Prosthetics, Neural

Gerald E. Loeb

Introduction

This article provides an overview of the physical components that tend to be common to all neural prosthetic systems. It emphasizes the biophysical factors that constrain the sophistication of those interfaces. Specific applications to neural prosthetic systems for sensory replacement and motor control are covered in PROSTHETICS, SENSORY SYSTEMS and PROSTHETICS, MOTOR CONTROL, respectively. Electrical stimulation of the nervous system is also being used to treat other disorders; examples include spinal cord stimulation to control pain and basal ganglia stimulation to control parkinsonian dyskinesias.

Electroneural Interfaces

Two types of physical system are known to be capable of real-time information processing: electronic circuits, in which information is carried by the flow of electrons in metal conductors, and neural circuits, in which information is carried by ions in water. Much contemporary research in computational neurobiology is concerned with discovering or exploiting common principles of information processing in these two systems. Thus, it is natural that real-time interfaces between these systems have been developed so that electronic instrumentation can be used to study neural systems. Neural prosthetics are clinical applications of neural control interfaces whereby information may be exchanged between neural and electronic circuits. Their technology to date has been derived largely from cardiac pacemakers, which themselves have evolved from the fixed-rate, single-channel stimulators of the 1950s to become programmable and adaptive systems equipped with sensors and sophisticated data processing.

In principle, information could be transferred into and out of the nervous system by any of several means, including chemical, magnetic, optical, and ultrasonic. In practice, neural prostheses require temporospatial resolution and physical portability, which have only been achieved with the types of electrical signals that are familiar to most electrophysiologists. Thus, the future of neural prosthetics depends heavily on the well-understood biophysical properties of excitable membranes and on the development of technology that can approach physical limits that are readily predictable from those properties.

In addition to the obvious goal of restoring function to patients with disabilities, the field of neural prosthetics offers important opportunities for pure research:

- The clinical and commercial value of neural prostheses justifies the development of technology that is also useful in basic research.
- The implantation of sophisticated neural control interfaces in sentient observers creates unique opportunities for a new class of psychophysical research into neural computation.
- The development of functional replacement parts for the nervous system forces researchers to examine and test theories of neural computing more rigorously than they might do otherwise.
- The development of neural prosthetic controllers that can deal successfully with the exigencies of daily life will almost certainly require advancement of principles and methods for neural networks and other forms of adaptive control.

Stimulation

Most neural prosthetic devices operate by injecting electrical current into the extracellular fluids surrounding excitable neurons in order to elicit action potentials in those neurons. Action potentials so elicited are indistinguishable from those that arise through the

natural mechanisms of sensory transduction or synaptic input. When these action potentials arrive at their destinations, the receiving cells respond to and interpret the signals as if they arose from naturally occurring neural activity. Thus, the goal of the neural prosthetic device is to recreate the temporospatial pattern of activity that would have occurred normally during the particular function that is being replaced or augmented prosthetically (see PROSTHETICS, SENSORY SYSTEMS, for a discussion of these factors in cochlear implants).

Biophysics. Topologically, a neuron in its resting state is essentially a charged spherical capacitor with elongated deformations comprising its axon and dendrites. The cell membrane is the dielectric, the ionic solutions on either side of the membrane constitute the plates, and differences in the concentrations of ions on each side generate the charging potential of about -70 mV (inside versus outside). In order to generate an action potential, the membrane capacitance must be discharged by about 15 mV in a small region. This results in a brief sequence of openings and closings of sodium and potassium channels in the membrane, which results in the flow of the action current. The action current depolarizes and then repolarizes adjacent regions of the cell membrane, giving rise to the propagating wave of activity known as an action potential or spike.

The process of evoking an action potential through extracellular stimulation is somewhat counterintuitive. In order to depolarize a capacitor, it is necessary to pass charge across the dielectric, i.e., into the cell body. However, neither the source nor the sink electrode of the stimulator is actually inside the cell. Instead, the stimulator creates a voltage gradient in the tissues surrounding the target cell. This gradient induces charge to flow across the cell membrane by capacitive conductance in response to the rate of change of the voltage gradient, i.e., dV/dt. The amount and extent of the depolarization so produced depend on the intensity and time course of the pulse of stimulation current, its propagation through the various conductances in the tissues through which it diffuses, and the physical dimensions and consequent electrical properties of the excitable target cell (Ranck, 1975).

The most important physical dimension of highly elongated neurons is their diameter, which affects the ratio of membrane surface area (which determines capacitance) to axonal cross-sectional area (which determines resistance to current spread inside the cell). The presence, thickness, and disposition of myelin are also important because myelin greatly reduces the capacitance that must be discharged in order to reach threshold depolarization. It should also be remembered that electrical current must form a complete circuit, so that any capacitive stimulation current that enters a cell at one point, depolarizing its cell membrane locally, must be balanced by equal current leaving the cell and causing some degree of local hyperpolarization in other regions.

