Introduction to Biomedical Engineering

Device/Instrumentation II – biomedical sensors

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Outline

- Chapter 9: Biomedical sensors
  - Biopotential measurements
  - Physical measurements
  - Chemical measurements
    - Blood gases and pH sensors
  - Biosensors
    - Enzymatic biosensors
    - Affinity biosensors

Introduction

- Transducer: convert energy from one form to another
- Integrated with other parts to “read” out the signal (electrically, optically, chemically)
- Some are used *in vivo* to perform continuous, invasive or non-invasive monitoring of critical <u>physiological</u> variables
  - pressure, flow, concentration of gas
- Some are used *in vitro* to help clinicians in various diagnostic procedures
  - electrolytes, enzymes, metabolites in blood

Introduction (cont.)

- in vivo: inside a living body (human or animal)
- ex vivo: outside the living body
- in vitro: in a test tube
- in situ: right in the place where reactions happen (could be in the cells, tissue, test tube, etc.)

Physical measurements

- Displacement
  - Inductive
  - Resistive
  - Capacitive
  - Ultrasonic
- Air flow
- Temperature

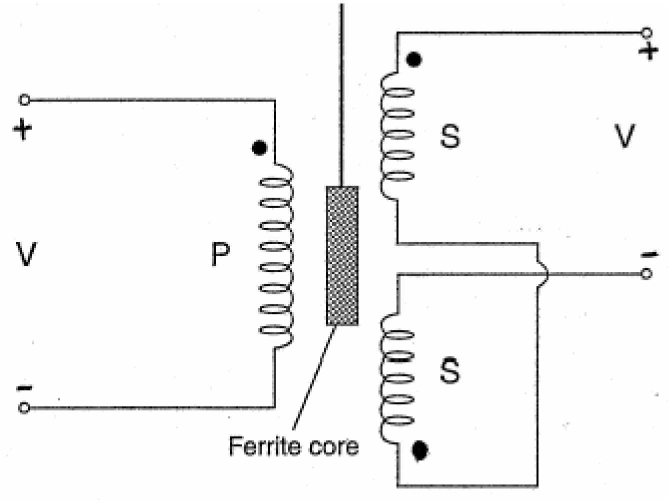
Displacement transducers

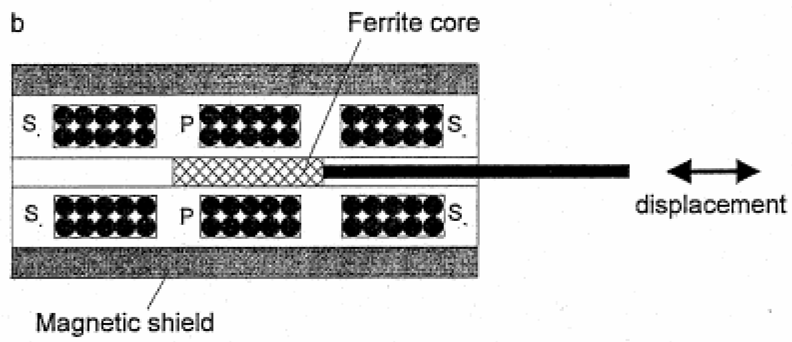
Linear Variable Differential Transformer (LVDT)

The primary coil P is excited by an AC current

The induced potentials at the 2 secondary coils are canceled due to the opposite polarities

When the core moves toward one coil, the induced potential in the coil increases and the voltage in the other coil decreases



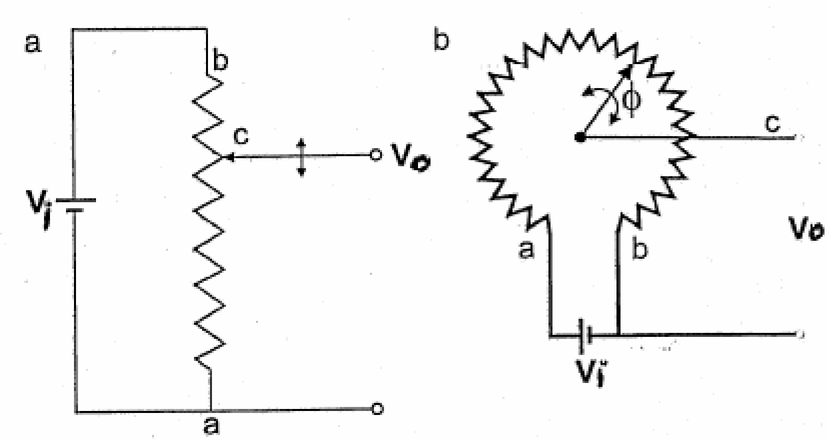


Induced voltage $\propto$ Displacement

Displacement transducers

Potentiometer: resistance is proportional to position

If the current through the resistor is constant, the displacement (linear c angular) will be proportional to



$$\Delta V = I\Delta R$$

Displacement transducers

<u>Strain gauge</u>: measures a <u>small change</u> in the length of an object as a result of an applied force

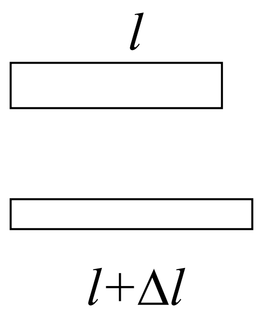
$$R = \rho \frac{l}{A}$$

Resistance of a conductive materiel with length l and cross-sectional area A. ρ is a constant (resistivity)

The fractional change in length of an object is called strain

$$S = \frac{\Delta l}{l}$$

Now consider a metal wire as a strain gauge



Original

Stretched

$$\Delta R = \rho \frac{l + \Delta l}{Al/(l + \Delta l)} - \rho \frac{l}{A} \approx 2 \frac{\Delta l}{l} R$$

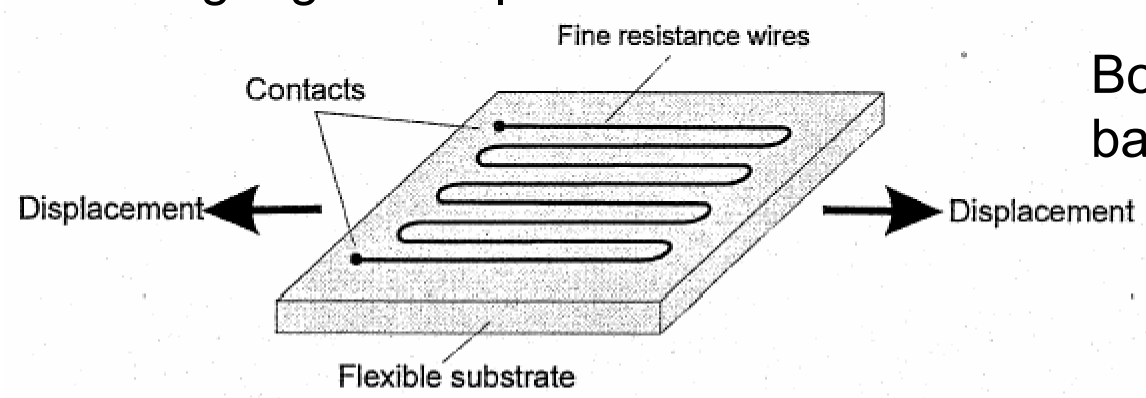
The gauge factor G

$$G = \frac{\Delta R / R}{\Delta l / l} = 2$$

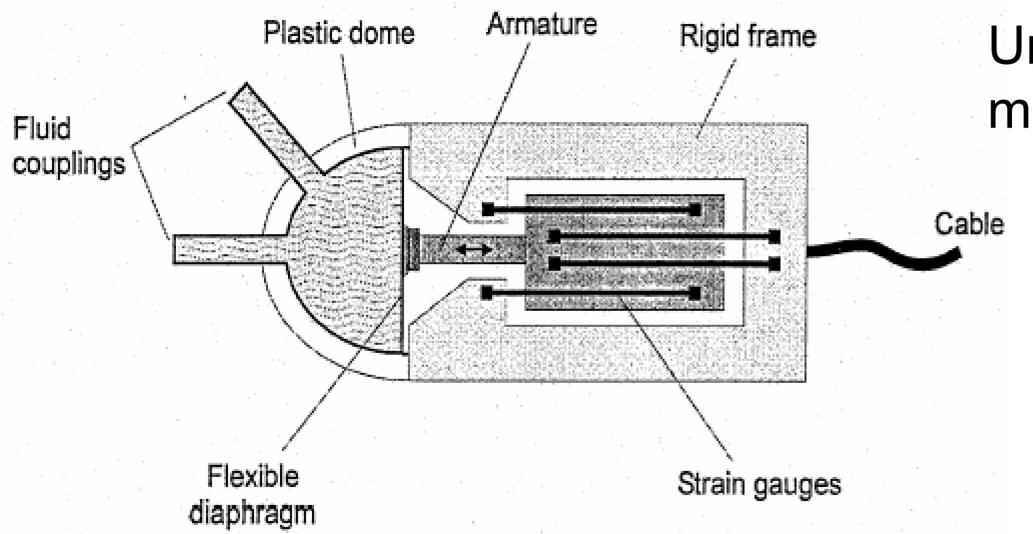
For silicon strain gauges, G > 100 (much more sensitive than metal)

