

## MICROELECTRODES

### BIOELECTRODES

#### MICROPIPETTES

Microelectrodes have traditionally been developed and used to measure voltage inside and outside biological cells, and much of our understanding of the nervous system has come from these recordings. Microelectrodes have been adapted with some clever arrangements to measure membrane voltage and ion concentrations simultaneously. More recently, microelectrodes capable of measuring partial pressures of various gases and concentrations of physiologically relevant chemical substances, such as neurotransmitters, have also been designed. The advantages of these microelectrodes is that they allow direct measurements within biological tissues to give information about the local microscopic milieu. Therefore, these electrodes must be small to minimize interference with physiological function and the damage generated by their insertion. Although these small structures are more fragile than macrosensors, they usually have better time constants.

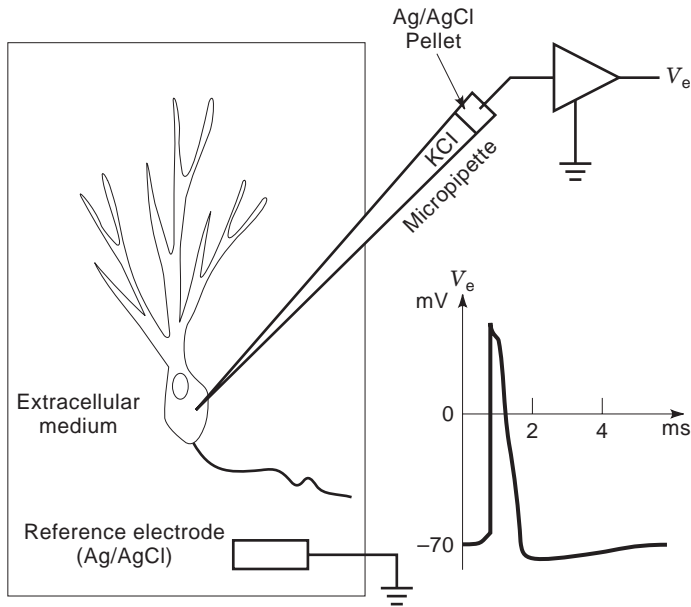
#### MEMBRANE POTENTIALS

All cells in the body have a nucleus and a cytoplasm surrounded by a lipid membrane. The cytoplasm is a good conductor with a resistivity varying between  $50 \Omega \cdot \text{cm}$  and  $300 \Omega \cdot \text{cm}$ . The cytoplasm is separated from the outside of the cell by a thin (7.5 nm to 10 nm), resistive and capacitive membrane composed almost entirely of proteins and lipids. Electrical potentials exist across this membrane in practically all cells of the body. The resting potential difference is generally around  $-70 \text{ mV}$ , and the inside of the membrane is negative with respect to the outside (See **Bioelectric potentials**). This resting potential is generated by the equilibrium of two forces, the diffusion of ions across the membrane through protein channels and the electrical force generated by accumulation of ions at the membrane. The resting potential is sustained by pumps that maintain diffusion gradients across the membrane. Some cells, such as muscle fibers and neurons, are excitable and generate large voltage signals (about 100 mV) either spontaneously or when stimulated. Figure 1 shows the resting potential and action potential in a neuron. The action potential is generated by nonlinear voltage-sensitive ion channels. Sodium (Na) channels are normally at rest and open when the membrane voltage reaches a threshold value. A large influx of Na current depolarizes the membrane to positive potentials. The Na channels turn themselves off (inactivation), and the potassium channels then open bringing the membrane voltage down to its resting value (1). This action potential is an all-or-none phenomenon and carries information from sensory inputs to the brain, from the brain to the muscles, and within various parts of the brain. Therefore, the measurement of the membrane potential is crucial to our understanding of the activity of excitable and

