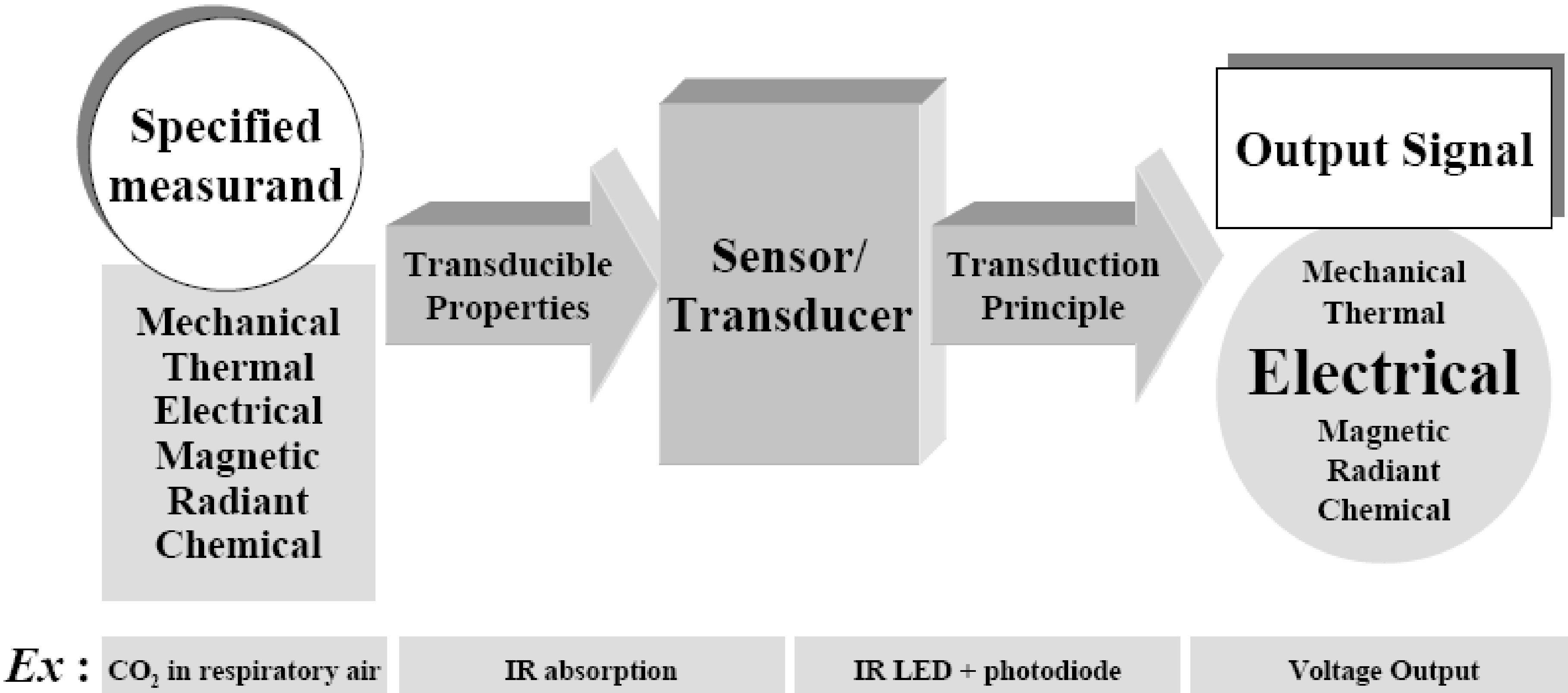
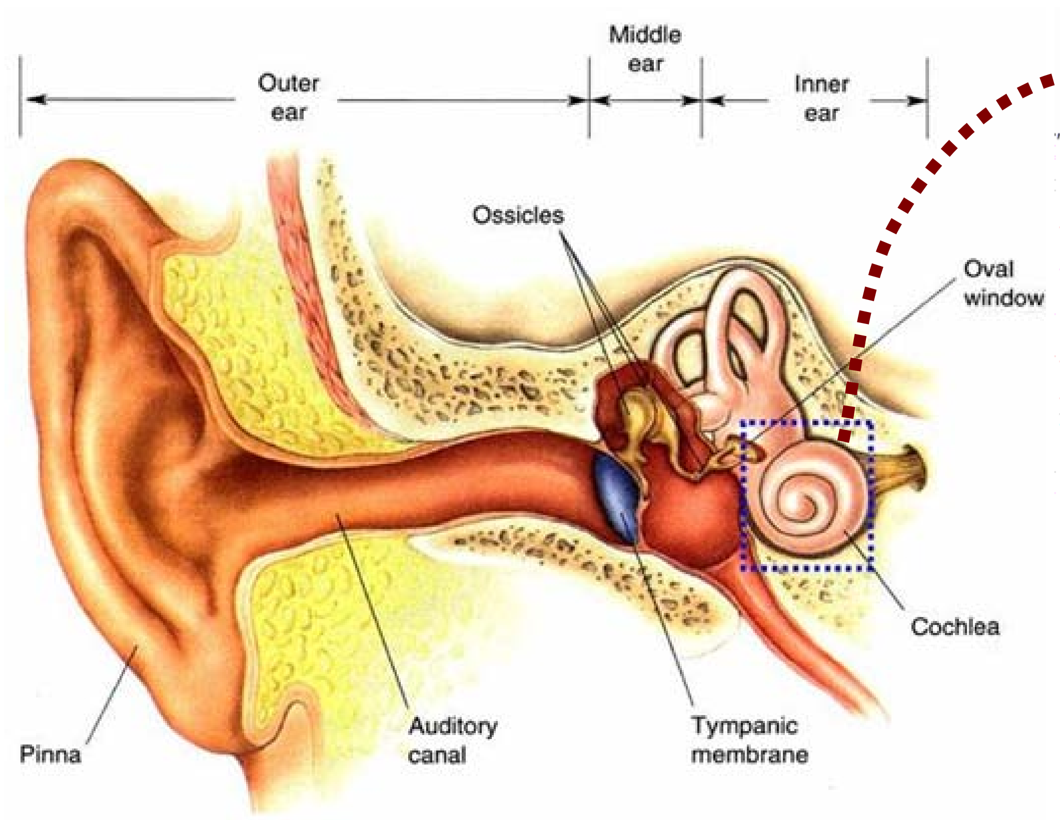
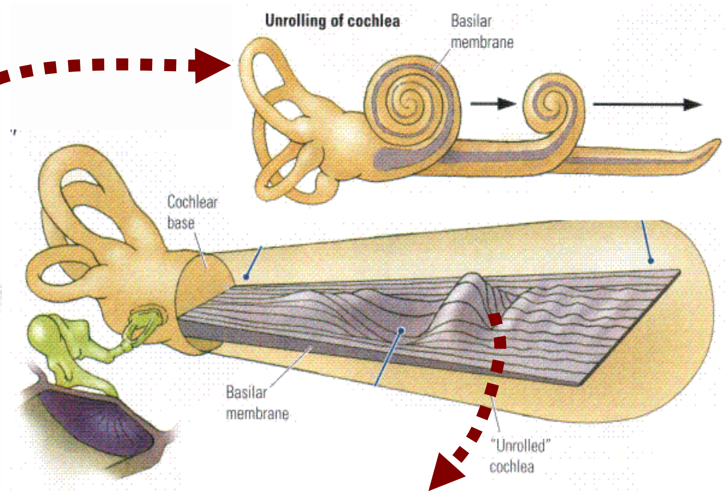
Biomedical Sensors

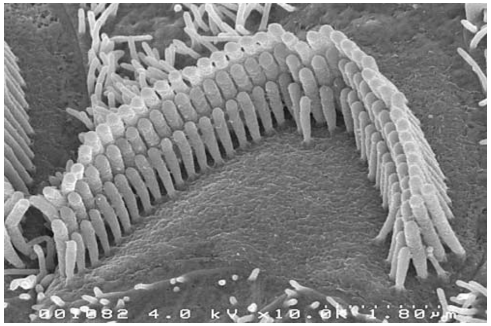
Transducer (=sensor)



Hair-cell as a natural transducer

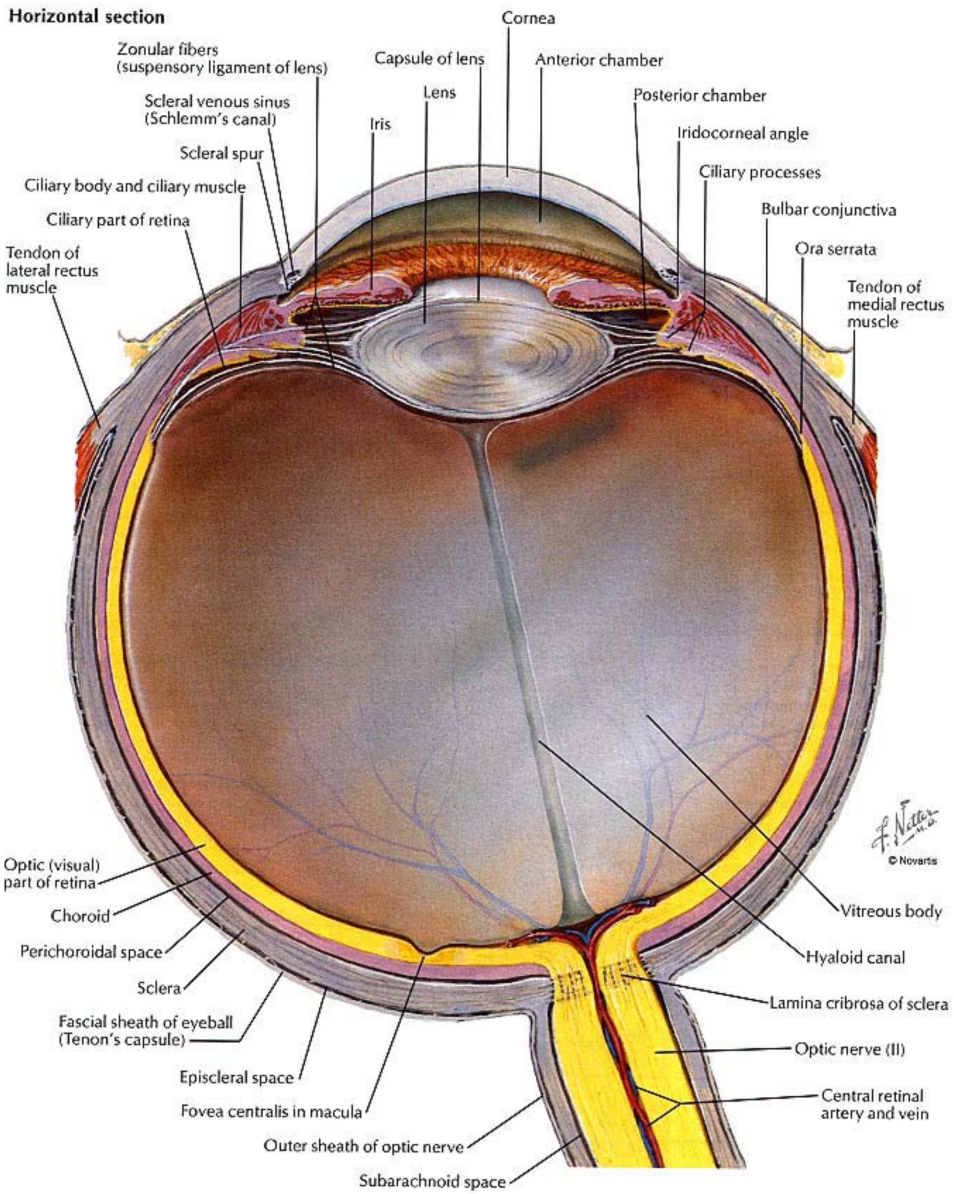






Eye structure

- **Retina (망막):** thin film of nerve tissue
- **Choroid (맥락막):** vascular tissue and layers
- **Sclera (공막):** opaque, fibrous, protective, outer layer
- **Optic nerve (시신경)**



Biosensor

- A device for the detection of an analyte that combines a biological component with a physicochemical detector component.
- Consists of 3 parts:
  - **the sensitive biological element**

    : biological material , a biologically derived material
  - **the transducer or the detector element** works in a physicochemical way : optical, piezoelectric, electrochemical, etc
  - **associated electronics or signal processors** that is primarily responsible for the display of the results in a user-friendly way.

Properties of biosensor

utilization of high sensitivity & selectivity of biological recognition

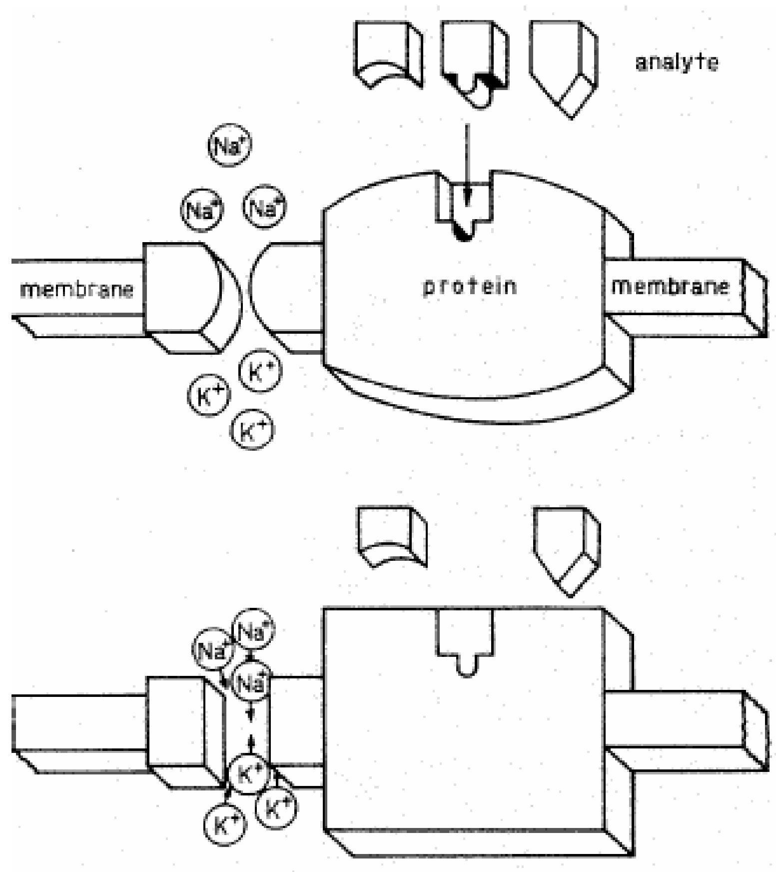
Ex : **natural chemoreceptor**

↑ binding substance ('acetylcholine')

↑ protein structure change

↑ ion channel open

↑ membrane potential change



Schematic of a natural chemoreceptor

Properties of biosensor

- **Merits of biosensor**
  - rapid response time / real-time sensing
  - continuous measurement / presence, absence or concentration of specific organic or inorganic substances
  - accurate & potentially low operating cost
  - easy to use / point-of-care diagnostics & home tests

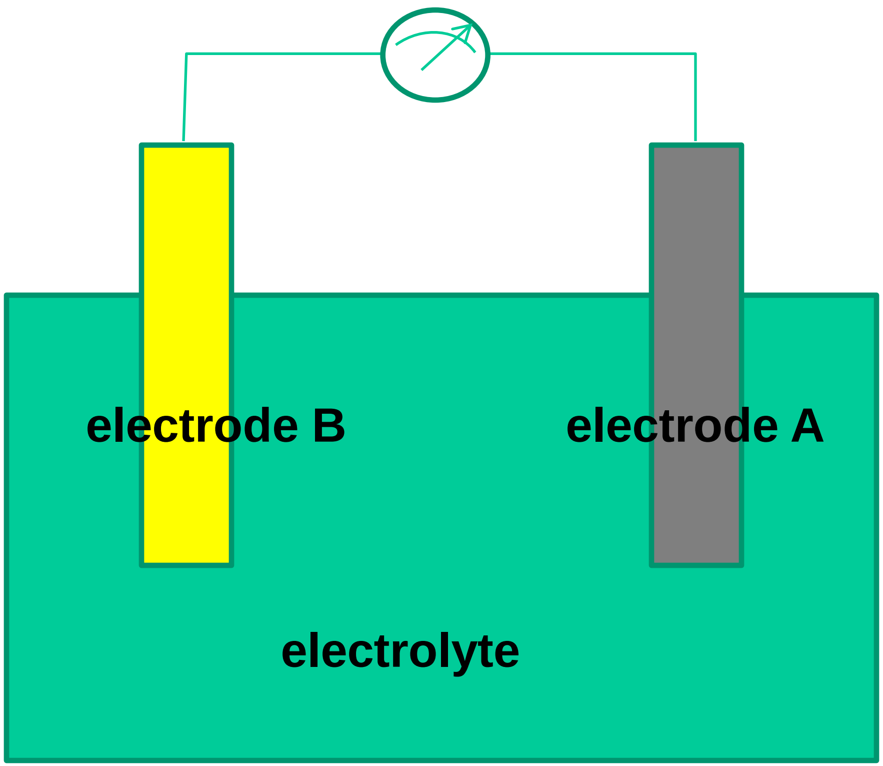
- **Drawbacks of biosensor**
  - need to design integrated, multitask systems
  - need for methods to improve sensitivity, stability, and selectivity
  - high production cost
  - slow development of noninvasive diagnostics
  - competition from conventional technology

Type of biosensor

- **Electrochemical sensor**
  - Biopotential sensors : ECG / EMG /EEG
  - Blood Gases and pH sensors
  - Bioanalytical sensors : Enzyme-based or Microbial biosensor
- **Mechanoelectrical sensor**
  - Hair-cell
  - Displacement transducer
  - Temperature sensor
- **Optical sensor**
  - SPR
  - Optical Fiber

