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Integrating Upper-Limb Prostheses with the Human Body: Technology Advances, Readiness, and Roles in Human–Prosthesis Interaction

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Abstract

Significant advances in bionic prosthetics have occurred in the past two decades. The field's rapid expansion has yielded many exciting technologies that can enhance the physical, functional, and cognitive integration of a prosthetic limb with a human. We review advances in the engineering of prosthetic devices and their interfaces with the human nervous system, as well as various surgical techniques for altering human neuromusculoskeletal systems for seamless human–prosthesis integration. We discuss significant advancements in research and clinical translation, focusing on upper limb prosthetics since they heavily rely on user intent for daily operation, although many discussed technologies have been extended to lower limb prostheses as well. In addition, our review emphasizes the roles of advanced prosthetics technologies in complex interactions with humans and the technology readiness levels (TRLs) of individual research advances. Finally, we discuss current gaps and controversies in the field and point out future research directions, guided by TRLs.

Contents

1. OVERVIEW

1.1. Scope of This Review Article

Seamlessly integrating an engineered prosthetic limb with the human body has been a fascinating concept, which ideally enables individuals with limb loss to restore normal daily functions and full body image. In the past two decades, engineers and researchers have pushed the boundaries of bionic technologies, including biomimicking mechatronics of prosthetic limbs, neural–machine interfaces for intuitive prosthesis control and restoration of haptic sensation, and novel surgical techniques for physical and neural prosthesis integration. More exciting, many of these new technologies have become clinically available or transferred into the medical device industry. Nevertheless, current technology is still very distant from the ideal bionic limbs (i.e., prosthetic limbs that feel and function just like biological limbs) portrayed in science fiction and media outlets. Additionally, clinical evidence about the benefits of these technological breakthroughs on individuals with limb loss has been scarce, regardless of the large and continually growing volume of publications in the field.

Hence, targeting audiences in the field of biomedical engineering, we present a review with the goals of (*a*) informing major research advances and clinical translation of technologies in the past two decades that enable seamless integration of humans and robotic prosthetic limbs, and (*b*) discussing gaps, controversies, and future research directions on the topic of human–prosthesis

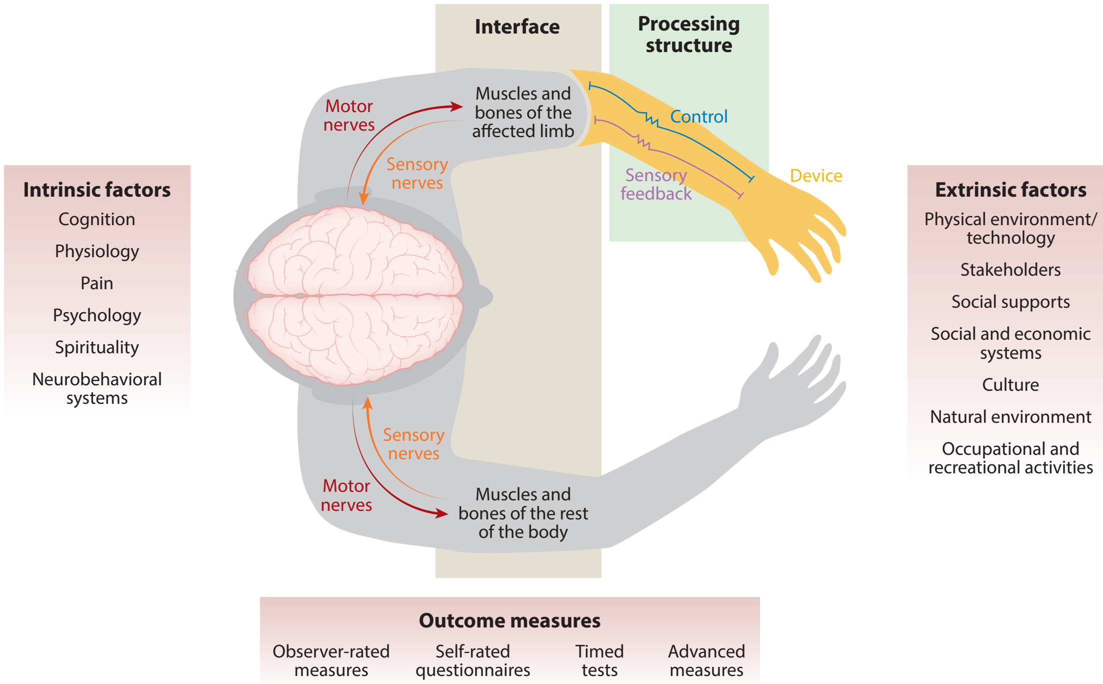

Figure 1

Intrinsic and extrinsic factors of human–prosthesis integration and interactions that influence clinical use of prosthetics technology and human user's function. Figure adapted with permission from Reference 1; copyright 2019 Elsevier.

integration. Note that we focus our review on upper limb prosthetics because of their heavy reliance on user intent for daily operation in contrast to lower limb prostheses that can be operated autonomously. Nevertheless, some reviewed neural or surgical technologies have also been explored for lower limb prostheses. In addition, distinguishing our review from several existing reviews on a similar topic (2–4), we lead the review of bionic technologies within the context of (*a*) their roles in complicated human–prosthesis interactions and integration and (*b*) technology readiness level (TRL) assessment.

1.2. Intrinsic and Extrinsic Factors for Human–Prosthesis Interactions and Integration

This review focuses on technological advances, assessing both their contributions and potential role in the complex web of human–prosthesis interactions illustrated in **Figure 1**. To keep this background in mind throughout the review, it is useful to sketch out the larger ecosystem, in which these technological advancements interact with humans.

There are several factors intrinsic to individuals that are part of the web of interaction with technological advances, including cognition, physiology, pain, psychology, spirituality, and others (1). The physiology of the person, for example, plays a key role in the impact of various technologies reviewed, such as implantable electrodes or osseointegration. Conversely, afferent neural interfaces have shown improvement of agency in users, which may be linked to self-forgiveness, playing a role in device acceptance (5). Thus, we see that intrinsic factors influence prosthesis integration and technology impact, and technology selection influences intrinsic factors such as a person's psychology.

It is noteworthy that people who typically integrate prosthetic technologies into their daily lives often value attributes of their prostheses differently than those who reject the usage of prosthetic technologies. For example, when asked what they would like to see improved, those who integrate prosthetic technologies typically ask for more—more feedback, more strength, more controllable finger digits, etc. (e.g., 6). In contrast, those who currently reject prosthetic technologies typically ask for less—less weight, less size, and fewer failed movements (e.g., 7). Acknowledging the lack of homogeneity among people with an amputation or congenital deficiency can help design technologies that meet the needs of unique cohorts (e.g., 8), and it is important to acknowledge that some technologies may not be suitable for all cohorts.

Factors extrinsic to the person and the technologies integrated into their users also play key roles in the web of impact. Different prostheses are appropriate for different tasks, and sometimes modifying the physical environment is more impactful than designing a new device. Similarly, the intrinsic factor of desire for autonomy is balanced with the extrinsic factor of available social support. Many of the technologies we reviewed are expensive, and the cost of these technologies must be balanced against the socioeconomic context of individuals. The amount of occupational training that individuals receive, while outside the scope of this review, has a significant impact on many of these technologies. When users of new technologies perform better, it is important to consider how much additional training they had received compared with users trained with conventional devices.

