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Sensory feedback for limb prostheses in amputees

Stanisa Raspopovic [1,2 ✉], Giacomo Valle [1,2] and Francesco Maria Petrini[1,2]

Commercial prosthetic devices currently do not provide natural sensory information on the interaction with objects or movements. The subsequent disadvantages include unphysiological walking with a prosthetic leg and difficulty in controlling the force exerted with a prosthetic hand, thus creating health issues. Restoring natural sensory feedback from the prosthesis to amputees is an unmet clinical need. An optimal device should be able to elicit natural sensations of touch or proprioception, by delivering the complex signals to the nervous system that would be produced by skin, muscles and joints receptors. This Review covers the various neurotechnological approaches that have been proposed for the development of the optimal sensory feedback restoration device for arm and leg amputees.

Limb amputation is a catastrophic event, impacting the health and quality of life of the person affected. The epidemiology of amputation worldwide is not homogeneous. In the United States, every year 242,230 lower-limb amputations are performed (averaged from refs. [1–3]) while 15,900 are executed on the upper extremities[3]. In the 27 countries of the European Union, 87,088 (averaged from refs. [1,2]) and 6,311 (averaged from refs. [4,5]) lower- and upper-limb amputations are performed per year, respectively.

Sensory feedback is an unmet need for prosthetic users

Limitations of prosthetics without sensory feedback. The upper- and lower-limb prosthetic devices currently available do not provide natural sensory information. Without realizing when the prosthesis meets an obstacle, lower-limb amputees may be subject to dangerous falls[6] and struggle to maintain symmetry during standing and walking[7]. Amputees may also experience an increased metabolic cost of normal physical activity, leading to fatigue and a twofold higher probability of heart failure[8] with respect to non-amputees, and also reduced mobility[7].

Sensory feedback is mentioned by upper-limb amputees as one of the main missing features of commercial prostheses[9], as they are not able to execute confident grip forces or undertake fine manipulations[10]. The lack of physiological feedback from the remaining extremity to the brain prevents the correct integration of the prosthesis in the body perception of the person[11]. This induces low prosthesis embodiment[12] and increased cognitive effort while using the devices[13], which affect their acceptability and ultimately reduce user confidence in the prosthesis[14]. The lack of physiological feedback from the remaining extremity to the brain also generates phantom limb pain, which is experienced by 50–80% of amputees[15]. All these limitations are responsible for an increase in the rejection rate or abandonment of prosthetic devices for both upper-limb[9] and lower-limb[16] amputees, which impedes the full reintegration of prosthetic users in the working society.

For all these reasons, the development of devices restoring sensory information to the prosthesis users is an important unmet clinical need. Several approaches have recently been adopted aimed at solving this issue, both in upper- and lower-limb amputees (Fig. 1).

Optimal sensory feedback restoration device. Sensory feedback restoration enables amputees to understand body–environment interactions or the actual movement of the device (Fig. 2a). This is achieved by a mechanism inspired by the somatosensory system of mammals, in which receptors in the skin or muscles transduce internal or external stimuli (for example, deformation of the skin) into electrical signals that travel to the brain. A set of sensors is added to the prosthesis using a glove, a sock or an insole (Fig. 2a). These sensors measure the pressure applied to the prosthesis (touch) and the movement of its joints (proprioception). Sensor readouts are obtained from a controller, which transduces them into electrical stimulation parameters, through dedicated mapping between artificial and natural sensory signals (sensory encoding algorithms). The stimulation parameters are delivered to a stimulator, which elicits the sensations perceived by the prosthesis user.

An optimal sensory feedback restoration device should evoke similar sensations to the ones perceived by the intact limb, in terms of quality and location. In other words, if an object is pushed against the tip of the little finger, the sensory feedback restoration device should elicit a sensation of pressure on the phantom little finger of the patient. The capability of the sensory neuroprosthesis to evoke sensations that match the quality of the external stimulus is described as homology, while the capability to evoke sensations that match the location is indicated as somatotopy. Homology and somatotopy maximize ease of use and acceptance of the device[14]. Consequently, the amputee does not have to spend long periods of training to interpret the inputs from the device. The elicited sensations are highly dependent on the approach used for the stimulation. In particular, by inducing signals directly inside the nerve, the resulting elicited sensations are somatotopic and homologous. Finally, in an optimal sensory feedback restoration device, all the communication between the controller, stimulator and prosthesis sensors need to be in quasi-real time with an unperceivable delay (as in the mammalian somatosensory system).

Somatosensory peripheral nerves. Human peripheral nerves are cable-like structures in which the axons are grouped through protective sheets of connective tissue (called endoneurium). Groups of axons (also named fibres) are organized into fascicles, which in turn are disposed into bundles. The nerve itself is enfolded in a protective sheet (called the epineurium), which is loosely connected to the bundles inside, enabling the fascicles to move. The nerve can thus deform under an external pressure. Afferent fibres convey the information from the periphery to the brain, and efferent fibres from the brain to the periphery. Afferents are connected in the periphery

[1]Laboratory for Neuroengineering, Department of Health Sciences and Technology, Institute for Robotics and Intelligent Systems, ETH Zürich, Zurich, Switzerland. [2]These authors contributed equally: Stanisa Raspopovic, Giacomo Valle, Francesco Maria Petrini. ✉e-mail: stanisa.raspopovic@hest.ethz.ch

Fig. 1 | Sensory feedback restoration devices tested in humans. Different approaches of sensory feedback restorations via implants and surgical interventions detailed in this Review are depicted. Different levels of amputation are shown: the left leg and arm depict transtibial and transradial amputations, respectively, while the right leg and arm show transfemoral and transhumeral amputations, respectively.

to different body 'sensors': cutaneous mechanoreceptors, proprioceptors and nociceptors. Cutaneous mechanoreceptors transduce the tactile stimuli applied on the skin into signals for the brain that travel along afferent fibres (thus also called tactile fibres).

