Invasive neural interfaces: the perspective of the surgeon

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ABSTRACT

Background: By implanting electrodes inside peripheral nerves, amputee’s intentions are picked up and exploited to control novel dexterous sensorized hand prostheses. Under the pretext of presenting surgical technique and clinical outcomes of the implant of invasive peripheral neural interfaces in a human amputee, this article critically comments, from the point of view of the surgeon, strengths and weaknesses of the procedure.

Materials and methods: Four multielectrodes were implanted in the medial and ulnar nerves of a young volunteer, which, following a car-crash, had a left transradial amputation. Both nerves were approached with a single incision in the medial aspect of the upper arm. Four weeks later, the electrodes were removed.

Results: Even if the trauma and the postamputation plastic processes altered the anatomy, electrodes were proficiently implanted with an overall success of 66%. Looking at the procedure from the surgeon’s viewpoint unveils few still open issues. Electrodes weaknesses were related to the absence of stabilizing structures, the cable transit through the skin, the implant angle, and the unproven magnetic resonance imaging compatibility. Future investigations are needed to definitely address the better anesthesia, number and sites of incisions, the nerves to implant, and the convenience of performing epineural microdissection.

Conclusions: Invasive neural interfaces developmental process almost completely relies on the efforts of bioengineers and neurophysiologists; however, the surgeon is responsible for intra and perioperative factors. Therefore, he deserves to play a major role also at the stage of specifying the requirements, to satisfy the requisites of a safe, stable, and long-lasting implant.

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Peripheral artery diseases and diabetes, work or road traumas, and cancers have caused the presence of almost 100,000 major upper limb amputees living in the European Community [1] and 41,000 in the United States [2]. In addition, in fighting countries, war-related injuries drastically play a major role. Looking forward, people living with the loss of a limb in the United States should more than double by the year 2050 [2]. Alas, today the hand transplant is still accompanied by huge immunologic unsolved issues [3]. To address the needs of those people to compensate what has been lost because of the amputation, bioengineers have begun to develop new hand prostheses, with independent controllable fingers [4] and embedded artificial sensors [5]. The deep-rooted control systems, mostly relying on the contraction of far spared muscles transmitted through hidden pulleys and cables or superficial electromyographic sensors, revealed to be inadequate for novel dexterous sensorized prostheses, especially in managing all the available degrees of freedom. To this aim, several new solutions have been tested so far. Recently, for instance, Prof Kuiken, Dumanian, and Collaborators developed the so-called “targeted muscle reinnervation”: the surgical transposition of the severed nerves previously devoted to the hand, toward the omolateral pectoralis major. It allows very proximal amputees to independently control several movements of myoelectric prostheses [6]. A further very promising approach is to put the electronic controller of the prosthesis directly in contact with peripheral nerves of the user.

In fact, the attempt to invasively couple with the bioelectrical activity of human peripheral nerves is relatively old. In the late 60s, two Swedish groups set up the technique for multifiber and single-unit neural signals recording [7,8]; few years later was conducted the first intraneural microstimulations [9,10]. The developmental process of novel nerve-stimulation devices has been further propelled forward by the birth, and the clinical applications, of functional electrical stimulation. This is intended as a stimulation produced to pursue a functional outcome, such as the artificially evoked foot dorsiflexion in the foot-drop [11], the management of the conjunct efforts of bioengineers and neurophysiologists, whereas the figure of the surgeon is considered quite marginal.

The progressive development of intraneural interfaces should, in the future, allow an intuitive control [14], the perception of tact [15], and other multimodal sensorial feedbacks [5]. The last are known to have a deep influence in the embodiment process, the degree of assimilation of the prosthesis in the user’s body scheme [16]. Bidirectional interfaces have the ability to manage neural signal flows in both afferent and efferent directions [17] and, in parallel of extracting user motor volitions, are able to translate and deliver to the nervous system information that artificial sensors have extracted from the surroundings.

Several electrodes, different in size, shape, and material, have been developed to be implanted in the peripheral nervous system, contiguous, around or inside a nerve trunk or a spinal root. The obtained bandwidth, signal-to-noise ratio, and selectivity of exchanged information are comparable with the ones achieved by implants in the central nervous system [18]. Unfortunately, the increase in selectiveness achieved by the intraneural electrode has consequent growth of invasiveness [18]. Invasive electrodes implanted inside the nerve, indeed, could potentially damage their hosting tissue. The damage could be related with three main processes: (i) the biocompatibility of the used materials and the inflammatory reaction that the body develops against what is considered a foreign body [19], resulting in the encapsulation of the electrode and in the alteration of tissue-electrode electrical impedance; (ii) the relative movements of the probe inside the nerve or in other words, the tissue-electrode mechanical mismatch; and (iii) the risk of the implanting procedure.

