BIOMEDICAL SENSORS

A biomedical instrumentation system (Fig. 1) consists of three main components: the sensor, the processor, and the recorder and/or display. This article is concerned with the sensor portion of the instrumentation system. As seen in Fig. 1, the sensor is the interface between the biological system and the electronic signal processing portion of the instrument. When we consider a biomedical sensor, we must be concerned about both the biological and the electronic aspects of sensor performance. Biological concerns involve the response of the biological system to the presence of the foreign sensor and the response of the sensor to the biological environment. Electronic concerns relate to the type of signal that the sensor provides and how this signal is interfaced to the processor portion of the instrument. Thus, in considering biomedical sensors we must look at both the biological and electronic performance of this component.

Biomedical sensors are classified in many different ways, as summarized in Table 1. Classifications are determined by the type of biological variable measured by the sensor, the technology used for sensing, the approach to obtaining the output signal from the sensor, and the interface that the sensor establishes with the physiological system. All of these concerns are important in classifying sensors, but depending on the sensor and the application, it may not be necessary to use all of the descriptors in the columns of Table 1 for sensor characterization. It is important to note, however, that the ways that biomedical sensors differ from sensors used in nonbiomedical instrumentation systems are found in these classifications. Although any sensor can be described by the variable measured and the sensing technology used, their interaction with a physiological system represents a special characteristic of biomedical sensors that is not generally of concern with similar conventional sensors. There are some biomedical sensors, for example, temperature sensors, that are identical to sensors of the same variable used for nonbiomedical applications. The application of these sensors to biological systems, not the technology, makes them unique. For example, a conventional temperature sensor, such as a thermistor, becomes a biomedical sensor when it is incorporated in a rapidly responding electronic oral thermometer with disposable protective sheaths.

Figure 1. Block diagram of a general biomedical instrument.

Biomedical sensors sense physical quantities, such as displacements or pressures, and they sense chemical quantities, such as the activity of hydrogen ions or partial pressure of oxygen. There is a special subcategory of chemical sensors of sufficient importance to be often listed as a separate category. This is the bioanalytical sensor that incorporates biological recognition reactions in sensing biochemical analytes.

There are various mechanisms whereby a sensor measures a specific variable. It may be possible to convert that variable directly into an electrical signal or the variable can produce an optical or mechanical representation. Chemical or biological responses are also obtained from sensors, and this is the case in nature's own sensors, such as in the nervous system of biological organisms.

Sensors are classified according to the way they convert a physiological variable to the output signal. In a single-step conversion process, the physiological variable, such as temperature, is directly converted to the output variable, such as an electrical signal. An example of this is a thermistor that directly converts its temperature into an electrical resistance functionally related to that temperature. In a multistep sensor, there are intermediate variables. For example, a glucose sensor does not directly convert the concentration of glucose to an electrical current, but rather an intermediate step occurs where the glucose determines the concentration of another substance, such as hydrogen peroxide, which in turn is converted into an electrical signal. Knowledge of whether a sensor produces its output by a single- or multiple-step conversion is often useful in determining what signals interfere with that sensor's response.

The previous classifications are based on the sensor technology used to measure a variable. Biomedical sensors are also classified in terms of how they are applied in making a measurement. Noncontacting sensors are located remotely from the biological signal source and do not actually touch the biological material being measured. A radiation thermometer is an example of such a device. Sensors are considered nonin-

Table 1. Classification of Sensors

Type of Variable Sensed	Technology Used for Sensing	Sensing Mechanism	Application to Biologic System
Physical	Electronic	Single step	Noncontacting
Chemical	Optical	Multistep	Noninvasive
Bioanalytical	Electrochemical		Minimally invasive
	Mechanical		Invasive
	Biologic		

Table 2. Examples of Physical Sensors Used in Biomedical Measurements

Sensor	Variable Sensed
Variable resistor	Linear or angular displacement
Strain gage	Strain (small linear displacement)
Linear variable differential transformer	Linear or angular displacement
Velocimeter (laser or ultrasound)	Velocity
Accelerometer	Acceleration
Thermistor	Temperature
Thermocouple	Differential temperature
Strain gage pressure transducer	Static and dynamic pressure
Load cell	Force
Electromagnetic flow meter	Flow of electrolytic liquids

vasive if they touch the body but do not enter its cavities or tissues. Sensors placed on the skin surface, such as a transcutaneous carbon dioxide sensor, are considered noninvasive. Minimally invasive sensors enter the body but only through normal orifices, such as the mouth or urethra. These sensors are often called indwelling sensors. A miniature pH sensor for measuring gastric pH might seem very invasive to the individual on whom the measurement is made, but in fact it is only minimally invasive because it enters a natural body cavity. Invasive sensors, on the other hand, must be placed surgically. Tissue must be incised or penetrated to position such sensors. Sensors located within the cardiovascular system, such as miniature intraarterial pressure transducers enter the arterial system only by a surgical cut-down or a skin-penetrating needle. The biomedical environment is extremely hostile especially for implanted sensors. Thus, special precautions must be made in packaging the sensors to minimize problems resulting from this environment.

In the following sections we look at examples of biomedical sensors based upon the variable sensed. We consider the operating principle of each sensor type and look at examples of biomedical applications.

PHYSICAL SENSORS

A physical sensor is one that measures quantities, such as geometrical, kinematic, electrical, force, pressure, and flow in biological systems. Table 2 lists examples of important physical sensors for biomedical measurements. Although similar sensing devices are used in biomedical and nonbiomedical applications, the realization of these devices as practical components is quite different depending on the application.

Sensors of Linear and Angular Displacement

A physical measurement frequently used in biomedical instrumentation is the determination of linear or angular displacement between two points. In biomedical measurements, such displacements are frequently determined dynamically to determine the function of an organ or organism. There are numerous sensors applied for this measurement. Some are applied in biomedical measurements, but others are useful only for nonbiomedical applications. In this section, we describe sensors with their primary application in biomedical measurement.

Liquid Metal Strain Gages. The liquid metal strain gage was described by Whitney (1) as a simple means of estimating changes in limb volume by measuring changes in the limb's circumference. The sensor shown in Fig. 2 consists of a thin, compliant silicone elastomer tube filled with mercury. Electrical contacts seal the mercury within the tube at each end and are connected to lead wires. If the tube is arranged in a straight line as shown in Fig. 2, the electrical resistance of the mercury column between the electrical contacts R, is given by

$$R = \rho \frac{L}{A} \tag{1}$$

where ρ is the resistivity of mercury, L is the length of the mercury column, and A is its cross section.

As the tube is stretched, the mercury column becomes longer but because its volume V must remain constant, its cross sectional area must decrease according to

$$A_1 = A_0 \left(\frac{L_0}{L_1}\right) \tag{2}$$

where A_0 and A_1 are the initial and final cross-sectional areas and L_0 and L_1 are the initial and final lengths of the mercury column.

Thus the change in resistance is given by

$$\Delta R = R_1 - R_0 = \frac{\rho}{V}(L_1^2 - L_0^2) \tag{3}$$

where R_0 is the initial resistance and R_1 is the final resistance.

A characteristic of a strain gage that describes its sensitivity is the gage factor γ which is defined as

$$\gamma = \frac{\Delta R/R_0}{\Delta L/L_0} \tag{4}$$

where L_0 is the initial length of the strain gage, ΔL is the change in its length, R_0 is the initial resistance of the strain gage, and ΔR is the change in the strain gage resistance when its length is increased by ΔL. Using (Eqs. (1–4), the gage factor for a liquid metal strain gage is given by

$$\gamma = \frac{L_1 + L_0}{L_0} \tag{5}$$

which for small displacements is approximated as 2.

