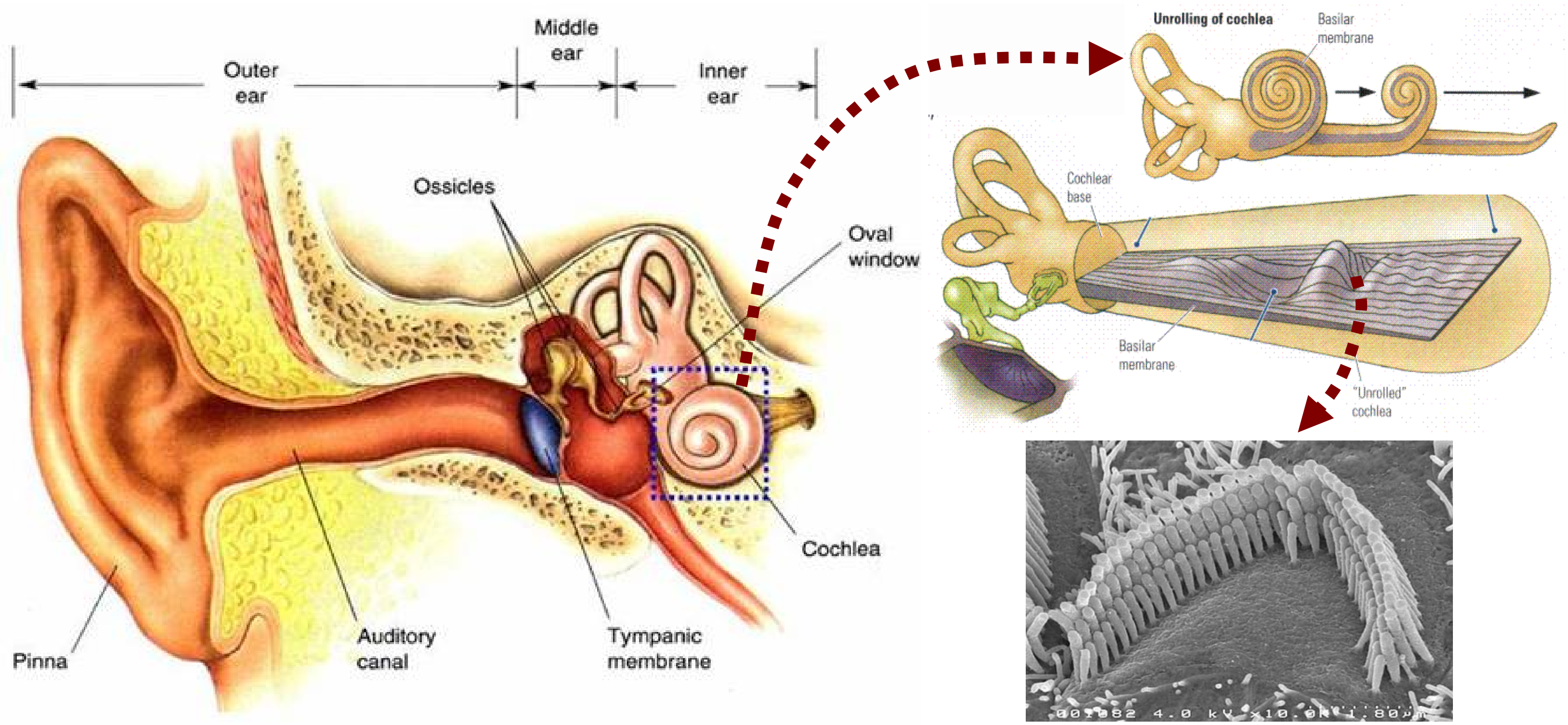
Biomedical Sensors

Transducer

- A transducer is a device, usually electrical, electronic, electro-mechanical, eletromagnetic, photonic or photovoltaic that converts one type of energy or physical attribute to another for various purposes including measurement or information transfer (for example, pressure sensor). A haircell in cochlea is a natural mechano-electric transducer.

Haircell in Cochlea



Biosensor

- a device for the detection of an analyte that combines a biological component with a physicochemical detector component.
- It consists of 3 parts:
  - the sensitive biological element (biological material (eg. tissue, microorganisms, organelles, cell receptors, enzymes, antibodies, nucleic acids, etc), a biologically derived material or biomimic) The sensitive elements can be created by biological engineering.
  - the transducer or the detector element (works in a physicochemical way; optical, piezoelectric, electrochemical, etc.) that transforms the signal resulting from the interaction of the analyte with the biological element into another signal (i.e., transduces) that can be more easily measured and quantified;
  - associated electronics or signal processors that is primarily responsible for the display of the results in a user-friendly way.

Biosensor

- The most widespread example of a commercial biosensor is the blood glucose biosensor, which uses an enzyme to break blood glucose down. In doing so it first oxidizes glucose and uses two electrons to reduce the FAD (a component of the enzyme) to FADH2. This in turn is oxidized by the electrode (accepting two electrons from the eledtrode) in a number of steps. The resulting current is a measure of the concentration of glucose. In this case, the electrode is the transducer and the enzyme is the biologically active component.
- Recently, arrays of many different detector molecules have been applied in so called electronic nose devices, where the pattern of response from the detectors is used to fingerprint a substance. Current commercial electronic noses, however, do not use biological elements.
- A canary in a cage, as used by miners to warn of gas could be considered a biosensor. Many of today's biosensor applications are similar, in that they use organisms which respond to toxic substances at a much lower level than us to warn us of their presence. Such devices can be used both in environmental monitoring and in water treatment facilities.

Principles of Detection– Photometric

- Optical biosensors based on the phenomenon of surface plasmon resonance are evanescence wave techniques. This utilises a property shown of gold and other materials; specifically that a thin layer of gold on a high refractive index glass surface can absorb laser light, producing electron waves (surface plasmons) on the gold surface. This occurs only at a specific angle and wavelength of incident light and is highly dependent on the surface of the gold, such that binding of a target analyte to a receptor on the gold surface produces a measurable signal.
- Surface plasmon resonance sensors operate using a sensor chip consisting of a plastic cassette supporting a glass plate, one side of which is coated with a microscopic layer of gold. This side contacts the optical detection apparatus of the instrument. The opposite side is then contacted with a microfluidic flow system. The contact with the flow system creates channels across which reagents can be passed in solution. This side of the glass sensor chip can be modified in a number of ways, to allow easy attachment of molecules of interest. Normally it is coated in or similar compound.
- Light, at a fixed wavelength is reflected off the gold side of the chip, at the angle of total internal reflection and detected inside the instrument. This induces the evanescent wave to penetrate through the glass plate and someway into the liquid flowing over the surface.
- The refractive index at the flow side of the chip surface has a direct influence on the behaviour of the light reflected off the gold side. Binding to the flow side of the chip has an effect on the refractive index and in this way biological interactions can be measured to a high degree of sensitivity with some sort of energy.
- Other optical biosensors are mainly based on changes in absorbance or fluorescence of an appropriate indicator compound. A widely used research tool, the micro-array, is basically a biosensor.

Principles of Detection – electrochemical

- Electrochemical biosensors are normally based on enzymatic catalysis of a reaction that produces or consumes electrons (such enzymes are rightly called redox enzymes). The sensor substrate usually contains three electrodes,a reference electrode, an active electrode and a sink electrode. The target analyte is involved in the reaction that takes place on the active electrode surface, and the ions produced create a potential which is subtracted from that of the reference electrode to give a signal. We can either measure the current (rate of flow of electrons is now proportional to the analyte concentration) at a fixed potential or the the potential can be measured at zero current (this gives a logarithmic response). Note that potential of the working or active electrode is space charge sensitive and this is often used.
- Another example, the potentiometric biosensors are screenprinted, conducting polymer coated, open circuit potential biosensors based on conjugated polymers immunoassays. They have only two electrodes and are extremely sensitive, robust and accurate. The signal is produced by electrochemical and physical changes in the conducting polymer layer due to changes occurring at the surface of the sensor. Such changes can be attributed to ionic strength, pH, hydration and redox reactions.

Principles of Detection – piezoelectric

- These utilise crystals which undergo an elastic deformation when an electrical potential is applied to them. An alternating potential (A.C.) produces a standing wave in the crystal at a characteristic frequency. This frequency is highly dependent on the elastic properties of the crystal, such that if a crystal is coated with a biological recognition element the binding of a (large) target analyte to a receptor will produce a change in the resonance frequency, which gives a binding signal. In a mode that uses surface waves (SAW), the sensitivity is greatly increased. This is a special application of the Quartz crystal microbalance in biosensor.

Applications

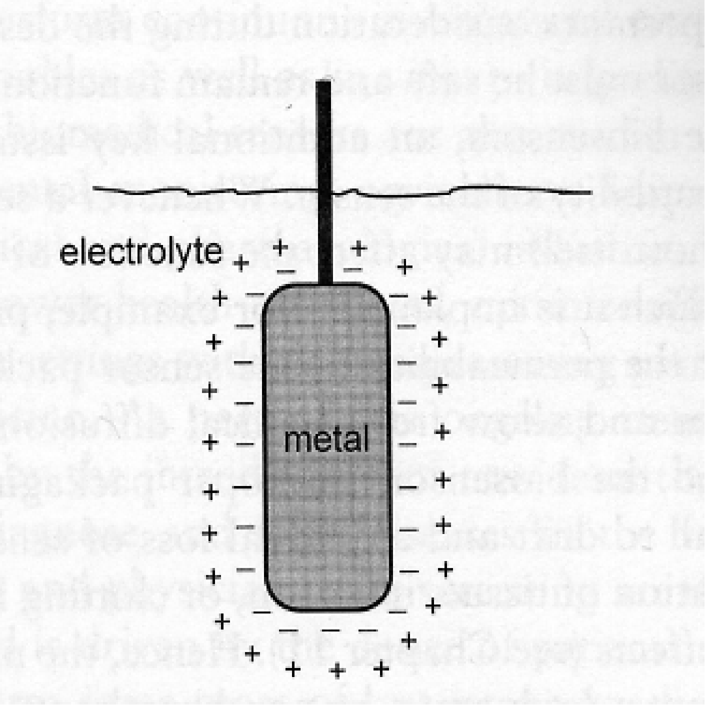
- Glucose monitoring in diabetes patients <-- historical market driver
- Other medical health related targets
- Environmental applications e.g. the detection of pesticides and river water contaminants
- Remote sensing of airborne bacteria e.g. in counter-bioterrorist activities
- Detection of pathogens
- Determination of drug residues in food, such as antibiotics in , particularly meat and honey.
- Drug discovery and evaluation of biological activity of new compounds.

Transducers

- Metal Electrodes for Biopotential Measurements
- Physical Measurements
- Blood Gas and PH measurements
- Temperature
- Bioanalytical
- Fiber Optic

2 Biopotential measurements

2.1 The Electrolyte/Metal Electrode Interface



Distribution of charges at a metal/electrolyte interface

- When a metal is placed in an electrolyte solution, a charge distribution is created next to the interface.

