

# Implanted Neural Interfaces: Biochallenges and Engineered Solutions

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## Key Words

neural prostheses, neural stimulation, neural recording, brain-machine interface, electrode, electrical stimulation

## Abstract

Neural interfaces are connections that enable two-way exchange of information with the nervous system. These connections can occur at multiple levels, including with peripheral nerves, with the spinal cord, or with the brain; in many instances, fundamental biophysical and biological challenges are shared across these levels. We review these challenges, including selectivity, stability, resolution versus invasiveness, implant-induced injury, and the host-interface response. Subsequently, we review the engineered solutions to these challenges, including electrode designs and geometry, stimulation waveforms, materials, and surface modifications. Finally, we consider emerging opportunities to improve neural interfaces, including cellular-level silicon to neuron connections, optical stimulation, and approaches to control inflammation. Overcoming the biophysical and biological challenges will enable effective high-density neural interfaces for stimulation and recording.

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## 1. INTRODUCTION

### 1.1. Neural Interfaces Enable Information Exchange with the Nervous System

Neural interfaces are intended to exchange information with the nervous system, and this exchange can occur in two directions. Hence, electrical stimulation, a tool that allows the introduction of information into the nervous system, can be used to exert external control, for example stimulation of a motor nerve to cause a muscle to contract. The application of electrical stimulation to restore function is commonly referred to as a neural prosthesis. Electrical recording also enables extraction of information from the nervous system. Such recordings can be used to determine the internal state of an organ or organism and as potential command or feedback signals to regulate a prosthetic device.

Communication and information relay within the nervous system is primarily through the rate and pattern of impulses called action potentials, and it is the number or spacing of these action potentials per unit time that code information in the nervous system. The nervous system has neuroanatomical and neurochemical architecture, and much of its information processing is achieved by action potentials and their spatiotemporal patterns. Therefore, information can be introduced into the nervous system by inducing action potentials or, conversely, the number, rate, and/or pattern of these action potentials can be read out to recover information from the nervous system.

Information exchange with the nervous system occurs at a number of different levels. Most peripherally, information can be delivered or recovered at the level of the end organ—a muscle in the case of the motor system—or a receptor or organ (e.g., eye or ear) in the sensory system. More centrally, at the level of peripheral nerves, information can be delivered by stimulation of the nerve and can cause some action at an end organ, or information can be extracted by recording signals from sensory nerve fibers that normally carry information from the periphery to the central nervous system (CNS). Further, interfacing can occur at the level of the CNS, whether it be within the spinal cord or within the brain; again, stimulation can cause some effect, or recording can be used to learn something about the state of these systems.

This review presents the underlying biophysical mechanisms of electrical stimulation and recording at the different levels of the nervous system. These fundamental principals are, to a

large degree, understood and can, to some extent, be controlled. However, the underlying principles also create fundamental biophysical and biological challenges. Here we consider some of these challenges as well as the engineering solutions that have been proposed to overcome these challenges and enable effective high-density neural interfaces for stimulation and recording.

## 2. INTERFACING TO THE PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system (PNS) is responsible for relaying information from the brain and spinal cord to the extremities, and vice versa. Because the PNS mediates both the instructions to the periphery for motor action as well as sensory feedback, damage or trauma can result in partial or complete loss of function. Peripheral nerve function is compromised in a variety of situations, including trauma, surgery in conjunction with associated tumors, and diabetic neuropathy. Interfacing to peripheral nerves is of interest to augment motor function or to discern the sensory information they carry so that appropriate prosthetic interventions can be implemented. Interfacing to peripheral nerves is also warranted when their connection to higher brain centers is severed in spinal cord injury; in such cases, the peripheral nerves are largely intact, enabling an artificial engineering driver that taps into peripheral nerves' efficient ability to initiate peripheral muscle contraction. The feasibility of peripheral nerve stimulation to achieve a desired motor output has been demonstrated (1) and is one of the major driving forces for PNS interfacing. Interfaces to the nervous system usually take the form of electrodes for stimulation and recording, though chemical stimulation and sensing are possible. Successful interfacing to peripheral nerves can revolutionize many neuroprosthetic applications and blunt not only the functional losses associated with peripheral nerve function but also those associated with spinal cord injury.

Electrical stimulation and recording of peripheral nerves enable study of the form and function of the nervous system and allow restoration of function following disease or injury. Examples of application of peripheral nerve stimulation include the treatment of pain (2), restoration of motor functions following spinal cord injury or stroke (3, 4), and treatment of epilepsy by electrical stimulation of the vagus nerve (5, 6). Examples of the use of neural recording include the study of coding properties of peripheral sensory neurons (7) and the recovery of nerve population activity for command and feedback signals to control prosthetic devices (8).

### 2.1. Structure of the Peripheral Nervous System

Myelinated nerve fibers, unmyelinated nerve fibers, and intraneural blood vessels constitute the endoneurium and exist in bundles as individual nerve branches or fascicles within compound peripheral nerve trunks. The endoneurium is a privileged space and maintains a microenvironment, separated from the general circulation by a blood-nerve barrier, appropriate to the function and health of the nerve fibers. Each fascicle is surrounded by a tough layer of tightly packed cells called the perineurium. The individual fascicles in a compound nerve trunk are held together by a meshwork of connective tissue and fat called the epineurium. Peripheral nerves contain both myelinated nerve fibers and unmyelinated fibers, but here the focus is on excitation and recording of myelinated nerve fibers.

Fascicles are arranged topologically according to their eventual anatomical targets. The classical anatomical studies of Sunderland (9) show that, in the more distal portions of a nerve trunk, motor axons are arranged into discrete fascicles that eventually branch from the main trunk to innervate single muscles or small groups of synergistic muscles. This conclusion has been corroborated by other anatomical studies (10), and recent data support the retention of topography at more proximal levels. Intraneural microstimulation has revealed that sensory fibers remain grouped

even in the more proximal regions of peripheral nerve trunks (11, 12), and horseradish peroxidase (HRP) staining has demonstrated that the digital axons within the median nerve of the monkey remain as discrete geometrical groups from the carpal tunnel to the proximal arm (13).

When interfacing engineered devices to peripheral nerves, there are challenges that arise due to the unique biological structure of nerve cables. Peripheral nerves are three-dimensional (3D) structures, with individual fibers connecting to, and coding for, unique motor and sensory information. The resolution of the information conveyed to or obtained from these nerves is determined by the resolution of stimulation or recording from individual nerve fibers buried in the 3D neural structure. The closer a stimulation or recording electrode is to a nerve fiber that is buried within the 3D nerve cable, the more selective or specific the signal evoked or recorded (14). Therefore, the biological constraints involve tolerance to electrodes placed close to nerve fibers, the number of such electrodes that can be tolerated, isolation of individual fiber signals within the cable from the nerve surface, or projection of current to stimulate individual fibers within the cable. Other challenges include the extent to which peripheral nerves can be reshaped such that buried fibers can be accessed. In the case of regenerative electrodes, where nerves are made to extend processes over implanted electrodes (in the case of amputation, for instance), the stability of such nerve endings without their natural end organ innervation is also of concern. Damage to peripheral nerves can cause loss of function, so it is desirable to minimize implant-induced trauma. Another biological concern is the inadvertent stimulation of pain fibers and discomfort associated with peripheral nerve interfacing. Electrical stimulation can result in hyperalgesia or hypoalgesia, depending on the frequency and duty cycle of the stimulation (15).

