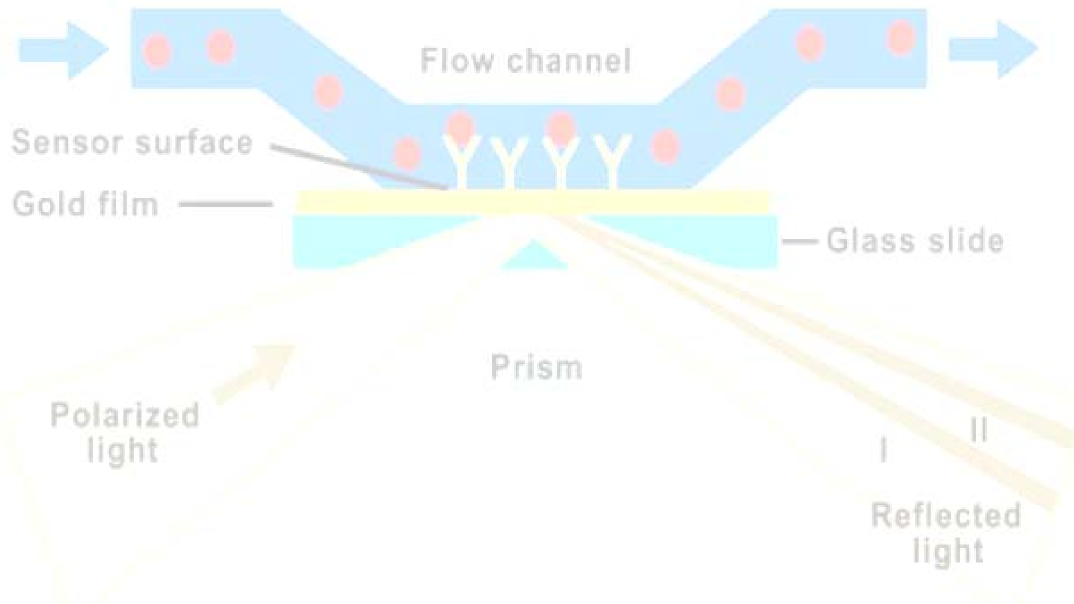
Commercial Biosensors



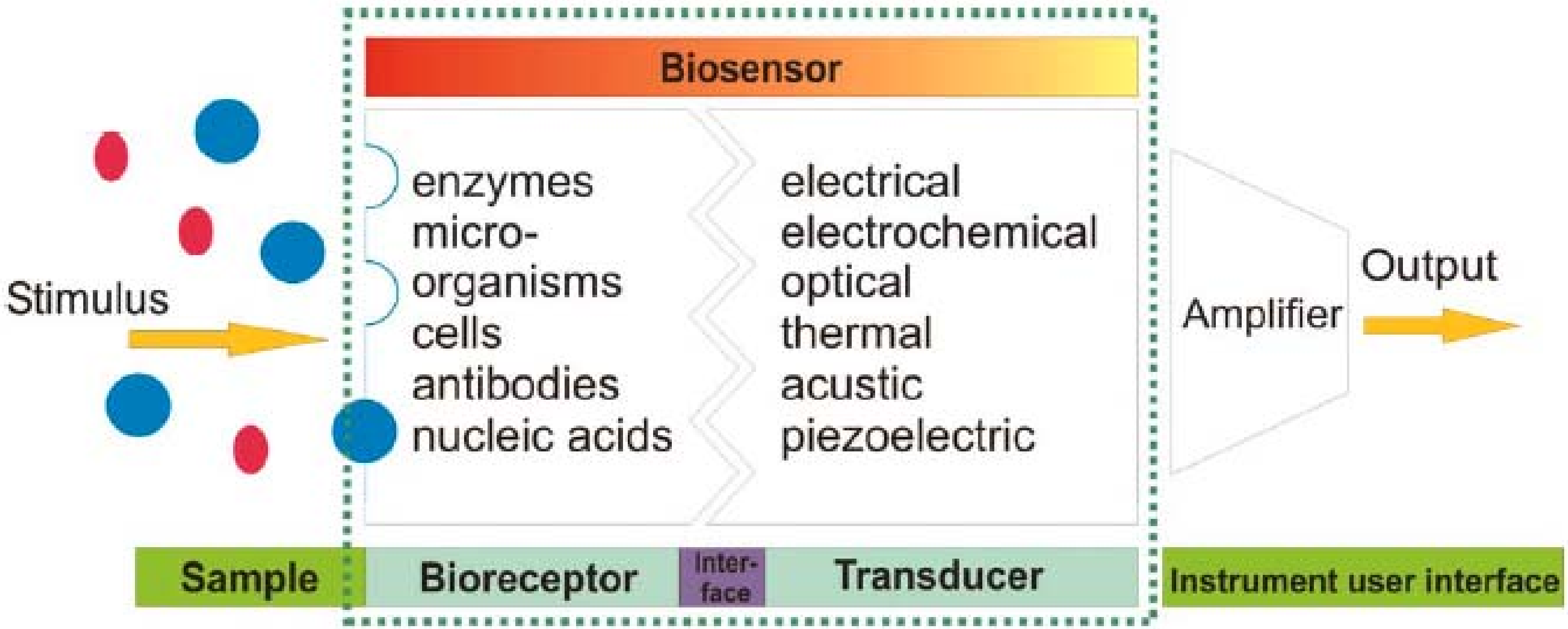
MB-JASS 2006

Nathalie Munnikes, TUM

Overview

- What is a biosensor?
- The biological component
    - Immobilization
- Some transducer principles
    - Electrochemical
    - Optical
    - Acoustic-Piezoelectric
- Some application areas
    - Diabetes
    - Marine observation
- Conclusion

Introduction



- Aim: combining the specificity and sensitivity of biological systems with the computing power of the microprocessor

[1]

The Analyte

In principle any substance that takes part in a biochemical process:

- Anorganic:
  - Gases
  - Ions (pH)
  - Heavy metals
- Organic:
  - Organic acids (→ proteins)
  - Carbohydrates (sugars)
  - Urea $(NH_2)_2CO$

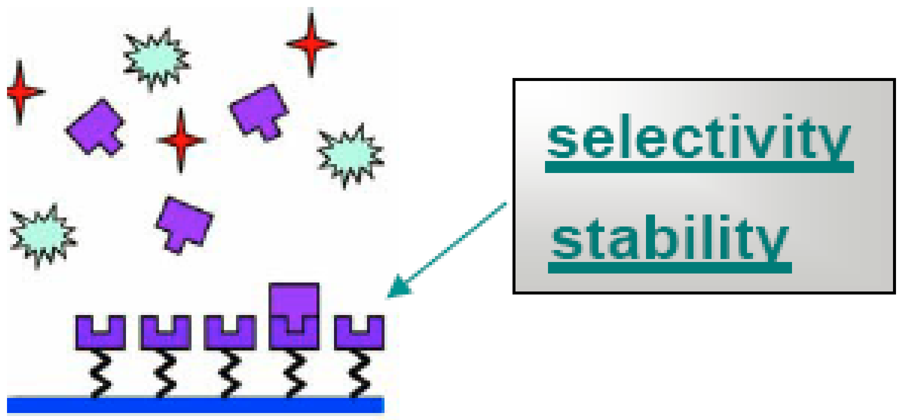
More generally: any unit, (part of) which is involved in a biochemical process:

- Microorganisms
- (Microbial) cells
- Antibodies
- Antigens

The Bioreceptor

Any biological substance that can attach itself to a particular analyte:

- Enzymes
- Antibodies
- Nucleic acids
- Receptors



...and unpurified material containing such a substance:

- Organisms, slices of tissue, cells, organelles, membranes

[1]