Displacement transducers

Strain gauge examples



Bonded to a semiflexible backing material



Unbonded configuration for measuring blood pressure

The change in resistance is quite small ⇒ amplifiers

Strain gauges are very sensitive to temperature ⇒ temperature compensation

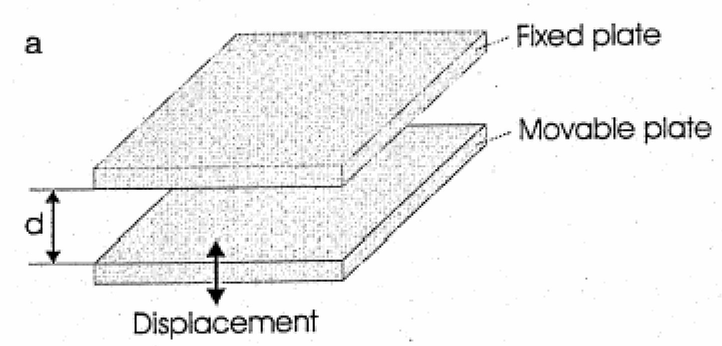
Displacement transducers

Capacitive: change in distance between two parallel plates (an insulating material sandwiched in the middle) results in a change in capacitance

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

A: area
d: distance between two conductors

where ε_0 is the permittivity of vacuum = 8.85×10^{-12} F/m
ε_r is dielectric constant of the insulating material



Displacement transducers

Piezoelectric transducer: certain crystal (such as quartz) generates a small electric potential when it is mechanically strained. The charge Q induced at surface is proportional to the applied force F

$$Q = kF$$

(k is a constant and specific to the material)

Then the voltage across the crystal is

$$V = \frac{Q}{C}$$

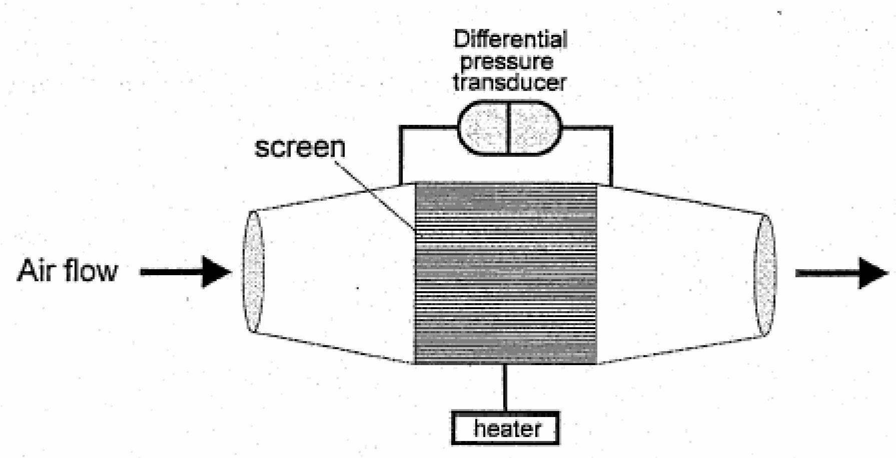
Not used for measuring DC (static) displacement due to internal leakage resistance that dissipates the surface charge

The inverse reaction can also happen $\Rightarrow$ apply an voltage across the crystal, and the crystal expands or contracts

In fact, piezoelectric transducers are often used to generate high frequency vibrations such as ultrasonic pulse transducers and resonant oscillators

Air flow

Fleish pneumotachometer

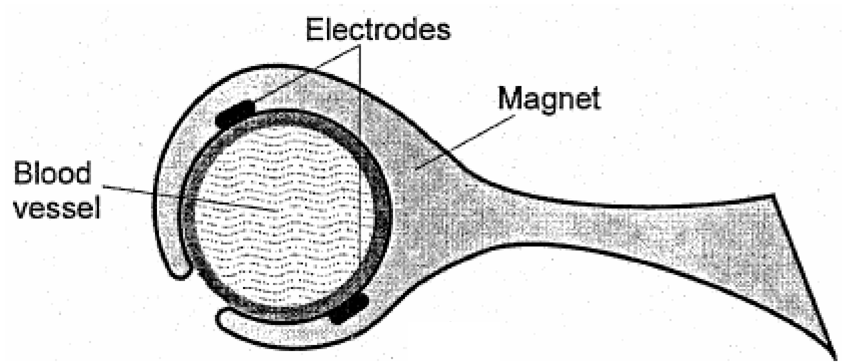


Flow rate $\propto \Delta P$

Pressure is measured at both sides of the resistive screen

The screen obstruction provides some resistance to the air flow and therefore generates pressure drop across the screen

Blood flow



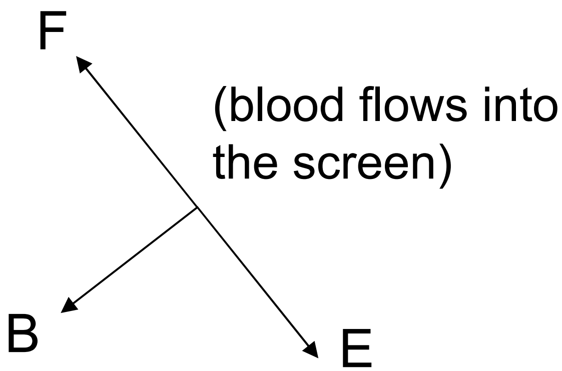
Apply a uniform magnetic field B across blood vessel

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

If velocity of blood flow is v, F is force experienced by charged particles in blood

This force causes movement of charges $\Rightarrow$ distribution of charges generates an electric field E

$$\vec{E} = \frac{V}{d}$$ d: diameter of blood vessel



For charged particles, there is a second force qE, at equilibrium:

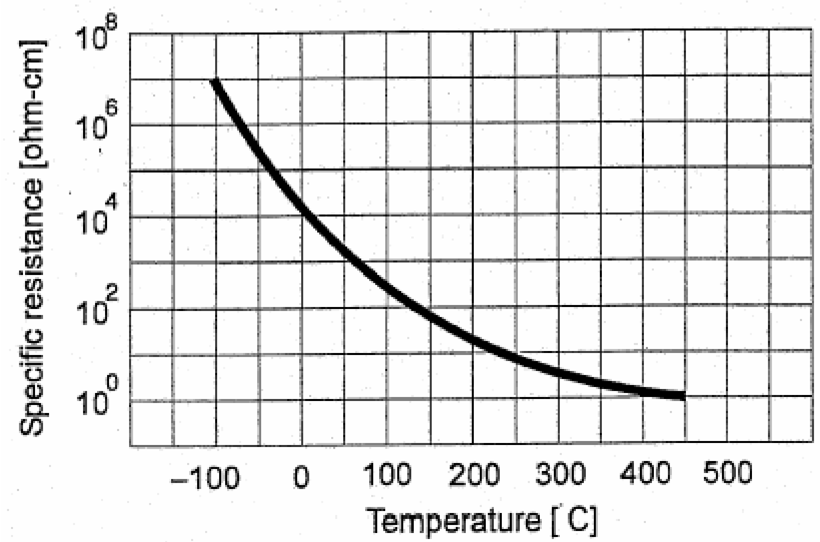
$$qvB = qE = q\frac{V}{d} \qquad \Rightarrow v = \frac{V}{Bd}$$

Temperature transducer

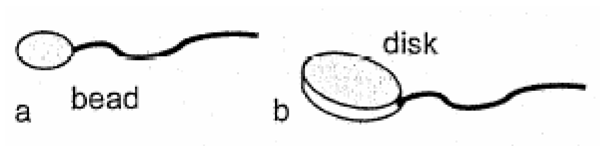
Thermistor: resistance is a function of temperature

$$R_T = R_0 e^{\beta(1/T - 1/T_0)}$$

where R_0 is the resistance at a reference temperature, T_0, and R_T is the resistance at temperature T. β is a material-specific constant. Both temperatures are expressed in degrees K

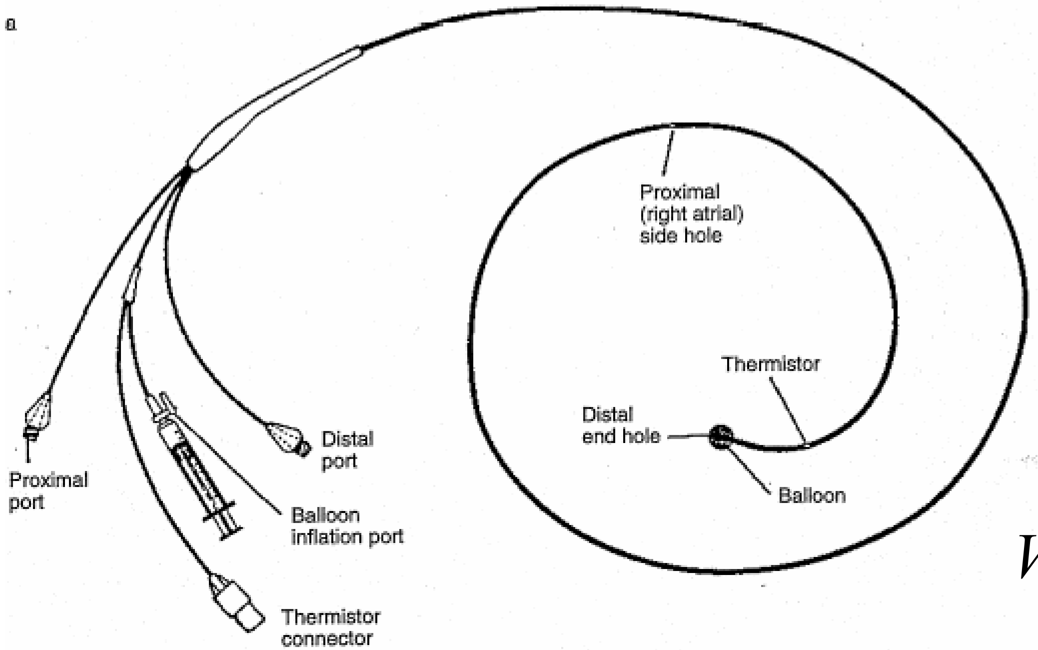


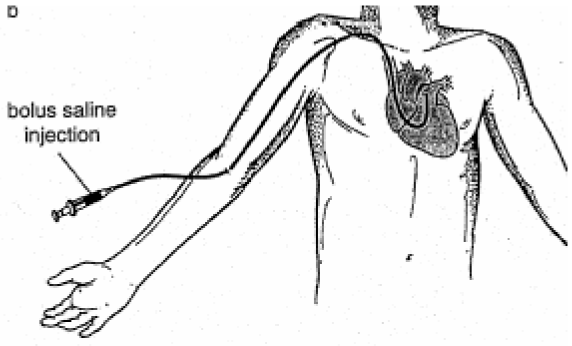
Common shapes of thermistors



The size and mass of a thermistor probe must be small to produce a rapid response to temperature variations