There are four types of tactile fibre and they are connected to four different mechanoreceptors in the glabrous skin (Fig. 2b). Fast-adapting type I (FAI) and type II (FAII) fibres respond only during dynamic phases of tissue deformation (for example, when
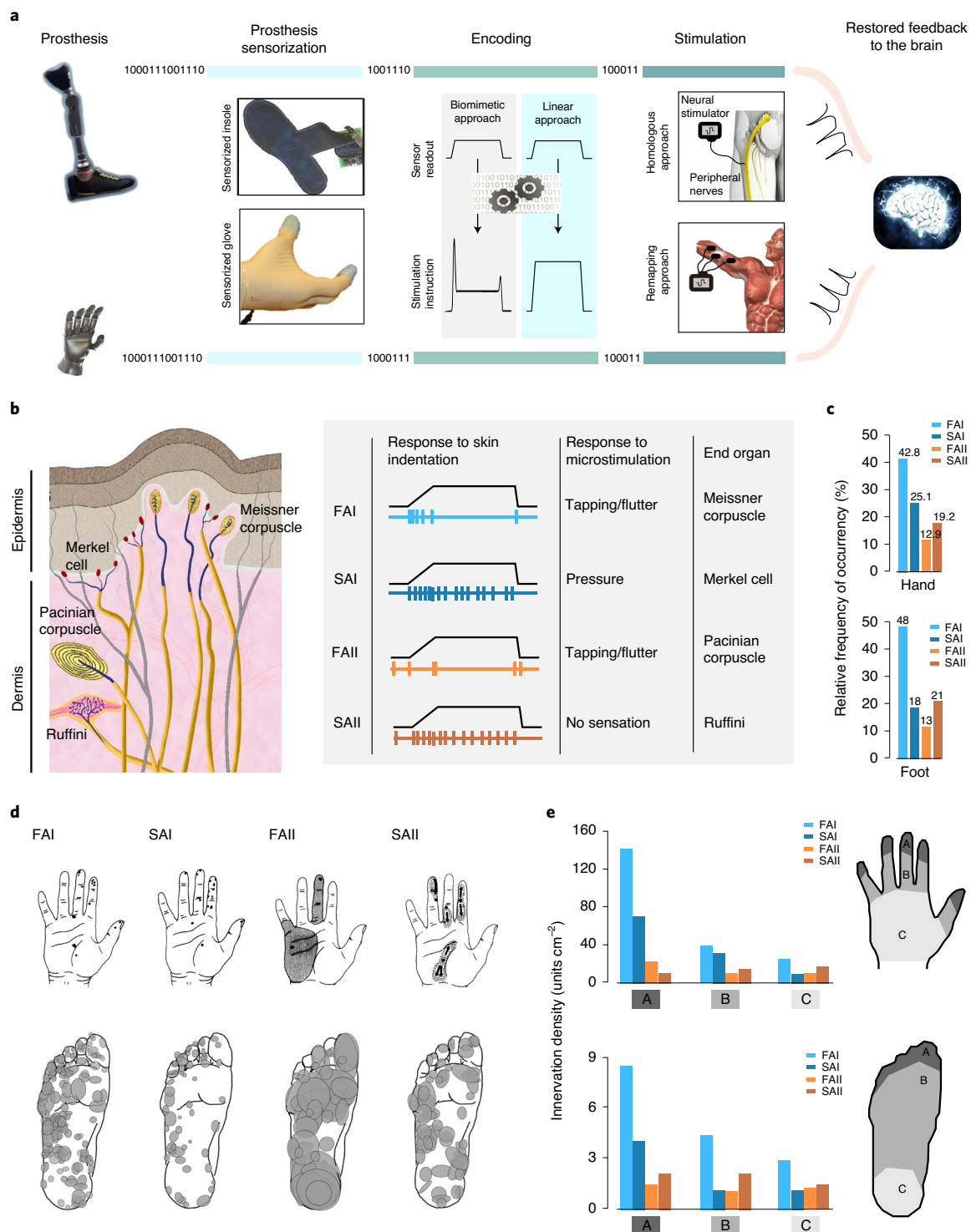
Fig. 2 | Artificial sensory feedback is inspired by nature. a, Working principle of a sensory feedback restoration device. Sensors are added to the prosthesis, whose readout is transduced (encoded) into the electrical stimulation of residual fibres. This mechanism is inspired by mammals. In the optimal system, the encoding and the stimulation generate a sensory nerve activation identical to the one that would have been produced by cutaneous mechanoreceptors and proprioceptors. **b**, Tactile afferents are connected to four types of cutaneous mechanoreceptor, which adapt differently to mechanical stimuli and responses to electrical stimulation[17,109,110]. **c**, There are varying numbers of tactile afferents (with FAI being the most represented). Data are extracted from refs. [18,111]. **d**, The receptive fields of tactile afferents are smaller for type I fibres[18,112]. **e**, Tactile afferents have different innervation densities throughout the inner hand and the sole of the foot[18,111]. Credit: **a**, Bottom left (grey hand) and far right (brain), reproduced with permission from pixy.org; bottom right (remapping approach), adapted with permission from iStock by Getty Images/Francesco Maria Petrini; bottom, second from left (sensorized glove), reproduced with permission from ref. [75], under a Creative Commons license CC BY 4.0; top, second from left (sensorized insole), adapted with permission from ref. [84], AAAS. **b**, Left, reproduced with permission from ref. [109], Elsevier. **d**, Hands, adapted with permission from ref. [112], Elsevier Biomedical Press; feet, adapted with permission from ref. [18], American Physiological Society

there is contact with a surface). Accordingly, intraneural electrical stimulation of these afferents usually elicits perception of intermittent tapping/flutter[17]. Slowly adapting type I (SAI) and type II (SAII) fibres respond to sustained deformations of the skin. SAI fibres encode static or low-frequency changes in tissue deformation (for example, maintaining contact with a surface) and evoke sensations of sustained pressure with electrical stimulation[17]. SAII fibres encode for skin stretches and generally, when stimulated, do not elicit a sensation[17]. FAI fibres are the most numerous (Fig. 2c). Type I fibres have smaller receptive fields—that is, the extent of skin activating the receptor in presence of a tactile stimulus—compared with type II afferents (Fig. 2d). Afferents innervate the skin progressively more towards the distal part of the extremities (Fig. 2e). In the foot, also the lateral part of the sole is more innervated than the medial one[18].

Tactile afferents deliver messages to the central nervous system, in two manners[19]: the rate code (the intensity of a stimulus is proportional to the firing rate of the fibre) and the population code (the intensity of a stimulus is proportional to the number of fibres that are activated). These strategies are used, for example, to convey the information of intensity of a stimulus[19]. Combinations or variations of these strategies are adopted to provide the brain with more sophisticated touch features. Embossed letters are coded through a spatial code: subgroups of fibres fire when they get in contact with a protuberance on an object, while others do not. Very small textures are communicated to the brain through a temporal code (that is, an exact sequence of spikes)[20]. Direct contact force or shape are encoded by the spike latency code: two groups of fibres fire with a specific latency[21].

Proprioceptors are responsible for the senses of posture and movement of the trunk and limbs, as well as of the sense of force. There are three main types of proprioceptive fibre in the muscles that are connected to two main proprioceptors[22]. (1) Type Ia fibres are connected to muscle spindles (which are embedded within the muscle fibres and make up the bulk of the muscle) and give information on the length of the muscle and the velocity of its change. (2) Type II fibres are similar to type Ia fibres but they only code for the length of the muscle. (3) Type Ib fibres are connected to Golgi tendon organs (embedded within the tendons) and give information on the force exerted by the muscles. Stimulation of these fibres does not often elicit a sensation[23]. These proprioceptors can be activated or inhibited through vibrations over muscle tendons[22]. Joint receptors are connected to slowly adapting afferents, and evoke a sensation of displacement or a deep sensation from the joint when targeted with electrical stimulation[23].

Remapping is not an optimal solution. Cutaneous stimulation of amputees' remaining extremities, not innervated by the afferents once connected to the missing limbs, is an example of technology that restores non-somatotopic sensations. Devices based on this technique (also named sensory remapping) have been developed and tested with volunteers[24,25]. Users are usually provided with coded stimuli (such as modulation of pulse rate) and learn to relate these codes to specific sensory information, for example, pinch force[26]. However, intensive cognitive load is usually required for a user to correctly interpret the coded signal[27]. Other problems of the approaches using remapped mechano-, vibro-tactile or electro-cutaneous feedback include: artefacts on the recoding system used for the prosthesis control due to the stimulation[28], the miniaturization of the systems, power consumption and the quality of the sensation elicited, which is not very pleasant. These issues probably prevent the clinical adoption of such technologies, despite the great advantage of not requiring any surgical intervention.

The device design is tailored with respect to the amputation type. The design of a sensory feedback restoration device varies for upper- and lower-limb amputees. The sciatic nerve, which innervates the foot and lower leg, is more than twice as large as the median and ulnar nerves, which run to the fingers and palms, and it is also difficult to reach through the big leg muscles. The density and placement of the receptors are different between upper and lower limbs. Upper-limb amputees can use their intact hand for almost all activities, while amputees that are missing part of the leg cannot ambulate without a prosthesis. A failed manipulation can lead to a broken glass, whereas a failed step could lead to a fall.

A more proximal amputation entails a greater disability[7,8] (different levels of amputations are depicted in Fig. 1), as persons with a more proximal amputation have less of a residual neuromuscular structure to interface via different surgery and implantable approaches. Also, more proximal levels of amputation require more complexity in the sensory feedback restoration, as larger amounts of information need to be transmitted; for example, the proprioception from the prosthetic knee is not needed for a transtibial amputee.

The role of materials in the development of neuroprostheses
Mimicking the nervous tissue through artificial materials. As the peripheral nervous tissue is composed of a matrix of optimally integrated axons and connective tissues, it is reasonably stiff; however, at the same time, it is soft, as axons and bundles can slide on each other guaranteeing accommodation to the movements of the body by bending and stretching. This is in clear contrast to the materials traditionally used for nerve interfacing, which are several orders sharper and stiffer, and can therefore be harmful to the tissue in which they are implanted. Simultaneously, the body may be a hostile environment for the implanted devices: to be used as materials for neural prostheses, implants have to withstand the body environment over the years. Typically, neural interfaces are made of a substrate, which gives structural stability and compliance with respect to the nerve, and active sites that are embedded within it, delivering electrical current into the excitable tissue. Different geometrical solutions have been tested (Figs. 1 and 3 and Table 1): implants can be placed around the nerves (such as cuff electrodes[29] and flat interface nerve electrodes (FINEs)[30], longitudinally through the nerves (such as wire and thin-film longitudinal intrafascicular electrodes (wire LIFEs)[31] and tf-LIFEs[32]), through the nerves via multielectrode needles (such as Utah electrodes[33]) or via shafts (such as transverse intrafascicular multichannel electrodes (TIMEs)[34]).