1. Electrochemical sensor

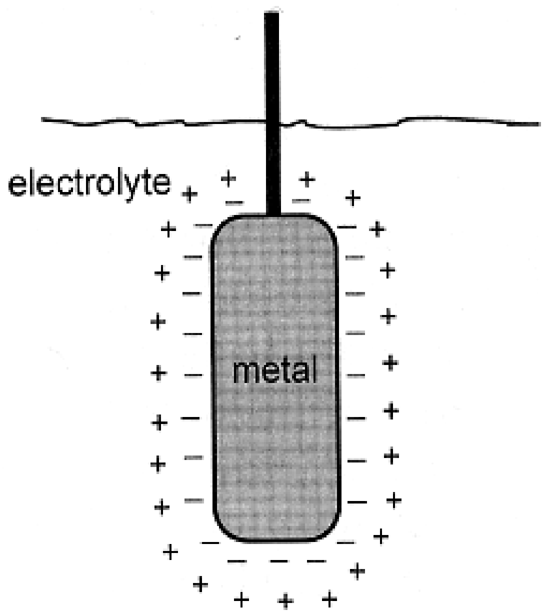
1.1 The Electrolyte/Metal Electrode Interface



<structure of Electrochemical cell>

- **Electrochemical cell**
  : two electrodes+electrolyte
- When potential $V_B < V_A$,
  Cell potential = V_A-V_B
- **Half-cell potential** : V_A, V_B
- **Electrolyte** : ion conductor
- **Electrode** : electronic conductor

Half-cell potential



Distribution of charges at a metal/electrolyte interface

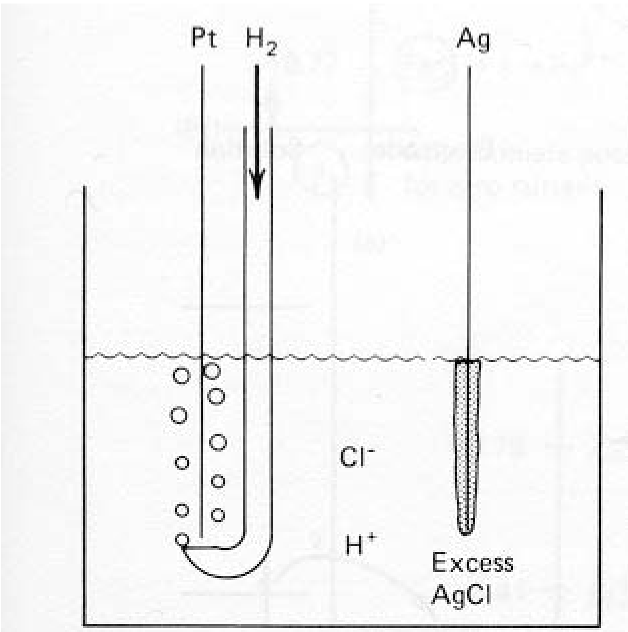
- **When a metal is placed in an electrolyte solution, a charge distribution is created next to the interface.**
- **This distribution causes a half-cell potential.**
- **Primary affecting factors: metal, ionic concentration, and temperature.**
- **NHE's potential is 0 by definition**

Table 1) Half-Cell potentials

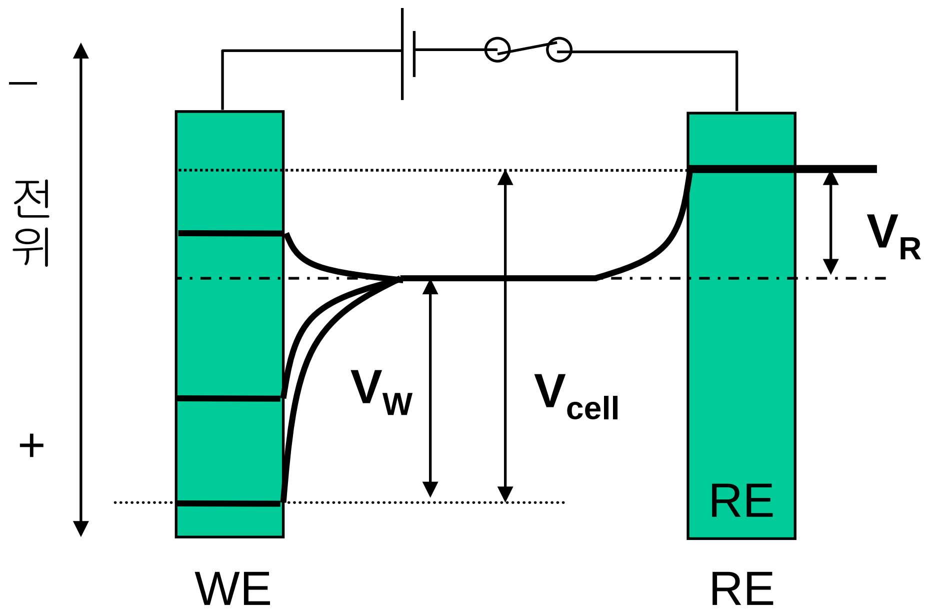
Primary metal and chemical reaction			Half-cell potential
Al	→	$Al^{3+} + 3e^-$	−1.706
Cr	→	$Cr^{3+} + 3e^-$	−0.744
Cd	→	$Cd^{2+} + 2e^-$	−0.401
Zn	→	$Zn^{2+} + 2e^-$	−0.763
Fe	→	$Fe^{2+} + 2e^-$	−0.409
Ni	→	$Ni^{2+} + 2e^-$	−0.230
Pb	→	$Pb^{2+} + 2e^-$	−0.126
H_2	→	$2H^+ + 2e^-$	−0.000 (standard by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

Normal Hydrogen Electrode(NHE)

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



Reference electrode



- A constant V_R in the Reference Electrode is desired for measuring

$$\triangle V_{cell} = \triangle V_w$$

Ag/AgCl

- two reactions

$$Ag \rightleftarrows Ag^+ + e^-$$

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

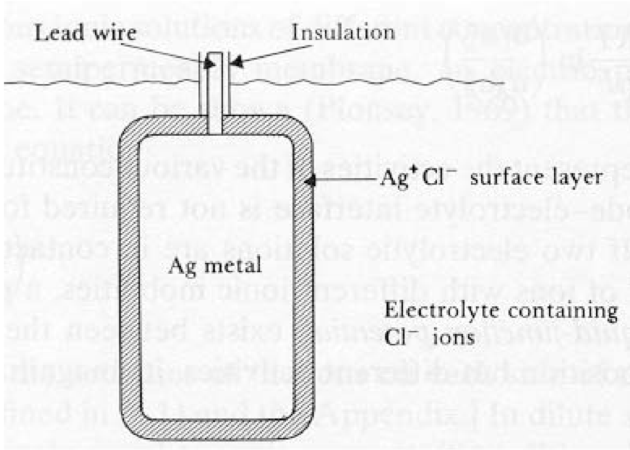


Fig 5.2 Ag-AgCl electrode

- The first reaction 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.

Examples of reference electrode

Table 2) Reference Electrodes

Electrode	Reaction	$E°/V$	E/V
(Pt) H_2 | H^+	$2H^+(aq) + 2e^- \rightleftharpoons H_2$	0	
Ag | AgCl	$AgCl(s) + e^- \rightleftharpoons Ag(s) + Cl^-(aq)$	0.222	Saturated KCl, 0.197
Hg | Hg_2Cl_2 (Calomel Electrode)	$Hg_2Cl_2 + 2e^- \rightleftharpoons 2Hg + 2Cl^-$	0.280	Saturated KCl, 0.2412 (SCE) 1 N KCl, 0.2801 (NCE) 0.1 M KCl, 0.3337
Hg | Hg_2SO_4	$Hg_2SO_4 + 2e^- \rightleftharpoons 2Hg + SO_4^{2-}$	0.613	
Hg | HgO	$HgO + H_2O + 2e^- \rightleftharpoons Hg + 2OH^-$	0.098	

The Electrolyte/Metal Electrode Interface

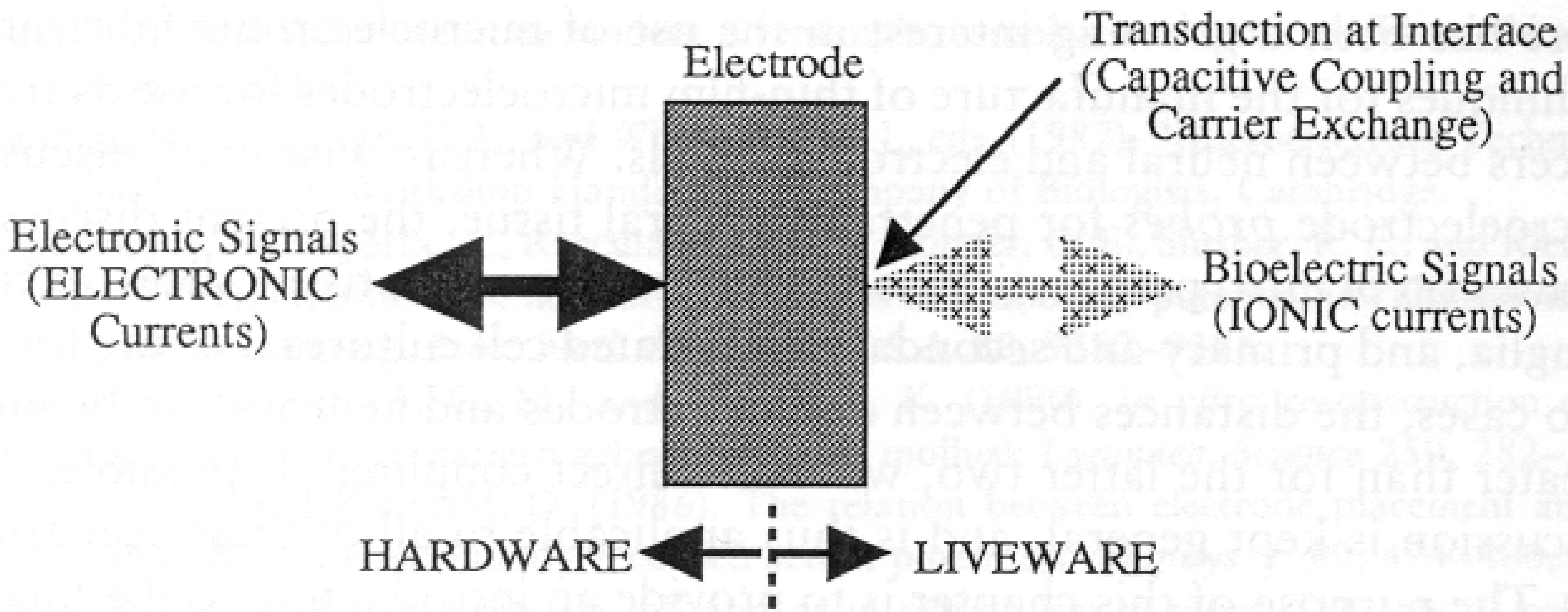
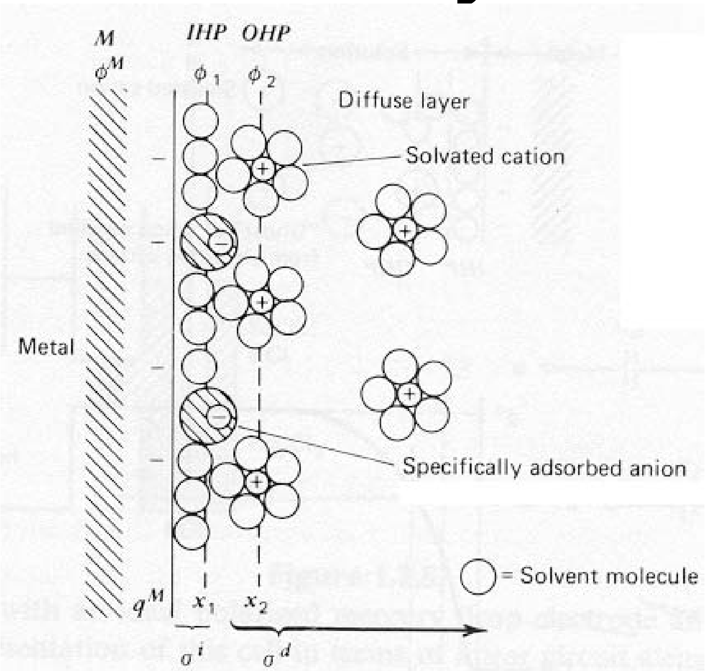


FIGURE 1 Diagram illustrating the transduction of signals between the physiologic and electronic environments.

Double Layer



- Helmholtz (Inner) layer: solvent molecules and other species specifically adsorbed (stuck at or near surface). IHP (inner Helmholtz plane) and OHP. The solvated ions can approach up to the boundary plane.
- Diffused layer is outside the OHP.

Double Layer

- **Metal charge (Qm):** excess or deficiencies of electrons in a very thin (<0.1A) layer on metal surface. Sm=Qm/A[mC/cm^2]
- **Solution charge(Qs):** excess of cations or anions in the vicinity of electrode surface. SS=Qs/A[mC/cm^2]
- **Double Layer:** the whole array of charge species and oriented dipoles existing at the metal-solution interface. Actual structure more complicated.
- **Double layer capacitance(Cd)** is defined at a given potential, typically in the range of 10 to 20 mF/cm^2.
- **Total excess charge density**

  Ss= Si+Sd=-Sm.
- **Thickness of double layer (including diffused layer)** depends on ionic concentration, but is around 300 A.
- **The field strength** is about 1E9 V/m/

Factors affecting electrode reaction rate and current

1. Mass transfer
2. Electron transfer at the electrode surface
3. Chemical reactions
4. Other surface reactions: adsorption, desorption, electrodeposition

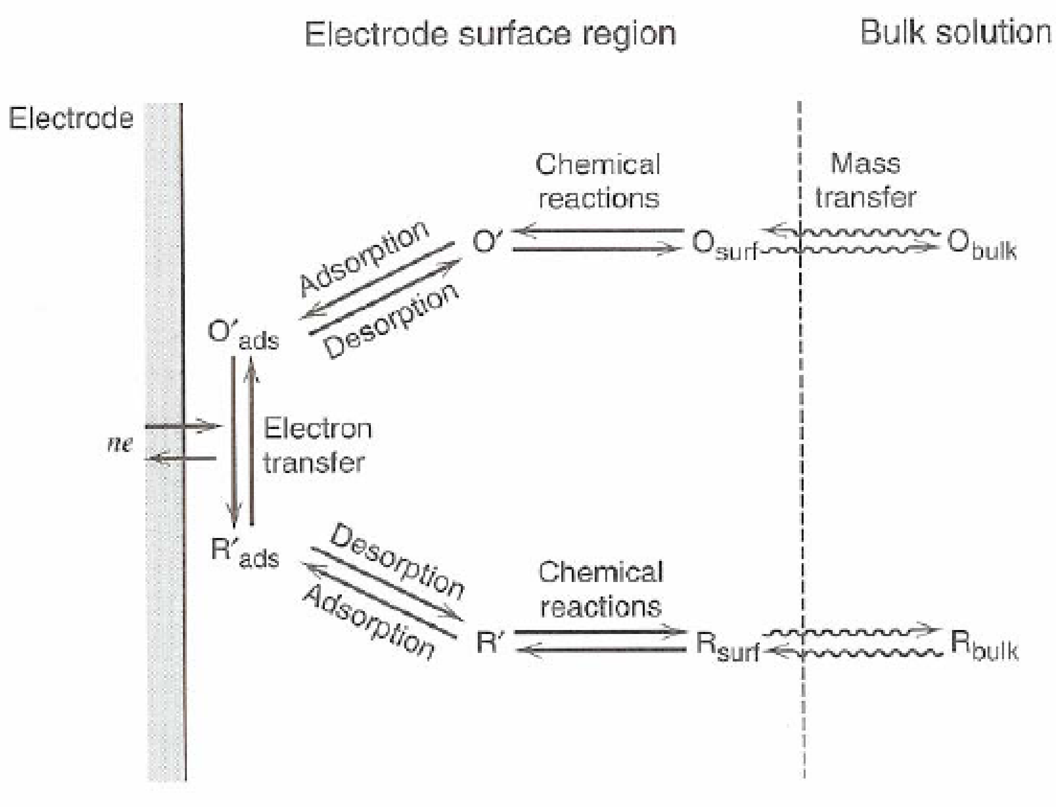
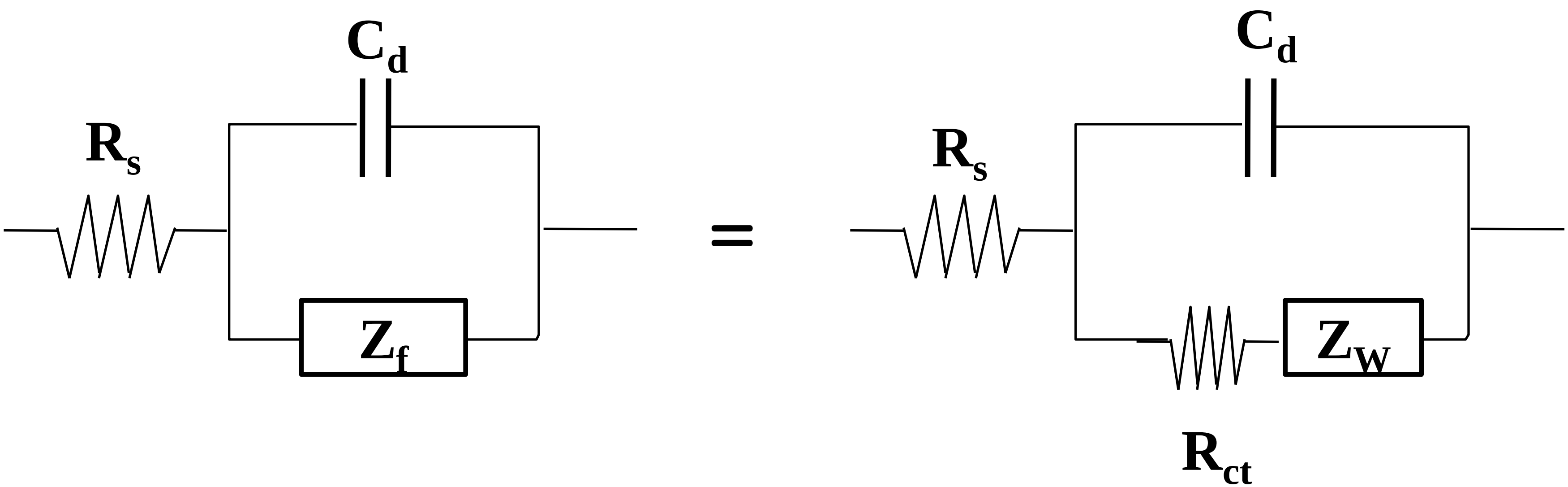


Figure 1.3.6 Pathway of a general electrode reaction.