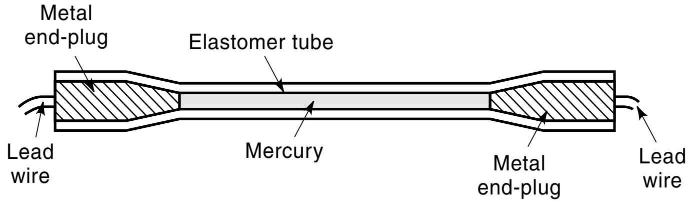

Figure 2. Cross-sectional view of a liquid metal strain gage (1).

The principal difference between the liquid metal strain gage and conventional foil or wire strain gages is the compliance of the structure. Conventional strain gages can be stretched only a very small fraction of their length and remain elastic. Liquid metal strain gages can be stretched as much as twice their length and still return to their original length when released.

Liquid metal strain gages are used for many applications in biomedical research and in some cases even in clinical medicine. The main concern about these devices is that the silicone tube is fragile and breaks, thereby exposing the subject to elemental mercury. Furthermore, oxygen diffuses through the silicone tube and oxidizes the mercury making the electrical signals from this sensor noisy after repeated use. Nevertheless, there are several common applications for this sensor. If one models a limb as a circular cylinder of fixed length, the cross-sectional area and, hence, the volume of the cylinder are determined by measuring its circumference. A liquid metal strain gage wrapped around a limb is used to measure changes in its circumference which then are used to estimate changes in the limb volume (1). This is used in clinical devices for determining whether any deep venous thromboses (blood clots) are in patients legs. If a strain gage is wrapped around an individual's leg and a sphygmomanometer cuff is placed on the upper leg, inflating the cuff to a pressure between arterial and venous pressure for the patient occludes the venous outflow from the leg but still allows blood to enter the limb through the arteries. This causes the limb volume and, hence, its circumference to increase until a new equilibrium point is reached. Releasing the cuff allows the blood to leave the leg via its veins, and the circumference returns to normal. By plotting the length of the strain gage as a function of time, a clinician determines the rate at which the blood leaves the leg and whether an obstruction is present. This technique is especially useful in evaluating patients following surgery because undetected venous thrombi can cause a pulmonary embolism which is life threatening.

Another application of the liquid metal strain gage is measuring breathing movements. By slightly stretching a strain gage and taping it to the chest or abdomen, it is possible to measure differences in displacement as the subject breathes. This simple sensor provides reliable breathing signals in infants studied in the hospital (2).

Inductance Plethysmography. The inductance of a coil of wire is approximately proportional to the cross-sectional area within the coil:

$$L \cong \frac{r}{2540}\left[7.353\log_{10}\left(\frac{16r}{d} - 6.386\right)\right] \quad (6)$$

where L is the inductance in microhenries, r is the coil's radius in millimeters, and d is the diameter of the wire in the coil in millimeters. By placing a compliant coil around a limb or the chest or abdomen, its inductance is proportional to the cross-sectional area of the structure it circumscribes, and this is used to determine volume or changes in volume. The problem with this arrangement is that a coil of wire is not as compliant as the liquid metal strain gage, and so it must be modified to become a compliant sensor. A simple way of doing this is to form a wire in a sinusoidal pattern and attach it to an elastic band so that the "wavelength" of the sinusoidal wire pattern increases as the band is stretched. The fact that the wire is in a sinusoidal pattern has no effect on the measurement of cross-sectional area if the sinusoid is in the plane of the surface of the structure being measured.

This device is used for measuring breathing effort, and, when appropriately calibrated, it provides a signal proportional to tidal volume (3,4). This makes it possible to use this device to detect airway obstruction, when breathing motion is still present (obstructive apnea), because the total volume change in thorax and abdomen is unchanged.

Sonomicrometer. Sound waves propagate in soft tissue at a velocity of approximately 1.1 mm/μs. One can measure the distance between two points in tissue by determining the time it takes an ultrasonic pulse to propagate from one transducer to another. The displacement is given by

$$d = ct \quad (7)$$

where c is the velocity of ultrasound in tissue, d is the distance between the two sensors, and t is the time it takes the pulse to propagate from one sensor to the other. Miniature ultrasonic transducers are made from piezoelectric ceramic or crystal materials and are as small as a 1 mm to 2 mm cube. These sensors are used to measure myocardial segment length by implanting them at different points in the myocardium (5), and they also have been used to dynamically monitor the dilatation of the uterine cervix during labor (6).

Measurement of Force

The measurement of forces in biology and medicine is important in understanding the biomechanics of organisms. As with displacement sensors, many of the force sensors used for this are the same as force sensors used in other applications. These force measurements are based on a load cell structure. Two variations of this fundamental device, however, are found frequently applied in biomechanical measurements. These are the force-sensitive resistor and the compliant dielectric-capacitance sensor.

Force-Sensitive Resistor. One of the simplest and therefore, least expensive force sensors consists of a carbon-loaded elastomer and metallic contact structure as shown in Fig. 3. The carbon-filled elastomer is electrically conductive and has a textured surface that contacts the metallic conductor. This has been exaggerated in Fig. 3 to illustrate the operating principle. When small normal forces are applied, the metallic conductor contacts only the tips of the loaded elastomer layer, but, as the force increases, the elastomer is compressed and more of the textured surface makes contact with the metallic electrode. This causes the electrical resistance between the electrode and the metallic contact at the base of the conductive elastomer to decrease.

Sensors of this type are frequently used for measuring forces between body surfaces and the external world. For example, with this type of device, it is possible to measure grasping, sitting, and standing forces and their distributions. By patterning the conducting contact, it is possible to have a force sensor array to measure the distribution of forces over an area. This is especially useful in studying seating pressures and the reduction of decubitous ulcers. The advantage of this type of sensor is that it is very thin and relatively

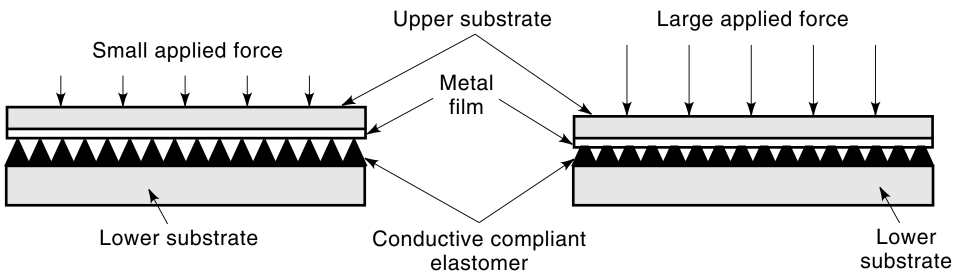

Figure 3. Cross-section of a force-sensitive resistor with small applied force (left) and a relatively large applied force (right).

inexpensive. Its limitation lies in the fact that it is not highly reproducible, and, because of the use of the carbon-filled elastomer, it has high hysteresis.