Different shapes and materials. Polyimide, silicone and parylene are the most commonly used materials for nerve electrodes substrates[35,36]. Silicones are polymers made of siloxane, and polydimethylsiloxane or PDMS is one of its most common types. An example of PDMS processing is spin coating, which is executed twice above and below a metal foil. Polyimides are synthesized by adding dianhydride and a diamine to a dipolar aprotic solvent (which generates poly at room temperature). Thermal imidization (that is, the removal of water through vapourization) of poly is the most common procedure to obtain polyimide. In contrast, to produce polyimide wafers, poly is spin-coated and then treated in a nitrogen atmosphere at a high temperature (~350 °C). Vapour deposition or sputtering are used to deposit metals on these wafers. The metal is then usually encapsulated with a second layer of polyimide, because of the low adhesion among these materials. Parylene (or polyparaxylylene) is a polymer made of the repetition of para-benzenediyl. Parylene-C (poly(dichloro-*p*-xylylene)) is the most common type used for biomedical applications. Usually parylene is processed through vapour deposition polymerization. The dimer of parylene is split into a monomeric gas, through heating. It is then polymerized on the target, by decreasing the temperature.

The most commonly used electrode is the spiral nerve cuff electrode[29], designed to be expandable so that it can be fitted around
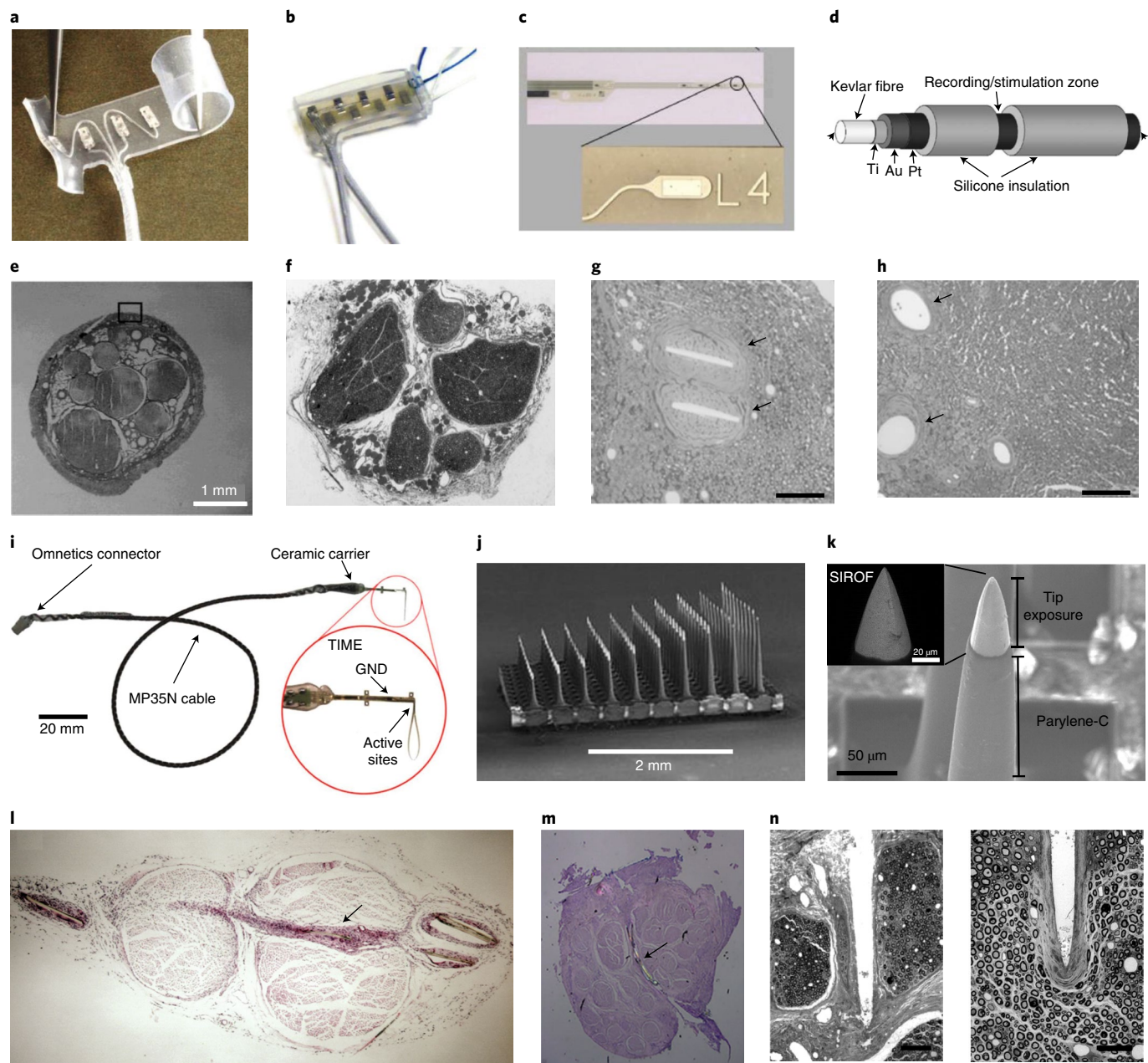
Fig. 3 | Electrodes used in human experiments. a, A cuff electrode[113]. **b**, A C-FINE[39]. **c**, A tf-LIFE[114]. **d**, A wire LIFE[40]. **e**, Cuff electrode biocompatibility in cats[49]. **f**, C-FINE biocompatibility in cats[39]. **g**, tf-LIFE biocompatibility[54] in rats. The arrows point to the electrodes. Scale bar, 100 μm. **h**, Wire LIFE biocompatibility[54] in rats. The arrows point to the electrodes. Scale bar, 100 μm. **i**, A TIME[63]. GND, ground electrode. **j**, A USEA[113]. **k**, Tip of microelectrode with iridium oxide sputtered[115]. **l**, TIME biocompatibility[116] in rats. The arrow points to the electrode. **m**, TIME biocompatibility in pigs[116]. The sample is a typical H&E (haematoxylin and eosin) staining microscopy image (×20) of the peripheral nerve, where the TIME electrode has been identified inside the nerve by the arrow. **n**, USEA biocompatibility in cats[56]. One electrode misses the nerve's fascicles (left) and another electrode tip is inside a fascicle and close to viable neurons (right). Scale bars, 100 μm (left) and 50 μm (right). Images of the biocompatibility are histological analyses (over long-term periods). Panels **e–h**, **l** and **n** are light microscopy images. Credit: panels reproduced with permission from: **a,j**, ref. [113], under a Creative Commons license CC BY 4.0; **b,f**, ref. [39], IOP; **c**, ref. [114], IEEE; **d**, ref. [40], Elsevier; **e**, ref. [49], Wiley; **g,h**, ref. [54], IEEE; **i**, ref. [63], Springer Nature Ltd; **l,m**, ref. [116], River Publishers; **n**, ref. [56], IEEE. Panel **k** adapted with permission from ref. [115], IOP

a nerve and accommodated to subsequent neural swelling. Cuffs (Case Western Reserve University and Ardiem Medical) have three active sites (cathodes), an anode and a screen electrode, presenting a good stability in human experimentation[37]. They are made of silicone, with platinum sites (Fig. 3a), and typically have an exposed area of 0.45 mm². However, the active sites of cuff electrodes have a structural barrier to stimulate the fibres in deep fascicles, as fascicles

themselves are transversally topographically located in a nerve[38]. To overcome this issue, the FINE reshapes the nerve into a flat geometry to increase the interfacing area by moving central axon populations close to the surface. It is fabricated by moulding a commercial silicone elastomer[30] and the stimulating contacts are evenly distributed in the top and the bottom half of the substrate (Fig. 3b). Contacts are produced using platinum foil, exposing a 0.4-mm-diameter

Table 1 | Material specifications used for the neural interfaces

Implant type	Substrate material	Active contact material	Area of sites (μm^2)
Cuff	Silicone	Platinum foil	441,562
FINE	Silicone	Platinum foil	125,600
C-FINE	Pliable silicon	Platinum foil	500,000
Wire LIFE	Insulated with medical-grade silicone	Kevlar fibre, with sputter-deposited titanium, gold and platinum	37,680
tf-LIFE	Polyimide	Platinum	5,256
TIME	Polyimide	Platinum coated with iridium oxide	5,026
USEA	Silicon wafers insulated with parylene-C	SIROF	5,026

The cuff electrode data are taken from the Ardiem Medical website for typical exposed contact area FINE[30], C-FINE[39,40], wire LIFE[31,41], tf-LIFE[114], TIME[46] and USEA[33] (Blackrock Microsystems).

window for the stimulation. C-FINE[39] is a version of FINEs optimal for anatomical locations near joints or organs, as it has a variable pattern of stiffness. Owing to the use of pliable silicone, C-FINEs guarantee stiffness along the width of the nerve to reshape it, while flexibility along its length allows for bending with the nerve.