Equivalent circuit



R_s : solution resistance

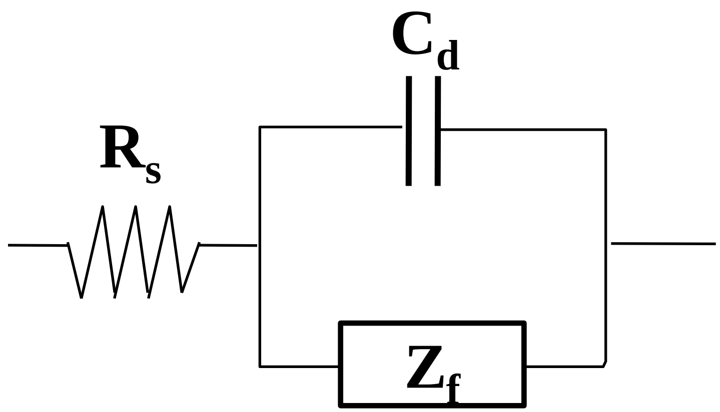
C_d : double layer capacitance

Z_f : impedance of the Faradaic process

R_{ct} : charge transfer resistance

Z_W : impedance to Mass transfer of the electroactive species

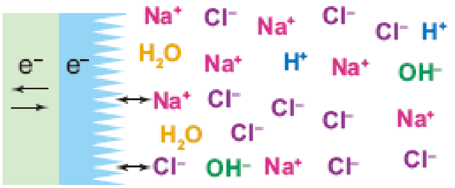
Current at the electrolyte/metal electrode Interface



- **<u>Capacitive current</u>** by C_d charging
- **<u>Faradaic current</u>** by chemical reaction and charge (e.g. electron) transfer related with Z_f

Charge injection mechanism

- Examples of capacitive & faradaic reaction material



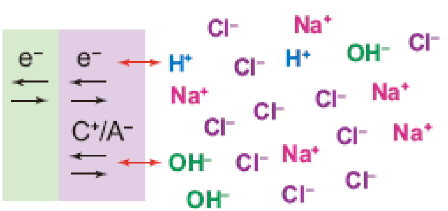
Titanium nitride

Double-layer charging
with a porous coating

Capacitive

(Chemically stable metal conductors, i.e., noble metals)

and (TiN, Ta/Ta_2O_5, carbon nanotubes))



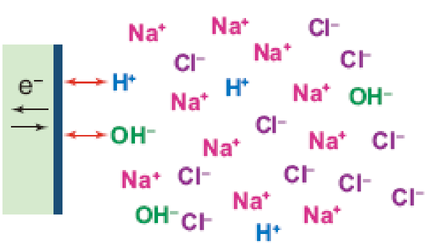
Iridium oxide

$Ir^{3+} \longleftrightarrow Ir^{4+} + e^-$

$Ir(OH)_n \longleftrightarrow IrO_n(OH)_{n-x} + xH^+ + xe^-$

Faradaic

(IrOx, PEDOT(a new polymer))



Platinum surface reactions

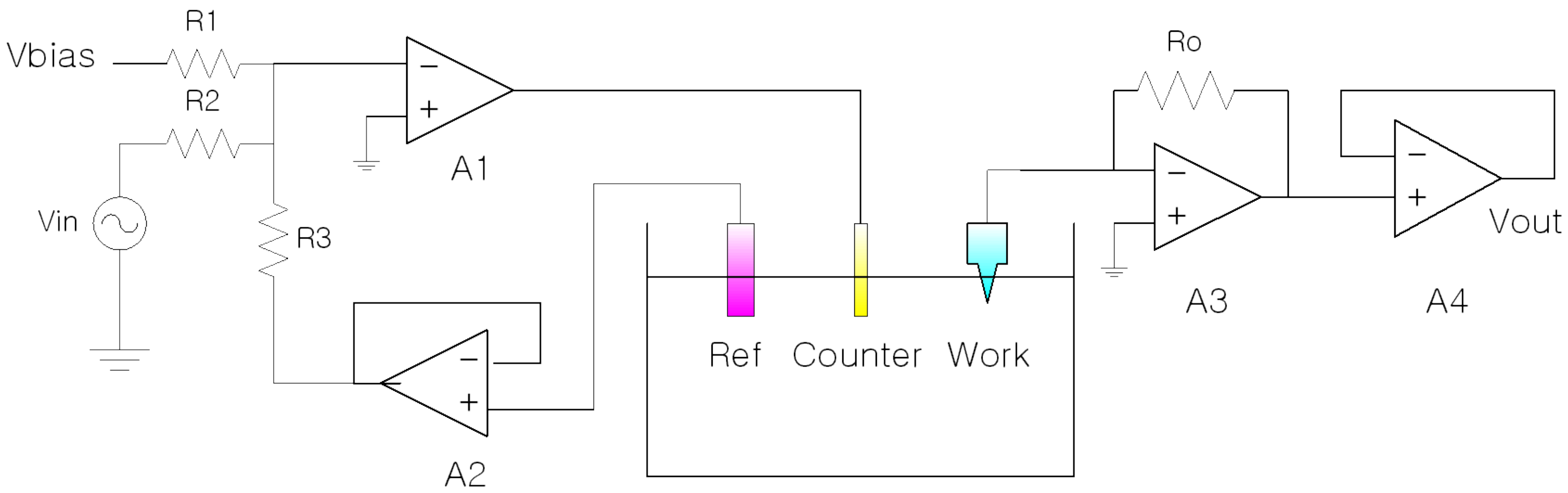
$Pt + H_2O \longleftrightarrow PtO + 2H^+ + 2e^-$

$Pt + H_2O + e^- \longleftrightarrow Pt\text{–}H + OH^-$

Capacitive & Faradaic

(Pt, PtIr alloys)

Impedance measurement (by Potentiostat)



$$R_{work} = -\frac{V_{ref}}{V_{out}} R_o = -\frac{V_{bias} + Vin}{V_{out}} R_o$$

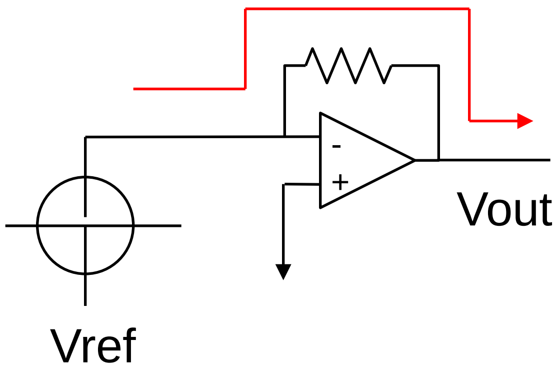
Potentiostat

- KCL applied at the stage A1 (-) input yields

Vout of A2 =
$$-\left(\frac{V_{bias}}{R_1}+\frac{Vin}{R_2}\right)R_3$$

- If R1=R2=R3, Vref = - (Vbias+Vin)
- Current flows from the Counter to Working electrode.
  - Counter electrode : low impedence
  - Ref. electrode : high impedence
- Now

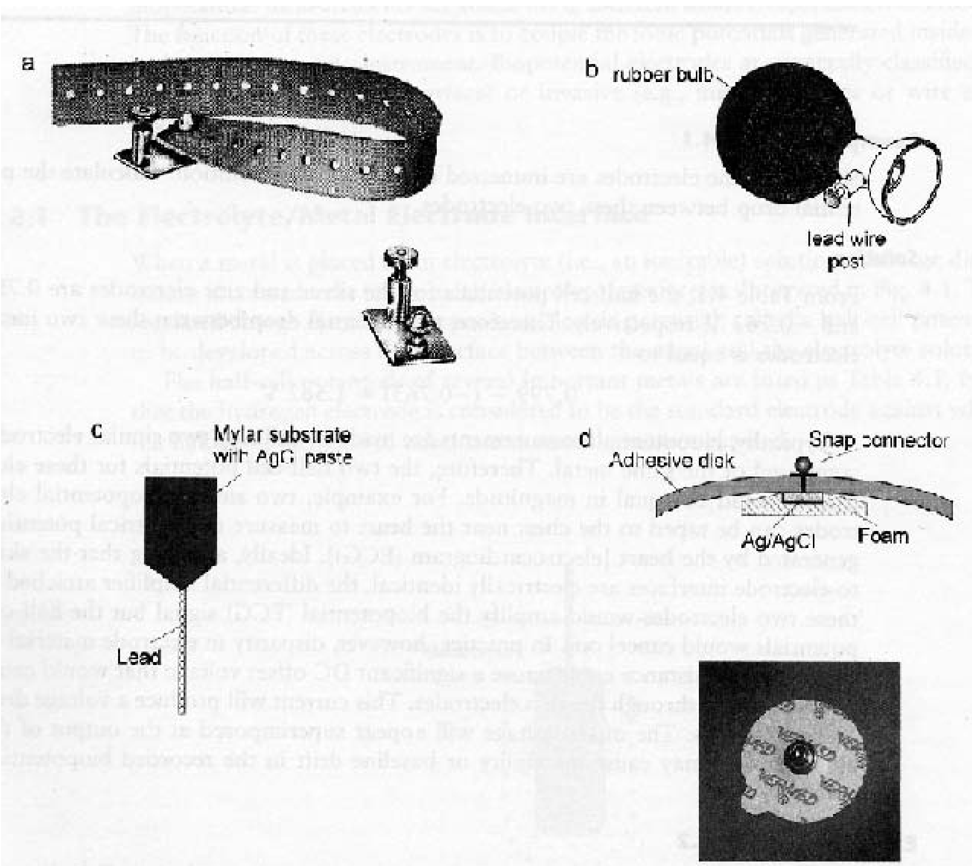
$$\frac{V_{ref}}{R_{work}}=-\frac{V_{out}}{R_o}$$



$$\therefore \quad R_{work}=-\frac{V_{ref}}{V_{out}}R_o=-\frac{V_{bias}+Vin}{V_{out}}R_o$$

- This means that we can measure the magnitude and phase of the R_{work} by looking at V_{in} and V_{out} .
- Advantage: There is no current through the Reference electrode. This electrode is preserved. The counter electrode may not be, but this does not affect the measurement.

1.2 Biopotential Sensors : 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

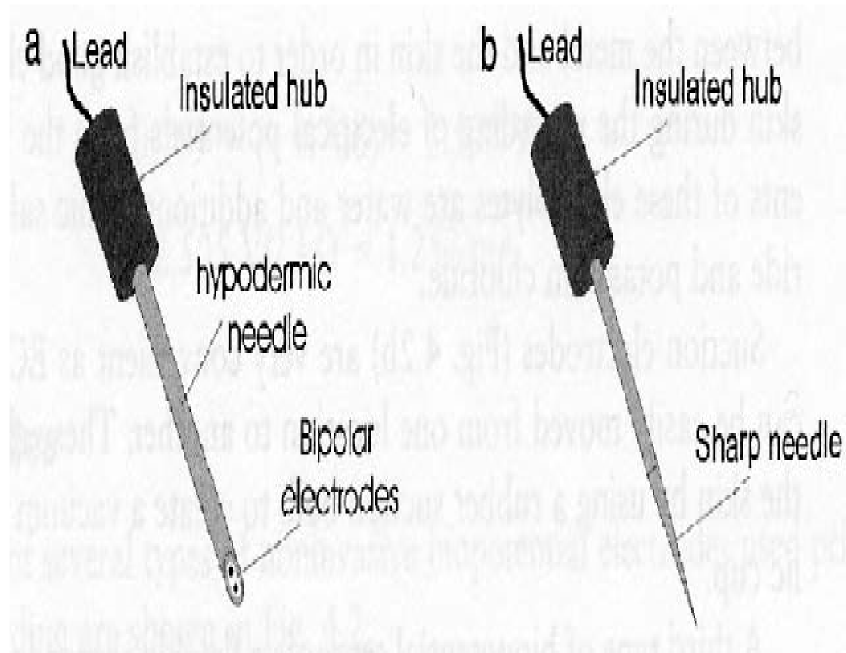
(courtesy of Vermont Medical, Inc., Bellows Falls, VT)

Electromyographic electrodes(EMG)

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.

Electroencephalographic electrodes (EEG)

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

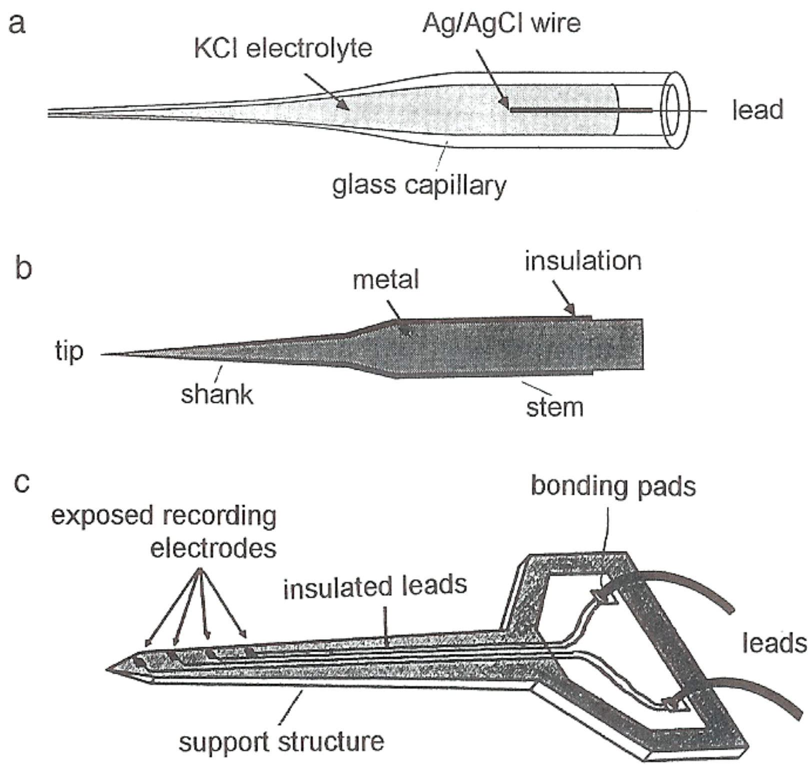
  -Cup electrode:

