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Review

Paradigms for restoration of somatosensory feedback via stimulation of the peripheral nervous system

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H I G H L I G H T S

- Damage to the somatosensory system can severely affect the execution of daily activities.
- Restoration of natural percepts after amputation demands direct interfacing to the available peripheral nerves.
- Data from single nerve stimulation to elicit multisensory sensations are discussed.

A B S T R A C T

The somatosensory system contributes substantially to the integration of multiple sensor modalities into perception. Tactile sensations, proprioception and even temperature perception are integrated to perceive embodiment of our limbs. Damage of somatosensory networks can severely affect the execution of daily life activities. Peripheral injuries are optimally corrected via direct interfacing of the peripheral nerves. Recent advances in implantable devices, stimulation paradigms, and biomimetic sensors enabled the restoration of natural sensations after amputation of the limb. The refinement of stimulation patterns to deliver natural feedback that can be interpreted intuitively such to prescind from long-learning sessions is crucial to function restoration. For this review, we collected state-of-the-art knowledge on the evolution of stimulation paradigms from single fiber stimulation to the eliciting of multisensory sensations. Data from the literature are structured into six sections: (a) physiology of the somatosensory system; (b) stimulation of single fibers; (c) restoral of multisensory percepts; (d) closure of the control loop in hand prostheses; (e) sensory restoration and the sense of embodiment, and (f) methodologies to assess stimulation outcomes. Full functional recovery demands further research on multisensory integration and brain plasticity, which will bring new paradigms for intuitive sensory feedback in the next generation of limb prostheses.

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1. Introduction

Obtaining feedback from our environment and estimating the internal states of our body is essential for decision making and survival. Humans constantly integrate inputs from multiple sensory sources in an unconscious fashion over all available channels. Millions of sensors located in the eye, ear, and skin collect hundreds of thousands of bits per second (Küpfmüller, 1974). Unconscious sensory integration and processing is necessary to prevent information overload from these sensory inputs. This intrinsic mechanism is essential to function, yet, overlooked under normal physiological conditions. The complexity of the sensory system becomes more evident when we aim to artificially mimic or replace some of its components.

The development of artificial sensors that reproduce the functions of innate human sensory receptors has been a long and uphill journey (Kappassov et al., 2015; Lucarotti et al., 2013). Alongside this, several modalities of sensory feedback, including mechanical and electrical stimulation of the skin (Clemente et al., 2016; Crea et al., 2015b; Dosen et al., 2017; Franceschi et al., 2017; Marco et al., 2017; Štrbac et al., 2016), and the use of implantable electrodes to directly connect these artificial receptors with the peripheral nervous system (PNS) (Alt et al., 2017; Badia et al., 2011; Boretius et al., 2010; Cogan, 2008; Saal and Bensmaia, 2015; Tyler, 2015) have been explored. While sensory feedback by electromechanical stimulation of the skin has improved the training experience of users wearing prosthetic limbs, intuitive control or intuitive sensory feedback with this modality is limited by the spatial resolution of the human skin (Fig. 1). Direct interfacing of the PNS by neural implants is the natural channel to achieve this goal, and recent results demonstrate that the development of long-term implantable systems for this purpose will be possible in the future.

Comprehensive reviews summarizing progress on implantable technologies are available (Borton et al., 2013; Saal and Bensmaia, 2015; Tyler, 2015), but an overview of the different stimulation paradigms for sensory restoration and its outcomes

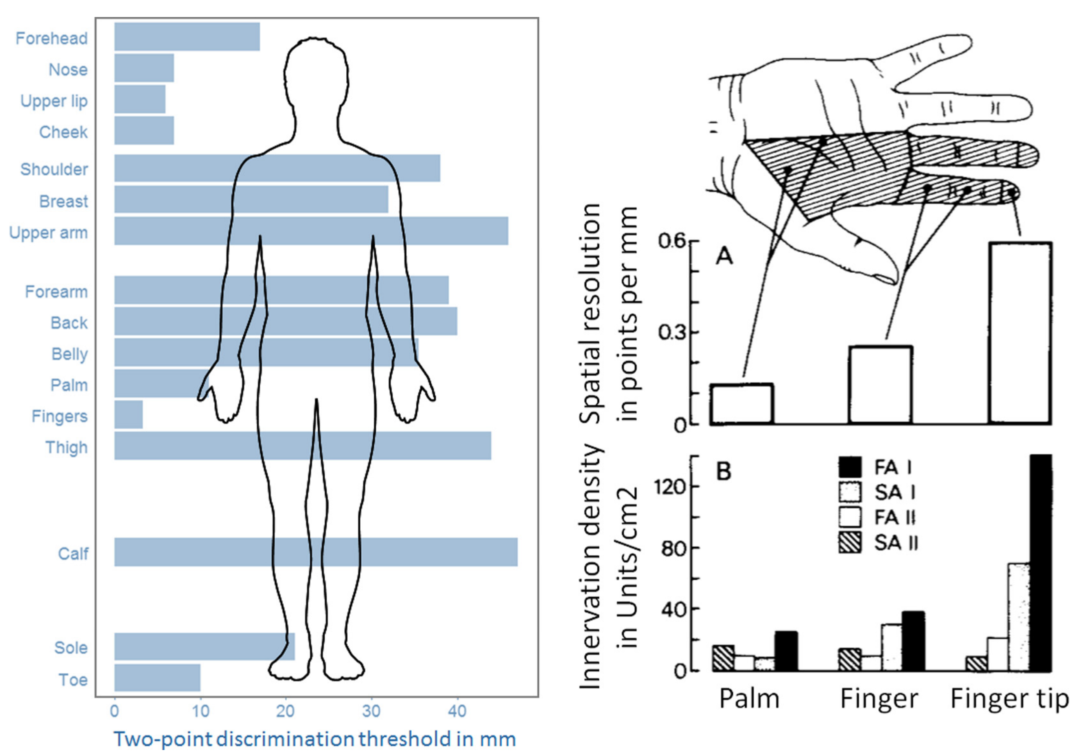

Fig. 1. Two-point discrimination threshold and the spatial resolution of the human receptors in the hand. The spatial resolution of the receptors located at the finger is much higher than the other parts of the human body. Adapted from Mancini et al. (2014) and (Johansson and Vallbo (1983), with permission.

