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Compliant peripheral nerve interfaces

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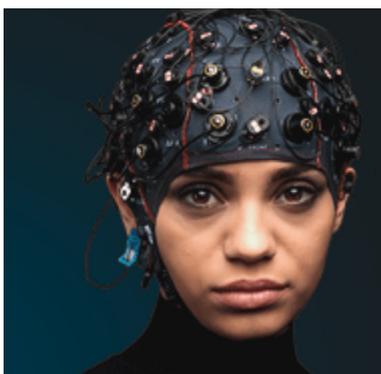
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TOPICAL REVIEW

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E-mail: silvestro.micera@epfl.ch and stephanie.lacour@epfl.ch**Keywords:** peripheral nerve interfaces, bioelectronic medicine, neuroprosthetics, flexible electronics, soft implants, nerve mechanics**Abstract**

Peripheral nerve interfaces (PNIs) record and/or modulate neural activity of nerves, which are responsible for conducting sensory-motor information to and from the central nervous system, and for regulating the activity of inner organs. PNIs are used both in neuroscience research and in therapeutic applications such as precise closed-loop control of neuroprosthetic limbs, treatment of neuropathic pain and restoration of vital functions (e.g. breathing and bladder management). Implantable interfaces represent an attractive solution to directly access peripheral nerves and provide enhanced selectivity both in recording and in stimulation, compared to their non-invasive counterparts. Nevertheless, the long-term functionality of implantable PNIs is limited by tissue damage, which occurs at the implant–tissue interface, and is thus highly dependent on material properties, biocompatibility and implant design. Current research focuses on the development of mechanically compliant PNIs, which adapt to the anatomy and dynamic movements of nerves in the body thereby limiting foreign body response. In this paper, we review recent progress in the development of flexible and implantable PNIs, highlighting promising solutions related to materials selection and their associated fabrication methods, and integrated functions. We report on the variety of available interface designs (intraneural, extraneural and regenerative) and different modulation techniques (electrical, optical, chemical) emphasizing the main challenges associated with integrating such systems on compliant substrates.

The peripheral nervous system (PNS) is the routing system of the body. Motor commands and sensory information are carried from and to the central nervous system (CNS) via the PNS. In addition, the PNS through the autonomic nervous system modulates internal physiology to maintain homeostasis, and regulates the respiration rate, heart rate, blood pressure, digestion and immune responses, among other bodily processes [1–4].

Neurotechnologies, which directly modulate and monitor activity in the PNS, have been employed for decades to treat PNS-related disorders and non-neurological conditions, and alleviate consequences of traumatic injury (figure 1) [1, 5–8]. Significant design and technological efforts have been dedicated to developing and improving implantable peripheral nerve interfaces (PNIs) that restore these impaired functions or alleviate debilitating conditions [9].

The first PNIs appeared in the late 1960s and consisted in simple lead wires or metal foils, insulated in silicone rubber, and were applied primarily to the phrenic nerve for diaphragm pacing [2, 10] and to sacral roots for bladder control [11, 12]. Since then, the spectrum of applications has widened, bringing to light specific opportunities and challenges related to different nerves and target functions in the PNS (table 1). PNIs are designed to interact with nerves of varying size and to modulate and record different types of neural activity (sensory, motor or autonomic) within a nerve or in a selected subsection of nerve structures. Additionally, recording is often occurring in the noisy innate environment of the peripheral nerves (PNs), where tiny neural signals may be shadowed by muscle activity [13, 14] or challenging to capture following PN injury [15, 16]. PNIs also need to mitigate the long and bundled anatomy of nerves,

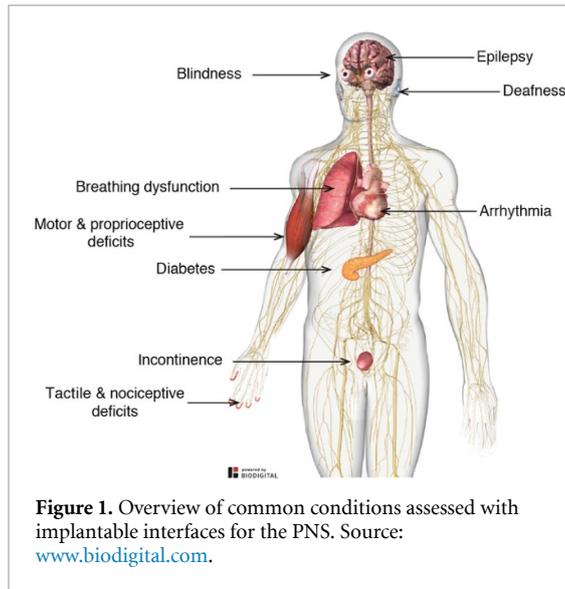


Table 1. Summary of PNI-specific functional goals and challenges.

PNI goals	
Functions	Sensory
	Motor
	Autonomic
Applications	Nerve modulation
	Nerve recording
	Nerve regeneration
PNS-specific challenges	
Selectivity	Spatial Fiber-type
Biomechanics	Dynamic and flexible system Up to 30% physiological stretch
Foreign body response	Increased immune surveillance

their dynamic environment [17], and innately high immune surveillance [18, 19]. While it is evident that multiple requirements should exist for different types of interfaces, the main common challenges consist in achieving high selectivity and a chronically stable performance, despite the structural complexity and unique biomechanics of the PNS. Consequently, in recent years, the field has evolved requiring not only expertise in neuroscience and engineering, but also in materials science to develop implantable interfaces with flexible and soft materials to minimize implant invasiveness and footprint [20].

In this review, we report on recent designs (extraneural, intraneural and regenerative) and materials for implantable and compliant PNIs that have been implemented both in *in vivo* animal models as well as in humans. We critically discuss results achieved with these techniques, highlighting intrinsic limitations and further exploring emerging solutions

that can minimize implant invasiveness, by focusing on the importance of the mechanical properties of nerves. Furthermore, we report on emerging PNI modalities, describing their possible advantages over conventional electrical devices and their integration within flexible substrates. We conclude on the remaining challenges and opportunities for the development of long-term and high resolution PNIs.

1. The peripheral nervous system

1.1. Anatomy and organization

The PNS conveys information between the CNS and the rest of the body, innervating specific targets such as organs, muscles or specialized sensory receptors. A typical PN consists in the axonal prolongation of multiple neuron bodies located in the spinal cord or spinal ganglia. Figure 2(a) illustrates the highly heterogeneous structure of a PN. Afferent and efferent signals travel through myelinated and unmyelinated axons that are individually embedded in a delicate tissue called endoneurium and are organized in bundles known as fascicles. The sinusoidal path of axons within their respective fascicles offer a great tolerance to stretch [21]. This feature also confers the dark-bright striped look characteristic of nerves, called bands of Fontana (figure 2(b)).

Each fascicle is kept together by a thin, yet tough and dense, connective tissue layer, the perineurium, that provides mechanical and biological protection from external agents. The perineurium forms the so-called ‘blood-nerve barrier’ (BNB), that biologically seals the fascicular environment, regulating protein diffusion and blocking external pathogens thanks to a slightly positive inner pressure [22]. Finally, multiple fascicles are bundled together by the epineurium, a loose areolar tissue that confers additional mechanical protection to the nerves, especially when close to articulation joints. The fascicles ensheathed in the epineurium split and merge with each other while travelling along the body: originating from the ganglia, nerves are initially constituted of a single fascicle, which branches out distally while reaching target locations and organs.

PNs receive nutrients through a dense and complex network of blood vessels and capillaries. These blood vessels run along the surface of the nerve and, thanks to multiple septa, penetrate all connective tissue layers to nourish the entire structure. To ensure proper blood supply during nerve stretching, the capillaries and the larger vessels are characterized by undulated, looping and redundant structures that minimize the risk of flow blockage [23].

In terms of organization and classification, fibers within the PNS exhibit different properties according to their role: motor, sensory or autonomic. Specifically, fiber diameter (0.2–20 μm), degree of myelination, conduction velocity (0.5–120 m s^{-1})

and function have been shown to be strictly correlated [24, 25] (figure 2(c)). Large myelinated efferent motor fibers ($A\alpha$ and $A\gamma$) are responsible for control of the musculoskeletal system. In the somatosensory system, large myelinated afferents ($A\alpha$ and $A\beta$) carry proprioceptive and mechanical information, while small thinly myelinated ($A\delta$) or unmyelinated (C) fibers are mainly responsible for transmitting thermal and noxious stimuli. Finally, small fibers (B and C) in the autonomic nervous system innervate smooth muscles regulating vital organs and providing information on the body's internal state. Fiber conduction velocity as well as excitability are influenced by fiber diameter (axonal resistance decreases with increasing diameter). Furthermore, the presence of myelin sheath on large fibers leads to a rapid saltatory conduction between nodes of Ranvier. In these sites, a high concentration of ion channels also contributes to an increase in the fiber excitability. As a result, large myelinated fibers have lower stimulation threshold compared to small unmyelinated ones, for comparable distances from the electrode site. In the same manner, large fibers generate higher amplitude action potentials (APs), meaning that these can be stimulated and successfully recorded from using less invasive electrodes [26].

Due to the complex anatomical and functional organization of the PNS, one of the main challenges in PNI design is to devise strategies to target different structures (i.e. whole nerve, multiple or single fascicles, multiple or single fibers) and functionalities (i.e. different fiber size), while also considering the implant's stability and efficacy in a mechanically dynamic environment.

1.2. Peripheral nerves and target disease

As PNs are involved in the regulation of a wide variety of functions across all areas of the body, naturally a significant number of clinical uses have emerged and different disorders can be treated through PNIs.

PN stimulation of motor nerves in upper (e.g. median, ulnar) or lower limb (e.g. sciatic, femoral, tibial) can be applied to paralyzed patients suffering from spinal cord injury (SCI), aiding with functions such as standing, walking or grasping [29–31]. Sacral motor roots are also a classical structure to modulate in view of restoring bladder function and erection following SCI [11, 12].

Among the spinal and cranial nerves, the phrenic nerve can be stimulated to regulate motor control of the diaphragm [10], while the vagus nerve is the most common target for clinical applications, as it drives a large number of autonomic functions. Treatment of epilepsy and depression are already implemented in the clinic and a new set of therapeutic applications are emerging for vagus nerve stimulation (VNS). These include stimulation for the alleviation of autoimmune and inflammatory disease, such

as rheumatoid arthritis [32], treatment of heart failure [33], obesity [34], improvement of sensory function after stroke [35] and enhancement of auditory processing in the case of tinnitus and hearing loss [36]. For a more comprehensive overview of emerging therapeutic applications of VNS we refer the reader to Guiraud *et al* [1].

Stimulation of the optic nerve has shown some promise in restoring vision in the blind [37]. Finally, neuromodulation of PNs to alleviate neuropathic pain has been implemented for more than 50 years, using various targets and with variable outcomes [5].

Efforts in recording from PNs have been dedicated to monitoring sensory and motor information. Signals from upper and lower extremities provide feedback control to prosthetic or paralyzed limbs [38–40], while afferents in the sacral roots can instead be used to aid in bladder voiding. Lastly, recordings from autonomic nerves can give insight on the body's internal state and may act as biomarkers for different pathologies: activity from the vagus nerve has been shown to be correlated with respiratory cycle and blood pressure [41, 42], while metabolic information derived from the carotid sinus nerve can be useful to treat type 2 diabetes [43].

