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Toward higher-performance bionic limbs for wider clinical use

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Most prosthetic limbs can autonomously move with dexterity, yet they are not perceived by the user as belonging to their own body. Robotic limbs can convey information about the environment with higher precision than biological limbs, but their actual performance is substantially limited by current technologies for the interfacing of the robotic devices with the body and for transferring motor and sensory information bidirectionally between the prosthesis and the user. In this Perspective, we argue that direct skeletal attachment of bionic devices via osseointegration, the amplification of neural signals by targeted muscle innervation, improved prosthesis control via implanted muscle sensors and advanced algorithms, and the provision of sensory feedback by means of electrodes implanted in peripheral nerves, should all be leveraged toward the creation of a new generation of high-performance bionic limbs. These five technologies have been clinically tested in humans, and alongside mechanical redesigns and adequate rehabilitation training should facilitate the wider clinical use of bionic limbs.

Prosthetics aim to substitute the loss of an extremity via technological means. Missing a limb leads to significant impairments in the capacity to move and to interact with the environment. This deficiency is associated with the actual functional loss of a body part and with the loss of sensation, and it can also affect the person's autonomy, basic societal functions and activities[1]. Requirements for prosthetic devices and the level of satisfaction of their users are affected by numerous factors, in particular the level of amputation (whether it is a unilateral impairment and whether it affects more than one extremity), cultural background, the type of fitting, and co-morbidities[1,2]. Also, the requirements and expectations for upper-limb and lower-limb prostheses are different. Whereas the lower extremities are mainly involved in cyclical locomotor tasks, the upper extremities are frequently engaged in more dexterous actions. Users of prosthetic limbs report that the most important priorities for upper-limb prostheses are function, comfort, durability, cost and appearance. These determine the overall appearance of the device, body language, and the general possibilities for the use of the device to interact with objects[3]. A survey of European and American amputees[4] noted that the most desired functional features are the ability to move separate fingers, avoiding the slipping of grasped objects, and proportional grip strength. Users of prosthetic limbs also conveyed the need for an increase in the range of motion and movement speed of the wrist, a more natural appearance, improvement in the socket temperature and transpiration management, reductions in weight and noise, and increased sensory feedback[5,6].

Although most lower-limb amputees feel confident in forward walking on level ground, maintaining balance and walking on uneven ground or on slopes remain a major concern[7,8]. This is especially prominent in patients with above-knee amputations, with reduced mobility, or with insufficient access to rehabilitation. Additionally, skin problems caused by wearing a socket affect lower-limb amputees to a greater extent, and results in significantly reduced walking distance and in prosthetic abandonment[9]. Indeed, because the major causes for lower-limb amputations are vascular diseases and diabetes[10], and conventional socket systems rely on the application of pressure on the residual limb, the use of lower-limb prostheses is associated with a high incidence of skin problems (24%–74% of prosthesis wearers; refs. [11,12]). And uneven loading on the lower limbs, which is a common problem, has been associated with a prevailing incidence of osteoarthritis on the intact limb[13].

Despite the different needs of upper-limb and lower-limb amputees, a natural appearance and natural control and reliability are desired characteristics in limb prostheses. For both groups of amputee, discomfort and problems with socket fitting are a common factor for device rejection[14,15]. In the past decade, the design of prosthetic limbs has aimed at reducing the overall weight of the prostheses and at mimicking the aesthetics and functions of the lost body parts[16–18]. Although further improvements are needed, developments in functionality have advanced to a degree that can't be fully exploited by the user[19–21]. For example, robotic arms and hands allow for dexterous manipulation[22–25] beyond the possibilities of volitional control available with current man–machine interfaces. These prostheses can be moved by actuating several degrees of freedom, and can measure the external environment with higher precision than humans can with their biological limbs[26]. Yet these possibilities are limited by constraints in the transfer of information to the user and from them.

Clinically available technology for interfacing active prostheses with the body has many limitations. One fundamental problem lies in the mechanical attachment of the device to the user's skeletal system. Most prostheses are connected with the body by sockets that prevent effective integration into the body scheme and that cause discomfort. Also, the currently employed neural connections for restoring volitional control and sensation are limited by an insufficient rate of information transfer. These biomechanical and neural challenges in interfacing technology are at the root of the gap between potentially revolutionizing bionic technology and clinical reality[19,27–29]. For example, clinically available technology for controlling upper-limb prostheses has remained almost unchanged for the past 50 years, and can still control at most two degrees of freedom (one at a time), and in an unnatural manner[30,31]. Moreover, there are practically no clinical prosthetic systems, neither for upper limbs nor for lower limbs, that transfer sensations to the user. The only sensory inputs available to users are vision and the sensations arising from compression forces at the socket. None of these systems are felt by the users as body parts; rather, they are felt as tools aiding in some functions of daily living.

The majority of amputees are fitted with prosthetic devices that have been available for decades. Yet the past few years have seen a few breakthroughs: targeted muscle reinnervation, chronically implanted sensors, advanced neural decoding algorithms, and osseointegration. These are examples of developments that may substantially impact the way prostheses are mechanically and neurally interfaced with amputees (Fig. 1). However, owing to their complex nature, only some of these advances have been tested in patients (and, in most cases, only with a relatively small number of users). The clinical implementation of these technologies requires interdisciplinary teams involving clinical, engineering and rehabilitation experts, and teams with all the needed expertise are rarely available in traditional healthcare systems. Moreover, the involved procedures for such early-stage medical technologies are exempt from conventional insurance schemes. This drives patients with limited financial coverage toward less-able yet standardized solutions. However, these breakthrough technologies are completing initial clinical tests, and we expect that their application in regular clinical environments will allow for critical refinements that will ensure that these solutions mature sufficiently and become the new clinical state-of-the-art. As more patients are being exposed to them, we foresee their implementation becoming optimized and standardized in the coming years, which would allow regulatory bodies to ensure long-term and high-quality user experiences across healthcare systems. In this Perspective, we discuss the most recent technological and clinical developments that will facilitate the design, fabrication and testing of the next generation of clinical prosthetic systems. Hence, rather than exhaustively overviewing technologies for prosthetic limbs, we limit our discussion to selected advances for both upper-limb and lower-limb bionic devices, highlight their scientific and clinical foundations, and analyse their common challenges and the most promising implementations.

Interfacing bionic limbs with the body

Interfacing robotic parts with the human body requires surpassing technical and practical considerations that become major obstacles when aiming at full clinical translation. The integration of bionic limbs with the body faces challenges spanning prosthetic attachments and human interfacing, prosthetic control, and user rehabilitation and training. In this section, we discuss each of these issues, outlining the advantages and disadvantages of the latest available implementations.

Biomechanical interfaces. Achieving biomechanical integration of robotic components with the body is challenging. Although socket technology — incorporated in the great majority of clinical devices — has advanced solutions that can adapt to different shapes of the residual limb, the interfacing socket remains highly unsatisfactory for patients[14,32], particularly for those with pathology-induced conditions such as heterotopic ossification[33]. Instead, attachment via a direct connection to the residual skeletal structures is more appealing. Direct attachment is clinically achieved by means of a metal implant inserted into skeletal structures and then connected to the prosthesis (**Error! Reference source not found.**). Termed osseointegration[34–36], it is currently the only clinically viable alternative to sockets for the mechanical attachment of prostheses. It is a more stable physical connection, it avoids pressure on soft tissues (and hence the ensuing discomfort and pain), and it allows for the transmission of forces directly to skeletal segments, hence enabling osseoperception[37–39]. Osseointegration also preserves the degrees of freedom of the joint, even for short residual limbs. For example, a residual humeral bone as short as 6–7 cm is sufficient for an osseointegrated implant that can preserve the entire range of motion of the shoulder joint[36]. Similarly, osseointegration of a lower-limb prosthesis with a short residual femoral bone can provide natural mobility to the hip joint[40]. Osseointegration also allows for the most effective use of the additional degrees of freedom that prostheses can provide.

However, a limitation of osseointegration is that the metal implant passes the skin barrier in a percutaneous configuration that may determine infections[41]. For this reason, its use over large scales should at least initially be limited as it can only be applied to patients with uncompromised immune systems and with a sufficient skeletal structure. If the risk of infections can be reduced, the presence of a percutaneous port in form of an osseointegrated attachment can in principle be exploited by implanted technology that transmits information in and out the user's body without the need for wireless technology[42–44]. Another limitation of osseointegration is that the absence of damping for impact loads (conventional sockets commonly provided load damping) can cause pain and discomfort, and even the failure of the interface. Although preliminary long-term assessments have indicated improved quality of life for individuals who have undergone osseointegration[45], large-scale cohort studies with long follow-up periods are needed to assess the safety and performance outcomes of the procedure. A survey of the veteran population in the on United States reported that only 28% of unilateral limb amputees and 13% of bilateral upper-limb amputees would consider osseointegration rather than traditional fixation of the device via a conventional socket or refraining from using any prosthesis[46].

Neuromuscular interfaces. A prosthesis can be controlled by using a variety of solutions, the choice depending on the level of amputation and the type of device (**Error! Reference source not found.**). For active control, the human neuromuscular system can be probed directly by interfacing either the brain, nerves or muscles, or by indirectly sensing the kinematics of available anatomical structures. Depending on the sensing method, the recorded signals are then processed to identify their prominent characteristics (features) so that a set of control signals can be mapped onto the targeted prosthetic joints.

Body-powered lower-limb prostheses employ hinge-like artificial joints that allow for free swing when sufficient power is exerted from able joints. In some cases, an autograft (such as rotationplasty) allows the transfer of an ankle joint, which when rotated can act as a knee substitute[47]. With a suitable passive lower-leg attachment, this procedure allows for voluntary gait restoration. However, modern-day powered devices[48] often use a hierarchical-control approach employing a finite-state machine[49] (a sequential control system that can transition among a finite number of states). These allow for the device to switch from one state or setting to another in response to a control input. At the lowest level of control, the position, torque or stiffness of the joints of lower-limb prostheses can be modulated on the basis of signals from mechanical sensors mounted on the prosthesis[50–52]. A finite-state machine is often used at the middle level of control to generate trajectories or to specify parameters for the lower-level controller to use or follow. Simple logic from mechanical sensors within the prosthesis is sufficient to switch between states within the finite-state machine to restore cyclic locomotion. The highest level of control generally provides an estimate of the user’s intention, to switch between locomotion activities. It can be as simple as using a key fob, or it can employ machine-learning algorithms or require an exaggerated body movement that is not typical of normal gait. This hierarchical-control approach has been incorporated into many microprocessor knees, and shown to provide functional outcomes that are better than those of purely passive devices. It has also been used to control locomotion modes for mechanically active devices when standing and walking on level ground, on slopes and on stairs[53–59]. However, this approach does not allow for full volitional control of leg prostheses.

Different from lower-limb devices that can to some extent operate autonomously, upper-limb prostheses always require a certain degree of volitional control. For example, cineplasty (one of the first control methods, and a simple yet powerful strategy) links contraction of proximal muscles of the upper limb to control more distal joints via transmuscularly implanted ivory rods[60,61]. However, owing to the need for extensive rehabilitation periods, cineplasty is no longer in use. Other strategies take advantage of gross movements of the shoulder and trunk to actuate more distal prosthetic functions[62,63] (and hence don’t need surgical intervention). Although simple, these body-powered prostheses are effective and used by many patients[64] because of their reliability, possibility of grip-force regulation, and durability, even when used for manually demanding work[65] or under challenging and competitive conditions[65,66]. Moreover, they provide natural sensory feedback, for example in association to the exerted force.

Contrary to body-powered systems, externally powered prostheses are controlled by decoding the user’s intention from the electrical activity of neural or muscle structures (**Error! Reference source not found.**). This approach has been used in the control of upper-limb prostheses for many years, but has only recently been applied to the lower-limb enabling volitional control of knee and ankle joints during non-weight-bearing situations[67,68]. Electrical signals from muscle can also improve the classification of locomotion modes[54,59,69–73]. In fact, electromyography sensors can enable a highly responsive volitional control of prosthetic ankle joints[74]. Nonetheless, for lower-limb prostheses these methods haven’t yet reached wider clinical implementation. One main challenge is that certain errors in classifying locomotion mode may lead to balance instability, which might threaten the user’s safety and confidence in the use of the prosthesis[71,75]. For upper-limb prostheses, however, volitional control has led to several clinically used active prosthetic arms and hands. Yet there is conflicting evidence as to the functional benefits of externally powered upper-limb prosthetic devices [64,76].

The most common control interface for powered upper-limb prostheses uses gross electromyography signals that are recorded from the surface of the skin covering residual muscles above the amputation site[31]. The use of electromyography for upper-prosthesis control is also based on the assumption that the user’s intention can be extracted from the activation of the remnant muscles. Therefore, the association between muscle signals and the commands for the prosthesis can either be unnatural or physiologically appropriate (that is, similar to the movements that would be generated by the biological limb). For example, for a prosthetic hand, supination and pronation can be associated to wrist flexion and extension, which are control tasks that are different from the produced movement. For many commercial prostheses, it is also common (yet unintuitive) to switch from the control of one function to the control of another via a brief co-contraction of antagonist muscle groups[16,31,77].