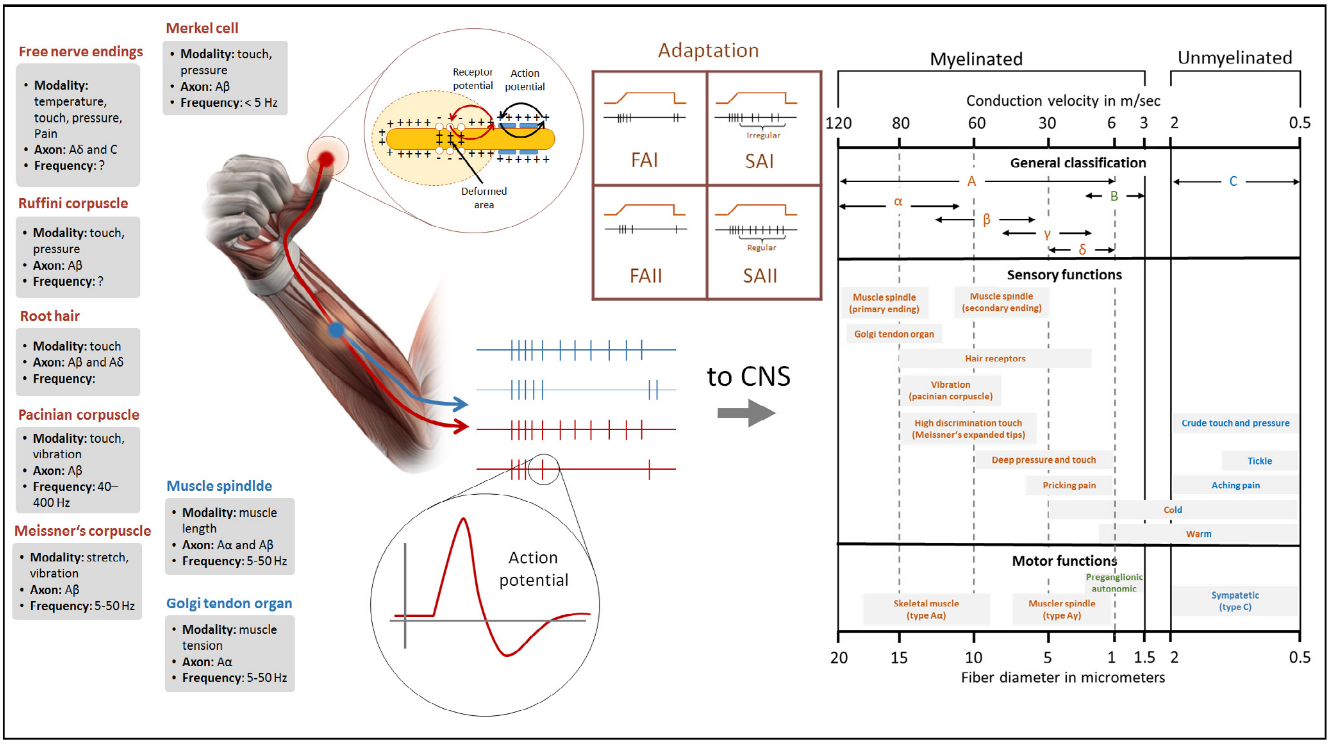

Fig. 2. Cutaneous and proprioceptive receptors of the skin send the information through the afferent pathway to the CNS. Sensory information is encoded in the frequency of the train of action potentials elicited by the receptor potential. Adapted from Johansson and Vallbo (1983) and Guyton and Hall (2006), with permission.

is lacking. This work compiles basic knowledge of the human somatosensory system, research progress on electrical stimulation of single fibers, and how this knowledge can be employed to reconstruct sensory percepts in humans. Successful developments that have driven the field toward an integrated understanding of the signal-encoding mechanisms connecting the human sensory receptors with the brain through the PNS are also examined.

2. The physiology of sensory feedback

Somatosensory information accounts for an important percentage of human perception, including tactile information such as touch, pressure and temperature, nociceptive stimulus of pain, tickling and itching, and proprioception such as joint angles and limb positions. The somatosensory system comprises the sensory receptors, the afferent peripheral nerves carrying the stimulus information, and the somatosensory cortex area of the brain. Tactile information is perceived by cutaneous receptors, while proprioception is sensed by specialized receptors located in the muscle belly and tendons in addition to cutaneous receptors (Johansson and Flanagan, 2009; Proske and Gandevia, 2012).

The physiology involving signal processing, sensor integration, and signal interpretation in the central nervous system (CNS) is beyond the scope of this article and available elsewhere (e.g., (Ackerley and Kavounoudias, 2015; Johansson and Flanagan, 2009; Panzeri et al., 2010; Saal and Bensmaia, 2014)). Likewise, specialized reading on the anatomy and physiology of human sensory receptors are available in the literature (e.g., (Abraira and Ginty, 2013; Butler et al., 2016; McGlone and Reilly, 2010; Saal and Bensmaia, 2014)).

2.1. How do humans transduce stimulus information?

The human glabrous skin is a highly sensitive organ with approximately 17,000 mechanoreceptors in the human hand alone (Johansson and Vallbo, 1983, 1979), which combine different sensory modalities to form the complex sense of touch. These mechanoreceptors include: The Meissner's corpuscles sensing skin stretch and vibration; Merkel cells and Ruffini corpuscles sensing skin touch and pressure; Pacinian corpuscle sensing skin touch and vibration; free nerve endings dedicated to temperature, touch, pressure and pain sensations; and the root hair plexus sensing touch.

Receptors located in the muscle belly and tendons monitor the status of muscle contractions. Muscle spindles sense muscle length, while Golgi tendon organs provide information regarding muscle tension. The human upper limb alone contains about 2500 Golgi tendon organs (Prochazka, 2012), while it is estimated that around 44,000 muscle spindles are contained in the human muscular-skeletal system with the number of spindles increasing in proportion to the fractional power of muscle mass (Banks, 2015).

Receptors are classified depending on their anatomical location (defining their receptive fields), their innervation density (defining their spatial resolution), and their response to ramp and hold stimuli (Fig. 2) (Johansson and Vallbo, 1983; McGlone and Reilly, 2010). This last classification defines how the receptor encodes and transduces a physical or chemical stimulus into information by means of electrical potentials. Some receptors are active only when the stimulus changes over time (velocity or acceleration dependent), which conveys different information from those that are active when the stimulus is constant (strength dependent). This has implications in how we perceive shapes and textures as well as in object manipulation. In addition, the sensations produced by cutaneous receptors are modulated (inhibited) during limb motion in proportion to the velocity of movement (Schmidt et al., 1990). One may already notice that different stimulation paradigms are required depending on the anatomical location where the electrical stimulation is applied and the type of information to be conveyed.