For a direct contact with deeper nerve fibres, LIFEs are used to pinch the nerve. They consist of a Kevlar fibre, metallized with sputter-deposited titanium, gold and platinum, and insulated with an approximately 1-μm-thick medical-grade silicone elastomer[31,40]. The stimulation zone consists of approximately 1 mm of a non-insulated portion of the metallized fibre and a tungsten needle is glued to the LIFEs, to penetrate the nerve's tissue and guide the electrode placement.

Recent widespread use of polymers, such as polyimide and parylene, has led to the use of flexible devices[36]. They can be produced with microfabrication methods, enabling reliable serial production, in contrast to prototype-based manufacturing. Polymer-based electrodes are not only flexible but also the arrays are generally much less thick (ranging between 10 and 20 μm) than rubber-based arrays. They also have a higher number of stimulating channels, as insulation can be provided even between only 10 μm close adjacent metallic tracks. FAST-LIFEs[41], combining longitudinal intrafascicular arrays and fascicular cuff electrodes, consist of a series of thin-film electrodes and traces deposited on a reinforced silicone substrate. Eight platinum intrafascicular electrodes are placed on the thin extension of the array and are distanced 0.5 mm from each another. Six cuff electrodes are integrated into the thicker part of the array. A combination of cuff electrodes (Ardiem Medical) and LIFE-like intraneural (double-sided filament electrode (ds-FILE)[32]) electrodes made from polyimide with active sites of platinum have also been also tested in humans.

To exploit further the transversal somatotopic disposition of peripheral nerves, TIMEs have been constructed[34] by micromachining and patterning polyimide substrate, insulation material and platinum electrode sites. A guiding needle is needed for LIFEs and TIMEs, to penetrate the resistant nerve surface, and guide the electrode placement, increasing the complexity and duration of the surgery required.

Utah slanted electrode arrays (USEAs) are selective wire-like multiple contact interfaces that tackle the nerve transversally, without the use of needles. They are developed starting with a silicon wafer and processed with common microelectromechanical system methods, have great spatial resolution and can be used to penetrate several regions in the nerve, via a single implant.

The platinum-plated tips are exposed with an area of about 0.005 mm². The more advanced version of USEAs[33] (marketed by Blackrock Microsystems) includes titanium, titanium tungsten and platinum sputtering[33]. The tips of the electrodes are coated with iridium oxide to facilitate electrical to ionic transduction, and the entire array, with the exception of the tip of each electrode, is insulated with the biocompatible polymer parylene-C. These electrodes are implanted by a pneumatic insertion device.

Higher charge storage through coating. Platinum is the most used material for active sites, because of its good biocompatibility and conducting properties. After implantation, the fibrotic response shifts[42] intraneural electrodes (LIFEs, TIMEs and USEAs) away from the excitable tissue; therefore, these devices could have an insufficient[43] injectable current in the tissue, to elicit neural response. In fact, the foreign body reaction pushes the interface away from the fibres, requiring increased currents to activate them. Specific coatings over the active sites, increasing their roughness and relative surface, can improve the conducting properties and injectable charge[43,44]. In fact, after the failure of stimulation in the first in-human polymer-based approach[45], this problem was addressed by developing a coating that increases the maximum injectable charge[44]. In the case of TIMEs, the iridium oxide layer acts as active site material with a sufficient charge injection capacity[46]. Since iridium oxide was introduced as an active coating via electroplating, maximal charge injection capacities have increased from 75 μC cm⁻² for bare platinum[47] to 2.3 mC cm⁻² for iridium oxide, which corresponds to a 30-fold increase[44]. Similarly, in USEAs, sputtered titanium and iridium oxide films (SIROF) were deposited, obtaining a higher charge injection capability[48].

Material stability and biocompatibility. Among implantable materials, there is a trade-off between invasiveness and efficacy, softness and stability. Their effect on the tissues is measured in complementary ways: through animal (or occasionally human) tissue processing after electrode explants and by observing their long-term functionality via chronic measurements during stimulation tests. Indeed, cuff electrodes were tested in cat experiments[49] revealing their long-term usability up to 28–34 weeks, with a pattern of mild morphological abnormalities, and especially the formation of an external layer of connective tissue. During an extensive human study, up to 160 weeks of cuff electrode use was achieved in humans[50]. Recently, the same electrodes were proven to be stable in human use[37] for up to seven years.

FINE electrodes squeeze the nerves; therefore, their effect on the tissue was carefully studied in rat[51] and cat[52] chronic experiments. The effects were studied on the tissue at regular timings post-implantation, observing moderate damage and concluding that FINEs that apply a small force can reshape the nerve without substantial changes in its physiology or histology. These results were translated to humans, resulting in successful electrode use for several years[53].