Compliant Dielectric Force Sensors. One can also measure biomedical forces with a structure similar to that of the force-sensitive resistor but in this case it is a capacitor. A compliant dielectric material is placed between the parallel plates of a capacitor as shown in Fig. 4, and, as a force is applied normal to the plane of this structure, the plates move closer together. Because the capacitance is given by

$$C = \epsilon \frac{A}{d} \tag{8}$$

where C is the capacitance, ϵ is the dielectric constant, A is the area of the capacitor plates, and d is the separation between these plates. As the force increases, the plate separation decreases as

$$\Delta d = \frac{F}{AE} \tag{9}$$

where Δd is the change in separation with an applied force F and E is the elastic constant (Young's modulus) of the dielectric material. Although the capacitance of such a sensor varies hyperbolically with applied force, the characteristics of the sensor are linearized by measuring the capacitance from depositing a known charge on the structure and measuring the voltage across the plates. This yields the relationship

$$C = \epsilon \frac{A}{d_0 - \Delta d} = \frac{\epsilon A^2 E}{AEd_0 - F} \tag{10}$$

$$V = \frac{Q}{C} = Q\left(\frac{d_0}{\epsilon A} - \frac{1}{\epsilon A^2 E}F\right) \tag{11}$$

where d_0 is the initial thickness of the compliant dielectric before the force F is applied. As with the force-sensitive resistor, it is possible to make capacitive sensors in arrays. These devices are applied similarly to the force-sensitive resistors, and in many cases their characteristics are more precise and are linear. An example of an application is a shoe pad containing several capacitive force sensors to measure forces at various points on the foot of a standing subject (7).

Pressure Sensors

The general design of a pressure sensor is illustrated in Fig. 5(a). It consists of a chamber coupled to the pressure being measured and a diaphragm as part of the chamber wall. The outside wall of the diaphragm is usually in contact with air at atmospheric pressure, but in some cases, such as miniature implantable sensors, a vacuum is on the other side of the diaphragm. Increasing the pressure within the chamber deflects the diaphragm, and the extent of this deflection is proportional to the pressure. Thus, one can produce a two-step pressure sensor by adding a displacement sensor to the diaphragm. In most cases a strain gage is used as the displacement sensor. Reusable strain gage pressure sensors coupled to the biological fluid by a fluid-filled catheter have been the mainstay of physiology laboratories for many years (8). These devices, however, are seldom used clinically anymore because it is necessary to sterilize them between applications, and they are not entirely robust. They have been replaced by disposable pressure sensor cartridges [Fig. 5(b)] with a semiconductor strain gage pressure sensor. In this case the strain gages that detect diaphragm deflection are integrated into a silicon diaphragm within the sensor cartridge. These diaphragms are manufactured by microfabrication technology, and they and the completed sensor are much smaller than the sensors previously described (9,10). These devices are produced inexpensively, so they are used on a single patient and then discarded rather than being cleaned and sterilized before use on the next patient.

Miniature semiconductor pressure sensors are also fabricated to allow introducing them into the vasculature or body

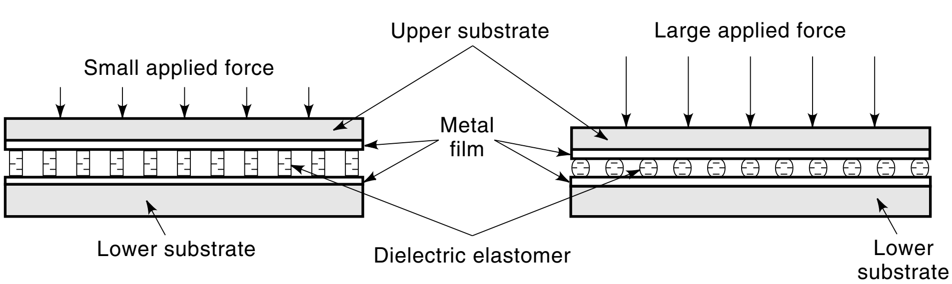

Figure 4. Cross-sectional view of a compliant dielectric force sensor with low (left) and high (right) applied force.

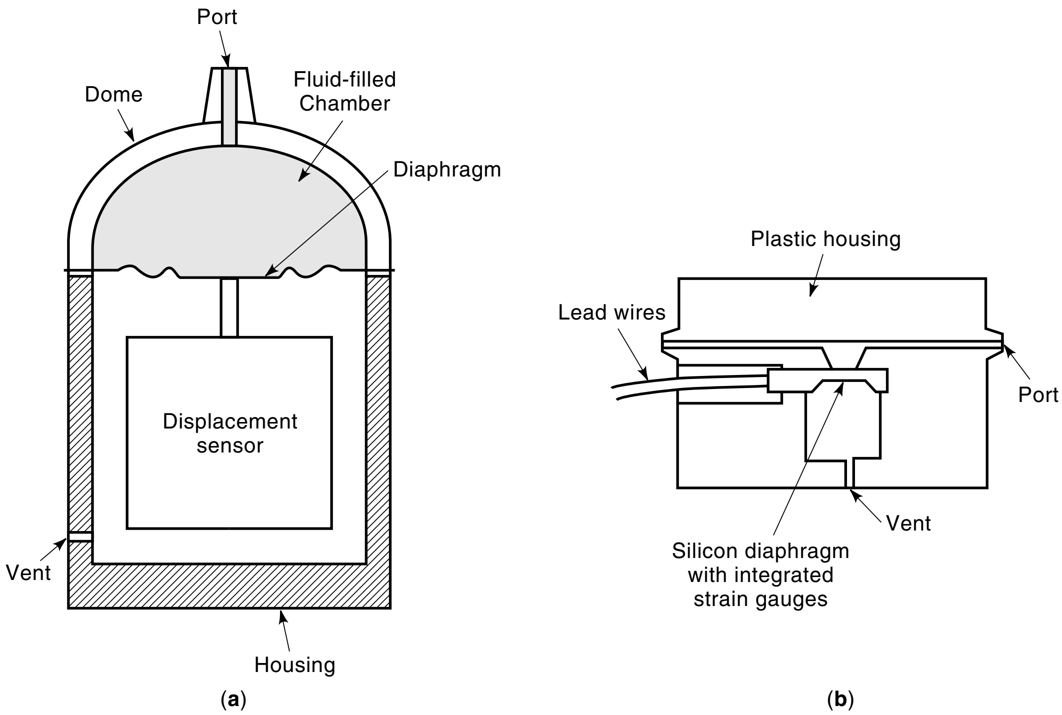

Figure 5. Fundamental pressure sensor structure (a) and disposable pressure sensor (b).

cavities. These so-called "catheter-tip" sensors are generally considerably more expensive than the external devices and must therefore, be reusable. There are methods to liquid or gas sterilize these devices to avoid cross-contamination from one patient to the next.

One of the advantages of the miniature, semiconductor-based pressure sensors is their small size. This means that the diaphragm and displacement sensors undergo considerably smaller displacement for a given pressure and have a much higher resonant frequency. Thus, these devices have much better frequency response characteristics than the older separate strain gage pressure sensors. The catheter coupling the pressure from the body to an external sensor also distorts dynamic pressure waveforms caused by the fluid characteristics of the catheter–sensor system. This results in further reduced high-frequency response, ringing, or motion artifact due to movement of the catheter. Catheter tip sensors avoid these problems.

Flow Measurement

A fundamental physiological mechanism is that of fluid transport through various vessels, ducts, and other anatomic structures to carry nutrients and waste, exchange materials with cells or tissue, and provide a conduit for transport of chemical signals. It is, therefore, understandable that one needs to measure fluid flow to describe and understand physiological mechanisms. Although there are many different types of sensors used to measure flow in pipes, only a few of these are appropriate for application to physiological systems. Some of these are described in the following paragraphs.

