

Biomimetic approaches to bionic touch through a peripheral nerve interface



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ABSTRACT

State-of-the-art prosthetic hands nearly match the dexterity of the human hand, and sophisticated approaches have been developed to control them intuitively. However, grasping and dexterously manipulating objects relies heavily on the sense of touch, without which we would struggle to perform even the most basic activities of daily living. Despite the importance of touch, not only in motor control but also in affective communication and embodiment, the restoration of touch through bionic hands is still in its infancy, a shortcoming that severely limits their effectiveness. Here, we focus on approaches to restore the sense of touch through an electrical interface with the peripheral nerve. First, we describe devices that can be chronically implanted in the nerve to electrically activate nerve fibers. Second, we discuss how these interfaces have been used to convey basic somatosensory feedback. **Third, we review what is known about how the somatosensory nerve encodes information about grasped objects in intact limbs and discuss how these natural neural codes can be exploited to convey artificial tactile feedback. Finally, we offer a blueprint for how these codes could be implemented in a neuroprosthetic device to deliver rich, natural, and versatile tactile sensations.**

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1. The importance of touch

Somatosensory feedback is critically important in activities of daily living, such as tying our shoe-laces, grasping objects, or even turning a door knob (Johansson and Flanagan, 2009; Marsden et al., 1984; Witney et al., 2004). Without touch and proprioception, these motor acts would require constant visual monitoring and would be slow, cumbersome, and error-prone. Touch is also an important way to communicate emotions to loved ones (Hertenstein et al., 2009). Finally, touch sensations are critical to the embodiment of our limbs, the feeling that they are a part of us (Botvinick and Cohen, 1998; Tsakiris and Haggard, 2005). Embodiment may help amputees think of the prosthesis as a body part rather than just a tool (Marasco et al., 2011).

Over the last decade, prosthetic hands have become increasingly anthropomorphic and state-of-the-art prostheses can nearly duplicate the functionality of human hands (Johannes et al., 2011; Reichel, 2004). Major strides have been made in the development of approaches to control these hands either by decoding motor intent from myoelectric signals (Fougner et al., 2012; Schultz and Kuiken, 2011) or from the activation of neurons in motor cortex (Bensmaia and Miller, 2014; Wodlinger et al., 2015). In contrast,

approaches to restore the sense of touch are still in their infancy. While tactile signals can be relayed through tactors arrayed on an intact skin region (Antfolk et al., 2013), methods of sensory substitution have limited throughput, at most can relay a few basic distinct signals, and often require extensive user training. To provide a richer and more natural form of feedback will require a direct interface with the neural circuitry that underlies natural somatosensation. All levels of the somatosensory system are active research targets for delivering somatosensory feedback, from the peripheral nerve to brainstem nuclei and cortical regions involved in processing somatosensory signals (see Weber et al., 2012 for a general overview).

In this review, we focus on approaches that target the peripheral nerve, where somatosensory signals originate, to restore somatosensation for upper-limb amputees. In contrast to brain interfaces, peripheral nerve interfaces offer a number of advantages. First, peripheral nerve procedures are associated with less risk to the patient than are brain surgeries. Second, neural coding is simpler and better understood at the periphery than it is in the brain. Third, nerve fibers provide parallel signals to the brain, so the complexities associated with electrical stimulation of the ill-understood microcircuitry of more central circuits are avoided with peripheral stimulation. Fourth, spinal reflexes (Schouenborg, 2008) and the spinothalamic pathways (important for affective touch, see McGlone et al., 2014) are engaged with peripheral interfaces while bypassed with brain interfaces.

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That directly stimulating the nerve can lead to natural and interpretable sensations has long been established: Microstimulation of single afferents elicits tactile sensations of certain qualities at distinct locations on the hand (Ochoa and Torebjork, 1983; Torebjork et al., 1987). Until recently, the main challenges to exploiting this phenomenon for use in upper-limb neuroprostheses were technical in nature. For one, peripheral nerve interfaces must be stable and safe for long-term use. Furthermore, to offer useful feedback requires that these interfaces provide multiple channels that interact with different populations of nerve fibers. Finally, each channel must selectively interact with small afferent populations to allow for greater versatility and naturalism in the evoked sensations. As we will show in this review, many of these problems are addressed by new developments in interface design. The challenge is to use these devices to deliver rich, natural, and behaviorally relevant information to the patient. First, we discuss the gross anatomy of the nerve and describe the state-of-the-art in peripheral nerve interfaces. Then, we describe how different types of tactile information are conveyed in the nerve of intact arms and how these natural neural codes can be reproduced through electrical stimulation. We provide a blue print for how to elicit naturalistic patterns of nerve activation with current peripheral nerve interfaces to evoke intuitive and verisimilar tactile sensations.

2. Overview of the peripheral nerve

Peripheral nerves carry bundles of fibers of both efferent and afferent neurons that send signals to and receive signals from distinct parts of the arm and hand. The human hand is supplied by three nerves – median, ulnar, and radial –, each of which innervates a different hand area (Fig. 1A): The median nerve innervates the lateral aspect of the palm, the palmar surface, and some of the dorsal surface of digits 1–3 (thumb, index, and middle finger), along with the palmar surface of the lateral aspect of digit 4 (ring finger). The ulnar nerve innervates the rest of the palmar surface of the hand, as well as the medial aspect of the dorsal surface of the hand. The radial nerve innervates the rest of the dorsal surface of the hand.

Each nerve carries both efferent fibers, which innervate muscles and thereby control movement, and afferent fibers, which relay information from cutaneous mechanoreceptors, proprioceptors, thermoreceptors, and nociceptors back to the central nervous system. Within each nerve, groups of fibers are bundled into fascicles, which provide a protective sheath (Fig. 1B). There are more fascicles, each carrying fewer fibers, as one proceeds from the shoulder to the wrist. At the wrist, each of the three nerves contains between 20,000 and 35,000 nerve fibers in total, most of which are sensory fibers as most muscles are proximal to the wrist. Of these, 17,000 or so are cutaneous afferents that respond

to non-noxious skin deformations (Johansson and Vallbo, 1979). The fingertips are most highly innervated by tactile afferents, reflecting their importance for object grasping, manipulation, and fine motor control (Vallbo and Johansson, 1984).