- This distribution causes a half-cell potential.
- In Table1, the half-cell potential of several important metals are listed.
- Standard electrode: hydrogen electrode

Electrode Processes

- Electrolyte: charge is carried by the movement of ions
- Electrode: charge is carried by electronic movement.
- Electrochemical cells: two electrodes separated by at least one electrolyte phase.
- Cell Potentials: difference in potential across the electrodes of a cell

Electrode

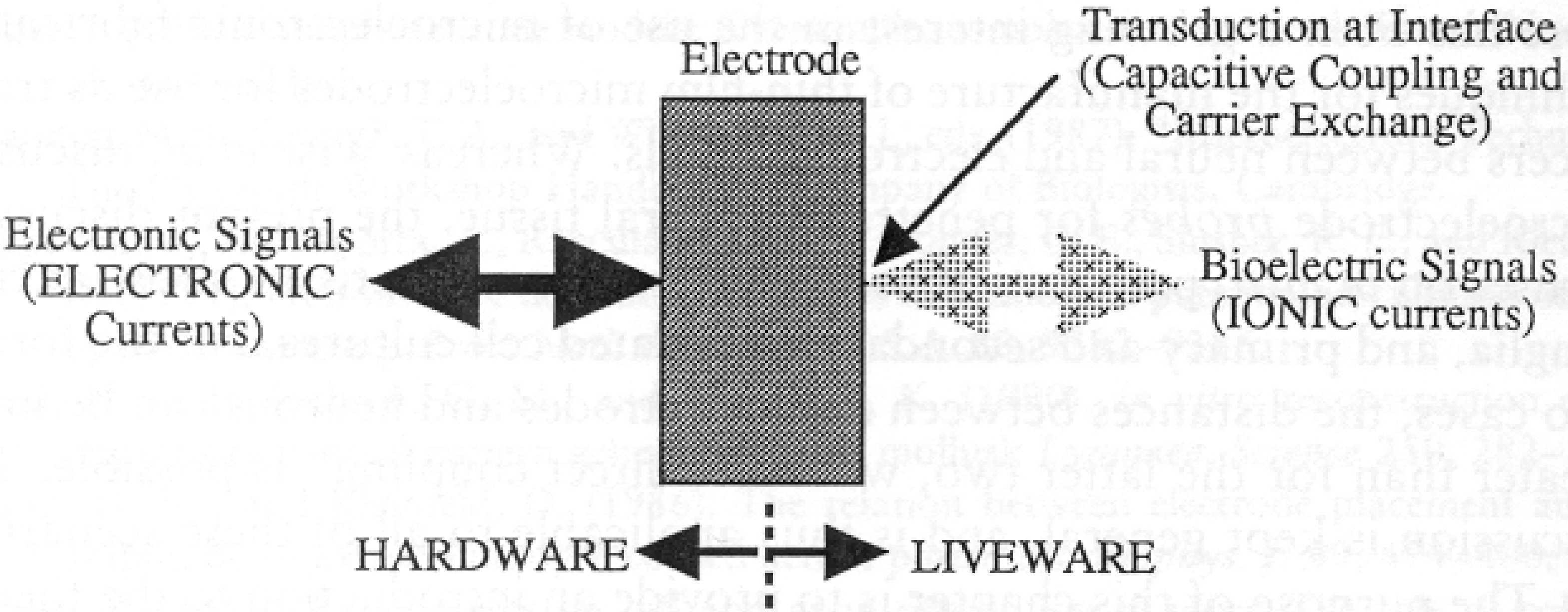


FIGURE 1 Diagram illustrating the transduction of signals between the physiologic and electronic environments.

Half Cell Potential

- The charge distribution at the interface induces this potential.
- Primary affecting factors: metal, ionic concentration, and temperature.
- NHE's potential is 0 by definition.

Normal Hydrogen Electrode(NHE)

- Internationally accepted primary reference
- defined as 0 volt
- Also called Standard Hydrogen Electrode
- $Pt/H_2/H^+$

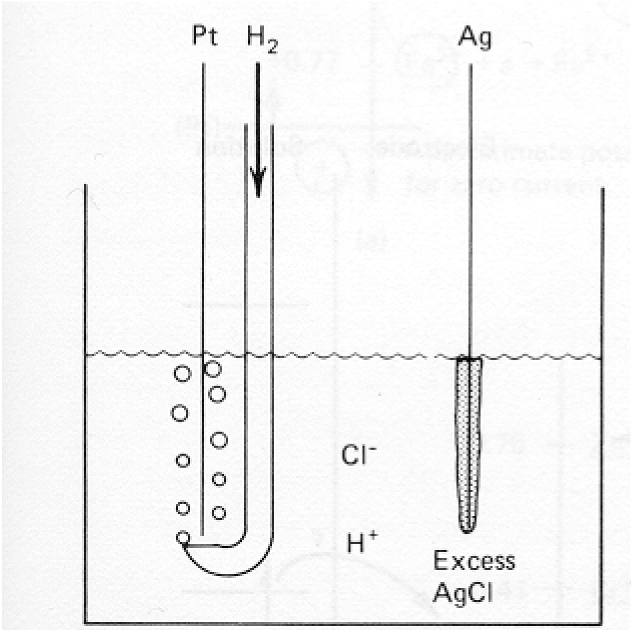
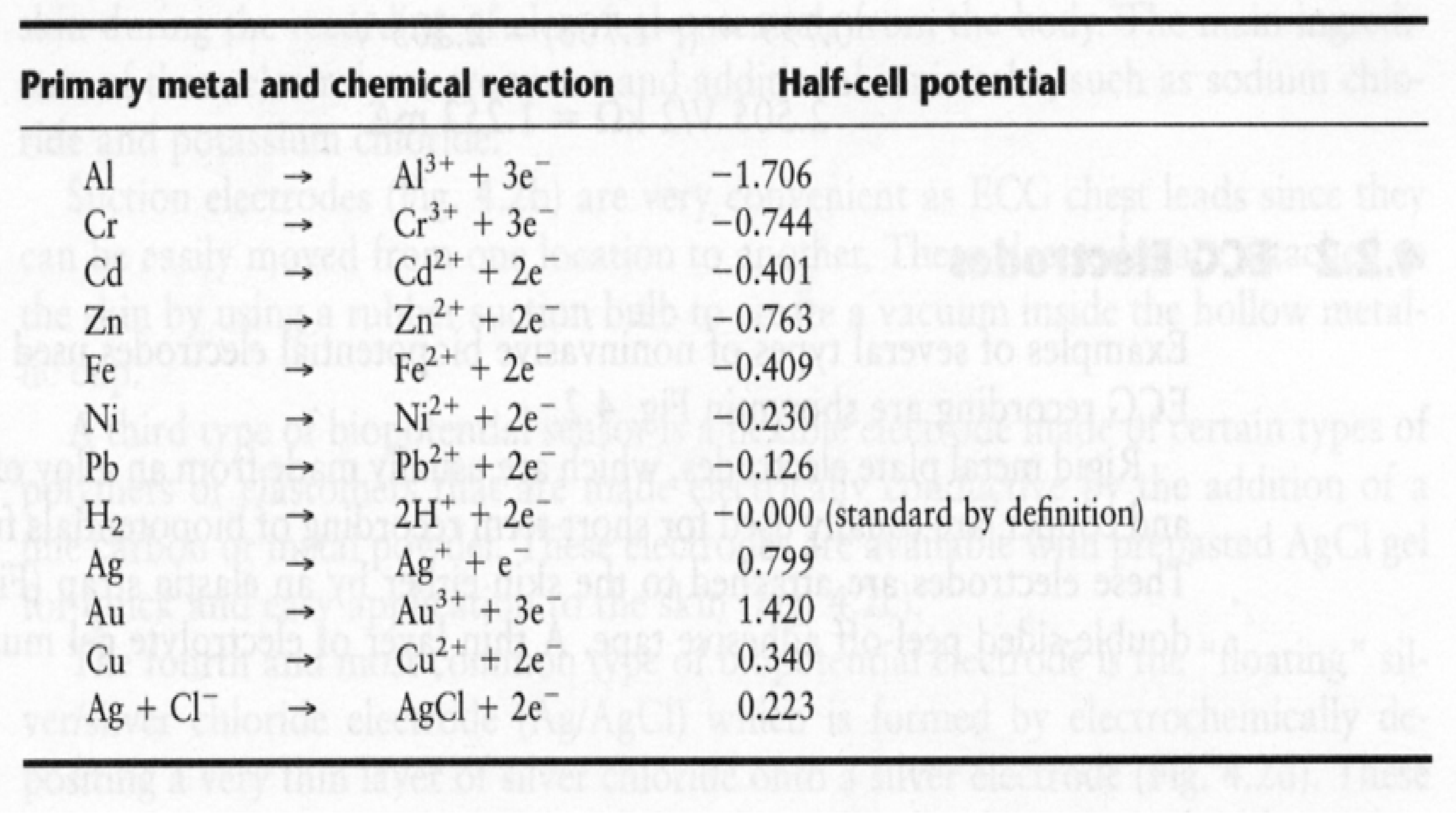


Table 1 Half-Cell potentials



Primary metal and chemical reaction			Half-cell potential
Al	→	$Al^{3+} + 3e^-$	−1.706
Cr	→	$Cr^{3+} + 3e^-$	−0.744
Cd	→	$Cd^{2+} + 2e^-$	−0.401
Zn	→	$Zn^{2+} + 2e^-$	−0.763
Fe	→	$Fe^{2+} + 2e^-$	−0.409
Ni	→	$Ni^{2+} + 2e^-$	−0.230
Pb	→	$Pb^{2+} + 2e^-$	−0.126
H_2	→	$2H^+ + 2e^-$	−0.000 (standard by definition)
Ag	→	$Ag^+ + e^-$	0.799
Au	→	$Au^{3+} + 3e^-$	1.420
Cu	→	$Cu^{2+} + 2e^-$	0.340
$Ag + Cl^-$	→	$AgCl + 2e^-$	0.223

Ag/AgCl

- Structure
-

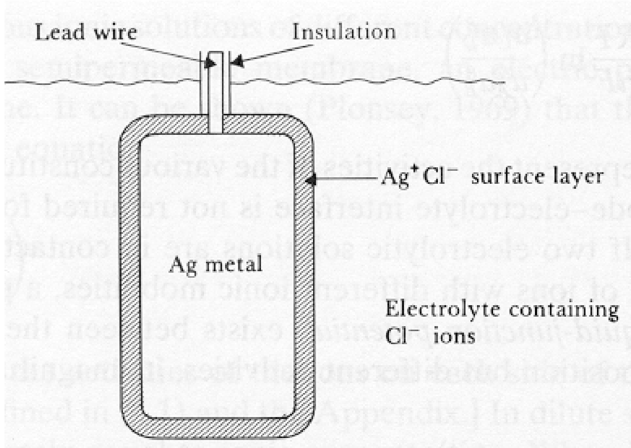


Fig 5.2 Ag-AgCl electrode

- two reactions

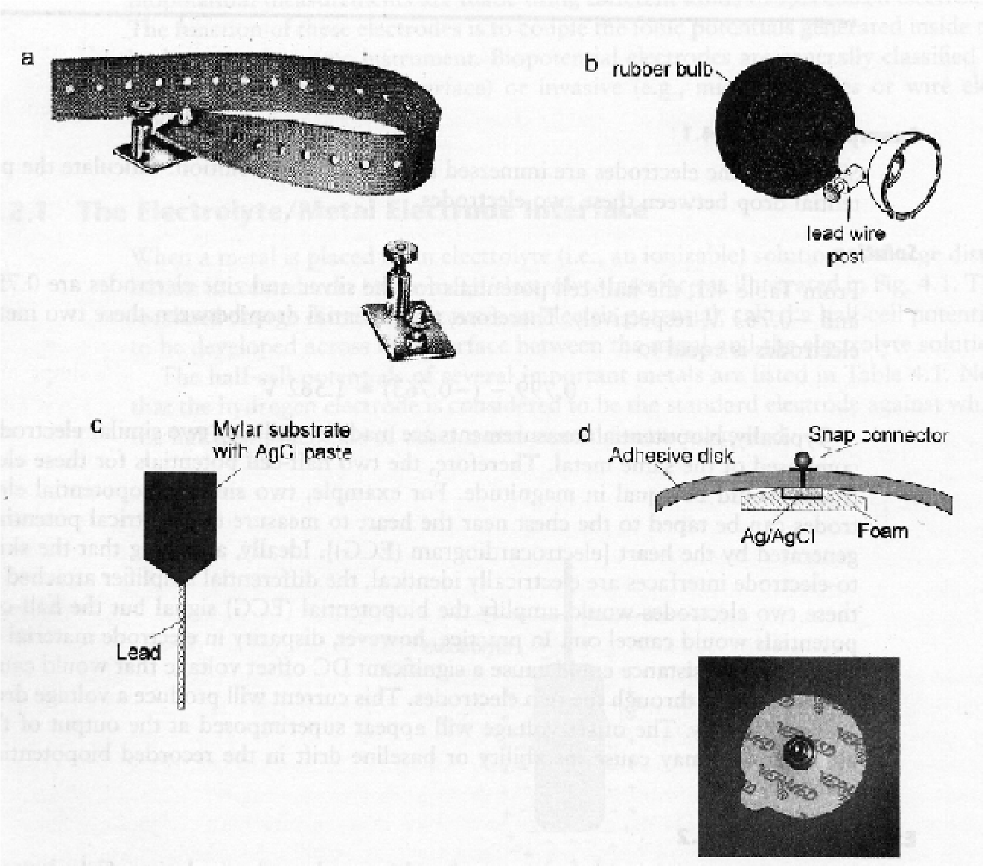
$$Ag \rightleftarrows Ag^+ + e^-$$
$$Ag^+ + Cl^- \rightleftarrows AgCl\downarrow$$

- The first is at the Ag metal, while the second is at the AgCl/Cl– interface: these reactions are reversable with the opposite reaction occuring at opposite electrode.
- The half cell potential of this electrode is maintained constant in Cl rich biological solutions.