2.2. How is sensory information encoded?

The essential communication unit for transmitting the stimulus information from the receptors to the CNS is the action potential

(AP) (Debanne et al., 2011). APs are rapid depolarizations and repolarizations of the cell membrane, producing a pulse-like change of the cells resting membrane potential. Every time a receptor is stimulated, it produces a graded potential eliciting a train of AP pulses in the connected nerve fiber, which travel through the axon (Fig. 2). Its frequency and timing is defined by the receptor's response profile. The stimulus intensity is encoded in the frequency modulation of the AP train (i.e. the number of action potentials), while the timing of occurrence of this train marks distinct events during sensory stimulation (Edin and Vallbo, 1990; Edin and Vallbo, 1990; Guyton and Hall, 2006; Kandel et al., 2000; Mackevicius et al., 2012; Muniak et al., 2007; Poulos et al., 1984).

Each receptor is characterized by its response to a ramp and hold stimulus as mentioned previously. Four cutaneous sensing units have been identified depending on their stimuli adaptation, including fast-adapting (FA) type I and II units (FA-I and FA-II, respectively), and slowly-adapting (SA) type I and II units (SA-I and SA-II, respectively). Transient responses (i.e., producing trains of APs only when the stimulus changes over time) are characteristic of FA units while steady responses (i.e., producing trains of APs only during sustained invariable stimuli) distinguish SA units, responding to dynamic and static events, respectively (Fig. 1). In the human hand, there are approximately 43% FA-I units containing Meissner endings, 13% FA-II units with Pacini endings, 25% SA-I units having Merkel endings, and 19% SA-II units with Ruffini endings (McGlone and Reilly, 2010). FA units drive the strength of cortical responses in the brain, while the timing of the cortical responses is modulated by Pacinian ending fibers (Saal et al., 2015).

Muscle spindle endings are divided into primary and secondary afferents, namely Ia and II, respectively (Matthews, 1964; Proske, 1997). Afferent endings of the Ia type carry information regarding the rate of change of muscle stretch, while type II afferents transmit information regarding muscle length (Cooper, 1961). The Golgi tendon organs afferent fibers are classified as slowly adapting units and named Ib (Jami, 1992; Moore, 1984).

As discussed later in this review, stimulating the afferent pathways of the PNS requires excitation of the cell membrane with a train of electrical impulses that mimic the dynamic and static response of the missing receptors. Again, depending on the location of the stimulation and the sensing information, the stimulation paradigm should also resemble the integration of multiple sensory modalities by exciting several sensory pathways at the same time.

2.3. The role of noise

Noise is inherently present in the peripheral nervous system. It has been shown that noise influences the nervous system from the molecular to the behavioral level (Faisal et al., 2008). Noise is a source of variation in the generation of APs, produced by random openings and closings of the membranes ion gate (channel noise) (White et al., 2000). Channel noise can modify AP timing, affecting its initiation and propagation (Faisal et al., 2008). The CNS deals with noise by averaging available information and the utilization of prior knowledge. Averaging exploits the redundant information available when several sources of noise affect the same signal carried out by different sensory units. Prior knowledge is used to detect noise in highly structured sensory signals (Faisal et al., 2008).

Noise can also lead to signal processing optimization (Faisal et al., 2008). Stochastic resonance, for instance, is the enhancement of a nonlinear system response to a weak signal by addition of noise. This phenomenon (referred in the field of neuroscience as stochastic facilitation (McDonnell and Ward, 2011)) has proven importance in muscle spindles in the human proprioceptive system (Cordo, 1996), in human tactile perception (Collins et al., 1996), and in sensorimotor and balance control (Collins et al., 2003).

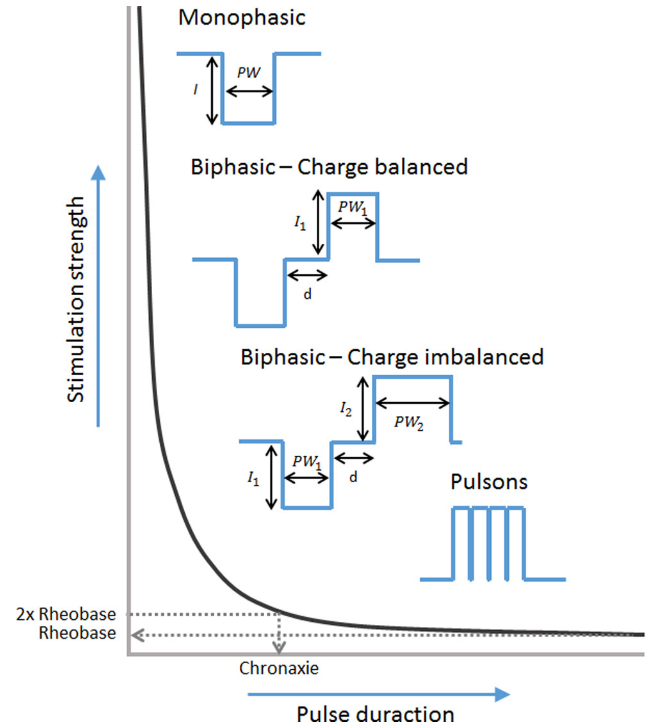

Fig. 3. Stimulation with square pulses. The duration (pulse width) and strength (amplitude) of the pulse define the amount of electric charge injected in the tissue, which is directly correlated to tissue and electrode damage. The shape of the curve is valid for rectangular pulses and might vary with different pulse shapes. Pulsons are square pulses divided in short bursts of square pulses. Energy optimal stimulation is achieved at chronaxie (Grill, 2015).

Currently, the role of noise in the encoding of sensory information is not fully considered in the design of stimulation paradigms, neither by considering the influence of random variation in the generation of APs nor observing the phenomenon of stochastic resonance to optimize sensory signal transmission.

3. Artificial encoding of sensory information

3.1. How are single fibers stimulated by electrical signals?

Sensory restoration by electrical stimulation comprises the activation of available axonal membranes to trigger a train of APs in response to an exogenous electrical stimulus. Such stimulation needs to be performed in a way that the brain interprets this stimulus as coming from a real, endogenous sensory receptor i.e. matching the response profiles of natural receptors described above. This involves emulating not only the time-frequency characteristics of the impulse train, but also characteristics of the impulses themselves, including their shape, amplitude, duty cycle, and polarity. Previous to eliciting any kind of sensory percept in humans, researchers have narrowed their focus to single fiber stimulation to elicit single APs. In this context, several simulation models have been proposed to understand the mechanisms of nerve fiber excitability (Basser et al., 2000; Mcneal, 1976; Meier et al., 1992; Rattay, 1999, 1987; Rattay and Aberham, 1993; Richardson et al., 2000; Rubinstein, 1991) and to develop novel neuroprostheses (Raspopovic et al., 2016, 2012). In general, stimulation with a square pulse (or a train of square pulses) has become the gold standard as it can provide rapid depolarization of the axonal membrane and it is relatively easy to implement by switching mechanisms (e.g., all-or-none electrical circuits). We will therefore describe first how the stimulation of single fibers with square pulses has been developed over the past decades. The effects of stimulating with other pulse shapes will be discussed in a later section.

