV). These long-term estimates could help provide forward prediction of how loading patterns from wearable robotic devices influence musculoskeletal structures over long time scales (*e.g.*, 100s of days).

Models of the neuro-muscular system can be personalized to each individual's morphology (*i.e.*, form) and host multi-scale formulations to understand how structural changes in molecular, cellular, tissue-scale mechanisms alter organ-scale form and therefore function [87]–[89]. In this context, the primary challenge is that of determining the body internal stimuli that initiate structural changes at (sub)cellular scales in different parts of the neuro-muscular system. As a result, current multi-scale formulations are not yet data-driven by an individual's neuromuscular biological signals and fail to reproduce *in vivo* function.

The framework we proposed in Section 3.1 (**Fig. 3A**) enables capturing neuro-mechanically consistent estimates of synaptic inputs to spinal motor neuron cells and resulting forces acting on musculoskeletal tissues. We propose that this information can be used to determine the stimuli acting on pools of motor neuron and musculotendon tissues as a way to drive predictive simulations of cellular-to-organ scale structural remodeling over longer time scales (*e.g.*, days to weeks to months). (**Fig. 3A and 3B**).

3.2.1. Models of musculoskeletal structural adaptation

We propose to employ discretized models of muscles and tendons [90]–[92]. These models are defined along with an initial configuration of the constituent structures from (sub)cellular, to tissues and organ scales. An initial configuration dictates the organ-scale force generating properties.

For instance, for a multi-scale muscle model, the initial configuration may include, at the tissue scale, the number of fascicles as well as the distribution of their lengths and their extracellular matrix stiffness. At the cellular scale it may include the number of fibers within a fascicle along with the distribution of their lengths. At the sub-cellular scale, configuration parameters may include the number of serial/parallel sarcomeres, which in turn dictates individual fiber length. At the molecular scale it may include titin and myosin isoform types, which in turn dictates sarcomere contractile properties [92].

Structural changes at (sub)cellular scales are propagated to larger scales, thereby dictating organ behavior (**Fig. 3B)**. A statistical model could be used to predict the likelihood of a mechanobiological trigger for a given muscle adaptation process. For example, if there is high likelihood that muscle strain rate exceeds a threshold value given a randomly sampled combination of muscle contractile variables (*e.g.*, motor unit firing rate, resulting force), duty cycle and input mechanical stimuli (*i.e.*, under/overstretch, under/overload), then new sarcomeres could be generated in the model adjusting the rest length of the muscle [93], [94].

In this context, given the number of cycles during which the muscle undergoes above-baseline stimuli (*e.g.*, over stretch) we propose to employ phenomenological laws to compute molecule-to-organ remodeling. In addition to an increase in serial sarcomere number, these could include upregulated

expression of myosin and titin isoforms, increase in fiber length, or increase in extracellular matrix stiffness [90], [95]. The process continues until tissue homeostasis is reached or stimuli go below baseline, thereby resulting in a new steady-state muscle-tendon structural configuration. [90]–[92] (**Fig. 3B).**

In this context, implementing phenomenological laws (as opposed to explicit finite element techniques), could provide a balance between physiological accuracy and computational tractability, central for translation to real-time closed-loop control scenarios (Section 4) [96]–[98].

3.2.2. Models of neural structural adaptation

We propose to model structural adaptation in the spinal cord using descriptive models built from spinal synergy theory [99]–[101], rather than predictive models as described in the previous Sections. Tissue composition in the spinal cord is more diverse than in muscles and tendons. While muscle composition is uniform across length scales and therefore suitable for being modeled via scale-specific mechanobiology theory, composition across spinal cord spatial scales is complex. A cross section of the spinal cord includes white matter, grey matter with motor neurons, interneurons, sensory, nociceptive fibers [20]. As a result, the concept of tissue and organ scales in the spinal cord is less appropriate. It would be more appropriate to talk about the existence of different spinal systems and circuits, composed of interacting cells [102].

We propose to employ HD-EMG-based techniques (Section 2.1) to determine changes in motor neuron behavior and how these reflect spinal circuit organization [18], [23]. In a first instance, this information can be inferred by applying dimensionality reduction techniques to alpha motor neuron spike trains in the time-domain (*i.e.*, NMF) [103]. Changes in muscle modularity (*i.e.*, either at the level of muscle weightings or non-negative factors) across mid-to-long time scales may indicate whether there has been structural reorganization in spinal motor circuitries (**Figs 2**).