Ag/AgCl- fabrication

- 1.Electrolyte process: Ag electrode as anode in KCl electrolyte with 1.5 V battery, reaction continues until I drops to about 10 uA. Weak under mechanical stress, leaving a portion of Ag exposed..
- 2. Sintering as in Fig. 5.3 using powered Ag and AgCl. Sintered at 400 C. Have more mechanical endurance.
- Other methods?
- AgCl has small conductivity. Enhance conductivity:
  - In case of 2: Enhance AgCl conductivity using Ag particles together with AgCl powder.
  - In case of 1:Light sensitive AgCl turns to atomic Ag momemts after fabrication.

2.2 ECG electrodes



Biopotential skin surface ECG electrodes:

(a) Rigid metal plate electrode and attachment strap,

(b) Suction-type metal electrode

(c) Flexible Mylar electrode,and

(d)disposable snap-type Ag/AgCl electrode

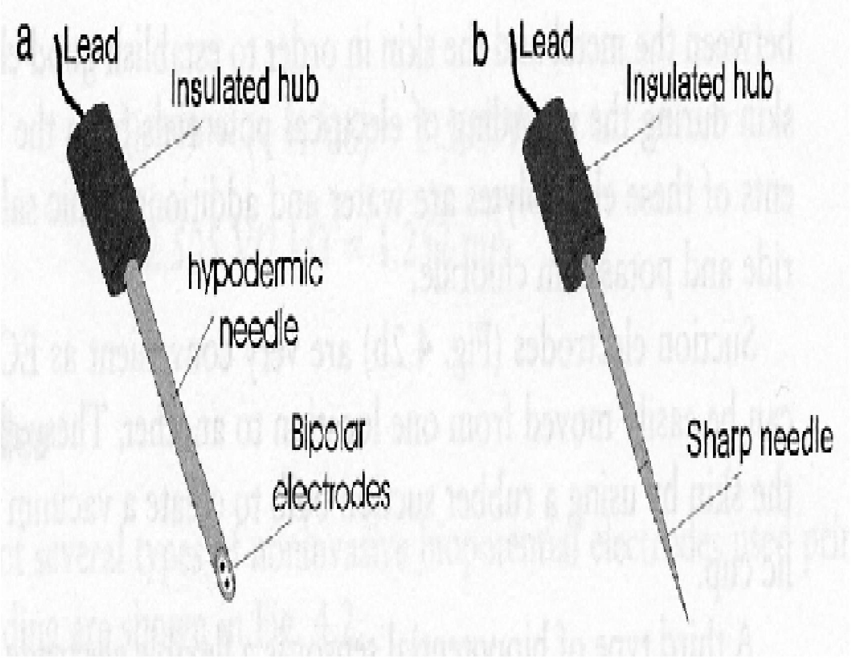
(courtesy of Vermont Medical, Inc., Bellows Falls, VT)

2.3 Electromyographic Electrodes

The shape and size of the recorded EMG signals depends on the electrical property of these electrodes and the recording location.

-The most common electrodes for noninvasive recordings are circular discs, about 1cm in diameter, that are made of silver or platinum.

-The electrodes for direct recording Are illustrated in Fig.



intramascular biopotential electrodes:
(a)bipolar and (b)unipolar configuration.

2.4 Electroencephalographic Electrodes

- The most commonly used elctrodes for recording signals from the brain[electroencephalograms (EEG)] are cup electrodes and subdermal electrodes.

-Cup electrode:

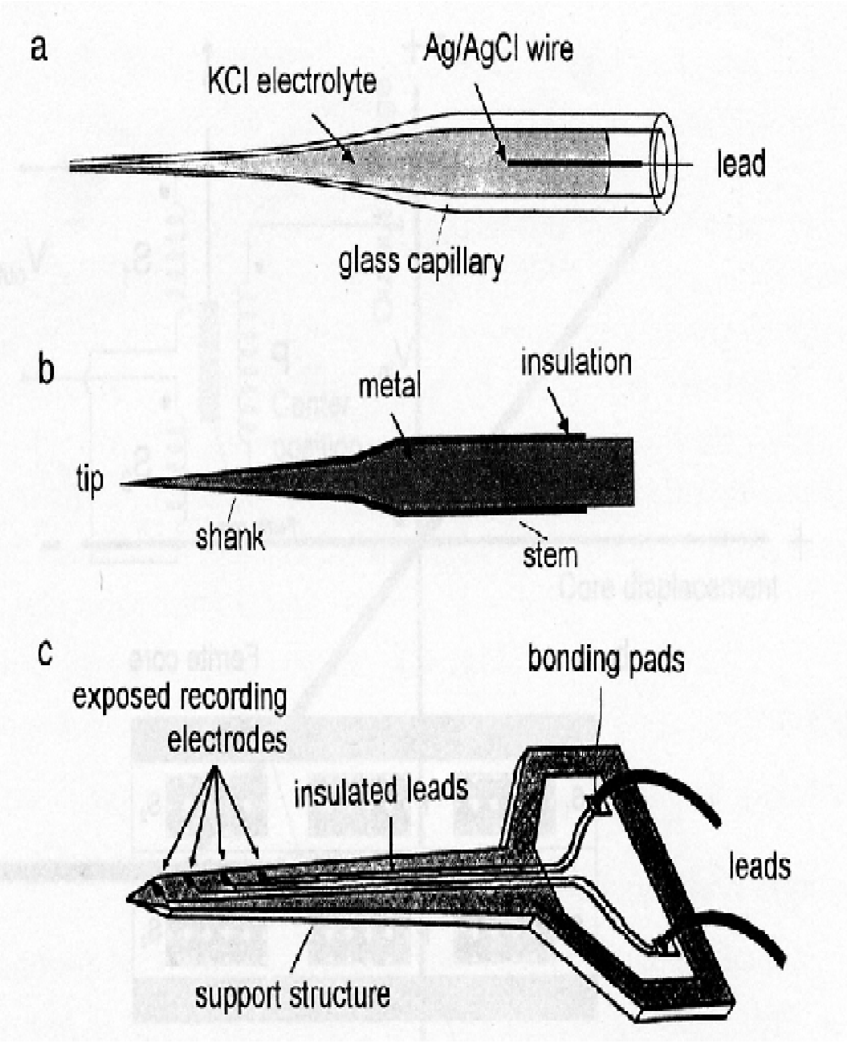
  - made of platinum

    or tin approximately 5-10mm in diameter
  - filled with a conducting electrolyte gel
  - Attached to the scalp with an adhesive tape

-Subdermal electrode:

  - Basically fine platinum or stainless-steel needle electrodes
  - 10mm long by 0.5mm wide
  - Inserted under the skin

2.5 Microelectrodes



Biopotential microelectrodes:

(a)**capillary glass microelectrode**

- 0.1~10um in diameter by a heating and pulling process

(b) **insulted metal electrode**

- a few micrometers by an electrochemical etching process

(c) **solid-state multisite recording microelectrode**

- the ability to mass produce very small and highly sophisticated microsensors with highly reproducible electrical and physical properties by solid-state microfabrication techniques

3 Physical Measurements

3.1 Displacement Transducers

- Inductive displacement transducer

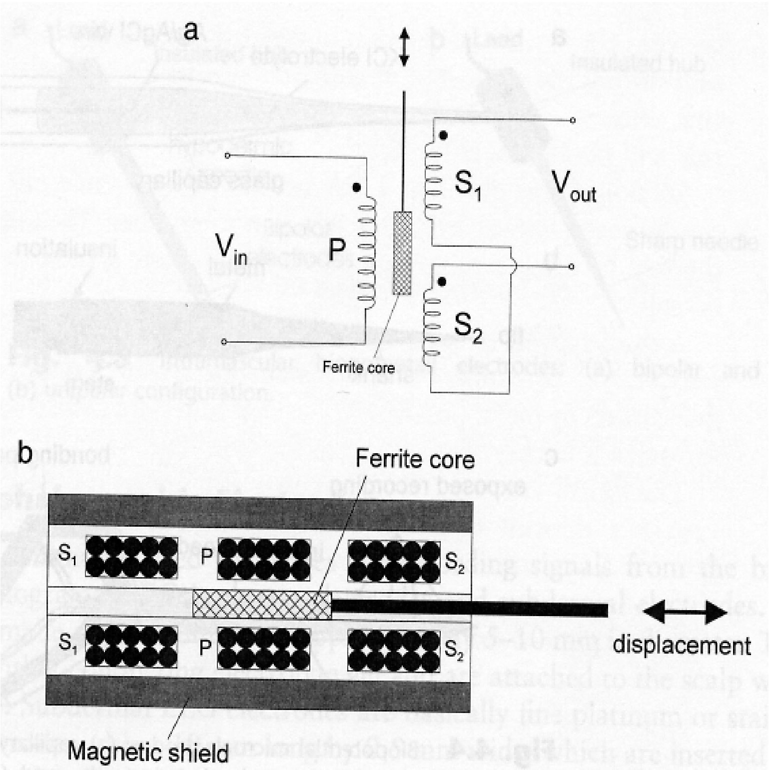
$$L = n^2 G\mu$$

G:geometric form constant

n: number of coil turns

μ :permeability of the magnetically susceptible medium inside the coil

- Measure displacement by changing either the self-inductance of a single coil or the mutual inductance
- The linear variable differential transformer(LVDT): widely used inductive displacement transducer