Pattern recognition of the surface electromyography aims to increase the number of functions that can be controlled using physiologically appropriate contractions. The natural patterns of muscle activation associated to specific movements are mapped by supervised learning to the corresponding tasks[78,79]. This approach, which has been extensively tested in laboratory studies, has shown that high levels of accuracy (>95%) can be achieved for a relatively large number of classes of task[80–83]. Yet its use in clinical and in at-home environments has been challenging, partly because of problems intrinsic to the detection of surface-electromyography signals. Electromyography signals collected by surface electrodes vary substantially with electrode replacement because of the donning and doffing of the prosthesis, and because they are influenced by skin conditions, have limited selectivity, and can be collected only from superficial muscles[84–86]. These changes in the signal characteristics of surface electromyography causes the performance of pattern-recognition systems to deteriorate[87]. Prosthesis-guided training[86] — a method used clinically to recalibrate control systems based on pattern recognition — can partly overcome these issues and has enabled home trials, which have shown that pattern-recognition control can produce better functional outcomes than conventional amplitude-control techniques after 6 weeks of at-home use[88]. Prosthesis-guided training has also been incorporated into a commercially available pattern-recognition control system (the Coapt Complete Control system, which is currently used by more than 200 patients[89]). Independent studies indicate acceptance rates greater than 70%, with most rejections caused by factors unrelated to the control system.

Many of the problems associated with signals from surface electromyography can be overcome with invasive electromyography technology[90–93], which uses sensors implanted into muscle, or over the surface of muscle yet below the subcutaneous layer. An analysis of chronic implantable systems (in particular, MyoPlant, ref. [94]; MIRA, ref. [95]; iSens, ref. [96]; and IMES, refs. [97,98]; Fig. 3), has shown that they can provide superior electromyography data quality than surface recordings[42]. For example, an IMES system consisting of eight electrodes implanted in the forearm of a transradial amputee (clinical-trial identifier, NCT01901081) led to safe application and to simple yet efficient simultaneous control over multiple degrees of freedom[92,97,99]. In lower-limb amputees, the same sensor system enabled reliable control over knee joints and ankle joints[100]. IMES implants have been stable for over 4 years[101]. Similarly, epimysial electrodes chronically implanted in patients have enabled high-quality direct control over months of operation[42].

User intent in lower and upper limbs can also be decoded from electrical activity recorded from efferent axons in peripheral nerves[102–105]. This requires direct nerve implants. Placing electrodes directly into nerves can solve the problems associated with non-invasive muscle recordings and, with respect to invasive muscle recordings, may also be applied in the absence of remnant muscle tissue. Motor information can in fact be decoded from neural recordings, with good performance[106–112]. However, electroneurographic signals have a low signal-to-noise ratio and limited stability[106], making it challenging to decode the activity of efferent fibres with intrafascicular nerve implants[113]. Also, nerve implants can potentially lead to damage of the nerve (which can self-repair to some degree[114]).

Alternatively, targeted muscle reinnervation — an established clinical intervention that consists in redirecting nerves that have lost their natural target muscles to other muscle tissues so as to biologically amplify the activity of the redirected nerve[115–119] — can provide a form of 'bioscreen' that displays, via muscle electrical signals, the neural activity of the transferred nerves. However, the transferred nerve branches may provide complex neural information from multiple functions, thus generating complex muscle signals reflecting the neural activity of multiple neural sources. Recently, the multiunit muscle signals generated following nerve transfers have been decoded by source separation algorithms[120,121118,122,123], thus providing a direct interface with spinal motor neurons[118,124–127].

As an alternative to decoding multiunit activity by source separation algorithms, the selectivity can be reached directly at the recording point. For example, myoblasts embedded in an electroconductive polymer, have been cultured directly onto the ends of transected nerves. These regenerative peripheral-nerve interfaces decodes the neural activity by selectively recording the muscular electrical signals generated by only a small number of nerve fibres, which increases the number of discrete signals available for prosthetic control[128]. A refined version of this strategy is known as the 'micro-targeted muscle reinnervation' procedure; it redirects individual peripheral nerves to small pieces of muscle that are devascularized and denervated. These individual groups of contracting muscle can then produce high-fidelity motor-control signals with favourable signal-to-noise ratios for the real-time control of a prosthesis[129–131]. Because the architecture of peripheral nerves at higher levels of amputation does not reveal distinct regions of functional topography that may be dissected towards specific (agonistic or antagonistic) muscle functions, this strategy is at the moment limited to distal amputation levels and to implantable electrodes that can pick up relatively low-energy myosignals.

As an alternative to approaches interacting with the peripheral neuromuscular system, a direct interface with the brain can in principle also be used for controlling bionic arms and legs. Implantable selective cortical electrodes can record from hundreds of cortical neurons, and this neural activity can then be associated with the online control of multiple degrees of freedom[132,133]. Such invasive brain interfacing is promising, yet it is limited by the need of brain surgery (which would not be accepted by most amputees) and by limited functionality (with respect to peripheral interfacing). Non-invasive brain-interfacing technology could be applied on a larger scale, but it does not provide the level of performance control that is typically required for prosthetic applications[134–136].

The recovery of function is of upmost importance to upper-limb and lower-limb amputees. High functionality can in principle be achieved fully on the basis of human adaptation. For example, able-bodied individuals equipped with an electromyography interface can simultaneously control a robotic arm with 7 degrees of freedom after limited training[137]; however, this approach is not intuitive.

To decrease cognitive load in the use of prostheses, it is evident that intuitive or 'natural' control — the continuous and simultaneous control over multiple degrees of freedom with physiological correspondence between (neural) intention and (prosthetic) action — is desirable[138]. It is also highly relevant for promoting embodiment (the user perceiving the prosthesis as a part of their body), which is also highly desired. Embodiment should indeed be in itself a driver for technology advances, as it would increase the satisfaction of the users of prostheses and their acceptance of the devices[138,139]. Natural control has been promoted by data-driven approaches that explore correlations between electromyography signals and motions[140–144]. When properly configured, it is superior to direct control and to sequential pattern recognition. Notably, continuous mapping of the kinematics of multiple degrees of freedom allows for better adaptation of the user to the interface than what can be achieved with classic pattern recognition[145].

Natural control can also be obtained by musculoskeletal models that predict joint moments from muscle activations[146–151]. This approach has been applied to both upper-limb and lower-limb prostheses[149,151,152]. Instead of exploring data patterns or correlations (as in data-driven approaches), forward musculoskeletal models mimic the biological process of musculoskeletal movement production, directly incorporate the physiological and biomechanical structures and constraints, and then estimate natural and coordinated limb motions[146]. Moreover, the use of targeted muscle reinnervation allows the detection of the neural activity of all nerves involved in the task (including those in missing muscles). Therefore, the combination of targeted muscle reinnervation and musculoskeletal models could allow for the reconstruction of the internal biomechanical representation of missing limbs[118,153].

Robust long-term control is a basic requirement for the clinical translation and embodiment of a prosthesis. Today's microprocessor-controlled knees and ankles are particularly robust prostheses that use relatively intuitive control methods. The mechanical signals incorporated into the prosthesis have low noise levels and are reliable. After the user has learnt how to operate the device, the prosthesis responds predictably, allowing the user to trust its operation. However, it is difficult to extend the number of locomotion activities that may be stored, and to allow for seamless and automatic transitions between activities. Yet machine-learning algorithms for the recognition of locomotion activities and of transitions between activities are promising. They can be developed to interpret information from mechanical sensors only[54,58,154,155], or from combined mechanical and electromyography information[59,69]. Electromyography signals can provide accurate intent estimates in powered knees[156] and ankles[157], provided that electromyography-signal changes, that can cause a deterioration of performance across multiple days, are corrected for[158].

Restoring robust control for upper-limb amputees has a different set of challenges. Upper-limb prosthetic limbs are used in an unconstrained environment, and do not typically contain as many mechanical sensors as lower-limb prostheses. Consequently, they rely primarily on volitional control by using electromyography signals. Conventional control approaches rely on skilled therapists and prosthetists to localize independent agonist–antagonist muscle pairs, to tune gains, to impose thresholds, and to create comfortable sockets that maintain consistent electrode positions when repeatedly donned. The clinical translation of more sophisticated approaches developed in research laboratories can be challenging because of the need to collect calibration data that is representative of the variable conditions in which the prosthesis might be used. For example, electromyography pattern-recognition systems are sensitive to electrode positions[87], residual limb-arm posture[159] and force variations[160] (among many other factors). Each of these problems can be mitigated by collecting an exhaustive set of training data, but this can be burdensome for the user. Alternatively, prosthesis-guided training can be applied for recalibration.

Adaptation via machine learning is also promising for the optimization of the use of electromyography signals for the control of bionic limbs. Adaptation is needed because of changes in electromyography-signal features and in the user's muscle-activation strategies. Completely unsupervised adaptation would of course be preferable, but a working system is currently out of reach[161]. With pattern-recognition systems, semi-supervised or piecewise-supervised approaches using labelled training signals are sufficient to counteract decreases in performance over days of use[162]. Co-adaptive systems[161,163,164] are limited to the calibration phase or to specific sets of tasks[165].

Unsupervised adaptation for lower-limb prostheses is probably more feasible than for upper-limb devices, particularly when estimating locomotion activities, because gait information can be exploited to help determine if the control system predicted the correct activity. Such an 'error signal' can be used to supervise the adaptation of electromyography classifiers[166,167]. It is even possible to adapt mid-level controllers by automatically adjusting control parameters to replicate normal gait profiles, or to adjust parameters to minimize a cost function based on electromyography activity from the affected or able limb while simultaneously enforcing normative kinematics.

Stability of the control can also be achieved by systems that are inherently robust to changes in conditions. For example, for the myocontrol of bionic limbs, variabilities from changes in posture can be substantially decreased by using intramuscular sensors, which also naturally eliminate the intrinsic variability of surface electromyography electrodes when donning and doffing the electrodes over repetitive uses[42,93]. Similarly, some electromyography-decoding approaches may be more stable than others to changes in signal characteristics. For example, electromyography-driven musculoskeletal models of upper and lower limbs for myocontrol may provide a 'solution space' for control that is less sensitive to changes in muscle coordination than data-driven machine-learning techniques[146,150,151]. This is because electromyography-driven musculoskeletal models directly incorporate physiological and biomechanical constraints that constrain the solution space. Alternatively, robustness could be promoted by allowing the systems themself to assist the user during the operation through a form of shared control[168,169].

Sensory feedback

Sensorimotor integration is a fundamental principle of motor control in humans. Therefore, substitutions of motor function should not prescind from the integration of sensory input. An ideal prosthesis should thus replace the motor and sensory functions of the lost limb. However, restoring sensory feedback in any capacity has proven to be highly challenging. It is indeed difficult to provide usable and explicit feedback that can be effectively integrated in the control and with the information gathered through other senses (such as vision)[170]. Moreover, when estimating the state of the environment, humans integrate information from multiple feedback sources as well as previous experience, so the delivered sensory information needs to be compatible within this internal framework[171]. For example, proprioceptive information requires the precise integration of sensory feedback from a variety of afferents; this is difficult to replicate.

A general strategy for the provision of sensory feedback involves the embedding of sensors in the prosthesis to measure joint positions, tactile pressure and grasping forces, and to transmit the information to the user by eliciting sensations in the remaining body structures. One approach is to stimulate the skin of the residual limb. This stimulation can be mechanical (acting on the tactile receptors via the use of, for instance, vibration motors[172,173], linear pushers[174,175], skin stretchers[176,177] or pressure cuffs[178]) or electrical[179–181] (via the delivery of low-intensity pulses of current through surface electrodes to activate cutaneous afferents or to induce transcutaneous electrical nerve stimulation[182–184] as well as through implanted microelectrodes for electrical stimulation of peripheral nerves[185]). The prosthesis state (sensor data) is communicated to the user as a time-varying pattern of stimulation. For example, the frequency or intensity of electrotactile or vibrotactile stimulation can be modulated proportionally to the measured grasping force[186–188]. These approaches can provide different sensations with respect to the natural sensing pathways (sensory substitution). It is also possible to elicit natural phantom-limb sensations by targeting sites on the skin that have been surgically reinnervated (targeted sensory reinnervation)[189–191]. Furthermore, natural feedback can potentially be restored through electrical stimulation of surgically formed muscle-actuated skin flaps (cutaneous mechanoneural interface[192]).

Because the direct stimulation of nerves can activate the same natural neural pathways conveying sensory information, its use with implanted electrodes[105] (Fig. 4) may be more effective at providing natural sensory feedback than non-invasive approaches[170]. Besides the inherent difficulty of artificially replicating the encoding of sensory feedback, apart from recent promising examples [44], a common challenge for these interfaces remains achieving long-term stability[193]. The implanted electrodes should be biocompatible with low electrical impedance, be flexible and mechanically stable, and provide large charge storage and injection capacity. This class of implants can establish natural tactile sensations[42,194–196,197–199,109,200–202], yet there are still significant financial and temporal efforts needed to transfer these results from the laboratory into human clinical trials and further on in commercial products.

