NEUROTECHNOLOGY

Bionic Limbs: Clinical Reality and Academic Promises

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Three recent articles in *Science Translational Medicine* (Tan *et al*. and Ortiz-Catalan *et al*., this issue; Raspopovic *et al*., 5 Feb 2014 issue, 222ra19) present neuroprosthetic systems in which sensory information is delivered through direct nerve stimulation while controlling an action of the prosthesis—in all three cases, arm and hand movement. We discuss such sensory-motor integration and other key issues in prosthetic reconstruction, with an emphasis on the gap existing between clinically available systems and more advanced, custom-designed academic systems. In the near future, osseointegration, implanted muscle, and nerve electrodes for decoding and stimulation may be components of prosthetic systems for clinical use, available to a large patient population.

The loss of an upper limb leads to a severe impairment, both from a psychological and a functional point of view. It therefore comes as no surprise that attempts to replace missing upper limbs with active artificial body parts can be traced back almost 70 years ago to a powered hand prosthesis in Germany (*1*). It has been evident since the earliest efforts in this area that the main difficulty is the interfacing between the artificial limb and the patient body. This problem is not only a mechanical challenge—mounting the artificial limb on the remaining skeletal structures—but also one of information transfer, allowing the user to intuitively control the actions of the robotic limb and to sense it. Surprisingly, the industrial and clinical state-of-the-art devices for interfacing robotic limbs with the human body have not made substantial progress since the earliest systems that were made available several decades ago (*2*).

Active robotic limbs currently available to patients are controlled by electric signals recorded from the remnant muscles above the amputation. The most common scheme in commercial systems is simple and comprises two signals that are used for a specific function—for example, hand opening and closing. Other functions can be controlled by the same signals after switching between functions, usually through co-contraction of the two muscle sites. These schemes are limited in functionality, unnatural, and unintuitive. For this reason, amputees often do not experience sufficient improvement in their daily activities to deem the use of an active prosthesis useful, which consequently results in a large abandonment rate [documented, with large variability across studies, with peaks of 40 to 50% and average rates of ~25% (*3*)]. The clinical reality of prosthetic reconstruction therefore leaves considerable room for improvement.

In three studies in *Science Translational Medicine* (*4*–*6*), including two in the current issue, researchers have expanded the prosthetic-user interface to incorporate a sense of touch with long-term implantation of electrodes in the nerves. They have shown that amputees can realize sensory-motor integration with a robotic limb by decoding motor intention from the remnant muscles above the amputation and encoding sensation with electrical nerve stimulation. In the two papers in this issue, Tan *et al*. and Ortiz-Catalan *et al*. (*5*, *6*), the implantations lasted between 1 and 2 years, the longest period of implanted electrodes in nerves documented in humans to date. During this time, the sensation induced by the nerve stimulation remained similar, proving the potential for permanent implants.

PROSTHETIC UPPER LIMBS

Academic research has addressed the problem of active upper-limb prosthetic control from many perspectives, including the possibility of using nerve or brain signals for control (Fig. 1) (*7*). Despite the potential impact of these modalities in the long term, the use of muscle signals for decoding motor intention remains the most robust and accurate interface for upper-limb prostheses. The ensemble electrical activity of a muscle—the electromyogram (EMG)—is generated by the neural activation sent from the output circuitries of the spinal cord and thus contains clear and robust information on the intended movement to be decoded. Accordingly, the three papers in *Science Translational Medicine* present neuroprosthetic systems that realize control of the prostheses by means of muscle signals (*4*–*6*). Future clinical systems will also be based on muscle recordings for decoding. Moreover, the recently developed surgical procedure of targeted muscle reinnervation (TMR) allows for the interfacing of nerves via muscle recordings (*8*): Nerves that formerly innervated the missing limb are redirected to remaining muscles in the region of the stump, the latter being used as biological amplifiers of specific nerve activity (Fig. 1).