Having sketched these intrinsic and extrinsic factors, we now acknowledge that the reviewed technologies and their evaluation in Section 2 fall across both intrinsic and extrinsic spectrums. In Section 3, we further discuss the existing controversy in the field and the need for valid outcomes in assessing psychological intrinsic factors, such as embodiment, to avoid nonrigorous claims when evaluating the impact of bionic technologies on humans.

1.3. Technology Readiness Levels (TRLs)

After 20 years of a boost of bionic technologies in research, it is exciting to witness the growth of the field, which has been well summarized in a recent review (3). Within the defined databases in that review, the expansion of the literature on bionic prosthetic arms increased from under 25 in 1997 to roughly 350 in 2017. However, this growing research community has developed a tendency to evaluate different bionic technologies as if they are at the same readiness levels. For example, researchers are constantly urged to show the clinical impact and real-life environment use of a novel bionic technology without solid and systematical engineering optimization, even when the technology is still in its infancy. We believe that such a tendency is detrimental to the field, and our goal is to guide reasonable outcomes appropriate to the maturity of the technology.

Here we employ the concept of TRLs, a scale used to assess the maturity of a technology for its real application (9). TRLs were initially developed by the US National Aeronautics and Space Administration in the 1970s and have been widely adopted in various domains, including medical devices (10). TRLs have nine levels, with TRL 9 being the most mature technology. In **Table 1**, we present the TRLs tailored for bionic prosthetic arms. At each level, we define the level, the needed development and evaluation methods, and the exit criteria to determine the technology development phase all the way to long-term translation and independent use in daily life. In Section 2, we illustrate the TRLs of the reviewed bionic technologies. In Section 3, we further discuss how to use the TRLs to guide research, technology development, and research translation in the field of prosthetics.

Table 1 Technology readiness levels for bionic prosthesis technologies

Level	Definition	Description and evaluation	Exit criteria
9	Longitudinal system evaluation in operational environments	Longitudinal evaluation of the system in daily life; evaluation on individuals with limb loss	Technology has been successfully deployed and proven under the full range of expected users, devices, and environments Longitudinal performance and use metrics have been collected Over-time efficacy and practical value to end users in daily prosthesis use has been determined
8	System evaluation in an operational environment	Evaluation of the system at home or in realistic environments; evaluation on individuals with limb loss	Final configuration of the technology developed Final configuration successfully tested in a home environment Performance and use metrics have been collected in a home/realistic environment Technology's ability to meet its operational requirements has been assessed and problems documented; plans, options, or actions to resolve problems have been identified
7	System evaluation in a lab environment	Evaluation of the system in lab with simulated daily tasks; evaluation on individuals with limb loss	Appropriate functional outcome measures are validated System has been validated on individuals with limb loss using functional outcome measures Fully stand-alone system has been demonstrated in a lab environment Appropriate performance and use metrics have been identified
6	System evaluation in abstract tasks on individual with limb loss	Online system evaluation of the prototype in lab with abstract physical or virtual tasks; experiments on individuals with limb loss; surgical implementations in humans	Human-in-the-loop system has been validated on individuals with limb loss using engineering metrics Solutions to the challenges/risks in use of technology on individuals with limb-loss is developed and validated Appropriate functional outcome measures are identified or developed
5	Online/in vivo system evaluation in abstract tasks using nontarget cohorts	Online/in vivo evaluation of the prototype in lab with abstract tasks; evaluation on nondisabled individuals or animal models iteratively	System has been validated using engineering metrics in nondisabled individuals or animal models How animal model responds to a surgery or implant is understood
4	Offline/in vitro system evaluation	Offline evaluation of the prototype based on offline data collected from amputees or nondisabled individuals or in vitro animal study (for surgical techniques/implants)	System has been validated offline using engineering metrics Feasibility of surgical techniques or implants is demonstrated
3	Component evaluation	Offline evaluation of each component based on benchtop test, computer analysis/simulation, or cadaver studies	Engineering evaluation metrics have been developed Components have been validated offline

(*Continued*)

Table 1 (*Continued*)

Level	Definition	Description and evaluation	Exit criteria
2	Technology concept formulated	Technology formulation based on principles in level 1; design based on computer modeling (mechanical device, signal, implantable/surgical interface) or cadaver studies	Applications of basic principles have been identified and published
1	Statement of gap and basic principles identified	Statement of gap and principles to fill the gap are observed and identified	Basic principles have been defined and published

2. RESEARCH MILESTONES IN THE PAST 20 YEARS

2.1. Advances in Mechatronics Design

We start this review with the advances in mechanical design and autonomous control of upper limb prostheses.

2.1.1. TRLs of prostheses in research and industry. **Figure 2** shows TRLs of existing prosthesis arm design, ranging from commonly used commercial components to research prototypes. In this review, we highlight the milestones of mechatronics advancements and their clinical use over the past two decades.

2.1.2. Design advances in anthropomorphic prosthetic hands. One of the major milestones in this field is the development and commercialization of anthropomorphic prosthetic hands (11). The TRLs for these devices are above TRL 5. Traditionally, active prosthetic hands or terminal devices have been single-jointed grippers driven by a dc motor. The appearance and function

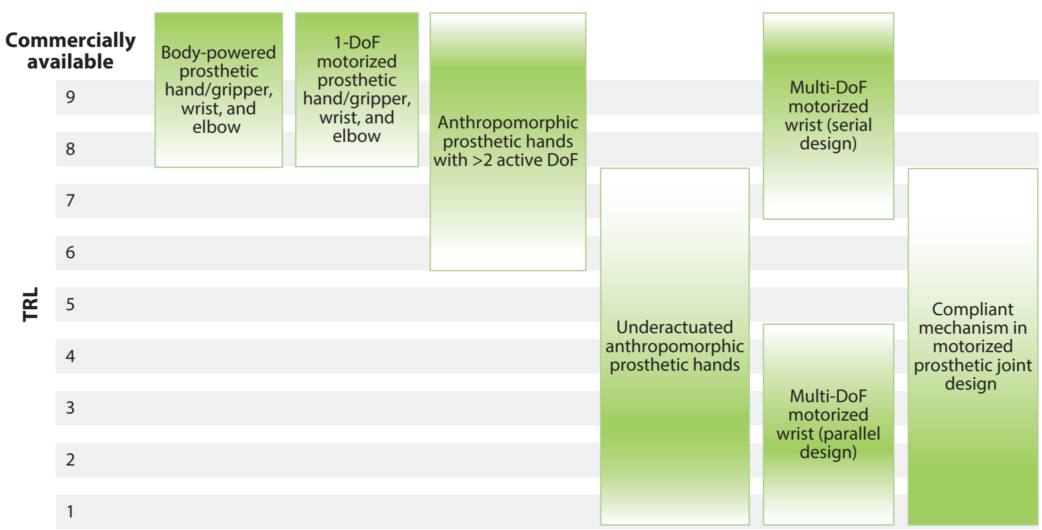

Figure 2

TRLs of existing prosthetic arms, focusing on mechatronics design mechanism. The vertical axis shows the TRL. Each technology in a block may span multiple TRLs according to the current literature. Darker shades indicate a larger number of existing publications in the reviewed technology at a certain TRL. Abbreviations: DoF, degree of freedom; TRL, technology readiness level.

of these monoarticulated devices are far from those of biological human hands. Advances in mechanical design and actuators have enabled the design of anthropomorphic prosthetic hands with polyarticulated fingers/thumbs. Several groups have reviewed the detailed mechanical design and actuation mechanisms for various anthropomorphic hands (11–13). In general, the finger design couples the actuation of metacarpophalangeal, proximal interphalangeal, and/or distal interphalangeal joints together. Thumb flexion/extension and thumb circumduction are separated joints that can be motorized or passively adjusted. Approximately 6–15 active actuators have been directly mounted on fingers/thumb, within the palm, or extended to forearm spaces to drive the hand via different transmission pathways (13). All mechatronics components are packed into a prosthesis hand unit as a stand-alone device that weighs approximately 200–600 g.