Cardiac output measured by thermodilution





- Inject cold saline into the right atrium (intravenous catheter)
- Measure temperature at the pulmonary artery over time
- Conservation of energy: The total heat content of the injected saline will be

$$V_i \Delta T_i \rho_i c_i = \rho_b c_b \int_0^T flow \cdot \Delta T_b(t) dt$$

Average blood flow (m^3/s)

ρ: density (kg/m^3)
c: specific heat capacity (J/kgK)
V_i: injection volume

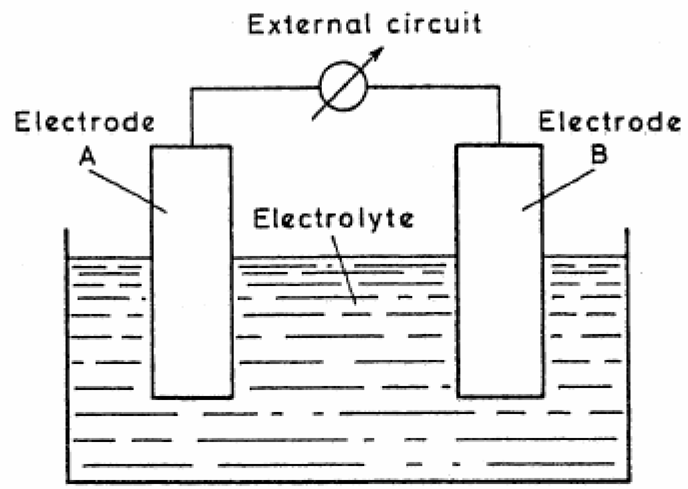
Chemical measurements

Important analytes and their normal ranges in blood, which indicate the physiological status of the body: gas pressure and related parameters, electrolytes, and metabolites

Blood Gases and Related Parameters		Electrolytes		Metabolites	
P_{O_2}	80–104 mm Hg	Na^+	135–155 mmol/l	Glucose	70–110 mg/100 ml
P_{CO_2}	33–48 mm Hg	K^+	3.6–5.5 mmol/l	Lactate	3–7 mg/100 ml
pH	7.31–7.45	Ca^{2+}	1.14–1.31 mmol/l	Creatinine	0.9–1.4 mg/100 ml
Hematocrit	40–54%	Cl^-	98–109 mmol/l	Urea	8–26 mg/100 ml
Total hemoglobin	13–18 g/100 ml				
O_2-saturation	95–100%				

Electrochemical cells as sensors

- Typically used for measurements of ion or gas-molecule concentrations
- The sensor consists of two electrodes and an ionic conductive material called an electrolyte
- Operation of electrochemical sensors is based on reactions and their equilibrium at the electrode surfaces (interface between electronic and ionic conductors)



Blood oxygen measurement

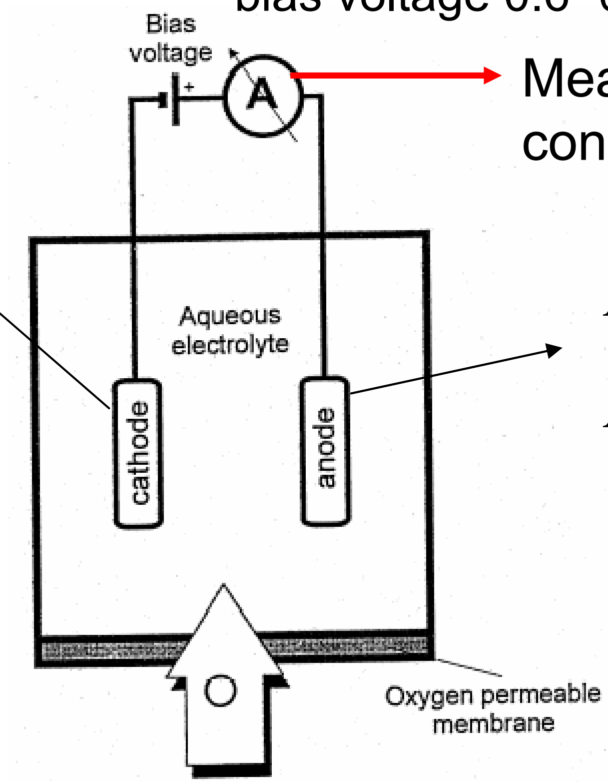
Measuring arterial blood gases pO_2: in operating room and intensive care unit to monitor respiratory and circulatory condition of a patient

Alternatively, oxygen saturation (% of oxygenated hemoglobin) can be measured and used to represent blood oxygenation

Clark electrode: measures partial pressure of O_2

bias voltage 0.6~0.7 V

$$O_2 + 2H_2O + 4e^- \leftrightarrow 4OH^-$$



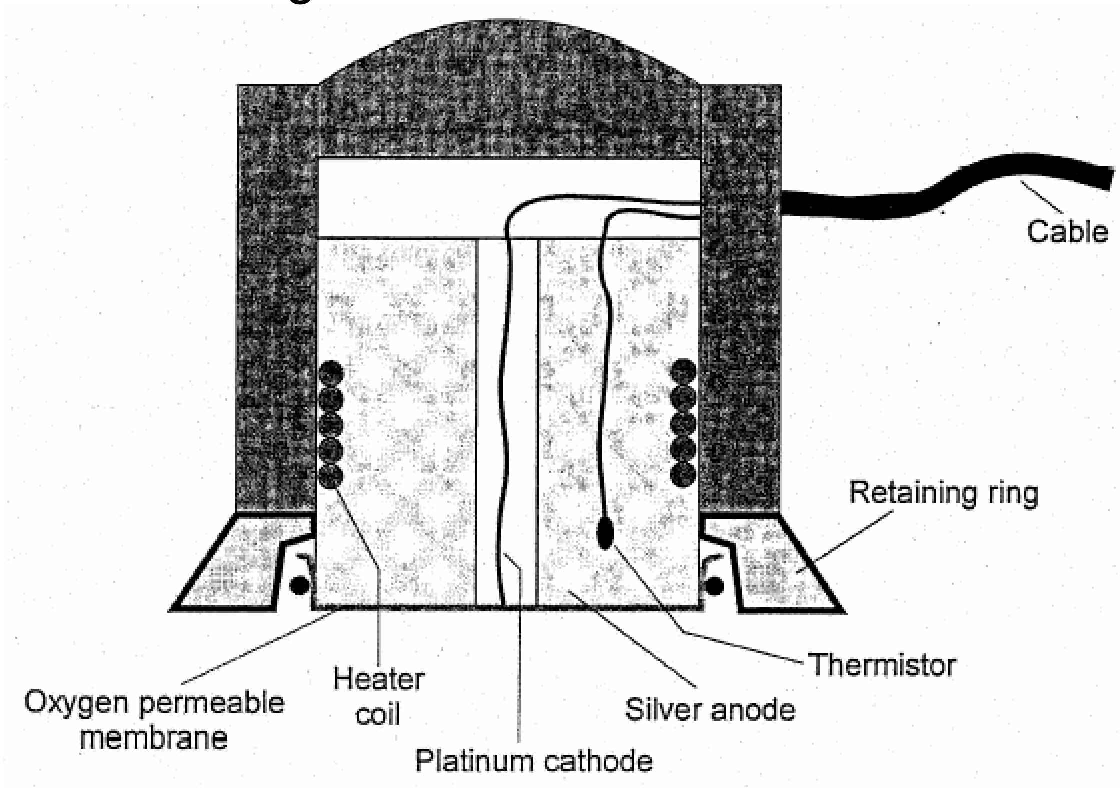
Measured current $\propto$ concentration of O_2

$$Ag \leftrightarrow Ag^+ + e^-$$

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

Transcutaneous pO_2 measurement

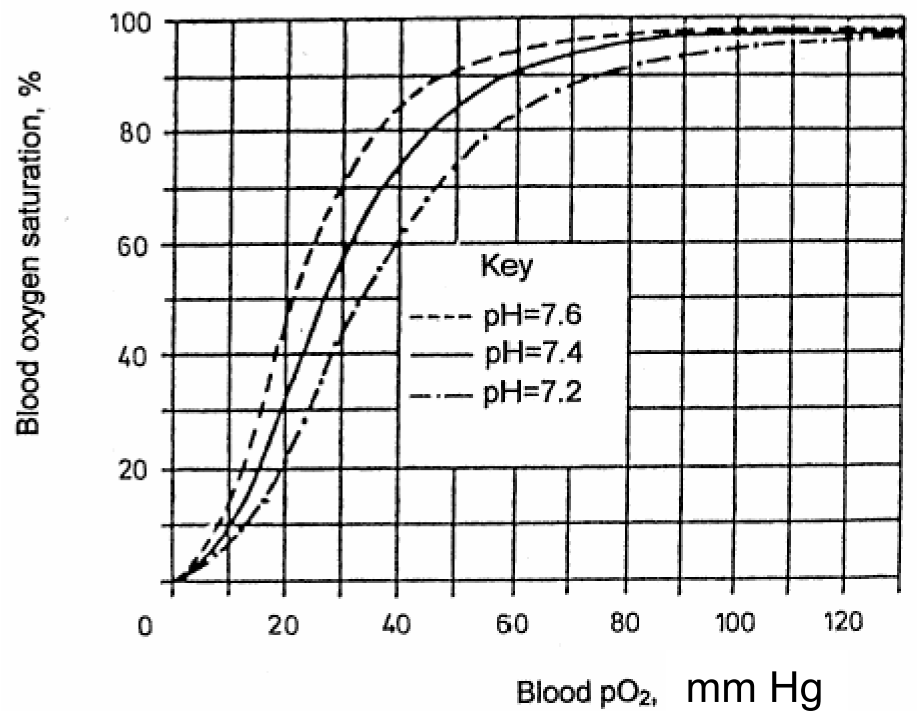
The skin is heated to 43°C to increase local blood flow and enhance diffusion of O2 through the skin