Alternatively, spinal circuitries organization can be inferred by applying frequency-domain analysis to HD-EMG-decomposed motor neuron spike trains [23]. In this context, we propose to use inter-spike coherence analysis to infer how synaptic input from spinal and supraspinal centers is projected onto alpha motor neuron pools [23], [104]. In this context, common and independent synaptic input can be inferred via coherence analysis, which is a measure of linear correlation (*i.e.*, commonality) in frequency domain. Common synaptic input refers to the proportion of the sum of excitatory and inhibitory inputs that are common to all motor neurons in a pool. Therefore, common input can be studied by applying coherence analysis between pairs of cumulative spike trains built from increasingly bigger sets of motor neurons. The number of motor neurons within each set at which coherence plateaus indicates the strength of the common input into the pool. The earlier it plateaus the more the proportion

of common *versus* independent input. Common input is the main determinant of force production *i.e.*, any synaptic input has to be common to all motor neurons in the pool for this command to regulate muscle force [25]. This has strong analogies with the concept of spinal synergies. We propose that alterations in the strength of common input can be used to infer short-to-long-terms spinal circuitries changes.

This multi-scale framework will enable capturing high-fidelity *in vivo* and *in silico* cellular activity in different parts of the neuro-muscular system and determine the potential that this has to induce structural changes in tissue/organ-scales. This will enable predicting how an individual's motor capacity evolves over time in response to physically interacting wearable devices.

The feasibility of the proposed approach is supported by our results along with colleagues. Recent developments enabled personalizing musculoskeletal models to match both an individual's morphology [49], [82], [105] and muscle force-generating capacity. This is central for characterizing the actual mechanical forces acting on musculotendon tissues, which drive structural adaptation. Multi-scale musculoskeletal models are being created to host formulations driven by EMGs [48], [86], [106] and by motor neuron cellular activity [18]. This is enabling the investigation of how neurally-driven musculotendon units interact with skeletal tissues and induce microstructural bone remodelling [84]. These multi-scale formulations are now being extended to study neuro-motor disorders underlying spasticity [48], *i.e.* **Fig 3.** This is providing the basis for modelling the neuromusculoskeletal system across spatiotemporal scales, *i.e.*, seconds/minutes for muscle signals and months for bone remodelling [86]. Validation of these models is being performed against *in vivo* loads from instrumented total knee replacements [83], *ex vivo* hip loads [84], and moments from inverse dynamics [49], [82].

4. STEERING SPINO-MUSCULAR FUNCTION AND ADAPTATION

The previous two sections proposed the development of clinically viable techniques to record motor neuron activity and muscle fascicle dynamics from the intact moving human *in vivo* (Section 2, **Fig. 2**) and then use it to drive numerical models of the composite neuromuscular system (Section 3, **Fig. 3**). Here we propose to use these data-driven models in real-time to determine the optimal combination of device stimuli required to alter ongoing neuromuscular function as well as its future adaptation, **Fig. 4.** This is the central step for moving beyond conventional wearable robots with fixed control parameter to a paradigm for continuously adaptive control over broad time scales.

The idea is to steer neuromuscular physiology in closed-loop, with the on/off timing and shape of wearable robot assistance patterns prescribed to interact directly with biological tissues. In practice, this would manifest as torque profiles sent to biological joints or electrical pulse trains sent to spinal neurons (**Fig. 1**). Exoskeleton-generated torque profiles could be parameterized, for instance, as a function of

peak torque, time to peak, and rise-fall times [5]. Pulse trains could be parameterized as a function of electrode-on-body position, pulse amplitude, width, and frequency. We the propose to develop online optimization-based controllers for exoskeleton and neurostimulator devices that close the loop with relevant neuromuscular states (*e.g.,* alpha motor neuron excitability, muscle operating strain and force, tendon tension, joint stiffness, **Figs 1, 3-4**). While subjects perform cyclic motor tasks (*e.g.*, walking or running), an online optimizer would periodically select a machine control law (*i.e.*, a combination of stimulation and/or actuation parameters) based on exploration in broad, but relevant parameter spaces spanning possible torque and electrical stimulation profiles. The effect on target neuromuscular structures would be captured *in vivo* via subject-specific, data-model fusion formulations (**Fig. 3**). An iterative process, whereby many candidate control laws and associated multi-scale physiological responses are explored and logged [5], it is expected that the online optimizer will have identified the optimal control law that brings target tissues closest to desired steady-state (**Figs 1 and 4)** [107].