Tissue encapsulation is of utmost impact for the correct function of any nonbiologic implant, as demonstrated at first for arterial prostheses, where the problem was deeply investigated in animals and, in parallel, in humans [20].

In the attempt to overcome the first two detailed issues, bioengineers and experts in biomaterials tested innovative flexible structures, smart coatings [21] and novel, more compliant and biocompatible, polymeric materials. Microwire electrodes have been mostly replaced by polyimide-based substrates, hosting multiple thin conducting metal wires and plates, made by platinum alloys [22]. Polyimide can be also fabricated as porous thin membrane [23], being porosity a well-known key factor for improving graft biocompatibility and for allowing drug delivery.

In animals, histologic evaluation of nerves that had intrafascicular electrodes implanted for 2–3 mo did not reveal axonal loss or demyelination [24], but only the presence of a mild scar confined around the electrode [25]. Innovation of intraneural interfaces starts with computational modeling and experiments in animals. However, when the application of those devices reaches its experimental phase in humans, the main actor of the surgical procedure becomes responsible for intra- and periprocedural factors that risk damaging the device or, worse, the patient who received the implant. Despite that, most of the invasive neural interfaces developmental process almost completely relies on the conjunct efforts of bioengineers and neurophysiologists, whereas the figure of the surgeon is considered quite marginal and involved only at the moment of the implant.

So far, intrafascicular electrodes implanted in amputees were able to record volitional motor activity used by the patient to control the grip of a single degree of freedom, tong-like, hand prosthesys [26], and the flexion-extension of a robotic finger [27]. Our group performed the first implant of multiple intraneural multielectrodes in multiple peripheral nerves of the stump of a human amputee, with the aim of controlling a sensorized cybernetic hand prosthesis and to deliver artificial afferent stimulations [28,29].

Under the pretext of offering a deeper description of the surgical technique and its clinical outcomes, this work is intended to exploit the knowledge gathered from this experience to critically comment, from the point of view of the surgeon, strengths and weaknesses of the surgical procedure and of used multielectrodes. A further comparison with possible alternative solutions would lead the reader toward how an ideal neural interface for peripheral nerves should be to satisfy the requisites of a safe, stable, and long-lasting implant.
2. Materials and methods

2.1. Ethics approval

This study was conducted or in accordance with the Helsinki Declaration of 1975 at the Hospital and at the Center for Integrated Research of Campus Bio-Medico University of Rome and was approved by the Campus Bio-Medico Ethics Committee and by the assigned office for active implantable device experimentation of the Italian Ministry of Health. The volunteer subject, in the presence of a witness from his family, signed an informed consent form.

2.2. Subject

The enrolled subject was involved, almost 2 years before, in a car-crash that produced a transradial, left arm amputation (Fig. 1). He is a right-handed, male, aged 26 years at the time of the experiment. Except for the amputation, he did not report any previous disorder. He demonstrated good intellective abilities and comprehension. Neurologic and neurographic/electromyographic examinations were normal, thus excluding possible functional degeneration in the forearm nerves fibers. Indeed, the sensibility of the spared part of the left arm, except for a dysesthesia and a sense of itching confined to the region of the scar, was normal. Central motor pattern integrity for median and ulnar nerve was tested by proving the ability to evoke motor evoked potential in biceps and triceps muscles, respectively, after the transcranial magnetic stimulation of the contralateral motor cortex. Motor evoked potentials were also present in the few spared fibers of the forearm stump, both in the flexor carpi ulnaris, as vehicle by the muscular branches of the ulnar nerve, and in the flexor digitorum profundus, as vehicle by the anterior interosseous nerve.

The left, severed upper limb presented a clean amputation along the line between the proximal and the middle third of the forearm (Fig. 1), produced by the surgery that the patient received to refine the traumatic lesion made by the car accident. A net scar was located in the medial face of the spared forearm, extending from the line of the amputation to the

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**Fig. 1** – The transradial severed left upper limb from different perspectives. Panel (A) frontal view of the trunk, panel (B) volar aspect of the arm, panel (C) medial aspect, and panel (D) lateral aspect of the arm. (Color version of figure is available online.)