3.1.1. Stimulation with square pulses

Fiber excitation with square pulses can be achieved by injecting electrical charge into the target tissue using current- or voltage-controlled stimulation following a step-like function of the same polarity (i.e., monophasic stimulation, Fig. 3) or with alternated polarity (i.e., biphasic stimulation, Fig. 3). Stimulating with biphasic pulses can be further performed either using a net charge of zero (i.e., balanced stimulation, Fig. 3) or with non-zero net charge (imbalanced stimulation, Fig. 3). A higher stimulation threshold is necessary with biphasic stimulation given that the AP elicited by the first phase might be arrested by the second phase (He, 2005; Van den Honert and Mortimer, 1979; Reilly et al., 1985). An advantage of this stimulation mode is that part of the charge delivered by the first phase is removed by the second phase, and this is beneficial in terms of reducing tissue damage (Grill and Mortimer, 1995; He, 2005). Lilly and colleagues demonstrated six decades ago that biphasic balanced stimulation helps preventing long-term cellular damage (Lilly et al., 1955). In deep brain stimulation, balanced biphasic stimulation is achieved by the second phase having a longer pulse width but smaller amplitude, maintaining the same area as the first phase (Coffey, 2008). Further, introducing a short delay between cathodic and anodic pulses partially reduces the requirement for a threshold increase (Gorman and Mortimer, 1983; Maciejasz et al., 2015) and balances out the physiological benefits of monopolar stimulation with those of safe stimulation (see below). Polarity of the stimulation pulse also influences stability of the implanted electrodes, as will be shown in further sections.

3.1.1.1. The relationship between strength and duration of stimulation. The charge injected during tissue stimulation with square pulses is defined by the strength of the stimulation (amplitude of the pulse) and the duration of the stimulation (width of the pulse t_{PW}). The amount of injected charge Q is an important parameter as it has direct consequences on tissue damage and stimulation efficiency (Horch and Dhillon, 2004). It is calculated as the mathematical interval of the current pulse with amplitude I over its duration t_{PW}. In the case of square shaped pulses, the injected charge can be easily calculated as the product of both parameters, i.e. $Q = I \times t_{pw}$. The strength-duration curve is a useful graph representing the relationship between these two parameters (Fig. 3) (Geddes and Bourland, 1985), and it is defined by Eq. (1):

$$I = I_r\left(1 + \frac{c}{d}\right) \quad (1)$$

where I_r is the rheobase current, d is the pulse width, and c is the chronaxie time. The rheobase current is the current used when the pulse width is infinite, while the chronaxie time is the pulse necessary to achieve a threshold current of twice the rheobase current. The chronaxie time characterizes the excitability of a given tissue with a given pulse shape.

3.1.1.2. Selectivity based on target localization and fiber size. The effect of waveform on stimulation selectivity has been extensively studied for square pulses. In general, electrical pulses excite thicker nerve fibers at lower thresholds than thinner one (Eq. (2), I_{th}: threshold current, D: diameter), and fibers closer to the electrode at lower threshold than fibers at a larger distance (Eq. (3), I_{th}: threshold current, I_R: offset, k: slope, r: distance) (Horch and Dhillon, 2004).

$$I_{th} = I_D + \frac{a}{\sqrt{D}} \quad (2)$$

$$I_{th} = I_R + k \times r^2 \quad (3)$$

Selectivity regarding fiber diameter depends on the pulse width, with shorter impulses increasing the difference in stimulation thresholds between fibers of different diameters (Grill and Mortimer, 1995). Conduction velocity increases with fiber diameter, and different conduction velocities are associated with different sensory modalities (Fig. 2). Thus, stimulation paradigms with increased fiber diameter selectivity are desirable when targeting a particular percept, including nociceptive feedback (i.e., small and slow conductive C fibers).

The pulse width also affects the spatial selectivity of the stimulation. Shorter pulses increase the stimulation threshold difference between fibers at different spatial location, with closer fibers stimulated first than distant ones (Grill and Mortimer, 1995). A pre-pulse can also modify the activation threshold of fibers of different diameters. Hyperpolarization and depolarization pre-pulses, for example, alter the initial state of the membrane (through changes in ion channel dynamics) bringing it into a transient refractory state and thus affecting its response to a subsequent impulse. Using hyperpolarization pre-pulses, APs can be elicited even with sub-threshold impulses (i.e., reducing the activation threshold), while the generation of an AP using a supra-threshold impulse can be inhibited by a depolarization pre-pulse (Grill and Mortimer, 1997, 1995). The delay between the cathodic and anodic phases (Fig. 3) also affects the stimulation selectivity of fibers with different diameters, reaching optimal selectivity when this delay is zero (Gorman and Mortimer, 1983). Fibers with different diameters can also be selectively stimulated by applying a train of pulses of high frequencies (600 Hz), mimicking the physiological recruitment order but requiring more energy (Baratta et al., 1989; Solomonow, 1984). Lertmanorat and Durand proposed a multipolar stimulation modality involving selective activation of individual fibers according to the activation function of the nerve diameter, which allowed thin fibers to be activated separately from thick fibers (Lertmanorat et al., 2004; Lertmanorat and Durand, 2004; Stieglitz, 2005). Efficiency and fiber selectivity can be also optimized by dividing each pulse in short bursts of square pulses, called pulsons (Fig. 3) (Qing et al., 2015).

3.1.2. Stimulation with non-square pulses

Stimulating with non-square pulses has advantages and disadvantages over square pulses, including different stimulation efficiency (Jezernik and Morari, 2005; Krouchev et al., 2014; Maciejasz et al., 2015; Wongsarnpigoon et al., 2010; Wongsarnpigoon and Grill, 2010) and selectivity (Fang and Mortimer, 1991; Hennings et al., 2005), as well as consequences on tissue damage (discussed in detail below). It has also been shown that the pulse shape modifies the chronaxie value in Eq. (1), as the current injection rate with non-rectangular shapes are non-uniform for the duration of the pulse, contrary to the constant rate produced with squared pulsed (Sahin and Tie, 2007; Wessale et al., 1992).