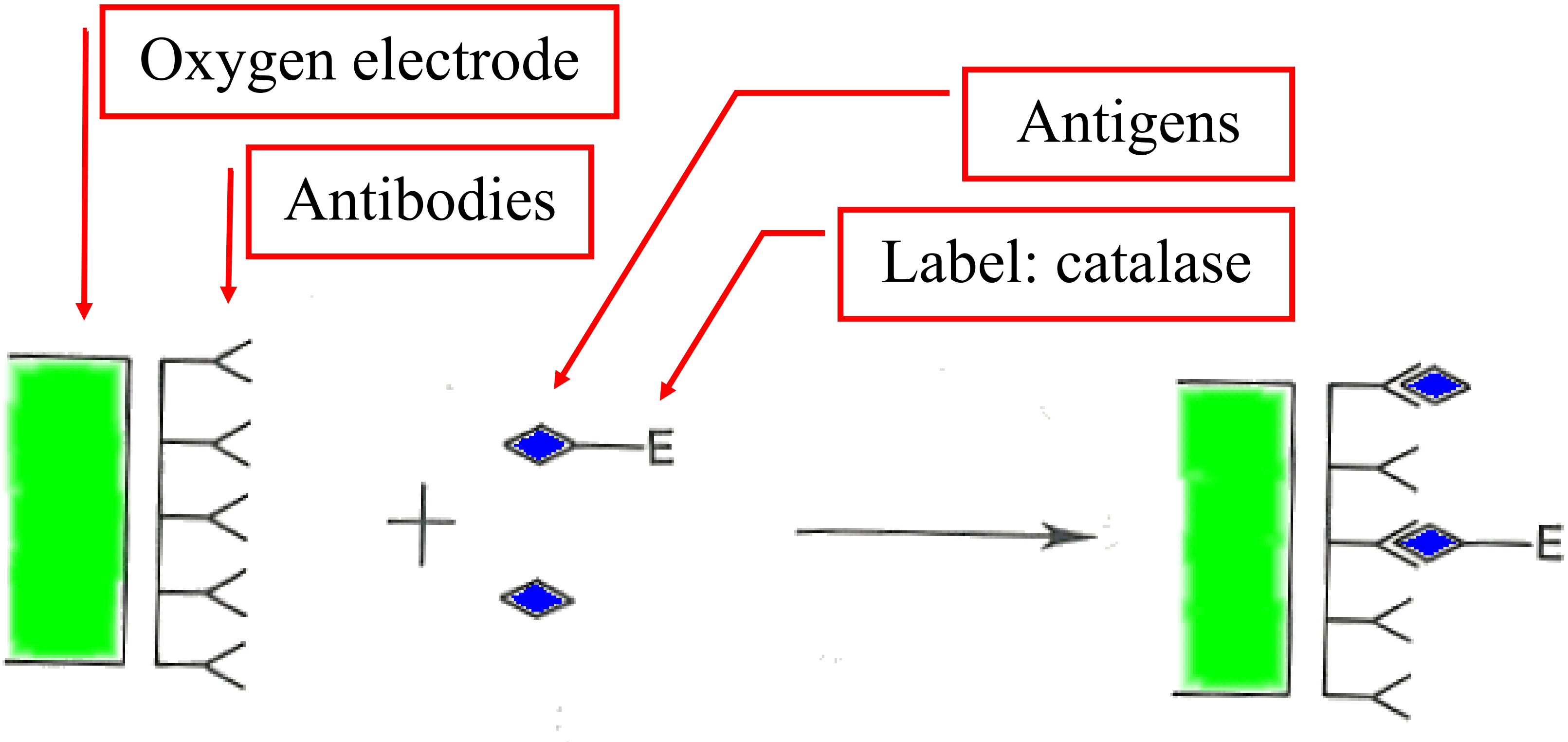
The Bioreceptor (2)

Catalytists

Based on bioaffinity:
binding & labelling

- Enzymes
- Antibodies
- Nucleic acids
- Receptors

Example: labelling antibodies

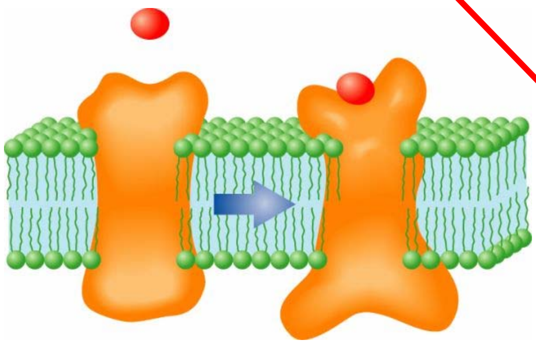


Catalase: $2\ H_2O_2 \rightarrow 2\ H_2O + O_2$

[11]

The Bioreceptor (2)

- Enzymes
- Antibodies
- Nucleic acids
- Receptors



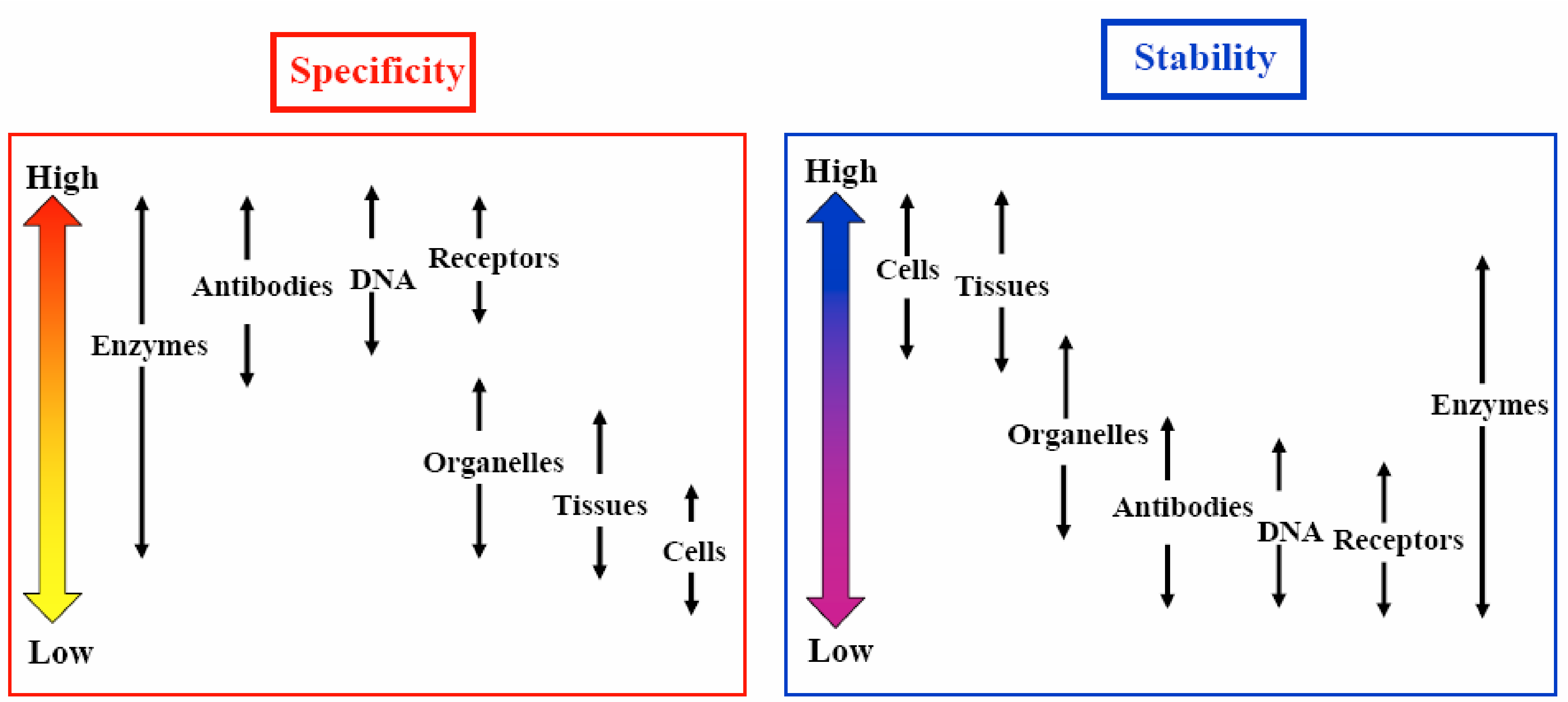
Catalytists

Based on bioaffinity: binding (& labelling)