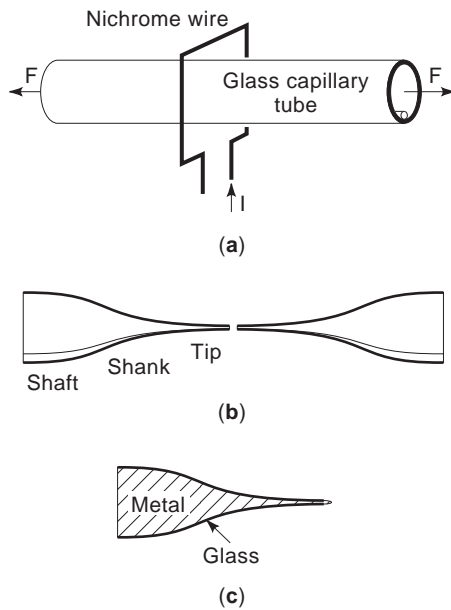
nonexcitable cells. To measure the electrical activity of a cell, the transmembranous voltage or transmembranous current must be evaluated. An electrode must be located directly inside or make electrical contact with the inside of the cell. Because the cells recorded from can be as small as  $1 \mu\text{m}$ , electrodes with submicron dimensions must be used to collect information without damaging the cell. This can be achieved with micropipettes. A micropipette as a microelectrode to record membranous voltage in muscle cells was first used by Graham and Gerard in 1946 (2).

#### GLASS MICROELECTRODES (MICROPIPETTES)

Micropipettes are made of very thin glass tubes filled with a conducting electrolytic solution. A 1 mm diameter borosilicate or aluminosilicate glass tube is placed in a pipette puller. The two ends of the glass tube are clamped to a pulling device, and a heating filament is placed in the middle of the glass [Fig. 2(a)]. As the heating filament melts the glass, the ends of the tube are pulled apart until separation takes place, forming two electrodes with very small diameter ( $<0.2 \mu\text{m}$ ) [see Fig. 2(b)]. The length of the electrode's shank is controlled by cooling the glass with an air puff following heating (3). The tip diameter and the taper of the electrode are also controlled to make various types of microelectrodes. Intracellular potential is recorded with submicron diameter electrodes filled with an electrolyte similar to that found within the cell. KCl is often used because the intracellular potassium concentration is high with respect to other ions. To facilitate filling the electrode, a small glass capillary is inserted in the tube by the manufacturer (Fig. 2). The other end of the electrode is inserted into an electrode holder which contains a reference electrode made of sintered Ag/AgCl. Then the electrode is connected to the input of a high impedance amplifier. The potential inside the cell is measured with respect to the voltage outside the cell using a reference electrode located in the extracellular space, also made of Ag/AgCl (see Fig. 1). Microelectrodes are also used to measure the voltage outside the cell (extracellular recording). The diameter of extracellular electrodes is larger than intracellular electrodes (around  $1 \mu\text{m}$  or  $2 \mu\text{m}$ ), and the electrodes are filled with NaCl because the sodium chloride concentration is significantly higher outside than inside the cell. A third type of microelectrode, the patch clamp electrode, is made to measure the current through the membrane and through ion channels (4). These electrodes are also pulled to a diameter of  $1 \mu\text{m}$  to  $2 \mu\text{m}$  but have a steep taper generated by pulling the electrode in a two-step procedure. Then the pipette is filled and placed on the surface of the cell. The glass forms a high impedance seal ( $\text{G}\Omega$ ) with the membrane. Then the patch of membrane inside the electrode is removed by applying a small amount of suction, and direct access to the cell is provided for voltage or current measurement (whole-cell patch clamp). By pulling the electrode and patch from the cell, an inside-outside patch is formed (cytoplasmic surface toward the bath). By pulling the electrode slowly away from the cell, an outside-out patch can sometimes form (extracellular surface toward the bath). The membranous current from these various combinations is obtained by clamping



**Figure 1.** Recording neural activity with a microelectrode. (a) Neuron and intracellular electrode. (b) Intracellular voltage obtained with electrode showing the resting potential and the action potential.



**Figure 2.** Microelectrodes. (a) Micropipette puller. A glass capillary tubing is heated and pulled. (b) Two small diameter electrodes are produced (c) Supported metal microelectrode with glass insulation.

the voltage at various values and measuring the current.

The impedance of these micropipettes significantly influences the measurement of both voltage and current. Intracellular electrodes, in particular, have high impedance and capacitance and require special circuits for signal processing (see later).