Stimulation efficiency is important to prolong battery life in implants (for a review see the work published by Grill (2015)). Table 1 provides an overview and general comparison of different stimulation pulse shapes. In a study using simulations and *in vivo* experiments, Wongsarnpigoon and colleagues tested the influence of square, rising exponential, decaying exponential, and rising ramp pulse shapes on stimulation efficiency (Wongsarnpigoon et al., 2010). They concluded that none of the waveforms can be simultaneously optimally efficient in terms of energy, charge, and power. It was also observed that for pulse widths shorter than

Table 1
Comparison of different stimulation pulse shapes (++: medium effect; +++: strong effect; PW: pulse width).

Shape	Selectivity	Efficiency		Reference
		Energy	Charge	
	+ +	+ +	+ +	Lilly et al. (1955) (Today: square pulses with charge balanced are commonly used)
				
	+ + +	+ + (PW < 0.1 ms)	+ + + (PW < 0.05 ms)	Gorman and Mortimer (1983), Grill and Mortimer (1995), Krouchev et al. (2014) and Wongsarnpigoon et al. (2010)
	+ + +	+ + +(2 ms < PW < 0.1 ms)	+ + +	Hennings et al. (2005) and Wongsarnpigoon et al. (2010)
	/	– – –	– – –	Wongsarnpigoon et al. (2010)
	/	+ + + (PW > 2 ms)	+ + +	Wongsarnpigoon et al. (2010)
	+ +	/	+ + +	Maciejasz et al. (2015)
	+ + +	/	/	Bhadra et al. (2006), Fang and Mortimer (1991) and Tosato et al. (2007)
	/	+ + +	+ + +	Wongsarnpigoon and Grill (2010)
	+ + +	/	+ + +	Qing et al. (2015)

0.1 ms, square and exponential pulses were equally energy-efficient, while for pulse width longer than 0.5 ms square pulses were the least efficient in terms of energy (Wongsarnpigoon et al., 2010). Krouchev and colleagues also agreed that for short pulses, rectangular pulses are frequently the most optimal for electrical stimulation (Krouchev et al., 2014). Charge efficiency was increased without jeopardizing the selectivity of stimulation by using a delayed discharge after the stimulation (Maciejasz et al., 2015). An optimal energy-efficient waveform was found using a genetic algorithm, approaching a truncated Gaussian shape (Wongsarnpigoon and Grill, 2010). Gaussian pulses were found also optimal along with linear and exponential decrease pulse shapes in terms of charge efficiency (Sahin and Tie, 2007).

Regarding selectivity, quasitrapezoidal pulses have been shown to block alpha fibers with lower current levels and activate gamma fibers at higher current levels by means of membrane hyperpolarization (Fang and Mortimer, 1991). Quasitrapezoidal pulses proved selective when stimulating the fibers of the vagal nerve (Tosato et al., 2007) and in the control of the urinary bladder (Bhadra et al., 2006; Stieglitz et al., 1997). Exponential rising waveforms have also shown increased size selectivity in motor fibers (Hennings et al., 2005). However, these methods require more energy than non-blocking pulse shapes.

3.1.3. Tissue damage and safe stimulation

Tissue (and electrode) damage depends on the stimulation waveforms as well as on the material chosen to fabricate the stimulation electrodes. The choice of waveform and material is defined by the mechanism of charge injection. There are two types of charge transfer mechanisms: capacitive and faradic charge transfers (Cogan, 2008; Horch and Dhillon, 2004; Merrill et al., 2005). During capacitive transfer there is no creation or consumption of chemical species, making it attractive to minimize electrode and tissue damage. However, except in the case of porous materials or coatings featuring a high dielectric constant, high charge injection rates are unattainable with this type of mechanism (Cogan, 2008). Faradic charge transfer involves the transfer of electrons and requires the oxidation or reduction of species at the surface of the electrode or in the solution (Cogan, 2008). This mechanism is less attractive due to higher risk of electrode and tissue damage, but provides the advantage of higher levels of charge injection during stimulation. Faradic or pseudofaradic electrodes are still state of the art and favorable in their performance after serious risk-benefit analysis (Cogan, 2008).

Pulse waveforms may influence tissue and electrode damage by corroding the electrode. This process is irreversible and therefore, undesirable. Counterintuitively, corrosion is more likely to happen during charge-balanced stimulation than with monophasic stimulation due to increased stimulation thresholds and a corresponding increase of electrode potentials reached during the reversal phase. A delay between cathodic and anodic phase of the stimulation pulse helps to minimize the increase in stimulation thresholds (Merrill et al., 2005; Scheiner et al., 1990). Charge-balanced stimulation at charge injections less than 0.4 $\mu C/mm^2$ is considered safer than monophasic stimulation for chronic implants (Mortimer et al., 1981). Beside corrosion, tissue damage may also be caused by overstimulation, producing the unnatural AP firing rates or durations. The creation of toxic electrochemical reaction products at intolerable rates is also a source of tissue damage (Merrill et al., 2005), while pH changes are not a main cause for tissue injury (Scheiner et al., 1990). Stimulation frequency and duty cycle have been correlated to early axonal degeneration (EAD), with less damage produced at 20 Hz than stimulating with 50 or 100 Hz (Agnew et al., 1989; McCreery et al., 1995).

Number of pulses and pulse duration is also associated to tissue damage, with damage decreasing with the number of pulses. The maximum damage threshold to stimulation threshold ratio (i.e., maximum range of safe stimulation) occurs at pulse durations near chronaxie. (Butterwick et al., 2007). During charge-balanced stimulation, damage can be reduced with shorter pulse widths

Table 2
Stimulation paradigms for eliciting sensory percepts (PW: pulse width, PA: pulse amplitude, IPI: inter-phase interval).

