Toward Replacement Parts for the Brain

Implantable Biomimetic Electronics as Neural Prostheses

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1 We Made the Deaf Hear. Now What?

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Neurons and modern digital electronic devices both process information in the form of all-or-none impulses of electricity, respectively called action potentials and logical states (bits). Over the past 50 years, electrophysiological techniques have been developed to provide sophisticated, safe, and reliable interfaces between electricity carried as ion fluxes in water and electricity carried as electron motion in metal conductors. Neural prostheses consist of the use of such interfaces to replace or repair dysfunction in the human nervous system. This chapter reviews the promises and the reality of what has been and might be achieved in the areas of sensory and motor prostheses, in the hope of providing some useful lessons and strategies for undertaking even more ambitious projects to repair higher neural functions such as cognition, memory, and affect.

Some years ago, the *New Yorker* printed a cartoon showing a bookstore patron gazing balefully at three aisles of books labeled, respectively, "nonfiction," "fiction," and "lies." That is a useful, if somewhat harsh and labile, way to categorize the status of a given scientific proposal to do something "difficult." Using an electronic device to fix a broken nervous system is certainly difficult. The first two *New Yorker* categories are akin to the distinction sometimes drawn between problems of "engineering" and those of "science," which raises the delicate question of what falls into the third category. Let us start with some examples drawn from other fields and then try to relate this categorization to actual or potential neural prostheses in order to understand their technical feasibility, clinical potential, and strategic risk.

The cliché question from the layperson is, "If we can put a man on the moon, why can't we cure cancer?" Putting a man on the moon is in the category of engineering because all the laws of physics required to demonstrate its feasibility are known, and calculations based on those laws can demonstrate that it is feasible. In fact, theoretical feasibility has been demonstrable for over a century, but practical achievement required a lot of technology, time, and money.

At some point between Jules Verne and the Apollo missions, putting a man on the moon shifted from fiction to nonfiction. I submit that the point occurred when someone, probably early in the history of modern rocketry, actually performed the myriad

calculations related to gravity fields, rocket acceleration, fuel efficiency, life-support systems, etc. and couldn't find any reason why it would not work.

In contrast, curing most cancers remains in the category of scientific research rather than engineering or clinical practice because we still do not know enough about what causes cancer or how cells control their reproduction to even identify a particular strategy for curing cancer in general. One can construct plausible scenarios for how it might be possible to cure cancer, but they must be based on suppositions or hypotheses about how cells work that are as yet unproven. Thus, such scenarios are a credible form of science fiction, permitting even scientists knowledgeable in those fields to indulge in a "willing suspension of disbelief."

Stories based on time travel, perpetual motion machines, or extrasensory perception, for example, represent a different form of science fiction. One can only suspend disbelief if one doesn't know enough about physics, thermodynamics, or neurophysiology to realize that the bedrock theory upon which those sciences are based makes those ideas fundamentally impossible, not just temporarily impractical. I submit that such stories become "lies" when they are offered up to the lay public with the promise that if they spend enough money on a particular fiction, it can be made real. They are particularly pernicious lies if one tells such stories to patients and their families, who would like to believe and use them as a basis for important personal decisions on alternative methods of treatment and rehabilitation.

This is not to say that scientific theory cannot be overturned; an eighteenth-century physicist would have dismissed a story about atomic energy and transmutations of the elements as such a lie. Nevertheless, it would have been prudent even then to recognize that the scenario could never be realized by alchemy and to wait for the eventual development of quantum mechanics. With the benefit of hindsight, we can look at the prior criticisms of research on neural prostheses to see if this categorization might have provided guidance in selecting projects that turned out to be useful.

Cochlear Implants

In the early days of cochlear implants (circa 1975), many knowledgeable auditory neurophysiologists believed (and some forcefully stated) that a functionally useful auditory prosthesis could not be built. Their arguments were not based on theoretical limits on the electrical excitability of the auditory nervous system. The biophysics of neurons in general had been well worked out 50 years earlier, and experiments in humans had already demonstrated that perceptions of sound could be produced by reasonable and safe electrical stimulation. Their objection was based on their personal hypotheses regarding how the central nervous system might process and perceive various temporospatial patterns of electrical activity in the ensemble of auditory neurons.