## METAL MICROELECTRODES

Although micropipettes can be made very small, they have large impedance and are also very fragile. Microelectrodes for recording the activity of small neurons can also be

made with sharpened and insulated metal wires. These electrodes have very small tips and can be placed within a few micrometers of the cell to be studied. Moreover, they can be stiff enough to penetrate tough tissue, such as the protective membrane around the brain or nerves. These electrodes can record neural activity but also provide very localized stimulation by passing current large enough to excite the neurons in the vicinity of the electrode (5).

The most common type of electrode uses tungsten etched to a sharp tip and insulated to within a few micrometers of the tip. These electrodes are shaped with a shallow taper to ease penetration. A more recent design uses iridium because it is stiffer than tungsten, is extremely resistant to corrosion, and can be electrochemically “activated (6).” In the recording mode, these metal electrodes operate at small voltages, and the impedance between the metal and the tissue is dominated by the double-layer capacitance. Therefore, the electrical model of the electrode consists of a small capacitance in series with the access resistance and the tissue resistance (see next section). The impedance is determined mainly by the size of the tip and can be in the  $M\Omega$  range. The noise generated by the electrode is typical thermal noise but does not come entirely from the resistance of the electrode. The electrochemical process, which generates the double-layer capacitance, involves movement of charge carriers and contributes to the noise (7). Therefore, low-noise recording amplifiers must be used to maximize the signal-to-noise ratio.

Metal microelectrodes can also be used to stimulate neuronal activity. Electrons are charge carriers in the metal, but in the body’s aqueous solution the current is carried by ions. A conversion must be made at the interface, which necessarily involves electrochemical reactions. Some of these reactions are reversible, but others are not. The irreversible reactions cause pH changes, gas formation, metal dissolution, and corrosion (8). All of these by-products are potentially damaging to the tissue but can be minimized by using biphasic current pulses which keep the voltage

across the interface below threshold values for these reactions and at least partially reverse some of the reactions. For microelectrodes designed to stimulate neural tissue, the charge-carrying capacity is the most important characteristic. This capacity is proportional to the surface area of the electrode. To increase the amount of charge which can be delivered by a small electrode, a layer of metal oxide (iridium oxide for an iridium electrode) is deposited on the surface. The oxide layer formation or activation is achieved by cycling the electrode between the anodic and cathodic voltages which generate electrolysis. Iridium oxide is a conductive layer which exchanges an electron for an hydroxyl ion across the interface. The charge-carrying capacity of the electrode is effectively increased by adding an iridium oxide layer. The impedance of the electrodes is also reduced by this activation process by an order of magnitude (6). The impedance decreases as a function of frequency and is best modeled by a capacitor in series with a resistor which has a 300 Hz cutoff.

Metal electrodes are insulated with various types of polymeric materials, such as Teflon or Parylene-C. Insulation at the tip of the electrode is removed with electric fields or lasers to burn the material away. By combining the properties of glass and metals, supported metal electrodes are fabricated [Fig. 2(c)]. A micropipette is filled with a metal which has a melting point below that of glass and is pulled to a fine tip. Thin metal films can also be deposited onto a solid glass rod pulled to a sharp point. Then the electrode is insulated with a polymer, except at the tip, to form a sharp microelectrode (9).

## ELECTRICAL PROPERTIES OF MICROELECTRODES

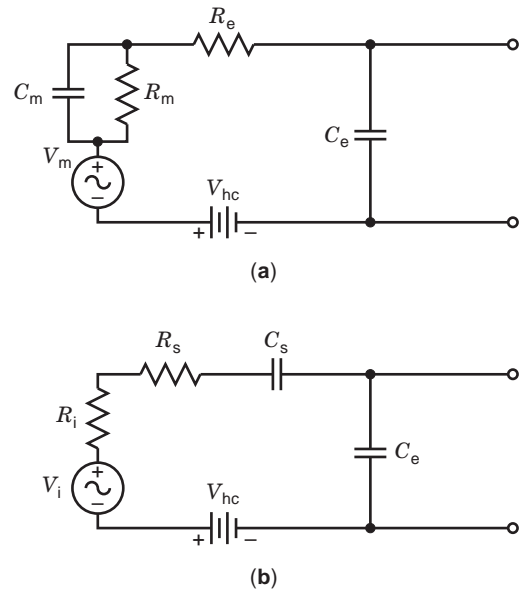
Micropipettes and metals microelectrodes consist of a conductive cylindrical core surrounded by an insulating layer made of polymer or glass. The electrode is inserted within a tissue which is a relatively good conductor (about  $100 \Omega \cdot \text{cm}$ ). The electrode is pulled to a very small diameter, and therefore the narrow shank region of the electrode generates large resistance. This region is usually tapered, and assuming a small amount of taper, the resistance is given by