For decoding, both Tan *et al*. (*5*) and Raspopovic *et al*. (*4*) used classic surface EMG electrodes (outside the body, on the skin), as in current commercial prostheses. The control method was that available in commercial prostheses (*5*) or a pattern recognition approach (*4*). The authors focused their main contribution on the characterization of the sensory pathway. In contrast, Ortiz-Catalan *et al*. (*6*) presented a fully implanted solution for control, in which the EMG recording electrodes were epimysial (on the muscle's connective tissue). It is likely that this epimysial solution will have substantial practical advantages over surface recordings, such as improved stability and greater sensitivity to small muscle activations, as noted anecdotally by the authors (*6*). For example, Ortiz-Catalan *et al*. noted a relevant improvement in the accuracy of proportional control when using implanted versus surface electrodes. Furthermore, for high-level amputations, as in the patient described by Ortiz-Catalan *et al*., TMR would further strengthen the control paradigm, because the information of the median, ulnar, and radial nerves, lost in the current fitting, could be recovered to provide intuitive recording sites for control.

Myoelectric prosthesis control has made progress in both signal transmission and interpretation. However, none of these advances have yet been translated into commercial systems (*2*), with the exception of a very recently developed controller called COAPT Complete Control (www.coaptengineering.com). Considering that several decades have passed since the first academic efforts in upper-limb prosthesis control, it is surprising that the basic control schemes based on two muscle signals are still the clinical state of the art and comprise the main commercial systems.

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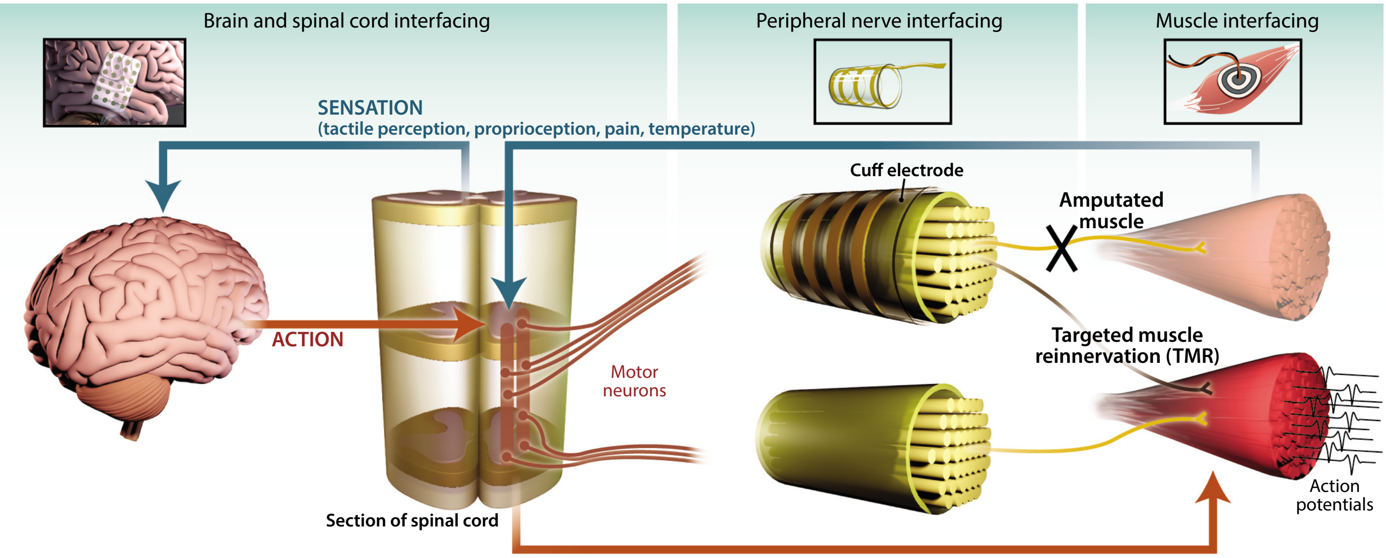