Mostly used on newborn babies in the ICU because their skin is thinner

Blood oxygenation

Relationship between arterial blood oxygen saturation and partial pressure of O_2

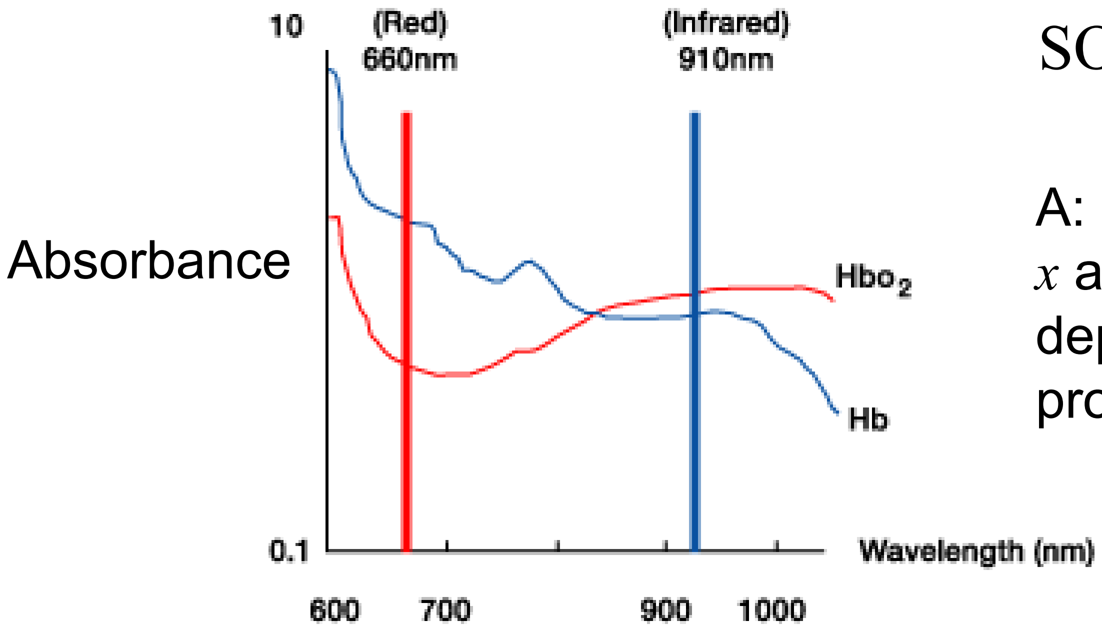


Note different curves at different pH values

Oxygen saturation

Saturation of O_2 $$SO_2 = \frac{[\mathrm{HbO_2}]}{[\mathrm{Hb}]+[\mathrm{HbO_2}]} \times 100\%$$

Oximetry: (color) measures light absorbance at one wavelength where there is a large difference between Hb and HbO_2 and at another wavelength (or more wavelengths)



$$\mathrm{SO_2} = x + y\frac{A(\lambda_1)}{A(\lambda_2)}$$

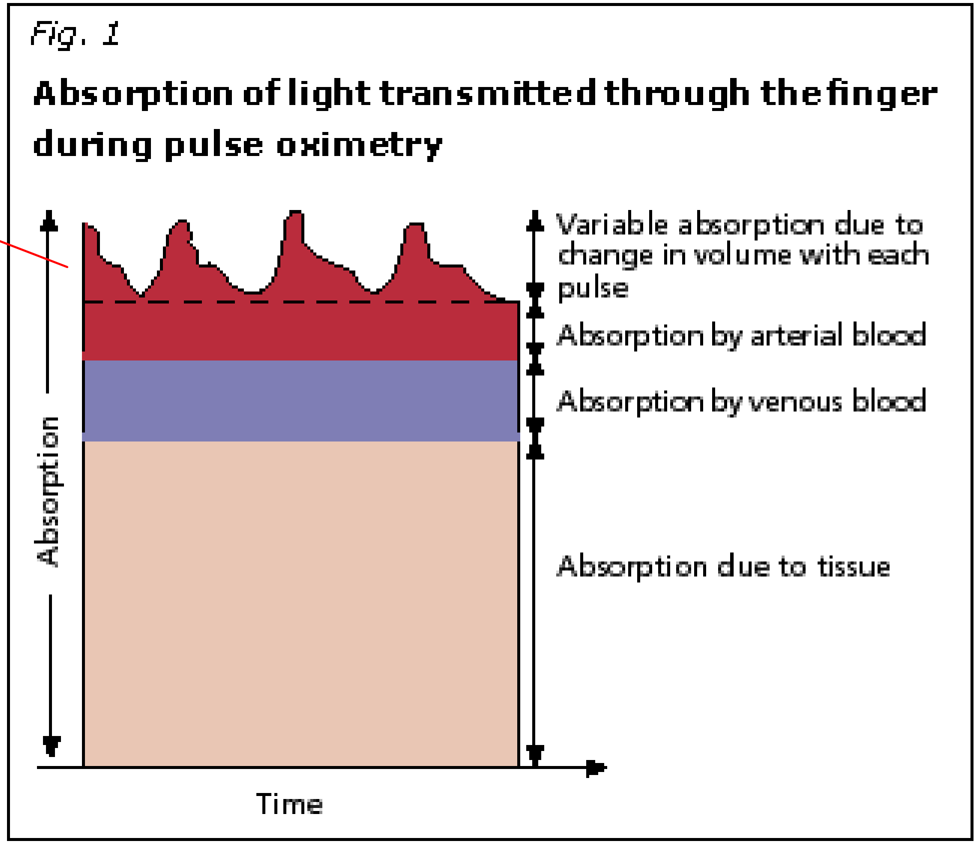
A: absorbance

x and y are constants depending on optical properties of blood

Oxygen saturation

Pulse oximetry: use the pulsatile (AC) component to extract oxygen saturation information and the non-pulsatile (DC) signal as a reference for normalization

Change in arterial blood volume associated with periodic contraction of the heart



pH and pCO_2 measurements

Membrane permeable to H^+ is located at the tip of the active electrode
The potential across the membrane (Nernst equation)

$$V = -0.059 \cdot \log_{10}[H^+] + c$$ c is a constant

$$pH = -\log_{10}[H^+]$$

For pCO2 measurement

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

$$[CO_2] = a(PCO_2)$$ a is a constant

It can be shown that

$$pH = \log[HCO_3^-] - \log k - \log a - \log PCO_2$$

Linear relationship over range of 10-90 mmHg

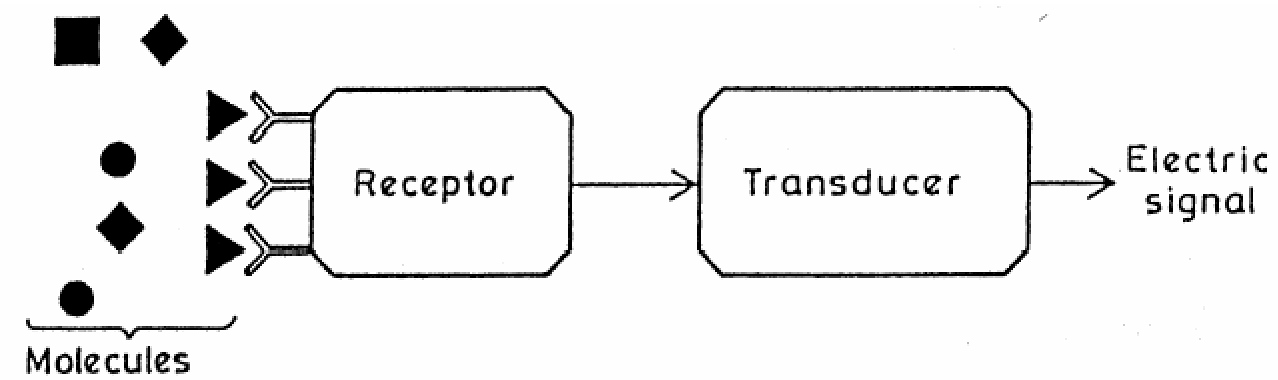
Biosensors

- Biosensor: is a sensor using a living component or a product of a living thing for measurement or indication. Generally a biosensor consists of two parts
  - A biological recognition element (enzyme, antibody, receptor) to provide selectivity to sense the target of interest (referred to as the analyte)
  - A supporting element which also acts as a transducer to convert the biochemical reaction into “signal” that can be read out and analyzed

Biosensors

Receptor provides selective molecular recognition

For example: enzymes, receptors, antibodies, nucleic acids, organic and inorganic small molecules, etc.