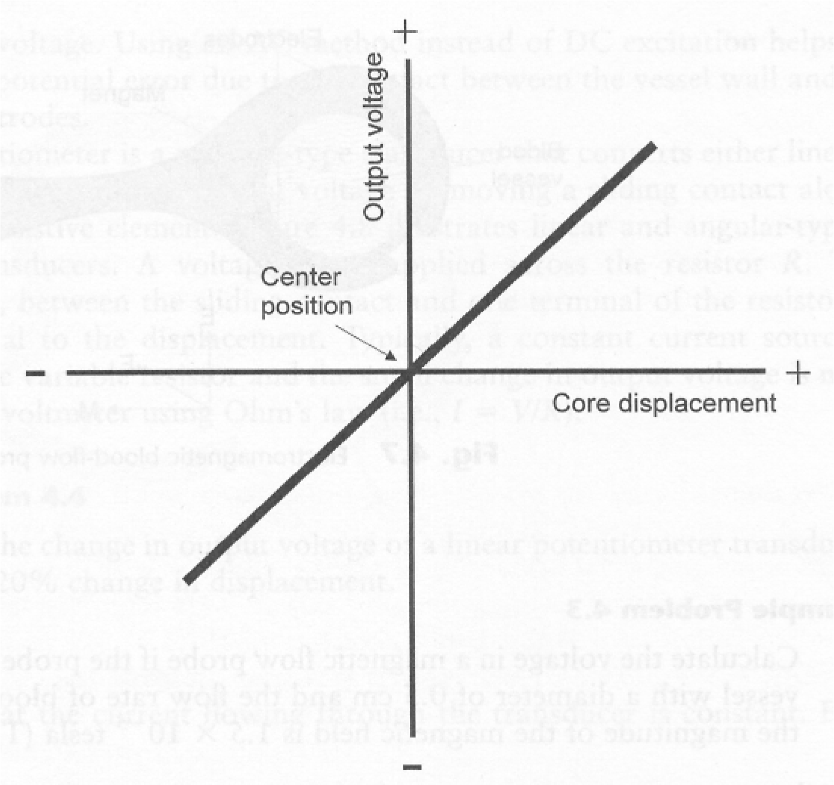
LVDT transducer

(a) electric diagram and

(b) cross-section view

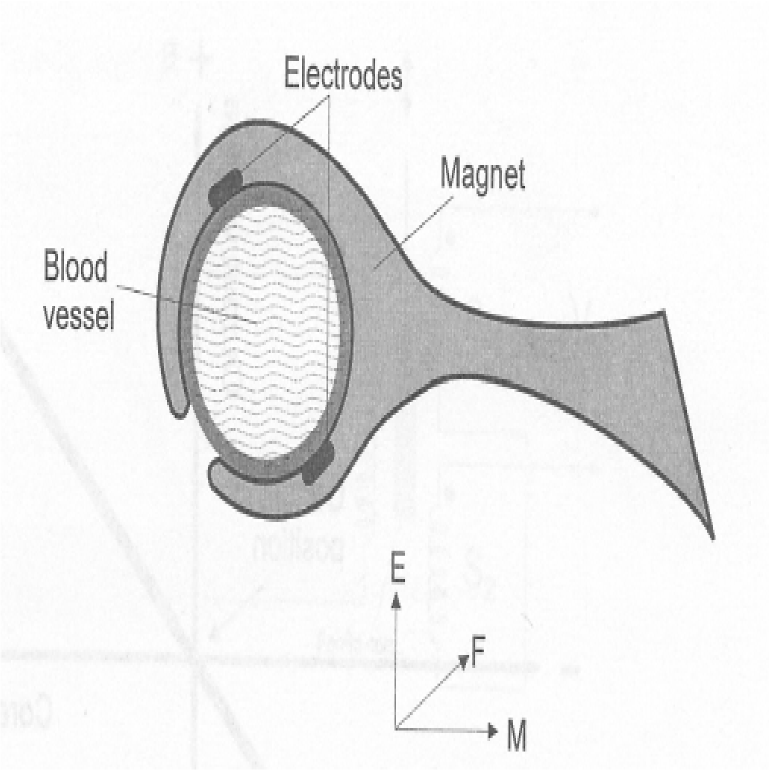
(c) P :primary coil

S_1,S_2 :secondary coil



Output voltage versus core displacement of a typical LVDT transducer

•Measuring blood flow through an exposed vessel



Electromagnetic blood-flow probe.

A clip-on probe that fits snugly around the blood vessel

- Contains electrical coils
- Coil is excited by an AC current.
- A pair of very small biopotential electrodes are attached.
- The flow-induced voltage is an AC voltage at the same freq. as the excitation voltage.

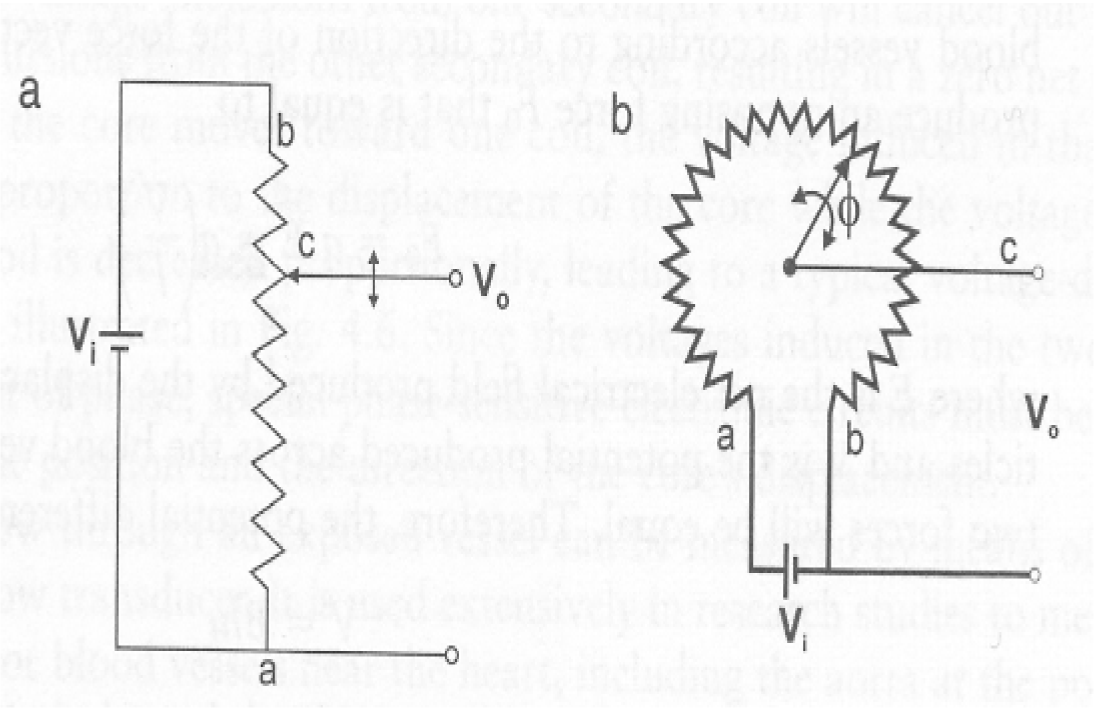
- Measuring blood flow through an exposed vessel
  - use an electromagnetic flow transducer.
  - blood vessel of diameter l
  - uniform velocity u
  - If the vessel is placed in a uniform magnetic field $\vec{B}$

    ions in the blood vessel experience a force $\vec{F}$

    $$\vec{F} = q(\vec{u} \times \vec{B})$$

    As a result , the movement of the deflected charged particle produce an opposing force $\vec{F}_0$

    $$\vec{F}_0 = q\vec{E} = q(\frac{V}{l})$$
  - In equilibrium, these two forces are equal: thus potential difference V is $V = Blu$

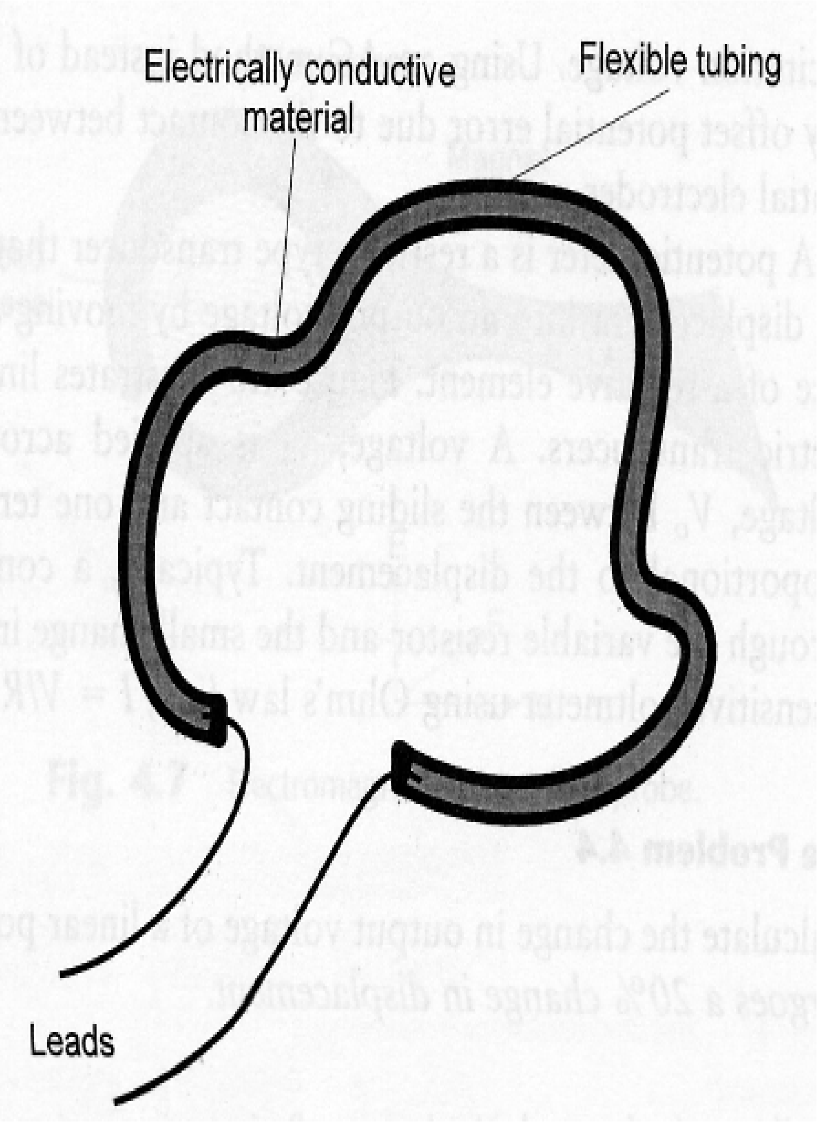


Linear translational(a)and angular (b)displacement transducers.

Potentiometer,Resistive-type transducer.

-convert either linear or angular displacement into an output voltage.

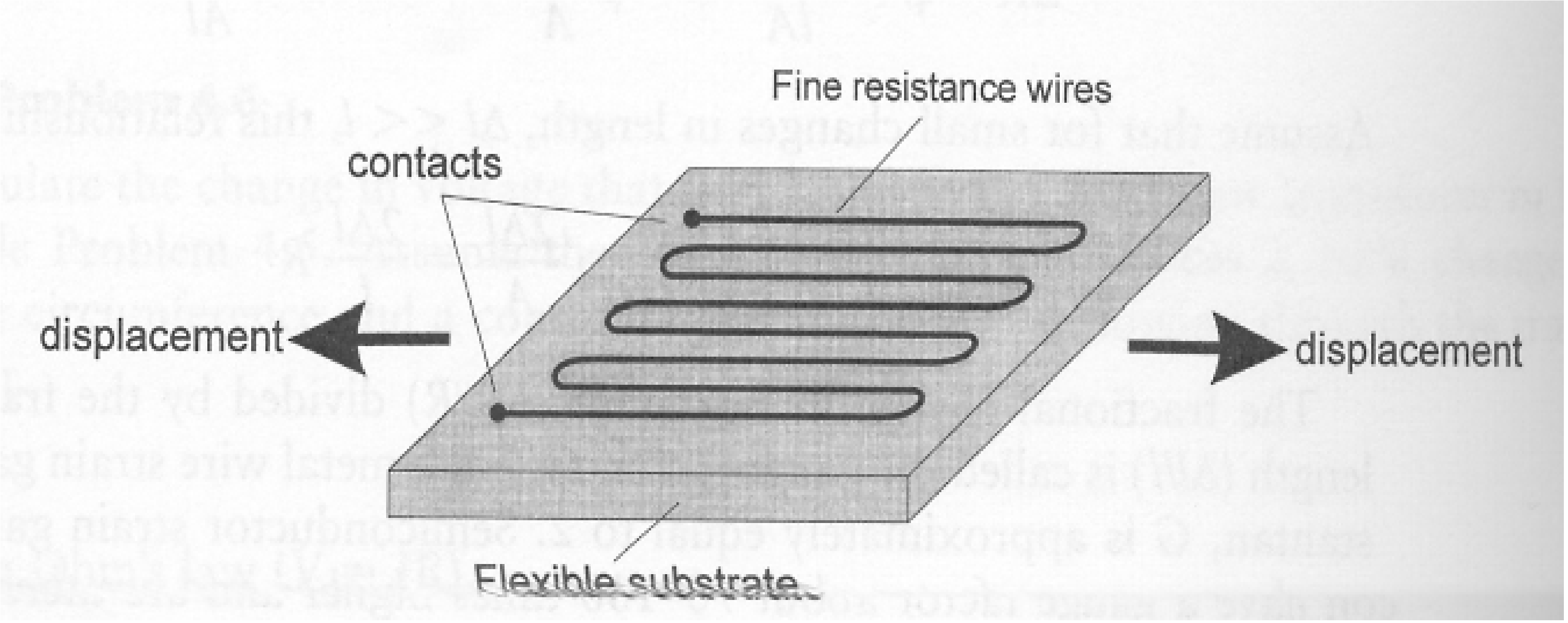
Plethysmography: volume-measuring method



Elastic resistive transducer.