**Fig. 2** – Panel (A) shows tf-LIFE4 System with needle, polyimide fiber, electrode filament, and ceramic connector; panel (B) shows tf-LIFE4 with its cable and external connector. (Color version of figure is available online.)
2.3. **Intraneural electrodes**

The multielectrodes chosen for the implant were thin film longitudinal intrafascicular electrodes generation 4th (tf-LIFE4s) [30]. The system combines a thin loop, which is the proper electrode, with a Kevlar filament loop and a thin tungsten needle. The latter is designed to be used as guidance for the implant, whereas it is removed after the procedure. The electrode is made of flexible polyimide thin films, whereas a ceramic connector collects all the tracks from the active sites and generates the cable that goes outside the body (Fig. 2).

The tf-LIFE4 microstructure consists of a polyimide substrate with overall thickness and length of 10 μm and 5 cm, respectively (Fig. 3). The tf-LIFE4s present eight Platinum 300-nm thick recording or stimulating sites and reference and ground electrodes on each side. Platinum and polyimide are nontoxic material chosen to improve the biocompatibility of the device. The high flexibility of polyimide reduces the mechanical electrode-tissue mismatch but, on the other hand, does not fulfill the minimum stiffness required to pierce the neural tissue. This issue is overcome with the use of the rigid tungsten needle, which creates the hole and acts as a tray for the whole system (Fig. 2A).

2.4. **Implantation and explant procedure**

The overall implantation procedure, conducted with the patient under general anesthesia, lasted about 4 h, of which the net surgical time took almost 1.5 h. To easily access the medial aspect of the left arm, the upper limb was located in the frontal plan, forming a 90° angle with the trunk and placed in extrarotation.

After superficial disinfection, the skin of the medial aspect of the arm has been cut from the middle upper arm following the medial edge of the biceps muscle for 10 cm distally. Incision ended about 6 cm above the elbow. The ulnar and the medial nerves have been exposed along their course for about 8 cm, through careful smooth dissection of the dermal and hypodermic structures, fascial bands, and muscles (Fig. 4A). The length of the incision was chosen to have enough space to introduce and stabilize two electrodes into each nerve, spaced at least 3 cm from one another and avoid possible conflicting interactions.

Following a partial epineurial microdissection, performed under a surgical microscope (Opmi Vario/NC33; Carl Zeiss Suricaus Inc., Germany) to visualize the fascicles, two tf-LIFE4s for each nerve (median and ulnar) were inserted into the nerve trunk, achieving a total amount of 32 channels opened toward the nerves.

The isolated nerve was stretched with the help of two surgical loops, to better control the resistance that it opposes when it was pierced by the tungsten needle (Fig. 2A). As soon as the needle came out from the opposite side of the nerve, the attached loop acted as a tray for the electrode (Fig. 4B). Hence, the whole system was pulled inside the nerve, until the active contacts, embedded in the two arm of the electrode, reached the targeted location, close in contact with the nerve fascicles. The kevlar ansa passes through the loop of the electrode, thus creating with the electrode a connection similar to the one existing between the two links that are part of a chain (Fig. 2A).

The distal electrode of the ulnar nerve was introduced perpendicularly, whereas all the other tf-LIFE4s were introduced 45° obliquely, with respect to the major nerve axis, to have a higher stability and useful interaction between the nerves fibers and the electrode.

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Fig. 3 – Panels A and B show snapshots of tf-LIFE4 under optical microscope at different magnifications. Panels C and D show schemes and measures. Ellipses highlight the tract that hosts the active contacts (green rectangles) that remain within the nerve as illustrated by panel E. (Color version of figure is available online.)
The selection of different fascicles to be implanted was slightly corrected according to the subject-referred sensations. To this aim, as soon as all the electrodes were placed, but before they were definitely fixed to the surroundings, the subject was awakened to report the sensations evoked by the stimulation of different sampled channels. Hence, the electrodes were gently moved up and down inside the nerve to obtain a satisfactory amount of channels able to evoke sensations.

Once the electrode reached its definitive location, the terminal tract of the ansa that came out through the nerve was anchored to the superficial epineurium, which covers the region of the nerve close to the exit hole, using an 8.0 nylon suture. The tungsten needle and the kevlar ansa were finally removed.