The glabrous skin of the hand contains four types of mechanoreceptors (Fig. 1C): Merkel's disks, Ruffini cylinders, Meissner corpuscles, and Pacinian corpuscles. Signals from individual (or small groups of) mechanoreceptors are carried to the brain by large myelinated (A β) fibers. Merkel's disks are innervated by slowly adapting type 1 (SA1) fibers, Ruffini cylinders by slowly adapting type 2 (SA2) fibers, Meissner corpuscles by rapidly adapting (RA) fibers, and Pacinian corpuscles by PC fibers. Each receptor confers to its respective afferent different response properties: SA1 fibers respond best to skin indentations, SA2 fibers to skin stretch, RA fibers to low-frequency skin vibrations (flutter), and PC fibers to high-frequency vibrations. SA2 and PC fibers respond to stimulation of large swaths of skin, whereas SA1 and RA fibers have small receptive fields. During natural contact with objects, all afferent types are activated and convey information about the objects' shape, size, texture and motion with respect to the skin (Saal and Bensmaia, 2014).

3. The state of the art in peripheral nerve interfaces

The development of anthropomorphic bionic hands and of algorithms to control these hands brought about a need to restore somatosensation, without which their dexterity would be severely limited. A variety of approaches were thus developed to interface with peripheral nerves to provide such feedback (see Fig. 2 for an overview). Here, we describe recent developments in peripheral nerve interfaces, along with their respective advantages and disadvantages (for a more in depth review of peripheral interfaces, see Navarro et al., 2005). In general, interfaces can be evaluated according to two criteria: stability – does each electrode interact with an identical population of afferents as time progresses? – and selectivity – does each electrode interact with a small afferent population? These two criteria are often at odds, with more selective interfaces being less stable and vice versa.

In the following, we highlight the main advantages and disadvantages of various peripheral nerve interfaces, focusing on their functional properties. For treatment of other important issues, such as biocompatibility and mechanical impedance, we refer the reader to other reviews (Grill et al., 2009; Micera and Navarro, 2009; Navarro et al., 2005). Furthermore, we focus on relatively mature techniques, most of which rely on electrical stimulation, and exclude other potentially promising approaches, including optogenetic stimulation (Towne et al., 2013) and direct stimulation using infrared light (Wells et al., 2007).

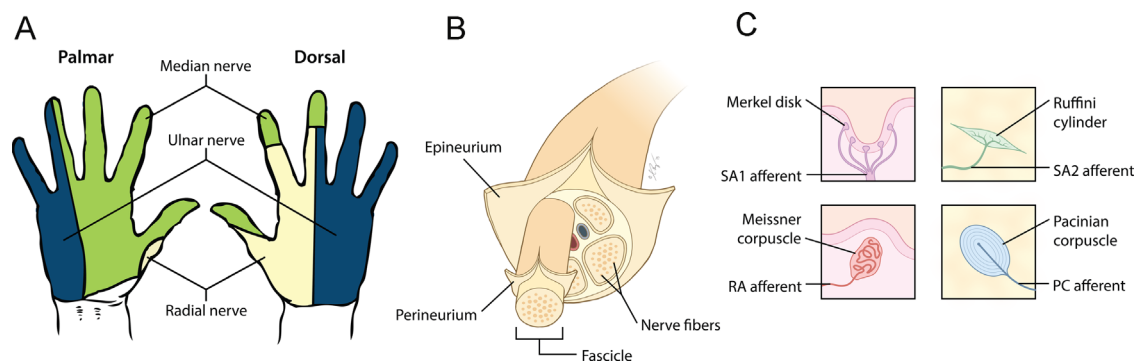


Fig. 1. A. Innervation of the hand by the three somatosensory nerves. B. Cross section of a nerve. C. Four mechanoreceptors mediate the sense of touch.

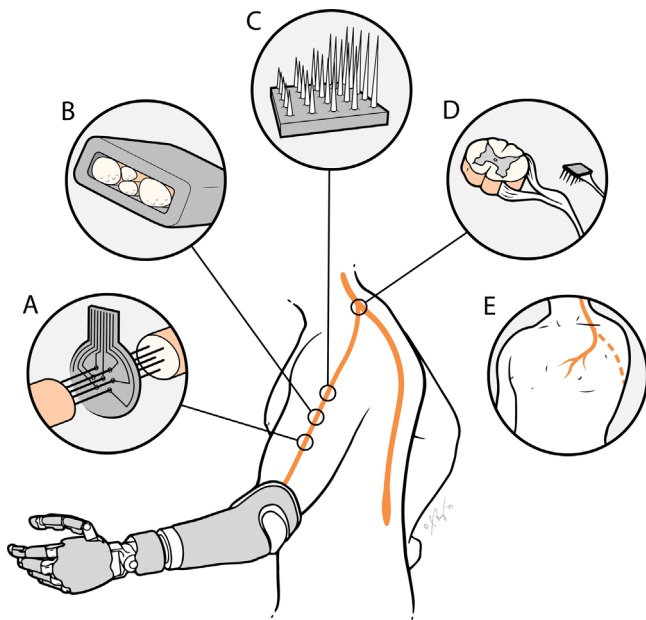


Fig. 2. Illustration of different approaches to restore the sense of touch through a peripheral nerve interface. A) Regenerative electrodes. B) Extra-fascicular electrodes. C) Intra-fascicular electrodes. D) Dorsal root ganglion implant. E) Targeted sensory reinnervation.