Even as practiced today with multichannel intracochlear electrodes and sophisticated digital signal processors, cochlear stimulation creates temporospatial patterns of neural activity that are greatly distorted from what would have occurred if those sounds had been presented acoustically to a normally functioning ear. It turns out that the brain is much more tolerant of some types of distortion than others and that it is possible to present this relatively crude electrical stimulation in ways that the brain accepts as quite natural sound. In fact, recent psychophysical tests in cochlear implant patients suggest that the intelligibility of speech as a function of number of information channels follows essentially the same curve in cochlear implant users as it does in normal hearing individuals. It levels off at about four to six channels regardless of how many stimulation channels the implant can provide (Wilson, 2000, 1997).

On the other hand, there are a lot of ways to present the same number of information channels that are not intelligible at all. In fact, a substantial minority (about 20%) of cochlear implant recipients never acquire high levels of speech recognition, for reasons that remain mysterious (Kessler et al., 1995; Loeb and Kessler, 1995). Thus, it was plausible but not provable to assert in 1975 that functional hearing would not be produced by multichannel cochlear implants. Fortunately for tens of thousands of deaf people and for the field of neural prosthetics in general, this assertion turned out to be wrong. Cochlear implants progressed from plausible science fiction to engineering and clinical fact, although it took 20 years to complete this transition.

There are still reasons for trying to increase the number of useful channels actually provided, but they fall into the category of incremental improvements rather than enabling technology. Such improvements might be expected to enhance performance in cluttered acoustic environments with background noise. They might also address the problematic minority who have difficulty using implants, but this is less certain. The underlying problem that limits the number of effective channels is related to the tendency for electrical stimulation currents to spread longitudinally in the fluid-filled scala tympani before passing through the subjacent bony walls into the spiral ganglion, where the auditory neurons are stimulated. Addressing this problem requires substantial changes to the design of the electrode arrays (for example, see figure 1.1), which raises various challenges for manufacturing techniques, surgical insertion strategies, and biocompatibility.

Alternatively, it may be more useful to address the temporal distortions produced by the present electrical stimulation waveforms. There are various speech encoding and stimulus waveforms in use (recently reviewed by Wilson, 2000), but they all introduce an unphysiological degree of synchronicity in the firing of the auditory neurons. The auditory nervous system is exquisitely tuned to decode temporal patterns (Loeb et al., 1983), so this may be more important than the simple rate coding that

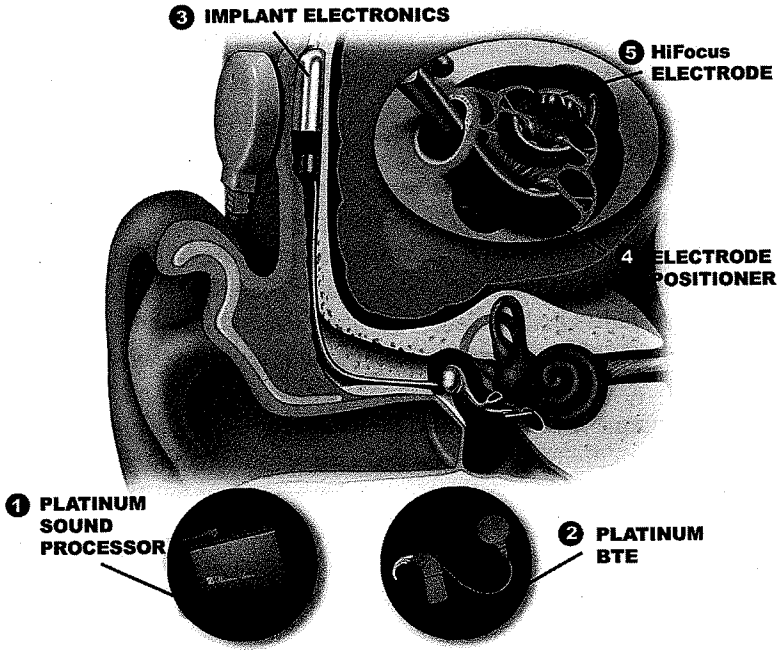

Figure 1.1
A cochlear prosthesis consists of an external sound processor (optional configurations shown in inserts 1 and 2) that transmits power and data to an implant (3) that generates complex patterns of stimulation pulses delivered to the cochlea by a multichannel electrode system. Insert 5 shows a new cochlear electrode array that attempts to improve the localization of each stimulation channel by pushing the array (4) against the medial wall of the scala tympani (closer to the spiral ganglion cells to be stimulated) and by incorporating silicone bumps between contacts to block the longitudinal spread of stimulus currents. (Illustration of the CLARION™ system with HiFocus™ electrode provided courtesy of the manufacturer, Advanced Bionics Corp., Valencia, Calif.)