As one example, this may enable neurologically injured patients to experience device-induced "physiological gait" (*i.e.,* reduced state of spasticity, paresis), which will gradually lead to pre-planned neural and musculoskeletal changes that structurally repair dysfunctional movement over time. This scenario may involve patients receiving mechanical torque and electrical stimuli simultaneously (**Fig. 1**). A similar approach may be employed in the context of robotic exoskeletons alone as inspired in part by recent animal work where *in vivo* muscle fascicle length recordings were used for the closed-loop control of muscle force [107]. In this context, we propose to develop data-driven models that can non-invasively sample muscle activation (*e.g.,* with HD-EMG) as well as fascicle length and velocity (*e.g,* with USG), estimate the force potential and then update the exoskeleton torque profile to steer fascicle dynamics as desired [107]. On longer time scales we envision semi-active exoskeletons with hierarchical feedback control structures that employ (1) online servo-based control of tissue strain (**Fig. 4A**) where the reference strain pattern is optimally prescribed by (2) a model-based control scheme that maps tissue strain to optimize mechanobiological processes and steer tissue properties in a targeted manner. For example, in concept, this novel class of hierarchical wearable robot controllers would be capable of applying continuously optimal exoskeletal loading patterns to non-invasively manipulate tissues *in vivo* to induce micro-ruptures that facilitate anabolic processes and promote growth and repair (**Fig. 4B**).

The key is the ability to non-invasively steer target neuromuscular structures with a high spatio-temporal resolution throughout everyday life. Since using a pure sensor-based approach is unrealistic *in vivo*, we envision the next generation of wearable robots will incorporate wearable sensing capable of directly extracting *in vivo* states (*e.g.*, electromyography surface electrodes, pulse oximetry units, and/or thin-film low-profile ultrasonography probes) or sampling a subset of states to drive forward subject-specific, neuromuscular models simultaneously running *in silico*. It is worth stressing that the

combination of *in vivo* and *in silico* processes observable via this hybrid approach (**Figs 3-4**) is more comprehensive than what is observable via signal-based or model-based approaches alone. This could provide a framework to inform wearable device controllers of the user's current physiological state [6], [108], and determine the optimal combination of device stimuli required to alter neuromuscular function and adaptation across time scales (**Fig. 4**).