Anthropomorphic prosthetic hands have been successfully introduced into commercial space. Although these devices may potentially improve prosthetic hand dexterity, the challenge lies in the need for multiple control sources to drive individual fingers, which often are not directly available in people with upper limb loss. Hence, instead of driving individual fingers, almost all the devices preprogram coordinated multiple finger motions to generate different grasping patterns for daily function. This approach significantly reduces the needed control dimension. The users are offered options to interface with the prosthetic device for the grasp section via either a mobile app or an electromyography (EMG)-based control (see Section 2.2). Companies continue optimizing commercial hands to improve the practical value of these devices, including weight reduction and improvement of durability, grip force, and speed. Nevertheless, as there are few publications evaluating the utility and impact on psychological intrinsic factors of anthropomorphic hands, it is unclear what design feature of the human-like hand affects its interactions with human users.

Another noteworthy research effort for anthropomorphic prosthetic hand design is the development of underactuated, compliant mechanisms for robust object grasping (14–17) (mainly in TRLs 2–4). Only one or two actuators were included to produce various grasping patterns. Catalano et al. (14) borrowed the idea of hand synergies in grasping to further reduce the actuation dimension. The underactuated design is achieved by a differential transmission mechanism. Similarly, Leddy & Dollar (15, 16) combined differential and other mechanisms to use a single actuator to produce three hand grasps. Liu et al. (17) adopted a compliant rolling-contact element joint design to enable multiaxis compliance. These clever mechanical designs allow stable object grasping and significantly reduce the need for control sources from the users. However, the adopted mechanisms lack robustness against, for example, dirt/dust or uneven wear among gears, challenging the use of the prosthetic hand in daily environments over time.

2.1.3. Design advances in prosthetic wrists. Traditionally, active prosthetic wrists power only pronation/supination (also called wrist rotation), although the posture of the wrist in the other two degrees of freedom (DoFs) is also important to facilitate object grasping and manipulation. An interesting study revealed that having more wrist DoFs was equally as important as (or more important than) having finger dexterity in a prosthetic arm design (18). These facts have inspired researchers to design multi-DoF prosthesis wrists, reviewed recently by Bajaj et al. (19). Either serial or parallel mechanics are proposed. In serial designs, wrist flexion/extension and rotation are designed as independent components and are connected serially. Besides traditional wrist rotators, motorized wrist flexion/extension components such as the MC Powered Flexion Wrist and ProWrist (Fillauer, Chattanooga, TN, USA) and DEKA arm (DEKA R&D Corp., Manchester, NH, USA) are commercially available. Although the serial design is simple and flexible to use, it adds weight and elongates the wrist dimension, challenging the device's fit for individuals with long residual forearms. A multi-DoF parallel kinematics prosthetic wrist has been proposed and designed but is mainly benchtop tested (20) (TRLs 1–4).

2.1.4. Autonomous prosthesis control. Another highlight in mechatronics design is the development of intelligent control to ease the user-level operation of upper limb prostheses. These autonomous, device-level controls require additional sensors mounted on prosthetic arms/hands and computer processors for closed-loop operation.

Intelligent control has been designed to facilitate object grasping. Many groups utilize embedded RGB cameras and/or depth cameras to capture the task context. Deep learning algorithms were applied to the captured images to predict the object to be grasped (21–26). Depending on the identified object, the prosthesis can automatically adjust the prosthetic wrist posture and plan a hand grasping pattern for object grasping. So far, this concept has been mainly validated in lab environments (TRLs 3–5). Another common application of intelligent prosthesis control is to achieve reflex-like actions, such as slip prevention (27). Studies have designed various sensors (such as force sensors, accelerometers, etc.) on the prosthesis fingertips to detect object slips using different mechanisms (e.g., measurements of normal and tangential force or fiction-based vibration). The detection of a slip triggers the motor in the prosthetic hand to increase the grasping force for slip prevention (28, 29). This feedback control typically reacts much quicker (on the scale of 10 ms) than the pure volitational control offered by neural–machine interfaces. Most of the intelligent controls have been benchtop tested (TRLs 2–4), while one commercial prosthetic hand incorporated slip-prevention mechanisms (Sensorhand Speed, Ottobock, Germany). These intelligent controls could improve the functionality of prosthetic arms and reduce the cognitive workload of users for prosthesis operations. Nevertheless, additional evidence is needed to show the benefit of these sensorized, intelligent prosthetic hands.

2.2. Efferent Interfaces: Neural Decoding Methods for Prosthetics

Efferent interfaces identify the human user's intent, such as closing a prosthetic hand, and then convert use intent into prosthesis control signals. An EMG-based interface has been far and away the most used source for efferent neural control of upper limb prostheses, although other neural interfaces (e.g., electroencephalography and peripheral neural interfaces) or control sources (e.g., ultrasound images of residual muscle movements, voice, tongue motion, and foot motion) have been explored recently (30). Therefore, our review focuses on advances in EMG-based efferent neural interfaces.

2.2.1. TRLs for electromyography (EMG)-based efferent neural interfaces. EMG is a technique that records myoelectric signals, which are the amplified efferent neural signals from the central nervous system that drive muscle contractions. EMG measurements can be recorded by electrodes on the skin surface or by intramuscular electrodes. **Figure 3** shows TRLs of existing EMG-based efferent neural interfaces for prosthetic arms.

2.2.2. Machine learning in EMG decoding. Conventionally, amplitude-based EMG control (TRLs 7–9) is used to drive a prosthesis, in which the magnitude of one EMG signal proportionally drives the motor speed in one direction. Usually, two isolated muscle activations are needed to control one prosthetic joint (31). The users can switch the operation joint or hand grasp patterns by muscle contraction–based triggers (such as double ballistic-like muscle contractions and cocontraction of the residual muscles). This control approach is not intuitive and has been limited to controlling only two to three DoFs.