Precept	Control mode	Polarity	PW (μs)	PA (μA/V)	IPI (μs)	Freq. (Hz)	Duration (s)	Ref.
Pain	Voltage	–	250	0.18–0.22	–	3, 5, 30	2–5	Ochoa and Torebjork (1989)
Touch, joint movement and position	Current	Monophasic or biphasic (charge balanced)	250	17–70	–	10–500	0.5	Dhillon et al. (2004)
Grip force and joint angle	Current	–	300	–	–	10–500	0.5	Dhillon and Horch (2005)
Object size and stiffness	–	Biphasic	290	–	75	20–200	–	Horch et al. (2011)
Tapping with a pen	Current	Biphasic (charge balanced)	–	100–180	–	8–20	–	Ortiz-Catalan et al. (2014)
Tingle, pressure, vibration, hair and air brush, and cold	Current	Biphasic (charge balanced)	200	1–100	100	1–320	0–60	Davis et al. (2016)
Touch	Current	Biphasic (charge balanced)	5–255	300 – perception	–	12–166	1–5	Graczyk et al. (2016)
Texture	Current	–	100	160	–	–	–	Oddo et al. (2016)
Contact between hand and object, and tingle, pressure and movement	Current	–	200	10–12	–	200	0.2	Clark et al. (2014)
Touch, object shape and stiffness	Current	Biphasic	–	Proportional to force level (limit is chemical safe charge of 120 nC)	–	50	0.5	Raspopovic et al. (2014)
Touch	Current	Biphasic (charge balanced)	24–60	1000–1200	–	100	–	Tan et al. (2014)
Force, embodiment	Current	Biphasic (charge balanced)	255	–	–	10–125	–	Schiefer et al. (2016)
Grasping force	Current	Biphasic (charge balanced)	50–500	10–500	50	30	–	Mastinu et al. (2017)

(McCreery et al., 1992). Charge density and charge per phase have been shown to interact synergistically in producing cortical tissue damage in cats (McCreery et al., 1990). Metrics for safe stimulation limits have been proposed and Shannon's k-factor is still used as a heuristic parameter to select safe stimulation parameters (Shannon, 1992). However, actual size and material of the electrodes as well as the targeted nerve and its pathophysiological status eventually determine if a stimulation protocol is safe or harmful. In addition, mechanical damage can occur, depending on the anchoring technique used during electrode implantation (Girsch et al., 1991; He, 2005).

3.2. How does fiber stimulation allow for restoring the senses of touch, force and proprioception?

Deeper comprehension of neural interface technologies (Navarro et al., 2005) has prompted the use of knowledge on single fiber stimulation and sensing physiology as described above to restore natural sensory feedback in humans. The hand has been the preferable target for sensory restoration to close the loop in the control of prosthesis. A summary of stimulation paradigms and their respective gain of function is provided in Table 2.

One of the first attempts to restore sensory information via electrical stimulation of afferent pathways was reported more than forty years ago (Anani et al., 1977; Clippinger et al., 1974). Although most of the outcomes of these studies were mainly related to paresthesia, this pioneering work enabled the production of artificial sensations by modulating the frequency and amplitude of electrical pulses. Later, Ochoa and Torebjoerk stimulated the C nociceptor fibers of the hand with intraneural microstimulation and successfully elicited sensations of pain (Ochoa and Torebjork, 1989). This study used voltage-controlled square pulse with 0.25 ms width and 2–5 s duration, stimulation frequencies of 3, 5 and 30 Hz, and varied amplitude ranging from 0.18 to 0.22 V.

Revived interest in this area expanded the repertoire of sensations that could be successfully delivered to the CNS to include contact timing between an object and the hand, grasping forces, location of the object relative to the hand and skin, and position of the fingers and hand in space. Researchers have chosen to deliver this type of information deliberately, to favor object manipulation over object exploration, as this is the main use of somatosensory information in humans (Delhaye et al., 2016).

3.2.1. Which sensations can be restored?

One of the first studies providing evidence that electrical stimulation of the peripheral nerves might restore somatosensory sensations in amputees was reported by Dhillon et al. (2004). Implanted intrafascicular electrodes were placed in eight amputees to elicit the sensations of touch, joint movement, and position. Rectangular pulses (monophasic, capacitively coupled, or biphasic, charge-balanced) with a duration of 250 μs and an amplitude of 200 μA were used to stimulate each electrode separately. The pulse amplitude was varied stepwise to determine the perceived threshold and upper limit for stimulation amplitude. A pulse train of amplitudes ranging between the perceived threshold and the upper limit (from 17 μA to 70 μA; pulse train durations of 500 ms) with varied stimulation frequency was then applied accordingly to the presented stimulus (distributed logarithmically and ranging from 10 to 500 Hz). With this paradigm, it was possible to produce discrete and graded sensations of touch (mainly referred to the finger tips) and, with practice, proprioceptive sensations, including movement of the whole finger and individual joints. A follow-up study by Dhillon and colleagues tested whether short-term training over time could affect the elicited sensory feedback when using similar electrical stimulation paradigms (Dhillon et al., 2005). However, no significant differences were present in the elicited sensations within the time frame of the study.

In another study, Dhillon and Horch reported a direct neural feedback framework for prosthetic control (Dhillon and Horch, 2005). This approach provided grip force and joint angle information back to amputees by means of intrafascicular electrodes implanted in the median nerve. The stimulation paradigm consisted of first identifying which electrode elicited sensations of touch and pressure, and which ones elicited proprioception. This was performed by using 500 ms pulse trains with a fixed pulse width of 300 μs and varying pulse amplitude in a current-controlled framework. Once the electrodes were identified, the frequency of the stimulation was varied to map the presented stimulus, ranging between 10 and 250 Hz for proprioceptive feedback and between 10 and 500 Hz for touch sensations.

Some years later, Horch and colleagues reported that object size and stiffness discrimination is also possible by electrically stimulating the peripheral nerves with intrafascicular electrodes (Horch et al., 2011). The stimulation paradigm in this study consisted on biphasic pulse trains with varied pulse frequency, varied pulse amplitude, constant pulse duration (290 μs), and a constant interphase interval (75 μs). Pulse amplitude was adjusted to a level the subject was comfortable with and stimulation frequencies ranged between 30 and 200 Hz for proprioception and between 20 and 170 Hz for touch percepts. With this stimulation paradigm, one of the two subjects participating in this study was able to distinguish between nine different objects with a performance statistically above chance.

After the pioneering work of Dhillon and Horch, several studies continued to report success stories of sensory restoration. Using a osseointegrated prosthetic arm, Ortiz-Catalan and colleagues provided long-term sensory feedback by means of electrically stimulation of the ulnar nerve with a cuff electrode (Ortiz-Catalan et al., 2014). In this study, the participant was able to distinguish pulses up to 8 and 10 Hz, where the projected field increased in proportion to current amplitude and train frequency.

Sensory information has also been delivered using an array of 96 electrodes (Utah Slanted Electrode Array- USEA) implanted intrafascicularly in an amputee to provide access to larger sensory pathways (Davis et al., 2016). Using current-controlled, biphasic, cathode leading stimulation (pulse amplitude ranging from 1 to 100 μA, train frequency raging between 1 and 320 Hz, pulse width of 200 μs and inter phase duration of 100 μs), Davis and colleagues were able to elicit sensory percepts of tingle, pressure, vibration, hair brush, air brush, and temperature (cold).