In summary, the biological challenges associated with peripheral nerve interfacing are (a) fidelity of the interface in terms of functional resolution; (b) relatively weak, noise-ridden electrical signals causing a challenging interface design constraint; (c) interface implantation-associated injury to nerve fibers of interest; (d) stability of the interface over time due to inflammation; and (e) managing inadvertent consequences such as pain or false sensory/motor stimulation due to physical movement or inflammation-associated triggering of neural activity.

## 2.2. Challenges and Solutions for Peripheral Nerve Interfaces

**Challenge 1: selective stimulation of peripheral nerve fibers.** Selectivity refers to the ability to activate one population of neurons without concomitant activation of another, often neighboring, population of neurons. In the peripheral nervous system, the challenge of selectivity arises from two fundamental properties of nerve fiber stimulation: the current required for extracellular stimulation of axons depends first on the distance between the electrode and the nerve fiber and second on the diameter of the nerve fiber (16). We review these two biophysical properties—the current-distance relationship and the current-diameter relationship—and then consider some recent approaches to overcome or exploit these relationships.

Transmembrane potentials generated by extracellular current are largest in the fibers closest to the stimulating electrode, thus less current is required to stimulate neurons in the proximity of the electrode. As the distance between the electrode and the fiber increases, the threshold,  $I_{th}$ , increases, and for excitation of myelinated nerve fibers with a point source electrode, this relationship is described by the current-distance relationship,  $I_{tb}(r) = I_r + kr^2$ . The offset,  $I_r$ , determines the absolute threshold, and the current-distance constant,  $k$ , determines the threshold difference between fibers at different distances,  $r$ , from the electrode (17).

Similarly, in response to an externally applied stimulus, larger diameter nerve fibers (by virtue of the larger spacing between their nodes of Ranvier) experience larger changes in transmembrane potential than fibers with small diameters (and smaller internodal spacing). Thus, larger diameter

fibers are activated at smaller stimulus amplitudes than the smaller diameter fibers, and for excitation of myelinated nerve fibers with a point source electrode, this relationship is described by the current-diameter relationship,  $I_{th}(D) = I_D + a/\sqrt{D}$ . The offset,  $I_D$ , determines the absolute threshold, and the slope,  $a$ , determines how rapidly the threshold declines as the diameter,  $D$ , increases.

**Solution 1A: multiple-contact nerve cuff electrodes enable selective stimulation.** Cuff-type electrodes include conductive electrode(s) embedded in an insulating sheath (cuff) that allows positioning of the electrode(s) in immediate contact with peripheral nerve trunks. Cuff electrodes enable selective activation of peripheral nerve fibers based on their position within a compound peripheral nerve or, in combination with specialized stimulation waveforms, based on their diameter (18, 19). Multi-electrode nerve cuffs, which position independently addressable electrode contacts around the nerve perimeter, exploit the current-distance relationship to enable selective and graded stimulation of an individual nerve fascicle lying closest to the electrode contact without stimulation of fascicles more distant from the contact (20, 21). Importantly, a distributed array of electrode contacts allowed selectivity to be achieved even when the electrodes were implanted without prior reference to the fascicular structure of the nerve (i.e., random orientation between electrodes and fascicles). The results of these initial acute in vivo studies were replicated in long-term chronically implanted electrodes, which demonstrated that selectivity was maintained over time (22). However, there was temporal variability of the recruitment properties of chronically implanted multiple-contact nerve cuff electrodes even after tissue encapsulation, and there was evidence of mechanically induced neural injury arising from the presence of the nerve cuff or lead cable (23, 24). The consequences of mechanically induced neural injury remain unclear, as in these studies there was no behavioral or electrophysiological evidence of the pathology that was observed histologically. The relationship between the magnitude and extent of neural injury and the behavioral consequences of such injury remains uncertain (25).

These studies served as the foundation for subsequent application of multiple-contact nerve cuff electrodes in humans with neurological disease or injury. The first application was to stimulate the human optic nerve in persons with blindness from photoreceptor loss. A multiple-contact nerve cuff electrode was implanted on the optic nerve, and stimulation through the different contacts was able to generate visual sensations (phosphenes) in different portions of visual space, consistent with the visuotopic organization of the optic nerve and the ability to stimulate selectively nerve fibers based on their positions within the nerve (26).

More recently, the feasibility of selective stimulation of peripheral motor nerves with multiple-contact nerve cuff electrodes was demonstrated in humans (27), and, subsequently, cuffs were chronically implanted to restore upper-extremity motor function in two persons with spinal cord injury. Initial human studies were conducted intraoperatively during nerve exposures that occurred during the course of other surgical procedures. The results demonstrated that both stimulation thresholds and stimulation selectivity were comparable to those measured in preclinical animal studies. Different electrode contacts enabled activation of target muscles from 27–97% of their maximum activation before activation spread to other muscles (27). Subsequently, four nerve cuff electrodes were implanted on proximal nerves innervating the upper extremity of a person with tetraplegia. The chronically implanted electrodes exhibited stable thresholds as well as the ability to generate functional movements, including shoulder abduction, elbow flexion, elbow extension, wrist extension, and finger extension, by selective stimulation via different electrode contacts (28).

In addition to the use of multiple-electrode contacts, cuff electrode designs that control the geometry of the nerve—and thereby the spatial arrangement of fascicles—are another innovative means to achieve elective stimulation. The flat interface nerve electrode (29) increases the

perimeter of the nerve, as compared with electrodes with round cross sections, thereby providing more space to position electrode contacts around the nerve. Further, the flat interface nerve electrode (FINE) reduces the height of the nerve, thereby reducing the distance from the electrode contacts to some of the fascicles, which might be positioned more centrally in the nerve when in a round configuration. These electrodes enable selective and graded stimulation of individual nerve fascicles as well as stimulation of subregions of individual fascicles (30).

**Solution 1B: intraneural electrode arrays enable selective stimulation.** Intraneural or intrafascicular electrodes are designed to reside within a nerve fascicle and enable selective activation of peripheral nerves. Initial modeling studies suggested that intrafascicular electrodes would enable more selective activation of regions of the nerve trunk than the extraneural approach (31), and experimental studies with implanted arrays demonstrated selective stimulation of individual motor units (one motor axon and the muscle fibers that it innervates) or small groups of axons.

Pairs of Pt-Ir wire electrodes implanted in the fascicles of the sciatic innervating the medial gastrocnemius and lateral gastrocnemius/soleus demonstrated stimulation selectivity within and between fascicles (32). The degree of overlap between the two fascicles ranged from 0.8–15.6% of the maximum force, and the degree of overlap within a fascicle ranged from –11.2 to 66.5%. However, the maximum evoked forces ( $12.9 \pm 2.9\text{N}$ ) suggested that the two electrodes stimulated only a portion of the nerve fascicle.