appears to dominate most sensory encoding systems. By applying very high stimulus pulse frequencies, the auditory neurons can be desynchronized to fire on random subharmonics of the stimulation frequencies, reducing this unnatural synchronization (Rubinstein et al., 1999). Unfortunately, such stimulation is less efficient in terms of the mean power consumption needed to produce a given level of perceived loudness. This would conflict with the emphasis on smaller, lighter prostheses that can be worn on the ear (see Figure 1.1, insert 2) or even fully implanted in the body. Given steady improvements in the power efficiency of digital signal processing, the power budget for cochlear implants is increasingly dominated by the power dissipated by pushing stimulation currents through electrodes and cochlear tissues. The combination of more channels and higher stimulus pulse rates would require substantially larger, heavier batteries or more frequent recharge cycles.

It is not clear whether either the temporal or spatial enhancement strategies will be useful in any particular patient, much less in all. There are some suggestions that cochlear implant patients and perhaps even normal hearing individuals vary considerably in their relative dependence on the wide range of partially redundant acoustic cues that distinguish speech. Conventional cochlear implants are based on replicating the Helmholtzian place-pitch encoding, but some listeners may depend more on decoding of the high-frequency temporal cues that arise from phase-locked transduction of complex acoustic waveforms (Loeb et al., 1983). For example, some subjects prefer interleaved patterns of biphasic pulses that avoid electrotonic summation between channels. Other subjects prefer and perform just as well with simultaneous multichannel stimuli consisting of complex analog waveforms obtained by bandpass filtering and compressing the dynamic range of the raw acoustic signal.

Despite the wealth of electrophysiological and psychophysical data that can be collected from patients with multichannel cochlear implants, no correlations have yet emerged that account for their often striking differences in performance and preference. Thus, it is not surprising that there are essentially no preoperative predictors to decide which patients should receive which cochlear electrode or which speech-processing system. This forces engineering teams to try to design into the implants a very wide range of signal-processing and stimulus generation and delivery schemes, greatly complicating what is already perhaps the most complex biomedical device ever built. That complexity, in turn, demands a high level of sophistication from the clinicians, who must decide how to program each implant in each patient, and a high level of design for the supporting software that allows those clinicians to navigate and manage all those options.

Despite (or perhaps because of) all these emergent complexities and competing strategies, cochlear implants remain the visible proof that sophisticated neural functions can be successfully replaced by well-designed neural prosthetic systems. They succeeded clinically and commercially because even the relatively primitive single-channel and multichannel devices that emerged in the late 1970s provided useful benefits for the large majority of patients in whom they were implanted (Bilger, 1983). This provided the impetus for much further research and development that vastly improved both the basic performance and general usability of cochlear implants. It also provided a wide range of improved general design and manufacturing tools and techniques that should be applicable to other neural prosthetic devices, provided that we understand their underlying basic science.

Visual Prostheses

Research on visual prostheses has been going on for even longer than cochlear implant development, but it is still stuck in the category of science fiction. In 1965,