Epidural stimulation of the spinal cord has been shown to evoke sensory precepts in the missing limbs of amputees[203]. Furthermore, direct cortical stimulation can also provide missing sensory feedback. By using floating microelectrode arrays, selected areas of the somatosensory cortex of a non-human primate can be stimulated to provide tactile sensation[204]. Similarly, optogenetics could provide highly accurate sensory feedback, and even read-out, by stimulating optically sensitive ion channels related to various neural circuits[205–209], though at present, these strategies have only been tested in animals.

There is only one commercial prosthesis type providing sensory feedback: an upper-limb device (the Vincent Evolution hand series) that provides vibrotactile feedback on the grasping force[210]. The limited clinical translation of sensory-feedback technology is partly a consequence of the uncertain functional advantages of including supplemental tactile feedback[211,212] or other rather simple sensory-feedback strategies. Although the benefits of sensory feedback may appear obvious for the user, without an improvement in function it is difficult to argue for the associated cost increase in the clinical devices. Hence, most research has focused on the sensorimotor integration of sensory feedback rather than on the intrinsic recovery of sensation[42,194,195,213]. For sensory-feedback technology to have clinical impact, it should show clear functional improvements.

The role of rehabilitation

User-centred rehabilitation is currently an essential part of functional recovery via prosthetic substitutions. Research efforts toward natural and intuitive control interfaces are essential, yet for functional tasks the user needs to adapt to the interface[214] and to systematically learn to interpret direct or indirect feedback[215,216,217]. Rehabilitation is also needed to treat co-morbidities, amputation-related overuse of joints in the contralateral extremity, neck and back, as well as pain syndromes. Especially after traumatic amputation, psychological support is crucial because the loss of any body part is a serious threat to the individual's core identity[218]. Amputation can trigger a disturbed body image and negative self-evaluation and psychological distress; in the absence of adequate therapy, these can cause a range of concealing[219] behaviours. Hence, prosthetic fitting should involve physical and occupational therapy as well as psychological and social support. A perfectly well-fitted advanced prosthetic device will not by itself enhance the quality of life of individuals who are not coping well with their amputation[220] or who have not never learnt how to properly use the device in their daily activities[214,221]. Rehabilitation and a team approach to care are vital to the success of complex prosthetic systems, but long rehabilitation periods (as were typical for tunnel cineplasty) can hamper it.

Quantitative evaluation measures that assess the accuracy of control in laboratory conditions are poor predictors of real clinical outcomes[222,223]. Also, the functional benefits of a bionic limb cannot be assessed separately from the rehabilitation program designed to train the user to interface with the robotic device (especially since depending on the rehabilitation a single prosthetic device can enable significantly different levels of function[224]). Objective and clinically relevant metrics of functional outcome are thus crucial for the design and delivery of effective rehabilitation.

Substantial prosthetic training is essential for the proficient handling of a myoelectric prosthesis (training usually starts before the user receives the device[225,226]). Pre-prosthetic training can involve virtual reality and augmented reality as well as training systems controlled via desktop computers[227] or smartphone apps[227–229]. The training protocol and the accompanying rehabilitation tools need to be matched to the user's prosthetic device and to the selected control interface[214]. In fact, the development of prosthetic functions, control strategies and sensory feedback needs to include appropriate protocols for rehabilitation[217]. It is thus important that, to enable the amputee to make best use of available technology, human–machine interfaces are developed alongside rehabilitation programs based on current knowledge of motor learning[215].

The next generation of clinical prostheses

We expect that the performance of the next generation of bionic limbs will broaden their clinical use by leveraging the breakthrough achievements of the past decade — osseointegration, cognitive bioscreens, implanted sensors, advanced control algorithms, and sensory feedback. Next-generation clinical prostheses should better meet patient requirements (most importantly, a more robust and natural control of the prosthesis) via improved prosthetic attachment to the residual limb, the implementation of a sensory-feedback interface that enhances the device's functions, and rehabilitation programs that are tailored to the user and based on motor-learning principles and on the unique features of each prosthesis.

Osseointegration has been fully certified in Europe and Australia, and the first implant system (OPRA) for above knee amputations has more recently been fully certified also in the US as it now holds a premarket approval by the United States Food and Drug Administration. It will eliminate the challenges and limitations inherent to socket design, especially for transhumeral and transfemoral amputations and for other challenging amputation levels. It will also provide the means to preserve the available degrees of freedom, and thus maximize the support provided by the additional degrees of freedom of the prosthesis. The extensive use of this procedure is currently mainly limited by the risks of infections, owing to the need for a percutaneous implant. However, long-term follow-up studies of large multicentre patient cohorts have documented that local infection rates are below 5%, and that revision rates are much lower[230]. Moreover, more precise pre-surgical assessments, improvements in surgical procedures, in materials for the port and in port-fixation design may further decrease the incidence of infection.

Next-generation prostheses should include robust control and chronically implanted electrodes. Muscles will remain the most likely signal targets for control; the limitations of nerve interfacing and brain interfacing are too severe. Intramuscular wireless sensors (such as the IMES and the MIRA) have been tested clinically and will become more common in limb prostheses. The iSens system, which combines intramuscular electrodes for control and nerve stimulation for sensory feedback is particularly promising (it may receive regulatory certification), but its high levels of energy consumption and its current incompatibility with osseointegration and other metallic implants may constrain its use. Implanted electromyography sensors employing algorithms similar to those developed for surface electromyography will be used for control and provide stable and high-fidelity signals over multiple uses of the prostheses. The combination of a muscular bioscreen[125] (via selective nerve transfers) and implanted muscle sensors (Fig. 5) should ensure robustness and offer the largest increase in functionality (with respect to current clinical systems). In this regard, the direct control of degrees of freedom is the most likely approach for clinical translation; more advanced control methods involving machine learning and musculoskeletal modelling approaches may be incorporated later, after refinement and thorough testing in research settings.

The inclusion of sensory feedback will be crucial. However, non-invasive sensory substitution presents fundamental problems, mainly related to the variability of elicited sensations for different locations of the actuators or electrodes. Although long-term nerve implants are feasible[103,114,195,231–234] and promising for versatile clinical and home uses[96,235], their wider clinical translation will require substantial developments regarding device stability, their integration into fully implantable systems, and the modularity of electrode–cable modules with implantable pulse generators. Moreover, establishing tactile sensory feedback while providing proprioception[236] is challenging[237,238]. Because of the primary clinical need for control and the open challenges in artificial sensory feedback, we expect that advances in prosthetic control will have clinical impact much earlier than developments in sensory feedback.

Certain groups of users of prostheses may receive greater benefits from next-generation bionic limbs (and hence adopt the devices earlier). In particular, patients with more than one impaired extremity extensively rely on prosthetic functions in order to master daily living activities, and therefore will benefit from new technologies to a greater extent[1]. For most patients, the available healthcare support will influence the choice of prosthesis. To ensure satisfactory implementation of next-generation technology and to maximize its reach, appropriate training will need to be provided to relevant healthcare professionals.

A few bionic-limb technologies, such as osseointegration and implantable myoelectric sensors, are ready to undergo large-scale clinical implementation. Suitable prosthetic technologies can increase the rates of return to work for the user population and thus justify the cost of the device[239,240]. However, funding constraints, access to a sufficiently large population of users, and ethical concerns can slow down the wider clinical use of the devices[241]. To maximize the chances of success, collaborative academic and industrial efforts should design well-powered clinical studies focused on the relevant user groups[242], and early-concept research studies should involvement advanced users and clinicians to ensure that the technology being developed meets actual needs and requirements[243]. For implantable technologies, appropriate animal studies should be used. Standardized and ethically considerate animal studies[244,245] should provide insights into the long-term stability of the technology and enable more efficient and informed transitions into human studies.

Realistically, the wider clinical application of osseointegration, targeted muscle reinnervation, implanted myoelectric sensors, advanced control algorithms, and implanted nerve electrodes for sensory feedback should occur within the next two decades. All of these technologies have been clinically tested, and shown to be safe and to provide performance advantages for lower-limb and upper-limb amputees. Bionic fittings leveraging these five technologies will, in aggregate, constitute a new generation of bionic limbs that we hope will substantially enhance the quality of life of patients and pave the way for longer-term visions of true limb replacement. Beyond breakthrough technologies, wider clinical success will require holistic support of the prosthesis-fitted individuals through tailored rehabilitation treatments.

References

1. Cordella, F. *et al.* Literature Review on Needs of Upper Limb Prosthesis Users. *Front. Neurosci.* **10**, 209 (2016).

2. Webster, J. B. *et al.* Prosthetic fitting, use, and satisfaction following lower-limb amputation: A prospective study. *J. Rehabil. Res. Dev.* **49**, 1493 (2012).

3. Biddiss, E., Beaton, D. & Chau, T. Consumer design priorities for upper limb prosthetics. *Disabil. Rehabil. Assist. Technol.* **2**, 346–357 (2007).

4. Kyberd, P. J. & Hill, W. Survey of upper limb prosthesis users in Sweden, the United Kingdom and Canada. *Prosthet. Orthot. Int.* **35**, 234–241 (2011).

5. Pylatiuk, C., Schulz, S. & Döderlein, L. Results of an Internet survey of myoelectric prosthetic hand users. *Prosthet. Orthot. Int.* **31**, 362–370 (2007).

6. Jang, C. H. *et al.* A Survey on Activities of Daily Living and Occupations of Upper Extremity Amputees. *Ann. Rehabil. Med.* **35**, 907 (2011).

7. Fogelberg, D. J., Allyn, K. J., Smersh, M. & Maitland, M. E. What People Want in a Prosthetic Foot. *J. Prosthetics Orthot.* **28**, 145–151 (2016).

8. Villa, C. *et al.* Cross-Slope and Level Walking Strategies During Swing in Individuals With Lower Limb Amputation. *Arch. Phys. Med. Rehabil.* **98**, 1149–1157 (2017).

9. Meulenbelt, H., Geertzen, J., Jonkman, M. & Dijkstra, P. Skin Problems of the Stump in Lower Limb Amputees: 1. A Clinical Study. *Acta Derm. Venereol.* **91**, 173–177 (2011).

10. NHS Scotland Information Services Division. *The Amputee Statistical Database for the United Kingdom 2004/05*. http://www.cofemer.fr/UserFiles/File/Amput2004_05.pdf (2005).

11. Dillingham, T. R., Pezzin, L. E., MacKenzie, E. J. & Burgess, A. R. Use and satisfaction with prosthetic devices among persons with trauma-related amputations: a long-term outcome

study. *Am. J. Phys. Med. Rehabil.* **80**, 563–71 (2001).

12. Koc, E. *et al.* Skin problems in amputees: a descriptive study. *Int. J. Dermatol.* **47**, 463–466 (2008).

13. Ding, Z., Jarvis, H. L., Bennett, A. N., Baker, R. & Bull, A. M. J. Higher knee contact forces might underlie increased osteoarthritis rates in high functioning amputees: A pilot study. *J. Orthop. Res.* 1–11 (2020) doi:10.1002/jor.24751.

14. Daly, W., Voo, L., Rosenbaum-Chou, T., Arabian, A. & Boone, D. Socket Pressure and Discomfort in Upper-Limb Prostheses: A Preliminary Study. *JPO J. Prosthetics Orthot.* **26**, 99–106 (2014).

15. Biddiss, E. a & Chau, T. T. Upper limb prosthesis use and abandonment: a survey of the last 25 years. *Prosthet. Orthot. Int.* **31**, 236–257 (2007).

16. Vujaklija, I., Farina, D. & Aszmann, O. New developments in prosthetic arm systems. *Orthop. Res. Rev.* **Volume 8**, 31–39 (2016).

17. Peerdeman, B. *et al.* Myoelectric forearm prostheses: State of the art from a user-centered perspective. *J. Rehabil. Res. Dev.* **48**, 719 (2011).

18. Belter, J. T., Segil, J. L., Dollar, A. M. & Weir, R. F. Mechanical design and performance specifications of anthropomorphic prosthetic hands: A review. *JRRD* **50**, (2013).

19. Farina, D. & Aszmann, O. Bionic Limbs: Clinical Reality and Academic Promises. *Sci. Transl. Med.* **6**, 257ps12-257ps12 (2014).

20. Ning Jiang, Dosen, S., Muller, K.-R. & Farina, D. Myoelectric Control of Artificial Limbs—Is There a Need to Change Focus? *IEEE Signal Process. Mag.* **29**, 152–150 (2012).

21. Castellini, C., Bongers, R. M., Nowak, M. & van der Sluis, C. K. Upper-limb prosthetic myocontrol: Two recommendations. *Front. Neurosci.* **9**, 1–4 (2016).

22. Bicchi, A. & Sorrentino, R. Dexterous manipulation through rolling. in *Proceedings of 1995 IEEE International Conference on Robotics and Automation* vol. 1 452–457 (IEEE, 1995).

23. Okamura, A. M., Smaby, N. & Cutkosky, M. R. An overview of dexterous manipulation. in *Proceedings 2000 ICRA. Millennium Conference. IEEE International Conference on Robotics and Automation. Symposia Proceedings (Cat. No.00CH37065)* vol. 1 255–262 (IEEE, 2000).