    - 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

Biopotential microelectrodes



(a) **capillary glass microelectrode**

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

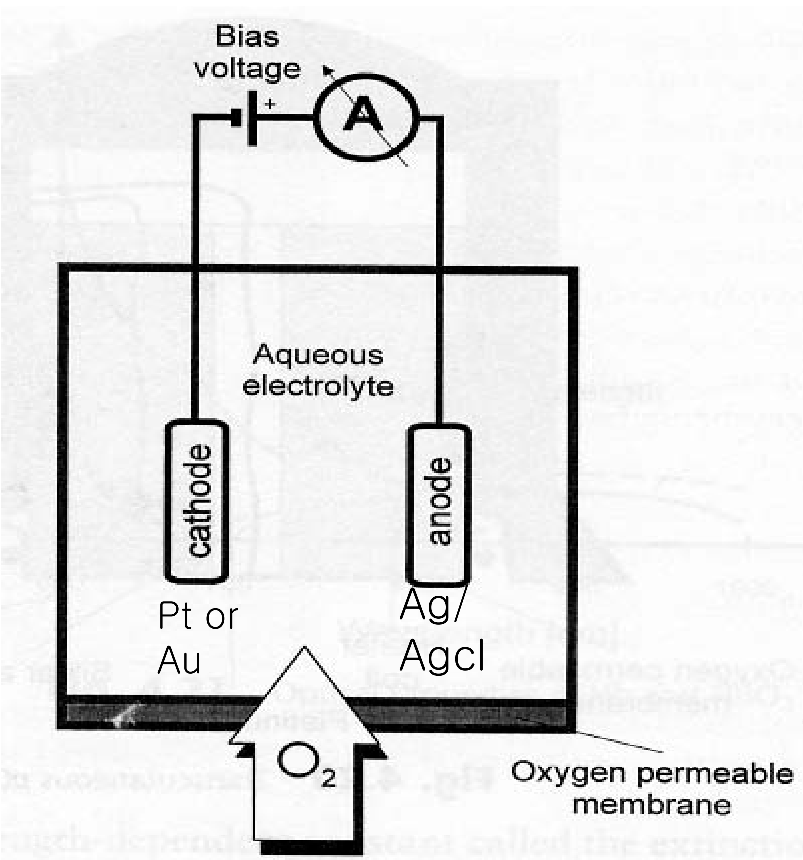
(b) **insulted metal electrode**

- 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

1.3 Blood Gases and pH Sensors : 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.

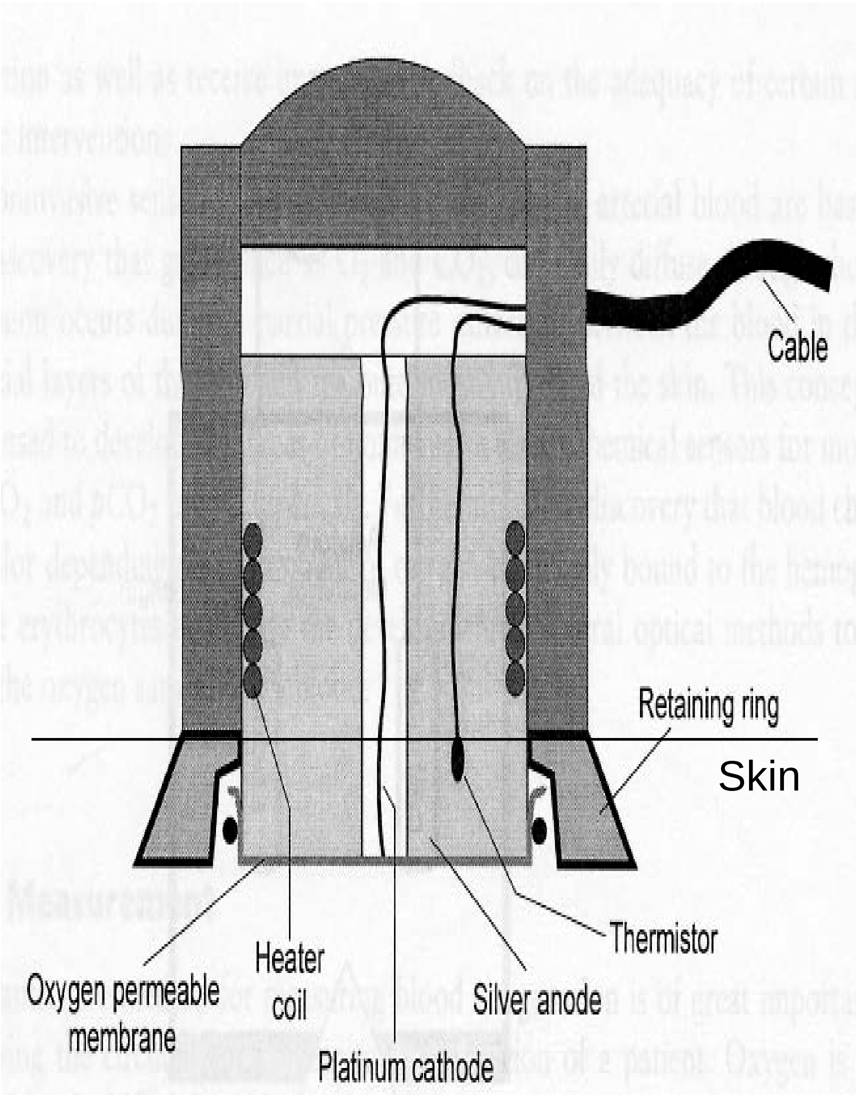
At cathode: $O_2+2H_2O+4e^- \leftrightarrow 4OH^-$ which moves to anode to flow current

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

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

The measured current is proportional to the pO2.

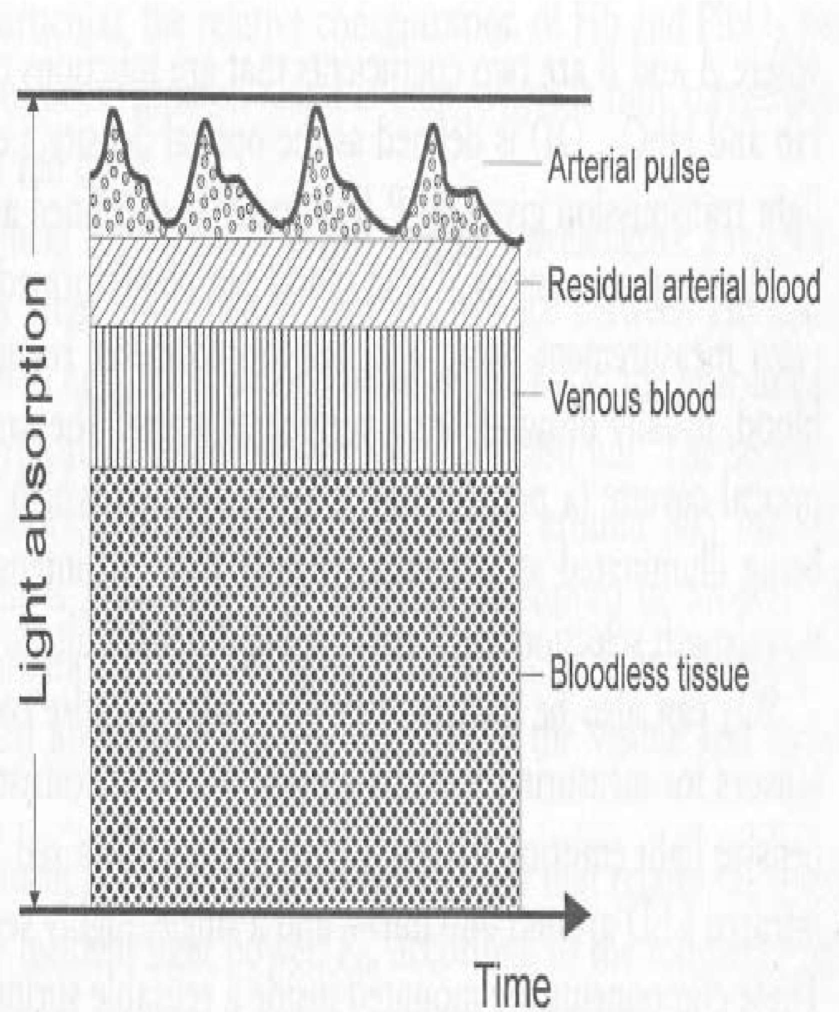
Transcutaneous pO2 sensor



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)

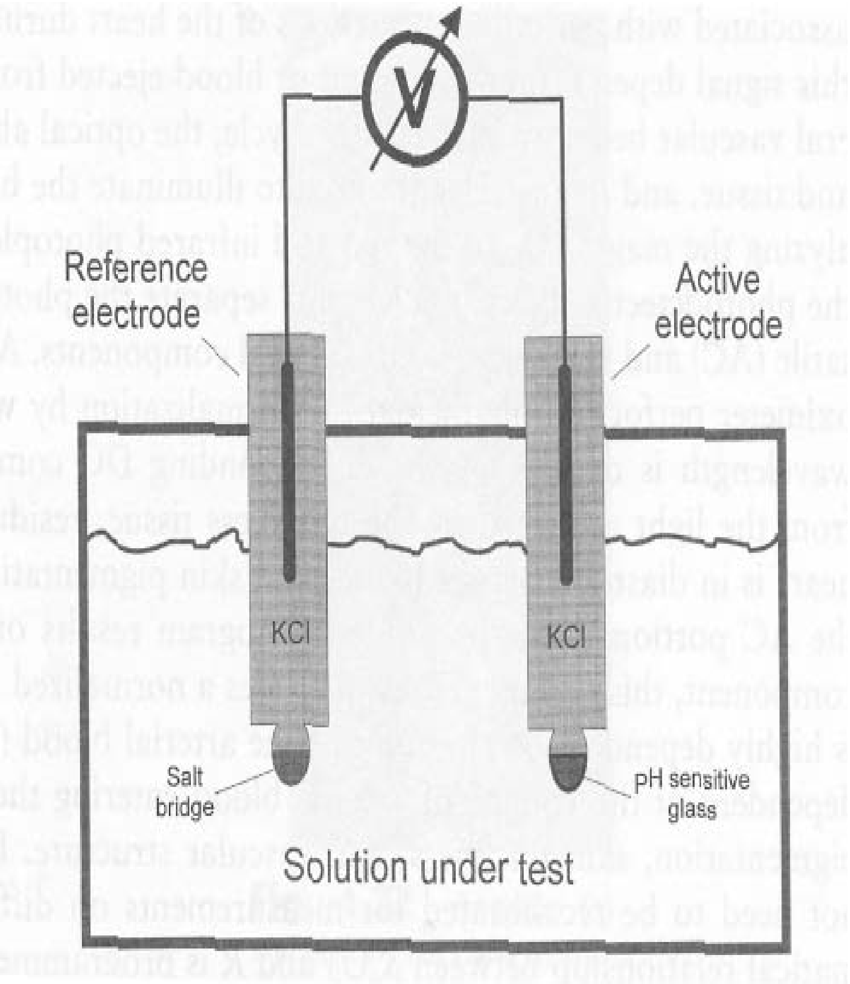
Photoplethysmography



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

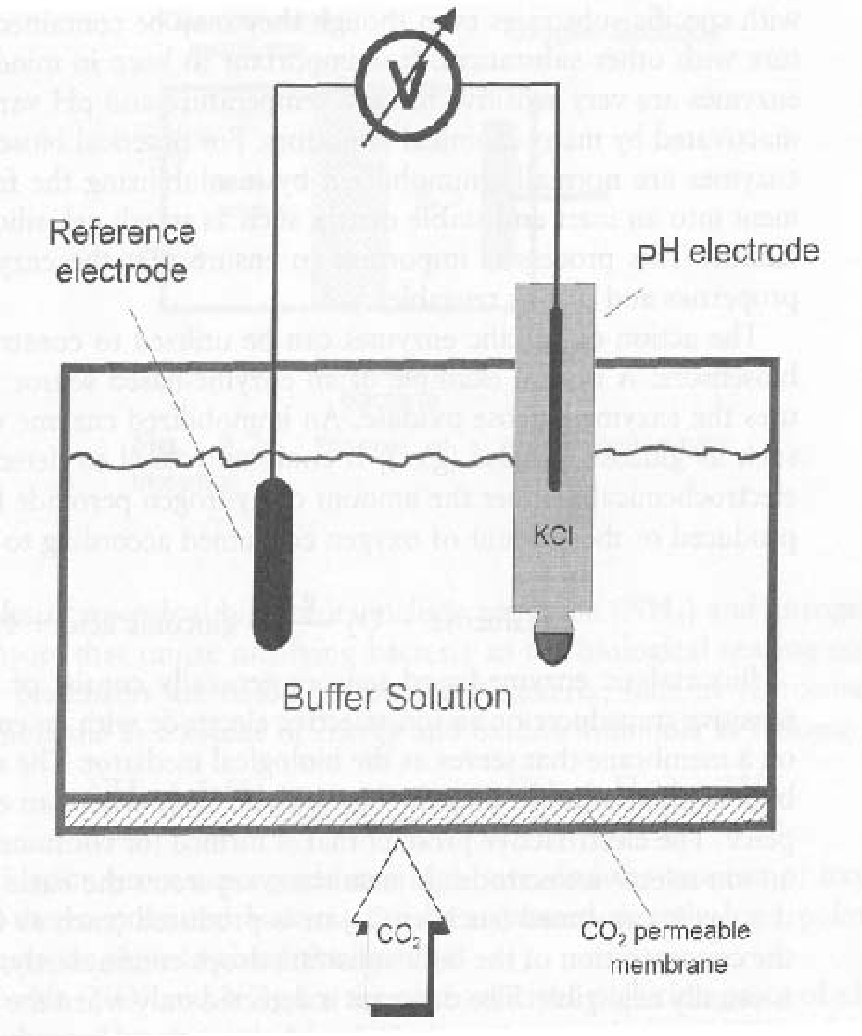
Pulse oximetry relies on the detection of the photoplethysmo-graphic signal. This signal is caused by changes in arterial blood volume associated with periodic contractions of the heart during systole.
(The IR signal reflected shows volume dependent absorption).

pH electrodes



- Two electrode:
- reference & active,
- Ag/AgCl wires dipped in KCl solution
- Reference electrode: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

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

1.4 Bioanalytical Sensors : 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.))

$$Glucose + O_2 \xrightarrow{g.o.} gluconic\ acid + H_2O_2$$

- Then either the amounts of either gluconic acid or H_2O_2 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.

Microbial Biosensors

- The operation of microbial biosensors

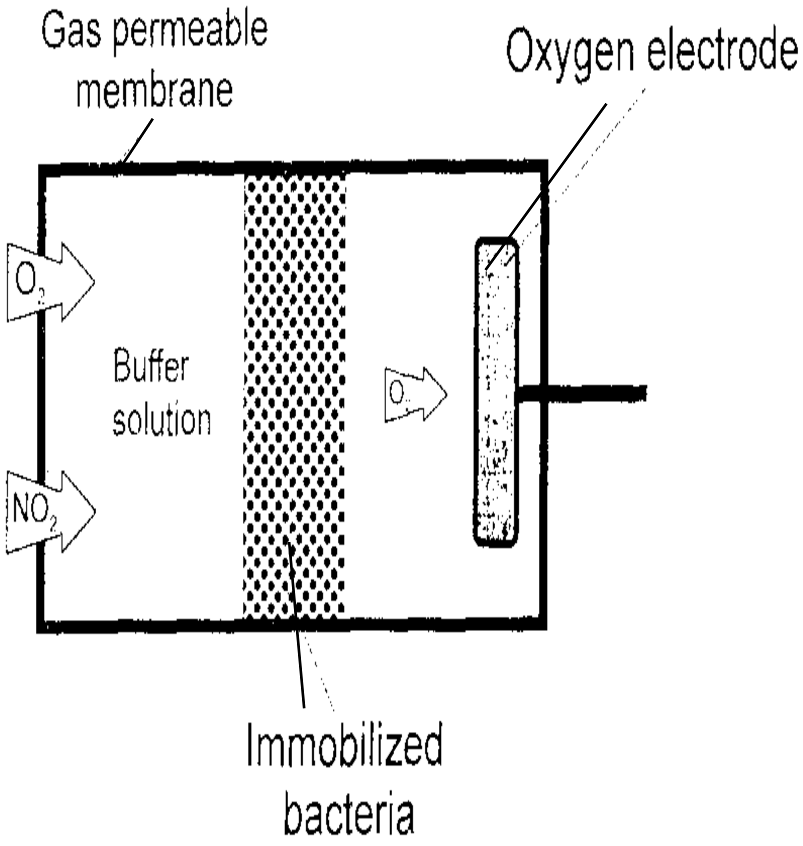
(1)The substance is transported to the surface of the sensor

(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 H_2, CO_2, or NH_3 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:

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

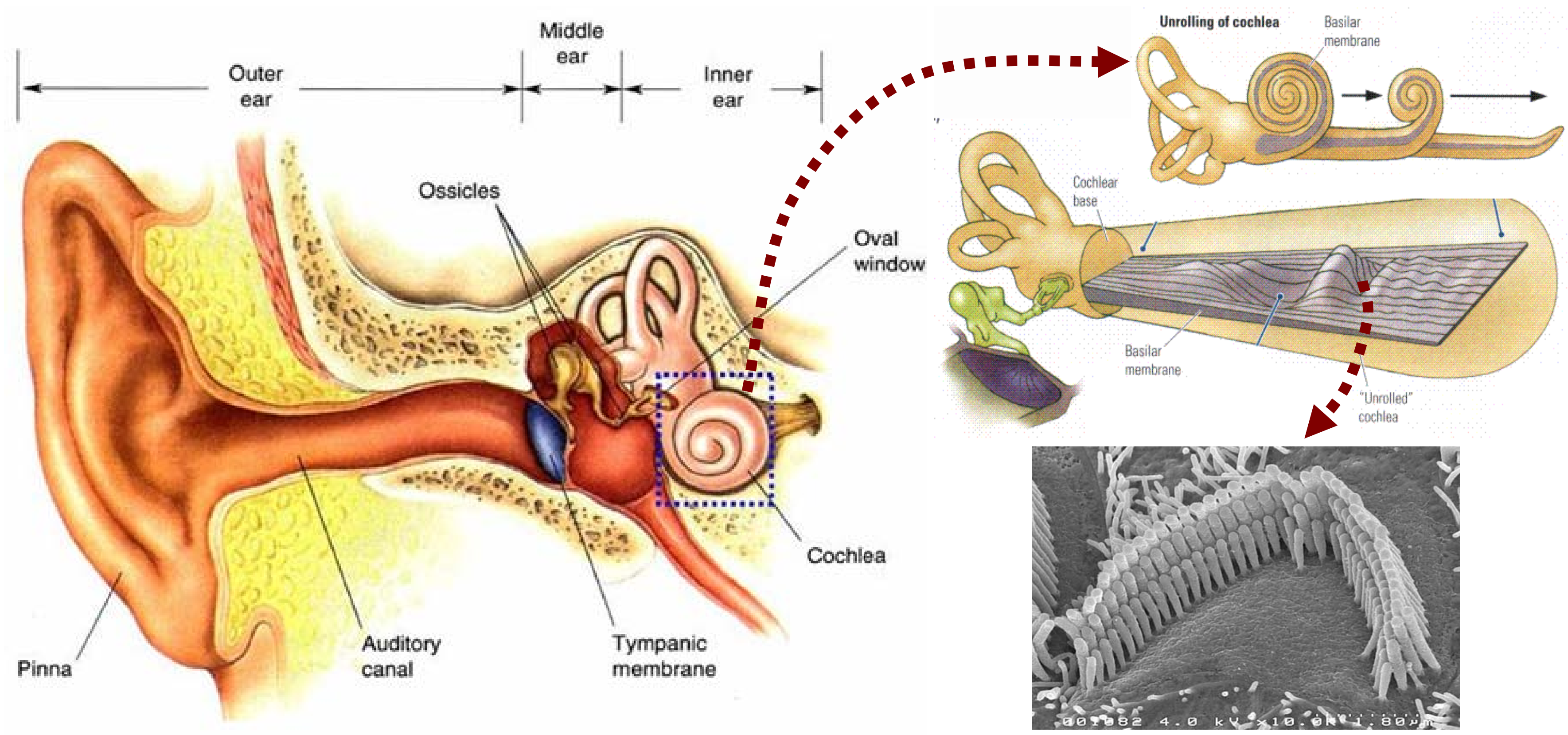
The consumption of O2 around the membrane is determined by an electrochemical oxygen electrode.