when the scientific community got wind of Giles Brindley's plan to implant an array of cortical surface electrodes in a blind volunteer patient, a secret conference was convened largely to vilify the attempt (notes from that conference can be found as an appendix to the proceedings of a later meeting edited by Sterling et al., 1971). As with cochlear implants, it was well known from biophysical theory and prior experimentation that electrical stimulation of the striate cortex (Brodmann's area 17, now known as V1) could produce sensations of light (Penfield and Perot, 1963). Contemporary hypotheses about visual perception suggested, however, that it would not be possible to create useful, stable percepts from such stimulation. In the event (a few months later), the patient reported seeing "phosphenes" that were much more stable and well defined than had been predicted (Brindley and Lewin, 1968). This led to about 10 years of aggressively pursued research to build a practical visual prosthesis based on this approach. It turned out that the surprisingly punctate phosphenes produced by relatively high levels of poorly focused stimulation were the product of the surround-inhibitory neural circuitry of cortical columns, which were discovered about this time. These same circuits, however, also produced uncontrollable nonlinear interactions between adjacent sites of surface stimulation when an attempt was made to combine them into images (reviewed by Girvin, 1988). In the end, this plausible attempt to convert science fiction into engineering fact had to be abandoned.

In order to overcome the problem of the interaction of stimulus channels, some researchers turned next to developing intracortical microstimulation. Very fine microelectrodes can be inserted about 2 mm into the cortex so that they stimulate just a few neurons within a cortical column, using microamperes of current rather than milliamperes (Ranck, 1975). Given the concurrent advances in the neurophysiology of vision, this approach is now primarily an engineering rather than a science problem. Unfortunately, it is a very large problem. Small arrays with a few microelectrodes have been used successfully to produce stable and apparently combinable phosphenes in patients (Schmidt et al., 1996; Bak et al., 1990). Scaling this up to hundreds or thousands of separately controlled channels to produce useful (but still crude) images poses daunting problems for fabrication, surgical implantation, biocompatibility, protective packaging, interconnections, power consumption, psychophysical fitting and programming, image acquisition, and real-time data processing. There are promising technologies under development for each of these requirements, but their combination into a clinically safe, effective, and practical system remains only plausible, not certain.

Over the past decade, attention has shifted toward the very different strategy of electrically stimulating the retina. Obviously this is not a viable strategy for blindness caused by damage to the retinal ganglion cells whose axons make up the optic nerve (e.g., glaucoma, retinal detachment, optic nerve compression), but it might work for patients with primary degenerative diseases of the photoreceptors (e.g., retinitis pig-

mentosa and macular degeneration). The problem is that the retinal cells are very small; biophysical theory predicts that they should be difficult to stimulate electrically. Initial experiments in patients with intact retinas (who were undergoing removal of the eye because of malignant tumors) appeared to confound this prediction because microampere currents produced sensations of light. In fact, this is an unsurprising consequence of introducing small biases in a system of photoreceptors and intraretinal circuitry that employs spontaneous activity to create very high sensitivity to weak but coherent incident energy, such as light reflected from dimly illuminated objects. The transduction systems of both the intact retina and the intact cochlea are built in this way. It has long been known that the first sensations induced by weak electromagnetic fields are visual and auditory auras. In the absence of this background activity from the receptors, however, the postsynaptic neurons that generate all-or-none action potentials to convey sensory information to the brain revert to their type-specific and predictable biophysical properties.

When electrical stimulation is applied to the vitreous surface of a retina without photoreceptors, the lowest threshold neural elements are the long, myelinated output axons of retinal ganglion cells coursing horizontally over the retinal surface on their way into the optic nerve. Any local subset of these axons would map into a wedge-shaped sector of the retina. The resulting "phosphene" would not be a promising primitive from which to create complex visual images. One clever alternative is to take advantage of the different membrane time constants of the myelinated retinal ganglion axons and the unmyelinated bipolar cells, which are local interneurons oriented perpendicularly to the retinal surface (Greenberg et al., 1999). Electrical stimulation becomes more efficient when pulse duration approximates this time constant (Ranck, 1975), so it is possible to selectively stimulate bipolar cells with much longer pulses ($\sim$2 ms) than normal ($\sim$0.2 ms). Long pulses may cause problems, however, if they also require high stimulus currents and repetition rates to produce stable phosphenes. A retinal prosthesis is likely to need large numbers of closely spaced, relatively small electrodes to achieve useful image resolution. The individual stimulus pulses may exceed the charge density limits of the electrode materials (Loeb et al., 1982) and the aggregate power dissipation may cause excessive heating of the retina. Initial experiments with relatively crude electrode arrays have been encouraging (Humayun et al., 2003).