In order to predict accurately the effects of stimulating a complex structure such as a part of the cerebral cortex or a muscle with embedded sensory and motor axons, it is necessary to have a great deal of quantitative information about the neural architecture and the disposition of the stimulating electrodes. There are some useful rules of thumb, however, that cover most of the important phenomena:

- The most important consequence of a stimulation pulse is the steepness of the extracellular field gradient that it produces in the vicinity of the target neurons. Small electrodes positioned close to excitable processes are most effective.
- The important stimulus variable is the charge of a pulse, which is current times duration. Voltage is not important, as most of the voltage tends to be dissipated across the metal-electrolyte interface (see below) rather than contributing to the voltage gradient in the tissue surrounding the neurons.
- Stimulation pulses are most efficient when they have a duration that is somewhat shorter than the membrane time constant of the target cells, which is usually on the order of 100–200 μs for myelinated axons and 500–1,000 μs for unmyelinated axons and cell bodies.
- The first recruited elements tend to be the largest, most elongated, and most myelinated elements, namely large-diameter myeli-

nated axons and large cell bodies attached to myelinated axons.
- Most body tissues (including bone and scar tissue) are sufficiently conductive that they tend, in aggregate, to act as volume conductors in which stimulus current density steadily decreases with distance from the electrode.
- Stimulation electrodes must be used in pairs (source and sink), but each contact tends to function as an independent monopolar electrode unless the two contacts are positioned closer together than the target neurons.

Electrochemistry. The rise of safe and effective neural prosthetic devices over the past 30 years is a consequence of the gradual elucidation of the electrochemical processes involved in converting electrical current from flow of electronics in a metal conductor to flow of ions in an aqueous one. In order for this to occur without cumulative deterioration of the electrodes or damage to the tissues, it is necessary that this be accomplished by entirely reversible chemical reactions. The typical reactions of electrolysis result in irreversible breakdown of water molecules into gases and acid or alkali solutions and shifts of the neutral valence of metals into positive-valence oxides with very different electrical, chemical, and biotoxic properties (reviewed by Loeb, McHardy, and Kelliher, 1982).

The most obvious fully reversible reaction is the charging and discharging of the capacitance between the metal electrode and the body fluids. Because the irreversible reactions of electrolysis all have minimal working voltages that must be exceeded before they occur (usually about ± 0.8 VDC), stimulating current can be passed into and out of the electrode safely as long as capacitive charging never reaches these working voltages. Thus, repeated brief pulses of electrical current can be applied safely, as long as an equal and opposite amount of charge flows in the opposite direction between each stimulating pulse.

The amount of charge that can be passed by this double-layer charging depends on the capacitance of this interface, which depends on the surface area of the electrode and the thickness of the effective dielectric boundary of the interface. A metal that forms little or no surface oxide, such as platinum, has a dielectric boundary thickness that depends on the thermodynamics of molecules bouncing off its surface. Metals that form stable nonconductive oxides, such as tantalum, can be anodized to build up their oxide thickness, reducing the capacitance but providing a barrier to inadvertent electrolytic reactions (Guyton and Hambrecht, 1974) and permitting them to sustain much higher voltages during stimulation pulses. Other reversible reactions available on some metal surfaces include absorption and desorption of hydrogen and oxygen. Iridium provides the highest charge density limit (about 3 mC/cm^2) of any biocompatible electrode material because it can be "activated" by growing a multilayer surface oxide that is electrically conductive and porous to ions (Robblee, Lefko, and Brummer, 1983). Iridium exhibits a range of stable positive valences from about $+3$ to $+4.8$, so that each atom in the oxide layer can absorb or release about two electrons, with concomitant release or absorption of two hydroxyl ions.

Electrochemical considerations are particularly important to attempts to extend neural prosthetic technology to provide denser multichannel interfaces with the nervous system. In order to provide more independent channels of stimulation in a given neural pathway, it is necessary to make the electrodes smaller and position them closer to their target neurons (Loeb, Peck, and Martyniuk, 1995). Such a microelectrode produces sufficient current density to activate local neurons selectively, while minimizing the spread of stimulation current to adjacent sites under the control of other microelectrodes. Unfortunately, the surface area of such electrodes tends to decrease faster than the amount of charge required to activate local neurons, pushing electrode materials to their safe charge density limits.

Recording

Electrophysiological recordings of interest to the control of neural prosthetics range from the potentials generated by large populations of cells (such as those seen in EEG and EMG) to the action poten-

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tials generated by individual neurons. All of these signals are small-amplitude AC signals (typically less than 1 mV) that must be detected against a background of interfering signals from other bioelectrical sources and various sources of noise. In most parts of the central and peripheral nervous systems, the activity of adjacent neurons is often quite distinctive, making it necessary to record and distinguish the action potentials of single units to use them as command and control signals. This has been accomplished for brief periods of time in many research applications, but techniques remain to be developed for stable, long-term recordings from human patients.