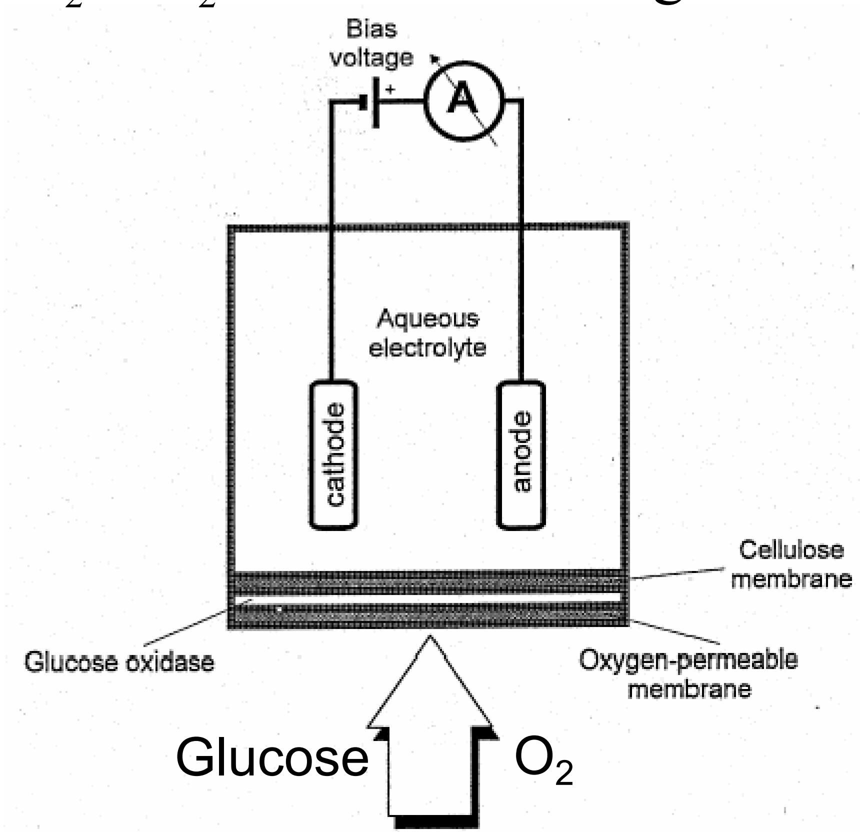
Transducer types in biosensors: calorimetric, electrochemical, optical, etc.

Enzymatic biosensors

- Immobilized enzymes as receptors
- Enzymes are catalysts for biochemical reactions
- Enzymes are specific to their substrates which can be the analyte

Example: glucose sensors

$$\text{Glucose} + O_2 + H_2O \xleftrightarrow{\text{glucuse oxidase}} \text{gluconic acid} + H_2O_2$$



Permeable to O_2 only

Enzymatic biosensors

Alternatively, the reaction product hydrogen peroxide can also be measured through reduction of H_2O_2

$$H_2O_2 \rightarrow 2H^+ + O_2 + 2e^-$$

Use a Clark-type electrochemical cell similar to the one for measuring O_2, but with a Pt or Au electrode at a positive potential 0.6~0.7 V

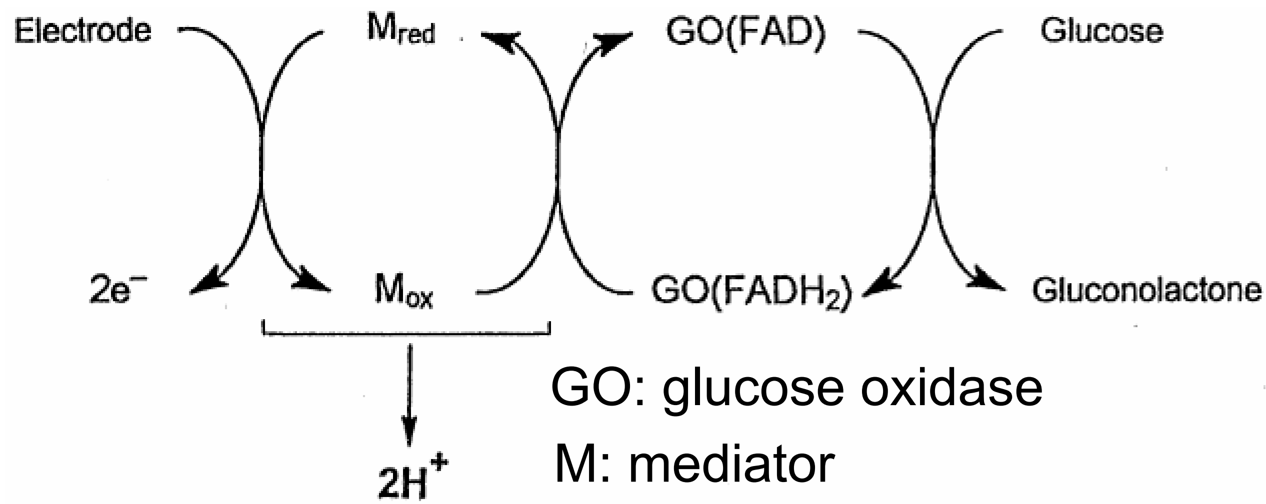
Electron mediators in enzymatic biosensors

In the membrane: $$S + O_2 \xrightarrow{\text{oxidase}} P + H_2O_2$$

At the anode: $$H_2O_2 \rightarrow 2H^+ + O_2 + 2e^-$$

Oxygen is consumed and later regenerated, therefore it only serves to transfer electron, which can be replaced by a <u>mediator</u>

Example: multi-cycle chemical electrochemical reaction chain for detecting glucose



GO: glucose oxidase

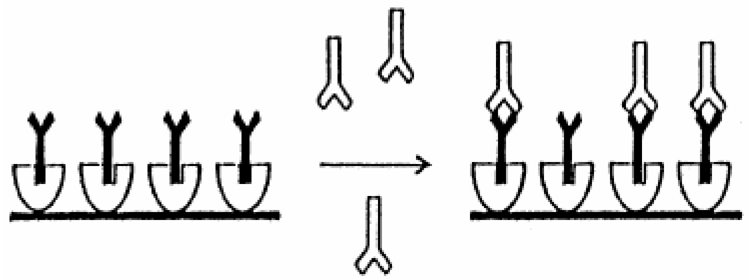
M: mediator

Affinity biosensors

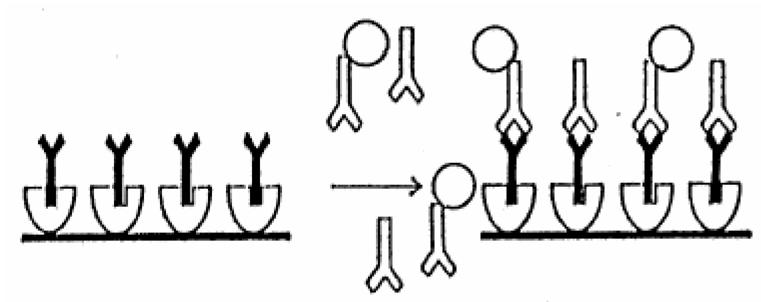
Immunosensors: based on highly specific antigen-antibody reactions

Detection of the reaction (binding/association) can be either direct or indirect (labeled)

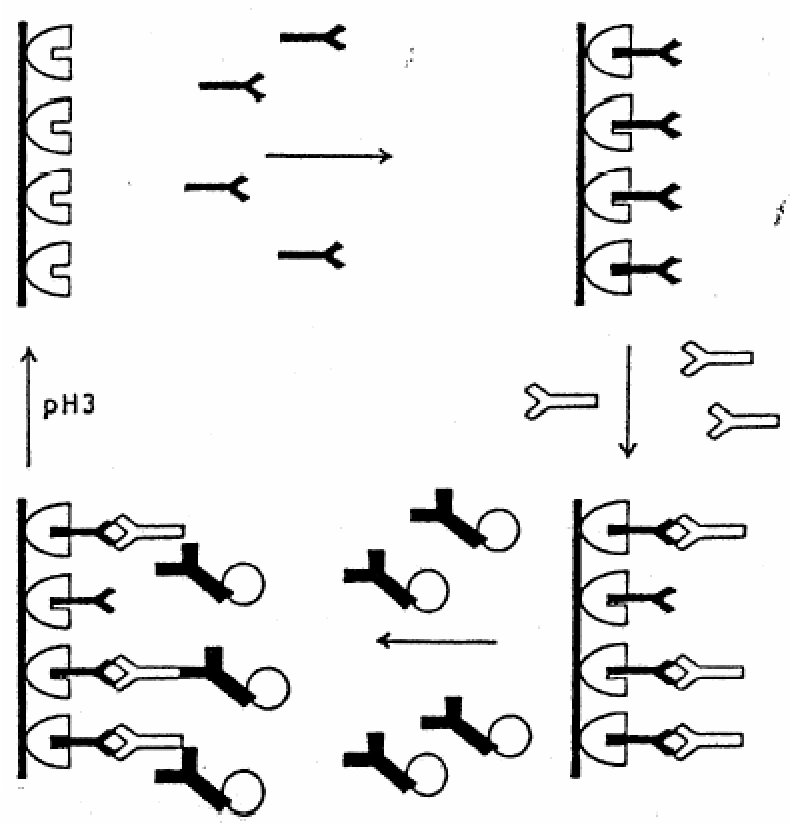
Direct

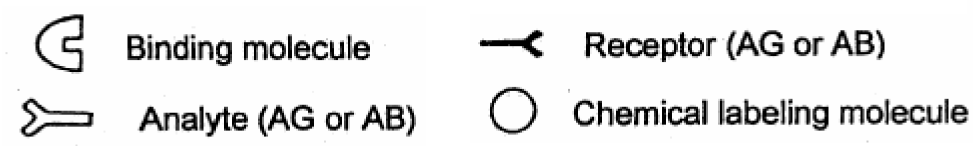


Indirect (competitive)