Machine learning has become a top-of-mind issue in recent years and has drastically improved EMG-based prosthesis control (32). EMG pattern recognition (PR) algorithms have been used to identify the user's intended discrete joint movements (e.g., different grasping patterns, opening the hand, wrist rotation) on the basis of patterns of multichannel EMG activity (33). PR allows individuals to control their prosthesis using physiologically appropriate muscle contractions and

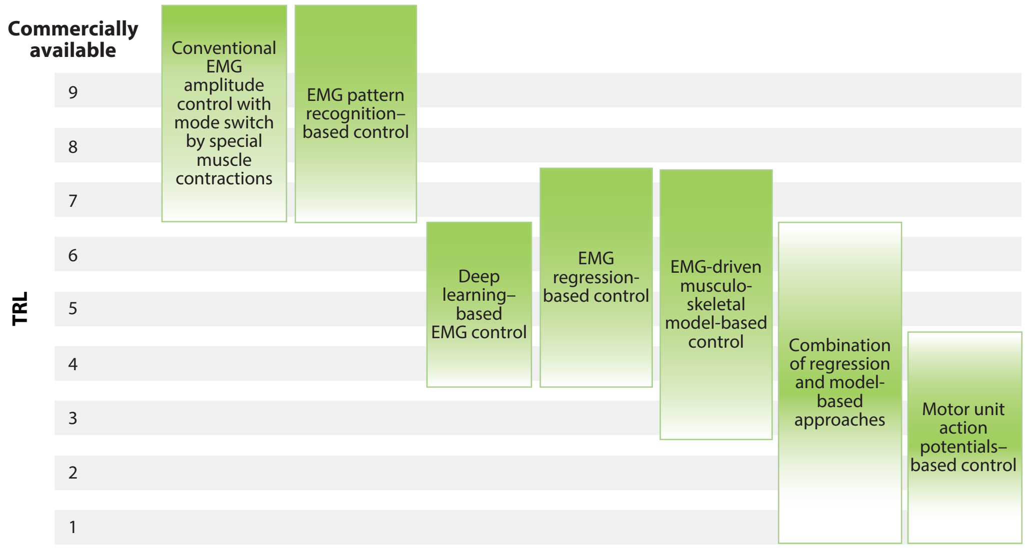

Figure 3

TRLs of existing efferent neural interfaces. The vertical axis shows the TRL. Each technology spans multiple TRLs according to the current literature. Abbreviations: EMG, electromyography; TRL, technology readiness level.

eliminates the need for complicated mode switching (33). Finding isolated myoelectric control sites, as used in conventional amplitude-based control, is largely unnecessary; PR allows individuals to use an EMG-controlled prosthesis despite having control sites with poor EMG signal separation or sites that pose a challenge for prosthesis fitting. A barrier to deploying EMG PR was providing the users with a mechanism to (re)calibrate their control if necessary (34). Currently, several companies (e.g., Coapt LLC, Chicago, IL, USA; Infinite Biomedical Technologies, Baltimore, MD, USA) have developed mobile phone apps that allows users to recalibrate the PR algorithm easily and quickly. PR systems using supervised machine learning for prosthesis control are operated at TRLs 7–9 and are commercially available.

Deep neural networks iteratively process information through multiple layers of interconnected neurons, each of which performs a specific function. Consequently, these deep networks have many parameters that need to be learned and typically require large amounts of data to be properly trained and more powerful processors to operate in a feed-forward manner. Efforts are ongoing to provide larger datasets that can be used to help train deep networks (35), but embedded system processing constraints have limited the real-time feed-forward evaluation of such network architectures using real prostheses in a tethered manner. Despite the limitations, deep learning has been tested on multichannel (36) or high-density EMG recordings (37) both offline and online (TRLs 4–6). It is reasonable to expect that more extensive research and evaluations in the coming years will show the potential of deep learning in neural prosthesis control.

Regression algorithms are also machine learning–based methods, used for myoelectric control of prosthetic arms (38, 39). The algorithms do not heavily rely on muscle-specific EMG recordings, making their application on residual limbs practical. Different from EMG pattern recognition that results in a discrete set of movements as the output, regression has been used to estimate arm/hand movement in multiple DoFs simultaneously and continuously. Nevertheless, in practice, thresholds need to be set such that low-level contractions do not cause inadvertent movements. Regression-based approaches are currently operating at TRLs 4–7.

2.2.3. Neuromusculoskeletal model-based EMG decoding methods. Despite the success of machine learning–based EMG decoding methods (often called black-box approaches), their performance depends on the quantity and quality of the training data. When a new EMG activity emerges (unseen in the training data), these machine learning methods may lose their capability for accurate intent estimation. Alternatively, the decoder can be structured with known human physiology. EMG-driven musculoskeletal model-based approaches have been developed (40–45). These decoders consist of components, such as Hill-type muscle models and a forward dynamic model of a human limb, to explicitly define the physiological mapping from neuromuscular control signals (i.e., EMG) to internal muscle forces, joint torque, and then joint motion. The model-informed approaches (referred to as white-box approaches) have allowed EMG-based decoding to remain functional even in situations where the training data are not considered. However, model-based approaches require optimization/personalization of high-dimensional parameters, which may take hours. In addition, they require muscle-specific EMG recordings, which can be challenging to apply to individuals with limb amputation. TRLs for this technical concept range between 3 and 7.

Motivated by the complementary benefit of machine learning and neuromusculoskeletal modeling methods, combining the two concepts together (defined as gray-box approaches here) may leverage their benefits for myoelectric control. One study hierarchically combined neural networks with a forward arm dynamic model to estimate hand and wrist motion using EMG signals (46). Reinforcement learning was used to train the neural network without running inverse dynamics (46, 47). This method enabled smooth coordinated prosthesis hand and wrist control. Nevertheless, the gray box is an emerging concept, and not many publications have addressed it yet.

2.2.4. Other major concepts for EMG-based prosthesis control. Here we highlight two other concepts. One idea is to leverage human motor learning capabilities to allow users to develop and use fixed, abstract EMG decoding mappings for prosthesis control (48, 49). In this case, the users do not need to make physiologically appropriate muscle contractions for prosthesis control. Although this method is not intuitive to use, users can adapt internal models of the control system mapping and successfully learn such mappings over many training sessions. Another emerging idea (TRLs 1–4) is to use motor unit action potentials (MUAPs) (decomposed from high-density or specially designed surface EMG electrodes) and neural drive for prosthesis control (50, 51). Since MUAPs represent the true activity of motor neurons, they could be more accurate for estimating user intent than surface EMG signals. This concept, however, has been challenged by the difficulty of real-time MUAP decomposition during dynamic movements.

2.2.5. Practical issues that limit clinical deployment of EMG-based interfaces. Regular use of myoelectric prostheses gives rise to various sources of signal disturbances that can degrade control performance (33, 52–55), such as EMG electrode shift or loss of contact due to changes in residual limb motion and socket loading, drift of skin–electrode impedance due to sweat, and wire failures during prolonged prosthesis use (53, 56, 57). All EMG signal decoding approaches are impacted by these challenges, including conventional amplitude-based control (58, 59). Several techniques have been developed to mitigate the effects of disturbances, such as advanced denoising techniques (60–63), use of redundant EMG channels (54), and adaptive machine learning methods (64–66). Some of these techniques have been implemented into commercial myoelectric prosthesis control for robust operation in daily environments.