Epiretinal stimulation is likely to lead to the same problems of subliminal channel interaction that were encountered with cortical surface stimulation. It is possible that the same fix will be feasible—using penetrating microelectrodes to inject current much closer to the target bipolar neurons, thereby reducing power requirements and channel interactions. However, the bipolar cells are biophysically much less excitable than cortical pyramidal cells, and the retina is a much more delicate place in which to implant such electrode arrays. Thus, for the time being, this strategy is plausible

science fiction in need of well-focused experiments to determine theoretical feasibility. If it is theoretically feasible, then the effort can shift to the formidable technical obstacles inherent in transmitting large amounts of data and power to dense electrode arrays that have to function for many years in the presence of saltwater and constant motion.

An alternative approach to retinal stimulation seeks to avoid the enormous complexity of external image acquisition and transmission of power and data to multichannel electrode arrays. The idea is to use integrated silicon arrays of photocells and electrodes implanted into the retina itself, between the superficial photoreceptor layer on the scleral side and the rest of the retinal ganglion circuitry on the vitreous side (Chow, 1991). It is a relatively simple matter to compute the maximal electrical current that can be derived from converting incident photons to electrons, assuming any reasonable photoelectric efficiency. Unfortunately, the answer is in the nanoampere range. There is no biophysical reason to expect such tiny stimulus currents to evoke action potentials in retinal cells deprived of background depolarization from photoreceptors.

Neuromuscular Reanimation

For the past 30 years, much of the technology developed for stimulating peripheral nerves and muscles has been predicated on the notion of getting paraplegics to walk. Despite substantial research efforts, there are no commercially available systems for locomotion; most research on functional electrical stimulation (FES) of the legs has retreated to the goal of providing FES-assisted standing. Paradoxically, the feasibility of electrically stimulating muscles to contract and move the limbs has been known since Luigi Galvani's discovery of bioelectricity in 1790. Is this an example of poor execution or unreasonable expectations?

The main challenge to the creation of clinically viable FES comes neither from science nor engineering but largely from selecting realistic objectives and tactics. There are many useful and practical clinical problems that can be addressed, given our present understanding of neurophysiology and currently available technologies, but getting paraplegics to walk is not one of them. Paraplegia presents a heterogeneous set of conditions in a relatively small population of patients. Moving around by wheelchair is readily available, relatively cheap, safe, and actually more energy efficient than normal walking or running. Equal-access laws have removed most mobility barriers in public places. Conversely, moving the legs with electrical stimulation of the muscles is highly invasive, cumbersome to program and to use, and inefficient and slow, even in a laboratory environment. In an uncontrolled field environment, it is likely to be quite dangerous as a consequence of inadequate strategies for coping with unpredictable footing and obstacles, the inability to control and min-

imize injury from falls, and the inability to get up after a fall. The kinematics and kinetics of unperturbed gait are easily measured in normal subjects, but the central neural strategies for achieving stability in the face of a wide range of perturbations and long delays in actuator response are not understood at all. Given these limitations, the resulting product would be unlikely to reduce health care costs or to improve the employability of paraplegics, in which case there would be no motivation for insurers to pay for it.

We have chosen instead to focus initially on the myriad secondary problems of muscle paralysis and paresis (Loeb and Richmond, 1999). Many of these result in substantial morbidity and large health care costs, but may be treatable with a modest number of stimulation channels and little or no real-time control. We have developed a modular, generic technology consisting of wireless intramuscular stimulators that can be injected nonsurgically into a wide range of sites (Cameron et al., 1997; figure 1.2). Each of these BION (*bio*nic *n*euron) implants receives power and digital command signals by inductive coupling from an external coil that creates an amplitude-modulated radio-frequency magnetic field in the vicinity of the implants (Troyk and