Based on hybridization: binding of a unique DNA/RNA sequence

Based on a physiological response e.g. neurotransmitters

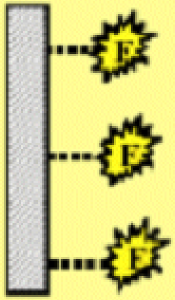
Receptors: specificity vs. stability



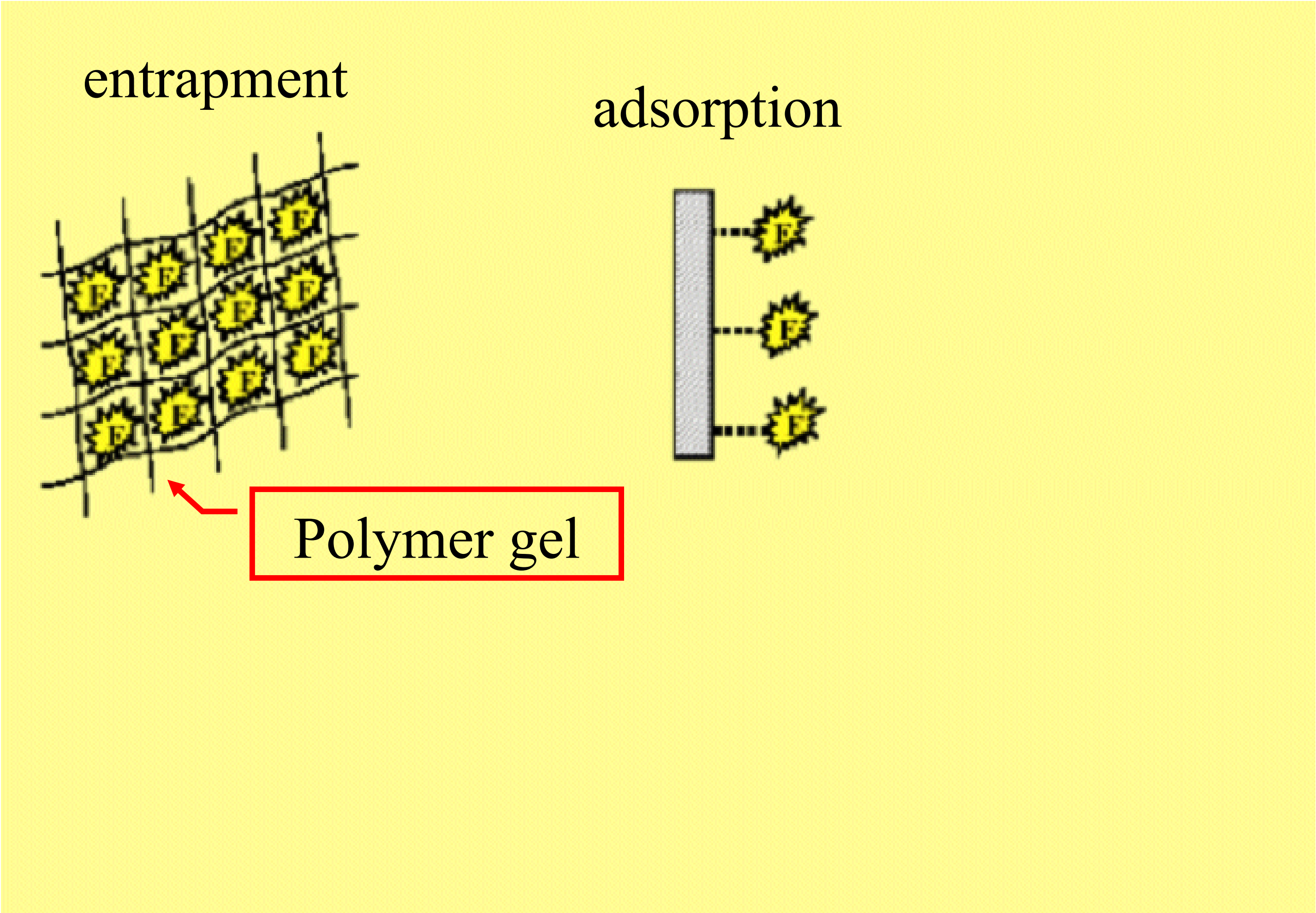
[1]