24. Shimoga, K. B. Robot Grasp Synthesis Algorithms: A Survey. *Int. J. Rob. Res.* **15**, 230–266 (1996).

25. Bicchi, A. Hands for dexterous manipulation and robust grasping: a difficult road toward simplicity. *IEEE Trans. Robot. Autom.* **16**, 652–662 (2000).

26. Fishel, J. A. & Loeb, G. E. Sensing tactile microvibrations with the BioTac — Comparison with human sensitivity. in *2012 4th IEEE RAS & EMBS International Conference on Biomedical Robotics and Biomechatronics (BioRob)* 1122–1127 (IEEE, 2012). doi:10.1109/BioRob.2012.6290741.

27. Sewell, P., Noroozi, S., Vinney, J. & Andrews, S. Developments in the trans-tibial prosthetic socket fitting process: a review of past and present research. *Prosthet. Orthot. Int.* **24**, 97–107 (2000).

28. Astrom, I. & Stenstrom, A. Effect on gait and socket comfort in unilateral trans-tibial amputees after exchange to a polyurethane concept. *Prosthet. Orthot. Int.* **28**, 28–36 (2004).

29. Ortiz-Catalan, M., Brånemark, R., Håkansson, B. & Delbeke, J. On the viability of implantable electrodes for the natural control of artificial limbs: Review and discussion. *Biomed. Eng. Online* **11**, 33 (2012).

30. Zhou, P. *et al.* Decoding a New Neural–Machine Interface for Control of Artificial Limbs. *J. Neurophysiol.* **98**, 2974–2982 (2007).

31. Scott, R. N. & Parker, P. a. Myoelectric prostheses: state of the art. *J. Med. Eng. Technol.* **12**, 143–51 (1988).

32. Lake, C. The Evolution of Upper Limb Prosthetic Socket Design. *JPO J. Prosthetics Orthot.* **20**, 85 (2008).

33. Potter, M. B. K. *et al.* Heterotopic Ossification Following Combat-Related Trauma. *J. Bone Jt. Surgery-American Vol.* **92**, 74–89 (2010).

34. Brånemark, R., Brånemark, P.-I., Rydevik, B. & Myers, R. R. Osseointegration in skeletal reconstruction and rehabilitation: A review. *J Rehabil Res Dev* **38**, 175–81 (2001).

35. Shelton, T. J., Beck, P. J., Bloebaum, R. D. & Bachus, K. N. Percutaneous Osseointegrated Prostheses for Amputees: Limb Compensation in a 12-Month Ovine model. *J. Biomech.* **44**, 2601–2606 (2011).

36. Jönsson, S., Caine-Winterberger, K. & Brånemark, R. Osseointegration amputation prostheses on the upper limbs: methods, prosthetics and rehabilitation. *Prosthet Orthot Int* **35**, 190–200 (2011).

37. Hagberg, K., Branemark, R., Gunterberg, B. & Rydevik, B. Osseointegrated trans-femoral amputation prostheses: Prospective results of general and condition-specific quality of life in 18 patients at 2-year follow-up. *Prosthet. Orthot. Int.* **32**, 29–41 (2008).

38. Hagberg, K., Häggström, E., Uden, M. & Brånemark, R. Socket Versus Bone-Anchored Trans-Femoral Prostheses: Hip Range of Motion and Sitting Comfort. *Prosthet. Orthot. Int.* **29**, 153–163 (2005).

39. Pitkin, M. Design features of implants for direct skeletal attachment of limb prostheses. *J. Biomed. Mater. Res. Part A* n/a-n/a (2013) doi:10.1002/jbm.a.34606.

40. Brånemark, R. P., Hagberg, K., Kulbacka-Ortiz, K., Berlin, Ö. & Rydevik, B. Osseointegrated Percutaneous Prosthetic System for the Treatment of Patients with Transfemoral Amputation: A Prospective Five-year Follow-up of Patient-reported Outcomes and Complications. *J. Am. Acad. Orthop. Surg.* **27**, E743–E751 (2019).

41. Al Muderis, M., Khemka, A., Lord, S. J., Van de Meent, H. & Frölke, J. P. M. Safety of Osseointegrated Implants for Transfemoral Amputees. *J. Bone Jt. Surg.* **98**, 900–909 (2016).

42. Ortiz-Catalan, M., Hakansson, B. & Branemark, R. An osseointegrated human-machine gateway for long-term sensory feedback and motor control of artificial limbs. *Sci. Transl. Med.* **6**, 257re6-257re6 (2014).

43. Mastinu, E., Doguet, P., Botquin, Y., Hakansson, B. & Ortiz-Catalan, M. Embedded System for Prosthetic Control Using Implanted Neuromuscular Interfaces Accessed Via an Osseointegrated Implant. *IEEE Trans. Biomed. Circuits Syst.* 1–11 (2017) doi:10.1109/TBCAS.2017.2694710.

44. Ortiz-Catalan, M., Mastinu, E., Sassu, P., Aszmann, O. & Brånemark, R. Self-Contained Neuromusculoskeletal Arm Prostheses. *N. Engl. J. Med.* **382**, 1732–1738 (2020).

45. Matthews, D. J. *et al.* UK trial of the Osseointegrated Prosthesis for the Rehabilitation for Amputees: 1995–2018. *Prosthet. Orthot. Int.* **43**, 112–122 (2019).

46. Resnik, L., Benz, H., Borgia, M. & Clark, M. A. Patient Perspectives on Osseointegration: A National Survey of Veterans with Upper Limb Amputation. *PM&R* (2019) doi:10.1002/pmrj.12147.

47. Van Nes, C. P. Rotation-Plasty For Congenital Defects Of The Femur. *J. Bone Joint Surg. Br.*

32-**B**, 12–16 (1950).

48. Azocar, A. F. *et al.* Design and clinical implementation of an open-source bionic leg. *Nat. Biomed. Eng.* **4**, 941–953 (2020).

49. Goldfarb, M., Lawson, B. E. & Shultz, A. H. Realizing the promise of robotic leg prostheses. *Sci. Transl. Med.* **5**, 225 (2013).

50. Grimes, D. L., Flowers, W. C. & Donath, M. Feasibility of an Active Control Scheme for Above Knee Prostheses. *J. Biomech. Eng.* **99**, 215 (1977).

51. Sup, F., Bohara, A. & Goldfarb, M. Design and Control of a Powered Transfemoral Prosthesis. *Int. J. Rob. Res.* **27**, 263–273 (2008).

52. Martinez-Villalpando, E. C. & Herr, H. Agonist-antagonist active knee prosthesis: A preliminary study in level-ground walking. *J. Rehabil. Res. Dev.* **46**, 361 (2009).

53. Simon, A. M., Hargrove, L. J., Lock, B. a. & Kuiken, T. a. Target Achievement Control Test: Evaluating real-time myoelectric pattern-recognition control of multifunctional upper-limb prostheses. *J. Rehabil. Res. Dev.* **48**, 619 (2011).

54. Young, A. J., Simon, A. M., Fey, N. P. & Hargrove, L. J. Intent Recognition in a Powered Lower Limb Prosthesis Using Time History Information. *Ann. Biomed. Eng.* **42**, 631–641 (2014).

55. Lenzi, T., Sensinger, J., Lipsey, J., Hargrove, L. & Kuiken, T. Design and preliminary testing of the RIC hybrid knee prosthesis. in *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* 1683–1686 (IEEE, 2015). doi:10.1109/EMBC.2015.7318700.

56. Lawson, B. E., Varol, H. A., Huff, A., Erdemir, E. & Goldfarb, M. Control of Stair Ascent and Descent With a Powered Transfemoral Prosthesis. *IEEE Trans. NEURAL Syst. Rehabil. Eng.* **21**, 466–473 (2013).

57. Au, S., Berniker, M. & Herr, H. Powered ankle-foot prosthesis to assist level-ground and stair-descent gaits. *Neural Networks* **21**, 654–666 (2008).

58. Varol, H. A., Sup, F. & Goldfarb, M. Multiclass real-time intent recognition of a powered lower limb prosthesis. *IEEE Trans. Biomed. Eng.* **57**, 542–551 (2010).

59. He Huang *et al.* Continuous Locomotion-Mode Identification for Prosthetic Legs Based on Neuromuscular–Mechanical Fusion. *IEEE Trans. Biomed. Eng.* **58**, 2867–2875 (2011).

60. Weir, R. F., Heckathorne, C. W. & Childress, D. S. Cineplasty as a control input for externally powered prosthetic components. *J. Rehabil. Res. Dev.* **38**, 357–63 (2001).

61. Brückner, L. Sauerbruch-lebsche-vanghetti cineplasty: The surgical procedure. *Orthop. Traumatol.* **1**, 90–99 (1992).

62. Kruit, J. & Cool, J. C. Body-powered hand prosthesis with low operating power for children. *J. Med. Eng. Technol.* **13**, 129–133 (1989).

63. Doeringer, J. A. & Hogan, N. Performance of above elbow body-powered prostheses in visually guided unconstrained motion tasks. *IEEE Trans. Biomed. Eng.* **42**, 621–631 (1995).

64. Carey, S. L., Lura, D. J. & Highsmith, M. J. Differences in myoelectric and body-powered upper-limb prostheses: Systematic literature review. *J. Rehabil. Res. Dev.* **52**, 247–262 (2015).

65. Schweitzer, W., Thali, M. J. & Egger, D. Case-study of a user-driven prosthetic arm design: bionic hand versus customized body-powered technology in a highly demanding work environment. *J. Neuroeng. Rehabil.* **15**, 1 (2018).

66. Riener, R. The Cybathlon promotes the development of assistive technology for people with

physical disabilities. *J. Neuroeng. Rehabil.* **13**, 49 (2016).

67. Hargrove, L. J., Simon, A. M., Lipschutz, R., Finucane, S. B. & Kuiken, T. A. Non-weight-bearing neural control of a powered transfemoral prosthesis. *J. Neuroeng. Rehabil.* **10**, 62 (2013).

68. Ha, K. H., Varol, H. A. & Goldfarb, M. Volitional control of a prosthetic knee using surface electromyography. *IEEE Trans. Biomed. Eng.* **58**, 144–151 (2011).

69. Hargrove, L. J. *et al.* Intuitive Control of a Powered Prosthetic Leg During Ambulation. *JAMA* **313**, 2244 (2015).

70. Peng, J., Fey, N. P., Kuiken, T. A. & Hargrove, L. J. Anticipatory kinematics and muscle activity preceding transitions from level-ground walking to stair ascent and descent. *J. Biomech.* **49**, 528–536 (2016).

71. Zhang, F., Liu, M. & Huang, H. Effects of Locomotion Mode Recognition Errors on Volitional Control of Powered Above-Knee Prostheses. *IEEE Trans. Neural Syst. Rehabil. Eng.* **23**, 64–72 (2015).

72. Khademi, G., Mohammadi, H. & Simon, D. Gradient-Based Multi-Objective Feature Selection for Gait Mode Recognition of Transfemoral Amputees. *Sensors* **19**, 253 (2019).

73. Spanias, J. A., Simon, A. M., Finucane, S. B., Perreault, E. J. & Hargrove, L. J. Online adaptive neural control of a robotic lower limb prosthesis. *J. Neural Eng.* **15**, 016015 (2018).

74. Au, S. K., Bonato, P. & Herr, H. An EMG-Position Controlled System for an Active Ankle-Foot Prosthesis: An Initial Experimental Study. in *9th International Conference on Rehabilitation Robotics, 2005. ICORR 2005.* 375–379 (IEEE, 2005). doi:10.1109/ICORR.2005.1501123.

75. Zhang, F., Liu, M. & Huang, H. Investigation of Timing to Switch Control Mode in Powered Knee Prostheses during Task Transitions. *PLoS One* **10**, e0133965 (2015).

76. Stevens, P. M. & Highsmith, M. J. Myoelectric and Body Power, Design Options for Upper-Limb Prostheses. *J. Prosthetics Orthot.* **29**, P1–P3 (2017).

77. Parker, P., Englehart, K. & Hudgins, B. Myoelectric signal processing for control of powered limb prostheses. *J. Electromyogr. Kinesiol.* **16**, 541–548 (2006).

78. Hudgins, B., Parker, P. & Scott, R. N. A new strategy for multifunction myoelectric control. *IEEE Trans. Biomed. Eng.* **40**, 82–94 (1993).

79. Graupe, D. & Cline, W. K. Functional separation of EMG signals via ARMA identification methods for prosthesis control purposes. *IEEE Transactions on Systems, Man and Cybernetics* vol. SMC-5 252–259 (1975).

80. Englehart, K., Hudgin, B. & Parker, P. A. A wavelet-based continuous classification scheme for multifunction myoelectric control. *IEEE Trans. Biomed. Eng.* **48**, 302–311 (2001).

81. Hargrove, L. J., Guanglin Li, Englehart, K. B. & Hudgins, B. S. Principal Components Analysis Preprocessing for Improved Classification Accuracies in Pattern-Recognition-Based Myoelectric Control. *IEEE Trans. Biomed. Eng.* **56**, 1407–1414 (2009).