Implantation of intrafascicular electrodes compromises the perineurium and the blood-nerve barrier, which serve to maintain the chemical and mechanical microenvironment necessary for the continued function of nerve fibers (33). Damage to the perineurium or blood-nerve barrier leads to endoneurial edema, an increase in endoneurial pressure, nerve fiber compression, and loss of nerve fibers, with the larger nerve fibers being the most vulnerable (33), and this sequence of events has been observed with chronically implanted intraneural electrodes (34). Chronically implanted intrafascicular electrodes resulted in endoneurial fibrosis and edema, loss of nerve fibers (34, 35), and variable shifts in threshold (34).

More recently, high-density arrays of integrated silicon-based electrodes have been used for selective stimulation of individual motor units in the cat sciatic nerve. Stimulation thresholds were almost an order of magnitude smaller than with cuff electrodes, and individual electrodes enabled selective activation of individual muscles (36). The small populations of nerve fibers stimulated by each electrode enabled the use of interleaved stimulation to reduce muscle fatigue occurring during prolonged activation (37). Rather than activating all motor units simultaneously, interleave stimulation uses asynchronous stimulation of subsets of motor units at lower frequencies to reduce fatigue. Chronic implants of the silicon electrode array yielded variable results with ~80% of the electrodes demonstrating stable input-output properties near the end of the seven-month implant period (38).

**Challenge 2: recording sensory information for control and feedback.** In most instances of neurological disease or injury, peripheral sense organs (e.g., touch, muscle stretch) are intact. Thus, peripheral nerves contain a wealth of sensory signals that might be used as command or feedback signals to control prosthetic devices. Alternatively, the distal nerve stump left following limb amputation might be used to recover prosthetic command signals from motor nerve fibers. The source of the signal that is recorded when an electrode is placed in tissue near an active neuron is the transmembrane current that flows during the action potential. During action potential propagation, the electrical potential in the extracellular space results from summation of shifted (in space and time) membrane currents originating from all active nerve fibers. However, the extracellular signals are small and, as discussed above, reside with the fragile, dynamic environment of the peripheral nerve. Further, since there is a linear relationship between the nodal area and

the nerve fiber diameter, the source current and thus the signal amplitude are dependent on fiber size, with the largest axons providing the dominant signal in multi-unit recordings (39). Finally, when recorded in proximity to contracting muscles, the neural signal is often contaminated by the much larger electromyogram or, when recorded in the presence of electrical stimulation, by large electrical artifacts.

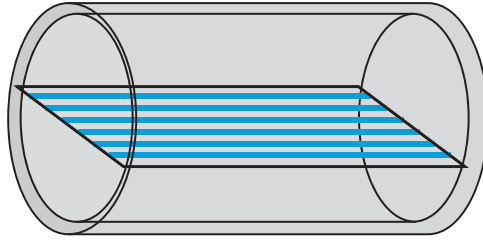
**Solution 2A: nerve cuff electrodes.** Cuff electrodes enable long-term stable recording of aggregate activity resulting from summation of the activity across a population of active nerve fibers within a nerve trunk to obtain prosthesis control signals and to study the role of sensory feedback in normal motor control (40, 41). As described above for stimulation, nerve cuff electrodes include an insulating tube surrounding the nerve trunk, and this insulating tube serves several important roles to facilitate peripheral nerve recording (39, 42). First, the insulating tube serves to cause all action currents to flow within the restricted volume conductor of the cuff-insulated nerve trunk rather than diffusely out of the nerve; this increases the recorded signal amplitude. Second, the insulating cuff serves to shield the recording electrodes from the externally generated electromyographic or stimulus artifact signals and, when combined with a balanced tripolar electrode configuration, results in strong rejection of these signals.

Nerve cuff electrodes are well developed for recording from peripheral nerves in animals (19, 23) and have been applied in humans to detect heel-strike for closed-loop control of electrical stimulation to treat foot drop (43) and to detect the onset of an object slipping from grasp for closed-loop control of electrical stimulation to restore hand grasp in persons with tetraplegia (44). In these applications, the recorded signal is an aggregate of the activity of all nerve fibers within the cuff (45). However, there are emerging methods of using individual electrodes within a multi-electrode cuff to achieve spatially selective recording from individual fascicles within compound peripheral nerve trunks (46, 47).

**Solution 2B: electrode arrays in the dorsal root ganglia.** Although intrafascicular microelectrodes enable high-fidelity recording from single afferent axons (7), even with modern electrode arrays, such an approach does not enable stable, long-term recordings as required for prosthetic applications. However, integrated silicon-based electrode arrays inserted into the dorsal root ganglion, to reside among the cell bodies of primary afferent neurons, enable long-term high-fidelity recordings from large numbers of primary afferent neurons (48). The signals obtained from simultaneous recordings of 8–10 single units can be combined to obtain high-fidelity estimates of limb position and velocity (49), and feedback of these estimates can be used for closed-loop control of electrical stimulation (50).

**Challenge 3: device and signal stability.** The average resting membrane potential of mammalian neurons is approximately  $-60$  mV, and during an action potential, voltages can reach the positive mV range (51). Electrodes that penetrate neurons intracellularly may see this level of signal (52), but signals recorded extracellularly are much lower (53); for example, regenerative electrodes measure signals on the order of several hundred microvolts (54a,b). In addition to the low amplitude voltages, there are many potential sources of noise when recording from the peripheral nervous system. The electromyogram (EMG) consists of electrical signals created by muscle activation, and this signal can overshadow the signals from peripheral nerves (38).

A fibrotic response around the electrodes can worsen what is a challenging signal-to-noise situation for extracellular recordings of peripheral nerve potentials. In the classic tissue response to foreign materials, implanted materials can eventually become covered in fibrotic connective tissue (55). After some time in the body, fibrosis of peripheral nerve implants does occur (24, 56a).



**Figure 1**

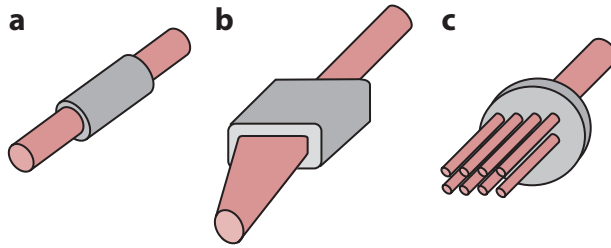
Aligned nanofibers (stripes) can be used to guide neural processes through peripheral nerve electrodes.

This encapsulation tissue has resistive electrical characteristics that change over time (56b), which means the magnitude and shape of recorded signals change over time as well.