- **consist of a thin elastic tube filled with an electrically conductive material**
- **The resistance of the conductor inside the flexible tubing is given by**

$$R = \rho \left(\frac{l}{A} \right)$$

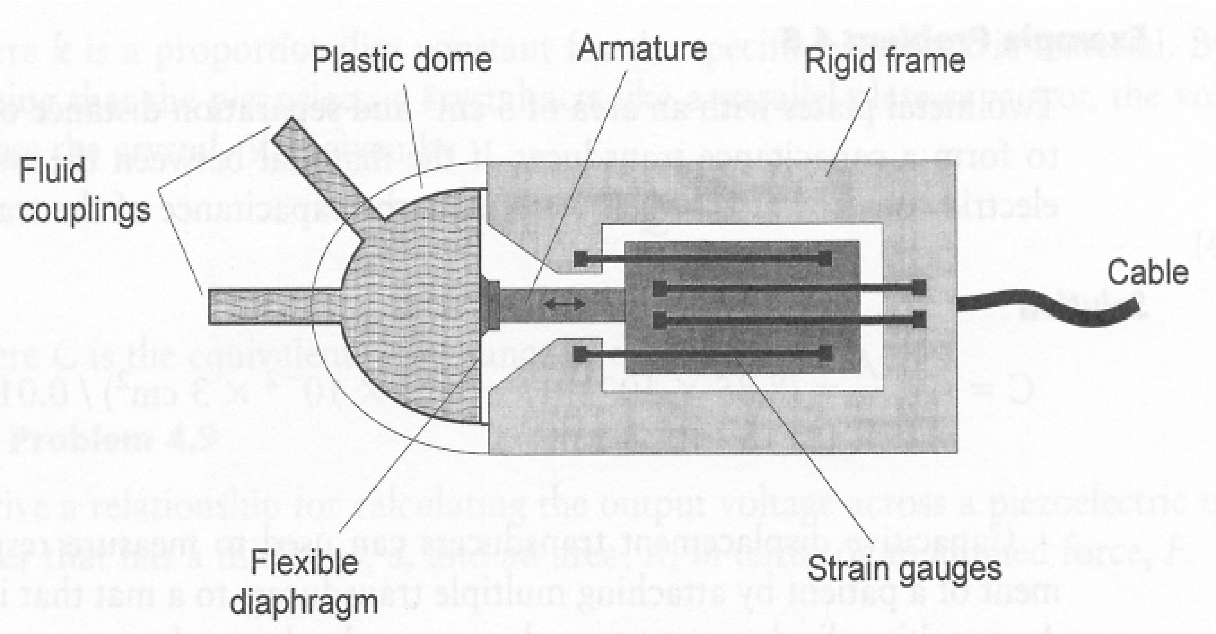


Bonded-type strain gauge transducer

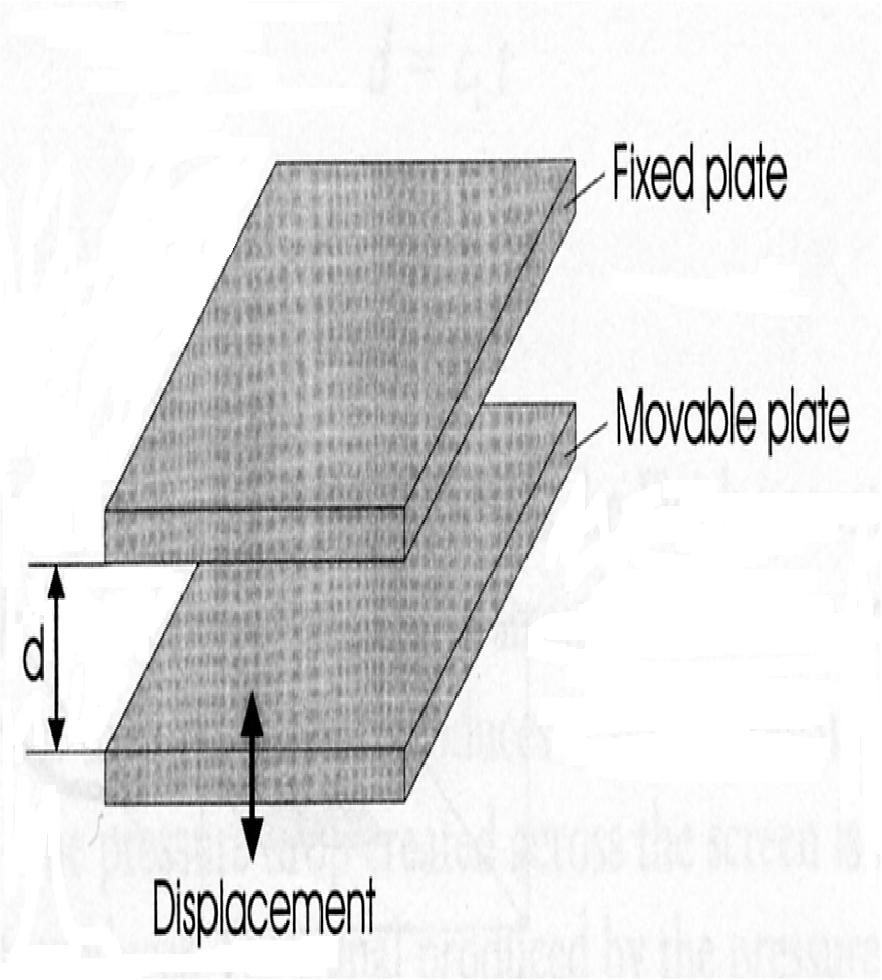
Strain gauge:bonded or un-bonded type

- In the case of bonded type, the strain gauge has a folded thin wire cemented to a semi-flexible backing material.
- Fractional change in the length (strain) is measured by fractional change in resistance.

Resistive strain gauge (unbonded type) blood pressure transducer



- Consist of multiple resistive wires(typically four) stretched between fixed and movable rigid frames.
- Changes in blood pressure during the pumping action of the heart apply a force on a the diaphragm that causes the movable frame to move from its resting position.
- This causes the strain gauge wires to stretch or compress.

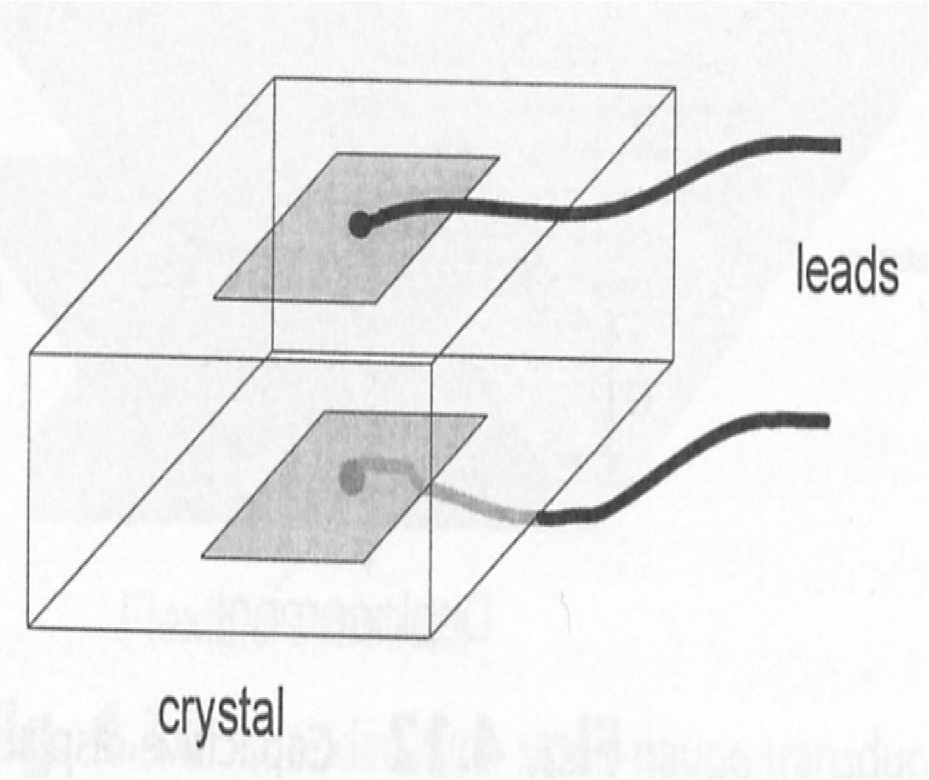


capacitive displacement transducer

The capacitance C between two equal size parallel plates

$$C = \varepsilon_0 \varepsilon_r \left(\frac{A}{d}\right)$$

The method that is most commonly used to measure displacement in capacitance transducers involve changing the separation distance d between a fixed and a movable plate.



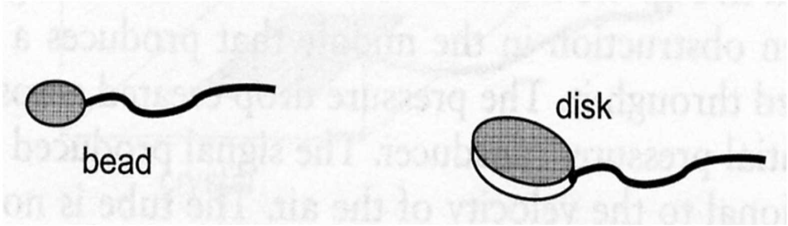
A piezoelectric transducer consists of a small crystal (usually quartz) that contracts if an electric field (usually in the form of a short voltage impulse) is applied across its plates.

Piezoelectric principle: asymmetric crystal is distorted by an applied force, the internal negative and positive charges are reoriented, causing an induced usrface charge, and this is proportional to the applied force.

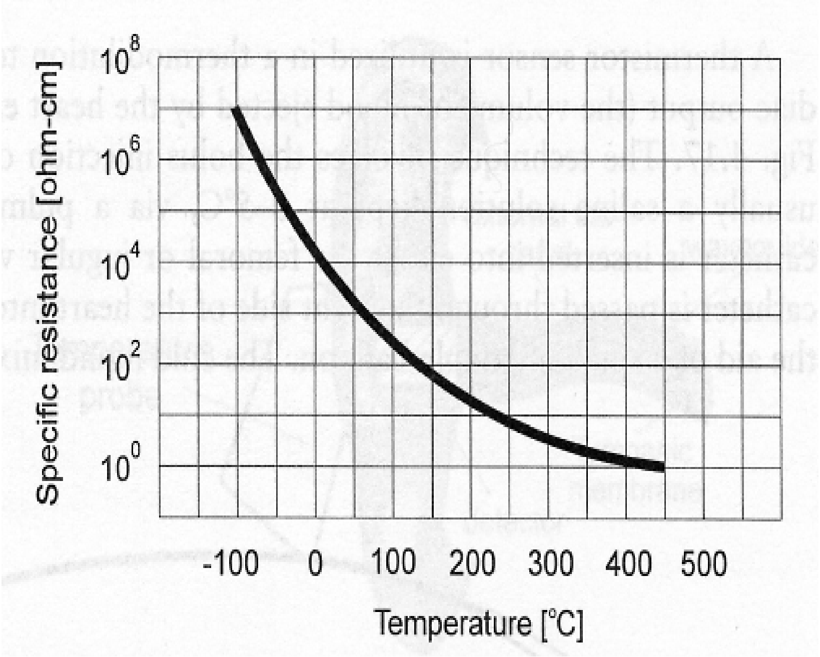
3.3 Temperature measurement

- Body temperature is one of the four basic vital signs.
- measured on Surface or inside
- Thermistor & Thermometer
  - Thermistor: require direct contact with the skin or mucosal tissues
  - Thermometer: noncontact,measure body core temperature inside the auditory canal

Thermistor



Temperature sensitive trasducer made of compressed sintered metal oxides (Ni, Mn, Co)



Resistivity versus temperature characteristics of a typical thermistor.