82. Englehart, K. & Hudgins, B. A robust, real-time control scheme for multifunction myoelectric control. *IEEE Trans. Biomed. Eng.* **50**, 848–54 (2003).

83. Scheme, E. & Englehart, K. Electromyogram pattern recognition for control of powered upper-limb prostheses: State of the art and challenges for clinical use. *J. Rehabil. Res. Dev.* **48**, 643–660 (2011).

84. Ohnishi, K., Weir, R. F. & Kuiken, T. a. Neural machine interfaces for controlling multifunctional powered upper-limb prostheses. *Expert Rev. Med. Devices* **4**, 43–53 (2007).

85. Light, C. M. & Chappell, P. H. Development of a lightweight and adaptable multiple-axis hand prosthesis. *Med. Eng. Phys.* **22**, 679–684 (2000).

86. Simon, A. M., Lock, B. A. & Stubblefield, K. A. Patient training for functional use of pattern recognition-controlled prostheses. *J. Prosthet. Orthot.* **24**, 56–64 (2012).

87. Hargrove, L., Englehart, K. & Hudgins, B. The effect of electrode displacements on pattern recognition based myoelectric control. in *2006 International Conference of the IEEE Engineering in Medicine and Biology Society* vol. 1 2203–2206 (IEEE, 2006).

88. Kuiken, T., Miller, L., Turner, K. & Hargrove, L. A comparison of pattern recognition control and direct control of a multiple degree-of-freedom transradial prosthesis. *IEEE J. Transl. Eng. Heal. Med.* **4**, 1–1 (2016).

89. Coapt LLC. Coapt engineering. http://www.coaptengineering.com/ (2016).

90. Cipriani, C., Segil, J. L., Birdwell, J. A. & Weir, R. F. Dexterous control of a prosthetic hand using fine-wire intramuscular electrodes in targeted extrinsic muscles. *IEEE Trans. Neural Syst. Rehabil. Eng.* **22**, 828–836 (2014).

91. Hahne, J. M., Farina, D., Jiang, N. & Liebetanz, D. A novel percutaneous electrode implant for improving robustness in advanced myoelectric control. *Front. Neurosci.* **10**, 1–10 (2016).

92. Pasquina, P. F. *et al.* First-in-man demonstration of a fully implanted myoelectric sensors system to control an advanced electromechanical prosthetic hand. *J. Neurosci. Methods* **244**, 85–93 (2015).

93. Weir, R. F. *et al.* Implantable Myoelectric Sensors (IMESs) for Intramuscular Electromyogram Recording. *IEEE Trans. Biomed. Eng.* **56**, 159–171 (2009).

94. Lewis, S. *et al.* Fully Implantable Multi-Channel Measurement System for Acquisition of Muscle Activity. *IEEE Trans. Instrum. Meas.* **62**, 1972–1981 (2013).

95. McDonnall, S., Hiatt, S., Crofts, B., Smith, C. & Merrill, D. Development of a wireless multichannel myoelectric implant for prosthesis control. in *Proceedings Myoelectric Control and Upper Limb Prosthesis Symposium (MEC 2017)* 21 (2017).

96. Graczyk, E. L., Resnik, L., Schiefer, M. A., Schmitt, M. S. & Tyler, D. J. Home Use of a Neural-connected Sensory Prosthesis Provides the Functional and Psychosocial Experience of Having a Hand Again. *Sci. Rep.* **8**, 9866 (2018).

97. Weir, R. F., Troyk, P. R., DeMichele, G., Kuiken, T. & Ku, T. Implantable myoelectric sensors (IMES) for upper-extremity prosthesis control- preliminary work. *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* **25**, 1562–1565 (2003).

98. Merrill, D. R., Lockhart, J., Troyk, P. R., Weir, R. F. & Hankin, D. L. Development of an implantable myoelectric sensor for advanced prosthesis control. *Artif. Organs* **35**, 249–52 (2011).

99. Baker, J. J., Scheme, E., Englehart, K., Hutchinson, D. T. & Greger, B. Continuous detection and decoding of dexterous finger flexions with implantable myoelectric sensors. *IEEE Trans. Neural Syst. Rehabil. Eng.* **18**, 424–432 (2010).

100. Kristjansson, K. *et al.* Prosthetic Control by Lower Limb Amputees Using Implantable Myoelectric Sensors. in 571–574 (2017). doi:10.1007/978-3-319-46669-9_94.

101. Salminger, S. *et al.* Long-term implant of intramuscular sensors and nerve transfers for wireless control of robotic arms in above-elbow amputees. *Sci. Robot.* **4**, (2019).

102. Jezernik, S., Grill, W. W. & Sinkjaer, T. Neural network classification of nerve activity recorded in a mixed nerve. *Neurol. Res.* **23**, 429–434 (2001).

103. Haugland, M. K. & Sinkjaer, T. Cutaneous whole nerve recordings used for correction of

footdrop in hemiplegic man. *IEEE Trans. Rehabil. Eng.* **3**, 307–317 (1995).

104. Hoffer, J. & Loeb, G. Implantable electrical and mechanical interfaces with nerve and muscle. *Ann. Biomed. Eng.* **8**, 351–360 (1980).

105. Navarro, X. *et al.* A critical review of interfaces with the peripheral nervous system for the control of neuroprostheses and hybrid bionic systems. *J. Peripher. Nerv. Syst.* **10**, 229–258 (2005).

106. Micera, S. *et al.* Decoding of grasping information from neural signals recorded using peripheral intrafascicular interfaces. *J. Neuroeng. Rehabil.* **8**, 53 (2011).

107. Raspopović, S., Capogrosso, M., Navarro, X. & Micera, S. Finite element and biophysics modelling of intraneural transversal electrodes: Influence of active site shape. in *2010 Annual International Conference of the IEEE Engineering in Medicine and Biology* 1678–1681 (IEEE, 2010). doi:10.1109/IEMBS.2010.5626826.

108. Kagan, Z. B. *et al.* Linear methods for reducing EMG contamination in peripheral nerve motor decodes. in *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* 3422–3425 (IEEE, 2016). doi:10.1109/EMBC.2016.7591463.

109. Davis, T. S. *et al.* Restoring motor control and sensory feedback in people with upper extremity amputations using arrays of 96 microelectrodes implanted in the median and ulnar nerves. *J. Neural Eng.* **13**, 036001 (2016).

110. Noce, E. *et al.* EMG and ENG-envelope pattern recognition for prosthetic hand control. *J. Neurosci. Methods* **311**, 38–46 (2019).

111. Petrini, F. M. *et al.* Microneurography as a tool to develop decoding algorithms for peripheral neuro-controlled hand prostheses. *Biomed. Eng. Online* **18**, 44 (2019).

112. Cracchiolo, M. *et al.* Decoding of grasping tasks from intraneural recordings in trans-radial amputee. *J. Neural Eng.* **17**, (2020).

113. Rossini, P. M. *et al.* Double nerve intraneural interface implant on a human amputee for robotic hand control. *Clin. Neurophysiol.* **121**, 777–783 (2010).

114. Wurth, S. *et al.* Long-term usability and bio-integration of polyimide-based intra-neural stimulating electrodes. *Biomaterials* **122**, 114–129 (2017).

115. Kuiken, T. A. *et al.* Targeted muscle reinnervation for real-time myoelectric control of multifunction artificial arms. *JAMA* **301**, 619–28 (2009).

116. Dumanian, G. A. *et al.* Targeted Reinnervation for Transhumeral Amputees: Current Surgical Technique and Update on Results. *Plast. Reconstr. Surg.* **124**, 863–869 (2009).

117. Kuiken, T. A., Dumanian, G. A., Lipschutz, R. D., Miller, L. A. & Stubblefield, K. A. The use of targeted muscle reinnervation for improved myoelectric prosthesis control in a bilateral shoulder disarticulation amputee. *Prosthet. Orthot. Int.* **28**, 245–53 (2004).

118. Farina, D. *et al.* Man/machine interface based on the discharge timings of spinal motor neurons after targeted muscle reinnervation. *Nat. Biomed. Eng.* **1**, 0025 (2017).

119. Aszmann, O. C. *et al.* Bionic reconstruction to restore hand function after brachial plexus injury: a case series of three patients. *Lancet* **385**, 2183–2189 (2015).

120. Muceli, S. *et al.* Decoding motor neuron activity from epimysial thin-film electrode recordings following targeted muscle reinnervation. *J. Neural Eng.* **16**, 016010 (2019).

121. Bergmeister, K. D. *et al.* Peripheral nerve transfers induce target muscle hyper-reinnervation and muscle fiber type switch. *Sci. Adv.* **(accepted)**, (2019).

122. Farina, D. *et al.* Noninvasive, Accurate Assessment of the Behavior of Representative

Populations of Motor Units in Targeted Reinnervated Muscles. *IEEE Trans. Neural Syst. Rehabil. Eng.* **22**, 810–819 (2014).

123. Kapelner, T. *et al.* Motor Unit Characteristics after Targeted Muscle Reinnervation. *PLoS One* **11**, e0149772 (2016).

124. Kapelner, T. *et al.* Classification of motor unit activity following targeted muscle reinnervation. in *2015 7th International IEEE/EMBS Conference on Neural Engineering (NER)* 652–654 (IEEE, 2015). doi:10.1109/NER.2015.7146707.

125. Bergmeister, K. D. *et al.* Broadband Prosthetic Interfaces: Combining Nerve Transfers and Implantable Multichannel EMG Technology to Decode Spinal Motor Neuron Activity. *Front. Neurosci.* **11**, (2017).

126. Ortiz-Catalan, M. Neuroengineering: Deciphering neural drive. *Nat. Biomed. Eng.* **1**, 0034 (2017).

127. Chen, C. *et al.* Prediction of finger kinematics from discharge timings of motor units: implications for intuitive control of myoelectric prostheses. *J. Neural Eng.* (2018) doi:10.1088/1741-2552/aaf4c3.

128. Urbanchek, M. G. *et al.* Development of a Regenerative Peripheral Nerve Interface for Control of a Neuroprosthetic Limb. *Biomed Res. Int.* **2016**, 1–8 (2016).

129. Frost, C. M. *et al.* Regenerative peripheral nerve interfaces for real-time, proportional control of a Neuroprosthetic hand. *J. Neuroeng. Rehabil.* **15**, 108 (2018).

130. Vu, P. P. *et al.* Closed-Loop Continuous Hand Control via Chronic Recording of Regenerative Peripheral Nerve Interfaces. *IEEE Trans. Neural Syst. Rehabil. Eng.* **26**, 515–526 (2018).

131. Vu, P. P. *et al.* A regenerative peripheral nerve interface allows real-time control of an artificial hand in upper limb amputees. *Sci. Transl. Med.* **12**, eaay2857 (2020).

132. Collinger, J. L. *et al.* High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet* **381**, 557–564 (2013).

133. Wodlinger, B. *et al.* Ten-dimensional anthropomorphic arm control in a human brain-machine interface: difficulties, solutions, and limitations. *J. Neural Eng.* **12**, 016011 (2015).

134. Courtine, G., Micera, S., DiGiovanna, J. & del R Millán, J. Brain–machine interface: closer to therapeutic reality? *Lancet* **381**, 515–517 (2013).

135. Lebedev, M. A. & Nicolelis, M. A. L. Brain–machine interfaces: past, present and future. *Trends Neurosci.* **29**, 536–546 (2006).

136. Rohm, M. *et al.* Hybrid brain–computer interfaces and hybrid neuroprostheses for restoration of upper limb functions in individuals with high-level spinal cord injury. *Artif. Intell. Med.* **59**, 133–142 (2013).

137. Ison, M., Vujaklija, I., Whitsell, B., Farina, D. & Artemiadis, P. High-Density Electromyography and Motor Skill Learning for Robust Long-Term Control of a 7-DoF Robot Arm. *IEEE Trans. Neural Syst. Rehabil. Eng.* **24**, 424–433 (2016).

138. Makin, T. R., de Vignemont, F. & Faisal, A. A. Neurocognitive barriers to the embodiment of technology. *Nat. Biomed. Eng.* **1**, 0014 (2017).

139. Tyler, D. J. Neural interfaces for somatosensory feedback. *Curr. Opin. Neurol.* **28**, 574–581 (2015).

140. Jiang, N., Rehbaum, H., Vujaklija, I., Graimann, B. & Farina, D. Intuitive, Online, Simultaneous, and Proportional Myoelectric Control Over Two Degrees-of-Freedom in Upper Limb Amputees. *IEEE Trans. Neural Syst. Rehabil. Eng.* **22**, 501–510 (2014).

141. Amsuess, S. *et al.* Context-Dependent Upper Limb Prosthesis Control for Natural and Robust Use. *IEEE Trans. Neural Syst. Rehabil. Eng.* **24**, 744–753 (2016).

142. Smith, L. H., Kuiken, T. A. & Hargrove, L. J. Real-time simultaneous myoelectric control by transradial amputees using linear and probability-weighted regression. in *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* 1119–1123 (IEEE, 2015). doi:10.1109/EMBC.2015.7318562.