3.1. Targeted sensory reinnervation

In contrast to the other methods presented below, targeted sensory reinnervation (TSR) does not involve a direct electrical interface with the residual nerve. Instead, the residual nerve is surgically rerouted to a different body region (usually the chest), causing both afferent and efferent fibers to reinnervate the skin and muscles, respectively (Kuiken et al., 2007). Touching the reinnervated patch of skin elicits sensations that are experienced at the former termination sites of the rerouted fibers on the hand or arm. For example, stimulating a patch of skin innervated by fibers that once projected to the index fingertip results in a sensation that is experienced as if originating from the index fingertip. This new hand representation is not somatotopically organized, however, so touching adjacent skin patches on the chest does not result in sensations that are experienced on adjacent parts of the hand (Kuiken et al., 2007). However, the sensitivity of the reinnervated skin is comparable to that of intact skin and the elicited sensations are natural (Marasco et al. 2009; Schultz et al., 2009).

In a tactile feedback system using TSR, an array of small tactors would cover the reinnervated skin region and stimulate the skin based on the output of sensors on the prosthetic hand. This technique has the advantages that (1) no foreign objects are implanted in the body, (2) no surgical procedure is required beyond the initial surgery to reroute the nerve, (3) the interface is stable in the long-term, and (4) stimulation of the reinnervated skin patch elicits sensations that feel natural instead of tingling or paresthesia, which can occur with electrical stimulation (see below). On the other hand, the quality of the sensory feedback evoked by TSR is limited by the capability of the tactor array to produce a wide range of sensations, by the limited spatial resolution set by the available area of skin and the size of the tactors, and by the lack of control over how the skin is reinnervated by the rerouted nerve. Furthermore, while it is possible to deliver tactile feedback, this method offers no natural way of restoring proprioception. Finally, taking the tactor array on and off together with the required calibration routines makes this option rather cumbersome for daily use.

3.2. Regenerative electrodes

Regenerative electrodes consist of a sieve with a large number of fine holes that sits close to the severed nerve. When the fibers regenerate, they grow through the holes (individually or in small bundles) and can then each be selectively stimulated (Kovacs et al., 1992). In principle, this technique can achieve a high number of contacts by decreasing the size and increasing the number of the holes. By delivering growth factors that target distinct neural populations (e.g., tactile and proprioceptive), it might even be possible to eventually guide different fiber populations to specific electrodes (Lotfi et al., 2011). As the nerve requires time to regenerate, several months can pass until the electrodes become usable. Furthermore, sometimes the nerve degenerates again after some time, leading to a loss of stimulation capability (Lago et al., 2005).

3.3. Extra-fascicular electrodes

Extra-fascicular electrodes do not penetrate the protective sheath of the nerve (the perineurium). The most common type of extra-fascicular electrode is the cuff electrode (see Walker et al., 1977 for an early example), which encircles the nerve and provides a number of distinct contacts around its circumference. A recent variant of the cuff electrode, the flat interface nerve electrode (FINE), yields a higher number of contacts and better selectivity in stimulating individual fascicles due to its elongated geometry (Fig. 2B)(Tyler and Durand, 2002). Because extra-fascicular electrodes do not penetrate the nerve, they tend to cause less damage to nerve fibers than their more invasive intra-fascicular counterparts (see below) and tend to be more stable in the long-term. However, since the contacts are separated from the nerve fibers by the perineurium, higher stimulation currents are required to achieve sensation than for intra-fascicular electrodes (Grinberg et al., 2008). These higher currents lead to a broader spatial spread, which leads to the activation of larger afferent populations and often entire fascicles (Leventhal and Durand, 2003). The resulting lack of selectivity might limit the ability of extra-fascicular electrodes to elicit naturalistic patterns of neuronal activation and evoke verisimilar tactile percepts. Indeed, when an intact hand contacts an object, each afferent fiber responds differently, depending on the afferent type and on the object features that impinge on the fiber's receptive field. In contrast, electrically stimulating a large population of afferents through a single electrode leads to synchronous activation across the population, which is highly unnatural and often evokes paresthesias (Tan et al., 2014). Note that the tendency to evoke paresthesias can be somewhat mitigated by temporally modulating the stimulation pulse trains (Tan et al., 2014), perhaps in part because it reduces the degree of synchronized activity in the nerve.

3.4. Intra-fascicular electrodes

As their name suggests, intra-fascicular electrodes penetrate the perineurium, so the stimulating lead is in direct contact with afferent fibers. These electrodes tend to have more contacts than their extra-fascicular counterparts. Various intra-fascicular interfaces have been developed that differ in the electrode layout and density, including the longitudinal intra-fascicular electrode (LIFE) with contacts aligned along the nerve (Dhillon et al., 2004), the transversal intra-fascicular multichannel electrode (TIME) with contacts aligned perpendicular to the nerve (Boretius et al., 2010), and the Utah slanted electrode array (USEA) with a 10×10 array of electrodes that penetrates the nerve to different depths (Fig. 2C) (Ledbetter et al., 2013). As alluded to above, intra-fascicular electrodes require lower currents to activate nerve fibers and thus

allow for the selective stimulation of small groups of fibers (Branner et al., 2001). These electrodes might even allow for stimulation of individual fibers, if low enough current amplitudes (around 1 μ A) are used (Torebjork et al., 1987), though this has not yet been conclusively demonstrated using the implants described here. Given the higher electrode density of intra-fascicular electrodes, they offer the potential of more fine-grained and naturalistic feedback as more and smaller sets of fibers can be stimulated individually. On the other hand, these electrodes tend to damage nerve fibers, because they move around inside the nerve so their long-term stability is compromised. Finally, a problem facing both extra- and intra-fascicular implants is that (depending on the implant location) stimulation can also excite motor fibers, causing residual muscles to contract, which might interfere with control of the prosthetic hand, particularly if it is based on myoelectric signals.