Pneumotachograph. One of the fundamental principles of fluid mechanics is Poiseuille's law which states that the pressure drop along the length of a fluid flowing in a tube is proportional to the volume flow through that tube. Thus, if one measures the pressure difference along a known resistance, such as a rigid tube, this pressure drop is proportional to the flow. Although it is not practical to make such a measurement in a blood vessel whose geometry changes according to physiological and fluid dynamic conditions, this principle is used for measuring gas flow.

The pneumotachograph is used for measuring the flow of air into and out of the airway, and hence, the lungs. By placing a known resistance, such as a metal screen or a corrugated foil in a tube through which the breathing air flows and measuring the differential pressure across this resistance, it is possible to obtain a signal proportional to the flow of gas through this system. This signal can then be electronically integrated to determine volume.

Pneumotachographs directly measure air flow into the respiratory tract because the actual gas entering the body must pass through the sensing system. They, therefore, are used only when there is a direct connection to the airway, such as when a patient is intubated or a nasal–oral face mask is used. Thus, this device is primarily used for diagnostic studies, such as in a pulmonary function laboratory.

Electromagnetic Flow Meter. It is known from electromagnetic field theory that charged particles moving in a plane transverse to a magnetic field experience a force mutually perpendicular to the direction of their velocity and that of the magnetic field. If blood or some other fluid containing positively and negatively charged ions flows with a velocity u in a direction perpendicular to a magnetic field B positive ions are deflected transverse to the field and the direction of flow, and negative ions are deflected in the opposite direction. This results in establishing an electrical potential e across the flowing fluid that is given by Faraday's law of induction. Thus, it is possible to measure a voltage across the fluid column that is proportional to the magnetic field strength and the velocity of the flowing blood:

$$e = \int_0^L \vec{u} \times \vec{B} \cdot dL \tag{12}$$

where L is the separation of the electrodes. For the ideal case of a uniform velocity profile u and a uniform magnetic field B Eq. (12) reduces to

$$e = BLu \tag{13}$$

This principle is the basis of the electromagnetic flow meter illustrated in Fig. 6. A magnetic field is set up transverse to the axis of a blood vessel by a permanent magnet or an electromagnet. Electrodes at right angles to the magnetic field direction through the blood vessel make contact with its outer surface and detect the voltage resulting from the flowing blood. For a fixed magnetic field, this voltage is a steady-state, dc potential when the flow is constant. This voltage, however, can be in error due to offset potentials on the electrodes which induce errors in the flow measurement. This problem is overcome by using an electromagnet driven by an ac current to generate a time-varying magnetic field. The resulting voltage seen at the electrodes due to the flow is ac, whereas the offset potentials continue to be dc. Thus the two signals can be separated. Although one problem is overcome by using ac magnetic excitation, another is introduced. There is an induced voltage, the transformer effect, if time-varying flux lines cross the area bounded by the electrodes, the vessel diameter between them, and the lead wires. Many practical approaches to minimize the transformer effect have been described (11,12).

Electromagnetic flow meters available commercially in various sizes and shapes are used for blood flow and cardiac output studies in animal models. Experimental versions of electromagnetic flow meters that can be introduced into the lumen of a blood vessel are reported (13), and these devices are introduced through a peripheral vein or artery without a major surgical procedure. It is important to note that electromagnetic flow meters measure flow velocity rather than volumetric flow. It is possible, however, to obtain volume flow information from them because placing the flow probe around a blood vessel requires a snug fit so that the electrodes make good contact with the vessel, and this fixes the inner diameter of the vessel where the flow measurement is made. The inner diameter is used to determine the cross-sectional area of the blood vessel and multiplied by the flow velocity, gives the volumetric flow.

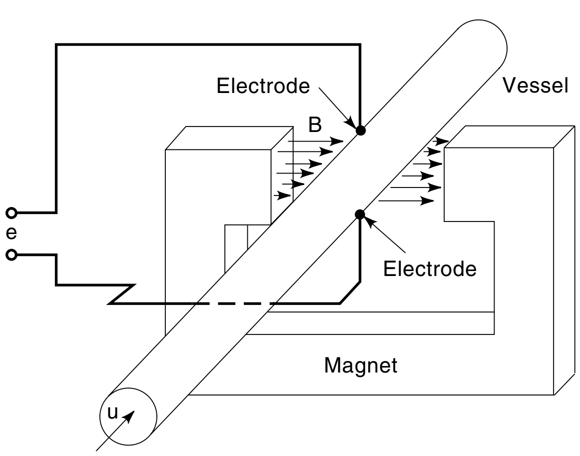

Figure 6. Schematic view of an electromagnetic flowmeter.

Ultrasonic Flow Measurement. The Doppler effect states that the frequency of a sound or ultrasound signal from a moving reflector is shifted according to the velocity of the reflector and the angle between the direction of the incident and reflected sound and that of the reflector:

$$f = \frac{2f_0u}{c}\cos\theta \tag{14}$$

where f is the reflected sound frequency, f_0 is the incident sound frequency, u is the velocity of the reflector, c is the velocity of sound and θ is the angle between the direction of the sound and that of the reflector velocity. This principle is applied to the direct and the indirect measurement of blood flow. In the former case, miniature transducers made of piezoelectric materials that produce and detect ultrasound are placed near or directly on a blood vessel so that they direct a beam of ultrasound into the vessel at an oblique angle. One transducer is used to generate the ultrasonic signal, whereas the other detects the diffusely scattered ultrasound waves from the moving blood cells. The reflected signal is shifted in frequency according to Eq. (14) and is used to determine the flow velocity of the blood. As with the electromagnetic flow meter, this method cannot directly determine the volume flow, but by constraining the diameter of the blood vessel it is possible to get a signal proportional to volumetric flow.

It is also possible to measure flow velocity of blood in vessels noninvasively using an ultrasonic imaging system. In this case a B-scan image of the vessel and its surrounding tissue is obtained, and small pixels of this image within the vessel are analyzed for frequency shifts in the reflected ultrasonic signal. In some ultrasonic scanners, the color of the image from within a vessel is varied according to this frequency shift and hence the flow velocity. Such images help clinicians to understand conditions of abnormal flow in major vessels caused by plaque formation or other anatomical anomalies. In the case of this noninvasive measurement of flow by imaging, it is not possible to determine volumetric flow because one does not know the vessel cross-sectional area or the angle between the incident ultrasound and the flow direction.

This latter problem is overcome with a new technique known as ultrasonic speckle tracking (14). In this technique, one considers the ultrasound image of the vessel and its contents as a motion picture taken one frame at a time. The vessel should lie within the image plane, and ideally the axis of the vessel should lie in the image. The pattern within the vessel lumen has a texture, the speckle, in one frame, and, if one looks at the next frame of the image taken shortly after the initial frame, the same speckle pattern appears as though it was shifted along the vessel. By recognizing this shift and knowing the time elapsed between the two frames, it is possible to calculate the flow velocity regardless of the angle between the ultrasound beam and the flow direction.

Measurement of Temperature

Sensors for measuring biomedical temperature are the same as those applied in other fields. Those most frequently used include the thermistor, thermocouple, and temperature-sensitive metallic wire or film resistors. The thermistor is by far the most common because of its relatively high sensitivity and small size. The latter is important in many biomedical measurements so that the instrument has rapid response time.