143. Hahne, J. M., Schweisfurth, M. A., Koppe, M. & Farina, D. Simultaneous control of multiple functions of bionic hand prostheses: Performance and robustness in end users. *Sci. Robot.* **3**, eaat3630 (2018).

144. Vujaklija, I. *et al.* Online mapping of EMG signals into kinematics by autoencoding. *J. Neuroeng. Rehabil.* **15**, 21 (2018).

145. Hahne, J. M., Markovic, M. & Farina, D. User adaptation in Myoelectric Man-Machine Interfaces. *Sci. Rep.* **7**, 4437 (2017).

146. Sartori, M., Llyod, D. G. & Farina, D. Neural Data-Driven Musculoskeletal Modeling for Personalized Neurorehabilitation Technologies. *IEEE Trans. Biomed. Eng.* **63**, 879–893 (2016).

147. Sartori, M., Farina, D. & Lloyd, D. G. Hybrid neuromusculoskeletal modeling to best track joint moments using a balance between muscle excitations derived from electromyograms and optimization. *J. Biomech.* **47**, 3613–3621 (2014).

148. Durandau, G., Farina, D. & Sartori, M. Robust Real-Time Musculoskeletal Modeling Driven by Electromyograms. *IEEE Trans. Biomed. Eng.* **65**, 556–564 (2018).

149. Crouch, D. L. & Huang, H. Lumped-parameter electromyogram-driven musculoskeletal hand model: A potential platform for real-time prosthesis control. *J. Biomech.* **49**, 3901–3907 (2016).

150. Crouch, D. L. & Huang, H. (Helen). Musculoskeletal model-based control interface mimics physiologic hand dynamics during path tracing task. *J. Neural Eng.* **14**, 036008 (2017).

151. Sartori, M., Durandau, G., Došen, S. & Farina, D. Robust simultaneous myoelectric control of multiple degrees of freedom in wrist-hand prostheses by real-time neuromusculoskeletal modeling. *J. Neural Eng.* **15**, 066026 (2018).

152. Sartori, M., Reggiani, M., Farina, D. & Lloyd, D. G. EMG-driven forward-dynamic estimation of muscle force and joint moment about multiple degrees of freedom in the human lower extremity. *PLoS One* **7**, e52618 (2012).

153. Sartori, M., van de Riet, J. & Farina, D. Estimation of Phantom Arm Mechanics About Four Degrees of Freedom After Targeted Muscle Reinnervation. *IEEE Trans. Med. Robot. Bionics* **1**, 58–64 (2019).

154. Young, A. J., Simon, A. M. & Hargrove, L. J. A training method for locomotion mode prediction using powered lower limb prostheses. *IEEE Trans. Neural Syst. Rehabil. Eng.* **22**, 671–677 (2014).

155. Simon, A. M. *et al.* Configuring a Powered Knee and Ankle Prosthesis for Transfemoral Amputees within Five Specific Ambulation Modes. *PLoS One* **9**, e99387 (2014).

156. Huang, H., Kuiken, T. A. & Lipschutz, R. D. A Strategy for Identifying LocomotionModes Using Surface Electromyography. *IEEE Trans. Biomed. Eng.* **56**, 65–73 (2009).

157. Jing Wang, Kannape, O. A. & Herr, H. M. Proportional EMG control of ankle plantar flexion in a powered transtibial prosthesis. in *2013 IEEE 13th International Conference on Rehabilitation Robotics (ICORR)* 1–5 (IEEE, 2013). doi:10.1109/ICORR.2013.6650391.

158. Spanias, J. A., Perreault, E. J. & Hargrove, L. J. Detection of and Compensation for EMG

Disturbances for Powered Lower Limb Prosthesis Control. *IEEE Trans. Neural Syst. Rehabil. Eng.* **24**, 226–34 (2016).

159. Scheme, E., Fougner, A., Stavdahl, Ø., Chan, A. D. C. & Englehart, K. Examining the adverse effects of limb position on pattern recognition based myoelectric control. in *2010 Annual International Conference of the IEEE Engineering in Medicine and Biology* 6337–6340 (IEEE, 2010). doi:10.1109/IEMBS.2010.5627638.

160. Scheme, E. J., Englehart, K. B. & Hudgins, B. S. Selective classification for improved robustness of myoelectric control under nonideal conditions. *IEEE Trans. Biomed. Eng.* **58**, 1698–705 (2011).

161. Sensinger, J. W., Lock, B. a & Kuiken, T. a. Adaptive pattern recognition of myoelectric signals: exploration of conceptual framework and practical algorithms. *IEEE Trans. Neural Syst. Rehabil. Eng.* **17**, 270–8 (2009).

162. Zhang, F. & Huang, H. Source selection for real-time user intent recognition toward volitional control of artificial legs. *IEEE J. Biomed. Heal. Informatics* **17**, 907–914 (2013).

163. Hahne, J. M., Dahne, S., Hwang, H.-J., Muller, K.-R. & Parra, L. C. Concurrent Adaptation of Human and Machine Improves Simultaneous and Proportional Myoelectric Control. *IEEE Trans. Neural Syst. Rehabil. Eng.* **23**, 618–627 (2015).

164. Yeung, D., Farina, D. & Vujaklija, I. Directional Forgetting for Stable Co-Adaptation in Myoelectric Control. *Sensors* **19**, 2203 (2019).

165. Edwards, A. L. *et al.* Application of real-time machine learning to myoelectric prosthesis control: A case series in adaptive switching. *Prosthet. Orthot. Int.* **40**, 573–581 (2016).

166. Spanias, J. A., Simon, A. M., Perreault, E. J. & Hargrove, L. J. Preliminary results for an adaptive pattern recognition system for novel users using a powered lower limb prosthesis. in *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* 5083–5086 (IEEE, 2016). doi:10.1109/EMBC.2016.7591870.

167. Du, L., Zhang, F., He, H. & Huang, H. Improving the performance of a neural-machine interface for prosthetic legs using adaptive pattern classifiers. *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS* 1571–1574 (2013) doi:10.1109/EMBC.2013.6609814.

168. Zhuang, K. Z. *et al.* Shared human–robot proportional control of a dexterous myoelectric prosthesis. *Nat. Mach. Intell.* **1**, 400–411 (2019).

169. Volkmar, R., Dosen, S., Gonzalez-Vargas, J., Baum, M. & Markovic, M. Improving bimanual interaction with a prosthesis using semi-autonomous control. *J. Neuroeng. Rehabil.* **16**, 140 (2019).

170. Bensmaia, S. J., Tyler, D. J. & Micera, S. Restoration of sensory information via bionic hands. *Nat. Biomed. Eng.* (2020) doi:10.1038/s41551-020-00630-8.

171. Berniker, M. & Kording, K. Bayesian approaches to sensory integration for motor control. *Wiley Interdiscip. Rev. Cogn. Sci.* **2**, 419–428 (2011).

172. Witteveen, H. J., Rietman, H. S. & Veltink, P. H. Vibrotactile grasping force and hand aperture feedback for myoelectric forearm prosthesis users. *Prosthet. Orthot. Int.* **39**, 204–212 (2015).

173. Dosen, S., Ninu, A., Yakimovich, T., Dietl, H. & Farina, D. A Novel Method to Generate Amplitude-Frequency Modulated Vibrotactile Stimulation. *IEEE Trans. Haptics* **9**, 3–12 (2016).

174. Antfolk, C., Balkenius, C., Lundborg, G., Rosen, B. & Sebelius, F. A tactile display system for hand prostheses to discriminate pressure and individual finger localization. *J. Med. Biol. Eng.* **30**, 355 (2010).

175. Antfolk, C. *et al.* Artificial Redirection of Sensation From Prosthetic Fingers to the Phantom

Hand Map on Transradial Amputees: Vibrotactile Versus Mechanotactile Sensory Feedback. *IEEE Trans. Neural Syst. Rehabil. Eng.* **21**, 112–120 (2013).

176. Bark, K., Wheeler, J., Lee, G., Savall, J. & Cutkosky, M. A wearable skin stretch device for haptic feedback. in *World Haptics 2009 - Third Joint EuroHaptics conference and Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems* 464–469 (IEEE, 2009). doi:10.1109/WHC.2009.4810850.

177. Wheeler, J., Bark, K., Savall, J. & Cutkosky, M. Investigation of Rotational Skin Stretch for Proprioceptive Feedback With Application to Myoelectric Systems. *IEEE Trans. Neural Syst. Rehabil. Eng.* **18**, 58–66 (2010).

178. Patterson, P. E. & Katz, J. A. Design and evaluation of a sensory feedback system that provides grasping pressure in a myoelectric hand. *J. Rehabil. Res. Dev.* **29**, 1 (1992).

179. Štrbac, M. *et al.* Integrated and flexible multichannel interface for electrotactile stimulation. *J. Neural Eng.* **13**, 046014 (2016).

180. Patel, G. K., Dosen, S., Castellini, C. & Farina, D. Multichannel electrotactile feedback for simultaneous and proportional myoelectric control. *J. Neural Eng.* **13**, 056015 (2016).

181. Scott, R. N., Brittain, R. H., Caldwell, R. R., Cameron, A. B. & Dunfield, V. A. Sensory-feedback system compatible with myoelectric control. *Med. Biol. Eng. Comput.* **18**, 65–69 (1980).

182. D'Anna, E. *et al.* A somatotopic bidirectional hand prosthesis with transcutaneous electrical nerve stimulation based sensory feedback. *Sci. Rep.* **7**, 10930 (2017).

183. Li, M. *et al.* Discrimination and Recognition of Phantom Finger Sensation Through Transcutaneous Electrical Nerve Stimulation. *Front. Neurosci.* **12**, 283 (2018).

184. Vargas, L., Shin, H., Huang, H. (Helen), Zhu, Y. & Hu, X. Object stiffness recognition using haptic feedback delivered through transcutaneous proximal nerve stimulation. *J. Neural Eng.* **17**, 016002 (2019).

185. Zollo, L. *et al.* Restoring tactile sensations via neural interfaces for real-time force-and-slippage closed-loop control of bionic hands. *Sci. Robot.* **4**, eaau9924 (2019).

186. Jorgovanovic, N., Dosen, S., Djozic, D. J., Krajoski, G. & Farina, D. Virtual Grasping: Closed-Loop Force Control Using Electrotactile Feedback. *Comput. Math. Methods Med.* **2014**, 1–13 (2014).

187. Saunders, I. & Vijayakumar, S. The role of feed-forward and feedback processes for closed-loop prosthesis control. *J. Neuroeng. Rehabil.* **8**, 60 (2011).

188. Schweisfurth, M. A. *et al.* Electrotactile EMG feedback improves the control of prosthesis grasping force. *J. Neural Eng.* **13**, 056010 (2016).

189. Marasco, P. D., Schultz, A. E. & Kuiken, T. A. Sensory capacity of reinnervated skin after redirection of amputated upper limb nerves to the chest. *Brain* **132**, 1441–1448 (2009).

190. Kuiken, T. A. *et al.* Targeted reinnervation for enhanced prosthetic arm function in a woman with a proximal amputation: a case study. *Lancet* **369**, 371–380 (2007).

191. Marasco, P. D., Kim, K., Colgate, J. E., Peshkin, M. A. & Kuiken, T. A. Robotic touch shifts perception of embodiment to a prosthesis in targeted reinnervation amputees. *Brain* **134**, 747–758 (2011).

192. S. Srinivasan, S. & M. Herr, H. A cutaneous mechanoneural interface for neuroprosthetic feedback. *Nat. Biomed. Eng.* (2021) doi:10.1038/s41551-020-00669-7.

193. Čvančara, P. *et al.* Stability of flexible thin-film metallization stimulation electrodes: analysis of explants after first-in-human study and improvement of in vivo performance. *J. Neural Eng.* **17**,

046006 (2020).

194. Raspopovic, S. *et al.* Restoring Natural Sensory Feedback in Real-Time Bidirectional Hand Prostheses. *Sci. Transl. Med.* **6**, 222ra19-222ra19 (2014).

195. Tan, D. W. *et al.* A neural interface provides long-term stable natural touch perception. *Sci. Transl. Med.* **6**, 257ra138-257ra138 (2014).

196. Mastinu, E. *et al.* Neural feedback strategies to improve grasping coordination in neuromusculoskeletal prostheses. *Sci. Rep.* **10**, 1–14 (2020).

197. Oddo, C. M. *et al.* Intraneural stimulation elicits discrimination of textural features by artificial fingertip in intact and amputee humans. *Elife* **5**, 167–174 (2016).

198. Petrini, F. M. *et al.* Six-Month Assessment of a Hand Prosthesis with Intraneural Tactile Feedback. *Ann. Neurol.* **00**, 1–18 (2018).

199. Valle, G. *et al.* Biomimetic Intraneural Sensory Feedback Enhances Sensation Naturalness, Tactile Sensitivity, and Manual Dexterity in a Bidirectional Prosthesis. *Neuron* **100**, 37-45.e7 (2018).

200. Risso, G. *et al.* Optimal integration of intraneural somatosensory feedback with visual information: a single-case study. *Sci. Rep.* **9**, 7916 (2019).