1.3. Biomechanics

The PN's structure has evolved to guarantee robust transmission of information under external stresses due to motion, trauma or diseases. In particular, the nerves routed in highly motile areas of the body, such as limb joints, need to withstand repeated elongations of up to 30% while being constantly sheared and compressed by the nearby contracting muscles [17].

PNs are heterogeneous anisotropic structures and, similarly to other tissues in the body [44], they display highly nonlinear and viscoelastic properties, stiffening at large strains, and they present stress relaxation behaviour when stretched. Moreover, like other organs, the behaviour at the microscopic level does not translate linearly to the whole nerve, making mechanical studies also scale-dependent [45].

Table 2 reports on the mechanical properties of PNs, characterized with different experimental methods and at multiple scales, from whole structure to single axon.

Until recently, the characterization of the mechanical properties of nerves has been primarily reported in studies in physiotherapy and post-traumatic rehabilitation surgery, focusing therefore on characteristics of the whole nerve such as the stiffness under large strain, tensile strength and transversal compression limits.

Yet, the design of a long-term PNI calls for a finer understanding of the nerve biomechanical properties. It is anticipated that a miniaturized PNI with matching nerve compliance would offer long-term stability and function.

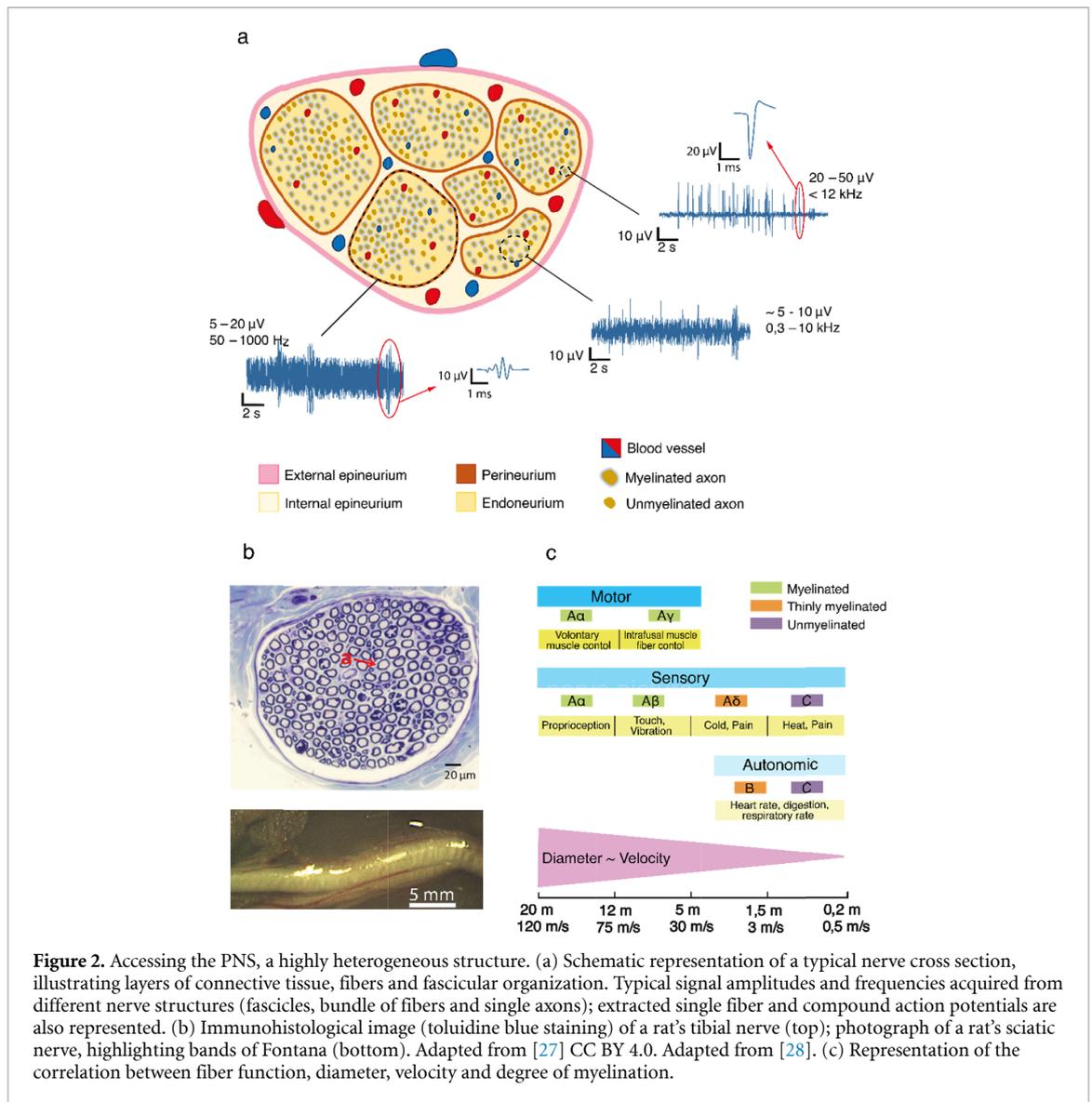


Figure 2. Accessing the PNS, a highly heterogeneous structure. (a) Schematic representation of a typical nerve cross section, illustrating layers of connective tissue, fibers and fascicular organization. Typical signal amplitudes and frequencies acquired from different nerve structures (fascicles, bundle of fibers and single axons); extracted single fiber and compound action potentials are also represented. (b) Immunohistological image (toluidine blue staining) of a rat's tibial nerve (top); photograph of a rat's sciatic nerve, highlighting bands of Fontana (bottom). Adapted from [27] CC BY 4.0. Adapted from [28]. (c) Representation of the correlation between fiber function, diameter, velocity and degree of myelination.

When defining the mechanical properties of a PNI, considerations on the size, target and function of the PNI itself are required. For example, in the case of a cuff PNI that encases the nerve, what is the maximal circular compression tolerable before causing ischemia [46]? At which speed and angle should a penetrating PNI be inserted in the nerve so that minimal damage is induced [47]?

Three different mechanical models have been reported in the literature to approximate the behaviour of nerves: linear elastic, viscoelastic, and hyperelastic, always considering the nerves as isotropic materials. The linear elastic approximation implies direct proportionality between strain and stress, defining an effective Young's modulus as measure of the nerve stiffness. Viscoelasticity and hyperelasticity models offer a more accurate view of the nerve mechanics [48, 49]. Viscoelasticity introduces time dependence, implying strain-rate dependent stiffness. Hyperelasticity instead accounts for

non-linearly elastic behaviour, thus strain-dependent stiffness.

To date, reported mechanical properties of the PN vary and strongly depend on the characterization method, illustrated in figure 3, scale of measurement, type and age of the animal model [50], and health condition [51] (table 2). For instance, macroscopic tensile measurements on the whole nerve report effective moduli in the range of tens of MPa [52–54]. The Young's moduli obtained with this technique span more than three orders of magnitude, indicating the sensitivity of the results to the selected protocol. Furthermore, microscopic probing of the nerve with atomic force microscopy (AFM) indentation indicates local (endoneurial), age-dependent, stiffnesses in the order of tens of kPa [50].

Fewer time-dependent mechanical characterization results are available, especially regarding the nerve's subcomponents. Endoneurium and perineurium are extremely thin and delicate tissues, requiring

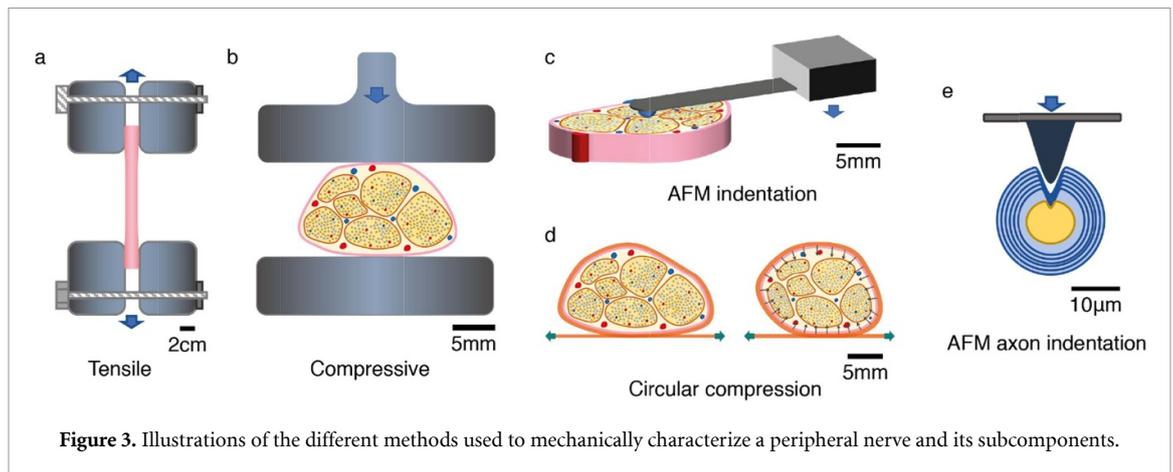


Table 2. Experimental measures of the biomechanical parameters of peripheral nerves. Characterisation methods are illustrated in figure 3.

Tissue	Animal model	Mechanical model	Value	Method	Ref
Whole nerve	Rabbit—sciatic	Linear	$E = 66.9$ kPa	Circular compres.	[46]
	Rat—sciatic	Linear	$E = 580$ kPa	Tensile	[55]
	Pig—tibial	Linear	$E = 7.43$ MPa	Tensile	[52]
	Rat—sciatic	Linear	$E = 13$ MPa	Tensile	[53]
	Human—median	Ogden	$\mu = 19$ kPa, $\alpha = 50$, $g = 0.37$, $\tau = 27$ s	Tensile	[49]
	Rat—sciatic	Linear	$E = 24.4$ MPa	Tensile	[54]
	Pig—sciatic	Linear	$E = 21.188$ kPa	Tensile	[56]
	Human—median	Ogden	$\mu = 12.9$ kPa, $\alpha = 6.5$	Compressive	[48]
	Rat—sciatic	Linear	$E = 772.8$ Pa; 4387 Pa ^a	Compressive	[47]
Perineurium	Rat—sciatic	Ogden	$\mu = 89$ kPa, $\alpha = 8.99$	Compressive	[57]
Epineurium	Rat—sciatic	Ogden	$\mu = 22$ kPa, $\alpha = 8.4$	Compressive	[57]
	Rat—sciatic	Linear	$E = 140$ Pa	AFM indentation	[58]
Endoneurium	Rat—sciatic	Ogden	$\mu = 55$ kPa, $\alpha = 6.95$	Compressive	[57]
	Rat—sciatic	Linear	$E = 390$ Pa; 131 Pa; 226 Pa ^b	AFM indentation	[50]
Myelin axon	Mouse—sciatic	Linear	$E = 31.4$ kPa; 55.8 kPa ^c	AFM indentation	[59]

^a Values measured by slow compression and small strain ($0.44\% \text{ s}^{-1}$, 0%–20%) and fast and large compression (1.3%, 20%–30%).

^b Values measured from rats 7, 30, 170 d old.

^c Values obtained applying compressive forces of 25 nN and 75 nN

Linear = Linear elastic model, Ogden = Ogden hyperviscoelastic

E : Young's modulus, g : Prony material constant, μ : Low-strain slope, α : High-strain curvature, τ : Relaxation time.

careful dissection and expensive microscale tools for characterization.