Another area of temperature measurement becoming important for clinical and home applications is radiation measurement of temperature. Inexpensive devices that measure the infrared radiation from the auditory canal are commercially available, and these respond almost instantaneously. Tympanic membrane (ear drum) direct temperature measurement using a miniature thermistor or thermocouple has been recognized as a minimally invasive method of determining core temperature (15), and the infrared radiation devices take advantage of this and the rapid response time of infrared detectors for making the measurement (16). Skin temperature over a portion of the body, such as the breast or abdomen is also measured by infrared radiation. The technique of thermography is useful in locating subcutaneous or deeper areas of inflammation such as in the case of some tumors or localized infection.

In addition to the applications previously mentioned, the most common medical application of temperature sensors is determining body temperature. This, along with blood pressure is one of the fundamental vital signs used to evaluate patients, and rapidly responding minimally or noninvasive sensors are desirable. The most common approach to this measurement is an electronic thermometer utilizing a low-mass thermistor placed orally. Because a nurse carries this device on patient rounds, an important aspect of its design is a protective disposable sheath that is placed over the temperature sensor before it is placed in a patient's mouth or elsewhere. This minimizes cross-contamination from one patient to the next, but it also increases the response time of the sensor because of the series thermal resistance and increased mass. Thus, an important aspect of this design is to minimize response time so that temperature is rapidly obtained and documented, thereby allowing the nurse more time for other patient interactions.

BIOPOTENTIAL ELECTRODES

The body produces many electrical signals that are useful in diagnosing and monitoring normal function and disease. The most frequently measured of these is the electrocardiogram (ECG) from the heart, the electroencephalogram (EEG) from the brain and the electromyogram (EMG) from muscle. Biopotential electrodes are sensors placed on or within the body to pick up these signals for processing and display by an instrumentation system (17). Thus, electrodes serve as the sensor for these instruments.

The basic operating principle of biopotential electrodes is converting an ionic current within the body to an electronic current in the electrode material and associated electrical circuits. For a charge to move from ions to electrons, chemical reactions known as redox reactions must occur.

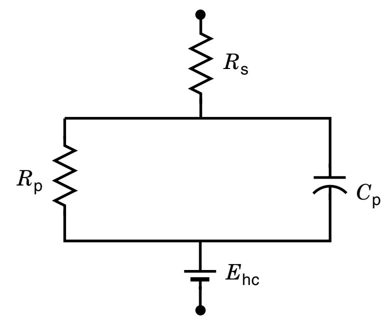

Figure 7. Equivalent electrical circuit for a biopotential electrode.

The following is a general form of these reactions:

$$\begin{aligned} M &\rightleftharpoons M^{n+} + ne^- \\ A + pe^- &\rightleftharpoons A^{p-} \end{aligned} \quad (15)$$

where M is a metal atom, M^{n+} is its cation, A represents a neutral atom of a material, and A^{p-} is an anion of that material. The numbers n and p are the valences of the atoms M and A, respectively, and are integers representing the number of excess positive or negative charges on the ions. Because these reactions occur on a metal surface in contact with an electrolytic solution, an excess positive or negative charge builds up at the interface between the metallic conductor of electrons and the solution of ions. This buildup of charge, known as polarization, results in electrical potential changes that are much larger when electrodes are moved than bioelectrical signals being measured. Thus, in many applications it is desirable to have electrodes that do not show or at least minimize this polarization. Although it is not possible to achieve an ideal nonpolarizable electrode in practice, silver/silver chloride (Ag/AgCl) electrodes come close (18).

Figure 7 shows the equivalent electrical circuit for a biopotential electrode. Capacitor C_p and resistor R_p result from the polarization at the electrode/electrolytic solution interface. The more polarizable the electrode is, the higher the values of these components become. Series resistance R_s represents the resistive component of the interface not associated with polarization, and the half cell potential E_{hc} arises from the redox reactions occurring at the electrode/solution interface. This potential is different for different materials entering into the redox reactions and hence is a function of the electrode material, the ions in solution, and the condition of the electrode surface. Typical values for these components for a disposable adult skin electrode are: $R_s = 200\ \Omega$, $R_p = 200\ k\Omega$, $C_p = 16$ nF, and $E_{hi} = 220$ mV.

It is possible to determine the source impedance of an electrode from the equivalent circuit, and this impedance, in general, is nonlinear. Individual component values are determined by electrode materials, surface area, and frequency of the signal measured. Very small electrodes, such as microelectrodes used for intracellular measurements, have very high source impedances because of their small effective surface area. Electrode source impedance is also affected by electrical current crossing the electrode/solution interface. Such current drives the reactions of Eq. (15) resulting in increased polarization due to the current. Thus it is important that electrode current is as small as possible. Ideally, it should be zero. One way to minimize electrode current is to have amplifiers with very high input impedance and low bias current connected to the electrodes.

Silver/Silver Chloride Electrode

Although electrochemists know of several different electrode systems that approach the behavior of a nonpolarizable electrode, only the Ag/AgCl electrode is used as a biomedical sensor. This use is generally limited to applications on the skin surface because the silver ion is toxic in the body. The Ag/AgCl electrode minimizes polarization because of the low solubility of silver chloride, resulting from oxidation of silver atoms on the electrode surface in the presence of chloride, the principal anion of the body (17). There are many ways to realize Ag/AgCl electrodes in practice (19). One of the most robust forms is a sintered electrode with a silver wire placed along the axis of a cylindrical mixture of finely powdered silver and silver chloride compressed to form a pellet. A layer of silver chloride is formed on a silver electrode surface by electrochemical oxidation in a chloride-containing solution. Exposing the silver metal surface to chlorine gas, such as in sodium hypochlorite, ordinary household bleach, also produces a thin layer of silver chloride. With the silver chloride surface on the electrode, electrical motion artifact and noise are of much lower amplitude than with unchloridized electrodes (20).

Examples of Electrodes and Applications

Figure 8 shows some of the common forms of biopotential electrodes. Skin electrodes are made from Ag/AgCl disks formed by any of the methods described in the previous section [Fig. 8(a)]. Often a silver foil or silver plated surface is used as the basis of these electrodes. It is possible to make electrodes in the form of a needle, as shown in Fig. 8(b), that is injected into a muscle to pick up EMG signals. Single or multipolar coaxial electrodes are formed by running an insulated wire through the lumen of a hypodermic needle and grinding it off at the needle's bevel.

The microelectrode is a very small miniature injectable electrode consisting of a glass micropipette drawn to a very fine point as small as 1 μm in diameter [Fig. 8(c)]. This point impales the body of a single cell, such as a nerve cell, to measure the electrical potential within the cell with respect to an extracellular electrode, thereby measuring the voltage across the cell membrane. An electrolytic solution within the micropipette couples the intracellular cytoplasm to an Ag/AgCl electrode in the shank of the micropipette.

Microelectronic technology has been used to fabricate miniature electrodes for various biomedical applications. Although these structures are not as small as glass or metal microelectrodes, they do allow fabrication in one- and two-dimensional arrays. The use of microelectronic technology makes it possible to batch fabricate the electrodes in highly reproducible forms and to distribute the production costs over a large batch of devices, thereby making individual devices relatively inexpensive. Sensors consisting of silicon probes with electrode arrays (21,22), miniature chambers that can contain the electrode chemistry (23), sieves with electrodes through which structures such as nerves can grow (24,25), and plaques of two-dimensional arrays have been fabricated and used for cardiac and neural recordings.