3.5. Interfaces with the dorsal root ganglia

Rather than targeting the nerve at a location along the residual limb, electrode arrays can also be implanted in the dorsal root ganglia (DRG), located close to the spinal cord (Gaunt et al., 2009). Sensation to the hand is supplied by three dorsal roots (which, incidentally, do not map one-to-one onto the three peripheral nerves) so full coverage of the hand would require the same number of implants as when targeting the peripheral nerves. An advantage of targeting the DRG is that these only contain afferent fibers so accidental stimulation of efferent (motor) fibers is not a problem. On the other hand, the surgery required for a DRG implant is more invasive and dangerous than its peripheral nerve counterpart. While this technique is still in its early days, it offers a promising alternative to implants into individual nerves, if long-term viability can be established.

4. Elicitation of tactile sensations using current technologies

In previous studies on sensory restoration through peripheral nerve interfaces, the residual nerve of amputated patients was typically implanted with an electrode, electrical stimulation was applied, and verbal reports or psychophysical judgments were gathered from the patient. Parameters of electrical stimulation were manipulated to elicit sensations of different quality or to produce sensations of a given quality but varying in sensory magnitude. One way to manipulate the evoked percept is to stimulate through different electrodes. Different electrodes will activate different afferent populations, with different receptive field locations and different submodality composition (mix of SA1, SA2, RA, and PC afferents). Consequently, stimulation through different electrodes can evoke sensations experienced in different locations on the hand, determined by the projection field of the activated fibers, that is, the location on the amputated limb where they terminated before injury and where the sensation is now experienced. Stimulation through different electrodes can also evoke sensations with different qualities, determined by the submodality composition of the activated population. For example, if an afferent population is dominated by SA1, RA, or PC fibers, evoked sensations will tend to be of pressure, flutter, or vibration, respectively (Ochoa and Torebjork, 1983).

Another way to manipulate artificial sensations is to change the stimulation intensity – the amount of charge delivered to the nerve – which can be achieved by changing the amplitude or width of stimulation pulses. Increases in stimulation intensity result in recruitment, that is, the activation of additional fibers. Finally, changing the stimulation frequency, or switching from a regular pattern to an irregular one, should also affect afferents'

responses and by extension perception. Indeed, tactile sensations are shaped in part by the timing of afferent responses, down to near millisecond precision (Mackevicius et al., 2012).

Next, we discuss how tactile information has been mapped onto regimes of electrical stimulation in previous studies with peripheral nerve interfaces. Most studies have focused on approaches to convey information that is key to grasping and manipulating objects, namely information about contact location, contract pressure, as well as hand conformation.

4.1. Contact location

When we grasp and manipulate an object, it is critical to know what parts of the hand are contacting it. Minimally, the thumb and one of the fingers need to make robust contact to pick up the object. As alluded to above, stimulating through different electrodes can evoke sensations that are projected to different parts of the hand. So, for example, if fibers that used to respond to the index fingertip are activated, a sensation will be evoked on the (now missing) index fingertip. As different electrodes impinge upon distinct groups of afferents, which originally innervated different parts of the hand, stimulation through different electrodes will result in sensations that are projected to different hand locations. Indeed, patients have been shown to reliably distinguish a small number of different contact points depending on which electrode was stimulated (Clark et al., 2014; Tan et al., 2015). One might expect intra-fascicular stimulation to produce more spatially localized sensations than does extra-fascicular stimulation, as a smaller number of afferents is activated through each individual electrode with the former than the latter. So far, however, both techniques have yielded projection fields whose sizes are roughly comparable (Raspovic et al., 2014; Tan et al., 2015).

One might ask the degree to which the nerve is somatotopically organized, with nearby afferents innervating nearby hand locations. Some evidence suggests that fibers in a single fascicle respond to a spatially restricted patch of skin (Ekedahl et al., 1997); as might be expected, then, stimulation of a fascicle elicits sensations that are projected to a spatially restricted patch of skin (Marchettini et al., 1990). Importantly, stimulation through a given electrode results in sensations whose location remains relatively stable over time, at least with extra-fascicular electrodes (Tan et al., 2015). Furthermore, the projection field grows systematically when stimulation intensity increases, as might be expected given the concomitant recruitment of more nearby afferents.

In a prosthesis, then, contact location could be signaled by matching sensors on the prosthetic hand with electrodes that have corresponding projection fields.

4.2. Pressure

Grasping and manipulating an object also requires that information about the contact force between skin and object be perceptually available (Witney et al., 2004): Too little force and the object will slip, too much force and the object or prosthesis might be damaged. In most studies, information about contact force is conveyed by manipulating the intensity of stimulation, with greater intensities corresponding to higher contact forces. Intensity has been manipulated by changing pulse amplitude (Raspovic et al., 2014), pulse width (Tan et al., 2014), or pulse frequency (Dhillon and Horch, 2005). Stimulation intensity ranges from the minimum charge that elicits a sensation to the charge that elicits pain or an unnatural tingling sensation (paresthesia). Within that range, graded sensations of pressure are evoked and patients are generally able to distinguish a small number of distinct pressure levels reliably (Dhillon and Horch, 2005; Raspovic et al., 2014; Tan et al., 2014).

4.3. Complex tactile signals

Of course, the sense of touch is highly multidimensional and comprises many different qualities. Stimulation of the nerve has been shown to induce a variety of sensations with complex qualities, such as tapping on the skin, vibration, tingling, stinging, brushing, and itch (Clark et al., 2014; Tan et al., 2015; 2014). However, sensation qualities have not been systematically explored nor has it been possible to reliably and systematically evoke a sensation with a specific quality. The quality of the sensation is often electrode-specific and grows in intensity with increases in the amount of charge delivered through the electrode. Differences in evoked sensations across electrodes likely reflect differences in the submodality distribution of afferents near the electrode, as evidenced by the fact that stimulation through electrodes with glabrous and non-glabrous receptive fields elicits distinct sensations, reflecting differences in the submodalities that innervate these skin regions (Tan et al., 2014). Some evidence suggests that afferents might to some degree be clustered in the nerve based on their submodality, because nearby fibers within a given fascicle are more likely to be of the same class than would be expected by chance (Ekedahl et al., 1997; Wu et al., 1999).