The design of the electrode does not provide any dedicated structure to fasten the device to the surrounding tissues, and especially to the nerve. To reduce the tissue-electrode mechanical mismatch and further stabilize the probe inside the nerve, we cared to suture to the contiguous fascial structures the ceramic connector and the wire that led the tracks from the active sites outside the body. Moreover, to the aim of uncoupling any possible traction accidentally delivered to the cables with forces applied to the electrode that could result in unwanted movements or in the extraction, two loops were arranged along the cable, one outside and one inside the body. The correct realization of the latter revealed to be a crucial factor in the mechanical stability of the whole system.

Four different holes were made in close proximity of the skin incision, two medially and two laterally, in the medial aspect of the upper arm for the electrode emission (Fig. 4 C).

Finally, the fascial bands, the subcutaneous structures, and the skin were sutured.

The four transcutaneous cables represented, however, open gates to the inner structures and, obviously, easy ways for spreading infectious agents. Antibiotic prophylaxis were executed through the administration of Cefazoline 2000 mg 30 min before the surgery and 1000 mg three times each 6 h after the surgery.

Four weeks after the implantation surgery, under general anesthesia, tf-LIFEs4s were explanted. By means of the same surgical access, the nerves were re-exposed and, once all the stabilizing sutures were removed, the electrodes were extracted. The skin incision has been sutured again and the four holes closed by adhesive sticks.

2.5. Interface-prosthesis system overview

The cables, coming from the implanted electrodes through the transit holes in the skin, plugged into the stimulation/recording apparatus. It is composed by four integrated four-channel amplifiers (Grass QP511 Quad AC Amplifier System; Natus Neurology Inc.), a two-channel stimulator (Grass S88X Dual Output Square Pulse Stimulator; Warwick, RI 02886 U.S.A.), and an analog to digital converter that interacts with the robotic hand. An on board PC was dedicated for signals analysis and processing. The used cybernetic prosthesis was a stand-alone version of the CyberHand prototype, designed to achieve functionality, dexterity, control, and cosmetics. It approximates weight and dimensions of the human hand. It has 16 degrees of freedom and 6 degrees of mobility achieved by six motors, five for the fingers flexion/extension and one for thumb adduction. Fingers motors are located in a forearm-like socket, whereas thumb motor is in the palm. As for the natural hand, the transmission is based on tendons-like cables and most of the degrees of freedom are underactuated (i.e., a single motor actuates several degrees of freedom). Further description of the CyberHand prototype is available in Ref. [31]. This configuration is not wearable and was set on a desk alongside the subject (Fig. 5). To test the movement controlled by median and ulnar nerve, the prosthesis was set to perform three different grips (pinch grip for median, flexion of the little-finger for ulnar, and power grip for both nerves) and rest.

Fig. 4 – Implantation surgery. Panel (A) median and ulnar nerves approached from the medial aspect of the upper arm. Panel (B) view under the microscope of the kevlar ansa pulling the electrode inside the nerve. Panel (C) cables passing through transit holes in the skin and arranged to form a loop outside the body. (Color version of figure is available online.)

Fig. 5 – Subject performing a palmar grip with the CyberHand prosthesis set closely on a desk. (Color version of figure is available online.)
The subject underwent a preimplant training, when he was instructed to practice for delivering motor commands. With his missing hand, he had to attempt replicating the grips performed by a virtual hand presented in a video. As soon as the electrodes were implanted, the classifier training phase started. The same videos showing alternating open-relaxed hand movements were synchronized with the recording system and were exploited to communicate to the classifier which grip the subject intended to perform and the onset of the grip.

The approach used for motor signals processing was based on two processes, the extraction of selected features exploited as input to an artificial neural network and wavelet denoising and spike-sorting of the neural signal using a template creation and matching approach [32]. Support vector machines and spike-sorting of the neural signal using a template created as input to an artificial neural network and wavelet denoising on two processes, the extraction of selected features exploited by the grip. The same videos showing alternating open-relaxed hand movements were synchronized with the recording system and were exploited to communicate to the classifier which grip the subject intended to perform and the onset of the grip.

3. Results

This section addresses clinical and surgical outcomes of the experimentation. An overall summary of the results of this study is also offered. However, the full description of the achieved prosthesis control or the consequent brain plasticity is outside the scope of this article and can be found elsewhere [28,33–35]. A detailed data describing requirements, specifics, and weaknesses for electrodes, surgical procedure, prosthesis, stimulation/recording system, classifier, and clinical protocol can be found in the Table.