Immobilization

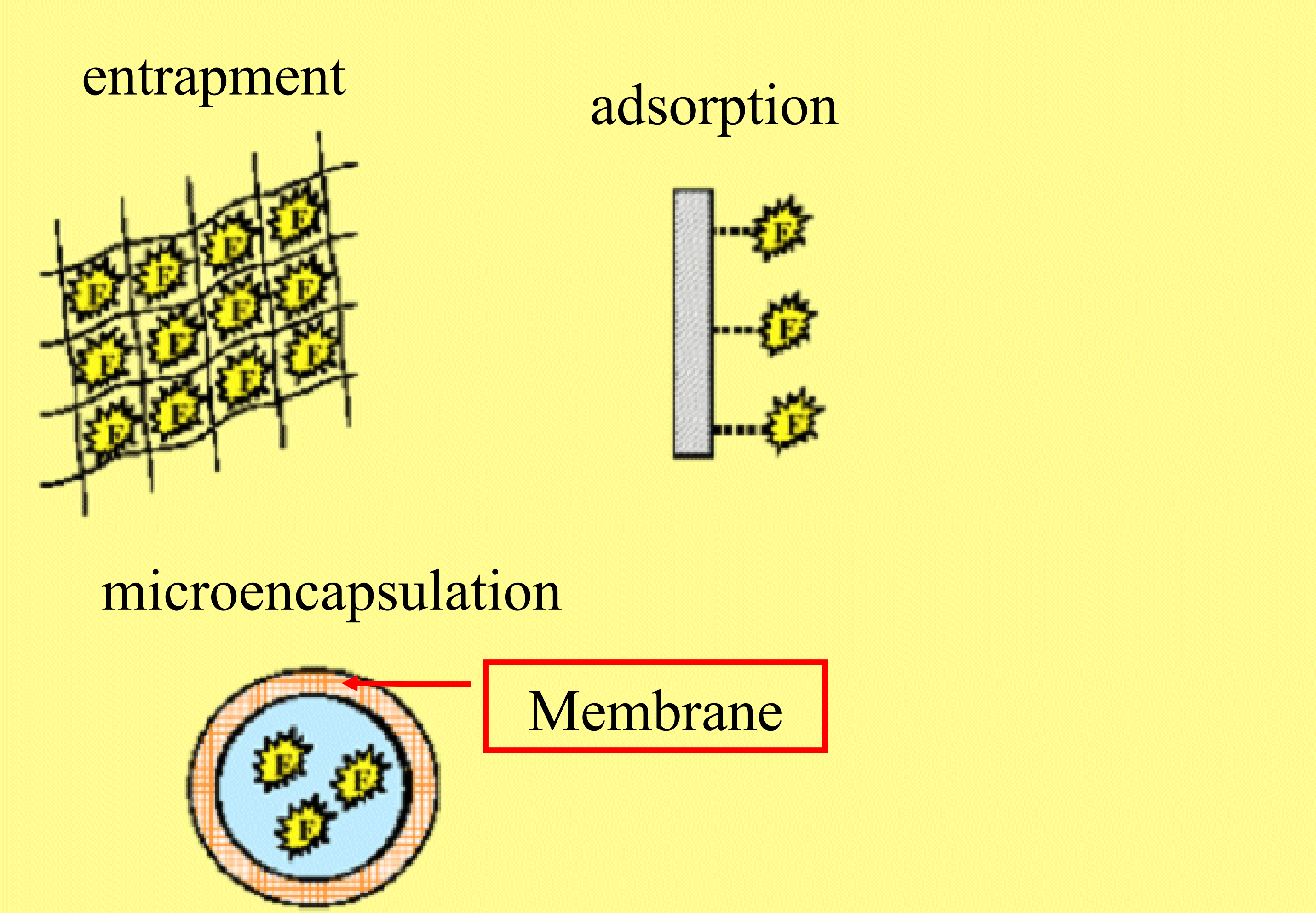
adsorption



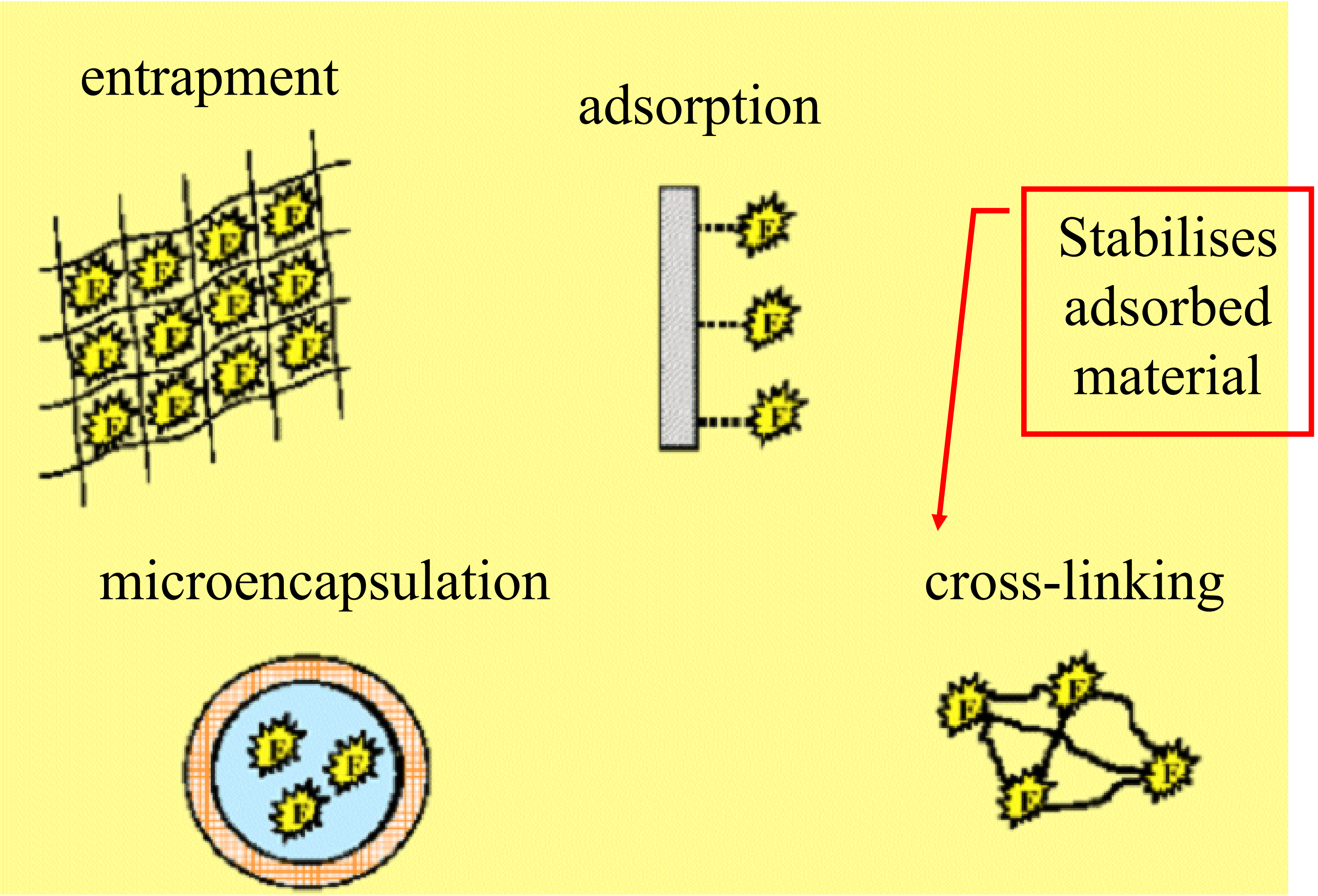
Immobilization



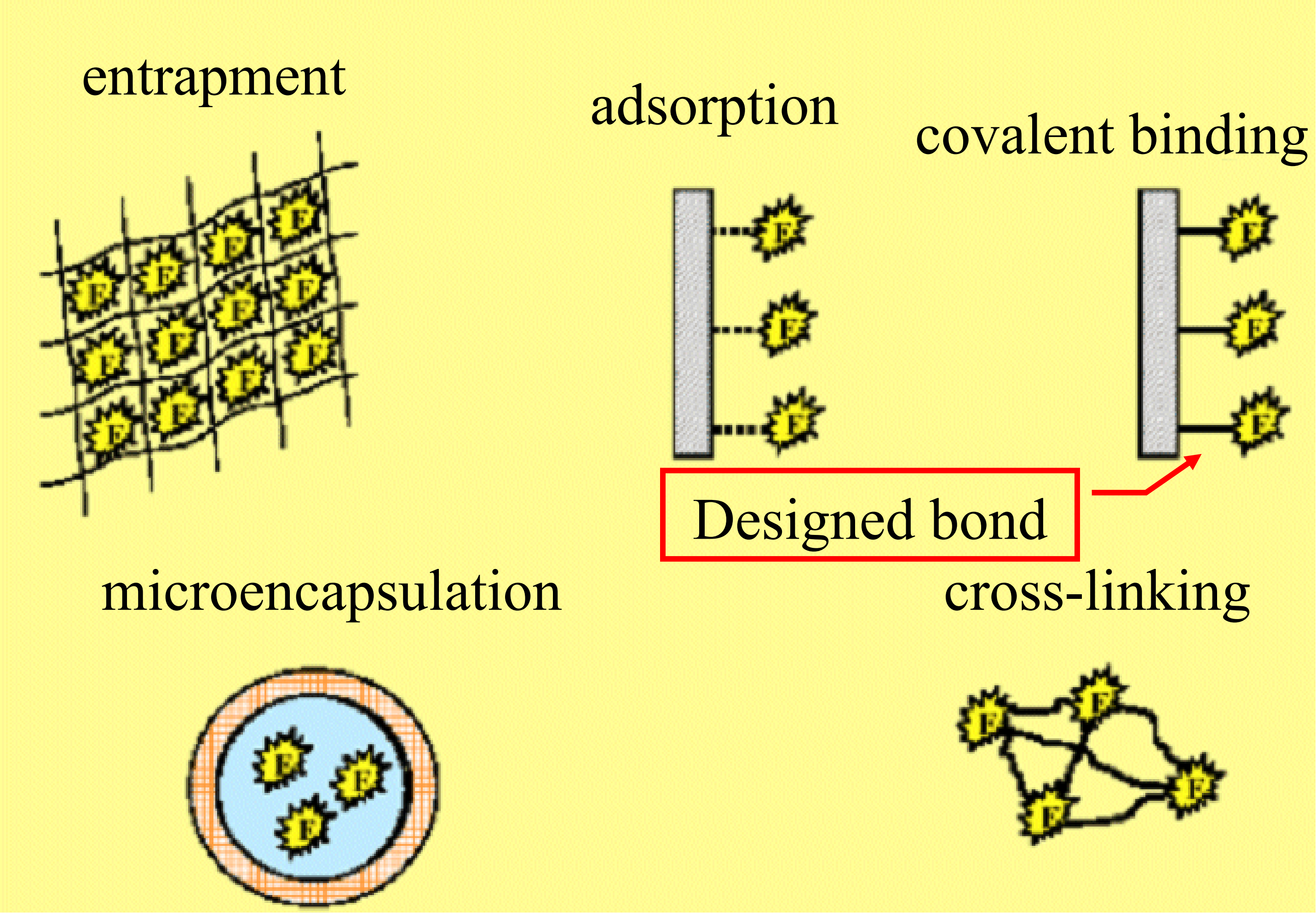
Immobilization



Immobilization



Immobilization



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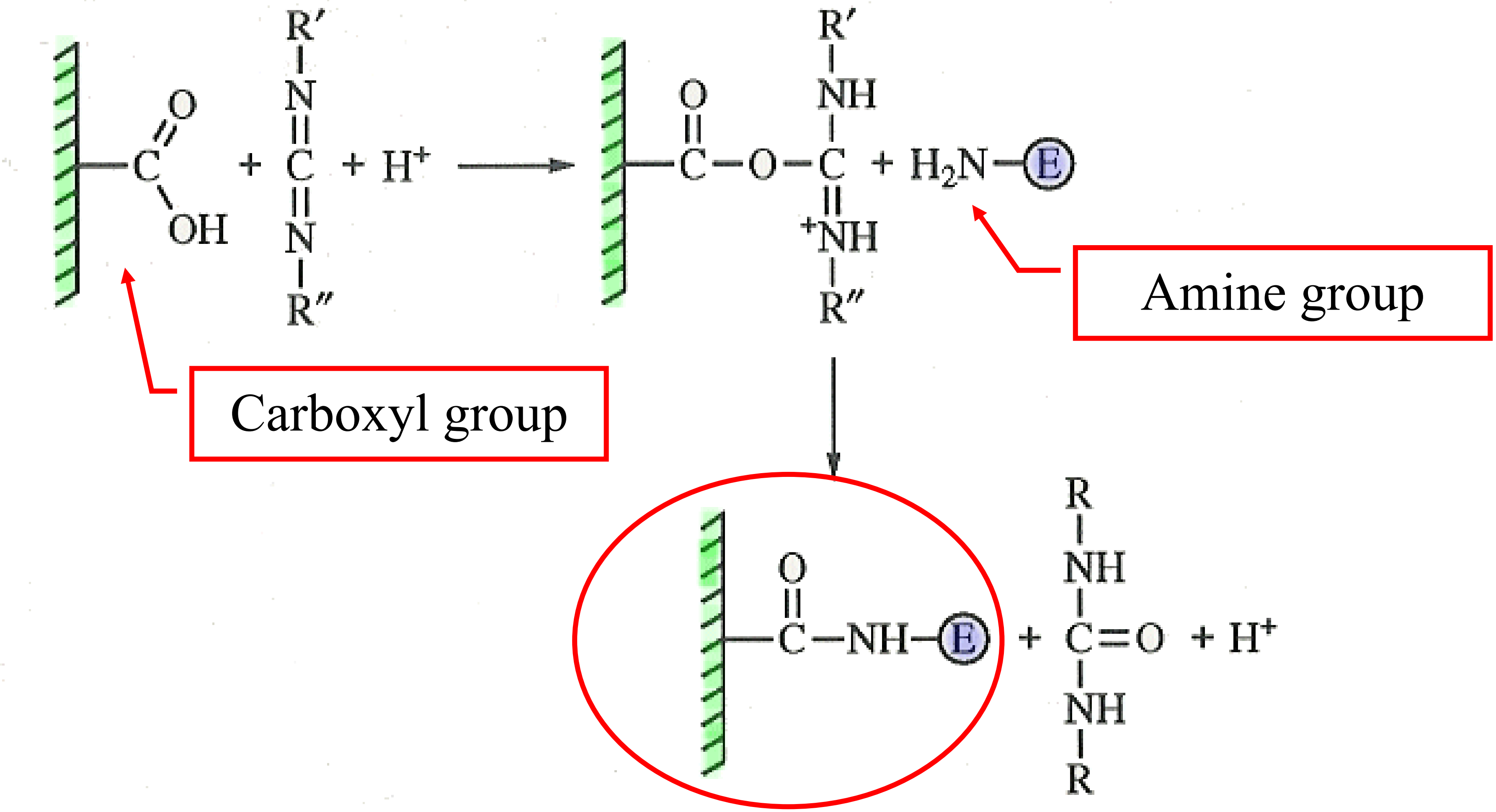
Example: covalent bonding