Fig. 1. Sensory-motor integration and human-machine interfacing for neuroprosthetics. Motor tasks are executed by means of supraspinal input to the spinal circuitries, which eventually converge to the spinal motor neurons. Motor neurons provide the neural activation to the muscles. Motor neurons are connected to muscles by their axons that innervate muscle fibers. Each task is made possible by feedback from the periphery. Integration of sensory input with movement occurs at the spinal and supraspinal levels (sensory-motor integration). Losing a limb implies the interruption of nerve fibers and the loss of muscles and anatomical structures. In this scheme, an amputation is represented by the "X." To replace the function of the missing limb, signals from the brain can be decoded for movement and the brain can be stimulated for sensation (encoding); however, interfacing at the muscles and nerves is preferable to the brain for decoding movement and encoding sensation in amputees. Owing to the stability of the neuromuscular junction, each action potential traveling along the axonal branches of a motor neuron generates action potentials in all of the innervated muscle fibers. Therefore, the electrical muscle activity contains the same neural information for decoding as the efferent nerve activity. A muscle can thus be seen as a "biological amplifier" of efferent nerve activity. In this scheme, the remnant muscle (bottom muscle) can be used to decode the nerve activity, either of its naturally innervating nerve or of a nerve previously innervating a muscle in the missing limb by using TMR. In the case of TMR, the natural innervation of the bottom muscle in this scheme would be surgically removed (not shown in the scheme). There are several electrode technologies for interfacing the brain, muscles, and nerves, of which only representative examples are shown here.

One of the characteristics that clinical prosthetic systems lack is feedback by means of natural sensory pathways. Apart from the technical challenges in providing sensory feedback, there are basic questions on sensory-motor integration with artificial limbs that remain unanswered. The recent neuroprosthetic studies published in *Science Translational Medicine* (*4*–*6*) all concern systems that include sensory-motor integration while at the same time emphasizing different, relevant aspects in bionic substitution of upper limbs. We discuss these studies' individual and combined contributions to the technical and sensory challenges below.

PROSTHESIS FITTING

The mechanical interface between the prosthesis and the human body is a practical, yet core challenge. Although socket materials have progressed, the same basic concept and problems in fitting the artificial limb to the body via a socket still prevail. Sockets are uncomfortable, can cause skin infections, show a decline in stability with changing temperature, and are difficult to fit under some conditions, such as when the stump is short or soft tissue is prevalent. The alternative to sockets is the direct integration of the prosthesis into the bone of the remaining limb by means of a procedure called osseointegration (*9*). Osseointegration offers several advantages over classic sockets because it replicates the normal anatomical structure, enabling, for example, full range of motion of the remaining shoulder joint. Moreover, it realizes a stronger coupling with the body through direct transmission of forces between the prosthesis and the bones. Although some risk of infection remains owing to the need for the bone-anchored interface to pass percutaneously, the incidence of infection in osseointegration has reportedly been relatively low (18%) when compared with skin infections developing because of the socket in traditional prostheses (34 to 41%) (*10*).

Ortiz-Catalan *et al.* (*6*) report a stable osseointegrated prosthesis in one patient with a trans-humeral amputation. This prosthesis was controlled with muscle signals and provided sensory input to the user through nerve interfacing (Fig. 1). The electrodes for decoding the control and encoding the sensation were all implanted and remained in place for more than 18 months at the time of publication; the goal is permanent implantation. The osseointegrated robotic limb equipped with sensory-motor integration was well received by the patient. According to the authors, the patient even occasionally sleeps with the arm prosthesis attached. This reveals the difference between the classic wearing of a prosthesis by using a socket (in which the user removes his or her prosthesis when not strictly needed) and the integration of the prosthesis into the patient's skeletal system (in which the device "becomes one" with its user). This integration constitutes a revolution similar to dental implants, which were the first example of osseointegrated artificial systems.