2.2.6. Evaluation of decoding algorithms. Evaluation methods for efferent neural interfaces depend on TRL (**Table 1**). When the TRL is below 5, offline analysis is used to check the accuracy and response time of the EMG decoding algorithm. This analysis guides optimization of the decoding algorithm design. When the TRL reaches 5–7, evaluation will be conducted with a human in the loop on abstract tasks in virtual or lab environments. Human intrinsic factors (**Figure 1**), such as variations in motor deficits and the level of human training beyond the decoding algorithm design, will influence online task performance. The evaluation metrics should include not only task performance measures (e.g., task successful rate) but also human behaviors (e.g., adaptation rate and physical and mental efforts of users during task performance). When the TRL reaches 8–9, evaluations will be conducted on prostheses users performing daily activities in clinics or at home. Both intrinsic and extrinsic factors (**Figure 1**) impact the outcomes that quantify over-time functional improvement, satisfaction or other psychological responses, and practical value of the technology.

Contradictory results exist on the correlation between offline algorithms accuracy (TRLs 3–4) and online task performance metrics (TRLs 5–7) (67, 68), potentially caused by human intrinsic factors that confound the online task performance measures. However, it does not necessarily mean that TRLs 3–4 can be skipped, since higher offline decoding accuracy has yielded a faster adaptation rate and less effort for human users in online task performance (69). For a new method stemming from an existing concept, comparisons with publicly available decoders using the same concept that have been tested in real time can be used for preliminary indication of performance (70). In addition, extreme care must be taken when reporting results to describe the systems under which the decoder was tested, and generalized conclusions must be limited to the performance under those test conditions.

2.3. Afferent Interfaces: Sensory Restoration and Augmentation

Afferent interfaces sense the state of prosthetic arms (e.g., joint position) and interactions of prostheses with the environment (e.g., contact force on prosthetic fingers when grasping an object) and convert the sensed information into stimulation patterns to elicit the users' sensation of the prosthetic arms.

2.3.1. TRLs of existing afferent interfacing technologies. **Figure 4** shows TRLs of existing afferent interfaces. Most commercial prostheses use incidental sensory feedback (e.g., visual feedback), but an active range of haptic devices for supplemental feedback have been considered across the TRL spectrum of research.

2.3.2. Importance of sensory feedback in prosthesis use. Sensory feedback is information about the effects of actions. In most situations in prosthesis control, it comes from many sources including incidental feedback (e.g., the visual perception of the position of the fingers, sense of shoulder motion, and cable force when operating body-powered prosthesis), ancillary feedback (e.g., the whine of a motor), and supplemental feedback (e.g., vibration intentionally stimulated on a subject's arm). In most situations it is used in many ways, including real-time corrections to actions (both internal to the mechanism and considering the human in the loop), updating internal models of cause-effect relationships, event confirmation, reinforcement of physiopsychological properties such as agency and embodiment, and the perception of pain (71). Sources of feedback differ in properties including how biased they are, how variable they are, how delayed they are, and how perceptible they are. People do an amazing job of integrating any and all sources of feedback to best accomplish a given task, but this fact makes the interplay of a single source of sensory feedback in the broader context of sensorimotor control challenging to untangle. Computational motor control provides a paradigm with which to analyze these various roles and contributions of sensory feedback (71).

2.3.3. Supplemental feedback through sensory substitution. Supplementary feedback is engineered artificial feedback that informs the user of the consequence of prosthesis control (e.g.,

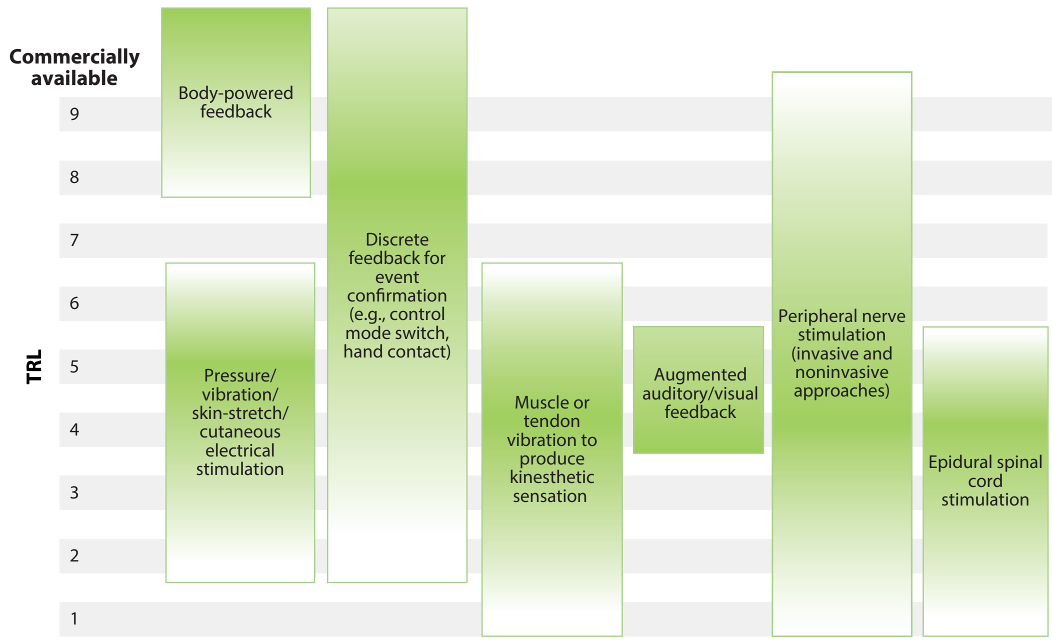

Figure 4

Technology readiness levels (TRLs) of existing afferent interfaces.

motion of the prosthesis joint or contact force on prosthetic fingers with an object). The supplementary feedback can be achieved by sensory substitution (i.e., inform the user of the sensed information measured from the prosthesis by stimulating another sensory modality that is available to the user) or afferent neural interface (i.e., inform the user of the sensed information measured from the prosthetic hand by stimulating residual afferent neural pathways that originally delivered such information from the missing hand to the brain). The last decade has seen a promising proliferation of success in employing supplementary feedback, as described in several review articles (71–74).

Sensory substitution has been investigated since 1912 (75). In the last two decades, there have been development efforts to design advanced haptic devices that incorporate multiple stimulation modalities (e.g., vibration and skin stretch) (76) or to design miniature devices that can be integrated into prostheses directly (77). Additionally, researchers have intentionally sought out feedback information, for which vision is a poor sensory source either because it has high variability (e.g., prosthesis joint speed) or a paucity of information (e.g., event confirmation restricted by occlusion) (28, 78, 79). Vibrotactile or electrotactile sensors are placed on the residual forearms or other places that map the prosthesis sensor readings or myoelectric control signals via modulation of magnitude and/or frequency of vibrating/electrical stimulations. A number of studies have recently demonstrated the usefulness of these approaches to improve performance and internal model acquisition (28, 78, 79). Nevertheless, these studies mainly operate at TRLs 2–6.

2.3.4. Supplemental feedback through stimulation of neural pathways.

Afferent neural interfaces seek to restore natural sensation in prosthetic hands through stimulation of the residual neural pathways that originally connected to the missing hand. One approach has used surgical techniques, such as targeted skin reinnervation (TSR) (80, 81) or agonist-antagonist myoneural interface (AMI) (82), to enable access to neural pathways for sensory restoration in people with limb loss. These surgical techniques for afferent feedback are reviewed in Section 2.4.