Indirect (sandwitch)

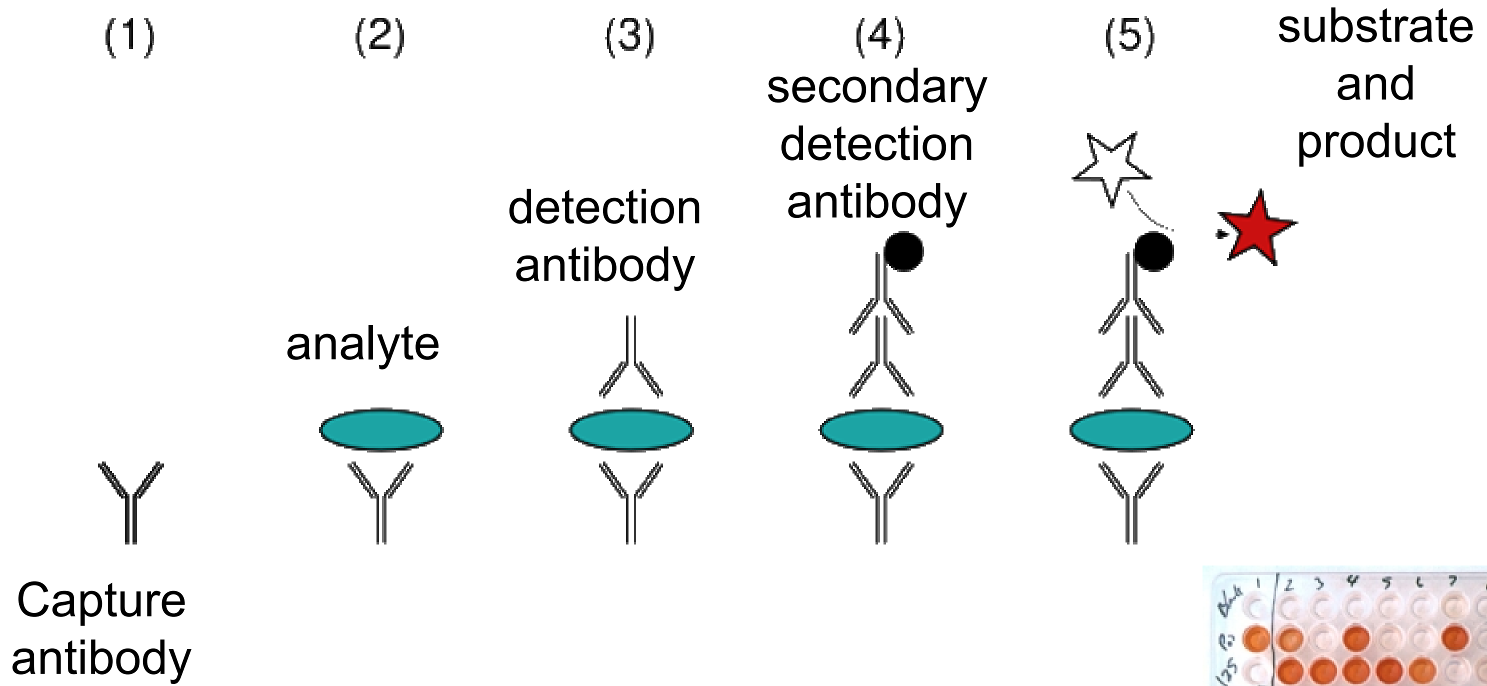


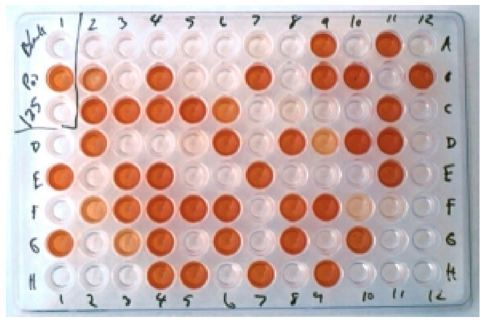


Indirect immunosensors

- Radioimmunoassay (RIA)
  - The labels are radioactive isotopes (for example ^{131}I)
  - Highly sensitive and specific but inconvenient and expensive
- ELISA (Enzyme-Linked Immunosorbent Assay)
  - Enzymes are used for labeling and signal is provided by reaction product
- Fluorescent immunoassay
  - Labeled with fluorescent dyes

ELISA

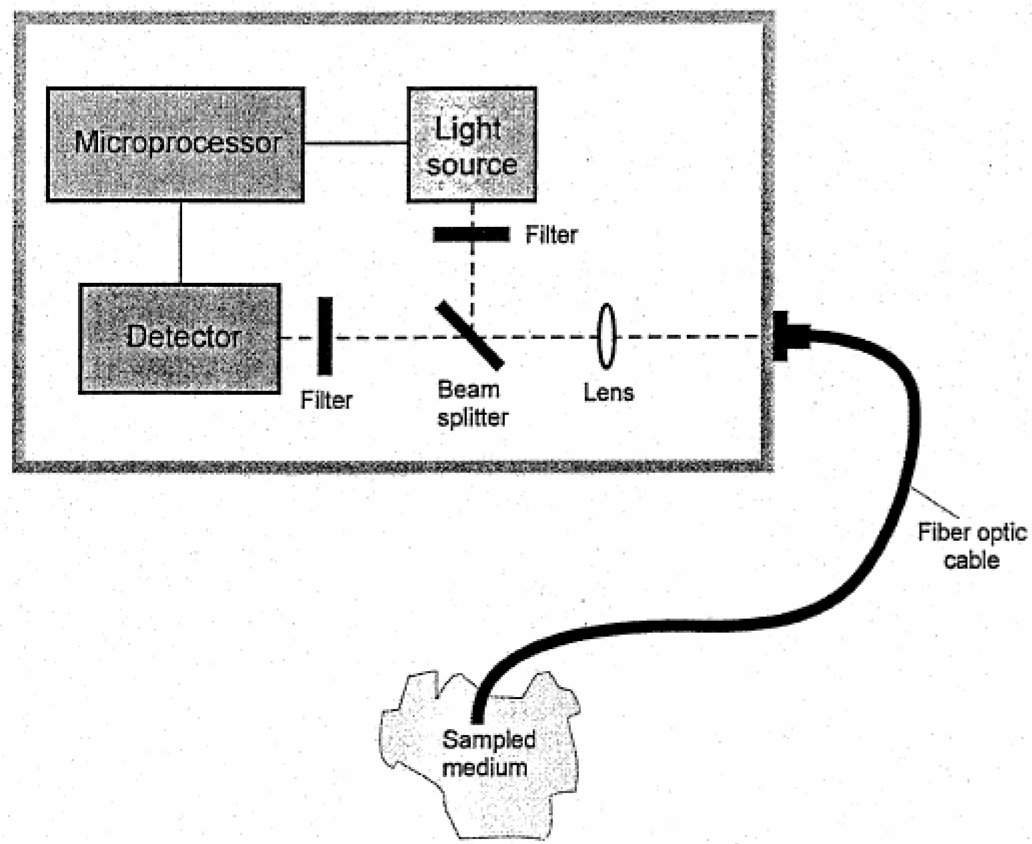




Typically colorimetric measurement (absorbance at certain wavelength $\propto$ analyte concentration)

Optical detection methods

Optical fibers are flexible and compact which are important features for applications that need miniaturization such as *in vivo* measurements



Optical fiber

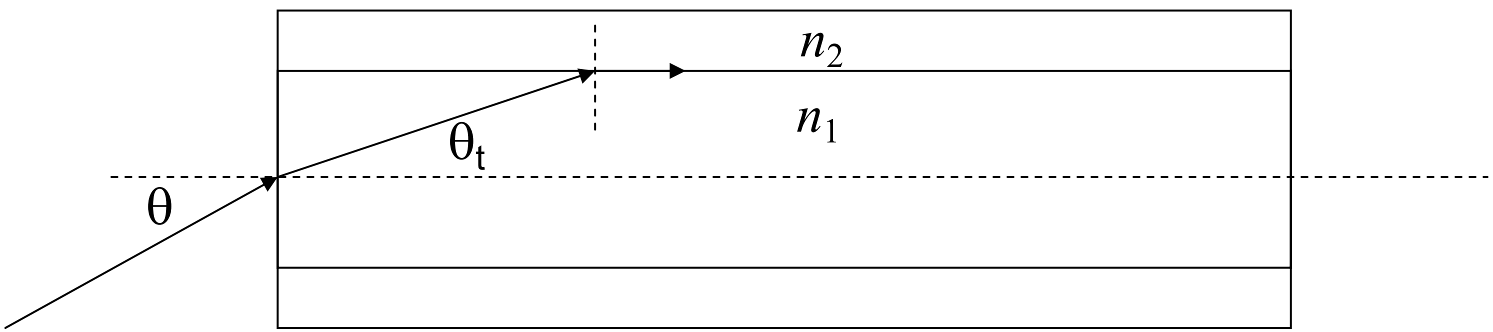
Typically made of glass SiO_2, and consisting of a core and a cladding layer