4.4. Proprioceptive signals

Stimulation of the nerve can also occasionally evoke proprioceptive sensations, for example sensations of movement of a finger or a joint or a specific hand configuration (Clark et al., 2014; Dhillon and Horch, 2005; Tan et al., 2015; 2014), though the quality and gradedness of these sensations has not been systematically explored. Restoring proprioception is an important goal as a lack of this sensory modality results in diminished movement accuracy (Gordon et al., 1995), especially for complex multi-joint movements (Sainburg et al., 1995; 1993), which are typical in day-to-day use of the hand. Furthermore, our ability to identify and manipulate objects or to perform most dexterous activities is severely impaired when proprioception is lost (Cole and Paillard, 1995). The benefits of proprioceptive restoration was demonstrated in a series of simple experiments in which it was shown that conveying proprioceptive as well as tactile feedback resulted in higher accuracy when distinguishing objects that differed in size and stiffness than did conveying tactile feedback alone (Horch et al., 2011).

5. Biomimetic artificial touch

5.1. The case for biomimicry

As described in the preceding section, peripheral stimulation of the nerve has the potential to elicit sensations that are highly localized, feel natural, and are thus easily interpretable by the patient. The main problem is that, to date, systematically and stably eliciting sensations with a specific quality has proven elusive. Ideally, we would be able to restore the sense of touch in a naturalistic way. This so-called biomimetic approach has the advantage that feedback is immediately interpretable and meaningful to the patients. Another approach would consist in creating systematic mappings between patterns of sensor activation and electrical stimulation of the nerve, in the hopes that patients might learn to interpret this artificial feedback (see Dadarlat et al., 2015 for an example with an intracortical interface). The feasibility of biomimetic artificial touch hinges on the extent to which natural sensations can indeed be evoked in a systematic and reliable way. The biomimetic approach faces two major challenges: The first is that neural interfaces are inherently limited in the number

of channels and the ability of individual channels to reliably and selectively stimulate individual afferents or small populations of afferents. About 17,000 cutaneous afferents innervate the hand (Johansson and Vallbo, 1979), two orders of magnitude more than there are channels in the densest peripheral nerve interfaces. Attempting to reproduce natural patterns of activation given the discrepancy between afferent count and channel count seems doomed to failure. The second challenge is that the stability of the implants, particularly of the ones with high channel count, is inadequate. Indeed, the biomimetic approach requires that electrodes impinge on afferent populations whose projection field and response properties are consistent over time.

On the other hand, there are several advantages to the biomimetic approach. Another type of peripheral neuroprosthesis, the retinal implant, has been shown to improve dramatically in efficacy when mimicking natural retinal signals even with a relatively low channel count (Nirenberg and Pandarinath, 2012), suggesting that biomimicry is beneficial even when stimulation is relatively coarse. Indeed, cochlear implants have been highly successful, despite their relatively low channel count (~20) (Eshraghi et al., 2012). There are further benefits to the biomimetic approach. First, while the brain is somewhat plastic, not all parts of the central nervous system are. For example, spinal reflexes involving tactile cues are shaped during development (Schouenborg, 2008) and likely remain relatively fixed throughout adulthood. Second, whether patients might be able to learn to associate arbitrary mappings with peripheral events remains to be demonstrated. Indeed, many peripheral stimulation regimes evoke paresthesias, i.e. tingling or prickling sensations (Tan et al., 2014). These sensations are likely to arise from 'unnatural' afferent responses and can be caused by both over-excitation of peripheral afferents or cross-talk between them (Ochoa and Torebjork, 1980). When caused by neuropathies, paresthesias are often chronic and do not improve over time, which might reflect an inability of higher processing areas to learn to interpret such aberrant neural responses. Third, in contrast to higher processing areas, where much about the neural circuitry and the representation of tactile signals remains unknown, our understanding of tactile encoding in the somatosensory nerves is far more sophisticated, in large part because tactile afferents can be divided into a small number of classes which each exhibit very stereotyped response properties. The challenges to reproducing natural patterns of afferent activation are thus technological rather than scientific.

5.2. Principles of biomimetic tactile feedback

As alluded to above, tens of thousands of cutaneous afferents innervate the skin of the human hand, and these fall into at least four classes: SA1, SA2, RA, and PC. Each of these afferent classes responds differently to stimulation of the skin. If the elicitation of complex realistic sensations requires fine-grained control over individual tactile afferents or at least small groups of afferents of the same type, then the biomimetic approach seems doomed to fail, as current devices deliver stimulation to populations of afferents of unknown size and class composition. However, there is reason to believe that such fine-grained control might not be required to reliably elicit complex sensations with given qualities. Indeed, while different afferent types were traditionally assumed to encode a single tactile feature, such as surface texture or tactile motion, recent reinterpretation of extant data suggests that information about most tactile features is encoded synergistically by all afferent classes (see Saal and Bensmaia, 2014 for a review). Importantly, signals from multiple afferent types converge at the earliest stages of processing in somatosensory cortex (and perhaps even before) (Carter et al., 2014; Pei et al., 2009; Saal and Bensmaia, 2014), allowing for the possibility that mimicking

naturalistic patterns of activation over small populations of afferents of mixed type will result in naturalistic patterns of cortical activation, culminating in verisimilar tactile percepts.