[11]

Transducers: an overview

- Electrochemical:
  - Potentiometry
  - Amperometry
  - Conductimetry
  - Field Effect Transistors
- Optical:
  - Ultraviolet-visible absorption
  - Luminescence
  - Laser light scattering
  - Internal Reflection Spectroscopy
    - Surface Plasmon Resonance (SPR)
- Mechanical-piezoelectric
- Acoustical-piezoelectric
  - Surface Acoustic Wave (SAW)
- Calorimetric

sensitivity
response time
miniaturization

Electrochemical transducers

- Potentiometry
- Amperometry
- Conductimetry
- Field Effect Transistors

Difference between indicator and reference electrode potential at equilibrium (i.e. zero current)

NH_3 → Urea, amino acids, creatinine
CO_2 → Urea, amino acids, enzymes
pH → Penicillin, DNA, RNA, glucose, pH-enzymes
I^- → Glucose, cholesterol, amino acids

The electrochemical cell

- Gibbs free energy of a half cell ($Ox + ne^- = Red$):

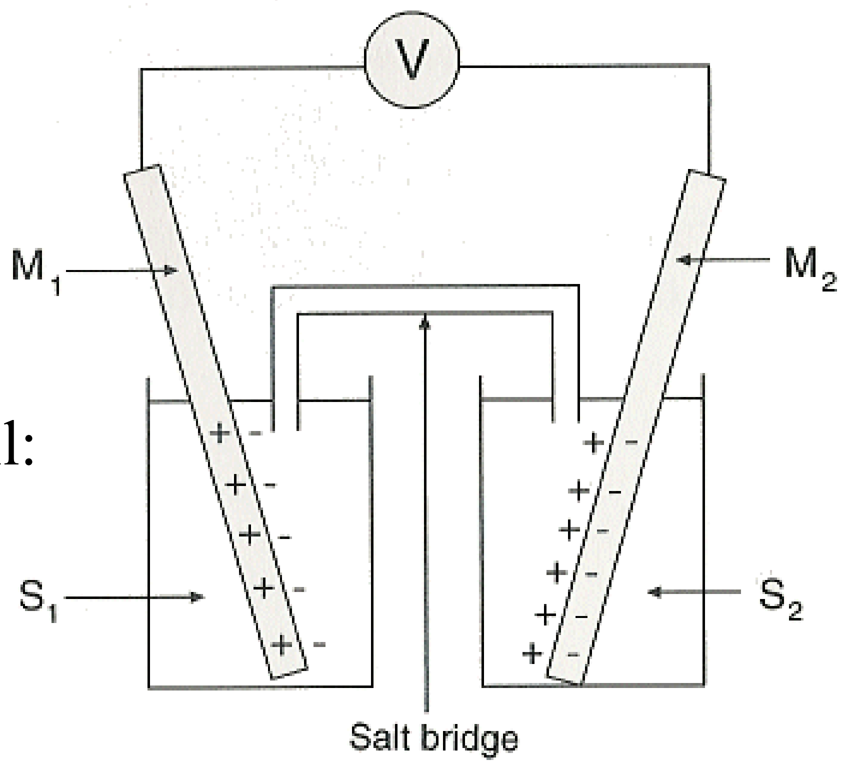
$\Delta G = -nFE = -RT \ln K$

→ Nernst equation for the electromotive force of a half-cell:

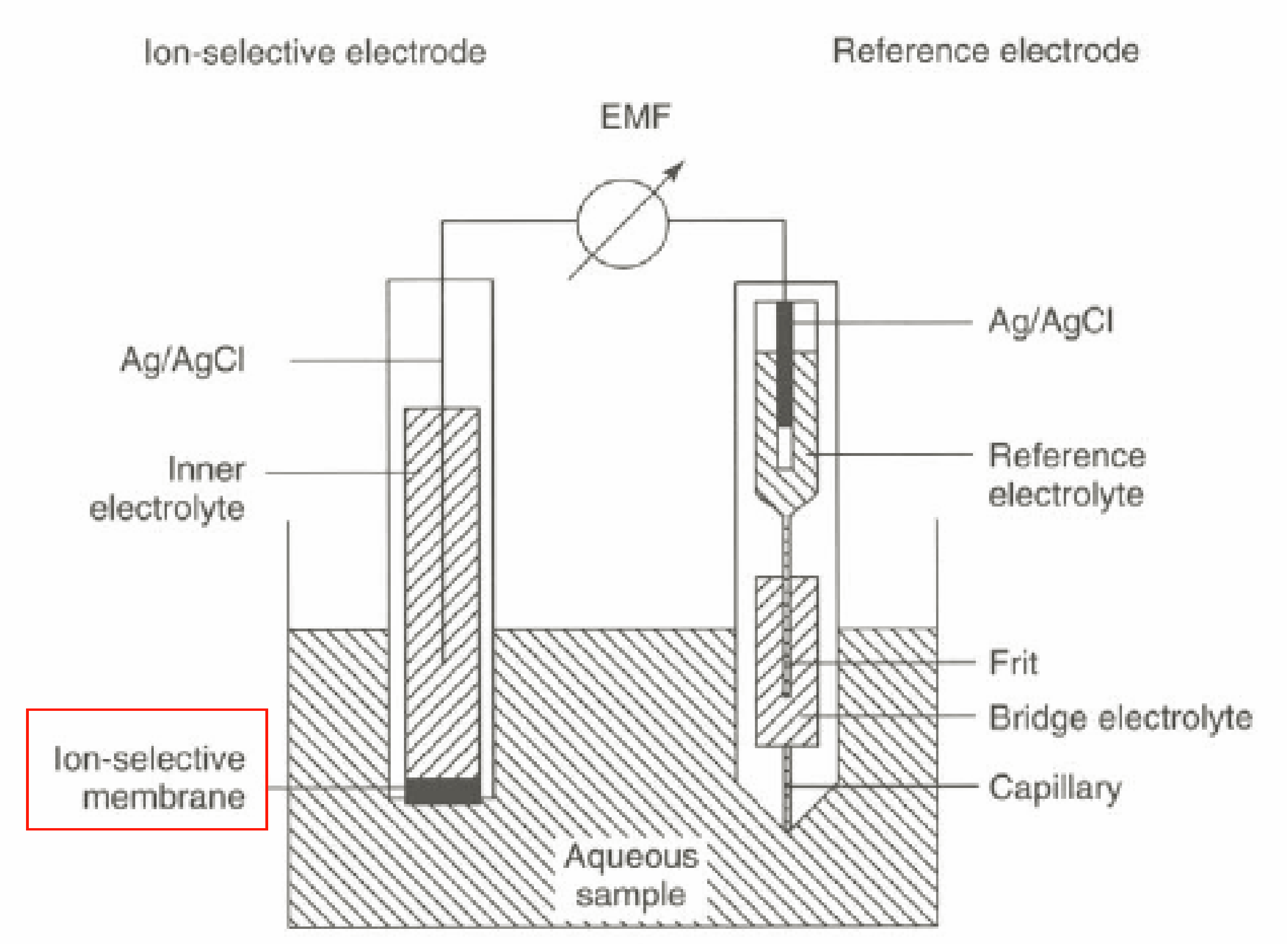
$E = E^* + RT/nF \cdot \ln (a_{Ox}/a_{Red})$

→ Measured potential:

$E_{cell} = E_{ind} - E_{ref}$



Ion-selective Electrode (ISE)



[1,10]

Electrochemical transducers

- Potentiometry
- Amperometry
- Conductimetry
- Field Effect Transistors

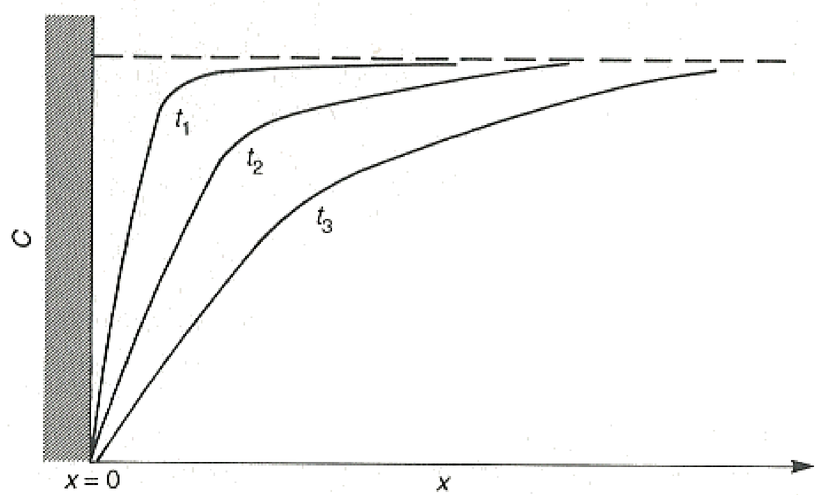
Difference between indicator and reference electrode potential at equilibrium (i.e. zero current)

Current flowing between working and reference electrode

Amperometry

- At t_0 a voltage is applied over the electrodes, causing the cell to "recharge".
- The diffusion rate of fresh Ox decreases.