Intracardiac electrodes are used with pacemakers to pick up cardiac electrograms to control whether or not the pacemaker generates a stimulus. Such electrodes are placed on a flexible probe, such as shown in Fig. 8(d) and introduced into the heart through a vessel. Often these electrodes are incorporated into the probe containing the stimulating electrodes for the pacemaker. There are many other examples of biopotential electrodes described in several general references (17,19,20,26,27).

CHEMICAL SENSORS

Biological organisms involve many complex chemical reactions, and so it is important to measure concentrations and

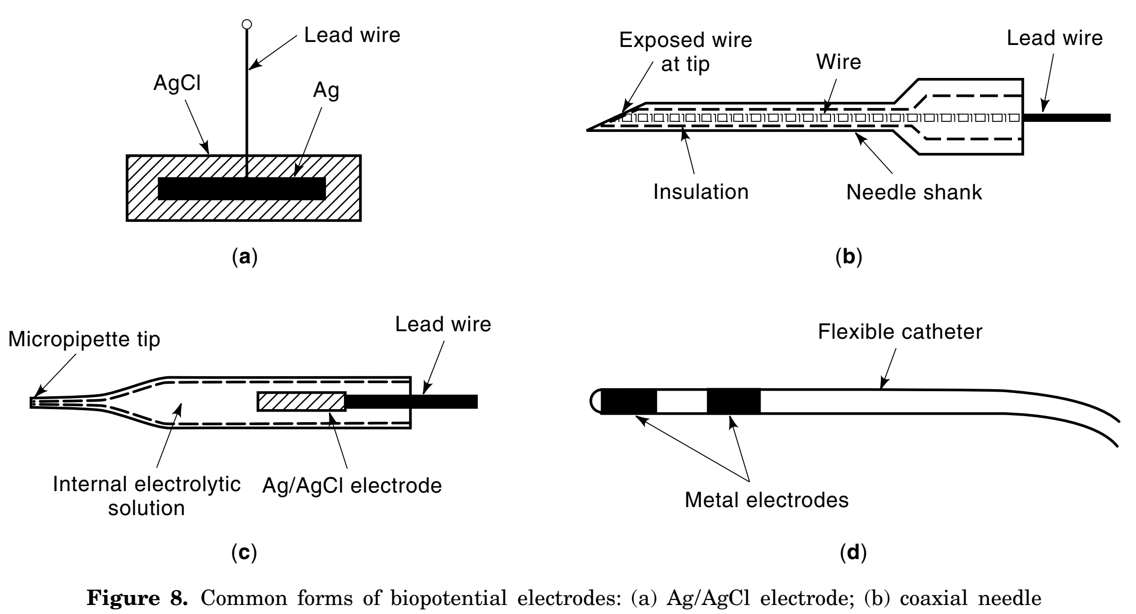

Figure 8. Common forms of biopotential electrodes: (a) Ag/AgCl electrode; (b) coaxial needle electrode; (c) microelectrode for intracellular measurement; and (d) intracardiac electrode for sensing and pacing.

Table 3. Classification of Chemical Sensors

Electrochemical
Amperometric
Potentiometric
Coulometric
Optical
Colorimetric
Fluorescent
Scattered light
Emission and absorption spectroscopy
Thermal
Calorimetry
Thermal conductivity

activities of various substances to understand biological function. Chemical sensors are devices that convert concentrations or activities of chemicals into electrical or optical signals related to these quantities. The major classes of chemical sensors are listed in Table 3. Electrochemical sensors convert the chemical substance being measured into an electrical quantity, such as voltage, current, or charge. Optical sensors have their optical properties changed by the chemical being measured or by light of a specific wavelength produced by the chemical. There are also thermal methods for detecting concentrations of substances and major analytical techniques, such as spectroscopy and nuclear magnetic resonance, that involve complete instrumentation systems and are beyond the scope of this article.

Electrochemical Sensors

Potentiometric sensors produce a voltage proportional to the activity of the chemical being sensed. Ion-selective electrodes are a common form of potentiometric chemical sensors. Their structure, shown in Fig. 9(a), consists of a chamber containing a solution of the analyte at a known activity. A portion of the chamber wall is a membrane specially formulated so that only ions of the analyte pass through the membrane. When this membrane is in contact with an unknown solution of the analyte ions, an electrical potential difference is generated across the membrane that is related to the log of the concentration difference across the membrane according to the Nernst equation.

$$E = E^0 - \frac{RT}{nF} \ln \frac{a_1}{a_2} \tag{16}$$

where E is the potential measured, E_0 is a constant potential associated with the membrane, R is the universal gas constant, T is the absolute temperature, n is the valence of the analyte ion, and a_1 and a_2 are the activity of the analyte ions on each side of the membrane. By placing a reference electrode (such as a Ag/AgCl electrode) on either side of the membrane and connecting these electrodes to a very high input impedance voltmeter, the potential across the membrane is determined. Because the activity of the analyte ion in the solution within the chamber is known, it is possible to determine the activity of the analyte ion in the external solution by measuring this potential.

Ion-selective electrodes have been developed for several inorganic ions of interest in physiology and medicine. These include the common pH glass electrode and sensors for other ions, such as potassium, sodium, chloride, calcium, lithium, and ammonium. Some of the ion-selective membranes are based on special glass formulations whereas others have a polymeric matrix, such as poly(vinylchloride), that is highly plasticized and contains ion-carrier molecules. In all cases the electrical source impedance of such sensors is very high, and measurements must be taken with a high input impedance voltmeter, such as an electrometer.

Amperometric sensors measure electron currents associated with redox reactions that involve the analyte being measured. The most common amperometric sensor used in biomedical applications measures the partial pressure of oxygen in solution. The redox reaction for oxygen at the cathode of

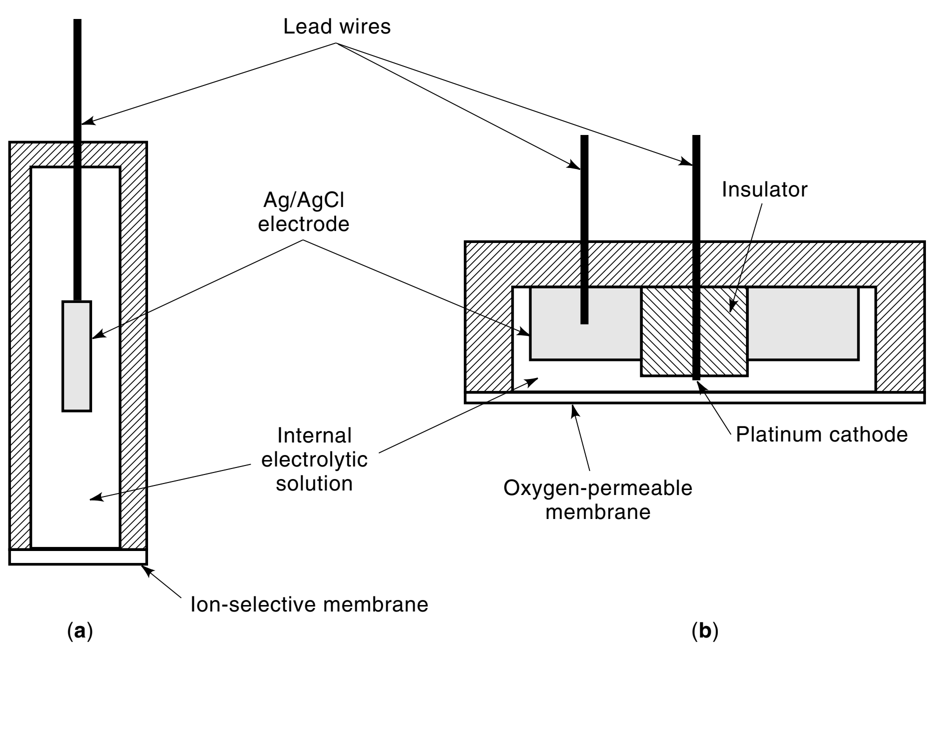

Figure 9. Examples of chemical sensors used in biomedical instrumentation: (a) an ion-selective electrode; (b) a Clark oxygen sensor (note: the electrolytic solution layer in this illustration is thicker than in practice).