Another approach is to directly stimulate somatosensory pathways. The majority of the studies use modulation of electrical stimulation frequency and magnitude to evoke somatotopically matched haptic sensation (touch or pressure) on finger digits (83–90). In one design, researchers have produced electrical stimulation to the peripheral sensory nerves of people with limb loss via transcutaneous high-density electrodes (91). Although it is noninvasive, the transcutaneous approach is very sensitive to electrode location and pressure applied to the electrode. Hence, it has only been tested in the lab environment with static arm postures (TRL 6). Another design is to stimulate sensory peripheral nerves by implantable peripheral nerve interfaces [e.g., extraneural multicontact nerve cuff (92) and intraneural transverse intrafascicular multichannel electrode (83)]. The implantable electrodes offer a more robust and reliable solution for practical use. Many research groups focus on high-density or multicontact design of the implantable neural interface to increase the stimulation selectively. This technology has been mainly evaluated on people with limb loss in the lab with psychophysical or closed-loop task testing (TRLs 1–7). Nevertheless, extraneural electrodes have been reported to provide functionally useful sensory feedback in daily life in longitudinal case studies for more than three years (90) (TRL 8–9). In the third design, a research group used implantable epidural spinal cord stimulators (ESCSs) to stimulate the dorsal root ganglia or dorsal column in the spinal cord to restore haptic sensation in the missing limb of people with limb loss (88). The resolution of the somatosensory response elicited by ESCSs is relatively low compared with that of peripheral nerve stimulation. ESCSs have only been tested in the lab briefly (TRL below 5) (88). It is noteworthy that, among all these reported studies, although some claimed that stimulate somatosensory neural pathways elicit a natural sense of touch in the hand, many have reported that electrical stimulation leads to tingling, numbness, or other unnatural sensations on the phantom limb.

Electrical stimulation of afferent neural pathways does not consistently evoke proprioception. To elicit proprioception, researchers have used tendon or muscle vibrations that can activate proprioceptors (such as residual muscle spindles or the Golgi tendon) and produce the illusion of movement of a missing limb in people with limb loss. Either wearable vibrators (93) or magnetic implants (94) have been used to show feasibility in a lab setting. The TRLs for these technologies have been low so far (TRLs 1–6).

2.3.5. Evaluation of supplemental sensory feedback. The supplementary sensory feedback component is often assessed to see if users can differentiate various signal levels, frequently using psychophysics tests such as the just-noticeable-difference threshold. In many of these studies, users are deprived of other sensory modalities such as vision (TRLs 5–6), which has limited transfer to real-life settings in which sensory modalities such as vision are present. More helpful evaluations characterize the impact of sensory feedback in the presence of other feedback sources and closed-loop form (e.g., TRL 7 and above).

The impact of supplemental sensory feedback on human–prosthesis integration has been evaluated by the following metrics: task performance and clinical outcomes measures of hand function, inductive or explicit measures of human behavioral responses (such as temperature as a proxy for embodiment, eye tracking, or inductive measures of internal model strength), prosthesis usage in a home environment (TRL 9), and surveys/questionnaires that probe psychosocial factors, including self-efficacy, prosthetic embodiment, social interaction, and quality of life (71, 86). A few studies have demonstrated impact of sensory feedback across all of these forms of evaluation. Given that almost no commercial prostheses provide supplemental feedback, it remains to be seen if the value added by supplemental sensory feedback is worth the cost in terms of money, reliability of devices, surgeries, compatibility with commercially available devices, and other intrinsic and extrinsic factors as shown in **Figure 1**.

2.4. Engineering Humans for Physical and Neural Interfaces

Using surgical and regenerative techniques to engineer a human neuromusculoskeletal system in the residual limb has shown great promise to enable seamless physical and neural human–prosthesis integration. Here, we review the advances in this important and novel topic in the research community.

2.4.1. TRLs for various surgical techniques. Surgical approaches to reconstruct the residual limb have gained popularity in the last two decades, and their TRL ranges from early theoretical conceptualizations to long-term implementations in daily life. **Figure 5** illustrates the TRLs of the different surgical approaches described in this section.

2.4.2. Surgical techniques for enhanced mechanical attachment and integration. Artificial limbs are commonly attached to the body via sockets. This approach causes discomfort, excessive perspiration, skin irritation, and compromised function of adjacent joints. An alternative

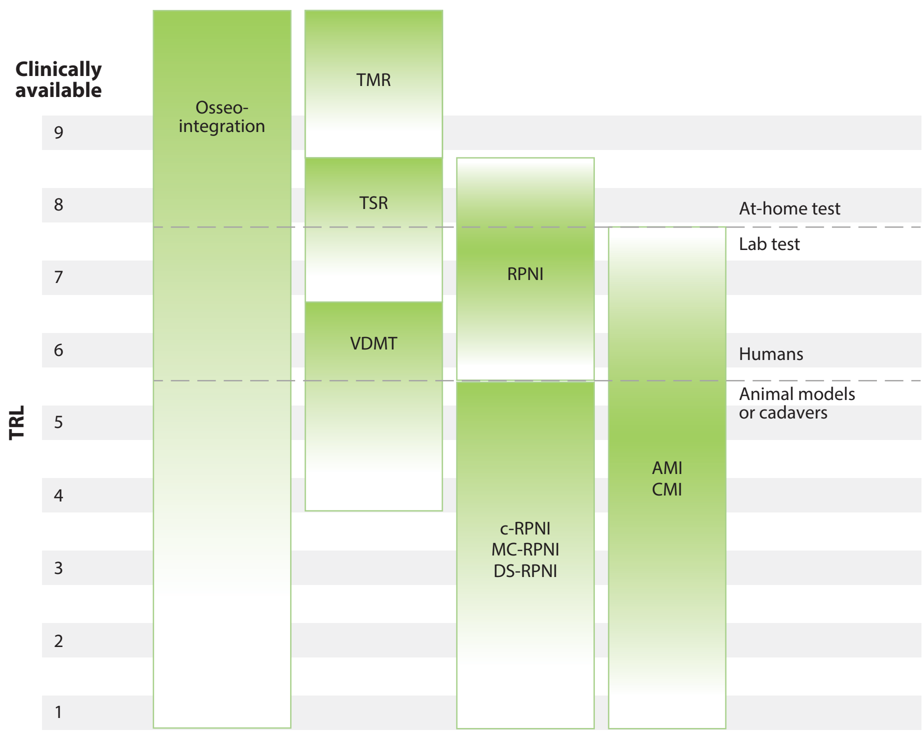

Figure 5

TRLs of various surgical techniques. The vertical axis shows the TRL. Each technology spans multiple TRLs according to the current literature. Darker shades indicate a larger number of existing publications in the reviewed technology at a certain TRL. Abbreviations: AMI, agonist-antagonist myoneural interface; CMI, cutaneous mechanoneural interface; c-RPNI, composite regenerative peripheral nerve interface; DS-RPNI, dermal sensory regenerative peripheral nerve interface; MC-RPNI, muscle cuff regenerative peripheral nerve interface; RPNI, regenerative peripheral nerve interface; TMR, targeted muscle reinnervation; TRL, technology readiness level; TSR, targeted skin reinnervation; VDMT, vascularized denervated muscle target.

technology to socket suspension is the direct skeletal attachment or bone anchoring of the prosthesis via osseointegration (95, 96). Osseointegration is primarily indicated for transfemoral amputations, in which socket suspension is challenging, such as in short residual limbs or compromised soft tissue. However, the indication for osseointegration has expanded to other amputation levels and is Conformité Européenne (CE) marked and US Food and Drug Administration (FDA) approved for transhumeral amputations. Several implant systems with varying biomechanical characteristics are currently being developed, and a few are already used clinically worldwide (97) (TRL 9).