By electrically stimulating the median, ulnar, and radial nerves of an amputee with square biphasic, charge-balanced, cathodal phase leading pulse trains, Graczyk and colleagues were able to manipulate tactile perception intensities by varying the pulse width and pulse frequency in a synergetic cooperative manner (Graczyk et al., 2016).

Recently, the work by Oddo and colleagues has further demonstrated that discrimination of different textural features are possible when electrically stimulating the afferent pathways of an amputee (Oddo et al., 2016). They used an artificial fingertip, which utilizes a mechano-neuro-transduction mechanism that approximates the firing dynamics of the SA1 afferents units. This mechanism was paired with electrical stimulation paradigms applied to the median nerve via implanted intrafascicular electrodes. The stimulation paradigm consisted of pulse trains with pulse duration of 100 μs and amplitude of 160 μA, which was triggered every time a spike from the artificial finger was produced.

3.2.2. How to close the afferent loop in hand prostheses?

The above mentioned studies have provided evidence that electrical stimulation of peripheral nerves may enable restoration of sensory feedback in humans. Major technological breakthroughs made it possible in some pilot studies to close the control loop of prostheses using artificial sensory feedback.

Clark and colleagues demonstrated that the USEA can be used to stimulate peripheral nerves to provide sensory feedback during online closed-loop control of a virtual hand (Clark et al., 2014). In this study, the stimulation of afferent nerves elicited sensations of contact events between the hand and a virtual target, while the hand was controlled with signals recorded on-line with the same electrode array.

Sensory information was also restored in real time while controlling a hand prosthesis in a study reported by Raspopovic and colleagues (Raspopovic et al., 2014). Intrafascicular electrodes were implanted for 30 days in the median and ulnar nerves to elicit sensations of touch in the index, thumb, and little fingers. The stimulation paradigms consisted of current-controlled cathodic rectangular biphasic pulse trains, stimulation frequency of 50 Hz, and stimulation time of 500 ms. The current amplitude was modulated in proportion to the force level sensed by the artificial sensors of the prosthetic hand. The provided sensory feedback assisted the amputee in correctly adjusting the force applied by the prosthesis during object manipulation, and to distinguish different object shapes and levels of stiffness, in an intuitive manner without visual or audible information (Raspopovic et al., 2014).

In the same year, Tan and colleagues also reported that touch perception delivered by electrical stimulation of an amputee's nerves with long-term implanted cuff electrodes improved the control of grasping force for a prosthetic hand (Tan et al., 2014). Here, the stimulation paradigm consisted of biphasic charge-balanced square pulse trains. Pulse trains usually had a frequency of 100 Hz. Constant pulse amplitude and varied pulse width (pulse width modulation with a 1 Hz sinusoidal function) produced a natural perception of pulsing pressure. When the pulse width excursion (i.e., range of variation of the pulse width) was reduced to around 5 μs, the sensation changed to a constant pressure. Paresthesia appeared during stimulation with constant pulse and width, the intensity of which was modulated by the frequency of the pulse train. The improvement in force control of a hand prosthesis was confirmed with a greater success rate in pulling the stem of cherries during a bimanual task. The same two study subjects were monitored after 2 years and it was reported that sensory feedback comparable to that of the initial assessment was achieved by applying the same set of stimulation paradigms during the control of a prosthetic hand in task mimicking activities of daily living (Schiefer et al., 2016).

Further hardware and software developments performed on the osseointegrated system presented by Ortiz-Catalan and colleagues allowed closure of the control loop with sensory information while grabbing different objects, including eggs and grapes (Mastinu et al., 2017). Constant amplitude (maximum ±500 μA) and pulse width (between 50 and 500 μs) with variable frequency proportional to the grasping force (maximum 30 Hz) were included in the stimulation paradigm with a maximum voltage of 10 V. The interpulse phase (i.e., the delay between pulses of different polarity) was fixed to 50 μs, and the amplitude and width of the secondary phase was reduced and delayed by a factor of ten, respectively. Ortiz-Catalan and colleagues have recently reported the use of this system for close-loop control during activities of daily life outside of controlled environments (Ortiz-Catalan et al., 2017).

3.2.3. Sense of embodiment

Successful sensory feedback in prosthesis would ideally not only provide tactile information but also proprioception and the sense of embodiment (Murray, 2008, 2004). Restoration of the sense of embodiment via electrical stimulation of peripheral nerves, which would recuperate the sense of ownership of the whole or a part of our body, has not yet been critically evaluated. Even though restoring motor function has been the highest priority, the lack of attention to eliciting embodiment sensations via electrical stimulation is remarkable, especially after the famous study of the rubber hand illusion reported by Botvinick and Cohen (1998), where congruent sensory stimulation of both a real and an artificial hand, resulted in the latter being felt as a real part of the subject's body. This finding extended to other parts of the body including the foot (Crea et al., 2015a) and the arm (Slater et al., 2008). This illusion emerges from adequate delivery of visual and cutaneous sensory feedback together with proprioceptive information, including the one provided by muscle spindles (Butler et al., 2016). Proprioceptive information appears to fuse with visual information to form an intermediate percept (Fuchs et al., 2016). The synchrony between the visual and tactile stimulus must have a maximum delay of 300 ms (Bekrater-bodmann et al., 2014). Experiments using neuromagnetic source imaging whereby subjects were subjected to the rubber hand illusion showed that modulation of the primary somatosensory cortex occurs upon visual information, making it possible to feel an artificial limb as part of their body (Schaefer et al., 2006).

Assessment of embodiment was reported by Schiefer and colleagues in two hand-amputated patients who were treated with implanted electrodes for two years (Schiefer et al., 2016). Assessment of sense of embodiment was performed using a survey protocol previously utilized by Marasco and colleagues (Marasco et al., 2011). Marasco and colleagues adapted the original rubber hand illusion protocol to evaluate sense of embodiment in patients who underwent targeted nerve reinnervation procedures. The results showed significantly greater sense of embodiment in both subjects when sensory feedback was provided by electrical stimulation. Further, embodiment has been reported in the case of osseointegrated prosthesis due to osseoperception (Lundberg et al., 2011).