The guiding-needle insertion of intraneural electrodes can damage the nerve, similarly to the pistol-based injection of USEAs, and therefore their biocompatibility is an important factor for their future adoption. Long-term histological and functional studies have revealed a good response of tissue to both wire-based and polyimide tf-LIFEs[54]. Regarding polyimide, a longitudinal animal study was performed, in which different time points of tissue response to polyimide were observed[42]. The selectivity, stability and biocompatibility were assessed in the sciatic nerve of 23 healthy adult rats for up to six months (note that one rat month is comparable to three human years[2]). A moderate increase in the stimulation threshold of the electrodes was reported during the first four weeks after implantation, remaining stable over the following five months. The time course of these adaptations correlated with the progressive
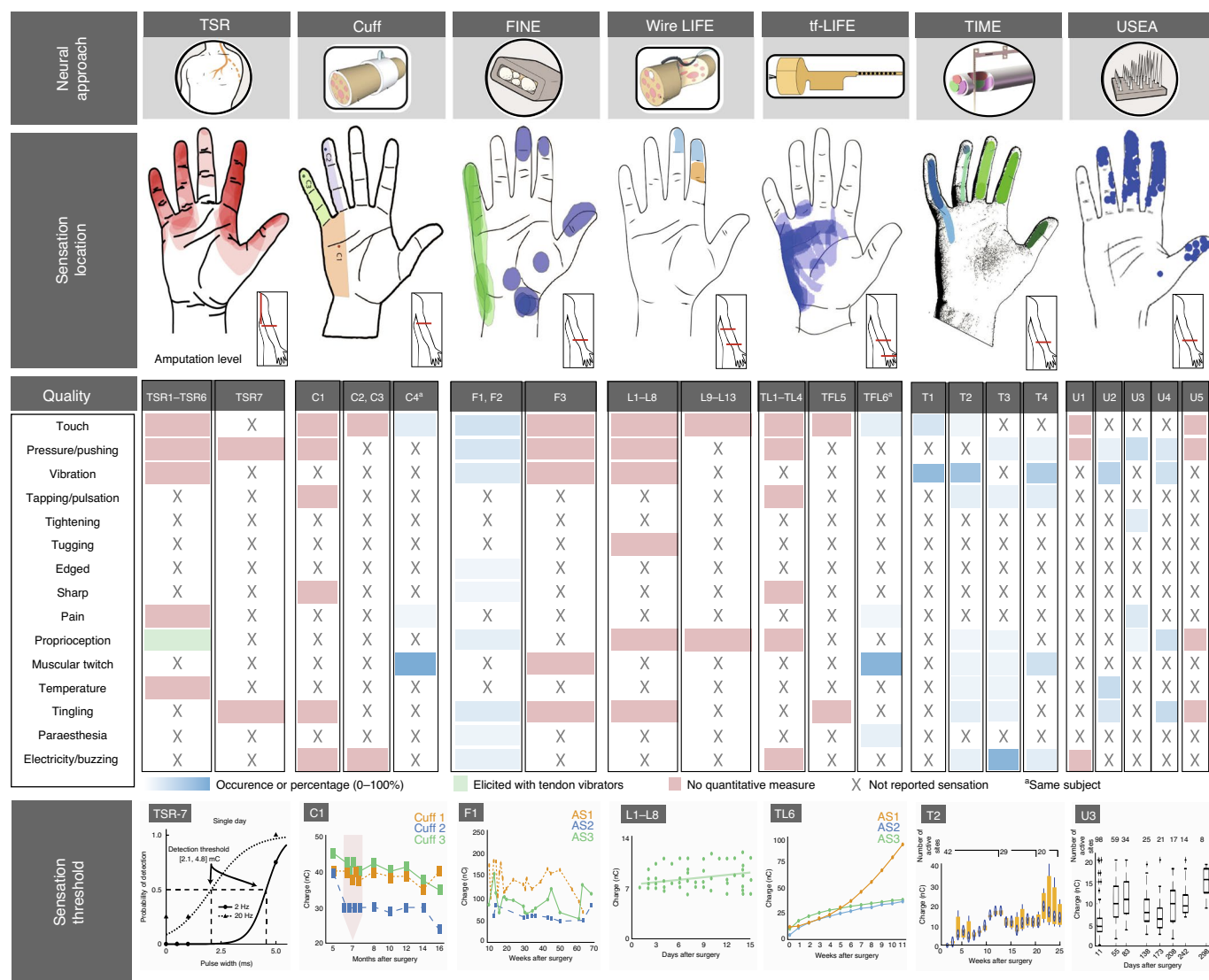
Fig. 4 | Sensation characterization for upper-limb amputees according to different neural approaches. Sensation location, quality and threshold related to the artificial sensations are shown. Only neural approaches tested in human experiments are reported. Results collected in transradial, transhumeral and partial amputees are shown. TSR1–TRS7, participants 1–7 with the targeted sensory reinnervation; C1–C4, participants 1–4 implanted with cuff electrodes; F1–F3, participants 1–3 implanted with FINEs; L1–L13, participants 1–13 implanted with LIFEs; TL1–TL6, participants 1–6 implanted with tf-LIFEs; T1–T4, participants 1–4 implanted with TIMEs; U1–U5, participants 1–5 implanted with USEAs; AS, active site. In the T2 and U3 boxplots, the central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers, and the outliers are plotted individually as crosses. Data are taken from refs. [80,81,88,99] for TSR, from refs. [37,68,69] for cuff, from refs. [53,75,117] for FINE, from refs. [61,67,99] for wire LIFE, from refs. [41,68] for tf-LIFE, from refs. [10,118] for TIME and from refs. [66,71,72,99,119] for USEA. Credit: TSR sensation location, reproduced with permission from ref. [80], under a Creative Commons license CC BY 4.0; cuff sensation location and plot, adapted with permission from ref. [69], AAAS; FINE sensation location and plot, adapted with permission from ref. [53], AAAS; tf-LIFE sensation location and picture, adapted with permission from ref. [41], IOP; TIME sensation location and plot, reproduced with permission from ref. [10], Wiley; USEA sensation location, reproduced with permission from ref. [71], IOP; USEA plot, adapted with permission from ref. [66], AAAS; TSR, FINE and USEA pictures, adapted with permission from ref. [99], under a Creative Commons license CC BY-NC-ND 4.0

development of the fibrotic capsule around the implants. The density of nerve fibres above and below the inserted implant remained unaffected. The impact of TIME electrodes on nerves was evaluated functionally and morphologically, through implants in the rats' sciatic nerve for two months[55]. The results indicated that implantation of devices in the nerve did not cause relevant axonal loss or demyelination.

USEAs have been studied histologically both in cats[56] and in humans[57]. During a six-month study, the morphology and fibre density of the nerve around the electrodes were found to be normal[56]. Implanted nerves were found to undergo a compensatory

regenerative response after the initial injury, which was highlighted in new axons growing around microelectrode shafts. Similar findings regarding inflammation have been observed in humans implanted with an USEA in the ulnar and median nerves[57].

Bionic limb applications

Limb amputation results in the loss of the extremity receptors and thus the sensory organs that interact with the environment. However, the somatosensory nerves and pathways conveying sensory information to the central nervous system remain functional[58]. Invasive procedures (that is, requiring surgical intervention) for

Table 2 | Characteristics and benefits of neural approaches to restore sensory feedback tested in humans with upper- and lower-limb amputations

Neural approach	Longevity (months)	Implants per patient	Channels per electrode	Sensations in closed loop	Motor control benefits	Feature recognition benefits	Cognitive benefits	Health benefits	Ecological use
Upper-limb amputees									
TSR	>9	1[a]	1[a]	1–6	Grasping force; dexterity	Stiffness hand posture	Embodiment	–	Yes
Cuff	>84	2	3–14	1–2	Slippage, manipulation and grasping performance; grip control	–	Embodiment; visuo-tactile integration	–	Yes
FINE	>84	3	4–8	1–2	Fine force control; prosthesis time use; manual accuracy; dexterity; ADL	Hand posture compliance size	Embodiment; visuo-tactile integration; QoL	PLP; mood states; distorted phantom limb perceptions	Yes
Wire LIFE	0.5	NR	1	2	Grasping force control	Hand posture compliance size	–	–	No
tf-LIFE	2.6	1–4	8–14	2	Slippage, manipulation and grasping performance	–	Embodiment; visuo-tactile integration	–	No
TIME	6	4	14	3	Fine force control; manual accuracy dexterity; motor coordination	Texture compliance shape/ size position hand posture	Embodiment; cognitive resources; visuo-tactile integration	PLP; mood states distorted phantom limb perceptions	No
USEA	14	2	96	3	Grip control; ADL; manual accuracy	Virtual texture; compliance; size	Embodiment	PLP	No
Lower-limb amputees									
AMI	>24	1[a]	–	1	Prosthesis control; stairs ambulation ankle torque control	Ankle posture	–	–	No
FINE	>24	3	16	2	Equilibrium; standing stability	–	Visuo-tactile synchrony; multisensory integration	–	No
TIME	3	4	14	4	Stairs ambulation; tandem waking falls avoidance; walking speed on uneven terrains	Touched positions; leg posture	Prosthesis confidence; cognitive resources; embodiment	PLP; metabolic cost	Yes

Data for upper-limb amputees taken from refs. [10,46,60,64][,75–78,83,85][–88] and for lower-limb amputees from refs. [82,97,98,100]. ADL, activities of daily living; QoL, quality of life; PLP, phantom-limb pain. [a]Surgery without electrode implants. NR, not reported.

implanting electrodes and directly stimulating the somatosensory nerves were first used in 1974 with single-channel cuff electrodes implanted around the median nerves for upper limbs[59], and in 1982 for the femoral nerve for lower-limb amputees[60]. Despite these proofs of concept, new technologies for sensory feedback restoration have only recently been successfully exploited in human clinical investigations.

Sensory feedback restoration for upper-limb extremities. Neural interfaces for sensory restoration were exploited in 2004, using wire LIFEs[61,62] implanted in the median and ulnar nerves of eight transhumeral amputees. These studies demonstrated that somatotopic sensations could be elicited from the missing hand. The authors showed for the first time that the intensity of the elicited sensation could be modulated by increasing the frequency or the amplitude of the neurostimulation. This was the starting point for subsequent studies in which sensations were connected to prosthesis pressure sensors, restoring grasping force regulation[10,53,63–66]. In 2010, a transradial amputee was implanted with a thin-film LIFE eliciting sensations perceived on the phantom hand[45]. The subsequent exploitation of the artificial feedback, delivered by wire LIFEs, was implemented in a prosthetic hand[67], enabling amputees to identify the size and stiffness of different objects with a myoelectric prosthesis without visual or auditory cues. More recently, polymer-based LIFEs (FAST-LIFEs and ds-FILEs) were successfully tested in humans[41,68].