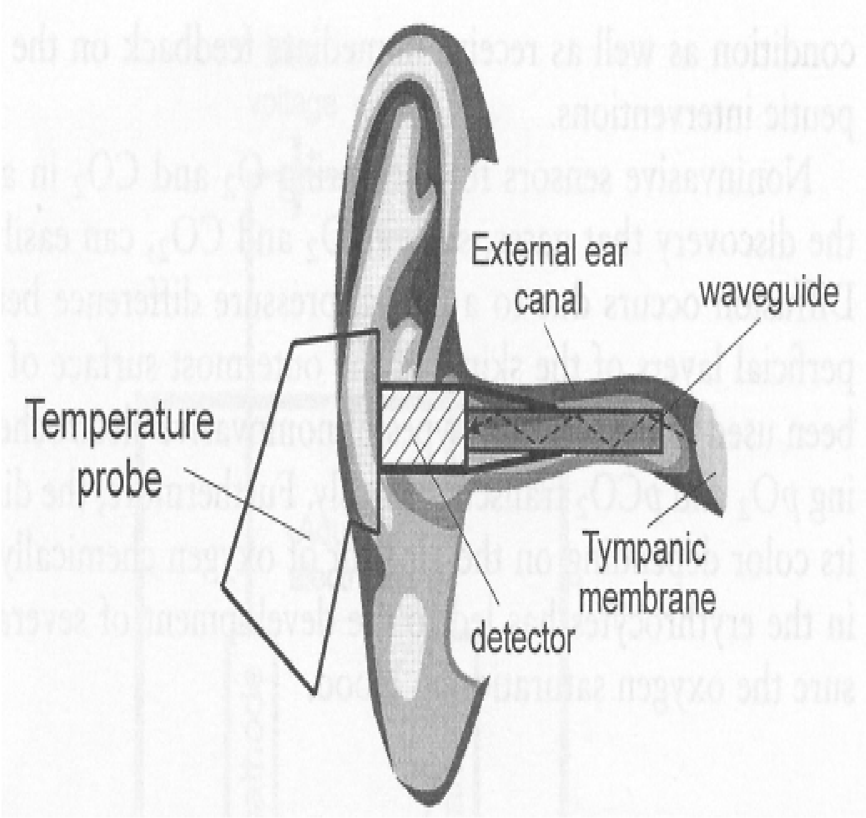
$R_T=R_0 \exp[B(1/T-1/T_0)]$

R_0 : the resistance at T_0 (in K)

R_T: the resistance at T (in K)

B: material constant

Thermometer

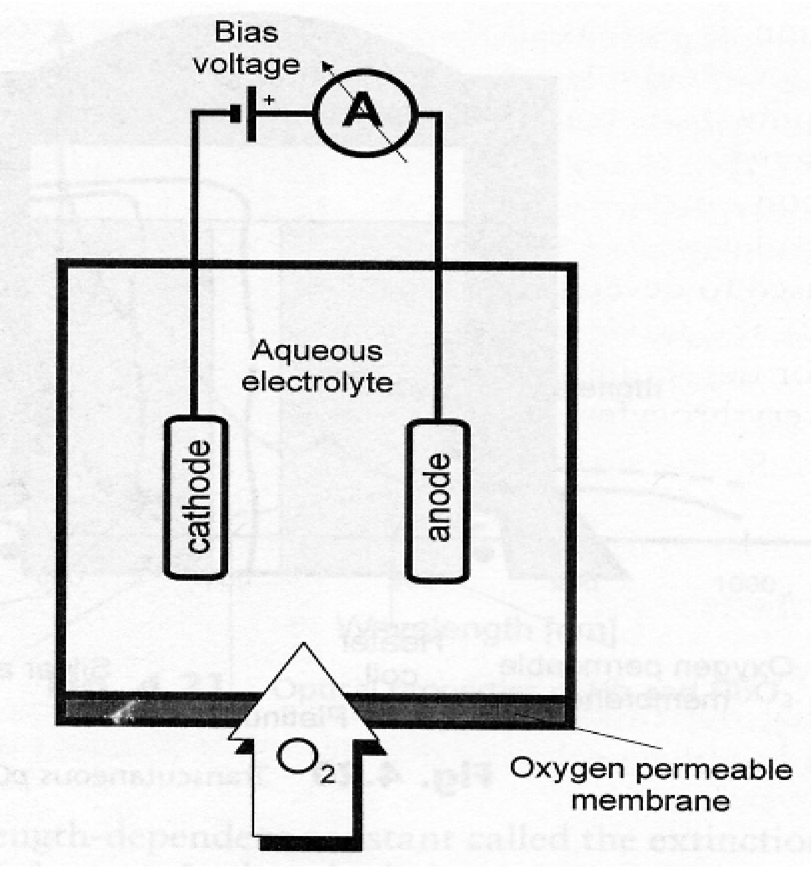


Non-contact type infrared thermometer

- measure the temperature of the ear canal wall near the tympanic membrane, which is known to track the core temperature.
- Infrared radiation from the tympanic membrane is detected by detector.
- Canal is gold plated for better reflectivity
- Sensor is a pyroelectric sensor (IR detector). Surface emissivity of the object at certain temperature and wavelength is calibrated for temperature change. (For example. T=300K and 3 um wavelength, 5 % change of emissivity corresponds to a temperature change of one degree.

4 Blood Gases and pH Sensors

4.1 Oxygen Measurement



Principle of a polarographic Clark-type pO2 sensor.

: measure the partial pressure of O_2 gas in a sample of air or blood.

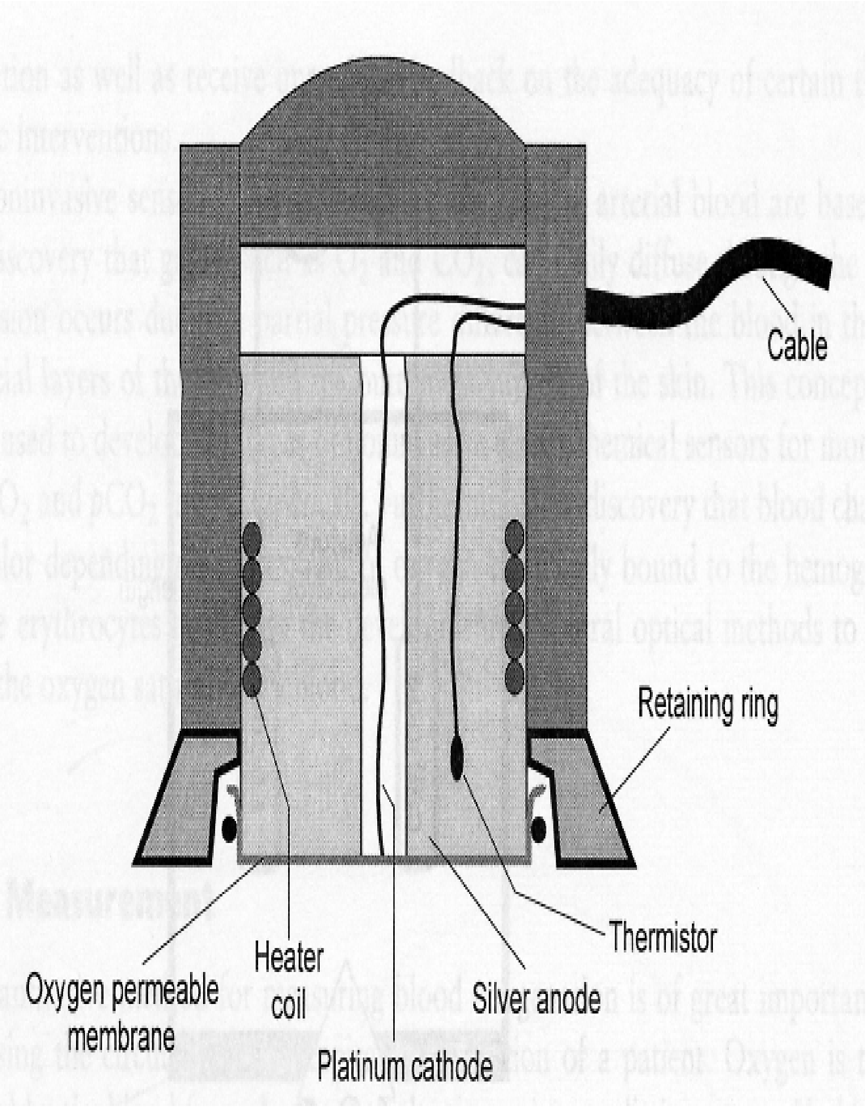
The measurement is based on the principle of polarography.

At cathode: $O_2+2H_2O+4e^- \leftrightarrow 4OH^-$ which moves to anode to flow current

At Anode: $Ag \leftrightarrow Ag^+ + e^-$

$Ag^+ + Cl^- \leftrightarrow AgCl$

The measured current is proportional to the pO2.



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Transcutaneous pO_2 sensor

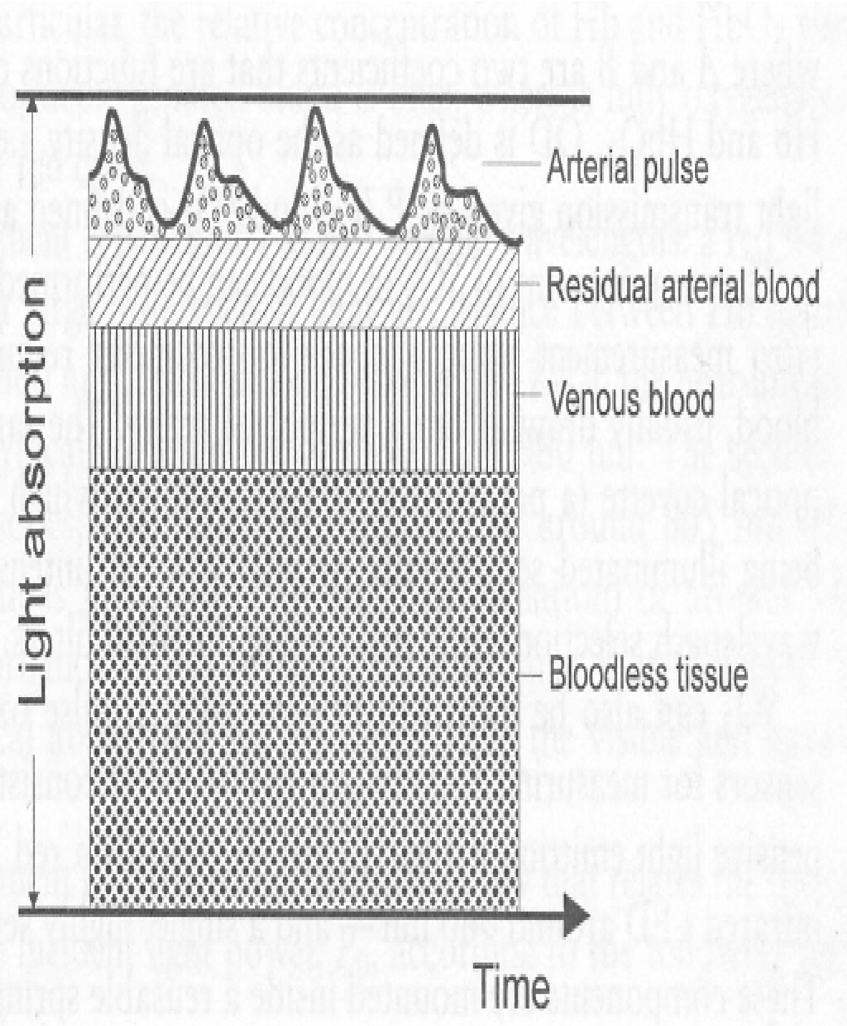
: cross section of a Clark-type transcutaneous pO_2 sensor

-essentially a standard polarographic pO_2 sensor

-attached to the surface of the skin by double sided adhesive tape.