201. D'Anna, E. *et al.* A closed-loop hand prosthesis with simultaneous intraneural tactile and position feedback. *Sci. Robot.* **4**, eaau8892 (2019).

202. Petrini, F. M. *et al.* Sensory feedback restoration in leg amputees improves walking speed, metabolic cost and phantom pain. *Nat. Med.* **25**, 1356–1363 (2019).

203. Chandrasekaran, S. *et al.* Sensory restoration by epidural stimulation of the lateral spinal cord in upper-limb amputees. *Elife* **9**, 1–26 (2020).

204. Klaes, C. *et al.* A cognitive neuroprosthetic that uses cortical stimulation for somatosensory feedback. *J. Neural Eng.* **11**, 056024 (2014).

205. May, T. *et al.* Detection of Optogenetic Stimulation in Somatosensory Cortex by Non-Human Primates - Towards Artificial Tactile Sensation. *PLoS One* **9**, e114529 (2014).

206. Anderson, H. E. & Weir, R. ff. On the development of optical peripheral nerve interfaces. *Neural Regen. Res.* **14**, 425 (2019).

207. Fontaine, A. K. *et al.* Optical vagus nerve modulation of heart and respiration via heart-injected retrograde AAV. *Sci. Rep.* **11**, 1–12 (2021).

208. Fontaine, A. K. *et al.* Optogenetic stimulation of cholinergic fibers for the modulation of insulin and glycemia. *Sci. Rep.* **11**, 1–9 (2021).

209. Fontaine, A. K., Gibson, E. A., Caldwell, J. H. & Weir, R. F. Optical Read-out of Neural Activity in Mammalian Peripheral Axons: Calcium Signaling at Nodes of Ranvier. *Sci. Rep.* **7**, 4744 (2017).

210. Vincent Systems. Vincent Evolution 2. http://vincentsystems.de/en/prosthetics/vincent-evolution-2/ (2016).

211. De Nunzio, A. M. *et al.* Tactile feedback is an effective instrument for the training of grasping with a prosthesis at low- and medium-force levels. *Exp. Brain Res.* 1–13 (2017) doi:10.1007/s00221-017-4991-7.

212. Strbac, M. *et al.* Short- and Long-Term Learning of Feedforward Control of a Myoelectric Prosthesis with Sensory Feedback by Amputees. *IEEE Trans. Neural Syst. Rehabil. Eng.* 1–1 (2017) doi:10.1109/TNSRE.2017.2712287.

213. Mulvey, M. R., Fawkner, H. J., Radford, H. E. & Johnson, M. I. Perceptual Embodiment of Prosthetic Limbs by Transcutaneous Electrical Nerve Stimulation. *Neuromodulation Technol. Neural Interface* **15**, 42–47 (2012).

214. Johnson, S. S. & Mansfield, E. Prosthetic Training. *Phys. Med. Rehabil. Clin. N. Am.* **25**, 133–151 (2014).

215. Wheaton, L. A. Neurorehabilitation in upper limb amputation: understanding how neurophysiological changes can affect functional rehabilitation. *J. Neuroeng. Rehabil.* **14**, 41 (2017).

216. Soyer, K., Ünver, B., Tamer, S. & Ülger, Ö. G. The importance of rehabilitation concerning upper extremity amputees: A Systematic Review. *Pakistan J. Med. Sci.* **32**, (2016).

217. Roche, A. D. *et al.* A Structured Rehabilitation Protocol for Improved Multifunctional Prosthetic Control: A Case Study. *J. Vis. Exp.* e52968 (2015) doi:10.3791/52968.

218. Dise-Lewis, J. E. Psychological Adaptation to Limb Loss. in *Comprehensive Management of the Upper-Limb Amputee* (eds. Atkins, D. J. & Meier, R. H.) 165–172 (Springer New York, 1989). doi:10.1007/978-1-4612-3530-9_15.

219. Gallagher, P. & MacLachlan, M. Psychological Adjustment and Coping in Adults With Prosthetic Limbs. *Behav. Med.* **25**, 117–124 (1999).

220. Hruby, L. A., Pittermann, A., Sturma, A. & Aszmann, O. C. The Vienna psychosocial assessment procedure for bionic reconstruction in patients with global brachial plexus injuries. *PLoS One* **13**, e0189592 (2018).

221. Sturma, A., Hruby, L. A., Prahm, C., Mayer, J. A. & Aszmann, O. C. Rehabilitation of Upper Extremity Nerve Injuries Using Surface EMG Biofeedback: Protocols for Clinical Application. *Front. Neurosci.* **12**, 906 (2018).

222. Vujaklija, I. *et al.* Translating Research on Myoelectric Control into Clinics—Are the Performance Assessment Methods Adequate? *Front. Neurorobot.* **11**, 1–7 (2017).

223. Ortiz-Catalan, M., Rouhani, F., Branemark, R. & Hakansson, B. Offline accuracy: A potentially misleading metric in myoelectric pattern recognition for prosthetic control. in *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* vols 2015-Novem 1140–1143 (IEEE, 2015).

224. Jarvis, H. L. *et al.* Temporal Spatial and Metabolic Measures of Walking in Highly Functional Individuals With Lower Limb Amputations. *Arch. Phys. Med. Rehabil.* **98**, 1389–1399 (2017).

225. Smurr, L. M., Gulick, K., Yancosek, K. & Ganz, O. Managing the Upper Extremity Amputee: A Protocol for Success. *J. Hand Ther.* **21**, 160–176 (2008).

226. Sturma, A. *et al.* Rehabilitation of high upper limb amputees after Targeted Muscle Reinnervation. *J. Hand Ther.* (2020) doi:10.1016/j.jht.2020.10.002.

227. Prahm, C., Vujaklija, I., Kayali, F., Purgathofer, P. & Aszmann, O. C. Game-Based Rehabilitation for Myoelectric Prosthesis Control. *JMIR serious games* **5**, e3 (2017).

228. Anderson, F. & Bischof, W. F. Augmented reality improves myoelectric prosthesis training. *Int. J. Disabil. Hum. Dev.* **13**, (2014).

229. Prahm, C., Kayali, F., Sturma, A. & Aszmann, O. PlayBionic: Game-Based Interventions to Encourage Patient Engagement and Performance in Prosthetic Motor Rehabilitation. *PM&R* **10**, 1252–1260 (2018).

230. Tillander, J., Hagberg, K., Hagberg, L. & Brånemark, R. Osseointegrated Titanium Implants for Limb Prostheses Attachments: Infectious Complications. *Clin. Orthop. Relat. Res.* **468**, 2781–2788 (2010).

231. Delgado-Martinez, I. *et al.* Fascicular nerve stimulation and recording using a novel double-aisle regenerative electrode. *J. Neural Eng.* **14**, 046003 (2017).

232. Tan, D. W., Schiefer, M. A., Keith, M. W., Anderson, J. R. & Tyler, D. J. Stability and selectivity of a chronic, multi-contact cuff electrode for sensory stimulation in human amputees. *J. Neural Eng.* **12**, 026002 (2015).

233. Micera, S., Caleo, M., Chisari, C., Hummel, F. C. & Pedrocchi, A. Advanced Neurotechnologies for the Restoration of Motor Function. *Neuron* **105**, 604–620 (2020).

234. Delianides, C., Tyler, D., Pinault, G., Ansari, R. & Triolo, R. Implanted High Density Cuff Electrodes Functionally Activate Human Tibial and Peroneal Motor Units Without Chronic Detriment to Peripheral Nerve Health. *Neuromodulation* **23**, 754–762 (2020).

235. Paggi, V., Akouissi, O., Micera, S. & Lacour, P. S. Compliant peripheral nerve interfaces. *J. Neural Eng.* **18**, (2021).

236. Srinivasan, S. S. *et al.* On prosthetic control: A regenerative agonist-antagonist myoneural interface. *Sci. Robot.* **2**, eaan2971 (2017).

237. Horch, K., Meek, S., Taylor, T. G. & Hutchinson, D. T. Object Discrimination With an Artificial Hand Using Electrical Stimulation of Peripheral Tactile and Proprioceptive Pathways With Intrafascicular Electrodes. *IEEE Trans. Neural Syst. Rehabil. Eng.* **19**, 483–489 (2011).

238. Schiefer, M. A., Graczyk, E. L., Sidik, S. M., Tan, D. W. & Tyler, D. J. Artificial tactile and proprioceptive feedback improves performance and confidence on object identification tasks. *PLoS One* **13**, e0207659 (2018).

239. Fernández, A., Isusi, I. & Gómez, M. Factors conditioning the return to work of upper limb amputees in Asturias, Spain. *Prosthet. Orthot. Int.* **24**, 143–147 (2000).

240. Burger, H. & Marinček, Č. Return to work after lower limb amputation. *Disabil. Rehabil.* **29**, 1323–1329 (2007).

241. Stieglitz, T. Of Man and Mice: Translational Research in Neurotechnology. *Neuron* **105**, 12–15 (2020).

242. van der Sluis, C. K. Scaling-up research in upper limb prosthetics. in *Compendium of the Trent International Symposium 2019* (2019).

243. Hickey, G., Richards, T. & Sheehy, J. Co-production from proposal to paper. *Nature* **562**, 29–31 (2018).

244. Vasudevan, S., Patel, K. & Welle, C. Rodent model for assessing the long term safety and performance of peripheral nerve recording electrodes. *J. Neural Eng.* **14**, 016008 (2017).

245. Sartoretto, S. C. *et al.* Sheep as an experimental model for biomaterial implant evaluation. *Acta Ortopédica Bras.* **24**, 262–266 (2016).

246. Boretius, T. *et al.* A transverse intrafascicular multichannel electrode (TIME) to interface with the peripheral nerve. *Biosens. Bioelectron.* **26**, 62–69 (2010).

247. Tyler, D. J. & Durand, D. M. Chronic Response of the Rat Sciatic Nerve to the Flat Interface Nerve Electrode. *Ann. Biomed. Eng.* **31**, 633–642 (2003).

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Author contributions

D.F. and O.C.A. conceived the project, and D.F., I.V., A.S. and O.C.A. edited the manuscript. All authors contributed to writing and revising the manuscript, and approved the final version.

Competing interests

L.J.H. and T.K. have a financial interest in Coapt Llc (www.coaptengineering.com). S.M. is a co-founder of Sensars Neuroprosthetics (www.sensars.com). T. S. is a co-founder and scientific advisor of CorTec GmbH (www.cortec-neuro.com) and neuroloop GmbH (www.neuroloop.de). R.F.W. is a co-founder and President of Point Designs Llc (www.pointdesignsllc.com). H.D. and B.G. are scientific managers at Ottobock SE & Co. KGaA. T.I. and K.K. are scientific officers at Össur Iceland. RB is the founder and chairman of Integrum AB. AMJB is co-founder and director of Biomex Ltd.

Additional information

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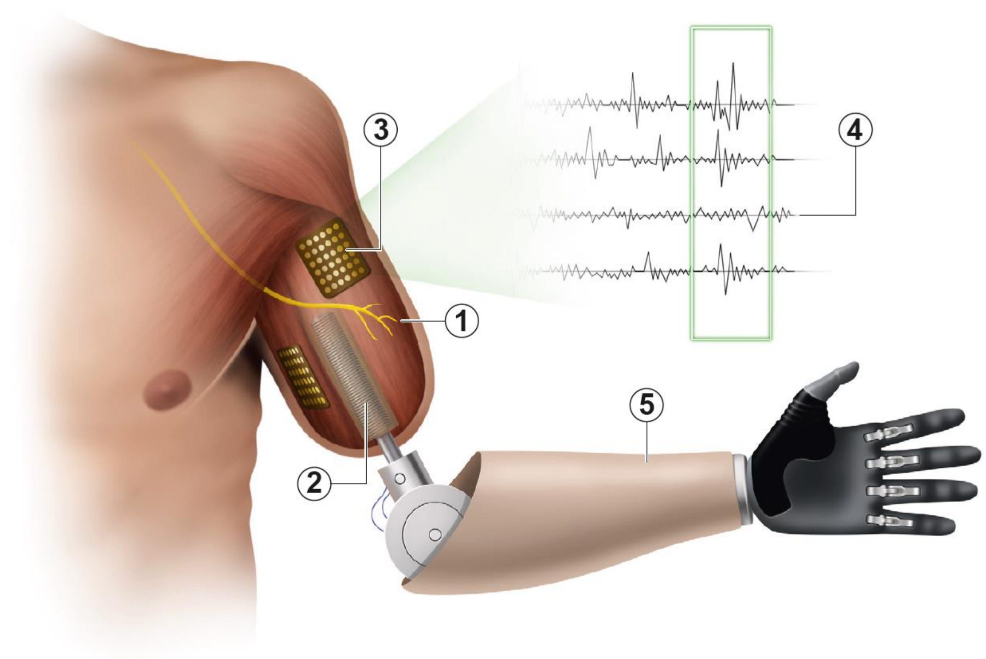

Fig. 1 | Advanced bionic-limb technologies. The most advanced technologies for the mechanical and neural interfacing of bionic limbs with the body are targeted muscle reinnervation (1), osseointegration (2), implanted sensors (3), advanced neural-decoding algorithms (4), that can be combined with modern multi-articulating prosthetic limbs (5). Credit: Aron Cserveny