an amperometric cell is as follows:

$$O_2 + H_2O + 4e^- \rightleftharpoons 4OH^- \quad (17)$$

A 600 mV bias is required for this reaction. An example of a practical realization of an amperometric oxygen sensor is the Clark electrode shown in Fig. 9(b). An oxygen-permeable membrane separates the measurement chamber from the external environment. Oxygen diffusing through this membrane into the inner electrolytic solution eventually makes its way to the cathode where it is reduced according to Eq. (17) to form hydroxyl ions and requiring electrons from the cathode to complete the process. As the partial pressure of oxygen increases outside of the membrane, more oxygen diffuses through the membrane into the inner solution and to the cathode where it is reduced. Thus, as the oxygen level increases in the environment of the sensor, the cathode current increases because of the greater availability of oxygen at its surface.

Coulometric sensors measure the actual amount of charge transferred in a redox reaction to determine the amount of a specific reactant in a solution. Although this is an important technique in the analytical laboratory, it is not used very frequently for biomedical measurements, and it is difficult to make this kind of measurement in vivo.

Optical Sensors

Optical transduction techniques are used for physical and chemical sensors. Most chemical sensor applications of optical devices are similar to applications involving colorimetric or fluorometric measurements with analytical laboratory instruments. These measurements involve looking at the color change or optical absorption (or reflection) of a chemical dye whose properties change as a function of the concentration or activity of a particular analyte that reacts with the dye. A simple example of this is litmus paper that changes its color in contact with a solution as the pH of the solution changes. Laboratory instruments use chemically sensitive dyes and measure their color changes photometrically when they are added to the solution being measured. Optical sensors carry out a similar function by immobilizing the dye at the tip of a probe in contact with the solution being measured. The probe illustrated in Fig. 10 consists of a fiber optic bundle with some of the fibers transmitting light from an external source to the dye and the remaining fibers returning the light transmitted through or reflected from the dye. This signal is processed at the proximal end of the probe photometrically and electronically to determine differences in the returned light compared with the transmitted light, which are related to the chemical substance being measured. Such devices are described for intravascular pH measurements where the probe is a part of a catheter introduced into a peripheral artery or vein (28).

The second general form of optical sensor based on analytical laboratory instrumentation consists of a similar fiber optic probe with a cuvette containing a different type of dye at its tip. The fluorescent properties of this dye are determined by the concentration of an analyte in a solution in contact with that dye. For example, it is known that oxygen quenches the fluorescence of certain dyes at the tip of a probe in contact with an oxygen-containing solution, such as blood (29). This principle has been used to build an optical oxygen sensor.

There is another way that oxygen in blood is measured optically. The red blood cells contain hemoglobin that is an oxygen carrier. The optical spectrum of oxidized hemoglobin is different from that of the hemoglobin molecule without oxygen. This is why that well-oxygenated blood is bright red, and blood with low oxygen content is a deep maroon color. By measuring the amount of light reflected from blood at various wavelengths, the fraction of oxygenated hemoglobin in the blood is determined. This is known as the percent hemoglobin oxygen saturation. By constructing an intravascular fiber optic probe that transmits light at two different wavelengths and returns the reflected light so that its intensity can be measured, the oxygen saturation of blood is determined. This process, known as oximetry, looks at the ratio of the intensity of light at two different wavelengths reflected through or from a blood specimen. One of these wavelengths should be an isosbestic point, such as 805 nm, a wavelength where the spectra of oxygenated and reduced hemoglobin are the same, and the second wavelength should be in the visible red portion of the spectrum, such as 660 nm, where there are major differences between the optical properties of oxygenated and reduced hemoglobin. The hemoglobin oxygen saturation is determined from the ratio by the equation

$$\text{oxygen saturation} = a - b(IR/R) \quad (18)$$

where a and b are constants based on the measurement conditions. It is important to note that oximetry gives the hemoglobin oxygen saturation, but it does not give the total oxygen concentration in the blood, because the hemoglobin content is unknown. If the hemoglobin is independently measured, however, it is possible to determine the total oxygen concentration. This is different from the oxygen tension (partial pressure of oxygen) in the blood. The partial pressure of oxygen in well-saturated hemoglobin varies over a wide range of values even though the saturation is close to 100%. Oxygen tension is determined only by an electrochemical sensor, such as the amperometric oxygen sensor, or by analytical laboratory methods, such as Van Slyke analysis (30).

Although optical oximetry has been a technique for blood analysis for over 60 years, only in recent years has it become a major measurement for critical care medicine because of the development of the noninvasive pulse oximeter (31,32). This optical method is based on the transillumination of tissue at the two wavelengths previously described. This is done by placing light emitting diodes (LED) of the desired wavelengths on one side of a finger, toe, or earlobe and using a light detector, such as a photodiode or phototransistor, on the other side opposite the emitters. Now the tissue between the light sources and detector is the cuvette that holds the blood, but it differs from the laboratory instrument or invasive oximeter case in that the blood volume being measured is variable because the tissue is not made up entirely of blood. As a matter of fact, the blood volume varies with time over the cardiac cycle because of the compliance of the vasculature. At systole a fresh bolus of arterial blood enters and distends the vasculature of the tissue thereby increasing the percentage of blood in that tissue with arterial blood. At diastole the pressure is lower, and so new blood does not enter the tissue. Blood continues to exit the tissue through the venules and veins, so that the total blood volume in the tissue decreases during diastole. These changes in blood volume result in simi-