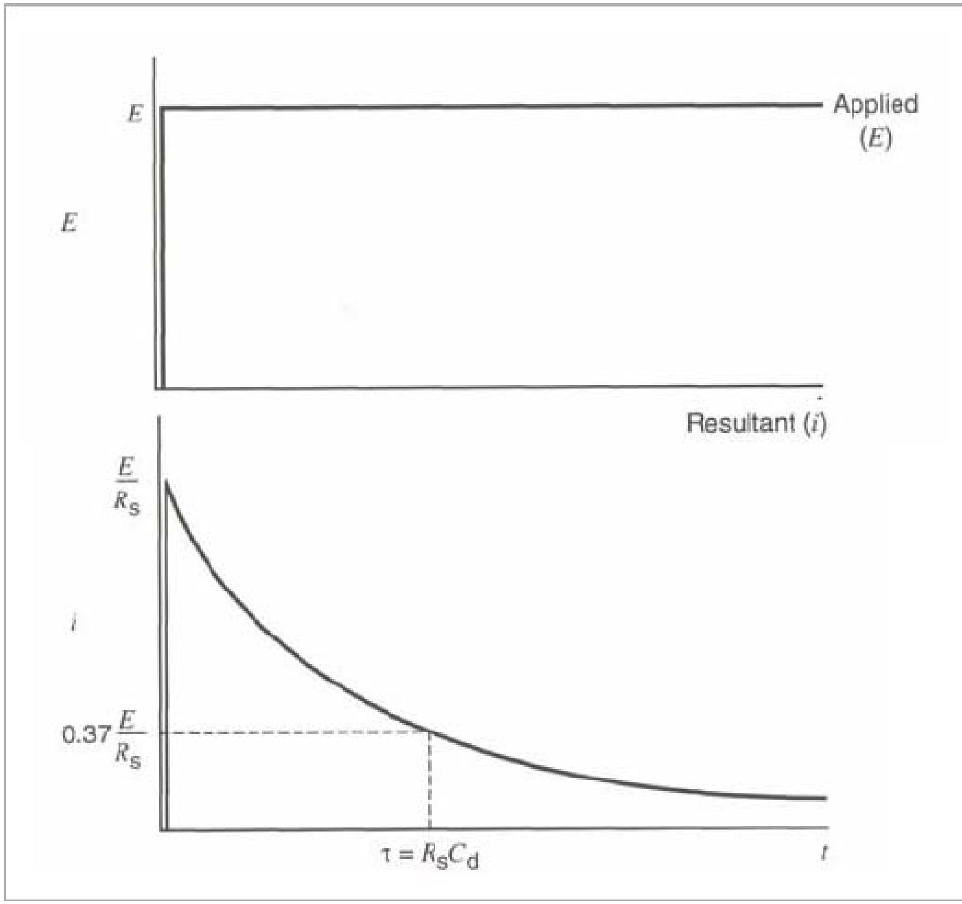
Fick's law: $dC/dt = D * d^2C/dC^2$



Amperometry (2)

→ The diffusion-limited current decays over time:

$i_d = nFADC_{Ox} / \sqrt{(\pi t)}$



Electrochemical transducers

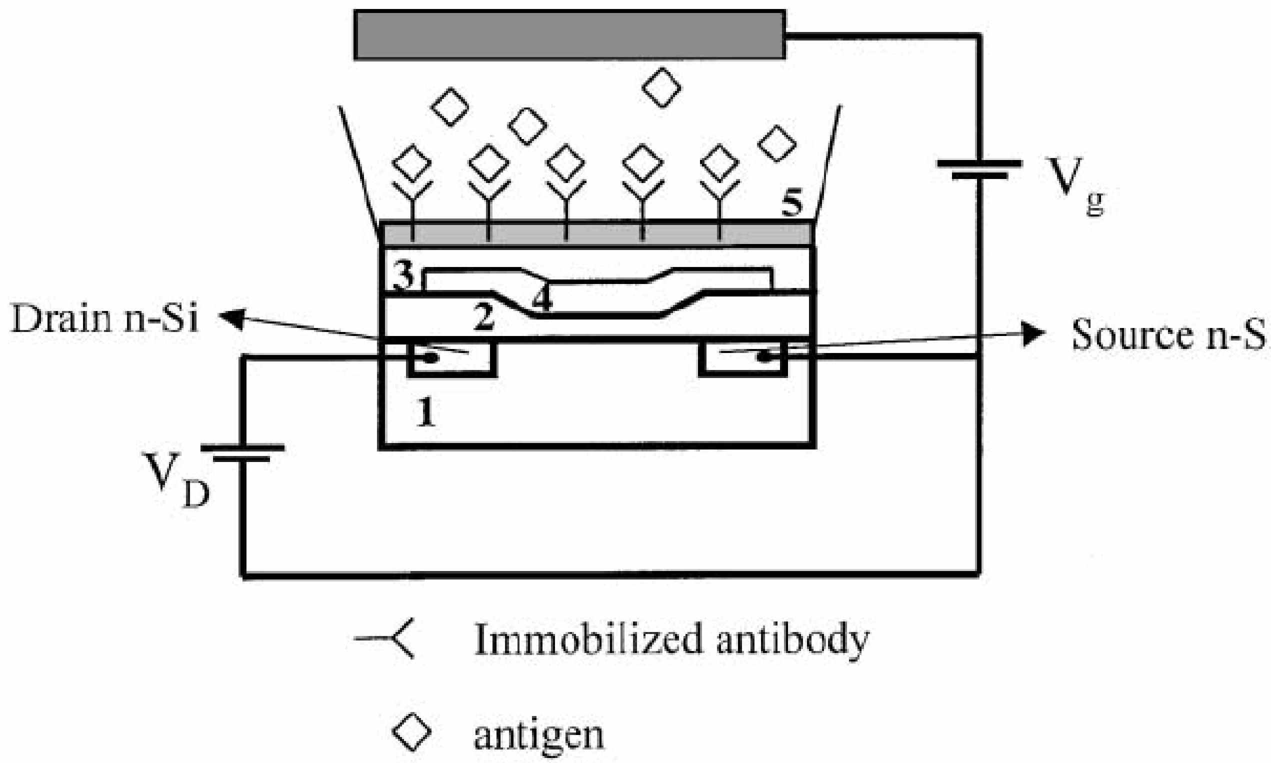
- Potentiometry
- Amperometry
- Conductimetry
- Field Effect Transistors

Difference between indicator and reference electrode potential at equilibrium (i.e. zero current)

Current flowing between working and reference electrode

Transistors where the gate metal has been replaced by a chemically sensing surface

Field Effect Transistor



1 Silicon substrate

2 Insulator SiO_2/Si_3N_4

3 Furrow Metals

4 Lacune (gap)

5 Selective coating

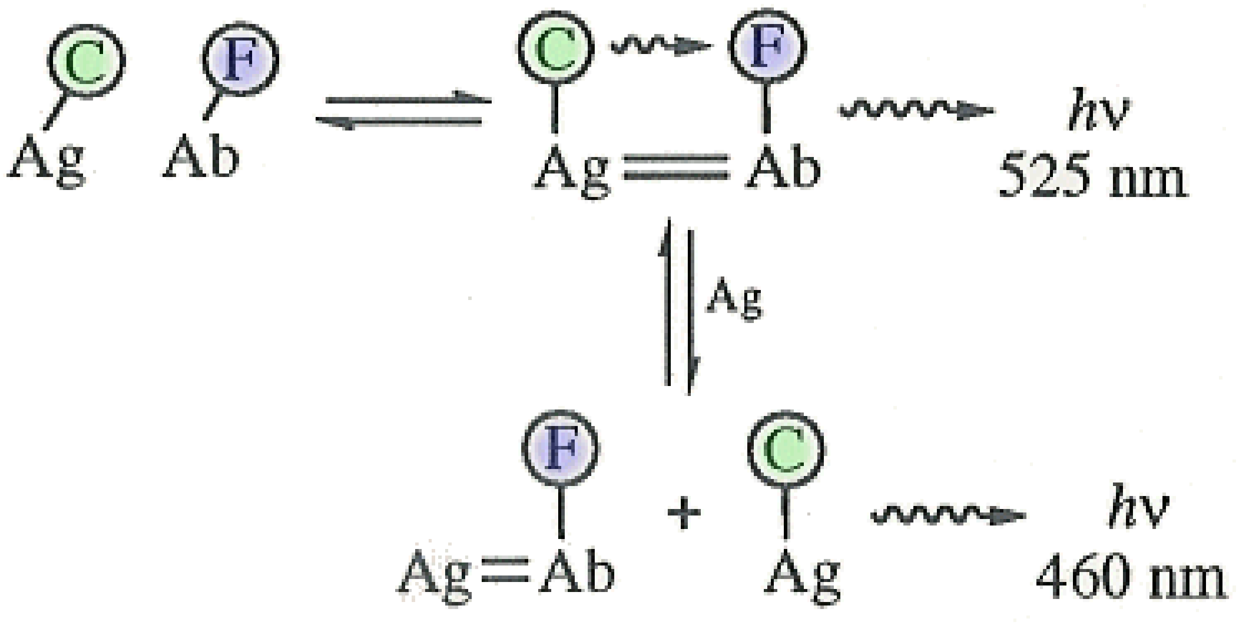
[1,9]