Type of biosensor

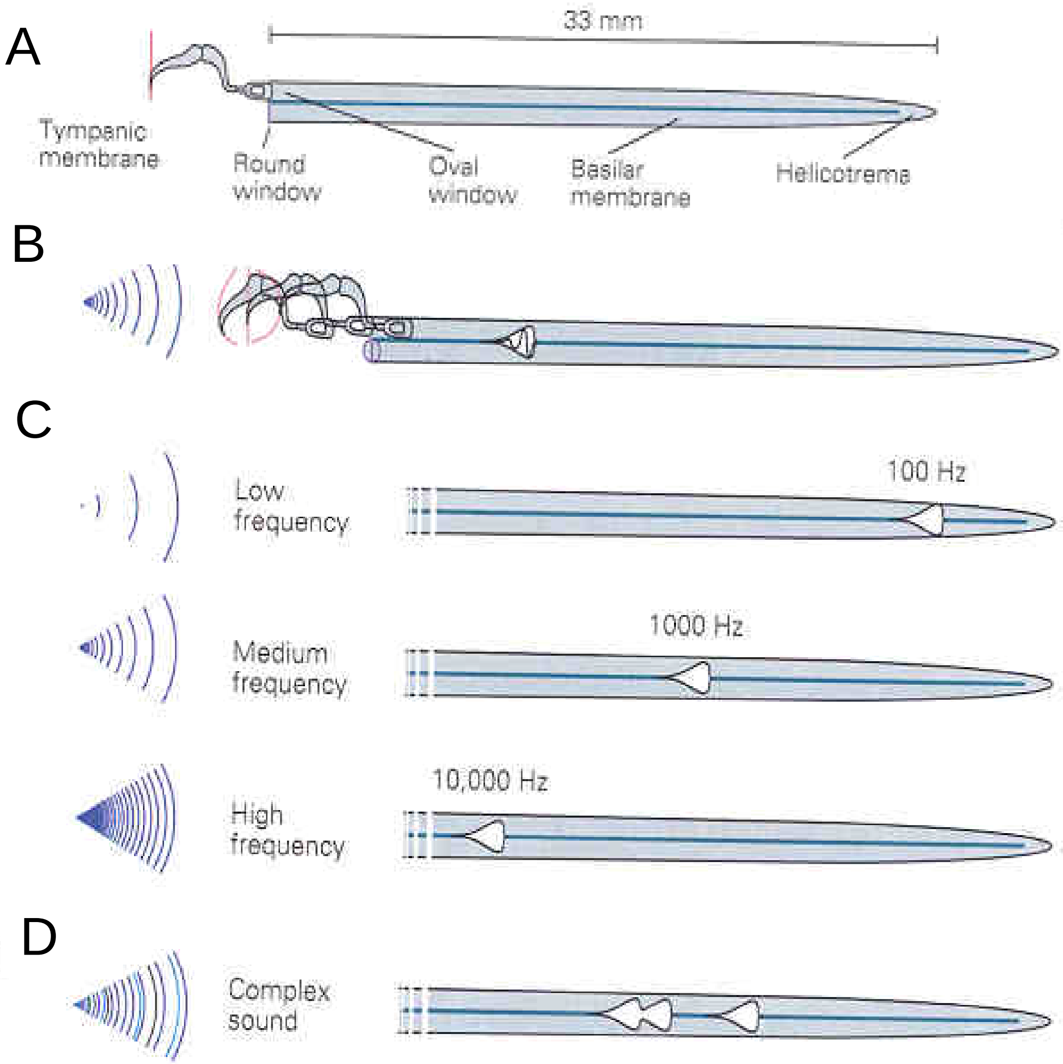
- **Electrochemical sensor**
  - Biopotential sensors : ECG / EMG /EEG
  - Blood Gases and pH sensors
  - Bioanalytical sensors : Enzyme-based or Microbial biosensor
- **Mechanoelectrical sensor**
  - Hair-cell
  - Displacement transducer
  - Temperature sensor
- **Optical sensor**
  - SPR
  - Optical Fiber