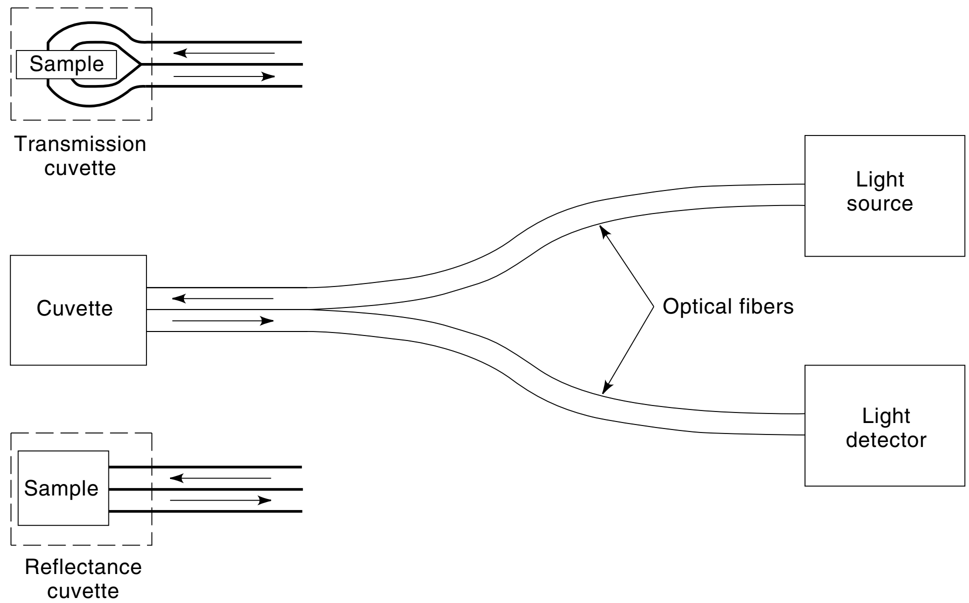

Figure 10. Fiber optic chemical sensor probe with transmission or reflectance sample cuvette that contains the sample itself or a dye in contact with the sample.

lar but inverted changes in the transmitted light through the tissue. The pulse oximeter measures these changes in transmitted light intensity and looks at the pulsatile component of this transmitted light. Because this pulsatile component results from the entry of arterial blood into the tissue, looking at the ratio of pulse amplitudes at the two different wavelengths using Eq. (18) gives a result related to the hemoglobin oxygen saturation of the arterial blood. Although a theoretical relationship can be calculated by light scattering theory, practical pulse oximeters use an experimentally derived relationship between the ratio of pulse amplitudes and hemoglobin oxygen saturation. In addition most pulse oximeters normalize the measured pulse amplitude with respect to the steady-state light transmission and average their results over several cardiac cycles to determine the oxygen saturation. This helps to minimize noise but also reduces effective response time.

The device is very easy to use clinically. All one needs to do is to tape or clamp the light emitting diodes and sensors to the tissue being measured. The instrument takes care of setup and calibration. Once the sensors are in place, information can be obtained. It is important to note that transmitted light is affected by the arterial pulse and also changes in venous blood volume and movement of the patient produce variations in transmitted light intensity. This results in errors in determining hemoglobin oxygen saturation, and these errors frequently are due to motion artifact. Because of this artifact, pulse oximeters are generally not useful for measuring actively moving subjects during exercise testing. Even with this limitation, pulse oximeters are widely used in clinical care because of their operating simplicity and ability to provide critical information.

Bioanalytical Sensors

Analytes of biomedical interest are often biochemicals with rather complex structures. Conventional electrochemical sensors often lack specificity in detecting these substances, and so other approaches are needed. One approach is to utilize biological recognition processes as part of the sensing mechanism. These sensors, known as bioanalytical sensors, take advantage of one of the following general types of biochemical reactions: (1) enzyme–substrate, (2) antigen–antibody, or (3) ligand–receptor. When these reactions are used, a sensor highly specific for a particular biological molecule can be developed. This sensor is usually has two or more stages. The first stage involves the biological sensing reaction, and this part of the sensor contains one of the components of the reaction, such as an enzyme or an antibody. The second stage of the sensor determines if, and to what extent, the biological reaction has taken place. This portion of the sensor consists of a physical or chemical sensor that senses the biological reaction based on changes in mass, electrical capacitance, electrical charge transfer, temperature, or optical properties. This section of the sensor may also consist of a chemical sensor that detects the product of a reaction or the depletion of one of the reactants. Bioanalytical sensors are described for many biological analytes. These sensors are often specific for a particular application (33–36). The most common example of a bioanalytical sensor senses glucose by using the enzyme glucose oxidase. The fundamental reaction involved is

$$\text{Glucose} + O_2 \xrightarrow{\text{glucose oxidase}} \text{Glucuronic acid} + H_2O_2 \quad (19)$$

This reaction occurs at the first stage of the sensor and is sensed in several ways: (1) by measuring the oxygen consumed, (2) by measuring the hydrogen peroxide produced, and (3) by measuring the heat produced by the reaction. Each technique has its advantages and limitations. For example, the oxygen consumed can be determined by measuring the partial pressure of oxygen in the vicinity of the glucose oxidase with an amperometric oxygen sensor. The problem with such a technique lies in the fact that it depends on the partial pressure of oxygen in the environment, and it is the change in oxygen tension that is really necessary to determine. This can be done with a differential sensor made up of two physically identical glucose sensor structures located adjacent to one another. The only difference between the two is that one contains the enzyme whereas the other does not. Thus, by measuring the difference in oxygen tension seen by these two sensors, one determines the amount of glucose present (37).

Bioanalytical sensors present special problems because they utilize biological substances. Often the stability of these chemicals depends on environmental conditions. Exposure to extremes of temperature or hydration lead to conformational changes of the sensing molecules that change their biological activity and hence the sensitivity of the sensor. Often bioanalytical sensors have limited lifetimes and must be stored using special conditions, such as in a dark, cool, humid environment, to remain functional. It is also important to note that not all biochemical reactions are entirely reversible, and so the bioanalytical sensors based on these reactions are also not reversible. Thus, the sensor can be used only for a single measurement.

Microelectronic technology has been applied to chemical and bioanalytical sensors as it has to physical sensors (23,36,37). This technology makes small, reproducible structures possible, which gives the sensors characteristics that are more similar than those from microsensors. Often the need for repeated calibrations can be reduced using this technology.

APPLICATIONS OF BIOMEDICAL SENSORS

The many ways in which bioanalytical sensors are used continue to grow as biomedical instrumentation becomes increasingly important as an adjunct to diagnosis and care. Sensors are finding their way into routine clinical care, the physician's office and clinic, nonhospital care facilities such as nursing homes, the patient's home itself and intensive care units where they are routinely used. The measurement is often carried out with noninvasive or minimally invasive sensors, but it is important that these are applied properly for greatest efficacy. Invasive sensors reliable and suitable for chronic applications for the most part still need to be developed to overcome major problems. These devices are desired for chronic applications, such as feedback sensors for rate responsive pacemakers, and they are expected to function for the remainder of the patient's life with little or no external intervention. Wireless telemetry devices are sometimes used with these sensors to communicate with instrumentation outside of the body. This avoids the necessity of having wires pass through the skin, a source of infection in chronic applications. Often it is not possible to calibrate implanted sensors once they have been placed in vivo, and they must have stable characteristics not only under in vitro laboratory testing but also in vivo. Issues related to the sensor-biological system interface still need to be understood and controlled. All foreign bodies implanted in tissue elicit a response from that tissue to reject or at least wall off the invading substance. Implanted sensors are usually surrounded by a fibrous capsule after 10 to 14 days' implantation as a result of the organism's foreign body response. This capsule is a barrier to transport of the analyte to the sensor thereby changing the sensor characteristics. Understanding the process of forming this capsule and its transport properties is needed to characterize sensors in vivo. Much work remains to be done in this area.

SUMMARY

Sensors serve an important function in biomedical instrumentation in that they are the interface between the electronic (or optical) instrument and the biological system being measured. The validity of the data provided by an instrumentation system is often linked to processes at this interface and to the functionality of the sensor itself. Although electronic signal processing compensates for some problems, in general the quality of a measurement is determined by the quality of the sensor making that measurement. Understanding the physics, chemistry, engineering, biology, and applications of sensors will lead to the development of better devices and their meaningful application to biomedical problems.

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