Optical transducers

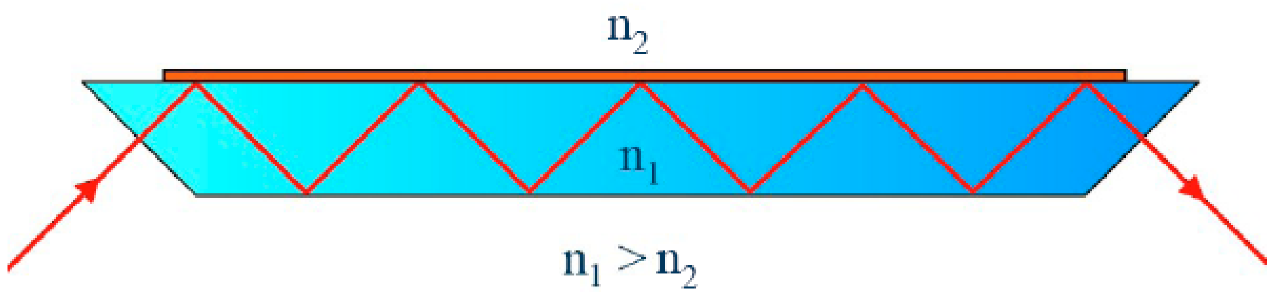
- Ultraviolet-visible absorption
- Luminescence
- Internal Reflection Spectroscopy
    - Surface Plasmon Resonance (SPR)
- Laser light scattering

Example: luminescence

- Combining chemiluminescence and fluorescence



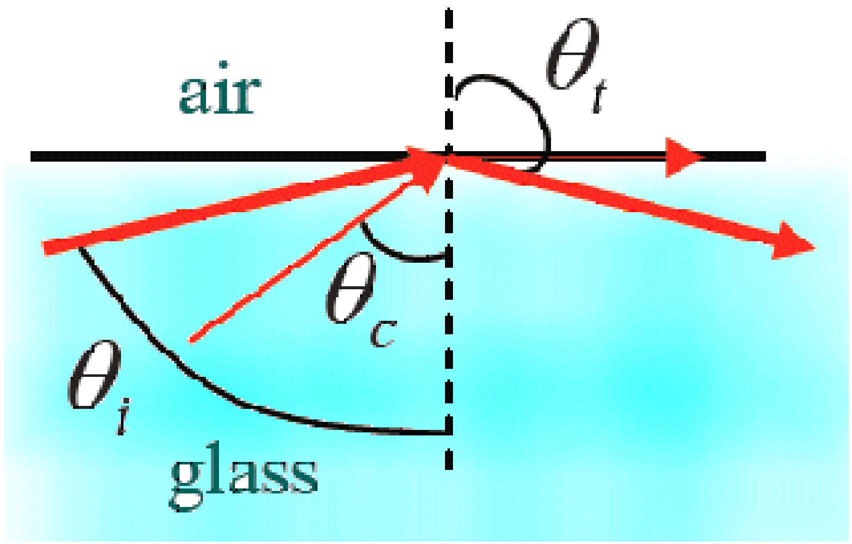
Total Internal Reflection (TIR)



- Snell's law:

  $n_1 \sin\theta_1 = n_2 \sin\theta_2$

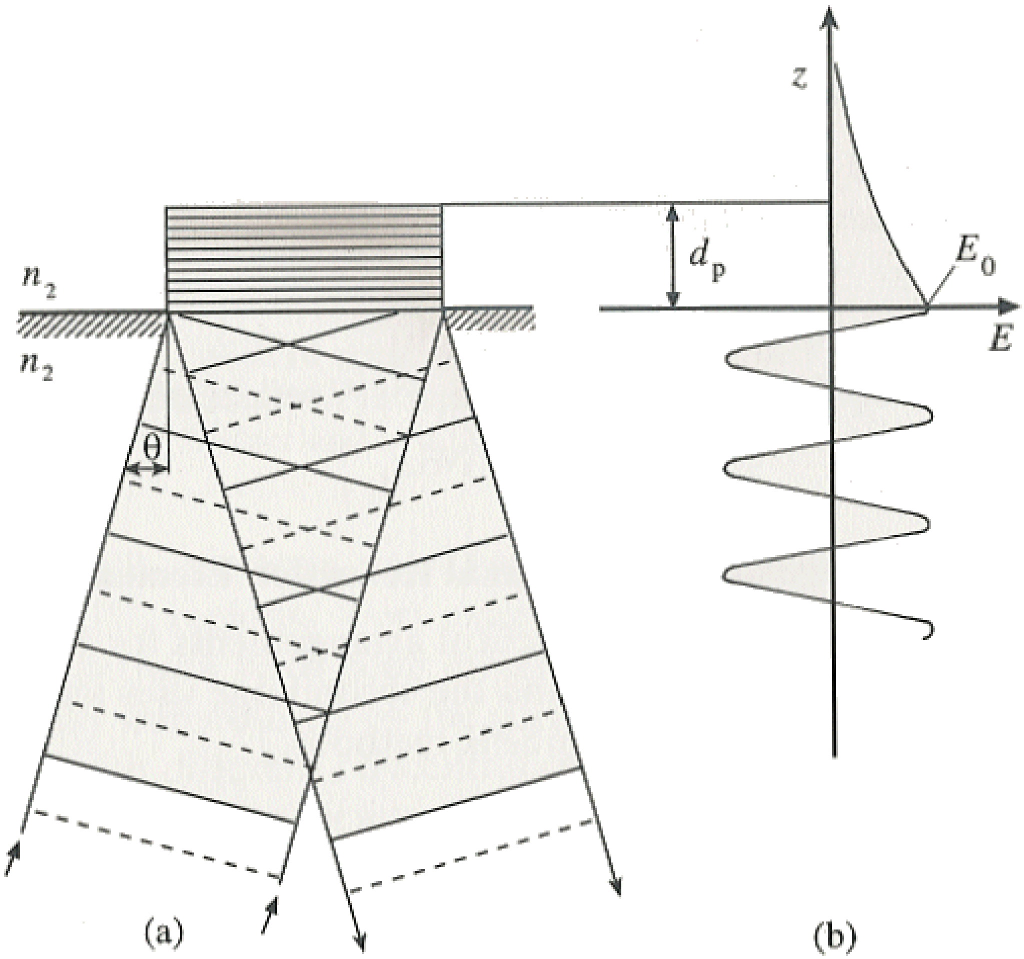
$\rightarrow \theta_c = \sin^{-1}(n_2/n_1)$