It should be also noted that these are difficult and time-consuming experiments to conduct, both in terms of access to the tissue and experimental method, which may account for the results heterogeneity. Furthermore, these isotropic models can offer a limited approximation of the nerve's anisotropic mechanics, especially at large strains and strain rates. Mechanical characterization along different directions is extremely challenging as it requires careful tissue handling and high spatial resolution tools such as AFM. However current finite element modelling (FEM) models,

although simplifying reality, have shown the possible benefits of numerical simulations for a better understanding of the interaction between nerve and PNIs.

Current PNIs are macroscopic devices with sub-millimetre features and therefore interact with the nerve at multiple levels. We believe further efforts are needed to better quantify the biomechanics of the nerve, especially given its structural (endoneurium, perineurium, epineurium, whole fascicles and nerves) heterogeneity [56, 60], and the variety of interface approaches (cuff vs penetrating). The difference between *in vivo* and *ex vivo* mechanical properties strongly depend on experimental conditions that

include the nerve storage protocol, time after explantation, hydration and temperature during measurements, and point to a need for more uniformity across the community.

We believe it would be extremely valuable to define standard characterization protocols, focusing on the most biologically relevant quantities needed for a better understanding of the implant–nerve relationship.

2. Challenges

Devices for PN stimulation and recording are among the most established and successful neural interfaces both in clinical practice and preclinical research. However, most available devices lack accuracy in stimulation and recording and can, for instance, cause unwanted motor or sensory side effects because of limited fascicular or fiber resolution. Furthermore, early failure can occur due to issues such as lead migration, breakage and infection [61], which are to be attributed to mechanical and biological aspects of the interfacing mechanism. Therefore, when designing PNIs, operating mechanisms as well as material selection should be guided by the need to address specific challenges, namely: selectivity, foreign body reaction (FBR) and device longevity, as summarized in figure 4.

2.1. Selectivity/resolution

Depending on the nerve size and animal model, the number of axons in a nerve ranges from hundreds to tens of thousands. While one-to-one (axon-electrode) interfacing is the ultimate concept, current PNIs only offer modest selectivity. The latter can be classified into two categories: spatial and functional [62]. The first refers to the ability to interact with fibers in a predefined and limited volume, while the second indicates the possibility to interact with only a single type of fibers, such as proprioceptive ones. The ability to selectively interact with fibers is therefore dependent on the technology and interaction modality.

PNIs dialogue with nerves via transducing sites, e.g. electrodes or light sources. An obvious technological solution to improve selectivity is therefore to increase the density of active sites in the PNI. However, technical and physical barriers limit the number of sites that can be integrated in a single device. Localized stimulation can be further achieved by exploiting multipolar configurations. For instance, tripolar electrodes that present evenly spaced rows of three contacts, can generate modulated transversal and/or longitudinal currents, targeting more superficial fascicles [63, 64].

In the case of recording, spatial selectivity is favoured by placing electrodes in direct contact with the fibers of interest. Compound signals from fascicles can be detected outside of the nerve, while

signals from small groups of fibers to single fiber require progressively more invasive solutions which can directly access the target structures (figure 2(a)). In particular, the proximity of the electrode to the nodes of Ranvier or the axon membrane is critical to record single fiber APs, especially given the conductive nature of the extracellular medium and the high density of axons packed into a nerve.

Functional selectivity relies on the ability to reach only one specific fiber type. This is challenging both in stimulation and recording modalities.

Fiber excitability is a function of the inverse of its radius [65], therefore larger fibers are inevitably stimulated when targeting smaller ones. Methods to ensure diameter-specific selectivity include designing optimized stimulation waveforms [66] or using high frequency stimulation to block either small or large fibers by modulating amplitude and frequency ranges [67, 68].

In terms of recording, distinguishing between different fiber types mainly relies on the amplitude of the extracellular electric field to be detected. Less invasive solutions are typically able to record compound APs from large myelinated fibers, while more invasive ones are required to detect the activity of small unmyelinated fibers [26]. Other techniques rely on post-processing of the signal. For example, the velocity of a signal can be extrapolated from multiple electrodes along the length of the nerve and can then be used to discriminate the different source fibers [69, 70]. However, these methods are primarily employed to detect evoked APs and not spontaneous activity. Functional electrical recording is also hindered by noise originating from nearby skeletal muscles. For this reason, electrode arrangement and placement, in particular the reference electrode, is critical to decouple neural and muscular signals and achieve higher signal-to-noise ratios (SNRs) [71, 72].

Modelling of signal propagation along nerves is a powerful tool to better understand and predict where to locate electrodes and how to tailor PNI designs. For example, FEM models have shown the effect of different electrode configurations and recording modalities on the reduction of artifacts derived from external sources such as muscles [72, 73]. Schiefer and colleagues have used FEM to derive the minimum number of extraneural electrodes to selectively stimulate axons and achieve individual activation of ankle muscles on paralyzed patients [74]. Numerical models have also analysed the effect of different waveforms on the stimulation selectivity, as thoroughly described by Grill [75]. Combining mathematical models of neurons and FEM studies, it has also been possible to obtain detailed information about the effect of electrode number and placement inside nerves, to then deliver accurate proprioceptive and sensory information through prosthetic limbs [76–78].

2.2. Foreign body reaction (FBR)

Implantation of a man-made interface in the body triggers an immune response, often called FBR. Implantation is followed by bleeding and protein absorption on the implant's surface, triggering the migration of immune cells, mainly fibroblasts and macrophages. These adhere to the device and secrete collagen and degradative agents, such as reactive oxygen species (ROS), to respectively isolate and damage the foreign material [79]. On the long term, multiple layers of fused macrophages (multinucleated giant-cells) accumulate around the implant, creating a dense fibrotic capsule that isolates the device from the host.

In the case of PN implants, the intensity of the adverse reaction is most pronounced when the BNB is breached, for instance when using invasive PNIs, such as intrafascicular or regenerative devices. Scarring is most pronounced at the entry and exit sites of the implant and often leads to significant increase in nerve volume during the first month post-implantation [80].

Deciphering the mechanisms for FBR in PNIs is an active field of research. Many parameters are known to trigger and maintain FBR, e.g. penetration trauma, material biocompatibility [84] and stress/strain induction due to the mechanical properties mismatch [85]. Sections 4.2 and 5.2 are dedicated to the strategies to reduce the FBR through different interaction mechanisms, drug eluting devices and soft biocompatible materials.

2.3. Longevity

PNI targeting lifelong applications, such as chronic pain relief or bionic limb control, require high stability possibly over multiple decades.

Like most implantables, they are continuously exposed to 'harsh' biological conditions: operating in a wet, warm and dynamic environment, they must guarantee selectivity and signal quality both when recording and stimulating.

Longevity is hindered by the FBR process, during which immune cells secrete ROS and proteolytic enzymes [86] to attack the implant: secreted chemicals such as peroxides can erode metallic electrodes and deteriorate insulators and substrates, potentially causing mechanical and/or electrical failure.

Flexible and stretchable implants, fabricated using thin film technologies or organic polymers, are further susceptible to ROS-mediated corrosion: bridging between electrodes, circuit opening and mechanical cracks are some of the potential issues that can present when using microfabricated implants [87].

Electrical stimulation also contributes to the degradation of metallic electrodes, as non-reversible electrochemical reactions may occur when injecting high currents [88, 89]. This effect is worsened by the FBR, as threshold currents increase over time due

to the growing scar tissue interposed between electrode and axons. In turn, dangerous chemical species released due to corrosion can worsen the immune response, resulting in a deleterious feedback loop.

As a solution, different active site sizes and materials have been developed to improve the stimulation performance by reducing threshold voltages and increasing the electrodes' chemical stability with coatings [48].

Moreover, PNIs placed on highly motile areas such as limbs are subject to continuous mechanical stresses due to the surrounding active musculoskeletal system [90]. This is worsened in the case of wired implants, as the connected cables can be another source of pulling forces [91].

The repetitive bending, stretching and twisting during the operation of the device can therefore cause mechanical failure at the electrode or connector level [92].

While current literature provides numerous examples of stability studies using extraneural electrodes, fewer are available when considering intraneural electrodes. The most recent study on the stability of intraneural implants, by Čvančara and colleagues, provides a useful insight of the stability of polyimide (PI)-based implants after 30 d of implantation in humans and rats [87]. Their results point out delamination between the substrate and the metallic electrodes over time and offer a potential solution with the use of a silicon carbide adhesion layer for >30 d stability.

3. Devices and technologies

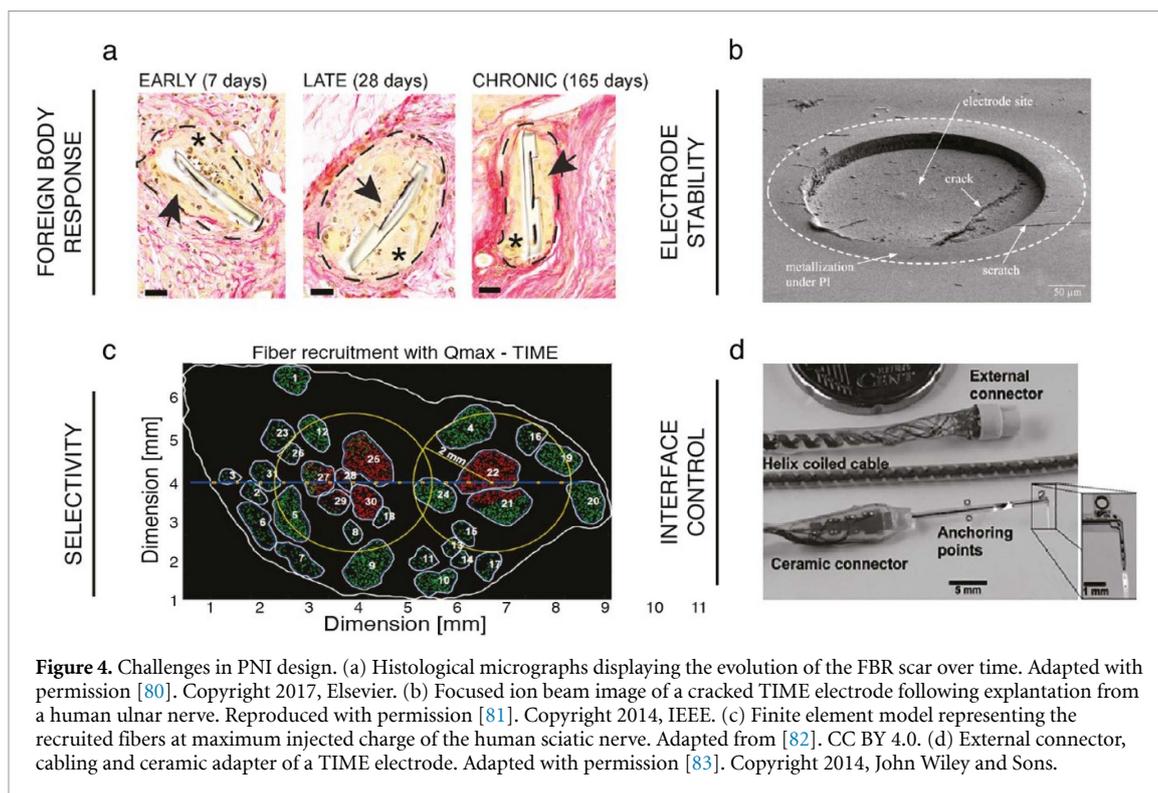
PNI can be classified based on their placement with respect to the nerve or on the mechanism used to interact with it. Modalities of interaction with peripheral axons are primarily electrical, chemical or optical.