$$R_E = \frac{4\rho L}{\pi d^2} \quad (1)$$

where  $\rho$  is the specific resistivity of the electrode's conducting material,  $L$  is the length of the electrode shank, and  $d$  is the internal diameter of the electrode. A distributed capacitance is also formed along the immersed part of the shank between the interior and the extracellular (or intracellular) space. This capacitance, again assuming a small amount of taper, is given by

$$C_E = \frac{2l\pi\epsilon}{\ln\left(\frac{D}{d}\right)} \quad (2)$$

where  $D$  is the outside diameter of the electrode,  $l$  is the length of the shank inserted into the tissue, and  $\epsilon$  is the dielectric constant of the insulating material. There are several impedances which affect the signal, and detailed



**Figure 3.** Microelectrode impedance. (a) Equivalent circuit for micropipette. (b) Equivalent circuit for metal microelectrode.

equivalent circuits of these microelectrodes have been presented (10).

For micropipettes, the impedance characteristic is dominated by the resistance  $R_E$  (about  $100 \text{ M}\Omega$  for an intracellular microelectrode) and the small capacitance  $C_E$  (a few pF) of the shank. The cell is modeled by an equivalent membranous resistance  $R_m$  and capacitance  $C_m$  in series with a voltage source  $V_m$ . A simplified equivalent circuit is shown in Fig. 3(a). The resistance of the cells  $R_m$  is often as large as the source resistance of the electrode. This can cause saturation of the amplifier when current is injected within the cell. Special circuits have been designed to remove this effect (see bridge circuit in next section).

For metal microelectrodes, the impedance is dominated by the metal-liquid capacitance  $C_s$  and the series resistance  $R_s$ . For extracellular recordings with a metal microelectrode, the source is modeled by a voltage generator  $V_i$  with a source resistance  $R_i$ . A simplified equivalent circuit is shown in Fig. 3(b). In both cases, there is a dc battery  $V_{hc}$  added to the equivalent circuit which takes into account all of the half-cell potentials throughout the circuit.

## ELECTRONIC CIRCUITS FOR MICROPIPETTES

The high resistance and capacitance of micropipettes can severely affect the signals recorded and require special circuits for processing (11). In particular, most researchers inject current inside through the cell to measure its input resistance or to depolarize the membrane. To inject current and record voltages with the same electrode, a circuit is used similar to that shown in Fig. 4(a). The membranous voltage is measured with the high impedance buffer amplifier (A). The injected current  $I_i$  is given by the following equation assuming that the input impedance of A is

infinite,

$$I_i = \frac{BV_s + V_m(AB - 1)}{R_s} \quad (3)$$

where  $B$  is a finite gain summing amplifier. If  $AB$  is set equal to 1, the circuit becomes a current source because the injected current equals  $BV_s/R_s$  and depends only on  $V_s$  and  $R_s$ .  $A$  is implemented as a high-impedance buffer and  $B$  as a summing amplifier with a gain of 1. The input resistance  $R_{in}$  of the circuit is obtained by considering that the resistance  $R_s$  is bootstrapped between the input and the output. Then the Miller theorem gives the resistance  $R_m$  as

$$R_{in} = \frac{R_s}{1 - AB} \quad (4)$$

The product  $AB$  can be designed to be less than but very close to 1 thereby generating a very high input resistance. Then this circuit allows voltage recording with high input impedance and current injection with a grounded voltage source.