In principle, the heterogeneity of electrically evoked sensations that has been observed on an electrode-by-electrode basis (see above) could be exploited to deliver more complex tactile feedback. Specifically, the quality of sensations evoked through each electrode could be identified in preliminary calibration tests. Then, electrodes with specific qualities could be activated when that quality is called for. This approach has several limitations: (1) it would require access to many electrodes with common receptive fields but different sensation qualities; (2) it would require that the quality of the sensations evoked through each electrode be highly stable over time given a consistent regime of stimulation; (3) it is unclear whether more complex sensations than basic ones, such as tapping and vibration, could be evoked or whether these basic sensations can be combined in a straightforward manner by stimulating simultaneously through multiple electrodes (e.g., stimulating a “brushing” and a “vibration” electrode to simulate texture). A more promising strategy would be to try to evoke different sensations by delivering spatiotemporal patterns of stimulation that evoke naturalistic activation patterns. Indeed, that different stimulation patterns can elicit qualitatively different and meaningful sensations has been described (Tan et al., 2014) but not fully explored. A major challenge is to predict how many and what tactile afferents will be stimulated by a given stimulation pattern through a specific electrode and how that pattern translates into a neural signal.

As discussed in more detail below, information about different tactile features is multiplexed in the spatial and temporal patterns of afferent activation. In a biomimetic prosthesis, spatial patterning can be achieved by stimulating different electrodes with spatially displaced projection fields, while temporal patterns can be evoked by temporally modulating the parameters – such as pulse width or timing – of stimulation delivered through each electrode. Next, we review how a number of key tactile features are encoded in the nerve and discuss how these coding schemes could be realized using current peripheral neural interfaces.

5.3. Contact location

As discussed above, information about contact location can be conveyed by stimulating through electrodes with somatotopically appropriate projection fields. Minimally, the interface should include an electrode with a projection field on each of the fingertips. To the extent that more projection fields are available, higher resolution will be available on each fingertip and greater coverage of the hand will be possible.

5.4. Contact pressure

With intact hands, we exert slightly more pressure than is needed to pick up an object, with the additional pressure acting as a safety margin against object slip (Westling and Johansson, 1984). While this safety margin is based in part on prior knowledge about the weight of objects as well as on visual cues, tactile cues that arise while grasping the object are used to rapidly correct the grip force, should it be insufficient (see Johansson and Flanagan, 2009 for an excellent review). The tactile signals underlying this correction are carried by SA1, RA, and potentially PC fibers: While the responses of SA1 afferents roughly track contact pressure, those of RA and PC afferents track changes in pressure. The combined population response is thus determined not only by contact pressure but also by its first and second derivatives (Dong et al., 2013; Kim et al., 2010). To mimic such a signal through peripheral feedback would require a scheme that not only takes the time-varying force signal into account, but also its derivatives. Likely such a scheme would improve the signaling of contact timing, i.e. the time when contact with an object is established and broken, by reproducing the large response transients that are observed, particularly in RA and PC fibers, at the onset and offset of contact (Fig. 3). More generally, information about pressure changes should be highly informative during early stages of the grasp when feedback about contact pressure is changing rapidly.

With electrical stimulation, increases in delivered charge (with higher amplitudes or wider pulse widths) are mostly associated with increases in the activated population, while increases in stimulation frequency are mostly associated with higher firing rates in the activated population. In the intact nerve, increases in pressure result in both an increase in the number of recruited fibers and an increase in the firing rates of those fibers already recruited (Muniak et al., 2007), which explains why changes in either the delivered charge or the stimulation frequencies result in changes in perceived pressure. It would be expected, then, that varying these stimulation parameters simultaneously would most accurately mimic the peripheral spiking patterns in the nerve, and, for example, might result in a larger number of pressure levels that can be perceived by the neuroprosthetic user.

5.5. Shape

Afferent signals from the hand convey information about the shape of objects. These signals allow us to position our fingers on the object such that it is at an appropriate orientation and configuration for further manipulation. Importantly, manipulating objects does not require vision. For example, we can effortlessly reach into our pocket, grasp our cell phone, and orient it correctly to dial a number, without the need to look at it. Before touch screens, it was even possible to dial a number and place a call

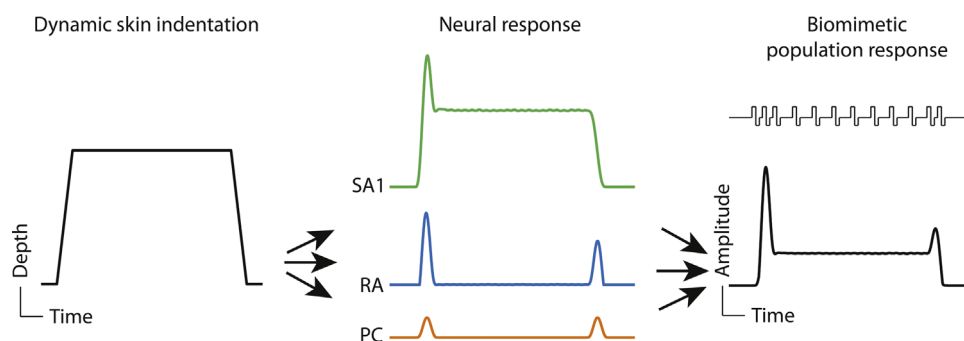


Fig. 3. Conveying dynamic pressure signals through peripheral stimulation. The peripheral response to an indented object is not just proportional to the indentation depth as RA and PC afferents also respond to the first two derivatives of time-varying depth (Dong et al., 2013; Kim et al., 2010). Combining responses from all afferent types leads to onset and offset transients as well as a sustained response, which can then be realized by modulating pulse train frequency.