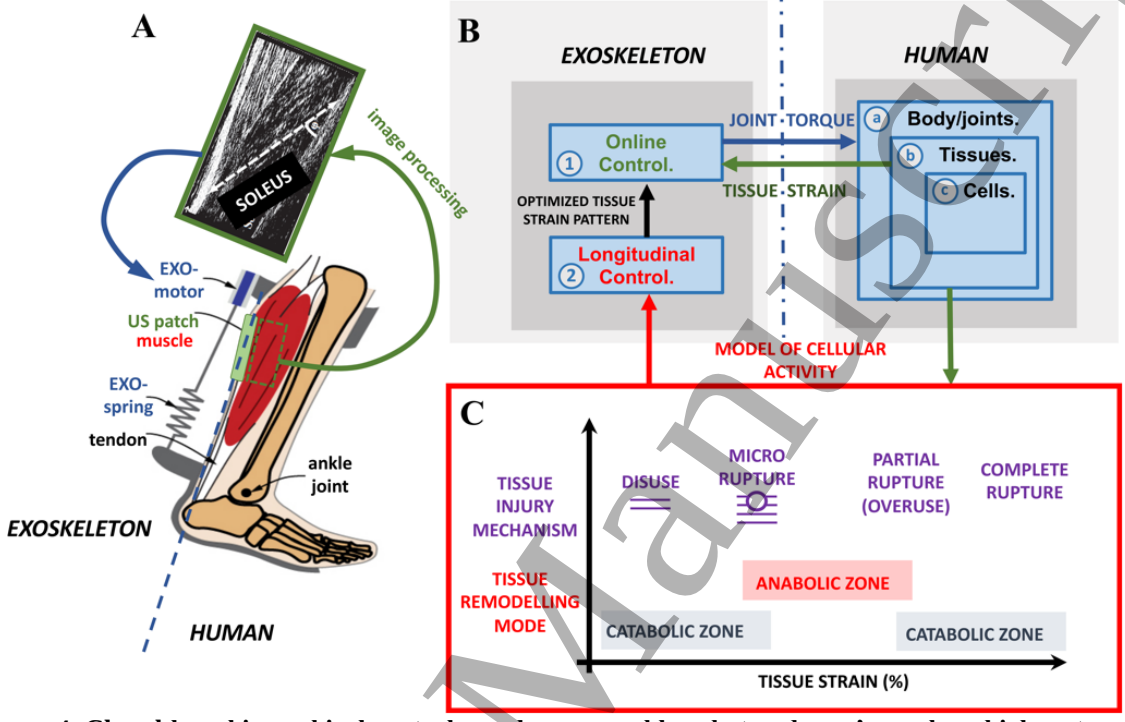

Figure 4. Closed-loop hierarchical control couples a wearable robot and user's mechanobiology to non-invasivley steer musculoskeletal tissue properties (A) The proposed exoskeleton system hardware includes an elastic actuator (EXO-motor and spring) that can apply torque about the ankle joint to modify loading on the human plantarflexor muscle-tendons (MT) and a non-invasive ultrasound (USG) sensor that can sample muscle fascicle and/or MT junction displacements in real-time. (B) The exoskeleton employs a hierarchical controller with (1) online (milliseconds) and (2) longitudinal (>minutes) components. The online controller sends commands to the exoskeleton motor producing torques that modify forces and strains of underlying tissues in order to maintain a desired 'optimized' reference strain pattern of the muscle or tendon based on real-time feedback of displacement from USG measurements. (C) The longitudinal controller feeds optimal strain patterns (*i.e.*, desired reference for (1)) using an adaptive model that can accurately map tissue strain to likelihood for tissue injury and/or atrophy/hypertrophy (*i.e.* also see **Fig. 3**). Sophisticated versions might employ machine learning techniques and a cumulative historical data set to continuously improve the mapping between an individual user's specific tissue strains and their unique biomarker derived mechanobiological states over time.

This is all in contrast with current techniques that operate neuromodulators and exoskeletons based on surrogate measures of body function. State of the art lower limb exoskeletons are designed to reduce lower-limb joint moments and powers as an indirect way to decrease metabolic rate of locomotion [6]. However, mounting evidence is casting doubt on the links between a user's metabolic energy consumption and measures of limb-joint moments and power. Indeed, changes in biological mechanical power at the center of mass, joint-, or muscle-level are unable to explain how exoskeletons alter users' metabolic rate [6]. Similarly, state of the art sub-threshold spinal cord electrical stimulation is used to

modulate neural activity and induce spinal plastic changes [109], rather than establishing functional neuroprostheses with bi-directional connections across the human-machine interface. In spinal cord injury [110] and stroke patients [111], sub-threshold stimulation can suppress severe lower limb spasticity and enable limb movement in motor-complete spinal cord lesions [112]. In this case, neuromodulation of the sub-threshold motor state of spinal excitability is the key to recovery[112], [113]. However, while spinal cord electrical stimulation has become a standard for treating chronic pain, its use for treating motor dysfunctions such as spasticity is limited [114]. In short, the fact that spinal cord stimulation methodologies largely operate in open-loop, irrespectively of motor neuron cellular activity and musculoskeletal forces, has hindered its utility.

The direct feedback that we propose to establish between wearable robot and human spino-muscular function may provide guidance for achieving a more complete symbiosis between human and robot. We contend that robots that can seamlessly estimate and then steer spino-muscular dynamics may provide greater locomotion performance benefits than current devices that reach beyond merely improving walking and running economy.

Our research with colleagues supports the feasibility of the closed-loop approach (**Fig. 1**). We have demonstrated EMG-driven modelling methods [11], [82], [85] to determine how a quadriceps weakness patient's would walk with the aid of a passive ankle-knee orthosis [115], and how a transfemoral amputee would walk using a microprocessor controlled prostheses[11], [51], [116]. Since then, we have translated these methods in order to operate in real-time [81], and demonstrated that stroke and SCI patients can voluntarily control bilateral a knee-ankle-joint exoskeletons in real-time [117], [118]. Ongoing work is aimed at demonstrating the possibility of decoding α-motor neuron discharges and approximating the distribution of their activity across lumbosacral segments in the human spinal cord [18] in order to infer how spinal motor neurons react to electrical stimuli in spinal cord injury patients [23]. Finally, we have recently demonstrated that it is possible to record EMG and B-mode USG images of plantarflexor muscle fascicles during locomotion with a robotic ankle exoskeleton, giving access to the necessary signals for closed-loop control schemes [29] (*e.g.*, **Fig. 4B**). These and future breakthroughs will enable new paradigms for closing the loop between neuro-muscular cellular processes and neuromodulation and mechatronic technologies.