The implant involved a large staff and voluminous instrumentation, such as the stimulation/recording apparatus, accessing the operating theater, which required a presurgical rationalization for a proficient management of the space and a decrease of the risk of environment infectious contamination.

Among six used tf-LIFEs, four were proficiently implanted, two in the median and two in the ulnar nerve, whereas two electrodes were broken during their insertion. This means that the overall achieved success percentage was 66%. The four electrodes successfully implanted, once have been anchored, remained almost stable in situ for the following 4 weeks.

The two electrodes broken during the implantation underwent the same kind of damage, thus probably unveiling a common weakness in the design of the system. Indeed, once the tungsten needle has pierced the nerve and came out from the opposite side (Fig. 4B), the two ansae (the pulling Kevlar ansa and the ansa of the electrode) had to go through the just done hole. However, in the point where they were interconnected in a chainlinks-like mode (Fig. 2A), the overall thickness of the system became double. This produced a strong resistance to the transit and further pulling resulted in the rupture of the electrode ansa, hence making the probe no more implantable.

Except for a mild-moderate pain confined to the implantation region, lasting few days and treated with paracetamol 1 g/d, the surgical procedure did not produce any complications or side effects. The third day after surgery, the patient was discharged and further surveyed daily in the outpatient service. No fever or other systemic or local signs of infections were reported.

Soon after the surgical edema was stabilized, the patient reached an acceptable control of the robotic hand. Elaboration of neural signals achieved a very low percentage of “false positive” unwanted movement and “false negative” classifications, that is, the command evokes no movement and a high percentage of correct classified grips, which improved from 75% of d 26 to 85% of d 28, thus unveiling a growing learning effect [14,28]. Stimulation evoked reproducible sensations congruent with the territory pertinence of the stimulated nerve, although its efficacy decayed after 10 d [17,28].

Even if the technique to explant the electrodes should be far easier compared with the implant, the second surgical procedure, surprisingly, lasted almost as long as the implant. The inflammatory reaction of the tissues involved 4 wk earlier in the first surgery was responsible for the rapid formation of postsurgical adhesions, which made the dissection of muscles and fascial connective tissue harder and slower.

During the explant procedure all but one of the electrodes were found in their original location, even if lightly mobilized. The distal electrode implanted in the ulnar nerve was found dislocated and broken. It was not possible to ascertain if that was due to some manipulation during the explant or if the patient accidentally broke the electrode shortly before the procedure. All the removed electrodes, except one, which was accidentally aspirated during the surgery, were collected for further experimental evaluation of their postexplant healthy state.

The visual inspection revealed huge presence of new fibrotic tissue along tf-LIFE cables, from the electrodes to the skin, compatible with a foreign body reaction. For obvious ethical reasons, the histologic evaluation was not performed.

The training to control the movement of the prosthesis and the regaining of sensitive feedback produced clinical improvement of the phantom-limb pain suffered by the patient, a normalization of the functional representation of the hand in the contralateral hemisphere of the brain [28] and of the intrahemispheric interaction [35] and between the two hemispheres [36].

4. Discussion

4.1. Postamputation remodeling

Surgeons must always keep in mind to deal with an arm that underwent a previous amputation, often of traumatic origin. The trauma, the surgical curettage performed to stabilize the amputation or the plastic processes, which underwent the arm neuromuscular structures in the attempt to recovery from the lesion, very likely altered the anatomic organization of the region [37]. Those considerations, alongside with the high probability of the presence of neuromas sited in the more distal tracts of severed nerves, should suggest the surgeon to be extremely cautious in making the decision to implant a patient and avoid sites close to the amputation edge.
4.2. Site to implant

Access to all the three main upper limb nerves (median, ulnar, and radial nerves) cannot be gained by means of a single surgical incision along the brachium or the forearm. For instance, the surgical access to easily expose the ulnar and the median nerves in the third distal of the upper arm is mostly based on two different skin incisions, along the medial and the anterior aspects, respectively [37]. However, we opted for performing a single incision to have enough space for a comfortable insertion of the electrodes.