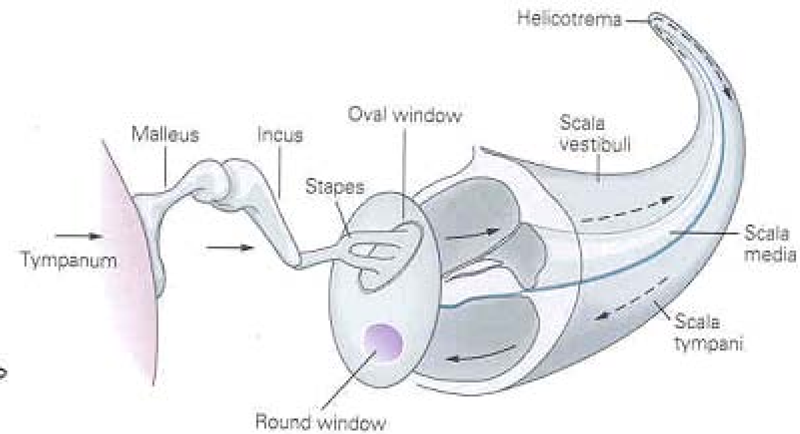
2. Mechanoelectrical sensor

2.1 Hair-cell as a natural transducer

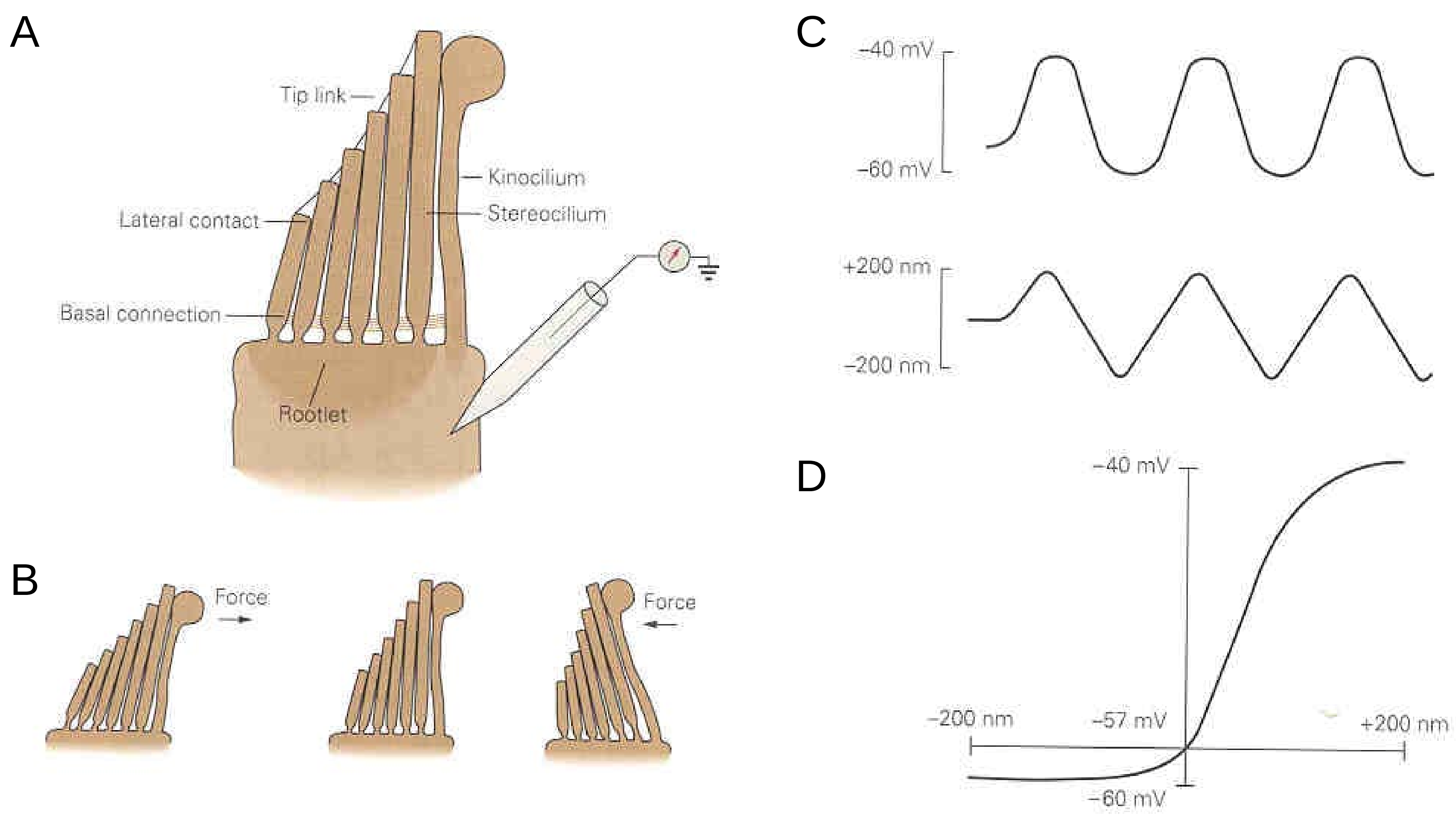


Motion of the Basilar Membrane

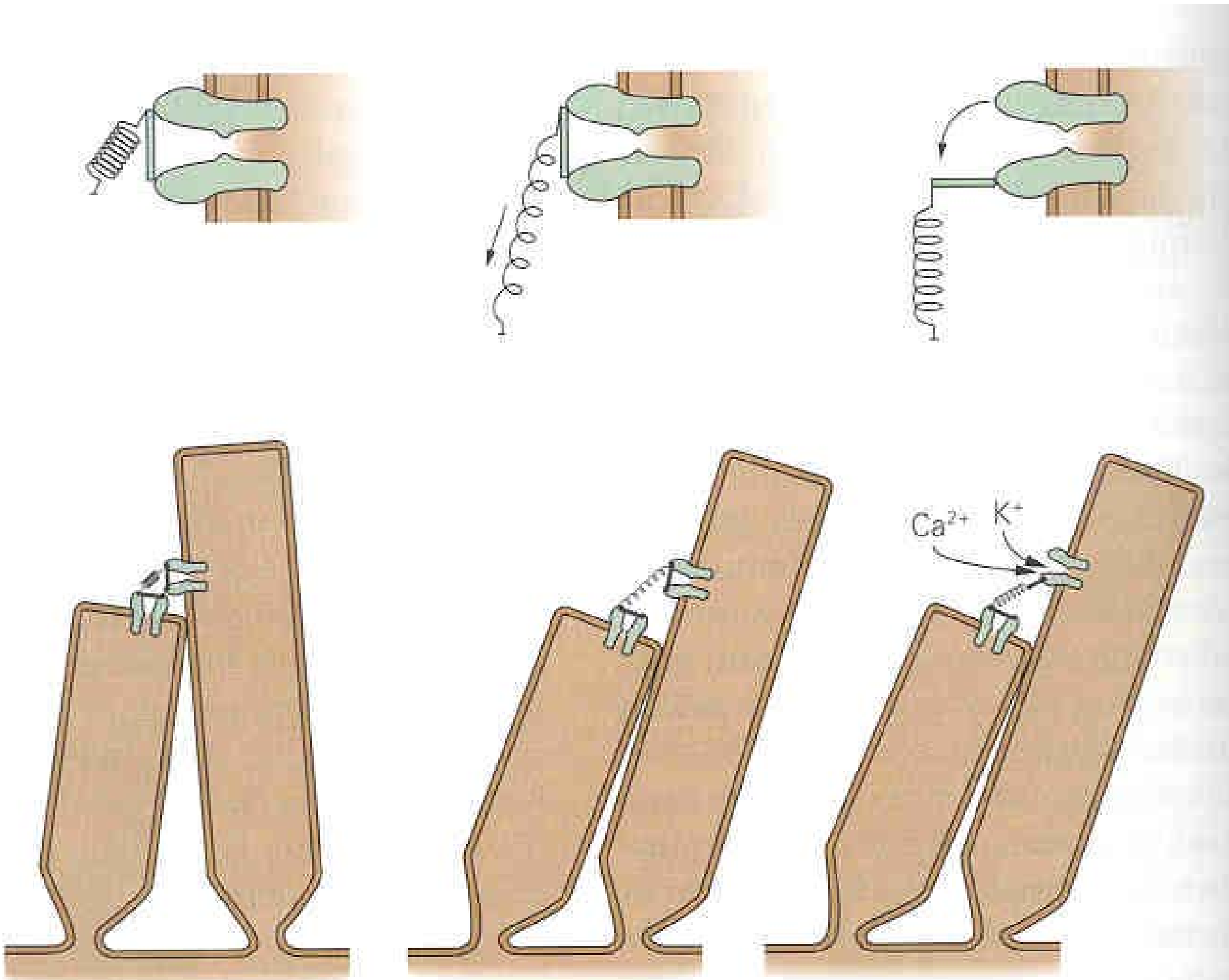




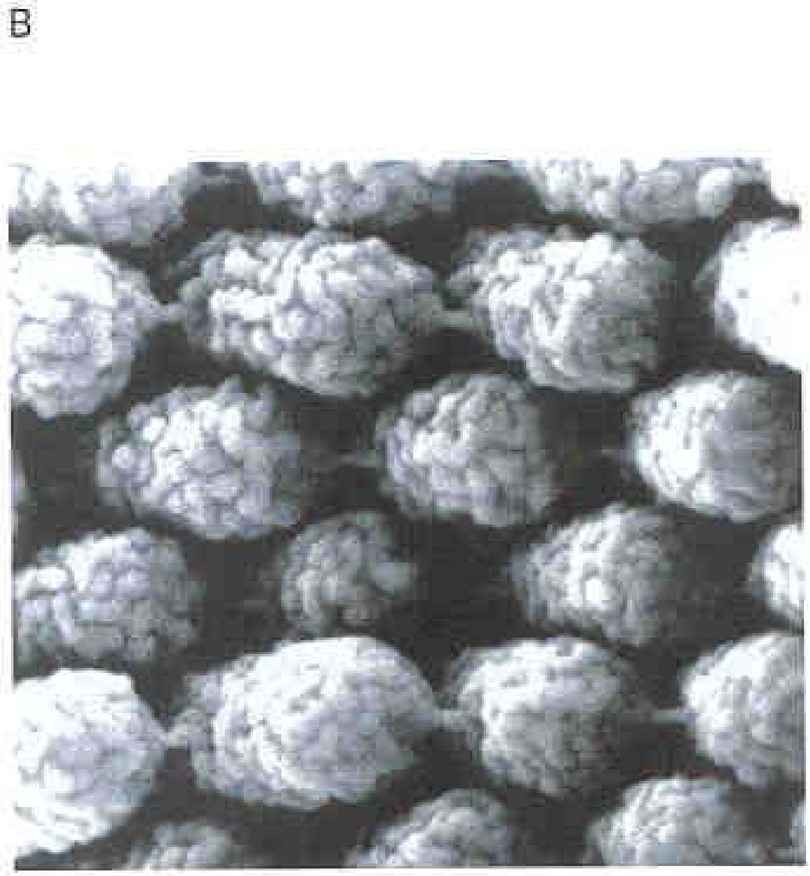
Mechanical sensitivity of a Hair Cell

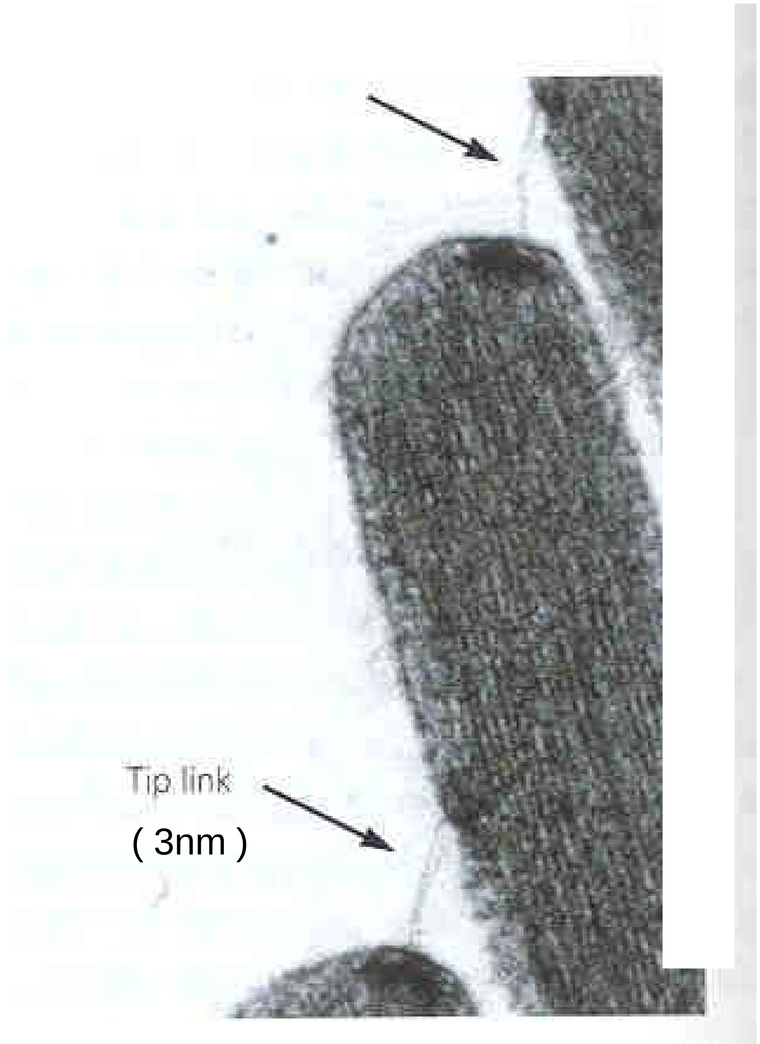


The mechanism of mechanoelectrical transduction by Hair Cell



A Scanning Electron Micrograph of the Stereocilia





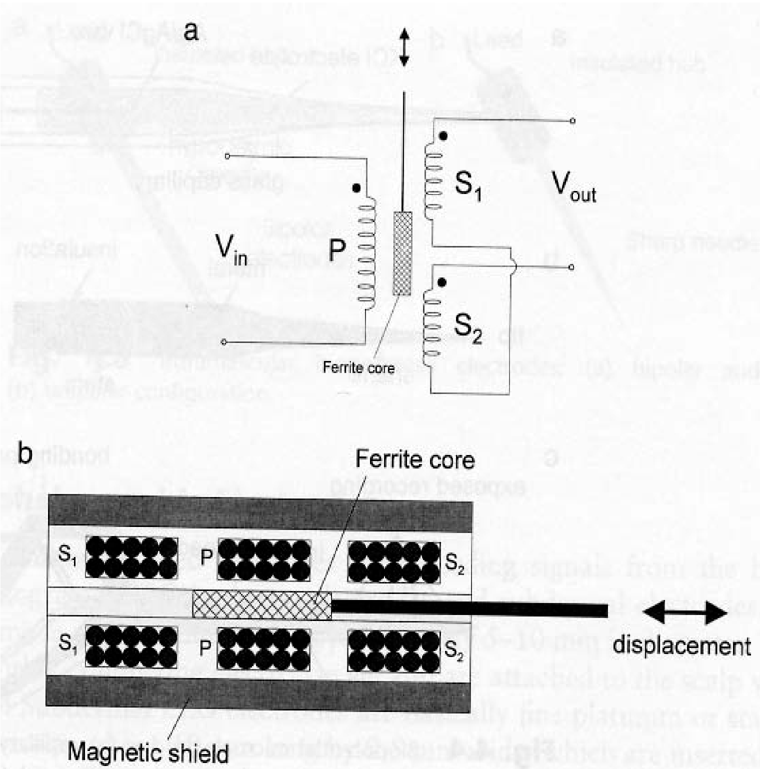
2.2 Displacement Transducers

- 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



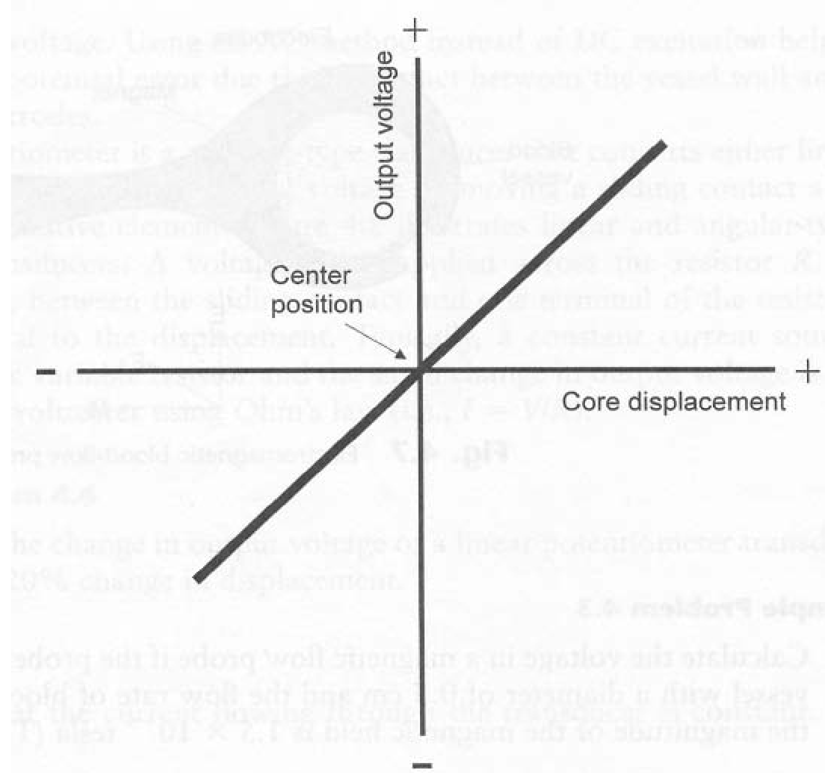
LVDT transducer

(a) electric diagram and

(b) cross-section view

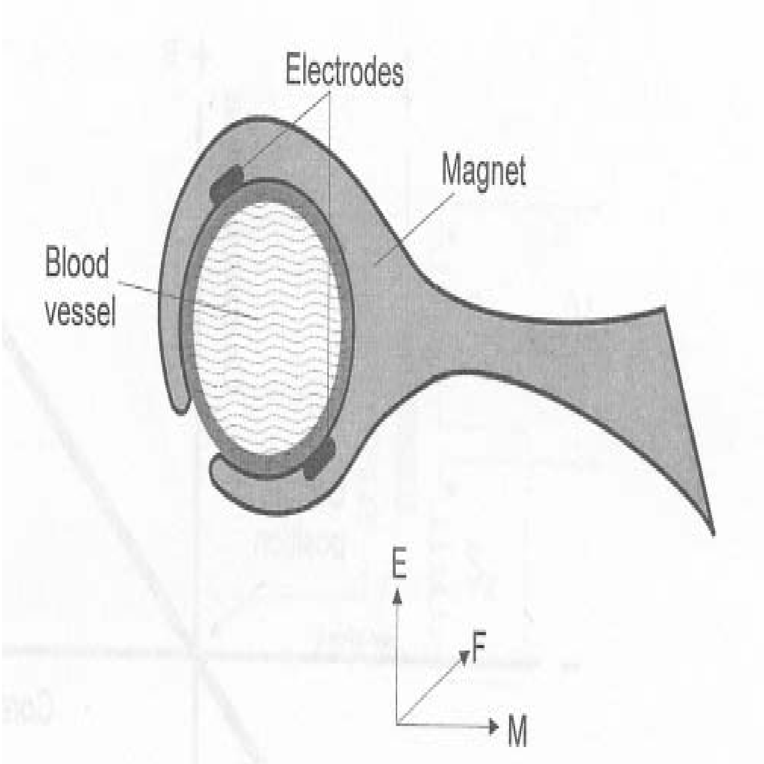
(c) P :primary coil

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 $\vec{F}$

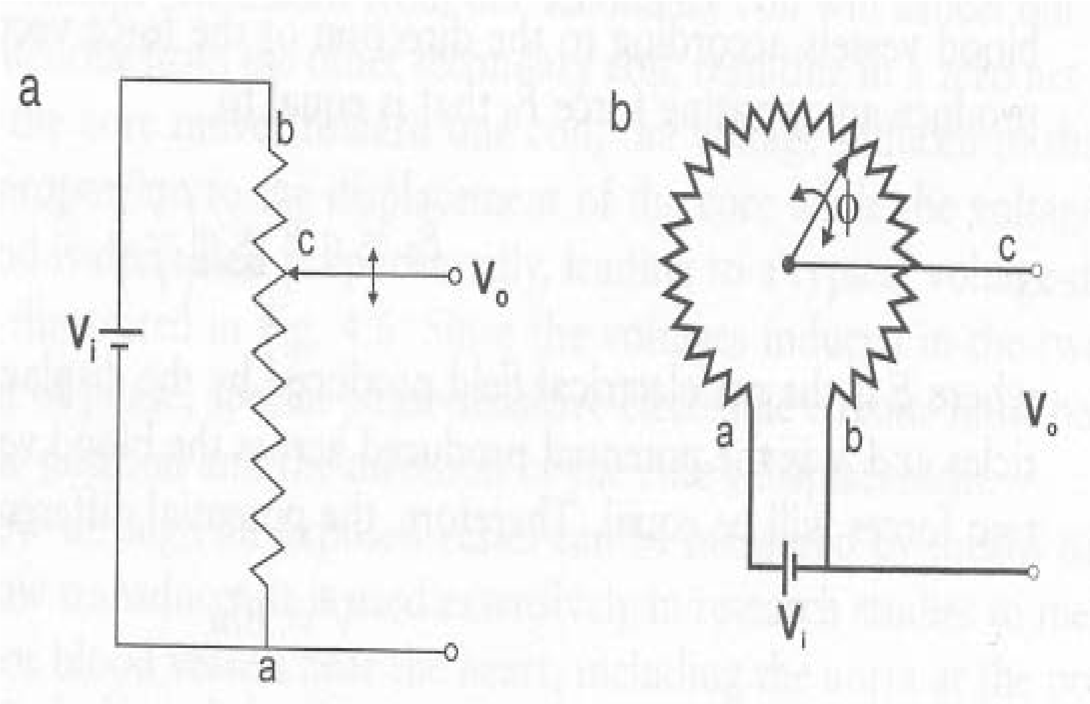
$$\vec{F} = q(\vec{u} \times \vec{B})$$

    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

$$V = Blu$$

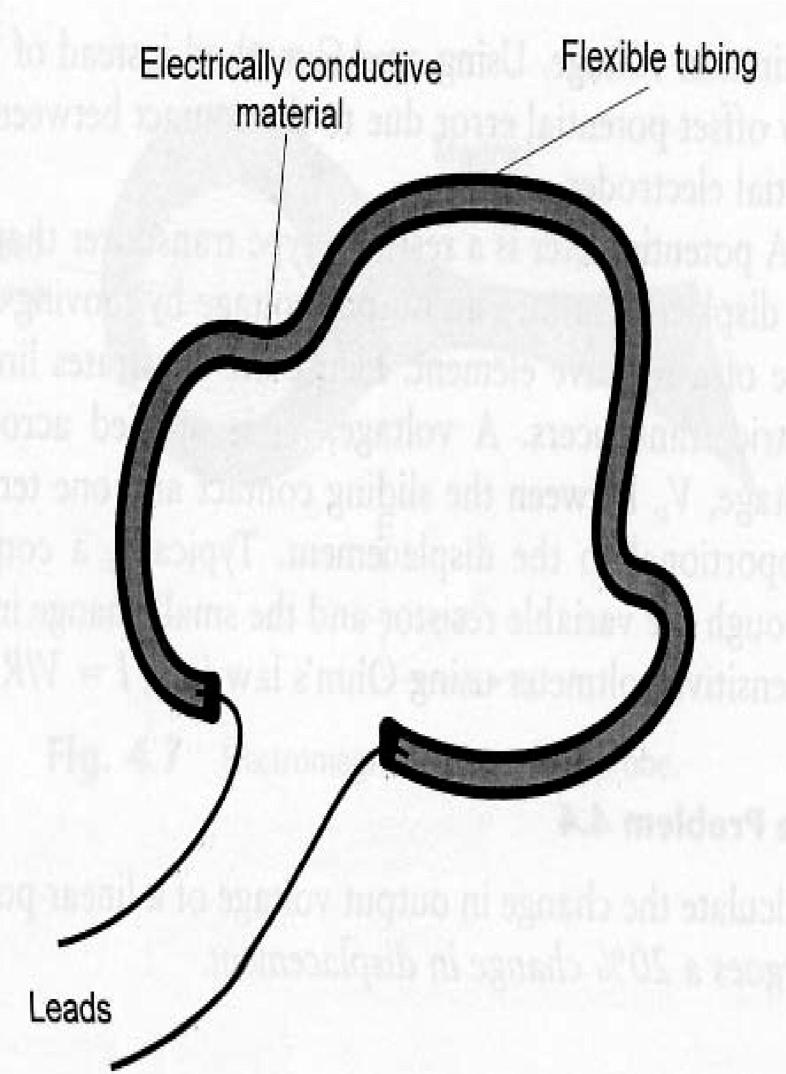


Linear translational (a)and angular (b)displacement transducers.

Potentiometer,Resistive-type transducer.

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

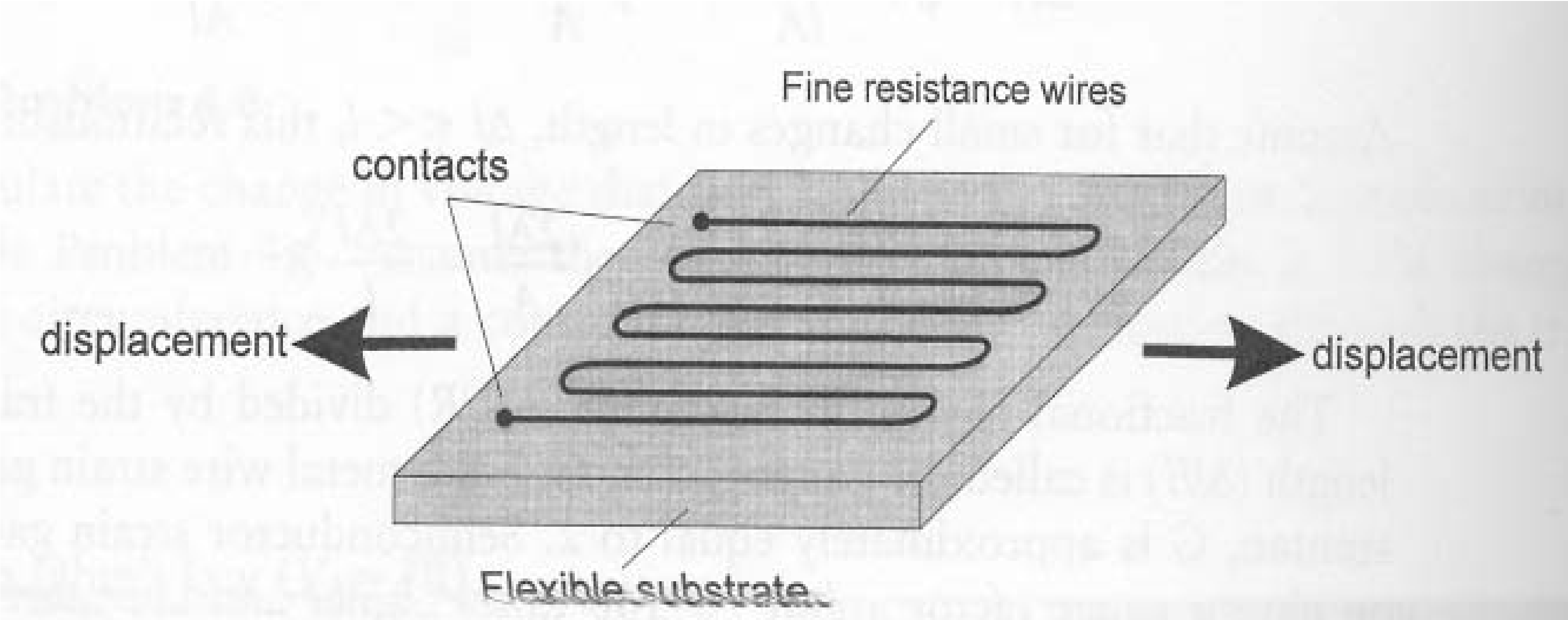
Plethysmography: volume-measuring method



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

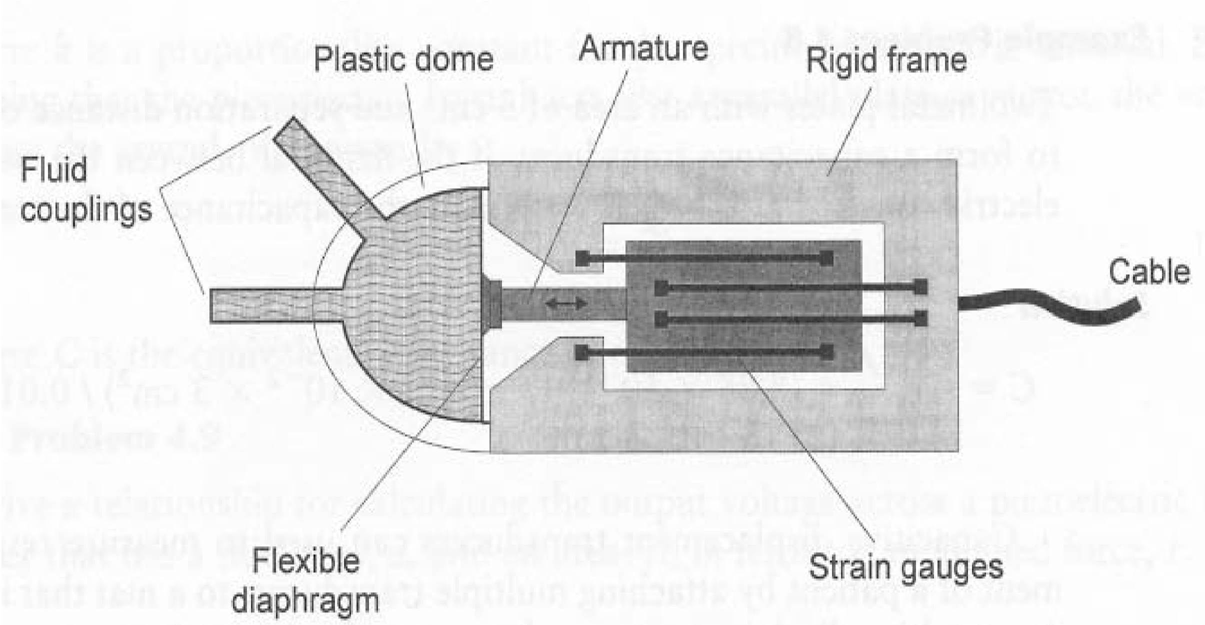
$$R = \rho\left(\frac{l}{A}\right)$$



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.