3.3. Stimulation outcome measures

3.3.1. Subjective measures

Three major approaches have been employed to perform subjective measurements of stimulation outcomes, namely psychophysical tests, questionnaires, and contralateral matching. Several studies on electrical stimulation of the peripheral nerves have used psychophysical tests to evaluate their research questions. Despite its early origins in the nineteenth century, the field of psychophysics continues to be actively used by neuroscientists (Read, 2015). A psychophysical test aims to quantify the perception of an applied sensory stimulus. This is usually performed by verbally reporting a value proportional to the perceived stimulus in a predefined scale. A psychometric function is then constructed by estimating the probability of detection of a certain level of the stimulus (Read, 2015). From this function, the just-noticeable difference (JND) is determined, which represents the change in the stimulus level that yields 75% chance of discrimination.

The JND has been used for instance in evaluating the discrimination of small increments in pulse width and frequency in the work of Graczyk and colleagues (Graczyk et al., 2016). Psychophysical testing was also used in two studies to test the response to different stimulation frequencies, mapped as the magnitude of the evoked sensation in an open numeric scale (Dhillon et al., 2005, 2004). In a different protocol, Oddo and colleagues utilized the three-alternative force-choice (3AFC) protocol to measure the discrimination of different surface textures using electrical stimulation (Oddo et al., 2016) (adapted from the work reported elsewhere (Gibson and Craig, 2005; Perez et al., 2010)). This protocol was used to test if two surfaces presented consecutively have the same or different textures (e.g., if one has larger spatial period of groves and ridges than the other).

Questionnaires have been used to estimate the modality of sensation elicited by electrical stimulation and to map the projected areas of the stimulation, as well as the level of embodiment. Questions regarding the modality of the sensory percepts (e.g., pressure, vibration), location, size, and intensity were used in several studies, where a map of the hand with dots representing the size and location of the stimulus was created (Clark et al., 2014; Davis et al., 2016; Dhillon et al., 2005; Ortiz-Catalan et al., 2014; Tan et al., 2014). As mentioned above, questions related to embodiment were used in the study published by Schiefer and colleagues, where adapted surveys from experiments with the rubber hand illusion were implemented (Schiefer et al., 2016). The main adaptation in this study was that the artificial hand is not touched by the investigator as in the rubber hand illusion, but it is stimulated when subjects grasp an object. This test helped to identify changes in the sense of embodiment when sensory feedback was provided.

Finally, contralateral matching has been used by Tan and colleagues to confirm that the frequency of a pulsatile pressure stimulus (i.e., a 1 Hz sine pulse) was successfully sensed by the study participant (Tan et al., 2014). When it applies to hand prosthesis, contralateral matching is performed by tapping on a manipulator with the contralateral intact hand (using the same stimulated-perceived- palmar location) in synchrony with the pressure stimulation pulse.

3.3.2. Objective measures

Objective measurements include the assessment of limb temperature, cortical involvement (i.e., brain source topography, response timing, and clustering of cortical connections), and success to failure ratio of task performance. Limb temperature is considered an indirect way of objectively measuring embodiment of an artificial limb as suggested by experiments with the rubber hand illusion (Moseley et al., 2008). Even though this has not yet been tested during electrical stimulation of peripheral nerves, the relationship between temperature and sense of embodiment has been demonstrated in tactile stimulation after targeted sensory reinnervation (Marasco et al., 2011). A system specifically designed to measure embodiment using the rubber hand illusion and measurements of body temperature has been recently reported (Benz et al., 2016). This system is suitable to assess embodiment after stimulating the peripheral afferents as it provides a coordinated visual and tactile stimulus that can be programmable, providing standardized and reproducible experiments for different stimulation paradigms.

Yet not via implanted electrodes but with microstimulation needles, cortical measurements have been used to test whether brain activity recorded with mechanical (natural) stimulation differed from brain activity recorded during electrical stimulation (Oddo et al., 2016). In this study, brain source topography, response timing, and clustering of cortical connections were investigated as ways of objectively measuring how realistic the precepts elicited by microstimulation were produced at the cortical level.

During closed-loop control with direct artificial sensory feedback, a measure that summarizes the outcomes of afferent nerve stimulation is the performance of a given manipulation task (i.e., motor control during manipulation or object recognizing during exploration). In this context, accuracy or the percentage of correctly performed tasks are the measurements usually selected by the experimenters (Horch et al., 2011; Raspopovic et al., 2014; Schiefer et al., 2016; Tan et al., 2014). Reduction in force exerted over an object has also been presented as positive outcomes of using electrical stimulation for sensory feedback restoration (Tan et al., 2014). Recently, a task force has been setup by the Defense Advanced Research Projects Agency (DARPA) of the USA to define measures of how improvements owing to sensory feedback can be assessed.

4. Conclusions and future directions

The past four decades have witnessed tremendous progress in understanding how human senses interpret the inner and outer world. This fundamental understanding has helped to develop procedures to successfully stimulate single fibers using electrical stimulation. More recently, advances in the technology to fabricate implantable devices have opened the door to the restoration of natural sensory feedback using artificially generated information. However, further research is necessary to achieve long-term stable stimulation of the peripheral nervous system that produces natural-like perceptions.

An adequate modulation of the amplitude and frequency of pulse trains is crucial. There seems to be an additional phase encoding in the stimulation patterns, which helps perceiving the presented stimulus without ambiguity. Reconstruction of sensory feedback demands increased stability of implantable devices and understanding of the physiological events occurring during and after simultaneous stimulation of several afferent fibers. Understanding the mechanisms responsible for deterioration of stimulation efficacy over time, and improved physiological models that explain the different percept elicited during electrical stimulation are crucial in moving forward.

Although long-term stability of implants is mainly determined by electrode fabrication techniques and materials, there is room for stimulation paradigms to help in this process. For instance, stimulating with alternative pulse shapes that minimize charge injection, reducing electrode and tissue damage may help developing more stable implants. Notably, restoration of sensory feedback in humans has only been attempted using square pulses. As we discussed above, stimulating with different pulse shapes or using subthreshold pre-pulses have proven to be useful to increase spatial and fiber size selectivity in animal models and simulations, but none of these paradigms have been employed to restore natural perceptions in humans. Although less well investigated, stimulation with noise may also prove useful to exploit the natural processes intrinsic to sensory signal transduction and processing in humans.

As new technologies emerge and we improve our understanding on human-machine interactions, the restoration of sensory feedback will become common practice in clinical settings. Results might be translated into increased controllability of prosthetic devices during object manipulation (upper limb) and improved balance and increased walking speed on unknown ground (lower limb). Enhancing intuitiveness and sense of embodiment warrant the change of perception of next generation prostheses from assistive devices towards real bionic limbs.

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Declaration of interest

None of the authors have potential conflicts of interest to be disclosed.

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