Several further considerations can drive the choice of the implant site. Very proximal amputations and shoulder disarticulations force the surgeon to look for the nerves in the axillary fossa at the level of the coracoid process, behind pectoralis minor, where the brachial plexus just produced its terminal branches [38]. This point of access has the advantage of easily locating all three main nerves of the arm and, if the amputation is not too proximal, likely to be spared by post-amputation remodeling. Do we know where, along the course of the nerves in the limb, neural interfaces are able to do their job better and achieve the better compromise in terms of stimulation/recording performance? Fascicles inside the more distal segment of peripheral nerves manifest a somatotopic organization, while this is not that clear for the most proximal tracts [39]. Somatotomy of the site receiving the implant is desirable because it allows maintenance of rigid organization among contiguous channels and targeted sensory-motor territories. Furthermore, we lack clear evidence in human to answer the previous question. However, the effects of intrafascicular multichannel stimulation of the upper limb nerves at the elbow and at the shoulder have been recently compared in monkeys. The selectivity of stimulation, in terms of muscle activation and somatosensory evoked potentials, showed to be comparable, but slightly higher at the elbow for all, but the ulnar, nerves [40].

In distal transradial amputation, median, ulnar, and radial nerves could be approached in several locations along the forearm. However, just below the elbow, those nerves already provided most of the terminal branches supplying the motor fibers to the hand and wrist muscles. This makes the implant targeting the upper arm preferred on those targeting the forearm. To extract motor commands useful for controlling the prosthesis, more proximal accesses have the advantage of a higher probability to contact survived fibers, innervating still functional muscles. Moreover, robotic hand pronosupination and elbow flexion-extension can be optimally controlled picking up commands from motor fibers originally devoted to biceps, brachioradialis, and pronators, which run in proximal nerve segments.

Despite that, we strongly suggest caution to implant too proximally. In the case of accidental damage to the nerve, a more proximal implant will involve greater consequences in terms of motor dysfunction and/or sensory dysesthesia.

4.3. Nerves to implant

The choice of the numbers and the nerves to implant should be driven by a strong methodologic rationale. The radial nerve could be traced with a posterior approach to the humerus by splitting the triceps, 13–15 cm proximal to the elbow joint line. For lateral approaches to the humerus, the radial nerve is located approximately 7.5–10 cm proximal to the lateral epicondyle. However, the exposure of the radial nerve at the median and distal third of the upper arm is almost invasive, due to the anatomic course of the nerve, located deep in the radial groove. The radial nerve-driven extension of carp and fingers is of paramount importance in reaching/grasping tasks, and in hand, functional electrical stimulation applications could justify the increased risk deriving from a further incision. However, this is not true in the case that the target task is the control of a robotic hand prosthesis, where the fingers flexion is controlled by the user, whereas the extension is autonomously actuated by the on board controller [33].

4.4. Insertion angle

Longitudinally implantable intrafascicular electrodes (LIFEs) have been designed to be inserted along the main axis of the nerve [41] (Fig. 6, A). Nevertheless, we found this solution uncomfortable for the surgeon, which should have pierced and extracted the needle from the same side of the nerve. This technique would imply the need of a huger dissection of contiguous structures, to make the nerves more prone to be displaced.

Similar considerations recently led to the development of multichannel electrodes designed to be implanted perpendicularly inside the nerve (Fig. 6, C) [42], thus achieving a higher selectivity of stimulation [43] with a good biocompatibility and comparable level of invasiveness [24].

However, transverse implantation could hide a major drawback. Indeed, although an accidental extraction of a longitudinally implanted probe may not be harmful, when the same pulling forces are applied to a transversally implanted electrode, it likely results in significant damage for the nerve.

4.5. Electrode stabilization

In the attempt to stabilize the electrode with the contiguous structures, we sutured the ceramic plate and the cable with the epineurium and with the contiguous connective tissue. However, it exposed the entire system to the risk of being damaged by the suturing needle. To overcome this issue, the new generation of transverse intraneural multielectrodes is endowed with dedicated slots for the suture [24].

![Fig. 6 — Different electrode insertion angles in respect to the nerve major axis. (Color version of figure is available online.)](image-url)
4.6. **Cable loops**

Often, pitfalls are hidden behind what apparently are easy steps of everyday surgery and details deserve the utmost attention. For instance, the loop that we arranged in the cables under the skin was planned to mechanically uncouple the electrode with forces applied to the portion of the cables outside the body. This common technique, often applied for surgical drains, worked perfectly in case the loop was performed upright in respect to the nerve (Fig. 7A), whereas when it was settled upside down (Fig. 7B) or along the opposite direction (Fig. 7C), the loop produced unexpected forces, which almost extracted the electrode.