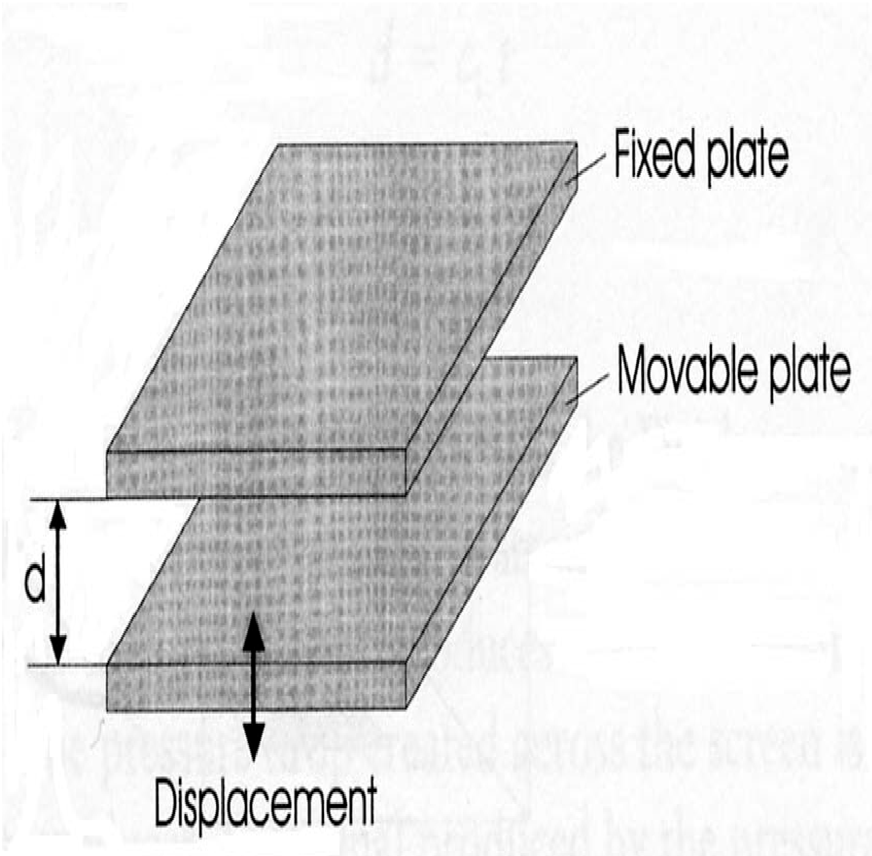
Resistive strain gauge

(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.



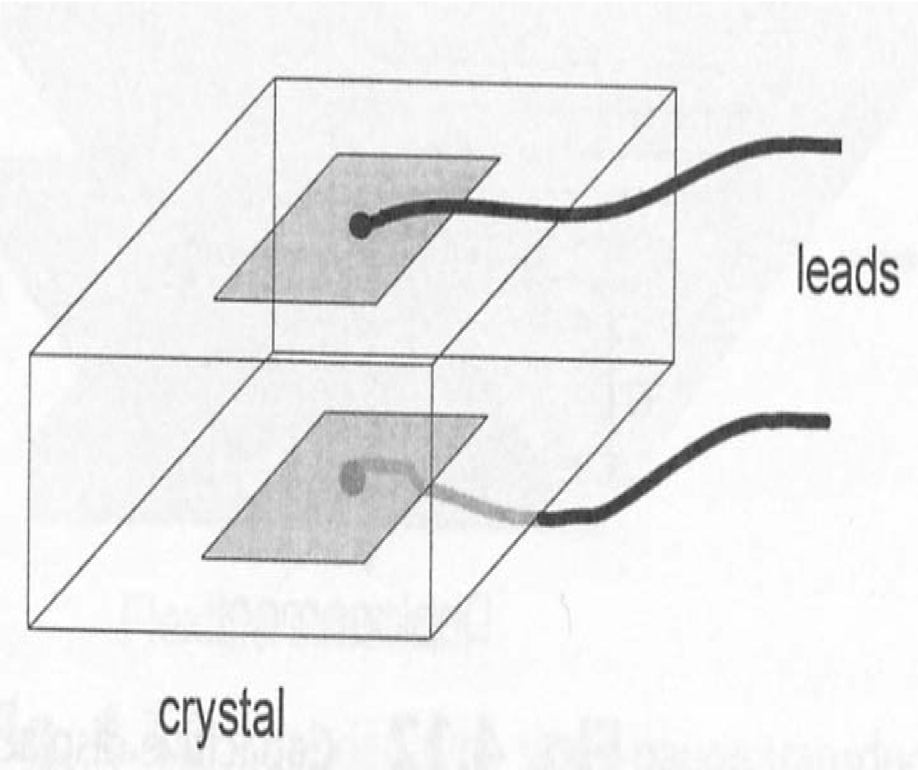
capacitive displacement transducer

The capacitance C between two equal size parallel plates

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

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)



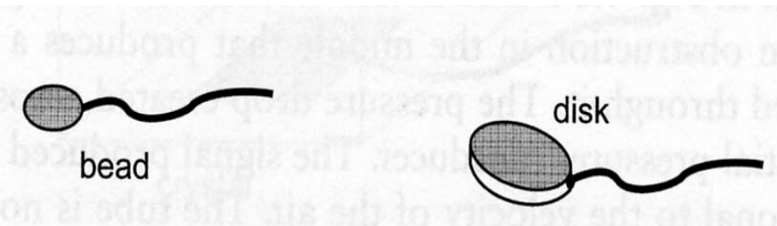
A piezoelectric transducer consists of a small crystal (usually quartz) that contracts if an electric field (usually in the form of a short voltage impulse) is applied across its plates.

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.

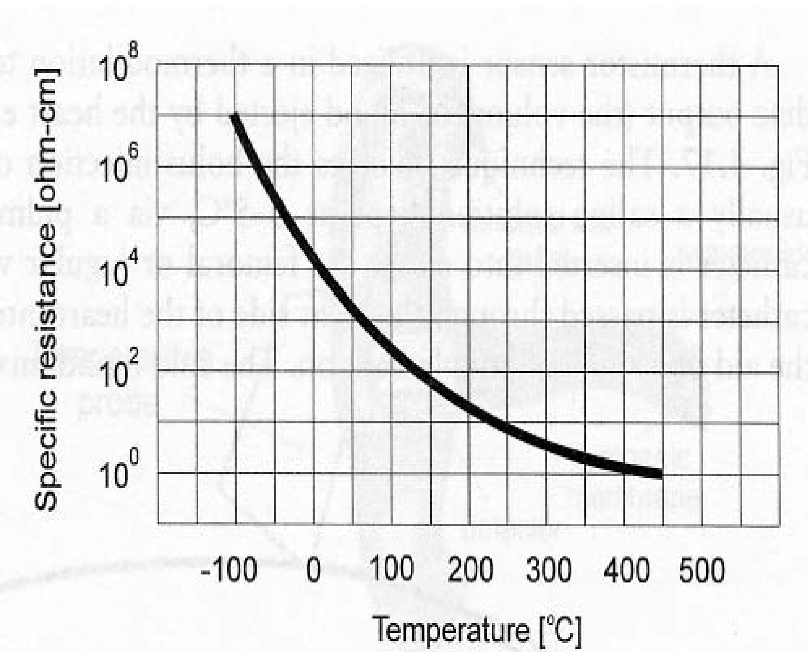
2.3 Temperature measurement

- 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.

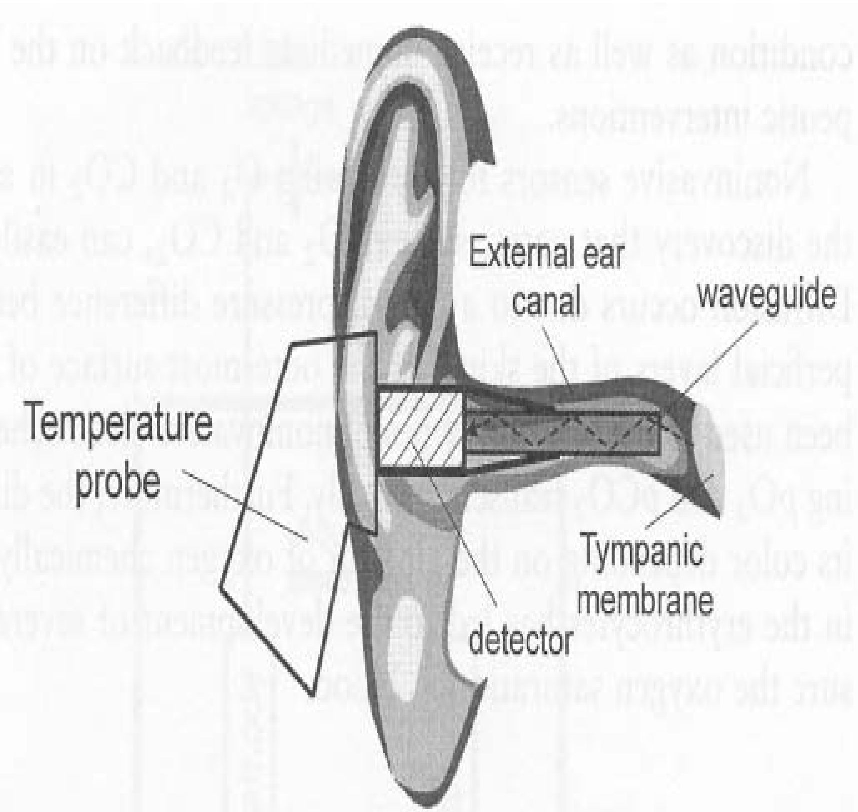
$$R_T = R_0 \exp[B(1/T - 1/T_0)]$$

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.

Type of biosensor

- **Electrochemical sensor**
  - Biopotential sensors : ECG / EMG /EEG
  - Blood Gases and pH sensors
  - Bioanalytical sensors : Enzyme-based or Microbial biosensor
- **Mechanoelectrical sensor**
  - Hair-cell
  - Displacement transducer
  - Temperature sensor
- **Optical biosensors**
  - SPR
  - Optical Fiber

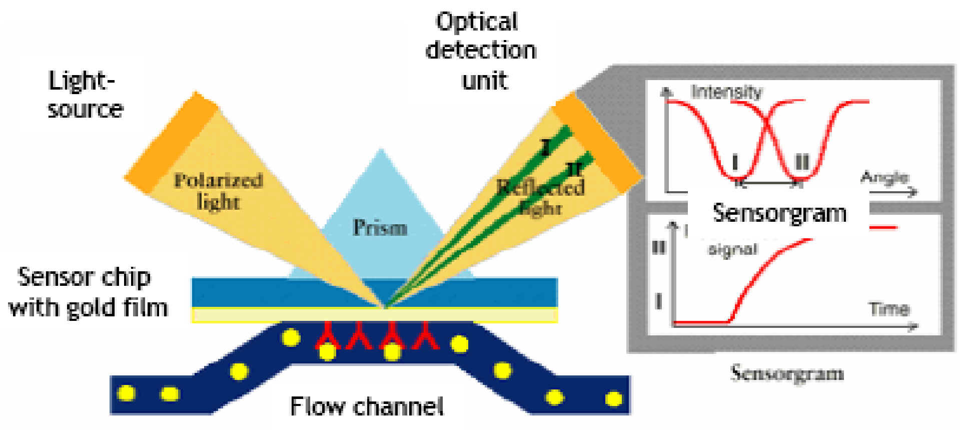
3. Optical Biosensors

3.1 Surface Plasmon Resonance(SPR)

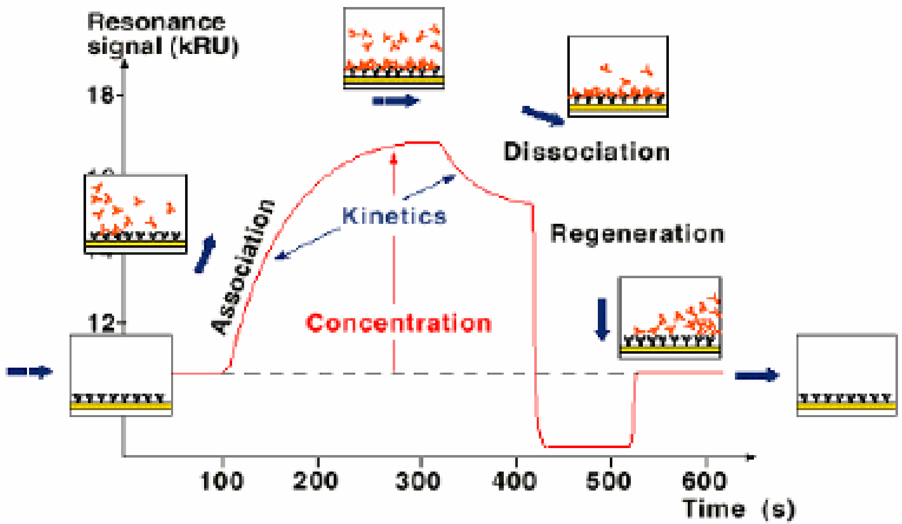
- When a light beam impinges onto a metal film at a specific (resonance) angle, the surface plasmons are set to resonate with the light. The resonance results in the absorption of light.
- When the SPR occurs within the spread angles, a dark line will appear in the band because of the absorption of light energy.
- Binding of biomolecules (antigen or antibody) on the metallic film as well as molecular interactions (antigen/antibody complex) will induce a change in the refractive index (RI) near the surface, thus giving rise to a shift of the resonance angle.
- SPR is an useful optical biosensor, because it is highly sensitive (10^{-4} to 10^{-6} RI units) and very local (10-100nm from sensing surface).

- 참고: http://biosensingusa.com/biosensing_instrument_spr_animation.html

SPR : concept



*The **SPR angle** is sensitive to the mass concentration of molecules close to the sensor chip surface.*

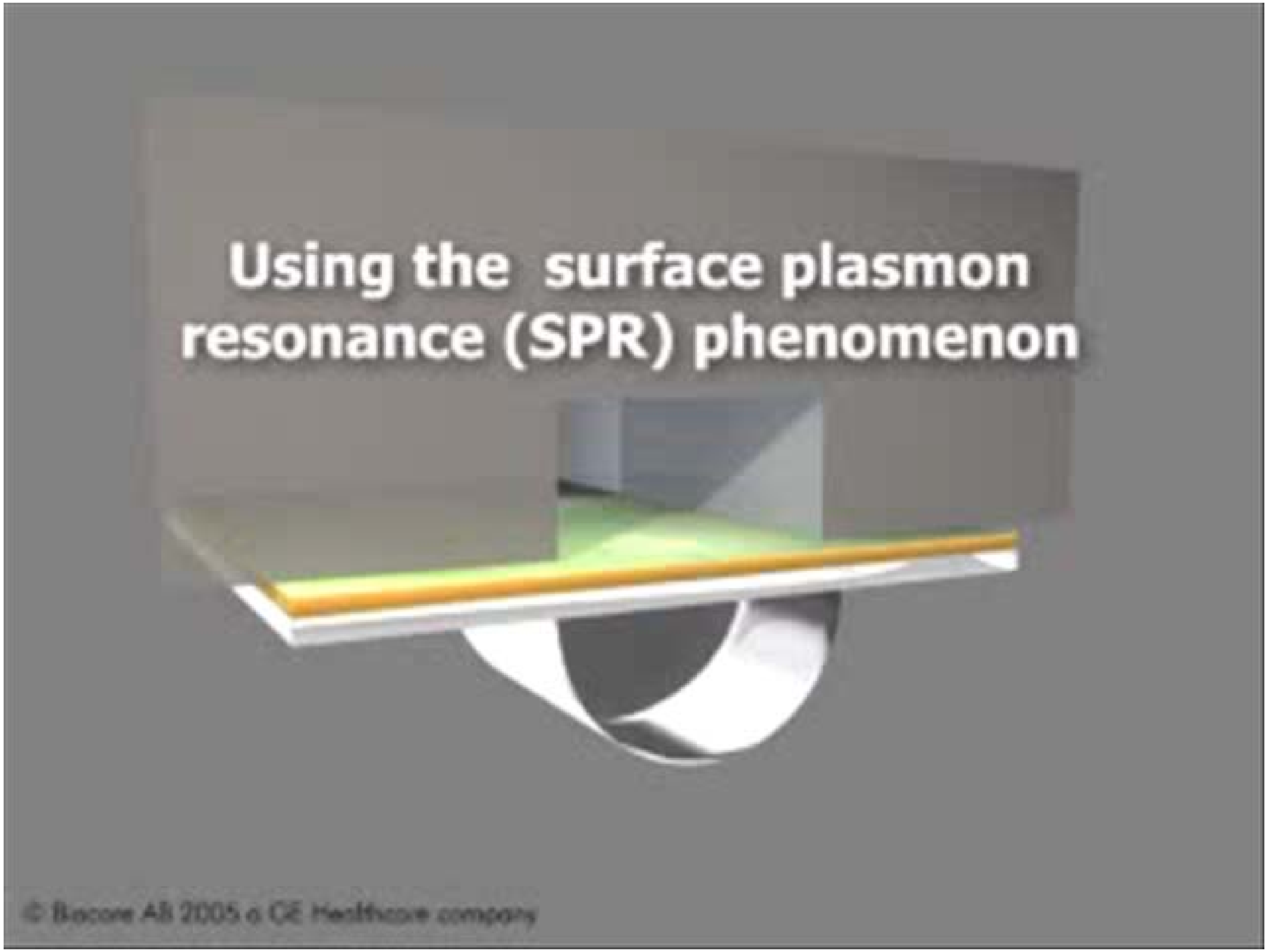


Sensorgram *A response of 1000 RU corresponds to a change in surface concentration of 1ng/mm².*