The high resistance of the electrode generates a large voltage in response to an applied current which is added to the cell's response. To remove the effect of the electrode resistance from the response of the cell, a bridge circuit shown in Fig. 4(b) is implemented. The circuit takes advantage of the fact that the electrode's time constant is significantly faster (in most cases) than the response of the cell to a step increase in current. A current generator injects the same current into a variable resistor that is injected in the cell. The voltage recorded by the electrode is subtracted from the voltage across the variable resistance. By varying the resistance, the effect of the electrode resistance can be removed from the recorded voltage. When the recorded signal is properly compensated for, then the resistance of the electrode is equal to the value of the variable resistance. Therefore, this simple circuit can compensate for the electrode resistance and allows direct measurement of the electrode resistance.

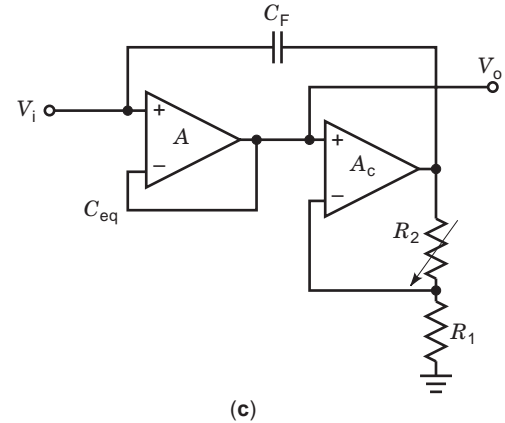
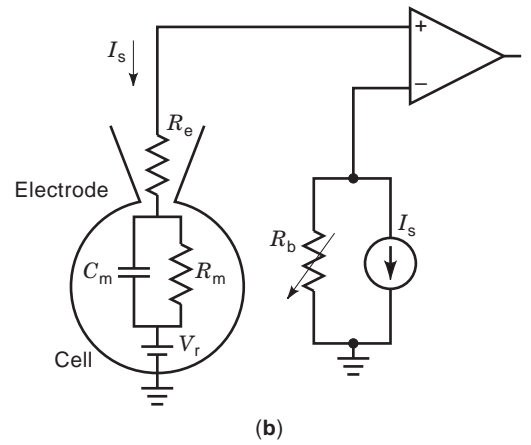
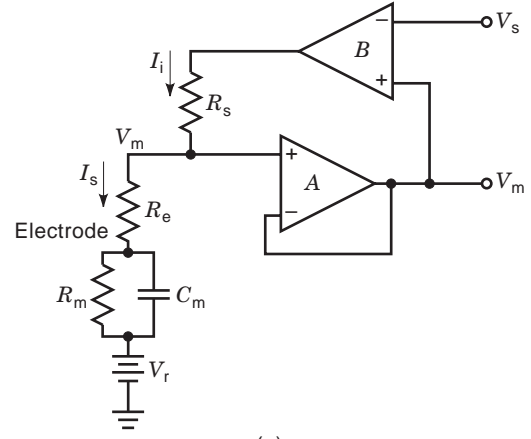
The bridge circuit depends on the relative speed of the rise time of the amplifier and the membranous voltage of the cell. The capacitance of the micropipette can be large enough to slow down the response of the amplifier until it is no longer possible to distinguish between the cell response and the electrode response. Therefore, a circuit compensating for the capacitance of the electrode has been developed. The circuit [Fig. 4(c)] introduces a negative capacitance at the amplifier input. The input impedance of the circuit, assuming an amplifier with an infinite input resistance is given by

$$Z_{in} = \frac{V_{in}}{I_f} = \frac{1}{(1 - AA_c)jC_F\omega} \quad (5)$$

where  $C_F$  is the feedback capacitor. Therefore, the input impedance of the circuit is the impedance of capacitor  $C_{eq}$  given by

$$C_{eq} = (1 - AA_c)C_F \quad (6)$$

If the product  $AA_c$  is adjusted to a value greater than 1, the input capacitance becomes negative and is placed in paral-



**Figure 4.** Circuits for microelectrodes. (a) Current injection and voltage measurement. (b) Bridge circuit for electrode resistance measurement and compensation. (c) Negative capacitance compensation.

lel with the capacitance of the electrode. Then the net capacitance is decreased, improving the frequency response and the rise time of the electrode-amplifier recording system (12). To implement the circuit, the amplifier ( $A$ ) is a buffer and is the same as in Fig. 4(a). The gain  $A_c$  amplifier is made variable and greater than 1.