Bone-anchored prostheses have been found to improve function (98), sensory awareness via osseoperception (99), self-perception (100), and overall quality of life (98). Whereas osseointegration is initially more expensive than a socket, the overall prosthetic cost over time and improved quality of life have been argued to justify it (101). On the downside, mechanical failures, skin interface stability, and latent risk of infections are some of the known complications of bone-anchoring implants (102–104). Osseointegration remains primarily used in individuals with remnant bone in the residual limb and without other comorbidities that can increase the risk of infections or failed osseointegration.

2.4.3. Surgical techniques to improve efferent interfaces. Research on the human–machine interface has focused on the machine side, with electrodes, processors, and stimulation devices. On the human side, initial efforts on surgical reconstruction procedures to make use of remnant neuromuscular structures, such as cineplasty (105), were proposed but poorly adopted. Renewed interest on the human side came with the clinical introduction of targeted muscle reinnervation (TMR) by Kuiken et al. (106), a procedure in which additional EMG control sources are surgically created by transferring nerves severed by the amputation to muscles remnant in the residual limb (80). The recipient (target) muscles have dispensable or no biomechanical function (no joint to actuate) and are first denervated to free muscle fibers for reinnervation by the transferred nerve. In upper limbs, TMR enables intuitive control of up to 3-DoF prostheses using EMG amplitude-based control (106), and functional outcomes have been further improved using EMG pattern recognition (31). This nerve transfer procedure—originally intended to improve the functionality of prostheses—is also helpful for postamputation pain (107–109). TMR has become the most widely used surgical reconstruction techniques for limb amputations at present (110) (TRL 9). Concerns have been raised concerning the potential formation of new painful neuromas in the native nerves transected to make way for the transferred nerves, as well as neuromas-in-continuity, due to the caliber mismatch between donor and recipient nerves. However, there are no published data regarding the incidence of these complications, which, in principle, could be mitigated by using vascularized pedicles around the coaptation (111).

Using free muscle grafts taken from different parts of the body as targets can help prevent denervating remnant muscles. This concept, presented as regenerative peripheral nerve interfaces (RPNIs), builds on the principle of using muscles as biological amplifiers of motor neural signals as in TMR but enables the control of more prosthetic joints. Instead of transferring the entire nerve to a single, relatively big muscle, its constituent fascicles are separated by longitudinal intraneural dissections, and then each is placed within a free muscle graft (112). This approach has been shown to produce additional myoelectric signals conducive to prosthetic control (113, 114) and alleviate postamputation pain (115). Nevertheless, since muscle grafts in RPNIs are much smaller than targeted muscles in TMR, it is challenging to use surface EMG electrodes for prosthesis control. Rather, using implanted electrodes is more suitable. Only case studies have been reported on the use of RPNIs for prosthetic control in laboratory environments (113, 114) and daily life (TRLs 6–8) (116, 117). Other RPNI variants exist, including muscle cuff RPNI (118) and composite RPNI (119); only the feasibility of these techniques has been demonstrated.

An alternative between nerve transfer to a native denervated muscle (TMR) and a free muscles graft (RPNI) is to dissect a portion of native muscle severing innervation but preserving vascularization (120), thus creating a vascularized denervated muscle target (VDMT). Preliminary results indicate that VDMTs can reduce postamputation pain (121), but they have not yet been used for prosthetic control (mainly at TRLs 5–6). In animal models, the concept of nerve transfer has been further investigated in procedures in which muscles are split to create more myoelectric signals (122). Increasing the number of myoelectric signals with ever more refined surgical procedures has been the motivation behind ongoing research on surgical human–machine interfaces.

2.4.4. Surgical techniques for afferent interfaces. Surgical approaches have also been used successfully to provide somatosensory perception (123). Initially discovered by accident during TMR (106), purposeful surgical transfer of sensory nerves (TSR) was later successfully demonstrated in upper limb amputations (80, 81) (TRL 6–7). TSR caused referred somatosensory sensations in the missing limb when the reinnervated skin in the residual limb was touched. The reinnervation maps are highly variable and often disorganized (124), but the perceived tactile sensations are reported as natural touch, a feature that can hardly be achieved by electrical stimulation (125).

Despite the fact that RPNIs are mostly intended to extract neural motor information, they can be stimulated to provide proprioceptive and tactile sensory feedback (126), also called sensory RPNI. Similarly, as for control, sensory feedback using RPNIs has not been implemented in daily life due to the lack of a transcutaneous interface. Other forms of sensory interface–based RPNI, such as dermal sensory-RPNI, have only been proposed and tested on animal models (127).

AMI is a new surgical method to restore proprioception in people with limb loss (82). AMI surgically reconnects a residual agonist-antagonist muscle pair with an artificial anchoring point. Stimulation of one muscle leads to its contraction and elongation of the other. The afferent nerves from muscle spindles and the Golgi tendon organ in both muscles elicit proprioception (e.g., muscle force, joint position). This technique has been applied in humans using native muscles, mainly on individuals with lower limb amputations (TRLs 6–7) (128). AMI was combined with the EMG-based efferent neural interface for a closed-loop operation of a robotic prosthetic ankle. Nevertheless, the clinical benefit of this surgical technology in the closed-loop neural prosthesis control has not yet been clear, given that individuals with lower limb amputations can use a direct EMG control paradigm to restore near-normal neuromechanics in dynamic postural control through training without any additional surgeries (129).

Regenerative AMIs using a principle similar to that of RPNIs have been demonstrated in animal models (130); however, it is yet uncertain if the forces exerted by reinnervated free muscle grafts will produce the desired dynamics to evoke proprioception. The same group also uses the composite tissue architecture of a muscle-actuated skin flap to evoke a haptic sensation. This technique is called a cutaneous mechanoneural interface (CMI) and has been demonstrated on animals only (TRLs 1–5) (131).

2.4.5. Combined human–machine interfaces used in daily life. Surgical and engineering approaches have been combined successfully in laboratory and daily life implementations. TMR and TSR have been used for closed-loop control of arm prostheses (5), including the provision of proprioception by vibrating reinnervated muscles (93). However, this approach is not yet used in daily life due to the lack of compact actuators that provide effective mechanical stimulation (TRL 7). The provision of both neural control and sensory feedback using noninvasive technologies has remained challenging, and the use of invasive (implanted) electrodes has been limited by the lack of transcutaneous bidirectional communication interfaces (132). Nerve transfers to large muscles allow for the use of skin surface electrodes to capture myoelectric activity, as in TMR.