Using different geometries, TIMEs[64], FINEs[53] and cuff electrodes[69] have been shown to be effective and functional neural interfaces, which provide sensory feedback in upper-limb amputees.
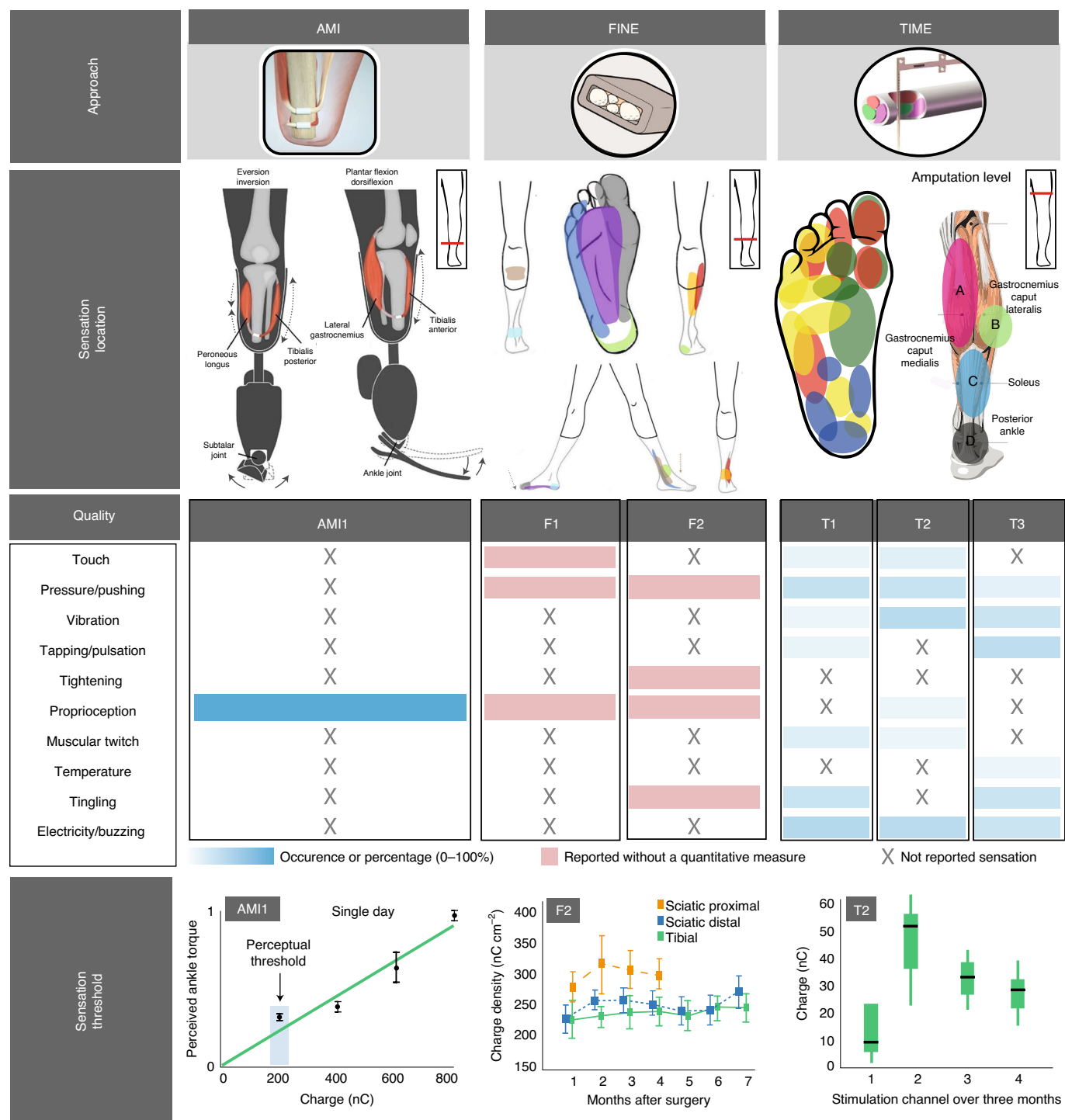
Fig. 5 | Sensation characterization for lower-limb amputees according to different neural approaches. Sensation location, quality and threshold related to the artificial sensations are displayed. Only neural approaches tested in human experiments are reported. Results collected in transtibial and transfemoral amputees are shown. AMI1, participant 1 with the agonist–antagonist myoneural interface; F1 and F2, participants 1 and 2 implanted with FINEs; T1–T3 participants 1–3 implanted with TIMEs. The error bars in the AMI1 and F2 plots are s.e.m. In the T2 boxplot, the central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers. Data are taken from ref. [86] for AMI, from ref. [82] for FINE and from refs. [83,84] for TIME. Credit: TIME sensation location, reproduced with permission from ref. [84], AAAS; FINE picture, adapted with permission from ref. [99], under a Creative Commons license CC BY-NC-ND 4.0; AMI sensation location and plot, adapted with permission from ref. [86], AAAS; FINE sensation location, adapted with permission from ref. [82], under a Creative Commons license CC BY 3.0

Using the neural stimulation delivered through TIMEs, an amputee was able to identify the object's position, shape and compliance. In addition, with FINEs and TIMEs, an improvement in force control has been demonstrated[53,64]. These were the first proofs of motor control benefits thanks to a real-time sensory feedback embedded in a prosthesis. Notably, in hand amputees implanted with TIMEs, the ability to provide information regarding textures was shown[70].

In 2016, the first use of an USEA for the peripheral nervous system (PNS) in humans was shown through recording of peripheral neural signals and providing sensory feedback[71,72]. In the past decade, many other benefits have been reported, connected to the use of direct nerve stimulation using neural interfaces (Fig. 4 and Table 2). Researchers have begun to demonstrate the benefits of the sensorimotor strategies related to prosthesis control[65,68]. The cognitive aspects of sensory feedback restoration have also been investigated considering prosthesis embodiment[65,73] and integration[74]. Health benefits have been related to the reduction in phantom limb abnormal representations[65,73,75] and phantom limb pain[10]. Sensory feedback restoration has also been proven to have an impact on how long a prosthesis can be used in everyday life[75].

More recently, notable stability[69,76] and also the home use of bidirectional prostheses using FINE[75] and cuff electrodes[37] for several years have been investigated and demonstrated.

In parallel with direct PNS stimulation, another approach has been developed, in particular for people with a high level of amputation called targeted muscular reinnervation (TMR)[77,78]. TMR is a surgical approach, in which, the residual nerve branches that once innervated the amputated hand are 'redirected' to another area of the body, such as the pectoral region (Fig. 1). The 'redirected' nerves re-grow and reinnervate the new muscles. Similarly, specific sensory nerves can be transferred so that the skin of the chest or the arm is reinnervated, which is called targeted sensory reinnervation (TSR)[78,79]. An arm amputee undergoing TMR to the pectoral region will be able to feel tactile cues on the chest as though they were originating from the missing hand[79]. To evoke this somatotopic sensation, this chest skin could be mechanically or electrically stimulated. A fully portable system was recently extensively tested with amputees at home using both TMR control and TSR provided by vibrators[80]. A similar method was also implemented by exploiting transcutaneous electrical stimulation of the reinnervated area[81].

Sensory feedback restoration for lower-limb extremities. Sensory restoration is also possible in lower-limb amputees (Fig. 5 and Table 2). By stimulating the sciatic nerve, it is possible to evoke the sensations referred on the phantom leg and foot: FINEs[82] and TIMEs[83,84] have been successfully tested in humans. Interestingly, FINEs have been adopted with transtibial amputees and TIMEs with transfemoral amputees, who are radically more disabled[7]. People implanted with FINEs perceived sensations on a few, spatially extended, areas under the phantom foot and on the phantom leg (Fig. 5), important for balance and locomotion. The neural sensory feedback delivered by TIMEs implanted in the tibial nerve were successfully exploited by transfemoral amputees. Distinct and spatially selective sensations of touch, pressure and vibration were elicited from more than 20 positions of the phantom foot, together with the contraction of the muscles of the missing leg (Fig. 5). Notably, this neural feedback was then exploited in motor tasks, which proved that this approach improved users' recognition of prosthesis movement and touch, mobility over stairs and obstacle avoidance[84]. When stepping out of the laboratory into an ecological environment, walking speed and self-reported confidence in the prosthesis increased, while mental and physical fatigue decreased for participants during neural sensory feedback compared with the no-stimulation trials[83]. This is an important health-related benefit since lower-limb amputees have a higher risk of having a heart attack[85]. Together with functional and health outcomes, the cognitive integration of the device into the participants' body schema was confirmed using the neuroprosthetic intervention[84], by measuring the prosthesis embodiment and cognitive effort while using the artificial leg. Finally, participants reported radically decreased phantom limb pain when provided with neural sensory feedback.