Microelectrodes have also been used for voltage and patch clamping of cells. These techniques allow researchers

to fix the voltage and measure the membrane current of a whole cell, a patch of membrane, or individual channels. The methods required specialized circuits which measure a current while maintaining the voltage of the membrane (4).

### ION-SELECTIVE GLASS MICROELECTRODES

By adding a membrane material to a glass micropipette, the activity of ions in sample solutions can be measured. The selectivity depends mainly on the type of membrane used. The pH of solutions can be measured with a glass membrane, and recent developments in polymer membranes have made it possible to measure the activities of  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Cl}^-$ , and other ions. These ion-selective microelectrodes are inexpensive and are small enough to measure the activity of ions in both extracellular and intracellular spaces. Abnormal cellular states often result from an imbalance of ionic concentration. Therefore, the fact the activity of ions (not just the concentration) can be measured with very small electrodes compatible with glass micropipette technology has provided researchers with a powerful method to analyze both the normal and diseased physiological states.

A membrane is chosen to allow the diffusion of certain ions selectively and then is inserted into the glass micropipette. The potential difference generated between an external reference electrode (Ag/AgCl, for example) and the ion-selective microelectrode immersed in the sample solution is given by the Nicolsky equation (13):

$$E_{\text{measured}} = V_r + \frac{2.3RT}{zF} \log(a_i + k_{ij}a_j^{2/x}) \quad (7)$$

where  $V_r$  is a constant and takes into account the voltages within the electrochemical cell,  $a_i$  is the activity of the ion in the sample,  $a_j$  is the activity of the interference  $j$ ,  $k_{ij}$  is the selectivity constant of the electrode for ion  $j$  relative to ion  $i$ ,  $x$  the charge of ion  $i$ ,  $R$  is the gas constant,  $T$  is the absolute temperature,  $z$  is the charge of the ion, and  $F$  is the Faraday constant. Typically, electrochemical cells have very large impedances, and the voltage difference must be measured with high input resistance amplifiers ( $\sim 10^{15} \Omega$ ), such as electrometers. The selective membranes can be grouped into three classes: glass, liquid, and solid state. Glass membranes are very sensitive to the concentration of  $\text{H}^+$  ions. Liquid membranes are commonly used in biological preparations for other ions. For example, potassium ion activity can be measured using a liquid membrane containing the antibiotic Valinomycin combined with a resin. When applied to the extracellular space of brain tissue undergoing epileptiform activity, the potassium concentration observed rises from its resting value of 7 mM to 11 mM. The rise in potassium activity is accompanied by increased neuronal activity and is similar to neural activity observed during epilepsy. The last class of membranes is made of solid-state material, such as crystals or insoluble salts. For example, a pellet of silver sulfide can be used to detect  $\text{Ag}^+$  with very high sensitivity.

### MICROELECTRODES FOR CHEMICAL MEASUREMENTS

The small size of microelectrodes makes them ideal for measuring local concentrations of various chemical species, such as neurotransmitters, or the partial pressure of various gases (see *Biosensors*). The carbon fiber microelectrode is very popular. These fibers have diameters as small as a few microns and can be inserted into glass micropipettes for insulation by exposing a short length of the electrode. Contact between the fiber and the electronic circuit is made by filling the electrode with mercury or silver paint and sealing it with epoxy. Then the assembly is inserted within physiological tissue and selective measurement of various compounds is carried out using a combination of selective membranes, enzyme coatings, surface modifications, and various electrochemical techniques. For example chronoamperometry has been used to detect the release of easily oxidized neurotransmitters, such as dopamine, serotonin, and epinephrine. In chronoamperometry, a constant voltage is applied between the carbon fiber and a ground electrode. The current is measured and is directly related to the level of oxidation. Carbon fiber microdisks are typically more useful than microcylinders since they provide a better geometry and excellent resolution. They are also more difficult to fabricate and have lower current amplitudes. A three-electrode system is used to generate a constant voltage between the working electrode and the medium around it. A reference electrode is located close to the working electrode to estimate the medium's voltage. Using feedback, a current is applied between the working electrode and a ground electrode to maintain a constant voltage. For the very low currents of microelectrodes and microdisks, a two electrode system is sufficient since the ohmic drop and polarization of the reference electrode are negligible. The amplitude of the current is modulated by oxidation of the compound to be measured and is proportional to its activity. To improve selectivity, a differential method is used whereby the current amplitudes obtained at two voltages are subtracted and the contribution of the interfering species, such as ascorbic acid, can be reduced or eliminated. The electrode can also be coated with selective membranes. Nafion is a commonly used membrane because it prevents various charged molecules from interfering with measurement. The surface of the carbon fiber can also be modified chemically or with a laser to improve the selectivity and sensitivity of the electrode (14). By depositing appropriate enzymes on the surface of the electrode, very selective electrodes can be made to measure glucose, nitric oxide, acetylcholine, etc.