4.7. **Epineural microdissection**

Biocompatibility tests of multichannel electrodes conducted in rat sciatic nerves have been performed piercing the whole compound composed by nerve and epineurium, probably as a consequence of the small dimension of this structure in rat [24,25]. Despite that, even if a careful microdissection of the epineurium could slightly increase the overall duration of the surgery, we are strongly in favor of the application of this procedure. It will preserve the probe from damages due to the transit through the resistant connective fibers proper of the epineurium and, during the insertion, allow the visualization of the underneath fascicles, impossible in human with an intact epineurium.

4.8. **Anesthesia**

Surgical procedures confined on the peripheral nerves of the upper limb and on contiguous structures are often performed with a brachial plexus nerve block, achieving a lower impact in terms of postsurgical recovery and side effects [44]. However, two main reasons push toward the use of general anesthesia in intra-peripheral nerve implant procedures: (i) the implant of such tiny devices in an often altered region can considerably increase the duration of the overall procedure, thus forcing the awake patient to sustain several hours in an uncomfortable position; (ii) the correct localization of the implanted electrode greatly benefits from an intraoperative check that, before the surgeon finally anchored the probe, needs the collaboration of the awake and feeling patient. In the case, the amount of perceived stimulations or recorded efferences is not acceptable; the electrode can still be gently moved to satisfy the criteria of a minimum number of working channels. This tricky but very helpful procedure is not compatible with the time latency and low manageability of a plexus block, whereas it can be conducted during a temporary period of lighter general anesthesia.

4.9. **Cable transit**

The duration of this experiment was kept <30 d, in accordance with the recommendation of the European Authorities inherent current delivering implantable medical devices still under scrutiny for human biocompatibility. Moreover, the reliability of the tissue-electrode contact in long-lasting implants is known to be a weakness of neural interfaces [45]. Although, from a clinical and surgical perspective, what mainly limited the duration of the experiment was the presence of cables that through holes in the skin (Fig. 4C) were plugged, outside the body, to the stimulation/recording apparatus. More than constituting a clear vehicle for the infectious contamination of area that received the surgery, their presence was perceived very uncomfortable by the patient and decreased his overall acceptability of the implant. To counteract this drawback, full implantable microelectronic systems, programmed for low consuming, to last a long time inside the body and wireless communicating with an external device, have been designed [46,47]. However, to the best of authors’ knowledge, none of them has yet reached the phase of validation in human.

4.10. **Magnetic resonance imaging compatibility**

The magnetic resonance imaging (MRI) compatibility of implantable intraneural interfaces is an underestimated topic and the literature, except for the work by Martinez-Santiesteban et al. [48], is strongly lacking of studies on the design or the application of magnetic resonance—compatible neural interfaces. However, MRI is today affirmed as the most powerful imaging method, especially when investigating soft tissues, and its applications are innumerable. Exposed to a high magnetic field, as under the scanner, a noncompatible device risks to be displaced, heated, or to deliver unwanted induced currents [49]. The very low amount and kind of conducting material used in the tf-LIFEs structure should not produce significant risks of tissue damaging nor of image artifacts. On the contrary, the loop constituted by the cables could behave as an antenna when particular resonance conditions are verified. Further efforts are needed to verify MRI compatibility of the present probes. We believe that MRI compatibility is an affordable specificity that we, as surgeons and clinicians, feel to request. This will allow to check after implantation the right location of the electrode and perform

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Fig. 7 – Cartoonish representation of the loop arranged in the cable below the skin in the correct manner (A), upside down (B), and in the opposite wrong direction (C). (Color version of figure is available online.)
We believe that, in the years we operate, most of the progresses of medicine go hand-in-hand with the innovation of the technologies developed to support them. In this scenario, clinicians and surgeons cannot be only, almost blind, final applicators of a ready-to-be-used technology. Invasive neural interfaces involve the use of multielectrodes arrays that need to be surgically implanted in the nervous system. In such an emerging field, the role of surgeons is becoming essential and being that they are the main actors of the electrode implantation procedure, we strongly recommend them to

### Table – Requirements, specifics, and weaknesses for electrodes, surgical procedure, prosthesis, stimulation/recording system, classifier, and clinical protocol.