**Solution 3A: decrease fibrotic encapsulation.** The fibrotic encapsulation of a peripheral implant can be reduced in several ways. In the CNS, the shape of an implant appears to have an influence on compatibility, as electrodes with larger cross-sectional areas and sharp features have a more severe initial tissue reaction than smaller implants with softer features (57a); this may apply to PNS implants as well, so electrode design is probably important to consider. Pharmacological blockade of tumor necrosis factor alpha (TNF-alpha) appears to limit the amount of early inflammation seen around electrode implants but does not have a significant effect on fibrosis (57b), though application of mitomycin C (a chemotherapeutic) does reduce the presence of fibrosis after peripheral nerve injury (57c). In the brain, it is possible to manage the fibrotic response by engineering electrode surfaces that are inherently anti-inflammatory (58) or by releasing anti-inflammatory compounds from coatings on electrodes (59), which may help to alleviate some of the fibrous encapsulation of implanted devices. Such a strategy may be useful for peripheral nerve electrodes as well.

**Solution 3B: bring the nerves to the electrode.** Another strategy to improve the nerve-electrode interface is to bring the nerves closer to the electrodes using axon guidance techniques (**Figure 1**). Topographical cues can be presented in the vicinity of electrodes to guide axons in regenerative electrode designs to bring the axons to the implanted electrodes (60, 61). Aligned poly (acrylonitrile-methacrylate) (PAN-MA) nanofibers have been shown to be more effective than random fibers in persuading nerves to regenerate directionally within conduits, and such control can potentially bring nerves closer to implanted electrodes (61). In addition to fibers, anisotropic presentation of growth factors, extracellular matrix (ECM) proteins, and other biological molecules can also guide axons (62, 63), making these substances potentially useful tools for the enhancement of peripheral nerve implant stability; they may also positively impact signal to noise ratio by increasing the proximity of nerves to electrodes.

**Challenge 4: implant-induced injury and adverse consequences.** Implants are made of a wide variety of materials, but regardless of the material properties, they can still cause damage to the nerve during insertion or after extended time in the body. There are several responses to peripheral nerve injury, which could be sustained from peripheral nerve implants, including Wallerian degeneration, neuropathic pain, and fibrosis (64a,b,c). Wallerian degeneration, or the breakdown of the distal stump of a severed nerve (65), can cause signal loss if the distal nerve is close to an electrode, as this nerve will no longer convey signals to the device. Fibrosis and scarring are not as disruptive in the PNS as in the CNS, perhaps because Schwann cells and fibroblasts



**Figure 2**

Examples of peripheral nerve interfaces. (a) A cuff electrode, which wraps around a nerve. (b) A flat interface neural electrode (FINE), which flattens the nerve so that fibers in the center of the bundle are closer to electrode contacts. (c) A regenerative sieve electrode that has holes to allow processes from a severed neuron to grow through.

mediate this response, rather than astrocytes and oligodendrocytes, which have been shown to produce compounds inhibitory to axonal outgrowth and possibly harmful to neurons (66).

In addition to general implant-associated injury, the specific types of peripheral nerve interfaces (Figure 2) each have their own consequences. Cuff electrodes may damage nerves they record from (25), and compression forces from flat interface electrodes can cause demyelination (67); this is undesirable because lost myelin could impede nerve conduction and therefore function. Some investigators, however, have reported only some fibrosis and no apparent nerve damage after electrode implantation and suggest that the choice of a region with minimal nerve flexion may be the reason for a favorable response (68). Nerve guidance implants are used to guide regenerating nerves to the correct target to be reinnervated, and the results of clinical trials look promising; biodegradable implants are preferred by physicians, but care must be taken not to implant too much material, as polyglycolic acid (PGA) and polylactide-caprolactone (PLCL) create an acidic environment when broken down, and large amounts of acid cannot be effectively buffered by surrounding cells, which could cause necrosis (69). Transected nerves can grow through sieve electrodes, but the resulting fibers tend to be small and covered by a thin layer of myelin, although some nerves emerge with no myelin, perhaps because of constriction by the sieve electrode holes (70).

**Solution 4: nerve-specific electrode design.** Some of the consequences of peripheral nerve implants, such as demyelination and nerve loss, appear to be alleviated by ensuring the proper fit of electrodes. When cuff electrodes are flexible and not tight on the nerve, minimal damage and fibrosis results (71). It has also been suggested that sieve electrode holes larger than 40 micrometers may allow for more regeneration and therefore greater signal-to-noise ratio (70).

In summary, peripheral nerve implants may be capable of revolutionizing current neuroprosthetics, but there are several key biological challenges that must be addressed before their widespread successful use. These challenges include recording and stimulation resolution, device stability, management of implant-induced injury, signal fidelity, and prevention of adverse implant consequences. Some strategies to address these challenges have been mentioned above, and such areas are research topics that are currently being addressed.

### 3. INTERFACING TO THE CENTRAL NERVOUS SYSTEM

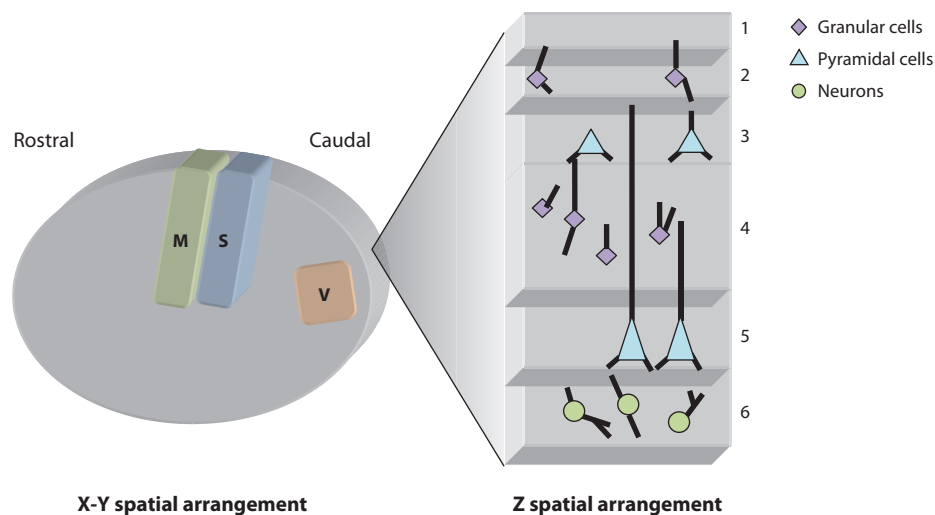
Interfaces to the CNS have become a major focus of neuroengineering research. There are many reasons to interface a device with the CNS, from regulating mood disorders (72), epilepsy (73), or

Parkinson's symptoms (74, 75) with deep brain stimulation (DBS) to controlling a brain-computer interface (BCI) (76). The underlying neural biology presents obstacles to neurointerfacing, the most common of which can be divided in two main categories: interfacing challenges and resolution challenges. Interfacing issues involve reducing the inflammatory response and gliosis around implants, which are suggested to be responsible for poor signal and chronic recording failure (77). Resolution challenges refer to the ability to collect signals from and send stimulation to a portion of the neuron-dense brain. The brain carries information that has regional specificity to certain functional areas, and yet sometimes this information may be coordinated over distances that are large relative to implant size; it is against this background that we are presented with the trade-off between invasiveness and spatial resolution. The application of a neural interface will typically dictate what level of invasion can be tolerated and what level of spatial resolution will be required to achieve a given goal.