-at 43 C, the measured pO2 is the same as that in the underlying artery

-applied to monitor newborn baby(for adult skin this does not work)

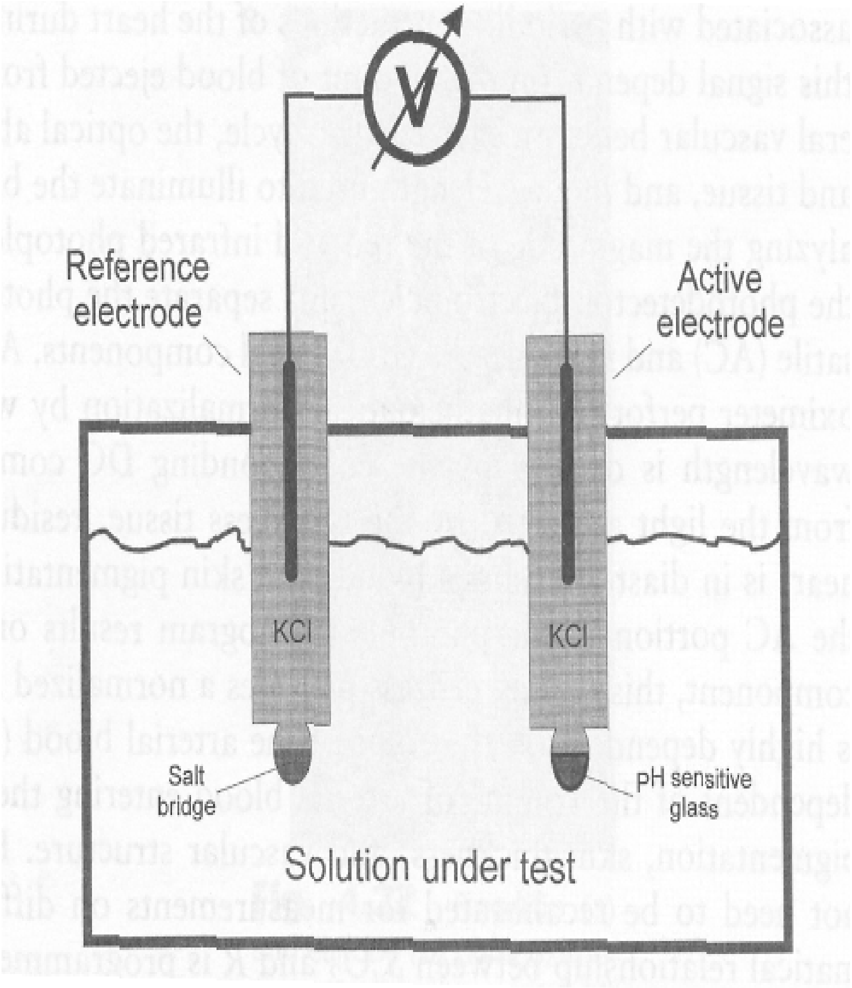


Time dependence of light absorption by a peripheral vascular tissue bed illustrating the effect of arterial pulsation

pulse oximetry relies on the detection of the photoplethysmographic signal. This signal is caused by changes in arterial blood volume associated with periodic contractions of the heart during systole.

(The IR signal reflected shows volume dependent absorption).

4.2 pH electrodes



Principle of a pH electrode.

- two electrode:

reference & active,

-Ag/AgCl wire dipped in KCl solution

-Salt bridge is permeable to all ions.

-Active electrode is sealed with H-impermeable glass except at the tip, where it is permeable only to H.

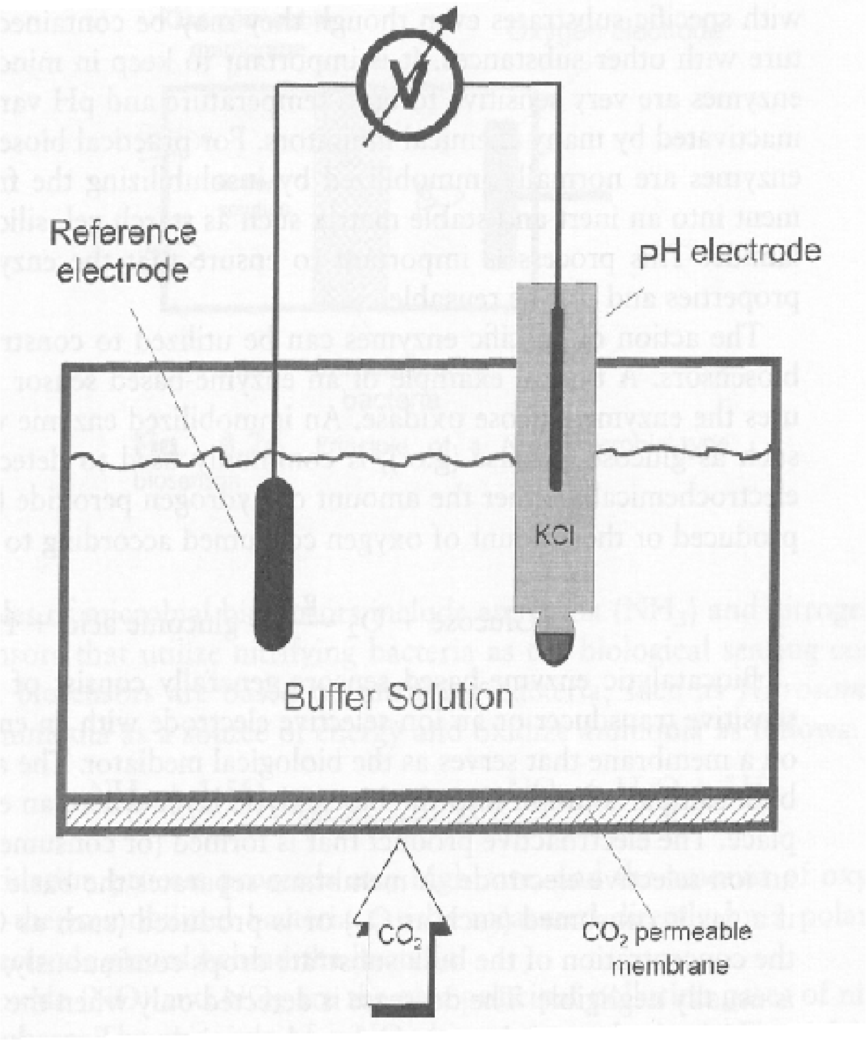
- V= -59mV*log10[H+]+C

(C:constant, 25C)

pH= -log10[H+]

V=59 *pH +C

4.3 Carbon Dioxide Sensors



Principle of a pCO_2 electrode

electrodes for measurement of partial pressure of CO_2 in blood or other liquid (based on measuring the pH)

$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$

Change of pH generates potential between the glass pH and a reference electrode(e.g., Ag/AgCl) that is proportional to the negative logarithm of the pCO_2

5 Bioanalytical Sensors

5.1 Enzyme-Based Biosensors

- Enzymes constitute a group of more than 2000 proteins having so-called biocatalytic properties.
- Most enzymes react only with specific substances.

  The soluble enzymes are very sensitive to

  both temperature and pH variations: also can be chemically inhibited.
- To ensure that the enzyme retains its catalytic properties and can be reusable, we use an inert and stable matrix such as starch gel, silicon rubber, or polyacrylamide.

- The action of specific enzymes can be utillized to construct a range of different biosensors.

ex)glucose sensor (using the enzyme glucose oxidase(g.o.))

Glucose + O_2 --g.o.→ gluconic acid +H_2O_2

- Then either the amounts of either gluconic acid or H2O2 are detected chemically or amount of consumed oxygen is measured.
- Biocatalytic enzyme-based sensors generally consist of an electrochemical gas-sensitive transducer or an ion-selective electrode ; with an enzyme immobilized in or on a membrane that serves as the biological mediator.

5.2 Microbial Biosensors

- The operation of microbial biosensors

(1)The substance is transported to the surface of the sensor

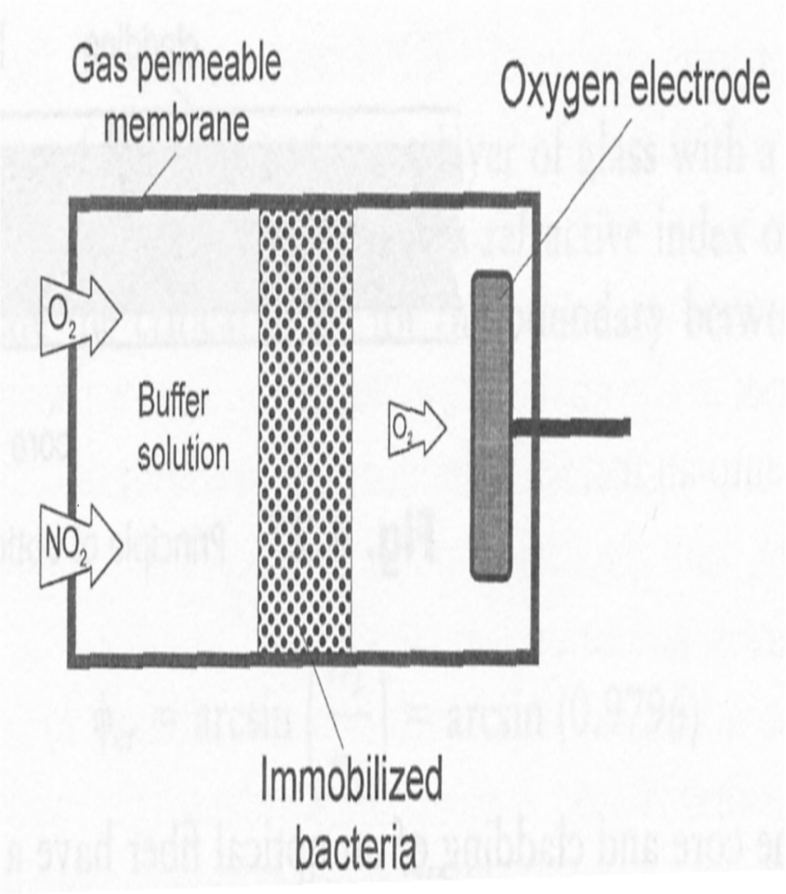
(2)The substance diffuses through the membrane to

the immobilized microorganism.

(3)A reaction occurs at the immobilized organism.

(4)The products formed in the reaction are transported through the membrane to the surface of the detector(products such as H2, CO2, or NH3 that are secreted by the micro-organism).

(5)the products are measured by the detector.



Principle of a NO_2 microbial-type biosensor.