3.1. Electrical interfaces

Electrical PNIs rely on the recording of extracellular APs and/or the stimulation of neural activity through modulated electrical fields. Therefore, the interaction between axons and implants is regulated by the physics of electric fields that propagate through space as a function of electrical permittivity and conductivity.

The electrical properties of PNIs have been characterized thoroughly also to enable the development of lumped electrical models and therefore realistic FEM simulations. Some of the key properties are the conductivity of the extracellular matrix (ECM) in the range of 10 mS cm^{-1} , the conductivity of an axon's core of about $70 \Omega \text{ cm}$, and the resistance and capacitance of the myelin surrounding the axons, that are about $2.8 \text{ M}\Omega \text{ cm}^2$ and 2 pF cm^{-2} , respectively [93].

Electrical fields are generated through currents or voltages applied on electrodes, that consequently induce the motion of extracellular ions until APs are



triggered. Conversely, the ion fluxes constituting the natural APs generate localized transient electric fields that are picked up by the implanted electrodes.

The nature of electric fields is such that selectively stimulating or recording the activity of axons is facilitated when electrodes are in their close proximity. For this reason, multiple interface designs have been proposed to access different nerve structures, from the fascicle to the single axon level.

In the following section, we present the current state of the art in electrical PNIs, with a focus on those established technologies that have been used in chronic experiments (from multiple months up to several years). Figure 5 illustrates the main design options.

3.1.1. Extraneural

Extraneural implants surround the nerve's epineurium, interacting with the neuronal tissue proximal to the outer surface of the nerve. This design is minimally invasive, as the nerve remains intact, but suffers from poor selectivity because of the multiple tissue layers interposed between axons and electrode(s).

Cuff electrodes are the most common device format: they fully encircle the nerve, both for interfacing and mechanical anchoring. Cuffs are usually built using flexible substrates (with flexural stiffness in the order of tens of kPa) [20]: silicones, PI and other polymers are the most commonly used materials together with thin film metals.

Different geometries have been developed taking into account PNI fabrication methods, insertion,

locking in place around the nerve, and electrode-nerve proximity. Different designs and materials therefore influence the implantation protocols and the long-term performance of the device, affecting parameters such as SNR and scarring [94].

The earliest [95] and simplest geometry consists of split-cylinders: the nerve is gently laid into the tube held split open and secured in place upon closing of the cuff. The split cylinder cuffs can integrate sutures, and rely on stiff backings [96] or chemical adhesives for locking into place and long term positional stability.

Spiral cuffs instead rely on the elasticity of the implant carrier material, e.g. silicone, to be wrapped around the nerve. This curling design allows a tight fit with a wider range of nerve diameters without the need of sutures or adhesives to secure the device [97]. Helix-shaped cuffs wrap around nerves in a corkscrew fashion and can be fixed using suture threads. As with spiral cuffs, this format accommodates a range of the nerve's diameter and local motion. Thanks to their open geometry, these PNIs are implanted easily, however, they also present a risk of excessive tightening around nerves due to tethering and pulling forces.

An interesting extraneural design that has proven successful in multiple translational studies is the flat interface neural electrode (FINE), designed by Tyler and Durand [98]. The FINE exploits the compliance of the nerve, increasing the contact surface with the implant by compressing the circular nerve into a flat elliptical shape. Overall, the FINES have shown improved selectivity with respect to standard circular cuffs while causing a mild FBR attributed to the

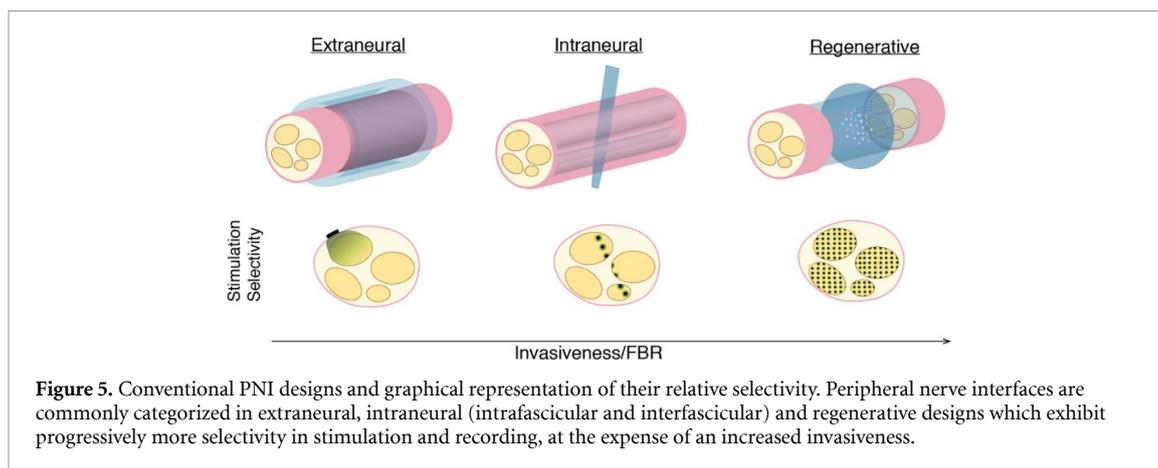


Figure 5. Conventional PNI designs and graphical representation of their relative selectivity. Peripheral nerve interfaces are commonly categorized in extraneural, intraneural (intrafascicular and interfascicular) and regenerative designs which exhibit progressively more selectivity in stimulation and recording, at the expense of an increased invasiveness.

compressive neuropathy. FINE devices of different sizes and electrode configurations have been successfully used chronically in a wide range of animals [30, 99, 100] and also in humans [101–103], both to stimulate and record the activity of PNs.

More recently, a new category of extraneural interfaces have emerged, relying on novel materials or original geometries, in order to improve anchoring to the nerves. These fill the gaps left by other standard cuffs, targeting the more delicate and small nerves (<200 μm in diameter) or simplifying the fabrication and implantation processes. An example is the paperclip-inspired wireless electrode developed by Lee and colleagues [104], that enables stimulation of small nerves such as the rat's pelvic nerve. Others used adhesives to either quickly lock the nerve inside a groove [105] or to easily and directly adhere the electrode onto the nerve itself [106, 107].

3.1.2. Intraneural

Intraneural interfaces penetrate the nerve, placing the active sites closer to the axons, and are commonly classified based on the position relative to the fascicles.

Interfascicular implants, the least common in literature, penetrate the epineurium placing active sites in the interfascicular space, ideally in contact with the perineurium. These devices provide a trade-off in performance and invasiveness: the sole breaching of the epineurium does not damage significantly the nerve functioning [23] while the vicinity to the fascicles allows for a reliable interaction with the adjacent fibers.

Tyler and Durand have developed a slowly penetrating interfascicular nerve electrode (SPINE) [108], that consists of a cuff integrated with protruding fin-like structures intended to pierce through the epineurium and settle close to internal fascicles. The SPINE device has shown promising results, with increased selectivity and reduced FBR. However, no further studies have been showcased using this device.

Intrafascicular electrodes penetrate all of the nerve's protective layers, breaching epi-, peri- and

endoneurium, potentially damaging axons and blood vessels during the insertion procedure. These implants enter the fascicles to minimize the distance between their active sites and axons, offering high SNR and fiber selectivity while causing a harsh adverse immune reaction as the BNB is compromised [109]. The reference rigid counterpart is the Utah Array (both standard and slanted), which achieves high spatial resolution at the expense of a harsh FBR [110].

One of the first examples of flexible intrafascicular implants is the thin-film longitudinal intrafascicular electrode (tf-LIFE) [111], that consists of a double aisle electrode array based on a PI substrate that is pulled longitudinally through a chosen fascicle using a needle with a loop of suture thread. Each tf-LIFE is implanted in a single fascicle, therefore multiple devices are needed to interact with nerves with a complex fascicular organization, such as the vagus nerve in humans and pigs.

tf-LIFE electrodes have been tested in rats for up to 3 months, showing a mild functional decline in the first month attributed to the implantation trauma, followed by a recovery to normal values in the following 2 months [112]. Histological studies at the end of the 3 months period have shown mild FBR reaction and ongoing inflammation associated with the harsh implantation and stresses due to the mechanical mismatch between implant and nerve. A variant of the tf-LIFE electrode, developed by Bossi and colleagues, includes thin film shape memory alloys (SMA) to enable thermomechanical electrode actuation [113]. By applying a current through the SMA tracks, it is possible to selectively move and therefore optimize the position of any electrode with respect to the nearby fibers, finally improving the device's selectivity.

The transversal intraneural multichannel electrode (TIME) design is inspired by the tf-LIFE except for the implantation direction, that is perpendicular with respect to the nerve's orientation [114]. This approach allows for the targeting of multiple fascicles using a single device, reducing therefore complexity

and allowing bionic limb control and other neuro-prosthetic applications with fewer implanted devices. In fact, TIME implants have been used extensively both to record and stimulate neural activity in chronic animal models and in acute mid-term human studies, for example in the context of a prosthetic leg with sensory feedback [76, 115] and bidirectionally controlled bionic hands [78]. Chronic studies of the FBR evolution have shown that TIMEs induce an immune response that stabilizes over time, therefore allowing reliable operation of the device for long-term implantation [116]. However, one of the drawbacks of TIMEs is the tendency to reposition themselves within the nerve, hindering the reliability of the signal in chronic settings [62].

Also, TIME devices with embedded integrated circuits have been developed to increase channel count through multiplexing and to improve recording quality through *in situ* analog amplification [117].

Self-opening intraneural peripheral interfaces (SELINES) are another evolution of the TIME: three-dimensional (3D) shanks protruding out of the main shaft provide improved mechanical anchoring and nerve coverage [118]. As in the case of TIME electrodes, SELINES are easily implanted by pulling with a needle and suture loop. However, such 3D designs are particularly suited for large nerves that offers sufficient space for the deployment of the lateral wings. Furthermore, one study indicates that the 3D design provides stable integration and axon selectivity following 1 month implantation, showing promise for future long term applications [80].

A challenge yet to be addressed in the design of intrafascicular electrodes is the application to small nerves, for which implanting through needle and suture may be quite destructive. Such designs call for innovation in materials and implantation techniques to further open up the road to precision neuroprosthetics.

3.1.3. Regenerative/sieve

Regenerative implants establish a bridge between the proximal nerve and distal connections of a transected nerve. They leverage the natural propensity of axons to regrow when cut. These PNIs are surgically inserted between the distal and proximal parts of the sectioned nerve. They support axonal growth through a tubular or sieve structure which may vary in diameter and length, and embed an electrode array. Ultimately, regenerative PNIs should allow for single fiber selectivity but this is hindered by the intense immune reaction and scarring following nerve repair intervention.

Different geometries and approaches to regenerative PNIs have been developed, using 2D and 3D electrode architecture.

Sieve electrodes consist of a flat array of contacts through which axons are forced to regrow. The advantage of using this format is its planar

design compatible with microfabrication techniques and selectivity. These implants are placed orthogonally to the nerve's length and are either sutured directly on the epineurium or are supported by tubes that hold onto the nerve itself. Multiple configurations have been exposed in literature, using perforated arrays [15, 119, 120] and slotted structures [121]. To increase the number of addressable electrodes for recording and stimulation, sieves have been also integrated with analog multiplexers [122]. A key parameter is the implant transparency, that is the ratio between the geometrical area of the entire device over the hollow surface of the electrodes. Larger transparencies favour regrowth but offer limited mechanical stability and electrode density [123].