5. DISCUSSION

Our goal was to establish a framework and outline the steps necessary to achieve HMIs capable of connecting spinal cord electrical stimulators and exoskeleton technologies to an individual's spino-muscular system. It is worth stressing this manuscript describes a possible roadmap for achieving steering robotic technologies within the next decade and not a set of readily available technologies that can be employed immediately.

Our proposed approach is based on three steps. First, the use of non-invasive wearable sensors including high-density wearable electrodes and transducers to record HD-EMG and USG data, from which decoding activity of spinal motor neurons and muscle fascicles with high spatio-temporal resolution (Section 2). Second, the use of decoded motor neurons and muscle fascicle activity to inform multi-scale models of the composite neuromuscular system. This enables observing a more comprehensive set of neuromuscular processes than would be possible via signal-based or model-based approaches alone (Section 3). Third, we propose to complement multi-scale models with statistical modelling to enable simulation of neuromuscular tissue adaptation and remodelling across time scales (Section 3). When incorporated within real-time control schemes (Section 4), this framework will enable direct tissue-machine interaction via multiple pathways. That is, interaction with a group of muscles or spinal circuitries will be achieved by altering both the neural drive (via spinal cord electrical stimulation) as well as the mechanical load (via exoskeletons or exosuits) to a given group of muscles.

In combination, this would allow for control of tissue states across a broad spatio-temporal range that has so far, been out of reach. Closing the loop between robot hardware, modelling software, and the user's biological systems (*e.g.*, both musculoskeletal and neural tissues) will lead to a new class of devices capable of steering human neuromechanical structure and function over both short and long timescales. On the shortest of time scales, robots that have access to neuromuscular state information have the potential to modify efferent neural drive to muscles (*i.e.* common synaptic input to motor neuron pool) [23] as well as sensory feedback (*i.e.* from muscle afferent fibers or mechanoreceptors) and augment dynamic balance and locomotion. On the longest of time scales, robots can gain access to biomarkers indicating cellular and tissue degradation in the composite neuromuscular system, *i.e.* maladaptation at the level of motor neuron excitability levels, muscle volume, or tendon stiffness. This information could be directly used in closed-loop controllers (**Figs 1 and 4**) to modify external electro-mechanical stimuli to the human body and shape remodelling in both nervous and muscular tissues to ultimately provide a neuro-mechanical benefit for the user, *i.e.* reduction in tissues peak loads to prevent tearing, preservation of tissue tension to prevent atrophy, reduction of muscle spasticity in patients to enhance voluntary limb control during rehabilitation [23], [107], [108].

Achieving this novel closed-loop HMI infrastructure will require tackling a number of challenges in the future decade. The HD-EMG recording and processing methods as well as the neuromechanical modelling techniques presented in Sections 2 and 3 need to be based on fully wearable sensing solutions and operate in real-time. This will require substantial innovation both at the level of hardware and software. New types of portable and wearable sensors will be required to measure HD-EMG- and USG-data during dynamic muscle contraction underlying tasks such as locomotion or rehabilitation exercises. Stretchable electronics represent good candidates for developing soft electrode grids that can interact

with and adapt to human limbs soft tissues, thereby always assuring electrode-to-skin contact [119]. Recent developments in printed tattoo-like electronics for EMG recordings showed potentials for assuring signal transmission at the electrode-skin interface [120]. More tangible solutions may also rely on stretchable textile electrodes directly embedded into smart sensor-equipped clothing [121]. This all will enhance electrode-to-skin stability, thereby achieving prolonged use in day-to-day scenarios. Similarly, thin-film transducers can be embedded directly in wearable garments to record USG data without hindering human movement [122].

The proposed HD-EMG decomposition techniques will have to be applicable to muscle dynamic contractions. This will require extending current HD-EMG decomposition methods, now suitable for muscle isometric contractions only, to operate during both eccentric and concentric contraction types. Relative movement between muscle fiber and electrode leads to non-stationarities in the recorded EMG, thereby distorting the shape of fiber action potentials over time as a function of fiber-to-electrode relative kinematics [123]. Despite challenges, recent work is supporting the possibility of HD-EMG decomposition during dynamic muscle contraction. Recently proposed data models enabled identification of motor unit firings from HD-EMGs, recorded during repeated dynamic muscle contractions from healthy individuals [21], [124]. Moreover, work applied to amputees' residual muscles EMGs proved the possibility of decomposing motor unit action potential during concentric muscle contractions, predominant in transhumeral and transradial amputees' muscles in the residuum [19], [125].