In addition to the osseointegration solution to mechanical interfacing, Ortiz-Catalan *et al.* (*6*) exploited this paradigm to improve the neural interfacing. One of the challenges in interfacing the human body for information transfer in prostheses is the need for wireless systems implanted in the body that communicate with receivers placed in the prosthesis. The issue is complex, as indicated by the fact that the proof of concept of a fully implanted wireless myoelectric system for prosthesis control in humans was just reported 2 months ago by Pasquina and colleagues (*11*). However, with osseointegration the cables of the implanted electrodes can be wired in and out of the patient's body through the bone-anchored mechanical conduit that passes through the human body percutaneously. Ortiz-Catalan *et al.* implanted electrodes in the patient's body, which could then communicate with the prosthesis with wires rather than wireless technology. This simple yet revolutionary concept may shorten the translational path of their upper-limb prosthesis by avoiding the need for wireless transmission.

SENSORY-MOTOR INTEGRATION

In addition to an accurate control, motor tasks require sensory information (Fig. 1) (*12*). Able-bodied individuals tend to underestimate the importance of sensory feedback during movement, because feedback is naturally integrated in each task. The lack of sensory information leads to difficulties in performing not only precise motor commands but also the simplest tasks (*12*). The three studies (*4*–*6*) included sensory integration with motor commands, providing sensory feedback through electrical stimulation of nerve fibers. Although each study has its own findings and goals, the collective contribution is the demonstration that it is possible to deliver sensations to the human brain by stimulating peripheral nerves for extended periods of time [for Tan *et al.*, up to 2 years (*5*)], concurrent with upper-arm prosthesis control (sensory-motor integration).

Ortiz-Catalan (*6*) and Tan (*5*) used cuff electrodes for nerve stimulation, which are wrapped around the peripheral nerve (Fig. 1). Stimulation was therefore not very selective, but the nerve integrity was preserved. Conversely, Raspopovic *et al.* (*4*) applied a more advanced electrode that was made of a very thin filament of polyimide inserted transversally into the nerve (transversal, intrafascicular electrode). In this electrode, stimulation was obtained by use of multiple sites in the nerve and was selective in each site. Although the impact of the type of electrode for encoding cannot be judged by comparing the three studies that used different protocols and implantation durations, the multichannel, selective, intraneural system used by Raspopovic *et al.* is in principle able to better tune the sensation by a larger number of selective stimulation sites (or combination of sites) than can cuff electrodes. However, there is a risk of intraneural scarring with irreversible nerve damage that was recently reported for this type of nerve electrode (*13*). For this reason, stability over longer periods of time needs to be proven for this extremely flexible and selective electrode structure. Raspopovic *et al.* (*4*) presented results from measures made in 1 week, whereas the cuff electrode interfaces were implanted in the other two studies for 1 to 2 years (*5*, *6*).

Fig. 2. No sensory feedback. Although sensory feedback is fundamental for natural movements, a good internal model of the prosthesis, obtained through training, and accurate feed-forward control together allow for the execution of certain tasks with a myoelectric prosthesis, without the delivery of artificial sensory input. This is in addition to the natural feedback available to amputees. A prosthetic user is here using the rich sensory information already available to him (vision and muscle afferent activity from the muscles used for control) in an activity of daily living requiring fine control, without additional sensory feedback. The patient is using an OttoBock Michelangelo hand activated by proportional, direct control from signal sites that have been maximally separated with TMR.

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SENSORY INFORMATION AND FUNCTION

Open questions remain with regard to the translation of these results into clinical devices, with special regard to the functional benefit of sensory feedback. Although it is evident that sensory feedback is important for natural motor tasks, it is less obvious that prosthetic users may benefit from additional sensory feedback during execution of prosthetic movements. A prosthetic user already relies on sensory feedback from vision and the muscles used to control the prosthesis. From here, a prosthetic user can build an internal model of the robotic limb and reliably exert a relatively precise force when grasping an object, without any additional artificial sensory input (*14*).