Field effect transistors (*FET*) have also been adapted to allow measuring various ions or chemicals. Ion-sensitive field-effect transistors (*ISFET*), for example, are enhanced *MOSFET* transistors but use an ion-sensitive membrane instead of gate metallization (14). Then the transistor is immersed in a solution containing the ions to be measured. An electrochemical potential is established at the interface between the solution and the gate dielectric. This potential is established with respect to a reference electrode located in the solution and can modulate the conductance of the channel under the gate. The electrodes can be made very small but have drift and selectivity problems.

## MICROELECTRODE ARRAYS

The silicon technology used to make integrated circuits can be adapted to manufacture arrays of microelectrodes. The activity of single cells can be recorded with the micropipette technology discussed previously. Neuroscientists are now increasingly interested in recording simultaneously from a large number of cells. Moreover, by stimulating a large number of cells in the spinal cord or in the brain selectively, it should be possible, in principle, to restore motor function in paralyzed patients or vision in blind patients, for example. Therefore, multiple arrays of electrodes capable of recording or stimulating the nervous system are clearly important to understanding nervous system function and to designing neural prostheses. Three silicon-based types of microelectrode arrays have been developed: (1) A 1-D beam electrode where a thin-film platinum-iridium is deposited on a thin layer of silicon substrate (15). This thin substrate provides a surprising amount of flexibility and can be utilized for the leads and the electrode pads. (2) A 2-D array for recording the activity of neurons grown in cultures and axons in nerves. A thin film microelectrode array is made of gold electrodes covered with platinum black on a silicon substrate. The assembly is built into the bottom of a neuron culture dish. Neurons grow over these electrodes and make direct contact with them (16). In another design, micromachining of a silicon wafer generates a matrix of 64 square holes with a side dimension of 90  $\mu\text{m}$ . Gold pads and leads are deposited near each hole. Then the thin wafer is inserted between the two sides of a severed nerve. As the axons grow inside the holes, it is possible to record from a selectively small groups of axons (17). (3) A 3-D array for cortical recording and stimulation. The 1-D beam electrode discussed previously can be assembled to form three-dimensional arrays. The longitudinal probes are inserted perpendicularly into a silicon platform. The leads from each probe are transferred to the silicon probe and are routed to a digital processing unit (18). Current work also involves including low noise amplification directly on the platform. Another implementation involving micromachining and etching techniques was used to fabricate a  $10 \times 10$  electrode array. One hundred conductive needlelike electrodes (80  $\mu\text{m}$  at the base and 1.5 mm long) are micromachined on a 4.2 mm  $\times$  4.2 mm substrate (19). Aluminum pads are deposited on the other side of the substrate and make contact with each needle electrode. The tips of the electrodes are coated with gold or platinum. A high-speed pneumatic device is used to place the array into cortical tissue because the high density of the electrodes makes insertion difficult. Then the microelectrode arrays are available for recording from a large number of cortical sites.

## NANO-ELECTRODES AND NANO-ARRAYS

Progress in nanotechnology has reduced the size of microelectrodes into the 1-100 nm range (20). These electrodes have improved spatial and temporal resolution for imaging and analytical measurements (20). Nano-wires arrays with integrated electronic circuits have been able to record neu-

ral activity along axons with a resolution of 400 nm (21). Electrodes as small as 1 nm have been fabricated (22). Concentrations as small as  $10^{-21}$  (23) have been measured with these nano-electrodes thereby getting closer to achieving single molecule detection.

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