An alternative design is the 'theta' design that consists of a hollow tube matching the nerve diameter and a flat ribbon with double-aisle electrodes that is centred in the tube mid-plane. As fibers regrow, electrodes can pick-up their activity [123]. Electrodes oriented in this direction can be considered mechanically transparent to the regrowing nerve and therefore favour natural regeneration. However, the natural disposition of regenerating neurons to avoid the implant walls often limits intimate electrode-axon contact or proximity [124].

A 'biomimetic' design is the third category of the regenerative PNIs: the implant consists of a bundle of 3D microchannels which host one or several electrodes spread along the channel length. Axons regrow along and within the microchannels to form 'mini-nerves'. The 3D structure is prepared using microfabrication and additive manufacturing techniques to form stacks or rolled implants [125–128].

Recently, investigators have developed devices increasing the number of controllable electrodes through the integration of integrated circuits [129]. Although no *in vivo* studies have been performed yet, these devices represent a first step towards massively dense implants that could enable new applications in neuroprosthetics.

3.1.4. Hybrid PNIs

A range of PNIs does not fall in any of the previously mentioned designs. These devices are meant to combine the advantages of different geometries, improving selectivity, increasing channel count and attenuating the FBR.

An example is the aforementioned SPINE, since active sites are placed on the extraneural part of the device making it a hybrid cuff-plus-interfascicular implant.

Fascicle-specific targeting of longitudinal intrafascicular electrodes (FAST-LIFEs) integrate the functionalities of a LIFE and a perineurial cuff device. FAST-LIFEs have been implanted in four human amputees, stimulating and recording from motor and sensory fibers localized in separate fascicles. Thanks to the specific intrafascicular nature of the implant,

it has been possible to achieve both spatial and functional selectivity. However, the implantation procedure appears to be more complicated with respect to other standard devices, requiring careful excision of the epineurium and clipping of the cuff around smaller and more fragile individual fascicles [130].

The cuff and sieve electrode (CASE) [131], an implant whose name is self-descriptive, exploits the tubular support present in regenerative implants by integrating additional extraneural recording sites on it. While CASEs are still very invasive because of the regenerative aspect, they can be easily implanted and can provide immediate recording feedback once in place thanks to the extraneural part.

3.1.5. Limitations of electrical PNIs

Electrical interfaces are the conventional choice for stimulating and recording from the PNS but they present some inherent limitations.

Neural tissues are good yet heterogenous conductors, which leads to current spread. For instance, Nicolai and colleagues described important side effects due to current spreading and undesired activation of fibers near the vagus nerve using helical cuff implants [132]. As a consequence, electrical stimulation suffers from a well-known selectivity-invasiveness trade-off, as previously introduced and summarized in figure 5.

Smaller electrodes could improve spatial resolution, although this would result in increased interfacial impedance and therefore higher stimulation amplitude requirements that can cause deleterious electrochemical reactions on the electrodes' surface [133]. In terms of recording, the measured extracellular signal decreases significantly with increasing distance between electrode and membrane/axon, due to the conductive nature of the extracellular medium acting as a shunt. For the same reason, electrodes also cannot avoid capturing signals from nearby sources such as other axons and surrounding muscles. While smaller electrodes could allow for more localized recordings [134] and denser packing, they also increase the interfacial impedance, deteriorating signal quality by worsening the SNR [135, 136]. In section 5.2 different material strategies to overcome this trade-off are briefly described.

As a result of these limitations of electrical interfaces, research has also focused on optimizing new techniques based on different stimulation and interfacing modalities.

3.2. Non-electrical interfaces

Optical, chemical, thermal and ultrasonic (US) strategies are studied as an alternative or complement to electrical peripheral neuromodulation. Significant work has been done to test optical, thermal and US mechanisms *ex vivo* and in acute settings with exposed nerves [137–141], while the effects of pharmacological agents has been exploited in the clinic

for years, mainly to achieve nerve conduction block with local anaesthetics [142].

One advantage of optical and US stimulation is that they can be delivered non-invasively using transcutaneous techniques [143–145]. Recent reports on US stimulation have shown that it is possible to non-invasively focus on PN terminations, which are difficult to access with implantable devices, directly targeting end-organs (e.g. spleen, liver) and thus reducing the risk of off-target effects [146–148].

Pharmacological agents are typically administered through injections, which directly target the nerve [149]. These methods, while non-invasive, suffer from poor spatial resolution and are not ideal for *in vivo* experiments. For instance, transdermal optical stimulation, performed via a laser, is often limited to superficial nerve endings [150, 151], as the light scatters within the tissue and can prevent the stimulation of deeper targets. In the case of pharmacological nerve block, syringe injections can be especially complicated as animals need to be restrained and small movements during the procedure can cause damage to the nerve [152]. By instead using flexible implantable devices, a more precise, localized and repeatable delivery may be achieved. Currently, chemical, optical and thermal PNIs have been developed, while the use of ultrasounds has been limited to a data and power transfer method for wireless implantable systems [153], and not as a sensing or stimulating technique. The fundamental mechanism through which ultrasounds interact with neural tissue is still unclear, with most theories being explored either through modeling [154] or acute experiments on exposed nerves [155, 156], which have often provided conflicting results. These are typically performed using conventional US transducers, while miniaturized systems integrated within a flexible device have only recently been developed but remain to be tested *in vivo* [157]. Such systems could potentially provide improved spatial resolution, thereby helping to elucidate the mechanisms behind US neuromodulation [158].

Lastly, the development of thermal implantables has not been thoroughly explored, although some examples have been reported in literature [159]. One primary concern relates to the possible damage to neural tissue which would derive from long-term use of heating or cooling strategies [138]. Cooling is known to reduce or silence neural activity, inducing physiological and behavioural changes [160]. Reducing temperature to 5 °C can produce an effective nerve conduction block and can be sustained for tens of minutes without neural damage. Nevertheless, delivering nerve cooling for only a few seconds would require an efficient heat exhaust mechanism, which is not trivial in an implantable device [138]. In terms of heating, safety limits are determined based on radiant exposure levels and frequency. Thermal damage to nerves occurs for radiant exposure above 0.7 J cm⁻². Effective stimulation with values below this threshold

can be safely delivered with frequencies up to 5 Hz, and for prolonged periods (~ 5 min) when stimulating at lower frequencies [161].

In the following, we therefore focus exclusively on optical, chemical and multimodal PNIs, which have all been successfully adapted to flexible and/or soft interfaces. These strategies have been primarily implemented for neuromodulation purposes, as an alternative to electrical stimulation. However, other successful applications have been reported, such as the promotion of nerve regeneration and the attenuation of FBR through optical and/or chemical mechanisms. In the following we review the main applications, delivery strategies and challenges of these devices, as summarized in figure 6.

3.2.1. Optical interfaces

The use of optical interfaces to modulate activity in the PNS has been explored in studies that either do not require genetic manipulations or involve optogenetic modification. Infrared and near-infrared light delivered to PNs through lasers and optic fibers provides neural activation through a local thermal process [162–164]. This method, whose activation mechanism is still not fully understood, can provide a local and selective stimulation of a limited number of axons even with extraneural interfaces, and has the advantage of minimal electrical noise or stimulation artifacts during concurrent recording.

In the past decade, however, the development of optical PNIs has been mainly oriented toward optogenetics, a selective neuromodulation technique, which has gained significant popularity in the field of neural interfaces. This strategy, which allows targeted activation or inhibition of specific fiber types, requires the expression of light sensitive proteins, called opsins, in specific nerve or cell-types. Therefore, by shining light onto the whole nerve, it is possible to interact only with opsin-expressing fibers, which respond exclusively to a preselected wavelength in the visible range. Aside from neuromodulation purposes, optogenetic techniques are also being applied to promote nerve regrowth from specific cell populations, which can allow a better understanding of axonal growth mechanisms [140, 165]. In the implementation of optogenetics, undesirable side effects, both at the cellular and neural circuit level, can arise due to: the presence of the light-sensitive proteins, the consequence of photothermal effects, and the activation or silencing of specific cell populations [166]. From a technological standpoint, one of the main challenges resides in the development of devices incorporating miniaturized and efficient light sources.

Different strategies have been implemented to obtain light delivery to target neural tissue. Historically, they have been developed for the CNS [167, 168]. However, in recent years, these light delivery methods, which employ stiff components such as optical

fibers and light emitting diodes (LEDs), have been adapted to the PNS. This transition is challenging because nerves, unlike the brain, bend frequently following body movement, making light delivery in freely moving animals difficult. The surrounding tissue may scatter light, making localized light delivery one of the priorities when designing optical interfaces. Moreover, the PNS is subject to a higher immune surveillance, which can hinder opsin expression after viral injection, reducing the efficacy of the optogenetic technique [169]. Recent research has provided new PNS-specific solutions both in terms of improved opsin transduction mechanisms and in terms of device design and optimized light delivery strategy.

The first proposed devices consist in implantable interfaces coupled to an external light source (e.g. laser) through an optic fiber. These are typically made of brittle materials such as silica, however they are sufficiently thin (~ 100 μm diameter) to allow for a certain degree of flexibility. By integrating the optic fiber within a soft cuff it is possible to keep the fiber in place and minimize FBR [170, 171]. This type of system is able to deliver high-intensity and thermally safe optical stimulation. Nevertheless, the use of such a device in long-term applications is unrealistic, as it requires tethering to an external light source.

A more adequate solution for chronic experiments consists in directly integrating the light source on the device, using bare micro-LED dies placed on flexible substrates, either through wire bonding or surface mount technology [172, 175–179]. These miniaturized components feature a relatively low power consumption, which makes it possible to employ wireless operation, whether it is through the use of an RF harvesting unit and rectifier circuit for power and data transmission [176] or through the use of a battery-powered headstage component [179]. As a result, a truly integrated implantable solution can be fabricated. However, integrating rigid components to the device adds complexity to the fabrication process, increases overall thickness (>50 μm), limits flexibility and represents a possible failure point. Lateral dimensions and thickness of commercially available micro-LEDs prevent the development of high density devices and complicate their use in small nerves, which require low bending radii. For applications in the CNS, these limitations have been partially overcome by fabricating thin film GaN micro-LEDs [180, 181], while similar approaches remain to be tested in the PNS. The increased flexibility promotes biointegration of the device, nevertheless its long-term use is still significantly limited by the requirement of a stable thin film encapsulation, a critical material choice in the design of active implantable systems [182]. Aside from providing flexibility, this approach enables the development of high density optical PNIs, which could potentially provide