In addition to PNS interfacing, a promising surgical approach has also been developed, using an agonist–antagonist myoneural interface (AMI) to restore proprioceptive sensations in a transtibial amputee[86]. The technique consists of connecting in series two opposing muscle-tendon ensembles (an agonist and an antagonist). The contraction and shortening of one muscle (by volitional intention or electrically activated) thus induces the stretching of the other muscle in series and vice versa. This linked motion enables the natural body sensors embedded in the muscle tendon to send signals to the brain, transmitting information on the muscle length, speed and force, which is then perceived as physiological joint proprioception. Multiple AMI pairs can be created for the control and sensation of multiple prosthetic joints.

All these findings provide the rationale for larger population investigations of the clinical utility of neuroprostheses that restore sensory feedback in leg amputees.

Restoration of proprioception using PNS. Proprioception is of crucial importance for the manipulation of objects[87]. It is known[22] that vibrations can elicit/inhibit proprioception, and thus tendon vibrators have been used to elicit the sensation of hand movements and postures in transhumeral participants with TMR[88]. In contrast, electrical stimulation of the nerve rarely evokes a proprioceptive sensation without also activating a muscular one. Indeed, using microstimulation, it has been proven that sensations of movement or position cannot be directly evoked by stimulating single muscle spindles[23]. Proprioceptive illusions are more difficult to induce than tactile sensations, as they require more than the mere additive activation of nervous fibres. However, the activation of a larger group of muscle spindle afferents could induce a sensation of joint movement[89], which probably explains the findings shown by adopting certain neural interfaces[67,72].

The difficulty in eliciting proprioceptive percepts is also related to how the proprioceptive afferents are distributed inside the nerve. The muscle spindle fibres are not grouped together within the nerve according to their function as the tactile afferents[90], instead they are clustered with motoneurons innervating the muscles[91]. Stimulating a group of only proprioceptive fibres is less likely than it is with tactile afferents: the active sites that induce muscle spindle fibres activation are also likely to easily evoke phantom muscle contractions. One relevant remark here is that the nerve fascicles could be not maintained at all levels, in particular in very proximal segments[92]. An alternative approach to conveying proprioceptive information is through sensory substitution, which consists of providing information on limb posture by electrically evoking a distinct cutaneous sensation[93]. This approach has not yet been tested in activities of everyday life.

Prospective and big picture
Technological limitations to overcome. Silicon- and polyimide-based cuff electrodes are currently in development for human certified use (for example, Neuros Altius System, USA, and Neuroloop, Germany). However, polyimide-based solutions (especially thin-film electrodes) could face major problems in terms of approval for use as active implantable medical devices, since they are associated with a risk of failure when implanted over the long term, and there has also been no previous use of medical-grade polyimide for this purpose[36]. However, the latest technological developments in iridium oxide coatings and in layers promoting adhesion between metal and polyimide have shown promising results with respect to long-term integrity and stability, and could facilitate the roadmap towards clinical approval for medical use[36]. The use of parylene-C and the coating of several medical devices could be a promising step forwards[94]. Indeed, USEAs already include parylene-C in their composition.

While developing these sophisticated technologies, the rudimental connection between the prosthesis and the stump is an often-overlooked limitation. At present, uncomfortable sockets are used, which in upper-limb amputees can compromise the stability of
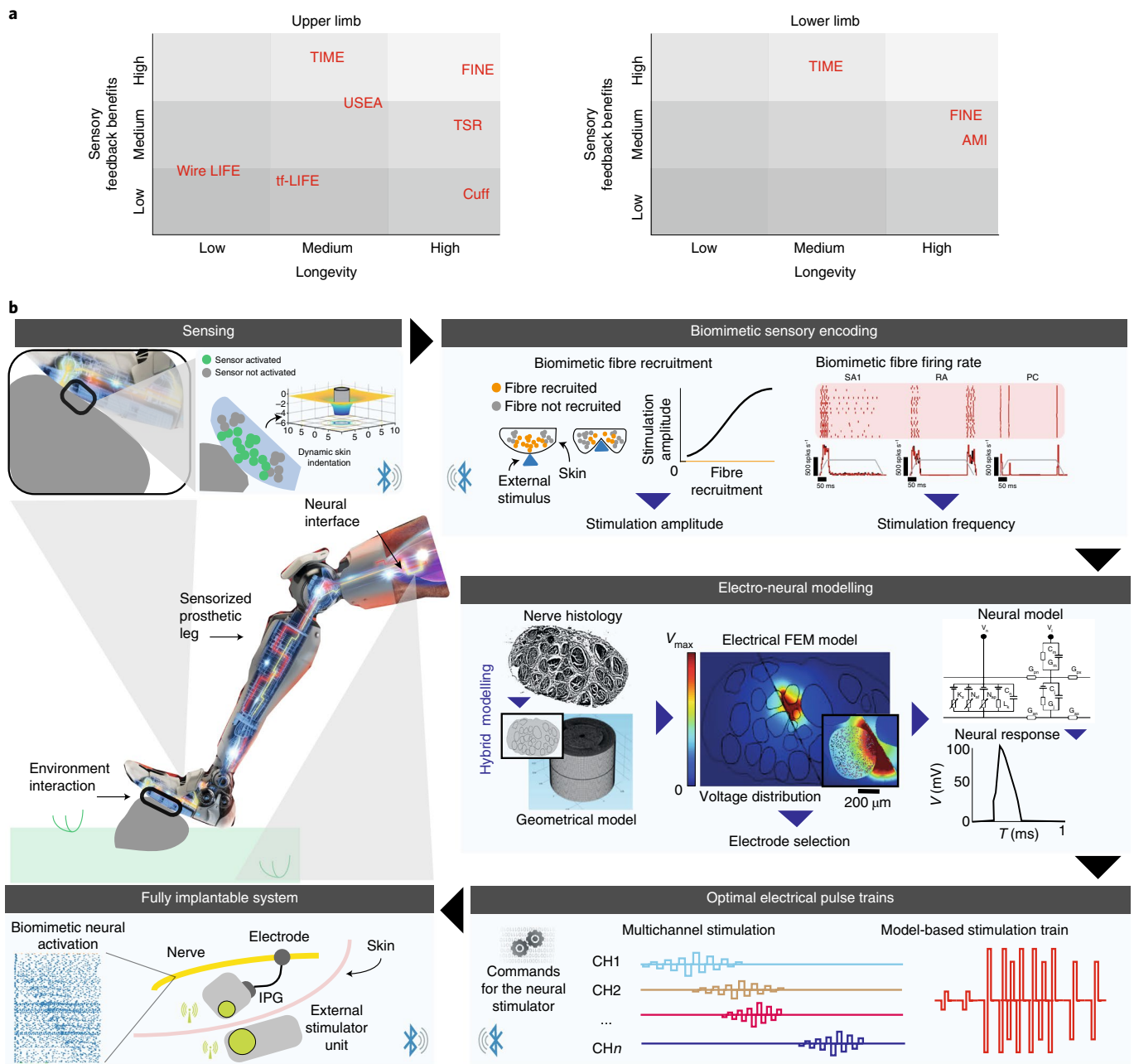
Fig. 6 | Biomimetic model-based encoding for natural sensory feedback. a, Comparison between sensory feedback benefits and longevity. Technologies for both upper and lower limbs are shown. **b**, The optimal neural stimulation should elicit a rich and natural perception generating a natural activation of the neural fibres. This can be achieved with a model-based approach in which, by interacting with the environment, the prosthesis can extract all the necessary information using advanced wearable sensors. Then, biomimetic sensory encoding algorithms convert sensor outputs and generate the optimal stimulation parameters based on the modelled fibre firing rate and recruitment. After this step, the electro-neural model identifies the optimal electrode configuration and the optimal electrical pulse trains are delivered using a multichannel neural stimulation. Finally, the electrical stimulation is injected into the somatosensory nerve through a fully implantable system. SA1, slow-adaptive fibre class 1; RA, rapid-adaptive fibre class; PC, Pacinian corpuscle fibre class; spks, spikes; IPG, implantable pulse generator; V, voltage; T, time; FEM, finite element method; CHn, channel n. N$_{af}$, fast sodium; N$_{ap}$, persistent sodium; K$_s$, slow potassium; L$_k$, linear leakage; C$_n$, C$_m$ and C$_j$, linear conductances; G$_m$, G$_j$, G$_{ax}$, G$_{an}$, G$_{pn}$ and G$_{px}$, resistances representing the myelin sheath. Credit: dynamic skin indentation in sensing panel and all of biomimetic sensory encoding panel, reproduced with permission from ref. [65], Elsevier; all of electro-neural modelling panel, adapted with permission from ref. [104], under a Creative Commons license CC BY 4.0