<u>Principle of immunoassays:</u>

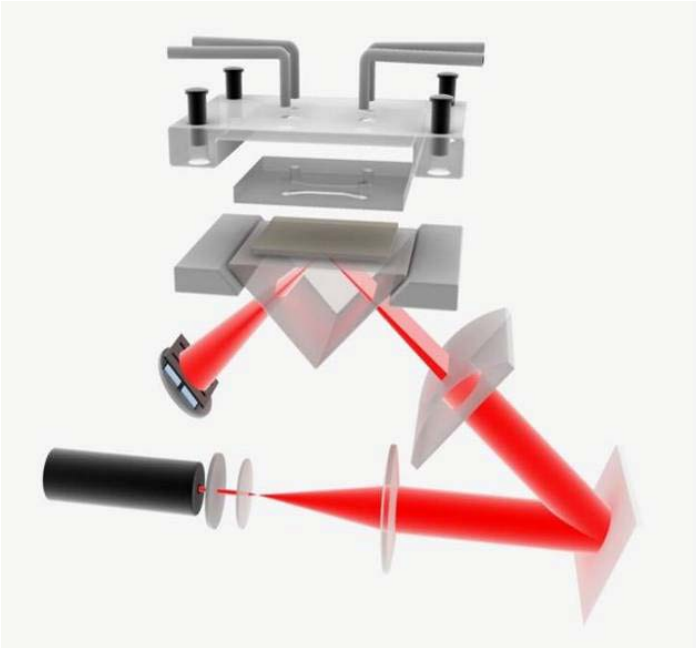
- *Reactions between two protein molecules can be extremely specific.*
- *One type of molecule (antibody) can be immobilised on gold sensor surface.*
- *The second (antigen) will bind changing the refractive index .*
- *This change is detected by changed angle (or wavelength) of surface plasmon resonance.*

SPR : concept



http://www.biacore.com

Features of SPR biosensor



•No Labeling

– No fluorescence dyes

• Real Time Measurement

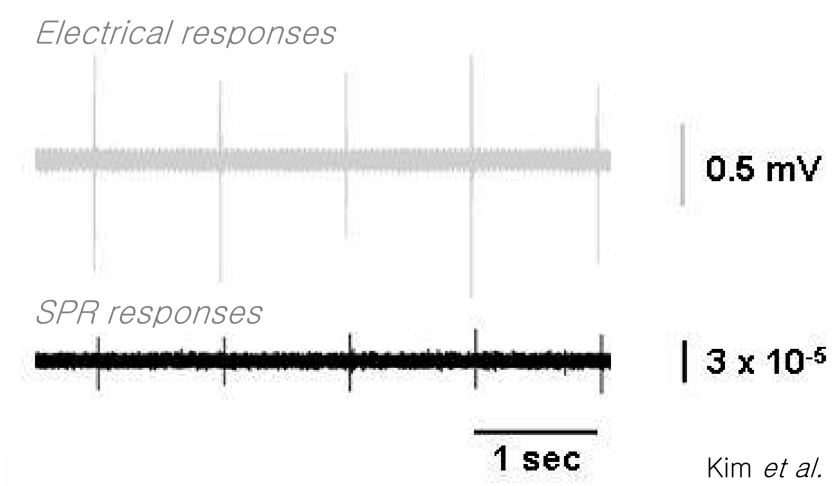
– Insight to dynamic nature of binding system and layer formation

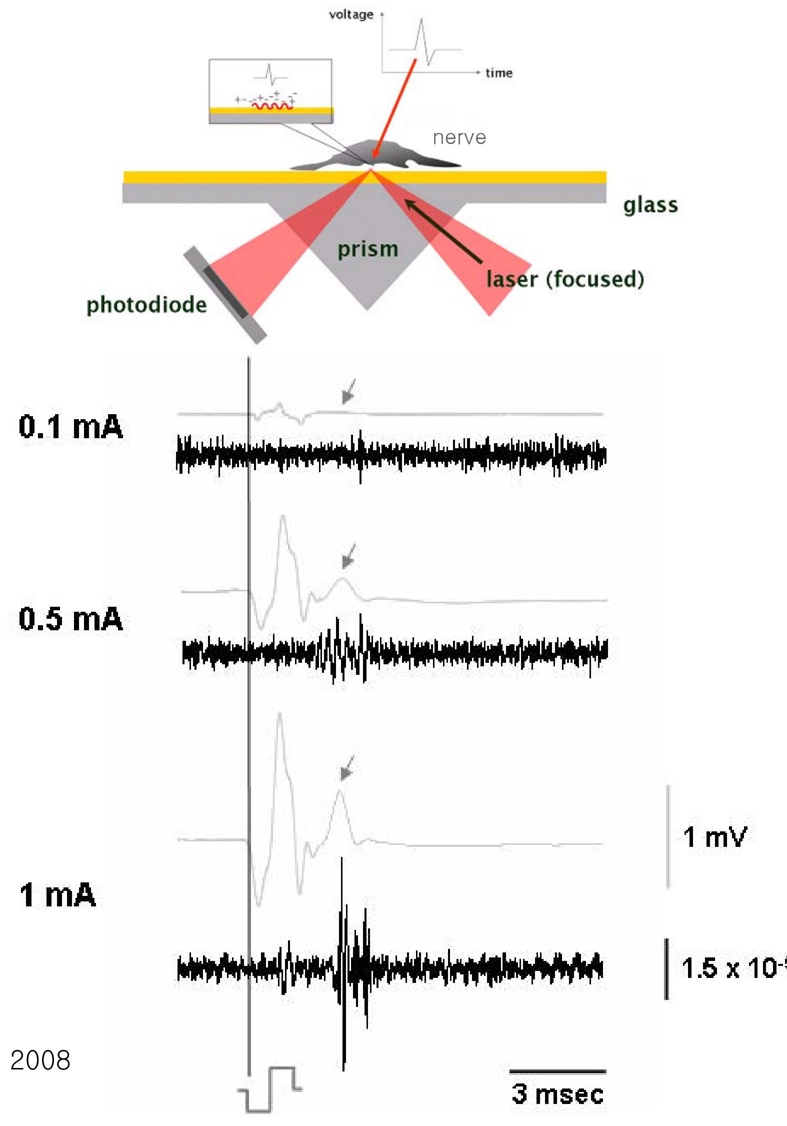
• Exceptional sensitivity within Localized Volume

– Small quantities of purified reagents are required

Extension of application

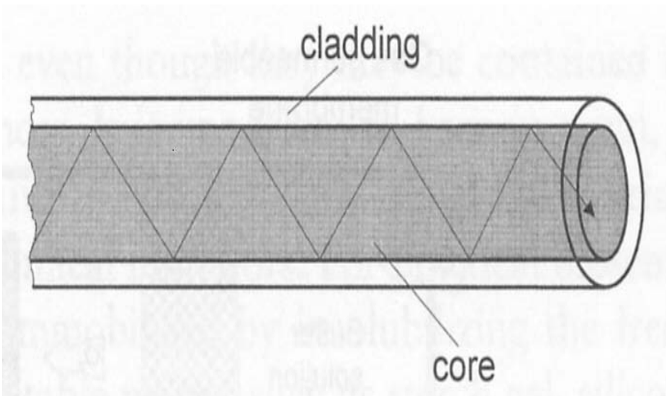
- Both the electrical (gray traces) and the SPR responses (black traces) increased in magnitude when the stimulation intensity was increased when supra-threshold stimulation currents were applied.
- The SPR responses were highly correlated with simultaneously recorded electrical responses.



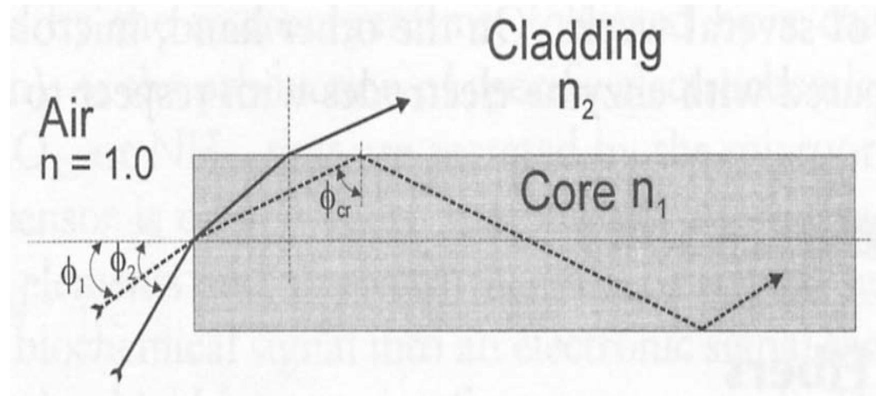


Kim *et al.* Opt. Letters 2008

3.2 Optical Fibers



principle of optical fibers.



Optical fiber illustrating the incident and refracted light.

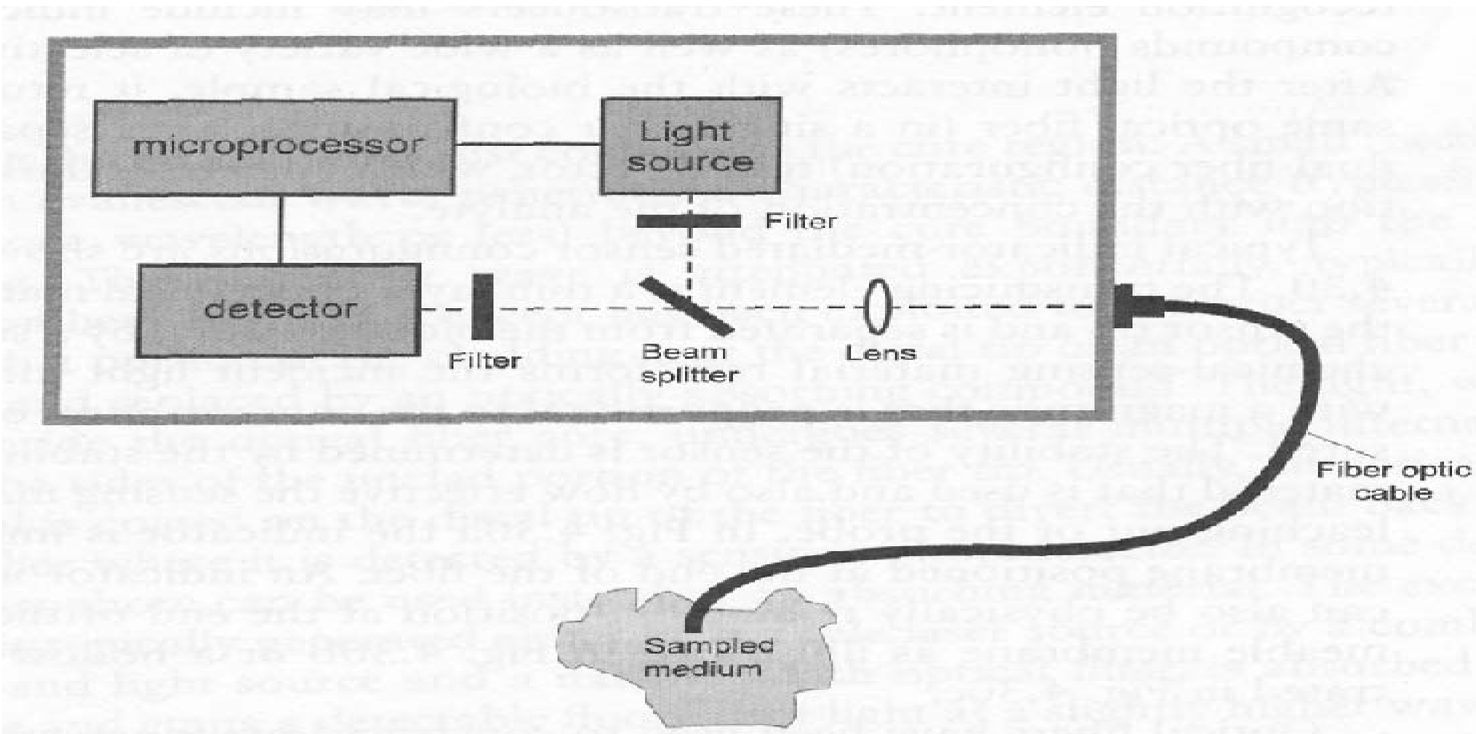
The solid line shows the light ray escaping from the core into cladding. The dashed line shows the ray undergoing total internal reflection inside the core.

- 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.

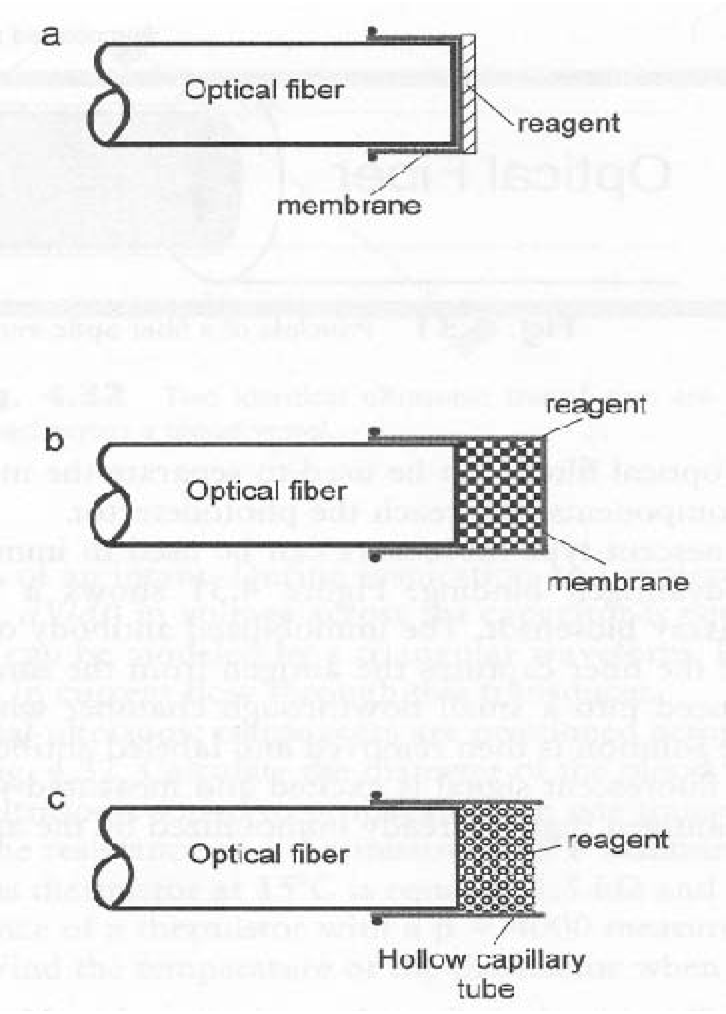
Sensing Mechanisms of Optic Fiber



General principle of a fiber optic-based sensor:

the common feature of commercial fiber optic sensors for blood gas monitoring

Indicator-Mediated fiber Optic Sensors



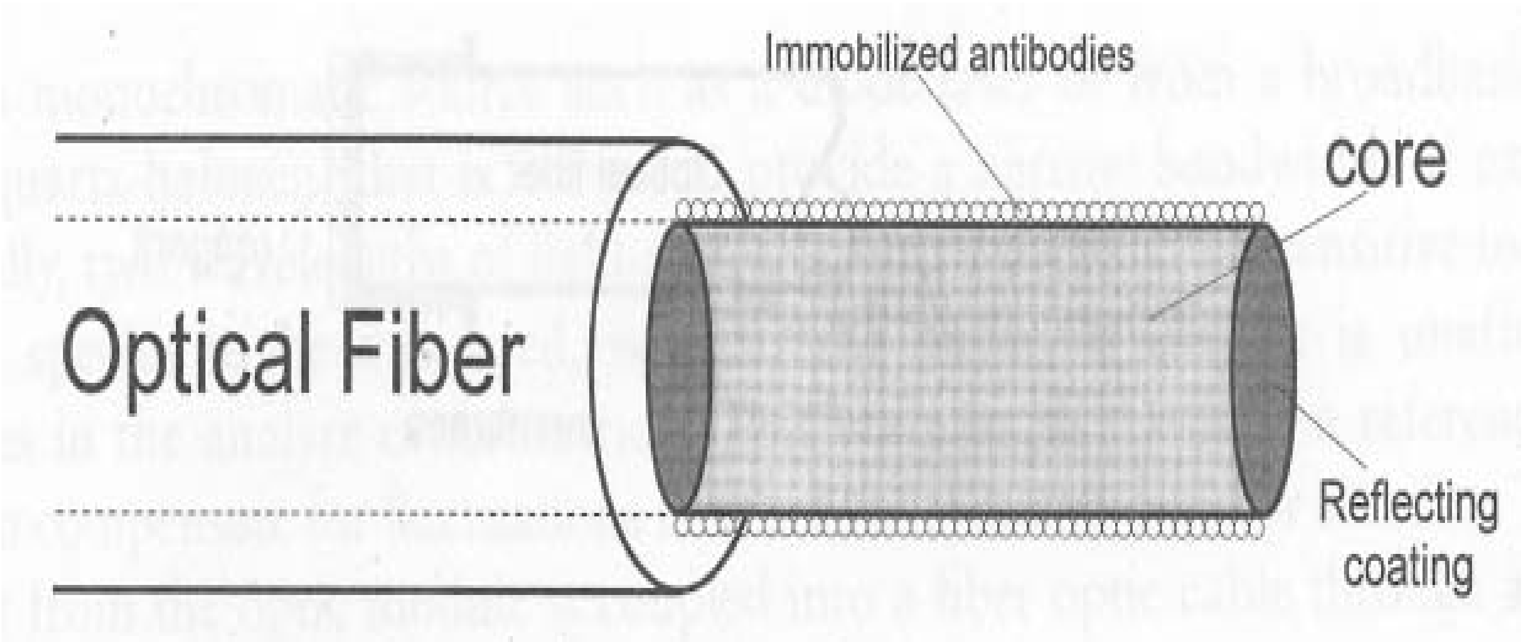
The return light signal has a magnitude that is proportional to the concentration of the species to be measured.

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