In addition to the biological challenges, there are biophysical challenges for CNS implants. Selective stimulation is key for eliciting desired responses from the CNS, and we discuss below a few specific strategies to achieve selective stimulation. Signals from the CNS are typically small in amplitude and deteriorate rapidly over space, which makes accurate recording difficult. Strategies to alleviate this problem are also discussed.

### 3.1. Structure of the Central Nervous System

The CNS consists of the brain and spinal cord and is essentially the central processing unit for the body. The brain can be divided into a number of functional areas (**Figure 3**). At the base of the brain lies the brainstem, responsible for controlling basic functions such as respiration. Located above the brainstem are the thalamus, hippocampus, basal ganglia, and other deep structures, known to play a role in various other functions such as emotional response to stimuli, memory



**Figure 3**

The three-dimensional spatial arrangement of the brain; the X-Y spatial arrangement corresponds to functional areas mapped out over the surface of the cerebral cortex, such as the primary motor (M), sensory (S), and visual (V) cortices, whereas the Z arrangement corresponds to cortical layers found at different depths below the brain's surface. Different cell types, such as pyramidal cells, granular cells, and neurons, occupy the different cortical layers.

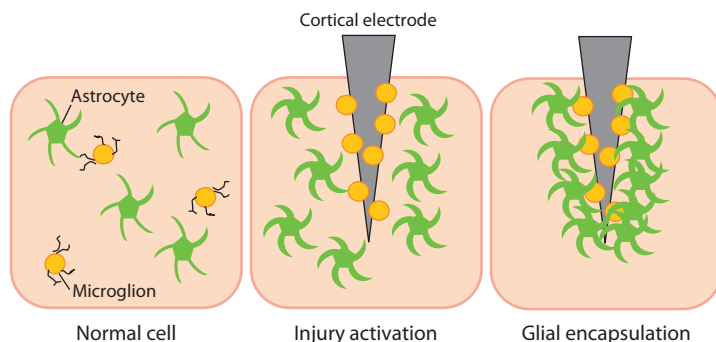
formation, and temperature regulation (51). The cerebellum, located at the lower posterior portion of the skull, receives motor and sensory input and appears to be responsible for posture and motor coordination. The highest centers of the brain are located in the cerebral cortex, which covers the brain's surface. The cortex consists of six layers, each of which houses different varieties of cells (or only cell processes, in the case of layer 1) that carry different kinds of information. Aside from the z-dimensional layers, the cortical surface can be divided into regions of functional specificity. Domains exist, such as the visual cortex, auditory cortex, somatosensory cortex, and motor cortex, that are primarily responsible for the initiation, execution, or processing of certain functions.

The stereotypical butterfly shape seen within the spinal cord consists of gray matter tracts running inside a white matter bundle. The dorsal side of the spinal cord carries sensory information, whereas the ventral portion of the spinal cord carries motor information. Interneurons are involved in spinal reflexes; typically, sensory or motor neurons synapse onto inhibitory interneurons, which in turn synapse onto other motor neurons, preventing certain muscle groups from activating during a reflexive movement. Along with neurons, multiple other cell types inhabit the central nervous system, including astrocytes, microglia, oligodendrocytes, Schwann cells, and neural precursor cells (66). The interactions of these cells in the CNS are key to alleviating some of the problems faced by CNS interfaces.

### 3.2. Challenges and Solutions of Central Neural Interfaces

**Challenge 1: host-interface response.** When a device is implanted into the brain or spinal cord for extended periods of time, an inflammatory response is initiated by the body (**Figure 4**). Cell types involved in the CNS injury response include astrocytes, microglia, oligodendrocytes, oligodendrocyte precursors, and menengial cells, all of which may manufacture products inhibitory to axon regeneration (66). Initial electrode insertion is believed to damage multiple structures, including capillaries, extracellular matrix, and cells, and blood-borne macrophages can enter through severed vessels (78). Microglia become activated and migrate to the site of injury; upon staining, they are found next to the electrode interface (79). Microglia have been shown to secrete reactive oxygen species as well as a number of inflammatory cytokines, some of which are neurotoxic at high concentrations (80, 81) so their proximity to neurons may be detrimental to long-term recording.

This initial microglial activation and migration are part of the acute response to CNS injury, and the chronic response is characterized by the encapsulation of the implanted electrode or device



**Figure 4**

Development of glial encapsulation on a cortical electrode. After injury, microglia become activated and migrate to the site of injury; astrocytes near the injury site become reactive. Over time, the reactive astrocytes encapsulate the electrode, forming a dense cellular sheath.

(78). The main component of this encapsulation is astrocytes (57). The astrocytic sheath grows in size for several weeks, after which the encapsulation layer becomes thinner and denser and stabilizes after approximately six weeks (57). Astrocytes are glial cells that normally perform some vital functions in the CNS, including buffering neurotransmitter and forming the blood-brain barrier. However, when astrocytes become reactive, they can secrete proteoglycans (82) and form a barrier around the implanted electrode. Astrocytes have also been shown to attach more strongly to neural implants over time (79). This encapsulation is of concern because it is suspected that the sheath increases tissue impedance and therefore diminishes the ability to record and stimulate (77), and it is inhibitory to axon regrowth (66, 83), which means that any neurons trying to grow processes into the sheath (and closer to the recording electrodes) will be thwarted. In addition to the presence of the astrocytic sheath, the number of neurons in close proximity to the electrode also appears to decrease, suggesting that neurons closest to the electrode either die or migrate away from the interface (84). To complicate matters, some cell types such as astrocytes and microglia, appear to allow axon regeneration at certain times and not at others (66).

**Solution 1: modulation of the interface.** Because the inflammatory response of the central nervous system is unforgiving, multiple strategies have been devised to circumvent these processes. Devices have been fabricated with different physical dimensions and geometries to test whether such changes influence the tissue response. Different tip geometries appear to result in different levels of acute inflammation; however, at time points longer than a few weeks, all inflammatory responses look similar (57). There is a correlation between electrode spacing and gliosis (79), so electrode design does govern certain aspects of the tissue response.

Aside from varying electrode design, another method to alleviate the glial response is to coat the electrodes with anti-inflammatory compounds, adhesion proteins, or bioactive molecules (78). Anti-inflammatory coatings seem to reduce the appearance of glial activation surrounding implanted chronic cortical electrodes (59), but it is yet to be determined if that is sufficient to improve the longevity of cortical recording. Adhesion molecules and growth factors have also been considered (58) and do appear to lessen the prevalence of glial scar. The exact amount of glial encapsulation that is tolerable for adequate electrical conductivity remains in question, but it is likely that the more the chronic glial response is alleviated, the better the prognosis for long-term implants.