However, this is challenging in small muscle targets, such as RPNIs, where implanted electrodes are more suitable, thus posing challenges for the clinical implementation of more refined surgical reconstruction techniques (133).

TMR and implanted electrodes have been used in daily life for open-loop control of upper limb prostheses (134). Similarly, TMR and osseointegration using surface (135) and implanted (89) electrodes for open-loop control have been reported in daily life use. Currently, the only report of a longitudinal daily life implementation of closed-loop control has been achieved using a neuromusculoskeletal interface comprising an osseointegrated implant and implanted electrodes (90). This neuromusculoskeletal interface has also allowed for more refined surgical reconstruction technics, such as RPNIs, to be used for prosthetic control in daily life (116, 117). However, these reports have been only case studies (TRLs 8–9). Additional research and an understanding of the role of these surgical technologies within the complex human–prosthesis interactions and ethics are necessary.

3. GAPS, FUTURE DIRECTIONS, AND RESEARCH GUIDELINES

3.1. Need for Home Trials and Evidence of Technology Effectiveness

One key future direction is to conduct more longitudinal evaluations in daily life (TRL 9). First, the evidence of the effectiveness of various technologies, compared with conventional approaches, is still limited. For example, although EMG pattern recognition is a mature technology, its clinical trials compared with the conventional amplitude-based control have been carried out only recently. Due to the small size and geographic dispersion of the population with upper limb loss and the complexity of human–prosthesis interaction (as shown in **Figure 1**), the clinical studies often yield a limited sample size and inconsistent conclusions (136–138). Second, when people with limb loss are given new prosthetic technologies, they need time to coadapt to the device (139). Cognitive function may also take time to develop through technology use. Nevertheless, the majority of studies in the current field are at TRLs 6–8 (short-term studies in the lab or clinics). Hence, more systematically designed longitudinal trials are needed to provide evidence of the potential of new bionic technologies (140).

We recognize that large-scale home-based clinical trials (TRL 9) are complicated by many factors (e.g., need for intensive resources, participant dropout, people more willing to test control strategies in a lab than during their day-to-day activities, etc.). Multisite collaboration on clinical trials can increase the sample size and produce more concrete evidence than case studies. In addition, the field would benefit from open-source or research-friendly proprietary systems that could integrate with a range of commercially available devices already in use.

3.2. Is Prosthesis Embodiment Necessary?

The concept of embodiment of the artificial limb, or prosthetic embodiment, has become a popular research topic in the field of prostheses. However, there is ambiguity in terms of the definition of the terminology (141, 142). For individuals who conduct translational research, embodiment is commonly understood to be the combination of agency (e.g., the person causes the artificial limb to move) and ownership (e.g., the person perceives the artificial limb as part of one's own body) (141–143). However, other concepts, such as body image (144), have also been used to describe embodiment.

The importance of prosthesis embodiment as a metric for evaluating the efficacy of bionic technologies is also in debate. Some think showing motor function improvement is essential to judge the efficacy of bionic technologies, while others have argued that embodiment leads to behavioral shifts that can result in less device abandonment even if they do not result in increased motor function and have advocated for the measurement of embodiment as an important metric (143). However, no evidence within the field of prosthetics has demonstrated that embodiment is a key user demand or that embodiment is linked to decreased device abandonment. Further work is needed to evaluate the strength of this claim.

More importantly, it is difficult to measure the subcomponents of embodiment (agency and ownership). While several metrics have been used and validated (142), they have typically been limited to laboratory experiments in carefully controlled experimental conditions (TRL 6). It is easy to dissipate the sense of embodiment, particularly in dynamic environments (141), and so it is not clear how robust various forms of prosthetic embodiment or the metrics that measure them are.

In summary, embodiment remains an intriguing area of study, but as a field, we need to be careful that we do not overextend the boundaries of what is proven or the confidence and robustness of the methods we are using.

3.3. TRLs to Guide Future Research and Development

Based on the review of the bionic technologies (**Figures 2–5**), different technical concepts are located at different TRLs. Even within the same concept, different approaches span across multiple TRLs. Hence, using one evaluation criterion to judge the soundness of a concept or technology is problematic. Sometimes there is a tendency of thinking in the community that various bionic technologies are at the same TRL. This wrong assumption leads to clinical translational studies of a premature technology and the rejection of novel ideas or systematic benchtop validation and optimization studies. Therefore, in this review article, we introduce TRLs and advocate using TRLs (**Table 1**) as an appropriate guideline when progressing with the development of bionic technologies, designing evaluation experiments, and disseminating the research outcomes. For example, researchers and engineers can first understand the TRL of their targeted technology in the existing literature and then formulate their technology advancement on the basis of the current and next TRLs. The TRL validation methods and exit criteria can guide the design of the evaluation protocol and outcomes. In addition, TRL can facilitate paper reviewers' ability to identify the study contributions and appropriateness of evaluation methodology. The healthy growth of our field needs research that covers the full spectrum of TRLs, including innovative concepts and feasibility studies, solid benchtop evaluation and optimization, and careful clinical translational research.

3.4. Need for Synergetic Approaches to Integrate Prosthetic Technologies

Notably, many of the milestones made over the past 20 years are synergistic. Researchers tend to integrate surgical techniques, advanced prosthetic devices, and efferent and afferent neural interfaces together to address the function of individuals with limb loss. In our opinion, the sum of optimized components does not necessarily yield the optimal system for human–prosthesis integration. Rather, components must match each other for the best outcomes for prosthesis users. For example, if amplitude-based EMG control is used as an efferent neural decoder, TMR surgery needs additional procedures (e.g., using fat tissues as insulators) to ensure the independence of EMG activities produced by each transferred nerve (106). However, if the efferent decoding method is based on pattern recognition, this additional procedure in TMR is less critical. Hence, a synergetic research collaboration among mechanical and biomedical engineers, clinical researchers, and surgeons is recommended to design the optimal prosthesis solutions for people with limb loss to improve their daily function. We suggest using theories or mechanisms behind human physiology and sensorimotor integrations [e.g., internal model (71, 145)] to serve as the basis behind a holistic framework to guide the appropriate integration of the discussed bionic technologies together to improve the mobility and quality of life of individuals with limb amputations.

4. CONCLUSION

This review article discusses the major research and technological advances that enable or enhance the integration of prosthetics with human users in the context of complicated human–prosthesis interactions. The review also aims to elicit awareness on the broad spectrum of readiness levels of the reviewed individual technologies. By clarifying the complexity of human–prosthesis interactions and technology readiness levels, we hope that our community can use TRLs to guide technology development and clinical translation procedures, keep an open mind to innovative ideas, precisely define the terminologies and outcome measures in reporting the technology benefits, establish holistic approaches for bionic technology integration, collaborate via resource and data sharing, and continue to advance the field to improve the quality of life of individuals with limb loss.

DISCLOSURE STATEMENT

M.O.-C. has consulted for Integrum AB, a company developing osseointegrated implants. L.J.H. is a cofounder of Coapt LLC, a company developing EMG-based prosthesis control. H.H. and J.W.S. are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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