Transmits light through the core (total internal reflection)

Diameter can be very small ~μm ⇒ very flexible

The angle of light rays that go into the fiber core and can be accepted (transmitted) by the fiber is dependent on the core and cladding materials

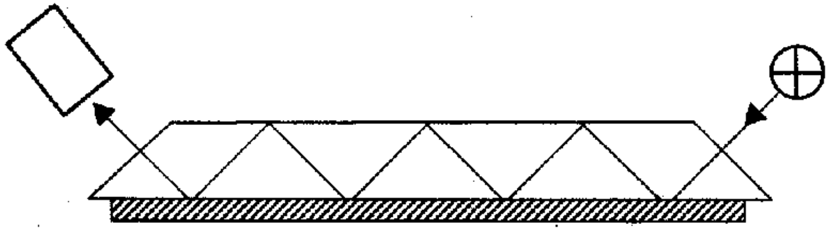
Incident angle of light rays going into a fiber must be less than θ



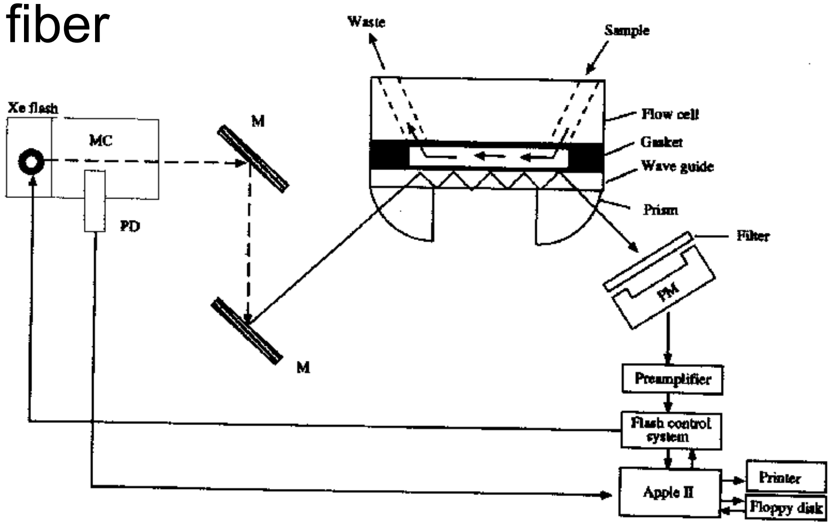
NA of an optical fiber = $\sin\theta = \sqrt{n_1^2 - n_2^2}$

Optical fiber sensor – examples

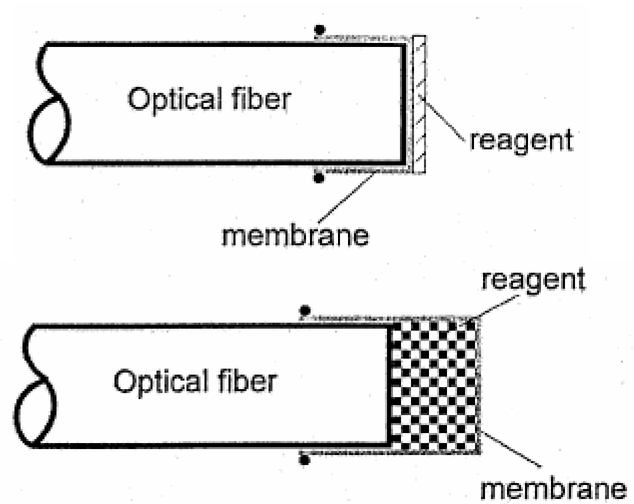
- Sensing area along side of an optical fiber

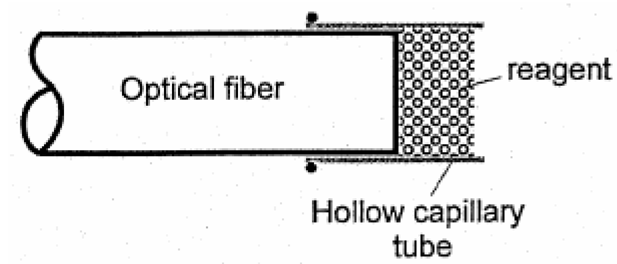


Total internal reflection
inside the fiber



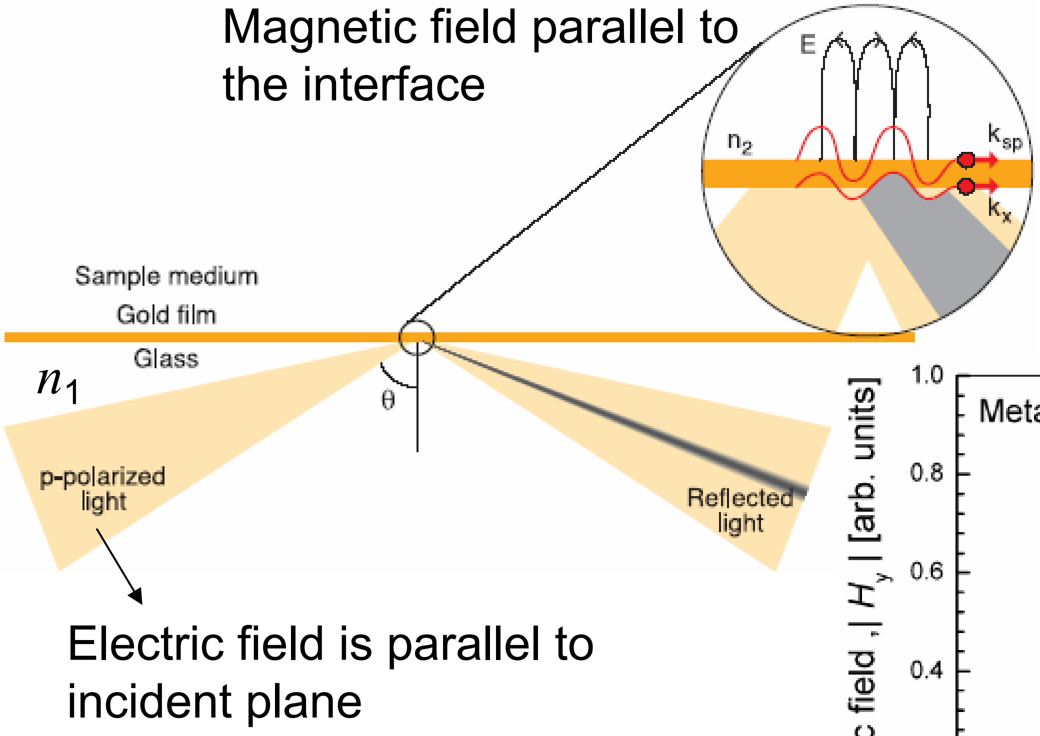
- Sensing area located at distal end surface of an optical fiber



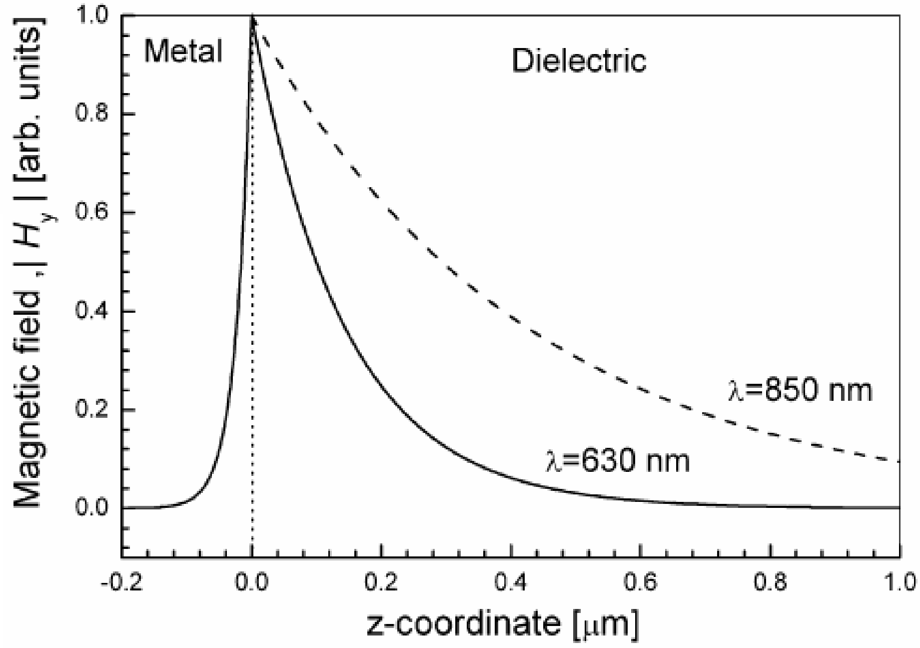


Surface plasmon resonance

A surface plasma wave (SPW) is an electromagnetic wave (due to charge density oscillation) which propagates along the boundary between a dielectric and a metal