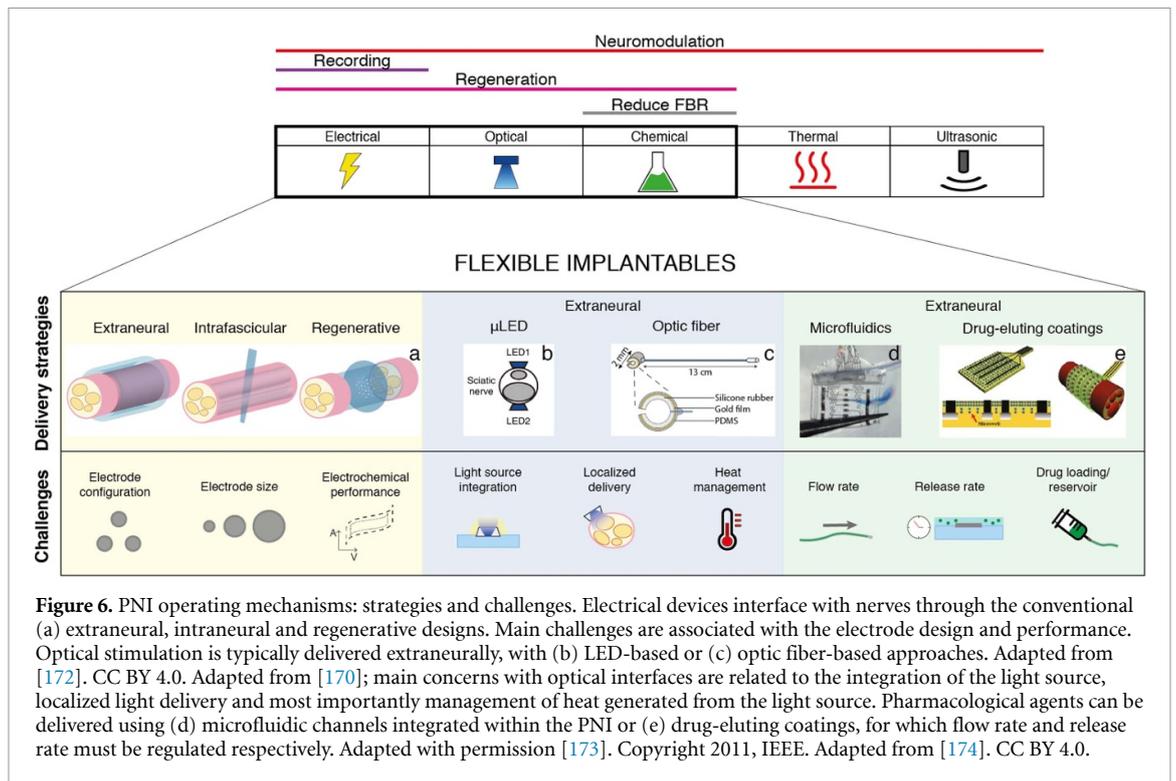


Figure 6. PNI operating mechanisms: strategies and challenges. Electrical devices interface with nerves through the conventional (a) extraneural, intraneural and regenerative designs. Main challenges are associated with the electrode design and performance. Optical stimulation is typically delivered extraneurally, with (b) LED-based or (c) optic fiber-based approaches. Adapted from [172]. CC BY 4.0. Adapted from [170]; main concerns with optical interfaces are related to the integration of the light source, localized light delivery and most importantly management of heat generated from the light source. Pharmacological agents can be delivered using (d) microfluidic channels integrated within the PNI or (e) drug-eluting coatings, for which flow rate and release rate must be regulated respectively. Adapted with permission [173]. Copyright 2011, IEEE. Adapted from [174]. CC BY 4.0.

improved spatial and fiber-type selectivity in either extraneural or intraneural approaches.

Currently, intraneural optical PNIs have only been proposed in the form of penetrating rigid optic fibers for infrared stimulation, like the Utah Slant Optrode Array [163], which penetrates the nerve and provides local heating to fibers. Similarly to electrical extraneural devices, optical cuffs cannot achieve the same level of localized light delivery as intraneural devices. They therefore require optimization of stimulation parameters to target fibers located within the nerve, by modulating the amplitude of current applied to LEDs in order to access either superficial or deeper structures [172].

Specifically, when designing optical interfaces for optogenetics, it is necessary to ensure a minimum irradiance in the range of $1\text{--}5\text{ mW mm}^{-2}$ to target fibers [183, 184]. Light source intensity is set to guarantee opsin response based on this lower limit and by taking into account light scattering effects in the nerve. Strategies to contain and localize light delivery include the use of reflective metallic layers around cuffs [170, 171, 177] as well as proper characterization of light propagation within PNs [172]. The consequences of light propagation and intensity are also relevant when electrically recording elicited neural activity: the generation of photoelectric artifact, whose waveform can be similar to an AP, can contaminate data and complicate our understanding of the results [185].

Lastly, a major concern for optical interfaces is the generation of heat associated with high intensity, duty cycle or frequency stimulation. Optostimulation

parameters reported in literature for modulation of the PNS vary according to application and experimental protocol, but typically cover ranges of 0–20 Hz for frequency, 0%–50% for duty cycle and 0–20 ms for pulse duration [172, 175–178]. The effects of these parameters require careful monitoring as an increase in temperature ($\sim 1\text{ }^{\circ}\text{C}$ – $2\text{ }^{\circ}\text{C}$) is known to harm tissue or provoke unwanted neural activity [187]. For this reason, preliminary *in vitro* tests are required to estimate limit values of stimulation parameters. A more reliable monitoring consists in measuring real *in vivo* conditions. A thermometer tip can be placed in close proximity to the light source in anaesthetized animals to verify safe stimulation conditions [177]. Ideally, a temperature sensor should be placed in contact with the LED to provide real-time information, which is necessary during chronic implantation, as efficiency could drop leading to an increased heat generation.

Currently only one solution of this kind has been proposed in the PNS, using negative temperature coefficient components [175], which are rigid and bulky, significantly affecting the overall thickness and flexibility of the device. Alternatively to temperature monitoring, heat generation in PNIs can be directly limited by mounting micro-LEDs on heat dissipating substrates such as stainless steel [188].

Despite the number of open issues in the application of optogenetics to the PNS, namely heat management and the immune response after viral injection [169], and, despite the currently limited translational prospective of this technique, optogenetics is becoming a well-established

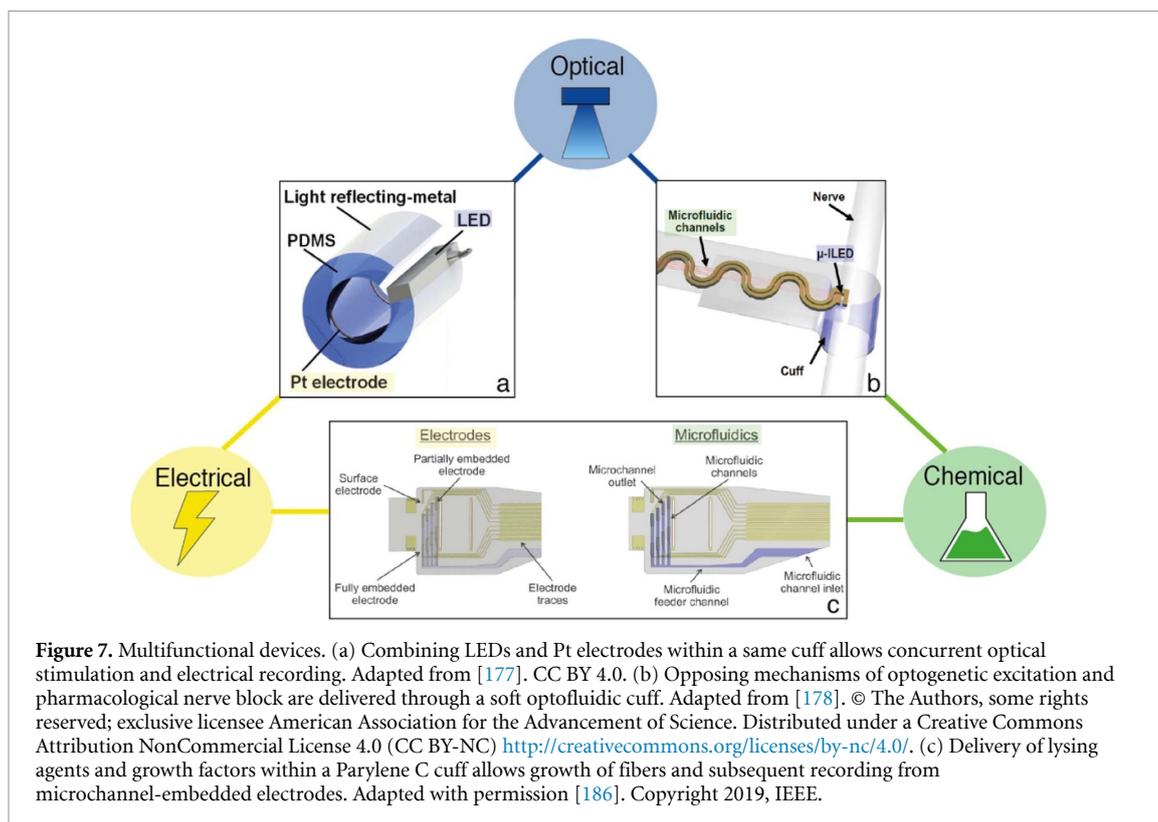


Figure 7. Multifunctional devices. (a) Combining LEDs and Pt electrodes within a same cuff allows concurrent optical stimulation and electrical recording. Adapted from [177]. CC BY 4.0. (b) Opposing mechanisms of optogenetic excitation and pharmacological nerve block are delivered through a soft optofluidic cuff. Adapted from [178]. © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) <http://creativecommons.org/licenses/by-nc/4.0/>. (c) Delivery of lysing agents and growth factors within a Parylene C cuff allows growth of fibers and subsequent recording from microchannel-embedded electrodes. Adapted with permission [186]. Copyright 2019, IEEE.

alternative to current electrical approaches. Thanks to its inherent functional selectivity of different fiber types, we expect it will be a main research topic in the field of flexible PNIs in coming years.

3.2.2. Chemical interfaces

Aside from optical and electrical mechanisms, pharmacological treatment represents a well-established alternative for neuromodulation, which does not require genetic treatment [189]. Local administration of drugs is achieved through perineural or intraneural injections, which can be repeated over time to obtain the desired effect. However, it is difficult to contain the spread of local anaesthetic, which can target nearby muscles, causing unwanted motor block [190]. Implantable drug delivery systems are promising approaches for local, chronic and repeatable pharmacological treatment using cuff-like devices incorporating a cannula [152, 191], without causing nerve trauma associated with intraneural injections [192].

One of the main features of chemical PNIs is the wide variety of effects that can be obtained based on the selected pharmacological agent. Nerve block using drugs such as lidocaine or bupivacaine [142] is a useful tool for neurophysiological research and an established clinical practice to temporarily block pain. Additionally, growth factors can be delivered to promote regeneration of axons [193].

A possible complication in the development of fully implantable systems is related to the drug delivery strategy. A common method for drug

delivery in flexible chemical PNIs consists in fabricating microfluidic channels on cuff electrodes [173, 178, 186] which can then be connected to external syringe pumps [186] to provide pharmacological treatment over time. More complex solutions integrate drug reservoirs and micropumps within the same device [178]. Alternatively, hydrogel-based [174] or nanofiber-based [194] drug-loaded coatings have been used, allowing a controlled release in a fixed time frame without any external supply (or source).

3.2.3. Combined strategies

The integration within a single system of multiple modalities (figure 7) to communicate with the PN is enabled by the introduction of precise fabrication techniques and miniaturisation. Concurrent electrophysiological recording from microelectrodes integrated with a drug delivery outlet allows for *in situ* verification of nerve blocking effects [195]. Selective stimulation and recording has been achieved by attracting axons to the electrodes thanks to the combined effect of lysing agents which remove connective tissue and neurotrophic factors to promote axonal growth [186, 196]. Drug delivery may be used to counteract immune response and promote the long-term use of PNIs by delivering anti-inflammatory agents [174, 194]. Lastly, an optofluidic cuff has been proposed, which can provide two opposing mechanisms, stimulation and inhibition of neural activity, through optogenetics and pharmacological agents respectively [178].