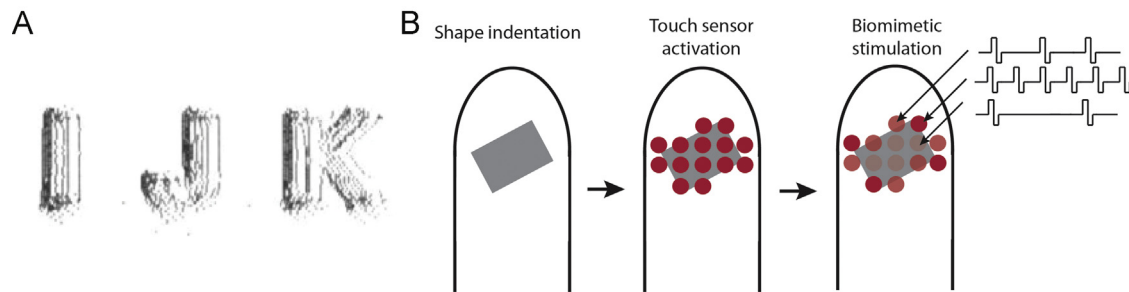


Fig. 4. A) Reconstruction of the response of SA1 afferents to letters scanned across the skin (reproduced from Phillips et al., 1988). The spatial structure of the stimulus is reflected in the spatial pattern of afferent activation. The neural basis of tactile form perception at the somatosensory periphery is thus similar to its visual counterpart in the retina. B) Conveying object shape through peripheral stimulation: An object indents the prosthetic fingertip, where a sensor array measures the spatial distribution of forces. Electrodes with projected fields corresponding to the touch sensor locations are stimulated in a manner that depends on the force applied on the associated sensors. Like in the intact nerve, afferents located close to an edge or corner respond more vigorously than afferents signaling a continuous part of the shape because the corresponding sensors experience more force.

without looking at the phone. Information about the three dimensional shape of objects is carried in the spatial pattern of activation evoked in SA1 and RA afferents. Indeed, the spatial configuration of the object is reflected in the spatial pattern of afferent activation, a representation that is highly analogous to the visual representation of shape in the retina. Specifically, afferents whose receptive fields are in contact with the object are activated whereas afferents whose receptive fields are not remain (mostly) inactive. Certain key features of the object, for example the presence and orientation of edges, are enhanced at the periphery due to skin mechanics (Fig. 4A) (Phillips and Johnson, 1981; Sripati et al., 2006) and the geometry of the receptive fields (Pruszynski and Johansson, 2014). Not only are the visual and cutaneous representations of shape analogous in the periphery, they are also analogous in cortex, both involving the decomposition of shape into a set of oriented contours (Bensmaia et al., 2008), then extracting increasingly complex stimulus features, such as curvature (Yau et al., 2013; 2009).

Biomimetic representations of shape could be achieved by activating electrodes whose projection fields correspond to the position of sensors that are activated during contact with an object. Thus, if an edge impinges on a fingertip, it will activate spatially aligned sensors, and result in the stimulation of afferents with spatially aligned projection fields (Fig. 4B). This strategy to convey spatial information will be limited by the spatial resolution of the sensor array on the fingertip and by the number of spatially resolved projection fields achievable by the interface. Currently available prosthetic fingers have spatial resolutions on the order of 2–3 mm (Johannes et al., 2011; Wettels et al., 2008), while the skin has a resolution of about 1 mm. The main spatial bottleneck, however, is the resolution of the interface, which has not been systematically quantified, but is likely to be around a fingerpad (~1 cm). As the channel count of peripheral interfaces increases – that is, as the number of distinct populations of afferents that can individually activated increases – the spatial acuity of artificial touch will improve.

Importantly, though, the perception of the three dimensional shape of objects – stereognosis – also requires proprioceptive information. Indeed, the interpretation of cutaneous signals is highly dependent on the configuration of the hand. Thus, to convey information about three dimensional shape will require that both tactile and proprioceptive feedback be restored, which constitutes a major challenge for peripheral nerve interfaces.

5.6. Slip and motion

Sometimes, our grip force is off or the grasped object is perturbed, and the object slips from our grasp. In this case, slip triggers rapid adjustments to the grip force that secure our hold on

the object. Again, grip control relies heavily on tactile feedback. Both RA and PC afferents are especially sensitive to skin slip and will respond vigorously at the onset of slip (Johansson and Westling, 1987; Srinivasan et al., 1990). Detecting slip from touch sensors embedded in a prosthetic hand will likely involve sensing the small vibrations that are elicited at slip onset.

Not only are we able to detect the onset of motion (or slip), we can also perceive the direction of motion (Pei and Bensmaia, 2014). This ability is thought to rely on the sequential activation of afferents with spatially displaced receptive fields (Gardner and Costanzo, 1980), as is also the case in the retina. To mimic the consequences of natural motion on afferent activity would involve sequentially activating electrodes with spatially displaced projection fields. As is the case with shape representation, the ability to elicit tactile motion percepts will require a relatively high density of electrodes with adjacent and preferably overlapping projection fields.

5.7. Texture

Texture information is conveyed through two mechanisms in the somatosensory nerve. Coarse textural features are encoded in the spatial pattern of activation in SA1 and perhaps also RA afferents (Connor et al., 1990; Connor and Johnson, 1992). At this spatial scale (on the order of millimeters), the code for texture is identical to that for shape. This spatial encoding mechanism is complemented by a temporal one, which mediates the perception of fine textural features. Indeed, we can distinguish textured surfaces with spatial periods that differ on the order of hundreds of nanometers (Skedung et al., 2013), a perceptual feat that is only possible when the skin moves relative to the surface. During texture scanning, high-frequency skin oscillations are elicited in the skin (Manfredi et al., 2014) that can travel the entire length of the finger (Manfredi et al., 2012) and as far away as the wrist (Delhay et al., 2012). These skin oscillations in turn evoke highly patterned and repeatable temporal spiking patterns in PC and to some extent RA fibers, and these millisecond precision spiking patterns convey information about textural features too fine to be encoded spatially (Weber et al., 2013).

Most bionic fingers comprise two types of sensors: an array of pressure sensors that can transduce spatially patterned but relatively slow deformations of the fingertip and a sensor that is sensitive to high frequency oscillations (for example, an accelerometer) (Fishel and Loeb, 2012; Johannes et al., 2011). The output of the sensor array can be used to drive a spatial pattern of stimulation that mimics the spatial layout of the coarse features of a texture. The output of the high-frequency sensor can be used to drive a temporal pattern of stimulation that mimics the texture-specific signature spiking pattern evoked in RA and PC afferents (Fig. 5).