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<td>Easiness of insertion</td>
<td>Tungsten guide needle</td>
<td>Weakness of the link between needle and electrode</td>
</tr>
<tr>
<td>Appropriateness to neural signal</td>
<td>Low impedance &lt; 10 kohm at 1 kHz</td>
<td></td>
</tr>
<tr>
<td>Large staff and voluminous instruments accessing the operating theater</td>
<td>Eight active channels (four on each side)</td>
<td></td>
</tr>
<tr>
<td>Electrodes implantation</td>
<td>66% of electrodes proficiently implanted</td>
<td>Weakness of the link between needle and electrode</td>
</tr>
<tr>
<td>Intrasurgical stimulation</td>
<td>Temporary lighter general anesthesia</td>
<td>Increased risks compared with nerve block</td>
</tr>
<tr>
<td>Post-surgical status</td>
<td>No fever or any other complication</td>
<td>Huge postsurgical adhesions</td>
</tr>
<tr>
<td>Electrode explant</td>
<td>Very long surgery</td>
<td></td>
</tr>
<tr>
<td>Electrode stability</td>
<td>One electrode was found dislocated and broken</td>
<td>Lack of dedicated structures</td>
</tr>
<tr>
<td>Anthropomorphism</td>
<td>- Size and shape of the human hand</td>
<td>Not wearable in the present configuration</td>
</tr>
<tr>
<td>- Hand weight 0.4 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tendon-like transmission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>- User control</td>
<td>Close-loop with user not validated</td>
</tr>
<tr>
<td>- Internal control of force, position and velocity with built-in sensors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation Recording system [28]</td>
<td>High signal to noise ratio</td>
<td></td>
</tr>
<tr>
<td>- Amplified factor 10,000–200,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Input noise 4 μV peak to peak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multichannels recording</td>
<td>- 16 channel parallel recording, 1 on audio</td>
<td>Not implantable</td>
</tr>
<tr>
<td>Safety stimulation</td>
<td>- Stimulation in constant current mode</td>
<td></td>
</tr>
<tr>
<td>- Compatible with the surgery room</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sterilization of the wires</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classifier [32]</td>
<td>Low training time</td>
<td>Not useful for intrasurgical recording</td>
</tr>
<tr>
<td>Low false positive and false negative</td>
<td>Correct classified grips &gt; 85%</td>
<td></td>
</tr>
<tr>
<td>Fast response</td>
<td>Analyzed several channels together Extracting features, wavelet denoising, spike-sorting, template creation, and matching approach for support vector machines</td>
<td></td>
</tr>
<tr>
<td>Clinical protocol [28]</td>
<td>Sensory stimulation</td>
<td></td>
</tr>
<tr>
<td>- Elicited tactile reproducible sensation</td>
<td>Stimulation decayed early after 10 d</td>
<td></td>
</tr>
<tr>
<td>- Modulation of frequency of stimulation progressively increases the sensation magnitude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor control</td>
<td>- Preimplant training phase</td>
<td></td>
</tr>
<tr>
<td>- Classifier training phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation of neuroplasticity [35,36]</td>
<td>- Changes before and after the training</td>
<td></td>
</tr>
<tr>
<td>Evaluation of changes in phantom limb pain [28]</td>
<td>- Improvement in phantom limb pain after the training</td>
<td>Improvement decayed after 3-mo follow-up</td>
</tr>
</tbody>
</table>
play also a major role at the stage of specifying the requirements of the interface. Invasive interfaces, indeed, further than the ability of managing high-quality neural signals, have to fulfill constraints of a stable implantation performed in a safe surgical act. In the case of the multichannel electrodes we used, they demonstrated to be capable of picking up signals with a good signal-to-noise ratio and to be safe for a 4-wk period in human. However, from the point of view of the surgeon, a critical analysis unveils the weaknesses related to the absence of dedicated stabilizing structures, the presence of the cable transit through the skin, the implant angle, and the unproven MRI compatibility, on which future developments have to focus.

Several issues regarding the type of exploited anesthesia, the number and the sites of incisions, the choice of the nerves to implant, and the convenience of performing epineural microdissection remain open.

Finally, given the increased risk connected with any experimental phase and the impossibility to furnish, at present, long-lasting and dependable solutions to our patients, ethical soundness is a pertinent topic. Hence, we strongly suggest to be extremely selective in volunteers’ enrollment, which should be finalized only after reaching a high degree of confidence that the subject has understood purposes and modalities of the experimentation and after a careful evaluation of his motivation. Motivation should be strong enough to withstand the cognitive and emotional loads deriving from two surgeries and from the tight scheduling of experimental sessions.

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This manuscripts has not been previously published in whole or in part or submitted elsewhere for review. It addresses clinical and surgical outcomes of the experimentation. The achieved prosthesis control is outside the scope of this article.

REFERENCES