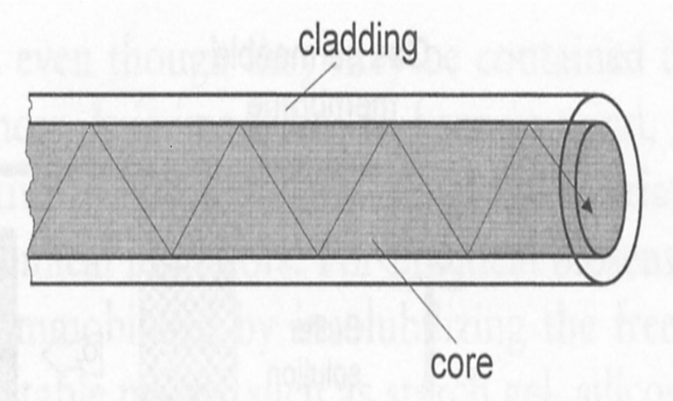
When a sample of NO2 gas Diffuses through the gas-permeable membrane, it is oxidized by the *Nitrobacter* sp. Bacteria as follows:

$$2NO_2 + O_2 \rightarrow 2NO_3$$

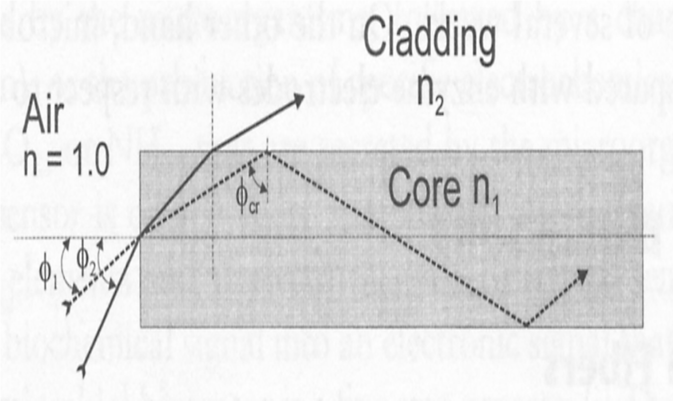
The consumption of O2 around the membrane is determined by an electrochemical oxygen electrode.

6 Optical Biosensors

6.1 Optical Fibers



principle of optical fibers.

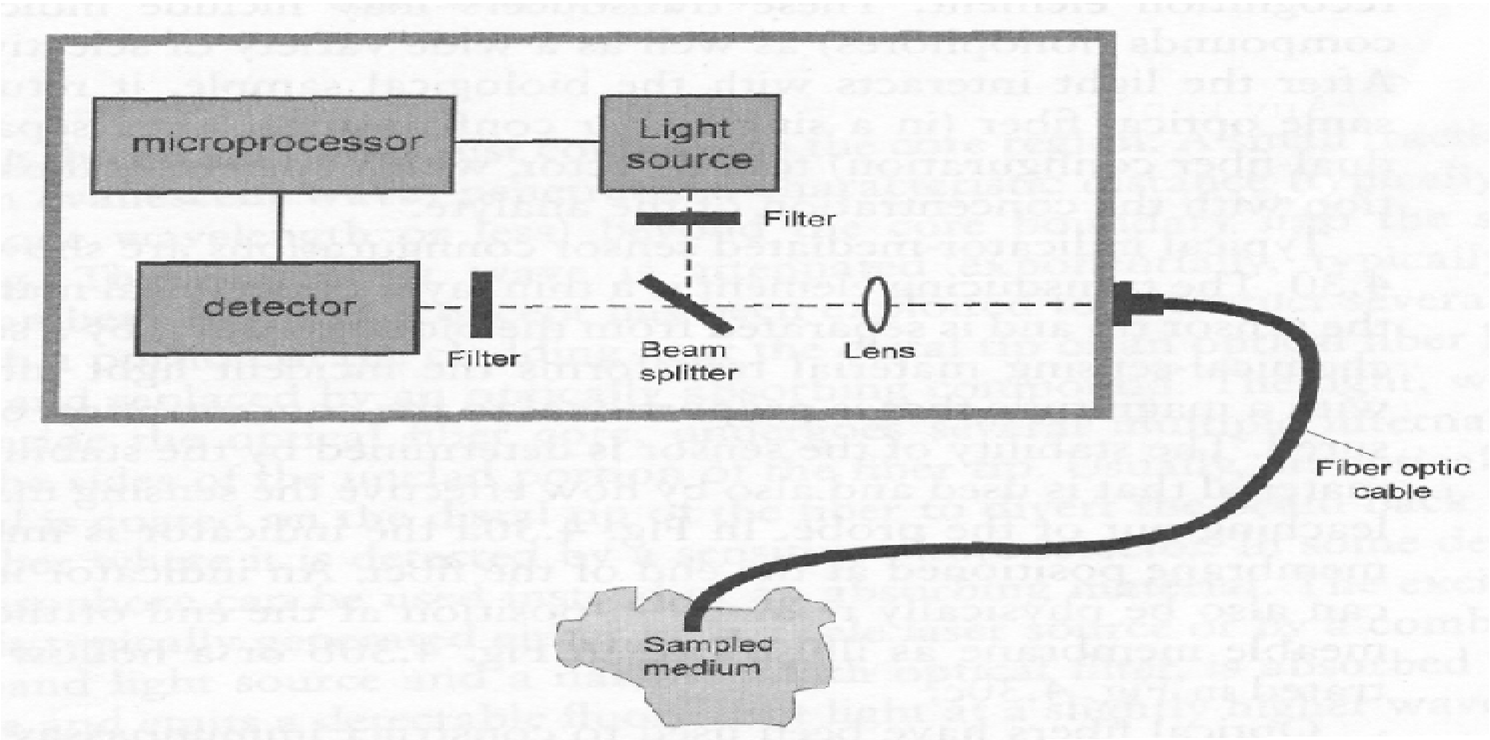


optical fiber illustrating the incident and refracted light rays. The solid line shows the light ray escaping from the core into cladding.The dashed line shows the ray undergoing total internal reflection inside the core.

- used to transmit light from one location to another.
- made from two concentric and transparent glass or plastic materials: core & cladding
- The index of refraction, n

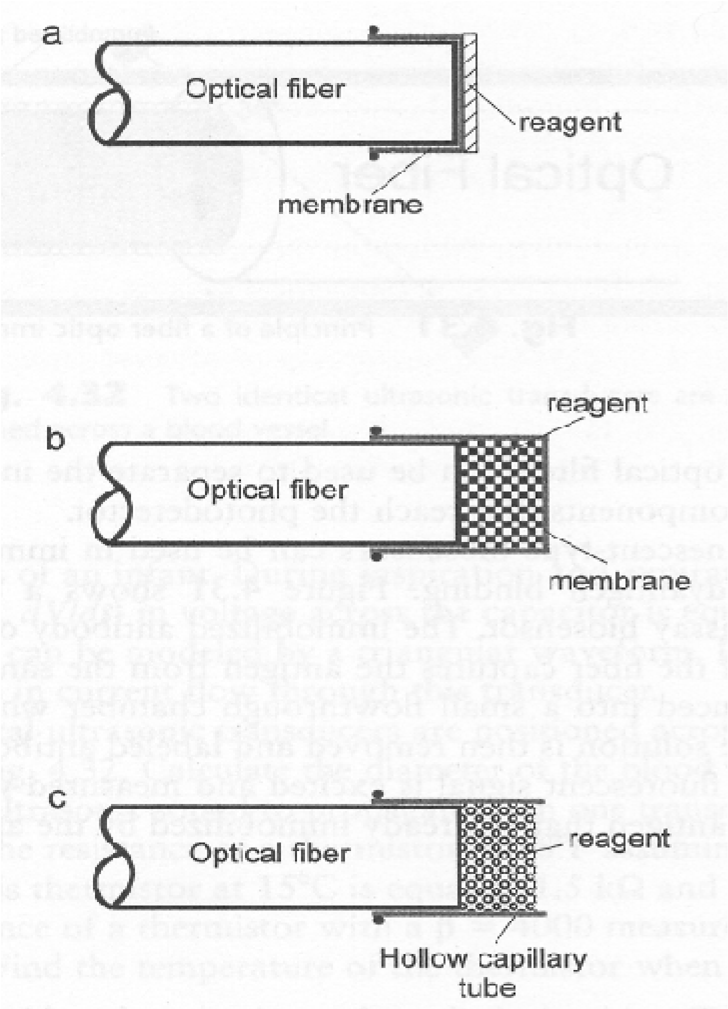
  core:n_1, cladding:n_2, $n_1 > n_2$
- Snell's law: $n_1 \sin Q_1 = n_2 \sin Q_2$
- If $\sin Q_2 = 1.0$, $\sin Q_{cr} = n_2 / n_1$
- Any light rays that enter the optical fiber with incidence angles greater than Qcr are internally reflected inside the core of the fiber by the surrounding cladding.

6.2 Sensing Mechanisms



General principle of a fiber optic-based sensor:
the common feature of commercial fiber optic sensors for blood gas monitoring

6.3 Indicator-Mediated fiber Optic Sensors



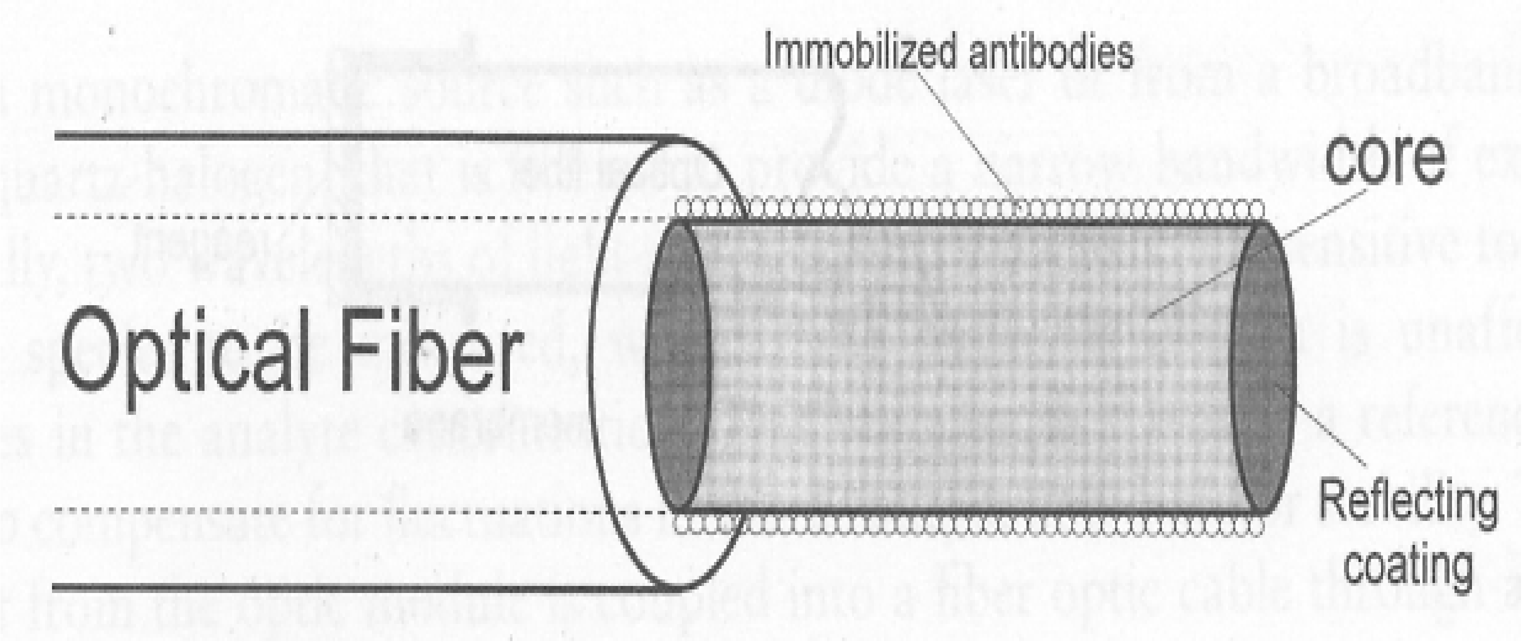
The return light signal has a magnitude that is proportional to the concentration of the specied to be measured.

Different indicator-mediated fiber optic sensor configurations.

(a) the indicator is immobilized directly on a membrane positioned at the end of the fiber

(b) an indicator in the form of powder can also be physically retained in position at the end of the fiber by a special permeable membrane

(c) or a hollow capillary tube.



Principle of a fiber optic immunoassay biosensor

- Uses Evanescence coupling of the light along fiber.
- Biosensor to detect antibody antigen binding.
- The immobilized antibody on the surface of unclad portion of the fiber capture antigen from the sample solution