Even when some sensory feedback is provided by a prosthetic system, this cannot exactly mimic the natural, multimodal sensory input to the brain during movement. The stimuli provided roughly resemble the real activity of some sensory pathways so that the brain can associate these stimuli to specific consistent interactions between the artificial limb and the external environment. The three studies in *Science Translational Medicine* (*4*–*6*) used this concept for closing the loop, and their contribution in showing reestablished sensory-motor integration is substantial. Nonetheless, with the exception of preliminary results by Tan *et al.* (*5*), they do not directly prove a functional advantage of the inclusion of the sensory stimulation with respect to the "open-loop" situation with vision only. Although accurate task-sensory information may provide advantages—such as for the task of separating the stem from a cherry (Tan *et al.*)—with appropriate training it becomes not strictly necessary (Fig. 2), especially when considering the limitations in the myocontrol algorithm accuracy and in the precision in force exertion by the robotic device.

Last, considering that there are limits to the number of physical variables that are coded, the choice of those that are functionally relevant is not an obvious task. For example, it can be argued that force is an important variable for the user because it cannot be estimated by vision. However, in experiments in which subjects were asked to exert a specific force level and were given different sensory modalities to accomplish this task, direct force feedback was not essential for the control of grasping force (*14*).

A SENSE OF OWNERSHIP

If the functional relevance of sensory feedback in prosthesis control is debatable, conversely it is certain that sensory feedback promotes a sense of ownership of the robotic limb; the robotic limb is psychologically integrated into the body rather than viewed as an external tool. Successful bionic substitution is indeed achieved when eliciting a shift in perception toward incorporation/embodiment of a prosthetic limb into the self-image of the amputee. The mechanisms for this embodiment are similar to those that determine the illusion that a fake rubber hand belongs to oneself when touched at the same time and location as the real hand (that is hidden in these experiments) (*15*).

Embodiment promotes activity in the brain areas dedicated to upper-limb control and thus decreases the cortical reorganization that typically follows the amputation (maladaptive plasticity) (*16*). Reducing this reorganization seems to be at the basis of the reduction of phantom limb pain (*17*, *18*). The use of a prosthesis that provides extensive sensory feedback to the brain in causal association with the interaction with the environment is an effective way to mimic the input from the lost arm and to counteract reduction of its cortical representation. Accordingly, a recent study (*19*) investigated the therapeutic efficacy of a myoelectric prosthesis with integrated electrocutaneous feedback on grip strength in the treatment of phantom limb pain. The authors showed that behaviorally relevant stimulation of the stump reduced the degree of limb pain.

Although only at an observational level in a few patients and without statistical support, the papers in *Science Translational Medicine* (*4*–*6*) all reported that the patients receiving sensory feedback experienced a substantial alleviation of phantom limb pain. This result and those presented in (*19*) are important achievements for the benefit of the patient and by themselves would justify the inclusion of explicit sensory feedback in prosthetic devices.

CLINICAL PERSPECTIVE

We began this article by discussing the gap existing in active prosthesis design and development between academic visions and promises and the devices present on the market. How do the three studies recently published in *Science Translational Medicine* (*4*–*6*) start to fill this gap? These studies make an important step forward in neuroprosthetics by proving that chronic implants in muscles and nerves in humans can realize artificial sensory-motor integration, without major degradation over time of the signals decoded or the electric impulses encoded. From these results, there is no doubt that a crucial future translational step in prosthetic devices for daily use will be the implantation of all the electrodes for recording and for stimulating.

The three studies also observed satisfaction of the users resulting from the receipt of sensory feedback and alleviation of phantom limb pain. Sensory feedback may therefore be an important component in next-generation prosthetic devices, at least because of the effect on embodiment of the artificial limb. Conversely, we believe that a proper demonstration of a substantial influence of sensory feedback, in addition to that naturally available to prosthetic users, in task performance, with the current control algorithms and the available robotic devices, will require further studies and data.

In the near future, osseointegration, implanted muscle electrodes for decoding, and implanted nerve electrodes for sensory feedback may be the key components of prosthetic systems for clinical use, available to a large patient population. These components, demonstrated in (*4*–*6*) in the first few patients, would certainly increase the clinical impact of bionic substitution and substantially decrease the relatively high current abandonment rate of active prostheses. Although not implemented in the three studies, we note the relevance of TMR as a further element in future clinical prostheses, for improving control and making the prosthetic's use more natural for the user.

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