The action potentials generated by individual neurons are produced by action currents of 1–10 nA lasting 0.2–2 ms, depending on the size and myelination of the cell. As in the case of the currents produced by electrical stimulation, the current density and the resulting potential gradient in the surrounding tissues drop rapidly with distance from the current source (Rall, 1962). Microelectrodes usually must be within 100 μm of a neuron to record a usable action potential. In order to be positioned that close to a neuron, such a microelectrode must be physically small, with a small surface area. For a metal microelectrode, double-layer charging of the metal-electrolyte interface provides the mechanism for converting a biopotential from ion fluxes in water to electron motion in a metal conductor. The small surface area of the exposed metal surface provides only a small capacitance, resulting in a relatively high impedance in the frequency band of the action potential (typically 100–1,000 kΩ at 0.5–5 kHz). The resistivity of the saline in the immediate vicinity of the microelectrode also presents a substantial impedance. High impedance is associated with high thermal noise, which adds to and obscures any biopotentials to be recorded.

Usually microelectrodes pick up signals from several adjacent neurons, which may need to be discriminated based on small differences in their waveforms. Even relatively low noise levels may degrade the reliability of such discrimination. Small movements of the microelectrode with respect to the neurons are likely to distort the relative amplitude and shape of the single unit potentials or change the sampled population entirely.

Systems Hardware

Power and Data Management

In order to improve the sophistication and capabilities of neural prosthetic interfaces, larger numbers of stimulating and recording channels must be positioned closer to their neural targets. This raises the problem of how to transmit more data to and from arrays of small electrodes located in delicate neural tissues.

One approach is to combine many electrodes into an array that includes active electronic processing so that a large number of separate signals can be multiplexed onto one data connection (Najafi, Ji, and Wise, 1990). Stimulation pulses are usually relatively brief ($\sim$100 μs) compared to their interpulse intervals ($\sim$10–100 ms), making it possible for a single stimulus channel to be multiplexed among many electrodes. Bioelectrical potentials are more difficult to multiplex because they usually have high concurrent bandwidths (1–10 kHz) on each channel, resulting in very high aggregate sampling rates.

Any active circuitry for multiplexing or demultiplexing requires DC power. Electrical leads and connectors carrying DC voltages are particularly difficult to insulate because even tiny amounts of saline leakage result in electrolytic corrosion (see below). The very low power consumption of some integrated circuit technologies has led to interest in the wireless transmission of power. Radio-frequency (RF) inductive coupling is now used routinely in cochlear implants and has been developed for injectable muscle stimulators (Troyk and Schwan, 1992). Infrared transmission and photoelectric conversion may also be possible over short distances.

Packaging

Active microelectronic circuitry is generally contained within a hermetic enclosure to protect it from moisture. This adds greatly to the physical bulk of the circuitry, particularly if large numbers

of input-output channels must be routed through feedthroughs and connectors incorporated into the package. The design of the package and the selection of hermetic materials (metals, ceramics, and glasses) are likely to be further complicated by the need to transmit RF or infrared energy to power and control the electronics. Embedding in epoxy, silicone, and other nonhermetic polymers was commonplace in the early cardiac pacemaker industry, but it is difficult to perform reliably on complex circuits. There is much interest in passivating monolithic integrated circuits so that they can be implanted directly into the nervous system with few or no attached leads.

Nonhermetic encapsulation and passivation depends on adhesion of the coating material to the substrate electronic components rather than impermeability. Water in the vapor phase tends to diffuse through all polymeric materials, but it does not cause electronic problems until it condenses onto the circuitry itself. Once condensation occurs, the water vapor forms an ionic solution by dissolving surface contaminants or the materials themselves. This solution represents an osmotic attractant, pulling additional water vapor out of the surrounding polymer and pressurizing itself so that it dissects along the surface, eventually bridging electrical conductors and resulting in corrosion and circuit failure. Condensation on hydrophilic surfaces can be prevented only if there are no voids and there is sufficient adhesive force between the encapsulant and all substrate materials. Even trace surface contaminants tend to interfere with adhesion, which usually depends on electrostatic bonding (Donaldson, 1987).

An alternative approach to chemical adhesion for certain geometries is to use hydrostatic pressure. This has proved useful in preventing electrical shorting from condensed water within connectors that must be opened and closed in the body. The encapsulant is pressurized mechanically as the connector is closed so that its hydrostatic pressure exceeds the maximal osmotic pressure of salt solutions (typically 200–250 psi) (Loeb et al., 1983).

General Conclusions

Serious attempts to build functional neural prostheses have been under way for about 35 years. Progress has been limited because it depended on concurrent developments in microelectronic and biomaterial technologies as well as on advances in understanding the neurophysiology of the functions to be restored. Once these thresholds have been passed for a given application (e.g., cochlear implants for the deaf; see PROSTHETICS, SENSORY SYSTEMS), dramatic functional restoration has been achieved, although the development of these complex and highly regulated medical devices remains much slower than that of comparable consumer electronics. As the armamentarium of applicable technology and basic neurophysiology enlarges, there should be a steady acceleration in the clinical application of neural prostheses.

Roadmap: Applications
Related Reading: Brain-Computer Interfaces; Brain Signal Analysis; Prosthetics, Motor Control; Prosthetics, Sensory Systems

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