Optical interfaces and optogenetics in the PNS have allowed a high degree of fiber-selectivity while guaranteeing a low level of invasiveness. Other hybrid approaches under development also aim at minimizing the overall invasiveness of PN experiments. Among these, strategies combining stimulation and recording in a single device allow real-time monitoring of elicited neural activity and closed-loop control without the need to implant additional cuffs or electromyography (EMG) electrodes. By integrating stimulation and recording electrodes in a single PNI, however, a major concern is associated with the generation of stimulation artifacts, which can lead to loss of recording information and requires specific signal processing or additional circuitry to be rejected [197]. Combined strategies, which merge optical stimulation with electrical recording on a cuff have shown to be less susceptible to stimulation artifact [177] and can provide a robust solution to modulate and monitor activity in freely moving animals.

The ability to manipulate nerves with combined approaches is of broad interest in the field of PNIs and could still potentially benefit from current technologies, such as multimaterial and multifunctional flexible fibers [198].

4. Materials and fabrication

4.1. Flexible substrates, electrodes and encapsulation

Progress in the field of flexible electronics has enabled the widespread use of polymeric substrates to develop flexible PNIs. Prominent choices, employed both as substrate and insulation layer, include PI and parylene C, which are advantageous due to their low Young's modulus (2–8 GPa), chemical inertness and electrical insulating properties [199]. Their compatibility with common microfabrication processes (dry etching, physical vapor deposition etc) allows for straightforward manufacturing of flexible devices in a variety of designs and form factors, also integrating metallic microelectrodes. As a result, these polymers have been used in recent decades to develop extraneural [186, 200, 201], intraneural [80, 112, 116, 202] and regenerative [123, 203, 204] devices alike.

In vitro evaluation as well as *in vivo* testing have shown material stability, no toxicity and limited FBR [202] of both PI and parylene C at chronic timepoints ranging from 2 to 6 months for different interface types, as highlighted in table 3. Despite well-documented use in animal models, chronic testing in human nerves [77, 205, 206] and existing commercial devices (NeuroNexus Nerve Cuffs), PI is still not approved by the FDA to be used in implantable devices such as PNIs.

The main concerns in the use of polymer-based implants are related to device encapsulation and long-term reliability and stability [207], and delamination within the multilayer structure that may be promoted

by the wet and ionic environment of the body. Current trends in neural interface design are focusing on improving the lifetime of polymeric thin films [208] and decreasing the risk of delamination at the substrate-metallization interface [87]. Furthermore, the encapsulation barrier properties can be improved by combining flexible layers (e.g. parylene-C or PI) with nm-scale insulating layers (e.g. Al_2O_3), having low water permeability. These can be deposited through atomic layer deposition, and further capped by an additional inorganic layer, such as HfO_2 , to limit issues related to water hydrolysis of alumina [209]. Alternatively, amorphous SiC has shown promise as an insulating film for cuff electrodes in chronic applications, thanks to its long-term stability in accelerated ageing tests [210].

Despite their non-negligible water permeability, silicone elastomers are extensively used to develop flexible PNIs, both in academic and industrial settings. The range of thicknesses commonly used (200–600 μm) is sufficiently high to ensure slow permeation across the entire encapsulation. Medical-grade silicones are employed to fabricate commercially available cuff electrodes for PN stimulation and recording (by companies such as CorTec, Ardiem Medical, MicroLeads). These devices rely on the attractive properties of silicones, including biocompatibility, low Young's Modulus ($\sim\text{MPa}$) and cost-effectiveness [199]. Human use of such implants has been reported for a variety of nerves in applications related to motor control and sensory feedback in neuroprosthetic limbs, for up to 11 years [211, 212].

The possibility of achieving such long-term functionality and stability of silicone-based cuffs has also been suggested in studies focused on the morphological and tissue response of nerves. Despite the significant thickness and pressure exercised on the nerve, the limited morphological changes observed after chronic studies in cats have been mainly attributed to damage from lead cables [213] and have been deemed negligible [214].

Similarly, other silicone-based extraneural interfaces, such as the FINE electrodes developed at Case Western Reserve University, have been implanted for up to 6 years restoring naturalistic sensation in upper limb amputees [103]. A variation of the FINE, the composite FINE (C-FINE) employs a combination of flexible materials, silicone and a layer of polyether ether ketone (PEEK), to modulate the device stiffness in different locations, flattening the nerve along its width and maintaining flexibility along its length [215].

Typically, metal electrodes are incorporated in these silicone-based implants in the form of patterned foils of Pt or PtIr with thicknesses in the range of tens of microns. Intraneural interfaces, instead, rely primarily on thin film (10–100 s of nm) lithographic patterning of noble metals (gold, platinum), which are the materials of choice due to their extensive use

in medical devices and their electrochemical stability. Decreasing electrode and interconnect size allows for higher electrode count and density, improving selectivity. These techniques are reliably used on PI and Parylene-based devices.

Conventional microfabrication techniques can also be employed to pattern microelectrodes and interconnects on stretchable substrates such as polydimethylsiloxane (PDMS). One technique consists in engineering stretchable microcracked interconnects through gold evaporation and has been successfully used to record PN activity in regenerative microchannel interfaces [126]. Hybrid approaches using both PI and silicone have been reported for cuffs [216] to combine the reliability and mechanical properties of traditional systems to the increased channel count and design flexibility of thin film devices. One drawback of decreasing electrode size is the resulting increase in impedance, which is detrimental for both nerve stimulation and recording and can lead to adverse electrochemical reactions and cell damage [133]. This can be typically overcome by roughening the electrode surface using porous coatings such as Pt black, which lead to a low interfacial impedance and a high charge injection capacity [217], providing a stable electrical performance over time.

Chronically interfacing the PNS with metal electrodes is challenging both from a mechanical and an electrochemical perspective. From a mechanical standpoint, the current trend is to move towards low flexural rigidity technologies. For instance carbon fibers [218] or carbon nanotube yarn electrodes [219] have allowed chronic interfacing and easy access to small nerves (sub-mm) which are typically difficult to target with thick conventional materials. Electrochemically, coatings such as Pt black, IrOx and TiN are known to improve safety and stability of stimulation delivery [133], and can decrease electrode impedance ensuring better quality recordings [220]. However they do not overcome the effects of the increase in impedance exacerbated by the fibrotic encapsulation, attributed also to the mechanical mismatch. As a result, current and future efforts should be focused on soft materials and defining fabrication strategies to integrate them in PNIs.

4.2. Soft materials and non-conventional fabrication strategies

The word 'soft' can have different meanings based on the context: in the field of microfabrication $E < \text{GPa}$, for additive manufacturing $E < \text{MPa}$ and for biology $E < \text{kPa}$. In this section we define as soft materials those that have a modulus below $\sim 10 \text{ MPa}$. While silicones also fall in this category, here we focus on materials with additional non-conventional properties, fabrication strategies and/or lower moduli. The need to match mechanical properties of nerves has favoured the development of PNIs integrating biomimetic materials, such as hydrogels, despite a number

of challenges linked to their processability. Recent research [58] has highlighted the importance of tailoring the elastic modulus of hydrogel coatings to match that of the host tissue. Coatings in the range of 1–10 kPa have been applied to cuff electrodes [58, 221] and have caused minimal growth of inflammatory tissue, compared to standard flexible cuffs with modulus in the GPa range, showing promise for long-term nerve neuromodulation.

Aside from reduced FBR, these materials show other favourable features for applications in PNIs, as illustrated in figure 8. The enhanced compliance of cuffs with hydrogel coatings allows for a more intimate contact between nerve and device [106, 107], which is crucial to guarantee an optimal electrical performance and to avoid cuff displacements.

In addition, the extensive use of hydrogels and natural ECM components in the field of tissue engineering has found a natural application in regenerative nerve interfaces. Hybrid tissue-engineered electronic nerve interfaces (TEENIs) have been developed to promote nerve regrowth within a hydrogel-based scaffold, while guaranteeing high precision in stimulation and recording through microelectrodes patterned on PI threads [232].

The composition and properties of soft materials can be specifically tailored to further enhance the functionalities of PNIs. For instance, shape memory polymers (SMPs) have become quite popular for cuff electrodes [233, 237] as they exhibit shape reconfigurability at a set temperature and elastic modulus tailoring, reaching moduli as low as 300 kPa. However, when using SMPs as substrate for neural interfaces an additional layer may be required (e.g. parylene C) to guarantee insulation [238]. Additionally, these devices have a fixed diameter and their composition needs to be properly adjusted to ensure the desired mechanical properties and a phase transition at physiological conditions. Nevertheless, the implantation procedure is simplified, not requiring additional surgical fixation, and relying entirely on the cuff softening around the nerve. The concept of shape reconfigurability and morphing has recently been demonstrated using viscoplastic materials [234], which can instead adapt to nerves growing by more than $2\times$ their original diameter, maintaining unaltered functionality and thus bypassing the need for device replacement over time. This opens up the possibility of using long term implantable interfaces in paediatric patients, an often overlooked category in the field.

Aside from exploiting the low Young modulus and biocompatibility of these materials, enhancing the conductivity of soft materials is an attractive solution to address both mechanical and electrical challenges, decreasing electrochemical impedance and lowering the mechanical mismatch at the electrode–tissue interface [174, 239]. This approach can improve the quality of recorded neural signals and can allow safe

Table 3. Conventional materials for flexible peripheral nerve interfaces implanted in animals and in humans.

Interface	Design	Substrate	Electrode	Animal studies		In human	
				Target nerve	Implantation time	Target nerve	Implantation time
Extraneural	Cuff	Polyimide	Thin film Pt (lithographic patterning)	Rat—sciatic [200]	2–6 months	—	—
			Thin film Pt/Au (lithographic patterning)	Rat—vagus [201]	Acute	—	—
			Thin film Pt (lithographic patterning)	Rat—sciatic [186]	Acute	—	—
			Thin film WTi (lithographic patterning)	Mouse—vagus [134]	12 weeks	—	—
			Stainless steel, Pt, PtIr (metal rings)	Mouse—vagus [222]	60 d 40 d	Acute	—
				Rat—facial [223]			
			PtIr (metal foil laser machining)	Rat—sciatic [90]	30 d	Acute	Median and radial [226]
			Pt (metal foil laser machining)	Rat—sciatic [224]	28–34 weeks	Radial, femoral, tibial and fibular [211]	11 years
				Rat—splanchnic [225]			
				Cat—sciatic [213]			
				Pig—radial [227]	Acute	—	—
FINE		Hybrid Polyimide-Silicone	Pt, PtIr (metal foil laser machining)	Cat—sciatic [228]	3 months	28 d	Femoral [229]
				Rat—sciatic [98]			Median, ulnar and femoral [103]
C-FINE		Hybrid PEEK-Silicone	Pt (metal foil laser machining)	Cat—sciatic [102]	2 years	7 months	1 year
Intraneural	tf-LIFE	Polyimide	Thin film Pt (lithographic patterning)	Rat—sciatic [112]	3 months	4 weeks	Median and ulnar [206]
			Thin film Pt (lithographic patterning)	Rat—sciatic [116]	2 months	32–37 d	Median and ulnar [115]
				Pig—median [83]	2–8 weeks	—	—
				Rat—sciatic [202]	6 months	—	—
Regenerative	Sieve	Polyimide	Thin film Pt (lithographic patterning)	Rat—sciatic [80]	12 months	—	—
			Thin film Pt (lithographic patterning)	Rat—sciatic [203]	3 months	—	—
			Thin film Pt (lithographic patterning)	Rat—sciatic [123]	—	—	—
			Thin film Au (lithographic patterning)	Rat—sciatic [204]	12 weeks	—	—
Microchannel		Polyimide	Thin film stretchable Au (shadow mask patterning)	Rat—sciatic [126]	10 weeks	—	—