**Challenge 2: resolution versus invasiveness trade-off.** Brain tissue has a complex organization. Not only are functional areas mapped over the surface of the cerebral cortex, but different cortical layers contain unique cell types and varieties of information. To exploit the organization of the brain, an implant must be able to access certain regions to gain desired information and elicit the desired response. This may necessitate a certain amount of intrusion into the tissue. Invasion into the CNS can have detrimental functional consequences, because trauma can partially or completely sever the electrical connections between proximal and distal processes, interrupting the flow of neural information. Such an interruption could be minor and cause only numbness in a limb or could be major and cause complete tetraplegia. Therefore, when determining what level of resolution is necessary, the functional consequences and outcomes need to be considered. As in the peripheral nervous system, there is an engineering trade-off in the CNS between the level of invasiveness and the spatial resolution gained from an implant.

We have already discussed that many of the interfaces used in the nervous system are electrical in nature, because the nervous system itself communicates using electrical (ionic) signals. When signals are recorded from the scalp or even the brain surface, they are the summation of many neural signals, and there is a limited amount of spatial information available (86). In contrast, penetrating

electrodes can have excellent spatial resolution, and some can even measure single-unit activity (87, 88). However, as we have explained earlier, the tissue response to implanted devices is neither inconsequential nor forgiving, and steps should be taken to alleviate it if possible.

**Solution 2: electrode design.** As in the PNS, careful consideration must be given to the level of invasiveness and the resolution required for a specific application, because invasion can damage tissue. Penetrating electrodes are not always necessary; for example, electroencephalogram (EEG) has been used to obtain signals for a BCI system (89). Electrocortigram (ECoG) electrodes are placed underneath the skull but above the brain and do not penetrate it; ECoG devices have also been used to gather signals for BCIs (90). By using surface electrodes to record signals, such arrays may cause a lesser tissue response. Takahashi and colleagues have had success stimulating nerves using a surface electrode array on the spinal cord (91).

In some cases, it may be necessary to stimulate or record from a region of the cortex, not just a single cell. Electrode arrays for this purpose have been devised and are commonly used in the literature. The ECoG devices mentioned above are used on the surface of the brain, and penetrating microwire arrays and silicon devices, such as the Utah array and the Michigan array, are also used. These devices can detect single units but cover a limited spatial region of the brain and are generally sufficient for stimulating or monitoring the activity of this small area. The drawback to these arrays is that they can produce more tissue damage because there are more parts physically protruding into the brain. However, such devices have been used in human and animal trials with success; for example, the Utah array has been used in both nonhuman primate (76) and human (87) studies.

**Challenge 3: lack of stimulation selectivity.** During electrical stimulation in the CNS, electrodes are placed in a complex volume conductor in close proximity to cells, dendrites, and axons. It is unclear which elements of which neurons are most susceptible to stimulation under different conditions. Application of currents may activate or inactivate (block) neurons and/or axons dependent on their morphology, distance from the electrode, orientation with respect to the electrode, discharge rate, and stimulus parameters (92). Effects on cells may differ from the effects on fibers of passage, and fiber activation will result in both antidromic and orthodromic propagation. In vitro measurements in cortical brain slices indicate that cells and fibers have similar thresholds for activation (93, 94). Similarly, in vivo measurements using microstimulation indicate that fibers and cells have similar thresholds for cathodic rectangular stimuli (92, 95, 96). Intraoperative studies with microstimulation in humans also indicate that local neurons and axons of passage have similar thresholds (97). Finally, computer modeling of the excitation of CNS neurons indicates that with conventional rectangular stimuli, axons of passage and local cells respond at similar thresholds (98, 99). Additionally, electrical stimulation may activate both pre- and postsynaptic elements, and the thresholds for generating direct and synaptic excitation are quite similar (96, 100). Thus, extracellular stimulation produces nonselective stimulation of an unknown group of neural elements over an unknown volume of tissue. The lack of selectivity of neural responsiveness complicates interpretation of the physiological basis for evoked responses as well as the ability to control the responses to stimulation in prosthetic applications.

**Solution 3A: stimulation waveforms.** Alteration of the stimulation waveform increases the selectivity in several applications of electrical stimulation of the nervous system (101). Conventional biphasic stimuli result in similar thresholds for different neural elements and nonselective stimulation of the CNS. Asymmetric stimulation waveforms, which are still charge balanced but contain a long-duration low-amplitude repulse followed by a short-duration stimulation pulse, increase

selectivity (99) by modifying the degree of inactivation of the voltage-dependent sodium channel (102). Asymmetric prepulse waveforms increase the threshold difference between activation of local cells and activation of axons of passage: Cathodic phase first waveforms enable selective stimulation of local cells, whereas anodic phase first waveforms enable selective stimulation of axons of passage (99). Although the results of preliminary testing of asymmetric waveforms were consistent with the model predictions (103), proving the utility of such waveforms awaits more rigorous evaluation. Alterations in stimulation waveform can also be used to increase the selectivity of peripheral nerve stimulation (101, 102) and are being explored as a means to increase the dynamic range of cochlear implants that stimulate the auditory nerve.

**Solution 3B: electrode geometry.** In addition to alterations in the stimulation waveform, changes to the electrode geometry are another approach to increase the selectivity of stimulation of the CNS. Although bipolar stimulation is widely employed and viewed to increase selectivity, biophysical analysis suggests the converse. During bipolar stimulation in the CNS, excitation can occur around both poles of the electrode (99, 104), and there is a low probability of activating neurons between to the two poles (104). A more fruitful approach appears to be electrode geometries designed for specific applications of brain stimulation. Modifying the physical electrode geometry by segmenting the electrode (105) or by changing the shape of the contacts (106) increases the spatial selectivity of stimulation. Ultimately, custom electrodes designed for specific patients (107) may increase the therapeutic window or the selectivity between the neural elements targeted for the desired clinical effect and the neural elements that produce unwanted side effects.

**Challenge 4: small amplitude signals that decline rapidly in space.** As with stimulation intensity, the amplitude of the signal recorded from an active neuron (or neurons) varies inversely with the distance between the neuron(s) and the recording electrode,  $r$ . For a monopolar source, the potential varies as  $1/r^{-1}$ , whereas for a dipolar source, more typical of transmembrane currents, the potential varies as  $1/r^{-2}$ . The decay of the extracellular potential is also dependent on the morphology and electrical properties of the recorded neuron (108, 109), and the steepness of decay varies from  $1/r^{-1}$  close to the neuron to  $1/r^{-2}$  further away. The historical rule of thumb is that to record isolated signals from single active neurons requires that the electrode lie within  $r = 100 \mu\text{m}$  of the active neuron. Data obtained by recording the same unit with different contacts of a multiple-contact recording probe are consistent with this rule of thumb (110, 111) and indicate that the recorded signal amplitude falls off rapidly as the electrode-to-neuron distance is increased. Further, the spike becomes broader (is low pass filtered) as the neuron-to-electrode distance increases (109) and thus is more challenging to discriminate from background activity and noise. The principal solution to this problem has been the use of high-density arrays of many electrodes, including metal microwires (112) and silicon-based probes (113, 114). However, the recording integrity of these arrays declines over time and solutions are needed to enable stable, long-term recordings from single neurons.