The proposed HD-EMG decomposition techniques will also have to be performed in real-time, something especially challenging when decomposing motor neuron function from multiple muscles simultaneously. This will require sampling hundreds of EMG channels simultaneously, *i.e.* 512 channels could be used to cover 8 to 16 muscles using 64-channels or 32-channels grids respectively. Real-time algorithms will have to assure fast data transfer from sensor to robot control logic as well as execution of multiple processing steps such as channel-to-channel cross correlation, signal whitening, orthogonalization, normalization, optimization of contrast functions (*i.e.* maximization of non-Gaussianity of estimated sources), computation of decomposition quality metrics (*i.e.* pulse to noise ratio or silhouette measure) [126]. Despite challenges, initial evidence of real-time decomposition possibility was recently provided on fewer EMG channels (i.e., < 200). Fast independent component analysis was recently developed to extract motor unit discharge events from high-density HD-EMG recordings from healthy individuals' extrinsic finger muscles [127]. Online decomposition via Convolution Kernel Compensation techniques was achieved during slow isometric ankle dorsiflexion contractions [128]. Recently, a fully automated convolutive blind source separation technique was proposed for extracting dorsi flexor motor unit activity from the recoded surface EMG in real-time [129]. Although the proposed method relied on an offline calibration step for computing an EMG

separation matrix, it enabled healthy individuals to control in closed-loop their own motor neuron activity (*i.e.*, by means of real-time bio-feedback of motor neuron activity), thereby demonstrating the possibility of real-time decomposition within closed loop control scenarios. Finally, recent work showed the possibility of approximating the complex and computational expensive convolutive blind source separation steps within a surrogate model based on deep learning recurrent neural networks [130]. Although the method relied on extensive offline training, it allowed relaxing computational constraints during the post-training execution phase, something crucial for future real-time control applications.

Similarly, to HD-EMG decomposition also the proposed data-driven neuromuscular models (Figs 2-3, Sections 2-3) will have to be made computationally efficient yet physiologically correct. This is also central for the controllers described in Section 4, which will require designing completely novel closed-loop schemes that efficiently process large data streams sampled in real-time from the spino-muscular system, *i.e.* spinal neuron discharges and innervated fascicle kinematics, **Figs 1 and 4**. These large data streams will have to be incorporated in numerical models to solve for numerical optimizations online (**Fig. 3B**), with objective functions evaluated based on multi-scale simulations, **Fig. 3A** [81]. A possible way forward is that of approximating sub-components of the proposed neuro-musculoskeletal modelling framework via computationally efficient surrogate models [131], [132]. Machine learning-based regression can be employed to approximate the full input-output relationship of key modelling components (**Fig. 3**), which would otherwise require substantial machine numerical power to be operated. This approach has shown to be promising for approximating complex three-dimensional musculoskeletal geometries [133] as well as HD-EMG deconvolution-based decomposition techniques [134]. Moreover, the use of software-tailored hardware such as FPGAs can further optimize algorithm runtime execution speed.

6. CONCLUSION

Over the next 10-15 years we anticipate the advent of cell- and tissue-in-the-loop control strategies that will enable a new class of wearable technologies that can steer neuromuscular form and function over short and long timescales. We propose a three-pronged approach that aims to merge multi-modal, non-invasive, acquisition of biological signals (**Fig. 2**) with multi-scale neuromuscular modelling (**Fig. 3**) and non-linear optimal robotic control theory (**Fig. 4**) within an integrative framework (**Fig. 1**). This novel class of steering technologies holds large potentials for improving quality of life. Applications ranges from enhancing limb-joint voluntary control in spastic patients, to altering sensory feedback for optimal rehabilitation in stroke survivors; to preserving Achilles tendon stiffness to counteract tissue degradation in aging, to improving healing following rupture of overstrained soft tissues. Developing wearable robotic systems that can truly incorporate neuromuscular physiology in the loop will require substantial innovation within the coming decade but, when successful, will enable new avenues for

inducing targeted repair of human motor capability at a level not considered before. Gaining more direct control over the stimuli that govern neuromuscular function over time will enable (chemo)electro-mechanical devices to co-adapt with the human body; an achievement that will disrupt the development of man-machine interfaces from neuroprostheses, to robotic limbs, to exosuits.

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