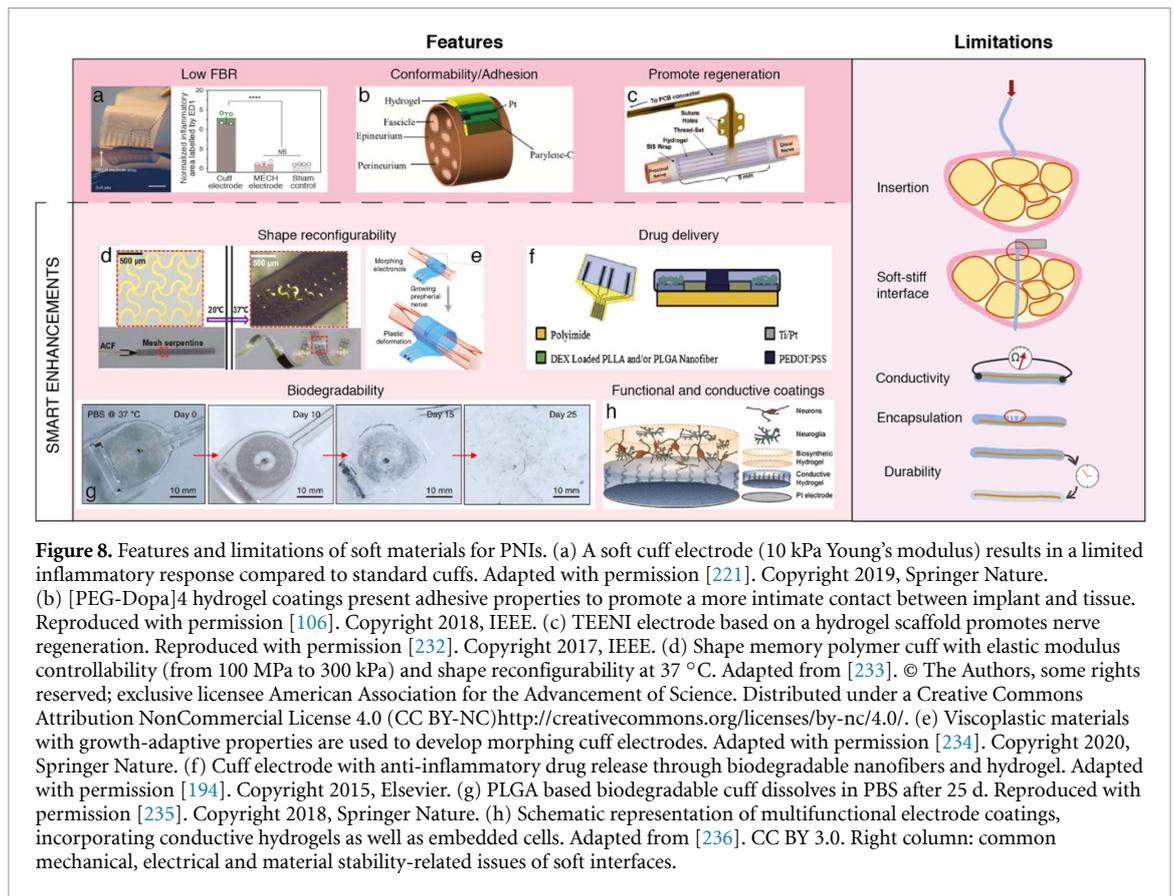


Figure 8. Features and limitations of soft materials for PNIs. (a) A soft cuff electrode (10 kPa Young's modulus) results in a limited inflammatory response compared to standard cuffs. Adapted with permission [221]. Copyright 2019, Springer Nature. (b) [PEG-Dopa]₄ hydrogel coatings present adhesive properties to promote a more intimate contact between implant and tissue. Reproduced with permission [106]. Copyright 2018, IEEE. (c) TEENI electrode based on a hydrogel scaffold promotes nerve regeneration. Reproduced with permission [232]. Copyright 2017, IEEE. (d) Shape memory polymer cuff with elastic modulus controllability (from 100 MPa to 300 kPa) and shape reconfigurability at 37 °C. Adapted from [233]. © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) <http://creativecommons.org/licenses/by-nc/4.0/>. (e) Viscoplastic materials with growth-adaptive properties are used to develop morphing cuff electrodes. Adapted with permission [234]. Copyright 2020, Springer Nature. (f) Cuff electrode with anti-inflammatory drug release through biodegradable nanofibers and hydrogel. Adapted with permission [194]. Copyright 2015, Elsevier. (g) PLGA based biodegradable cuff dissolves in PBS after 25 d. Reproduced with permission [235]. Copyright 2018, Springer Nature. (h) Schematic representation of multifunctional electrode coatings, incorporating conductive hydrogels as well as embedded cells. Adapted from [236]. CC BY 3.0. Right column: common mechanical, electrical and material stability-related issues of soft interfaces.

electrical stimulation in applications requiring continuous operation, such as neural block [174]. One way of achieving this consists in the synthesis of conductive polymers, such as poly(3,4-ethylene dioxythiophene), within a preformed hydrogel network, poly(vinyl alcohol) [240]. Other examples of multifunctional hydrogels include drug-eluting coatings, which can further improve implant biocompatibility by releasing anti-inflammatory drugs such as cyclosporine A, through loaded microspheres [174]. Lastly, using tissue engineering approaches which allow integration of neurons directly in the coating has been thought to provide a more direct connection between implant and neural tissue [236].

A final category of materials finding applications in PN stimulation and recording are bioresorbable substrates and electrodes. These transient devices, which consist of biodegradable polymeric dielectric layers, such as poly (lactic-co-glycolic acid) (PLGA), and electrodes (Mg, Mo), can be useful in case of short experimental and therapeutic timelines and to avoid complications associated with explantation [235].

While the advantages of these non-conventional materials are evident, integration within the device can be challenging. Patterning strategies for hydrogel coatings remain limited, as these materials are not typically employed in MEMS-based processes, being sensitive to high temperatures and strong organic solvents. Standard methods, including casting, dip-coating, transfer processing and printing [199] are

limited in resolution. Sub-100 μm features have been obtained using traditional photolithography on ion-gels successively converted into hydrogels via water exchange [221].

Aside from fabrication-related issues, the use of soft materials entails a number of complications associated with the device functionality itself.

While using soft materials could provide relevant benefits in the long-term performance of extraneural and regenerative implants, the same property could prejudice the development of inter- and intra-fascicular devices. Shanks fabricated using materials with a low modulus are more likely to buckle than their rigid counterparts and, moreover, cannot provide the sharp tips necessary to pierce through tissues. Therefore, it is necessary to develop custom insertion methods: some inspirational examples are already available in literature, as in the case of PI implants that are pulled through the nerve using a needle and some suture thread, or as in the case of PDMS based electrodes, that are pulled in using a syringe needle under vacuum [241]. PNI designers could also get inspired by the implantation methods used with brain implants, for example by using stiff resorbable coatings [199].

Soft conductors do not offer electrical conductivity levels similar to their rigid counterparts such as gold or platinum: elastomeric blends and electrically conductive hydrogels can have conductivities up to 10 000 S cm^{-1} and 40 S cm^{-1} respectively while

noble metals can offer values up to $600\,000\text{ S cm}^{-1}$ [242, 243]. Therefore, larger track resistances introduce higher thermal noise when recording and larger applied voltages for the same injected currents when stimulating.

Another challenge linked to soft materials is electronic insulation. Considering water permeability and electrical permittivity, soft materials such as hydrogels cannot compete with standard insulators like alumina or silicon oxide. Water and ions can infiltrate into the device in a shorter time and deteriorate its electrical performance over the long run. There is therefore a need for soft materials engineered with lower permeability and improved dielectric properties.

The soft implants should maintain stable mechanical and electrical properties in a harsh wet environment characterized by the presence of ROS, pH variations, electrochemical reactions and continuous mechanical stresses. Nevertheless, there are very few examples of chronic implantations using soft materials and further investigations are necessary to assess the durability of these technologies over the long term.

Soft materials finally need to be interfaced with standard, rigid, electronics, and consequently designers must engineer reliable and durable solutions to link the two parts. The mechanical mismatch at the interface could cause the accumulation of mechanical stresses on the soft side, potentially causing peak bending and twisting that can result in mechanical failure and loss of electrical functionality. Gradients in stiffness, obtained either through geometrical or material designs, could uniformly distribute stresses and ensure higher reliability over time. The electrical performance at the soft-stiff interface is also important, as it is necessary to have a stable electrical contact to guarantee signal quality with minimal noise. Soldering is not possible when using soft conductors and alternative technologies should be considered, such as those based on surface adhesion treatments [244].

To summarize, the latest achievements in the implementation of soft PNIs have shown promising results, especially related to the reduced biological footprint. However, they still lag behind established PNIs in terms of electrical performance and improved conductors and insulators must be engineered. Finally, the chronic stability of soft materials remains an open question to be addressed, both by research and regulatory agencies.

5. Conclusion

The efficacy and stability of flexible and implantable PNIs has progressed in recent years thanks to the technological advancements in polymer microfabrication and materials science. By tackling challenges related to FBR, academically developed devices

show promise for unaltered decade-long use in animals and humans. As for other neural interfaces, focus on miniaturization, soft materials, multimodal approaches and improved packaging, including wireless strategies, is desirable to overcome common issues in accessing the PNS. While PNIs are already used in a variety of clinical applications, the new possibilities offered by recent devices remain to be implemented and could further widen the spectrum of applications. Improved spatial and fiber type selectivity achieved thanks to thin film microfabrication and new techniques, such as optogenetics, are expected to provide more accurate therapy, with reduced side effects which would normally appear due to activation of undesired fibers or fascicles. A possible evolution of optoelectronic implants is tightly bound to the advances in optogenetics and light source miniaturization. Indeed, an implant with a dense array of light sources, coupled with modified fibers sensitive to specific wavelengths depending on their type, could provide the ultimate neuromodulation tool with high spatial and functional resolution. However optoelectronic implants are not yet able to be used for recording applications, although promising results are coming from *in vitro* experiments with cultured neurons exploiting voltage-based fluorescence or electrochromic materials [245, 246].

Issues arising in clinical devices, such as infection or implant migration, are limited when appropriately selecting materials which match the mechanical properties of nerves, can adapt to their frequent movements and are designed to ensure a better contact with the tissue. Because of the benefits brought forth by these techniques, we could even envision a more widespread use of typically invasive designs (intra-neural, regenerative), which are still somewhat uncommon, compared to their extraneural counterparts. To minimize the invasiveness of these devices it is also essential to better understand the fine mechanics of PNIs. This should be achieved through shared mechanical characterisation frameworks that can enable the formulation of universal physical models and therefore catalyse the development of new designs and tailored materials for PNIs.

Meanwhile, the community developing PNIs should also monitor the evolution of the equivalent devices applied in the CNS, specifically brain implants. The technologies developed in this context can be a source of inspiration for PN applications: a recent example is the fully polymeric and stretchable optoelectronic array developed by Liu and colleagues [247].

Examples provided in this review have highlighted this current trend towards flexible, soft and multimodal technologies. We expect future devices to further exploit these features singularly or merged together, providing long-term, high-resolution PN stimulation and recording.

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