the prosthesis, and in lower-limb amputees can be a source of pain. Connecting the residual bone to the prosthesis via an implanted biocompatible screw, called osseointegration[69], offers a solution. It improves the long-term stability of such devices and provides greater comfort for patients, especially as it alleviates the problem of the perceived weight of the prostheses[95]. It also provides the perfect

space for implantable neurotechnology leads to pass through the body to connect with external electronics[69].

Capturing sensory information external to the limb is one of the main technological drawbacks of the technologies described in this Review, since prosthetic limbs are not equipped with sensors. Future prostheses will need this data as input to optimize

neurostimulation. To attain this goal, important attention has been paid to developing prosthetic electronic skin[96]: a high-density matrix of sensors implemented over a flexible material that can be applied over the hand or leg. While various sensory signals[97] have been acquired using this technique (such as pressure, movement or temperature), the robustness and real-life use of these technologies are yet to be proven. Indeed, studies[83,84] suggest that for leg amputees, a limited number of sensors (such as three for the foot and one for the knee) may be sufficient. In contrast, in the hand, a high density is needed to implement the biomimetic paradigms[65,98,99].

Uniform performance metrics are required. Many studies report data in different ways, which hinders our ability to understand the relevance of the findings: sensations should be reported uniformly[100] together with their time evolution. In this way, clinical efforts globally could provide unified information regarding the behaviour of these devices and provide solutions to common problems.

In addition, common metrics should be defined (Table 2), which should be simple while meaningful, and therefore implementable in different scenarios. One example of such an indicator could be the time of use[75] of the device for upper-limb prostheses with and without intervention. This could help decrease the prosthesis abandonment rate[9]. Regarding lower-limb amputees, the most direct indicator of an intervention's success is an increase in mobility[101]. This then leads to improvement in the cardiovascular system[83], and potentially also to social and economic reinsertion.

Despite their differences, several general rules can be drawn from the studies described in this Review: typically, extraneural electrodes (cuffs and FINEs) exhibit a higher stability, at the price of lower selectivity (and therefore efficiency), compared with intraneural electrodes. This trade-off between invasiveness and selectivity has already been reported in animals[102] (Fig. 6a). However, this is more evident in leg applications: in fact, when interfacing the nerves of the arm, the maps of the elicited sensations are similar across different interfaces (Fig. 4). This is most probably because leg nerves (tibial and sciatic) are much bigger than those in the arm (median and ulnar), making it more difficult for extraneural devices to stimulate inner fascicles (Fig. 5).

Transforming paraesthesia into touch increases device acceptance. Although direct neural stimulation through neural interfaces has extensively shown its ability to evoke a large spectrum of tactile feelings, these sensations, referred to the phantom extremities, have often been described as unnatural and more similar to paraesthesias[103]. Biomimetic sensory encoding strategies[99] (that is, that resemble natural tactile coding) hold the promise of providing more pleasant sensations and therefore of increasing device acceptance[14].

Various encoding strategies have been used to translate the readout of sensors embedded or added to the prosthesis into stimulation parameters (amplitude, pulse width, frequency and duration of pulse trains). The linear modulation of injected charges[10,53,64,69] or frequencies[62,67,71] has been adopted to translate sensor information into neural modulation. This is in accordance with the physiology of afferent tactile fibres, which deliver information on the intensity of a sensation to the brain through population recruitment or changes in firing activity[19]. Recruitment and firing are controlled by modulating stimulation amplitude and frequency, respectively.

Despite the fact that these techniques are easy to implement in closed-loop systems, the perceived naturalness of the electrically evoked sensations is often rated as very low by the patients[63] (Figs. 4 and 5). In fact, the natural touch coding and the relationship between natural sensors and neural activity is more complex than intensity coding alone (Fig. 2). A major problem is that these types of stimulation induce highly synchronized neural firing in the entire population of recruited fibres[99]: it is impossible with the current technologies to separately stimulate different afferent types with the same active site.

Recent studies have presented more complex approaches[53,65,66], which stimulate the implanted fibres following the close-to-natural ensemble activation of tactile afferents (called biomimetic[99]; Fig. 6b). The results showed that biomimetic stimulation elicited more natural sensations than the previously presented strategies, with consequent benefits in terms of control of the prosthesis and its embodiment. Similar results were also confirmed with a participant implanted with a USEA with biomimetic sensory encoding strategies adopted[66].

Computational modelling for optimization. Electrodes used for stimulation can have different geometries, numbers of stimulating contacts, placement and stimulation protocols. This high-dimensional problem cannot be solved by empiric brute-force approaches, but requires exact computational models, exploiting accumulated knowledge. These hybrid models combine the electromagnetic solution of the field induced in the nerves by the electrical stimulation, with the consequent, nonlinear response from the axons[104] (Fig. 6b), and are implemented in in silico nerves. Different electrode materials and configurations (that is, electrode placement, shape and dimensions) can be tested in the model, thus obtaining the optimal geometrical selectivity (for example, stimulation of the sole fascicles innervating the forefoot with respect to the heel). The model computation of the axon activation of target fascicle(s) with respect to all fascicles could be used to evaluate the specificity and therefore the efficiency of the proposed designs. In parallel, different stimulation strategies could be tested obtaining the optimal fibre recruitment, expressed as a lower threshold and smaller curve steepness of activated fibres. Models can therefore give direct indications to manufacturers both for the design of the materials and their shape, used in electrodes, and also for the optimal algorithms to be ported onto the system controllers and implantable units.

Towards widespread use. The main goal of these technologies is to pass from proof-of-concept studies to clinical reality. To achieve this, several technological and regulatory steps are required[105]. The electrodes should be easy to implant with minimally invasive surgery. Due to all the problems with percutaneous wires (including possible infections), the development of fully implantable systems communicating with outside sensors (Figs. 1, 2 and 6b) is a mandatory next step. Commercial neurostimulators have pre-programmed stimulation protocols, without the need for continuous transcutaneous communication. Contrary, in bionic limbs, a high burden of information has to be transmitted through the skin to enable bidirectional communication. This involves an important constraint to battery capacity and implant size, which represent notable technological challenges.

However, even if the perfect system is achieved, providing some benefits for patients, this will not be sufficient for wide clinical use. Health and quality-of-life benefits should be assessed and documented, helping healthcare systems to save spending that would otherwise be necessary for the treatment of patients. This would increase the likelihood that these neurotechnologies can be reimbursed by insurances and healthcare systems, therefore guaranteeing their widespread to all patients in need.

Future developments could be systems that provide more selective or less invasive interfacing with nerves, such as optogenetics[106], conductive polymers[107] and ultrasound based[108], which today are at the stage of animal experimentation. The neurotechnologies presented have enormous potential in terms of social and health impacts, and after the recent discoveries, we are a bionic step closer to their achievement.

Data availability

The data and calculations that support the findings of this Review are available from the corresponding authors upon reasonable request.

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Competing interests

S.R. and F.M.P. hold shares of SensArs Neuroprosthetics Sarl, a start-up company dealing with the commercialization of neurocontrolled artificial limbs. G.V. declares no competing interests.

Additional information