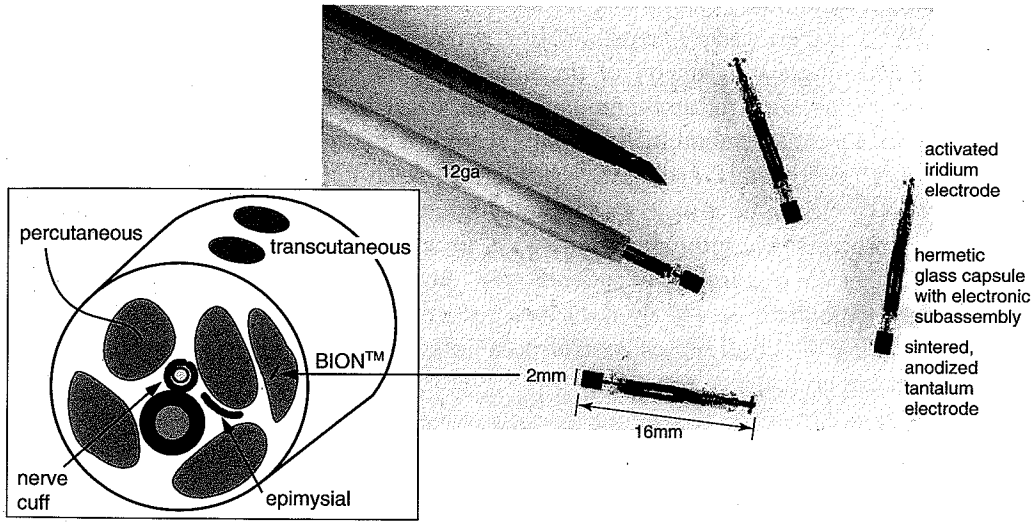

Figure 1.2
Various approaches to stimulating muscles include transcutaneous and percutaneous electrodes and surgically implanted multichannel stimulators with electrodes attached to nerves and muscles. BION implants are shown as they would be injected into muscles through a 12-gauge hypodermic needle. Each implant receives power and digitally addressed and encoded commands from an external controller and transmission coil. This system is in clinical trials to prevent disuse atrophy and related complications of upper motor paralysis, such as stroke and spinal cord injury. In principle, coordinated stimulation of many muscles could reanimate a paralyzed limb, but this will require substantial advances in sensing command and feedback signals from the patient and in emulating the complex and poorly understood control circuitry of the brain and spinal cord.

Schwan, 1992). The patient is provided with a portable controller (Personal Trainer) that creates preprogrammed sequences of stimulation to exercise the muscles.

The first clinical applications of this technology have aimed to prevent or reverse disuse atrophy of paretic muscles (Dupont et al., 2004). One clinical trial now under way involves stimulation of the middle deltoid and supraspinatus muscles of stroke patients to prevent chronically painful subluxation of the flaccid shoulder. Another involves strengthening the quadriceps muscles to protect an osteoarthritic knee from further stress and deterioration. Other applications in the planning phase include prevention of venous stasis and osteoporosis in patients with spinal cord injuries, reversal of equinus contractures of the ankle in cerebral palsy patients, and correction of footdrop in stroke patients. Still other clinical problems that may be candidates for such intramuscular stimulation include sleep apnea, disorders of gastrointestinal motility, and fecal and urinary incontinence. For most of these applications, clinical utility is as yet uncertain, morbidity would be unacceptable, and cost will be paramount. The generic, modular, minimally invasive and unobtrusive nature of BIONs makes them feasible to apply first to relatively simple clinical problems that might not justify the expense and morbidity of surgically implanted multichannel systems.

The BION technology is suitable for more ambitious FES to reanimate paralyzed limbs, but first the present microstimulator technology must be enhanced to include sensing and outgoing telemetry of the signals required for command and control. Work is under way to accommodate bioelectrical signals such as electromyography (EMG), motion and inclination as sensed by microelectromechanical system (MEMS) accelerometers, and relative position between implants, which can be used as a form of electronic muscle spindle to compute joint angles. These will be combined in progressively more ambitious ways to address various deficits of grasping and reaching in quadruplegic patients who have partial control of their arms. Such applications are less likely than locomotion to run afoul of our still-primitive understanding of sensorimotor control because speed, energy efficiency, and safety are much less critical.

Conclusions

The clinical and commercial success of cochlear implants has greatly increased the credibility of the field of neural prosthetics in general and the levels of technology and funding available to pursue new applications. That this success was achieved despite knowledgeable naysayers should not be cause for hubris. The laws of physics apply equally to bioelectricity and to conventional electronics, so they cannot be ignored. They represent the first and most easily predictable of many scientific, medical, and logistical hurdles that must be overcome to produce any useful neural prosthesis.

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