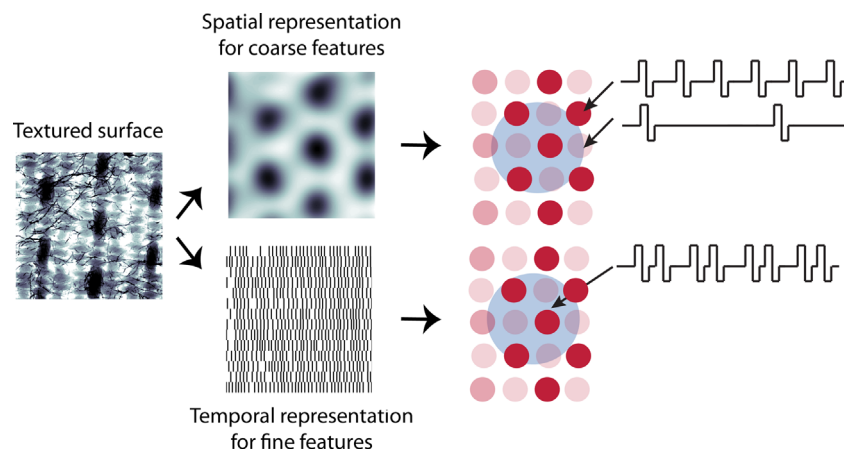


Fig. 5. Multiplexing of spatial and temporal codes. Different aspects of tactile sensation are signaled by different neural codes, which can be active simultaneously. In this example, coarse textural features are signaled through a spatial code (i.e., through the differential activation of SA1 afferents with different receptive fields), while fine textural features are signaled through a temporal code (i.e., through the precise spiking patterns of RA and PC afferents). Textures with both coarse and fine features trigger both codes at the same time.

One caveat of the schemes outlined above is that they often rely on simultaneous stimulation through many different electrodes. In concurrent stimulation, however, different electrodes cannot be treated as independent but rather interact (Branner et al., 2001; Sweeney et al., 1995). Future models will have to explicitly take such interactions into account.

6. Towards general and versatile somatosensory feedback

In the previous section, we reviewed what is known about how tactile information is encoded in the nerve, and provided suggestions as to how these neural codes could be implemented with a peripheral nerve interface. We were motivated by the notion that the more biomimetic the tactile feedback is, the more natural, rich, and meaningful it will feel to the patient. One could imagine a neuroprosthesis in which some or all of these codes (such as edge enhancement) are implemented as separate modules that are activated when applicable.

An alternative approach would consist in simulating the complex mechanics of the skin and mechanotransduction given a pattern of sensor activation. In other words, how would the skin and embedded mechanoreceptors respond were this pattern of forces applied to it? We can then use these models to estimate the response of the entire nerve given this pattern of sensor activation and this simulated response could then be realized in the patient's nerve with appropriate patterns of electrical stimulation. As discussed above, the implementation of these spiking patterns would be subject to the limitations of the interface. However, to the extent that the skin mechanics and mechanotransduction models capture the behavior of the skin and the resulting responses of mechanoreceptive afferents, the coding schemes described above will naturally arise. Such a model would likely generalize better to the infinite world of possible tactile encounters than more limited approaches designed to solve specific problems.

A general model simulating the spiking responses of large populations of afferents to arbitrary spatio-temporal stimuli does not yet exist, but it is within close reach. Indeed, sophisticated models that simulate different aspects of transduction do exist. These include skin mechanics models, which simulate the mechanical deflection of the skin resulting from arbitrary spatio-temporal stimulation of the skin (Dandekar et al., 2003; Manfredi et al., 2012; Sripathi et al., 2006); single unit mechanotransduction models, which recreate with millisecond precision the spiking patterns of individual tactile afferents of different classes to skin

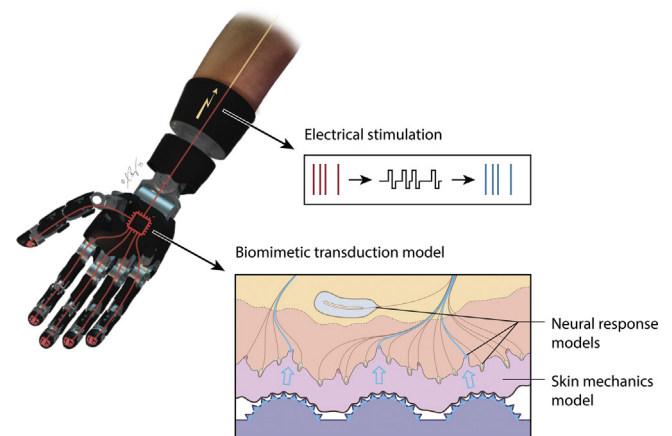


Fig. 6. Delivering somatosensory feedback using a biomimetic transduction model. Touch sensors on the prosthetic hand measure spatio-temporal distributions of pressure, which provide the input to a skin mechanics model. The resulting biomimetic skin strains form the input to precise single-afferent spiking models. Finally, the output of these models (red spikes) is transformed into electrical stimulation pulse trains (black trace) that elicit realistic spiking patterns (blue spikes) in the peripheral nerve.

deflections (Dong et al., 2013; Kim et al., 2010); and finally population models, which aggregate the responses of whole afferent populations to tactile stimulation of the hand (Gerling et al., 2014). These models can be combined to convert the output of sensors in the prosthetic hand into spatio-temporal activation patterns in the peripheral nerve that mimic those that would be produced given an intact limb (Fig. 6). At first, the evoked response will be a coarse approximation of the natural response, as the selectivity of stimulation will be limited by the technical abilities of current neural interfaces. But as interface technologies improve in their selectivity and stability, these computational models of touch will allow for increasingly rich and verisimilar artificial tactile sensations.

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