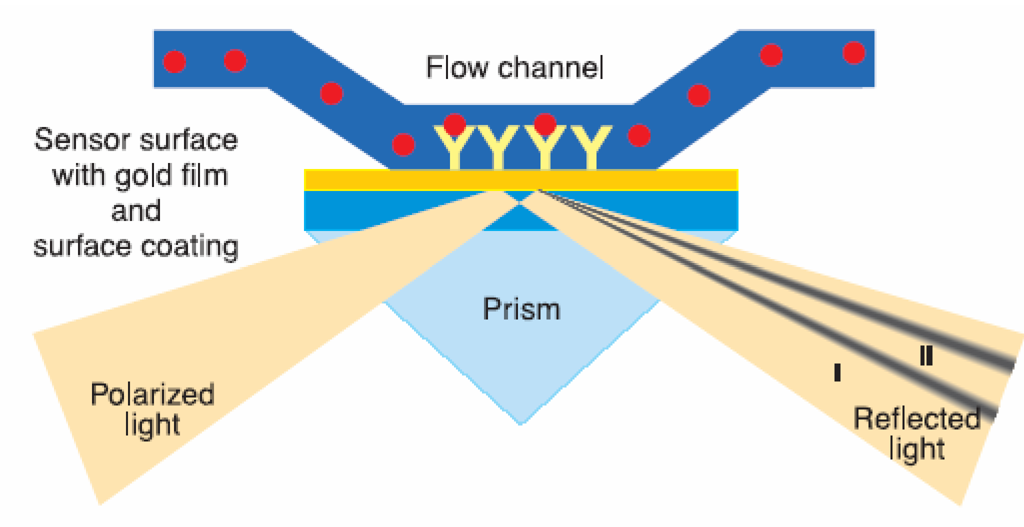
The magnitude of the surface plasmon wave decreases exponentially into both dielectric and metal media



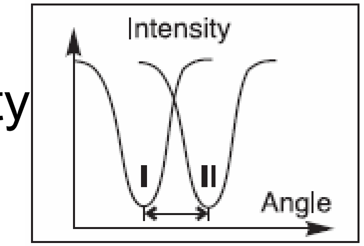
SPR biosensors

A surface plasmon wave can be excited optically: the propagation constant β of the incident light and the SPW are equal in magnitude and direction for the same frequency of waves

This corresponds to a certain angle of incident light at a fixed wavelength that the reflected light reaches its minimum



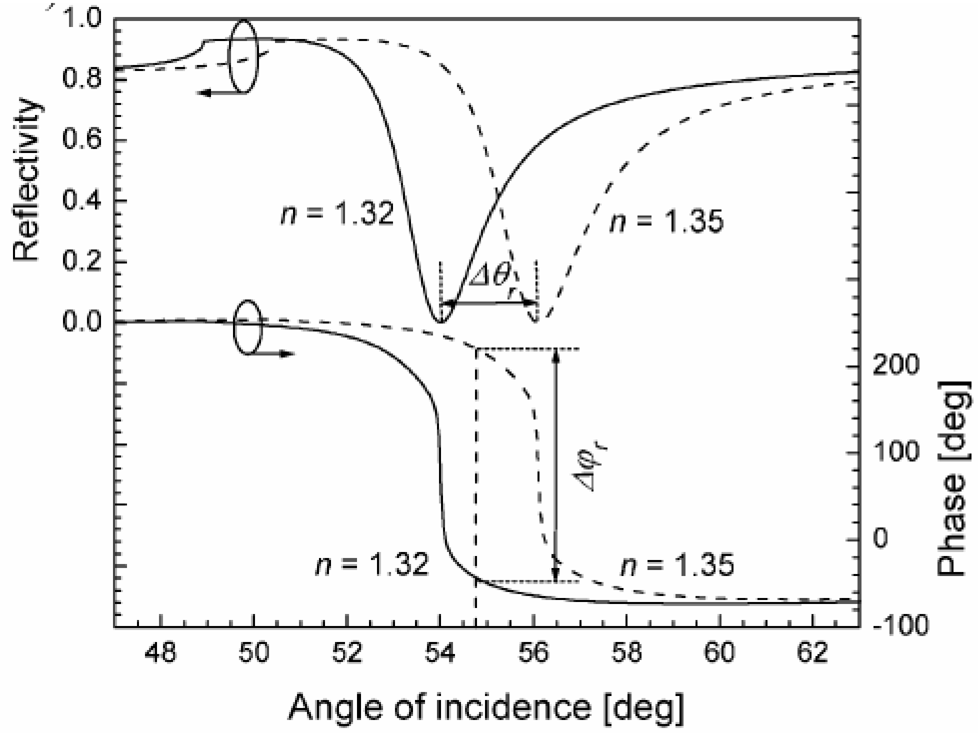
reflectivity

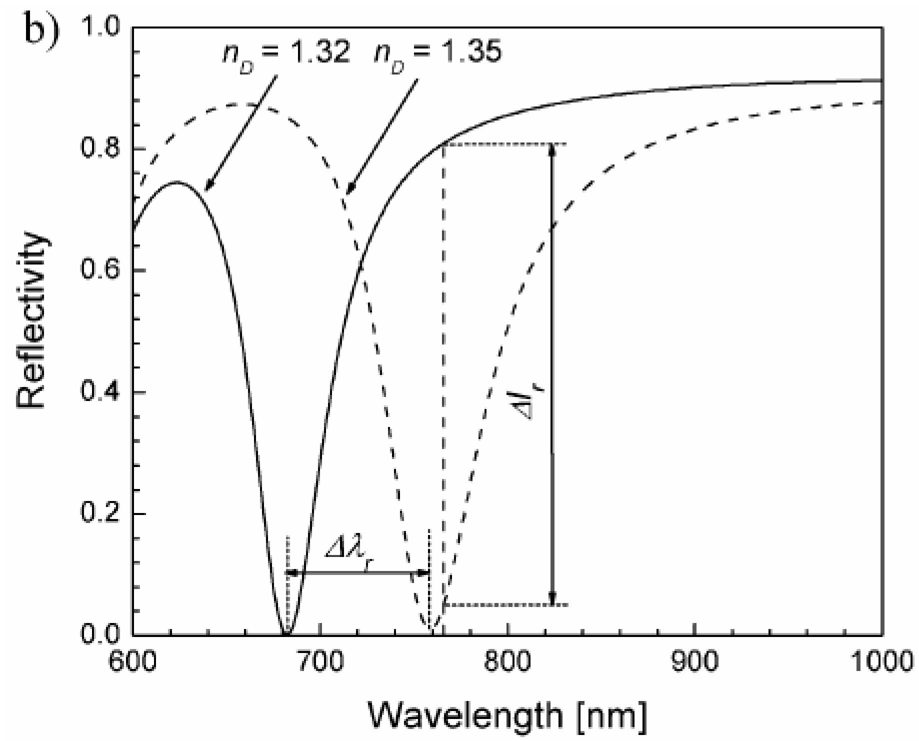


Binding induced change in propagation constant of SPW is proportional to the refractive index change in the sample ⇒ the angle of incident light also changes

SPR biosensors

Different parameters are measured in SPR biosensors to indicate the refractive index change in the sample (due to binding)



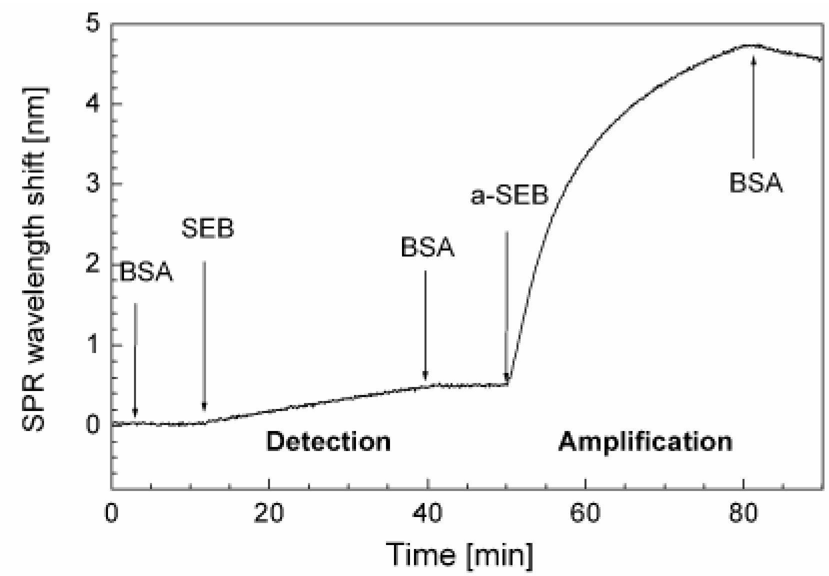


Angle of incident light
Phase shift of reflected light

Wavelength of incident light
Intensity of reflected light

SPR biosensors

The kinetics of binding events can be monitored continuously - **sensorgram**



Analyte: SEB (staphylococcal enterotoxin B)

BSA: bovine serum albumin, used to non-specific binding

a-SEB: antibody against SEB $\Rightarrow$ sandwich binding

SPR biosensors

- No need for labeling
- High sensitivity
- Fast $\Rightarrow$ real-time monitoring
- Used with sample in liquid $\Rightarrow$ important for biological samples
- Relatively simple device, which makes multichannel parallel detection easier $\Rightarrow$ high throughput

Trends in biomedical sensors

Centralized laboratory → Point of care

Centralized laboratory → Patients' home

in vitro → in vivo

Single test → Multiple tests in a single run

Key technologies for miniaturization of biomedical sensors and realization of biochips: microfluidics, semiconductor fabrication processes, microelectromechanical systems (MEMS)

Equally important are: the development of more stable and effective biomolecules used for recognition; search for new target analytes that are of diagnostic and/or biological significance

Biochips

- Miniaturized and highly integrated
- Provide analytical or diagnostic function
- Substrates can be glass, silicon, polymer, plastic, etc
- Desired features: high sensitivity and specificity, high speed, small size, small sample requirement, multi-channel and parallel analyzing, reliable

References

- Medical Instrumentation: Application and Design, edited by John G. Webster
- Sensors in Biomedical Applications: Fundamentals, Technology & Applications, by Gábor Harsányi
  - Ch7: Biosensors