**Solution 4: dynamic spatial tracking of single units.** Loss of signal during chronic recordings of single units may be due to relative movement between the electrodes and the neurons. The brain moves by 10–30  $\mu\text{m}$  during respiration, and displacements of 10–60  $\mu\text{m}$  occurred during head movements (115). These displacements are comparable to the dimensions of the cell body of recorded neurons and could easily move the neuron or electrode outside of the 100  $\mu\text{m}$  distance required for recording. Dynamic tracking of single units may provide a solution to maintain recordings in the face of tissue or electrode movement (111, 116). In such systems, the template of currently recorded neural activity is compared with previously recorded neural activity, and the

probe is moved within the brain to account for relative movements and maintain a stable spatial relationship between the recorded neuron and the electrode.

## 4. EMERGING OPPORTUNITIES

### 4.1. Single-Cell Electronic Connections

The intimacy and density of neural interfaces promise to be dramatically increased by connections between single electrical transistors and either single ion channels or single neurons in culture. Direct interfaces between small networks of nerve cells and synthetic devices promise to advance understanding of neuronal function and may yield a new generation of hybrid devices that exploit the computational capacities of biological neural networks. A silicon–neuron hybrid circuit was created by culturing a presynaptic nerve cell atop a capacitor and transistor gate and a postsynaptic nerve cell atop a second transistor gate (117). Application of voltage to the capacitor excited the presynaptic neuron, and this activity was recorded with the first transistor. Firing of the presynaptic neuron generated excitation of the postsynaptic neuron, presumably via an excitatory synapse, and the activity in the postsynaptic neuron was recorded with the second transistor. Further, short trains of activity in the presynaptic neuron appeared to increase the strength of the excitatory synapse between the cells, creating a memory trace within the circuit. These results demonstrate the ability to use integrated capacitors and transistors to stimulate and record from cultured neurons. The neuron–silicon hybrid provides a tool to study formation and plasticity within small neural circuits and may lead to novel computational devices.

The intimate contact established on these devices also enables capacitive stimulation of neurons. In general, the size of stimulating electrodes is limited by their ability to pass charge from the electronic charge carriers in metal electrodes to ionic charge carriers in the tissue, which is related to the surface area of the electrode. Exceeding the limits on the charge per unit area of the electrode can lead to damage to the electrode through dissolution (corrosion) or damage to the tissue by generation of chemical species as a result of reduction or oxidation reactions (redox or Faradaic reactions) at the electrode–tissue interface. However, stimulation of neurons with capacitive currents by coating the electrode with a dielectric avoids electron transfer and thus redox reactions at the interface. Guyton & Hambrecht (118) pioneered such an approach with the introduction of the tantalum pentoxide capacitor electrode, and subsequent *in vivo* testing (119) suggested that rather than electrochemical reactions, which were avoided under the tantalum electrodes, neuronal damage was caused by some other source—later attributed to the synchronous activation of large numbers of neurons.

A cellular-level interface-enabling capacitive stimulation was fabricated by depositing titanium dioxide, an effective dielectric, over a conductive (doped silicon) electrode (120). Neurons were cultured atop the dielectric layer, and the surrounding electrolyte served as the other plate in a classic parallel plate capacitor. Sawtooth voltage waveforms were applied to the doped silicon plate of the capacitor. Recall that capacitor current is proportional to the time derivative of the capacitor voltage. Thus, this generated a biphasic, rectangular current pulse. A train of such sawtooth waveforms generated a steadily increasing change in transmembrane potential that eventually led to an action-potential-like response. Thus, weak capacitive stimuli were able to generate neuronal stimulation without passing charge through Faradaic electrochemical reactions.

Efforts to move this technology from *in vitro* to *in vivo* are particularly exciting, as this could enable synaptic-level selectivity among electrodes and neurons. Initial efforts demonstrated that neurons could be cultured in the wells of silicon-based electrodes and that neurons could grow extensions out from the probe *in vivo* (121). However, it proved difficult to maintain the integrity

of the cultured neurons in the probe for long periods, as the neurons appeared to migrate from the probe.

## 4.2. Optical Stimulation

Conventional electrical stimulation uses electromagnetic radiation in the very low to ultra low frequency region—corresponding to wavelengths of tens to hundreds of kilometers. However, optical stimulation offers an alternative strategy to activate neuronal tissue, and recent demonstrations support the feasibility of direct activation of tissue as well as indirect activation of tissue via genetic introduction of exogenous light-responsive ion channels.

Following on the classic work of Fork (122), who demonstrated that laser illumination could produce excitation of molluscan neurons through a reversible, but unknown mechanism, Hirase et al. (123) used modern two-photon techniques that enabled the laser light to be focused much more precisely. They demonstrated excitation of pyramidal neurons in brain slices from mouse visual cortex at short latency, and the probability of excitation was modulated by both the intensity and wavelength of illumination. The experiments suggested two potential mechanisms by which laser illumination could generate neuronal activation. First, the data support that light-induced membrane depolarization resulted from a photochemical reaction that produced reactive oxygen species adjacent to the cell. The second potential mechanism was a transient perforation of the membrane that quickly resealed after the light was discontinued.

Laser illumination was also used to excite directly the rat sciatic nerve, and the amplitude of the evoked muscle response could be graded by the intensity of the light (124). The laser-based stimulation could be restricted to subcomponents of the sciatic nerve, thus illustrating the concept of selective stimulation. The mechanisms underlying stimulation are not understood, but potential mechanisms include photothermal injury (transient membrane perforation), photomechanical stimulation, or, as suggested by the work of Hirase and colleagues (123), a photochemical reaction.

An alternative to direct optical stimulation is genetic introduction of light-responsive channels to make neurons light sensitive. Recent advances are driven by the genetically controlled exogenous expression of chromophore-linked ion channels that impart light sensitivity to neurons not normally responsive to light. This optogenetic approach is distinct from both direct optical stimulation of excitable cells—which is still being pursued, but requires quite high illumination intensities—as well as light-induced uncaging of bound neurotransmitters with light, which causes light-triggered excitation of all neurons possessing receptors for that transmitter. Rather, these optogenetic tools provide the promise of highly selective stimulation of targeted cells—both temporally and spatially—and may form the basis of a new generation of neurotechnology solutions to neurological disease and injury as well as powerful new approaches to study neuronal function.

Zemelman and colleagues (125) demonstrated genetic manipulation to make only certain neurons responsive to illumination. They expressed genes in cultured hippocampal neurons coding for elements of the invertebrate retina. The retinal elements produced a light-controlled source of excitatory current in the affected cells, as they would in the native retina. When exposed to light, the neurons that were transfected with the retinal elements depolarized and generated action potentials at latencies between less than one second and several tens of seconds. The pattern of firing ranged from single spikes to bursts of spikes, as would be observed during conventional intracellular recording, and the firing frequency could be increased by increasing the light intensity. The variable nature of genetic transfection was presumably the cause of the variability in responsiveness across neurons.