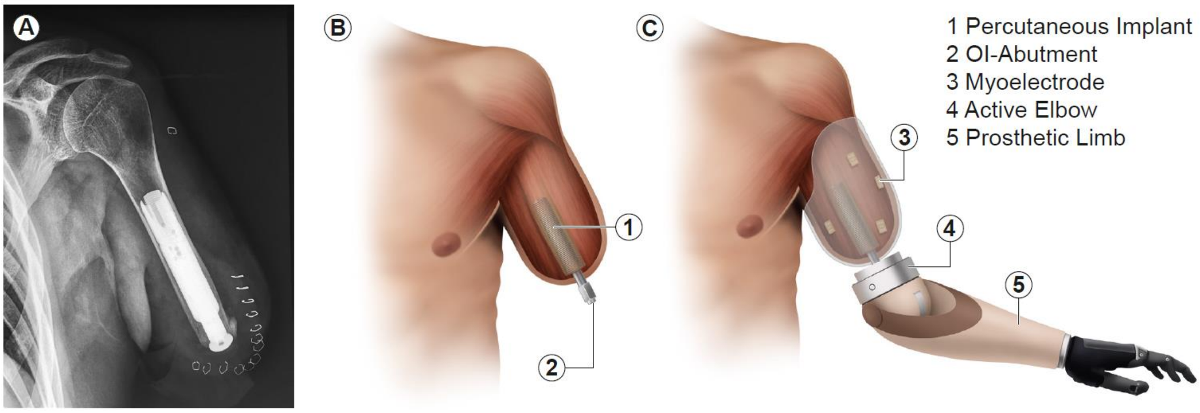

Fig. 2 | Osseointegrated implant in a transhumeral amputee. a, Radiography of the metal implant in the residual humeral bone. **b**, Schematic drawing of the percutaneous implant where the prosthesis is attached. **c**, Schematic drawing of a prosthetic fitting using osseointegration. Credit: Aron Cserveny

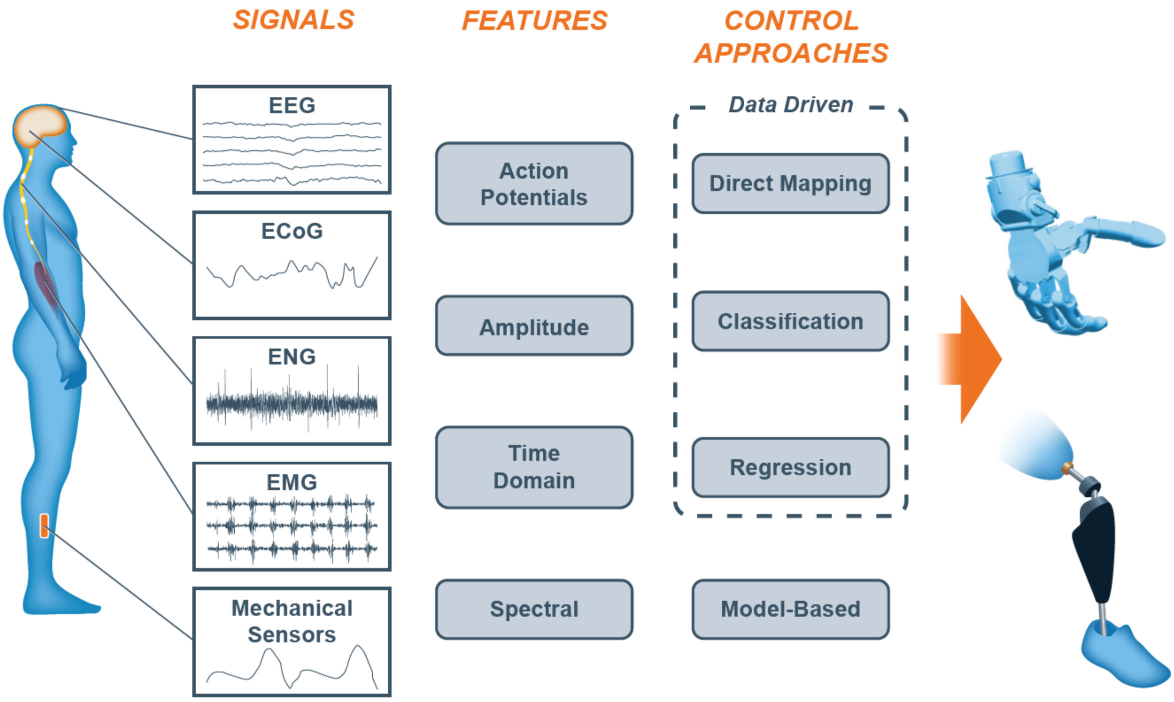

Fig. 3 | Approaches for neuromuscular interfacing, and their mapping into commands for driving externally powered prostheses. The human neuromuscular system can be interfaced at different levels using various probing methods. Biological signals that can be used for interfacing are invasive cortical recordings (most notably, from electrocorticography; ECoG) and non-invasive recordings (typically from electroencephalography; EEG). Electroneurography (ENG) records peripheral nerve activity, and electromyography (EMG) records electrical signals from muscle. Mechanical sensors are commonly used to monitor the resulting body motions. All these signals can be processed to extract characteristics (features) that are algorithmically mapped into control commands. Control strategies can extract the underlying user intention from the signal features to generate commands for the control of the designated joints in the bionic limb. Credit: Aron Cserveny

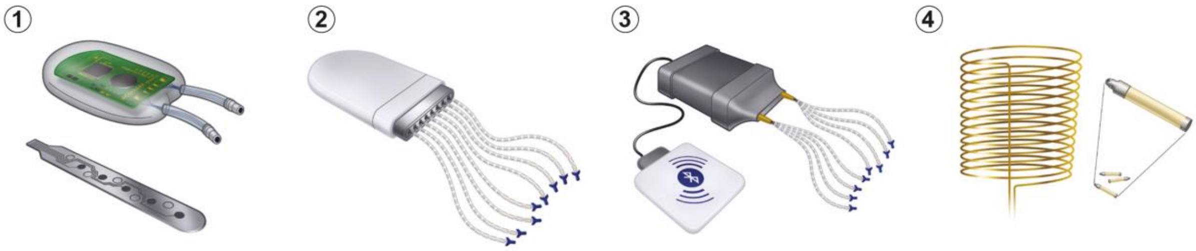

Fig. 3 | Chronically implantable electromyography systems. Chronically implantable EMG recording devices that have been tested in clinical settings: MyoPlant is an induction powered wireless sensor that enables distributed bipolar epimysial recordings **(1)**, MIRA is a multi-lead (32 sensors per lead) fully implantable recording system that transmits digitized EMG signals to the external transceiver via infrared light **(2)**, iSens allows multichannel recordings with Bluetooth enabled functionality (this system can be further extended to extraneural recordings and stimulation (see Fig. 4)) **(3)** and IMES is a system of up to 32 individual active implants that can be implanted in order to record intramuscular EMGs which are powered using an external coil **(4)**. Credit: Aron Cserveny

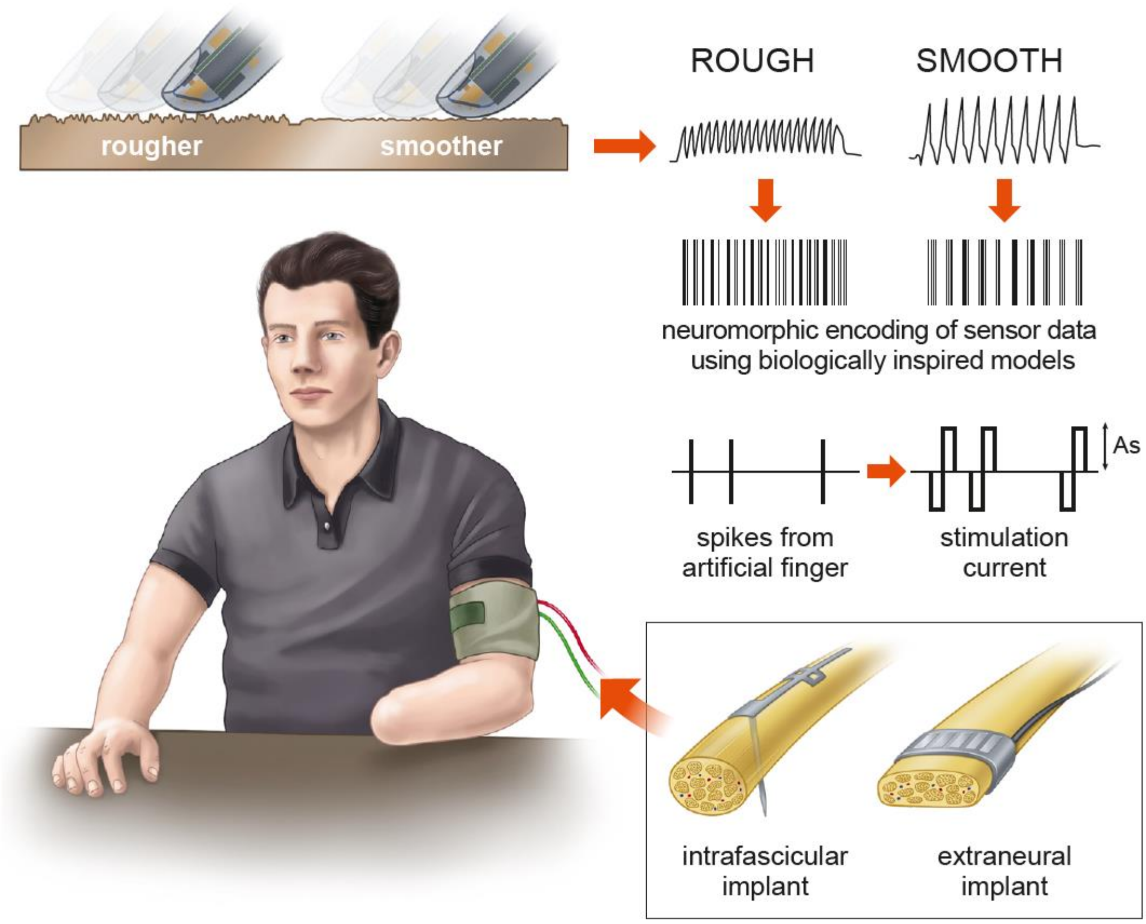

Fig. 4 | Nerve implant for stimulating afferent fibres to restore sensation. When in contact with a rough surface, sensors embedded in the tip of a bionic finger (top left) detect and code information of texture in the form of a current stimulus (right). To restore the sense of touch, the electric signal is then fed back to the user (bottom left) via implanted electrodes (bottom left, transversal interfascicular multichannel electrode[246] (TIME); bottom right, flat Interface nerve electrode[247] (FINE)). Credit: Aron Cserveny

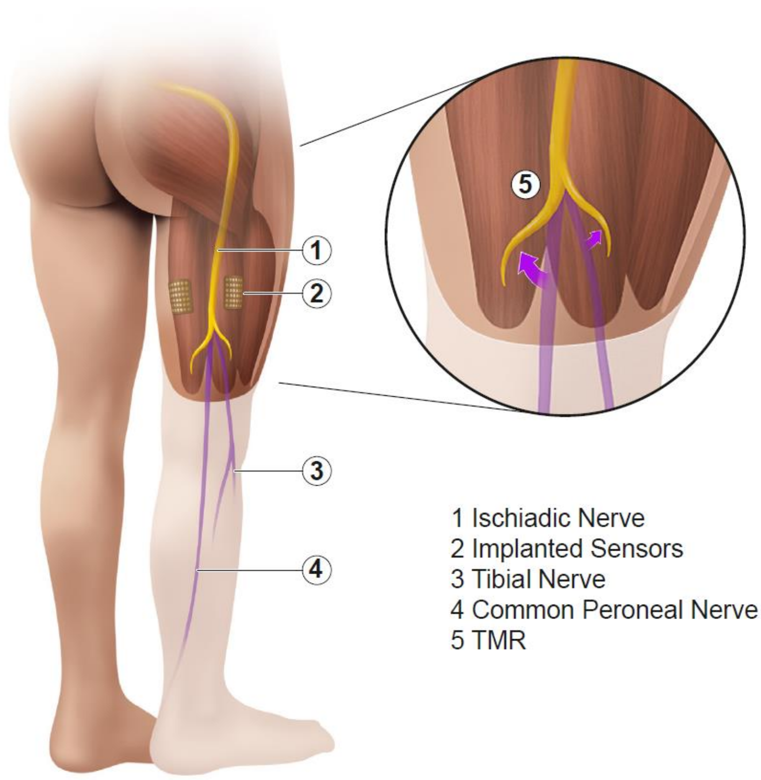

Fig. 5 | Invasive technologies for interfacing bioscreens. The combination of implanted sensors and selective nerve transfers can enhance the robustness and functionality of prostheses. The nerve fascicles of the tibial nerve (3) and common peroneal nerve (4) are transferred to muscles of the thigh to enable intuitive control of a prosthetic ankle joint. Credit: Aron Cserveny