This approach was extended by Banghart et al. (126) by development of a potassium channel that was responsive, via opening and closing, to different wavelengths of light. Normally, such

ion channels are responsive to changes in the potential across the cell membrane. In these experiments, the channel was joined with a photosensitive molecule (azobenzene) to make it responsive to light. The conformation of the azobenzene determined whether an attached channel blocker (tetraethylammonium, TEA) could or could not reach the channel pore. The engineered channels were then expressed in cultured neurons from rat hippocampus. Application of UV light at 390 nm caused a conformational change in the azobenzene, removing the TEA blocker and allowing potassium to flow out of the cell. Conversely, application of visible green light at 500 nm altered the shape of the azobenzene such that the pore blocker plugged the channel and halted the potassium efflux. The resulting photoswitch, through modulation of potassium flow into and out of the neurons, enabled different colors of light to turn neuronal firing on and off. Such a channel, for example, could be used to restore photoreceptor-like function in cases of retinitis pigmentosa and thus may offer an alternative approach to the visual prostheses being pursued with direct electrical stimulation of retinal or cortical neurons.

Increased temporal control was achieved by expression of the algal protein channelrhodopsin-2 (ChR2), a chromophore linked to a cation permeable transmembrane channel, in neurons of the hippocampus. Stimulation *in vitro* of the neurons with pulses of light evoked excitatory synaptic responses in cells in the hippocampal slice with high temporal precision (127), and this technique has been extended to applications *in vivo* (128). A glimpse of the power of these approaches was provided by Bi et al. (129), who achieved long-term expression of ChR2 in the inner retinal neurons of rats. The transfected neurons responded with membrane depolarization and action potential firing in response to light stimuli. Subsequently, they demonstrated expression of ChR2 in the retinal ganglion cells of photoreceptor-deficient mice and found that light stimuli resulted in evoked potentials in the visual cortex that were comparable in amplitude to those evoked in control animals.

These results demonstrate the feasibility of optical stimulation of genetically encoded light-responsive channels as a technique for neural interfacing and potentially for rehabilitation. The potential advantages of both direct and indirect optical activation of neurons include achieving selective stimulation of only the targeted neurons without activating neighboring neurons, eliminating electrical artifacts that complicate recording of neuronal activity in the presence of electrical stimulation, and eliminating the electrochemical reactions that occur at the electrode-tissue interface and lead to electrode dissolution or tissue damage.

The challenges to realizing the potential of these techniques are myriad. First, the ability to express at high levels exogenous proteins over chronic periods is still developing. Further, doing this in anatomically or type-distinct subsets of neurons remains a daunting task. In addition, although the concept of a fiber-optic-based system for selective neural stimulation holds tremendous appeal, this type of optical stimulation will still exhibit the same intensity-distance relationship as conventional electrical stimulation. The light intensity, and thus robustness of neuronal activation, will drop off as the distance between the light source and the neurons increases.

### 4.3. Electrode-Associated Inflammation

Management of the host response is critical for long-term implant stability (58), as this can help preserve neurons near the interface. In addition, the distance between neurons and recording elements can be minimized by encouraging neuronal growth toward electrodes. The ultimate goal of inflammation management is to ensure that long-term interfaces are stable, both from a neuronal-network standpoint as well as a device standpoint. Some of the methods employed to alleviate electrode-associated inflammation include reducing insult by shrinking the devices,

modulating stiffness, engineering anti-inflammatory surfaces, and coating the devices with adhesion and trophic factors.

Logically, if the insult to neural tissue can be minimized, perhaps the host response can also be minimized. Szarowski et al. have shown that silicon probes with smaller cross-sectional areas appear to have an astroglial response containing fewer cells than the response to larger electrodes initially, though after several weeks the gliotic response looks similar for all designs (57a). Nanoscale electrodes could prove useful for cortical implants, but insertion and efficient fabrication are concerns that must be addressed before their widespread use. In addition, mechanical stability is necessary for the electrodes to remain unbroken during the duration of implant, possibly years for human applications. A variety of carbon nanotube electrodes have been fabricated (130, 131) and have been shown to be biocompatible or at least capable of allowing cell growth (132), making them an interesting substrate for future neural implants.

It has been postulated that the stiff silicon electrodes may be responsible for exacerbating some of the adverse host responses toward chronic implants (133). To this end, alternate materials have been used to fabricate neural electrodes. Various types of polyimides, which have a lower Young's modulus (stiffness) than silicon, have been used to manufacture sieve, cuff, and cortical electrodes (133). Parylene, another flexible polymer, has also been used to manufacture neural electrodes (134a).

It is conceivable that the inflammatory response to chronic implants could be modulated by anti-inflammatory coatings. Dexamethasone injections result in less glial activation, as does insertion of construct containing dexamethasone into the rat brain (134b). Dexamethasone coatings on neural probes resulted in reduced staining of microglia and macrophages by the activated macrophage marker ED-1 and chondroitin sulfate proteoglycan staining by CS56 at one week post-implant; less astrocyte reactivity and more neuronal process survival, evidenced by neurofilament 160, was seen at one and four weeks post-implant, as compared to uncoated control probes (59). Alpha-melanocyte stimulating hormone (MSH), a potent anti-inflammatory peptide, has been shown to reduce the amounts of Interleukin-1 (IL-1) and TNF-alpha, both inflammatory cytokines, present in *in vitro* cultures, and reduce ED-1 staining of activated microglia and GFAP staining of astrocytes when coated on electrodes inserted *in vivo* (58). Anti-inflammatory compounds will likely be a vital part of reducing the host response to chronic electrodes, and long-term studies should be conducted to monitor the effectiveness of such coatings for long time points, possibly more than one year.

Stabilization of the implant-neuron interface may also be enhanced by the application of adhesion and trophic factors. Brain-derived neurotrophic factor (BDNF) released from microtubes in an implanted hydrogel has been used for promotion of neural regeneration after spinal cord injury (135). Laminin coatings on cortical electrodes result in more ED-1 staining at one day post-implant but then a reduction in ED-1 staining four weeks after insertion (136). In the same study, He et al. showed a reduction in GFAP intensity around the electrode tracts at four weeks, indicating a less severe glial response than for uncoated electrodes.

Methods to reduce implant-induced tissue reactions may be the key to long-term chronic electrical recordings and implant acceptance. The strategies presented here are a few of the methods being developed, and we hope future advances will mitigate the tissue response that plagues implanted devices today.

## 5. CONCLUSION

Seamless integration of external electronics with the nervous system has the potential to revolutionize our understanding of the brain and to significantly enhance the quality of life in individuals

with compromised neural function due to disease or trauma. We have presented here some of the design challenges in communicating in a bi-directional fashion with the CNS and PNS and have discussed some of the engineering solutions that will hopefully propel us to the ultimate goal of seamless interfacing with the nervous system.

## DISCLOSURE STATEMENT

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