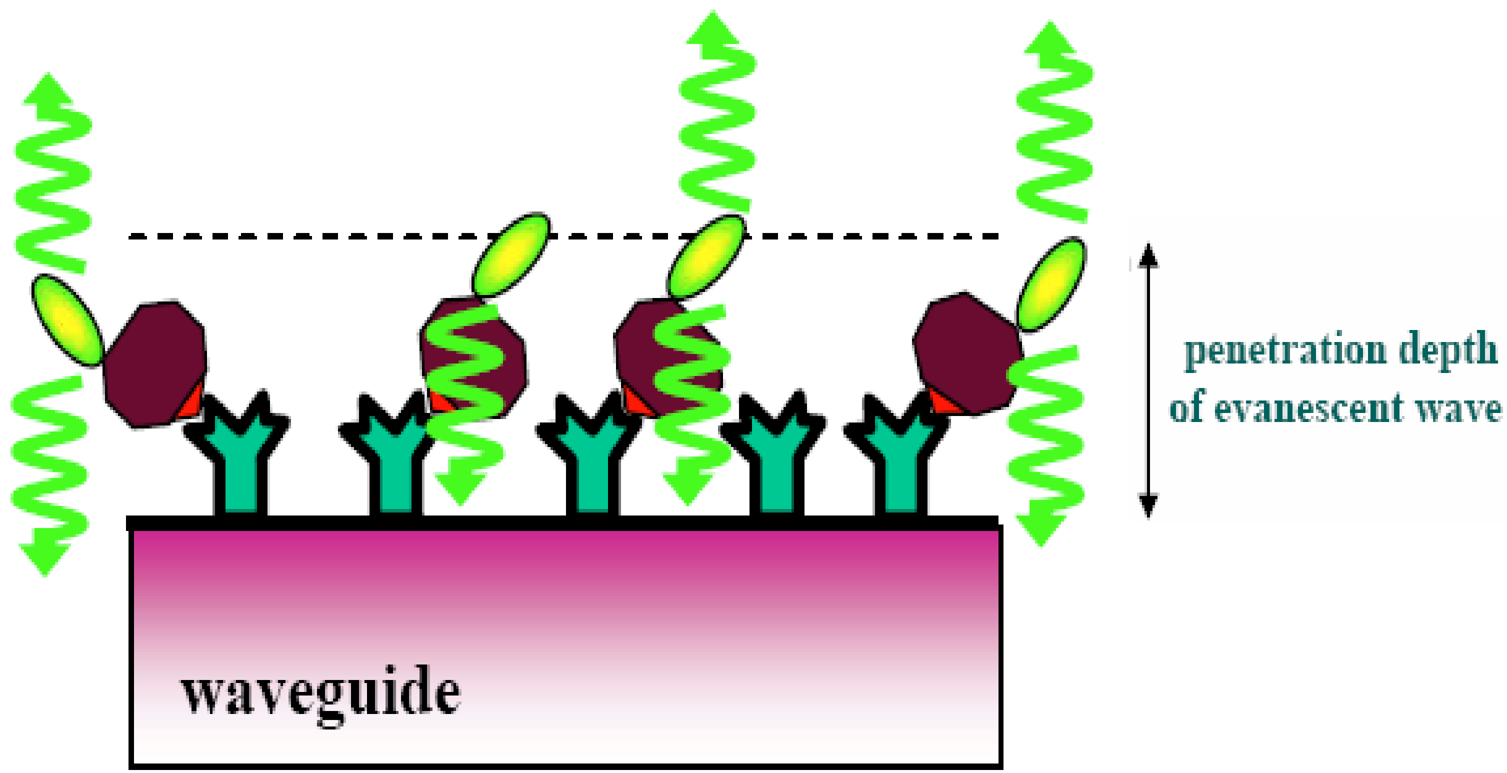
The evanescent wave

$$E_Z = E_0 \exp\left(- z/d_p \right)$$

$$d_p = \frac{\lambda}{2\pi n_1 \left[\sin^2\theta - \left(\frac{n_2}{n_1} \right)^2 \right]^{1/2}}$$

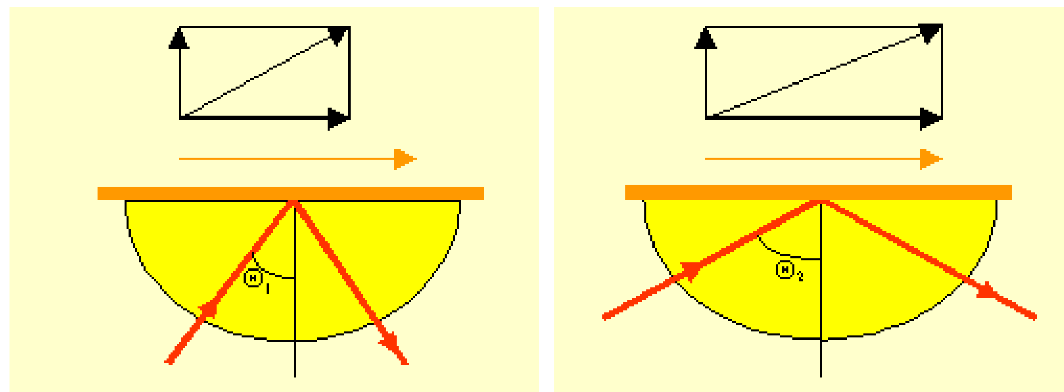


Total Internal Reflection Fluorescence



Plasmons & TIR

- A plasmon is a quasiparticle, belonging to a collective oscillation of the free electron gas in (semi)conductors.

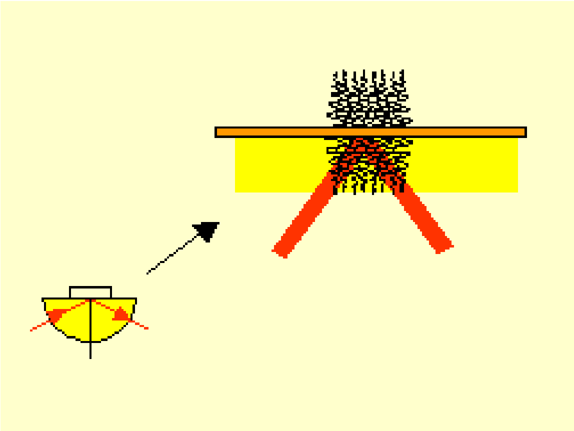


- An evanescent wave at a dielectric/conducting medium interface can excite surface plasmons

[12]

Plasmons & TIR (2)

→ Gap in the reflected light intensity

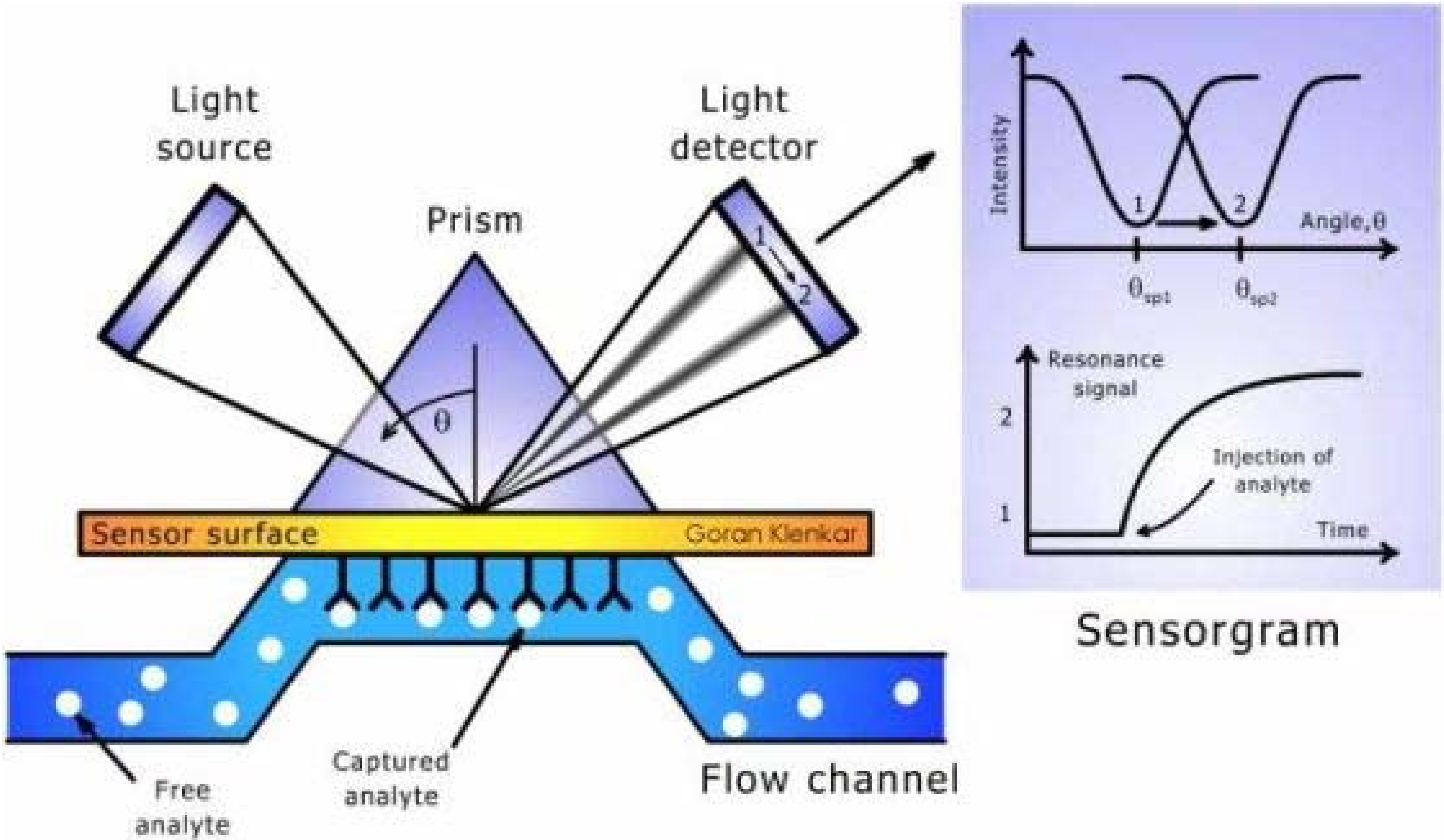


- How to involve biomaterial in this?

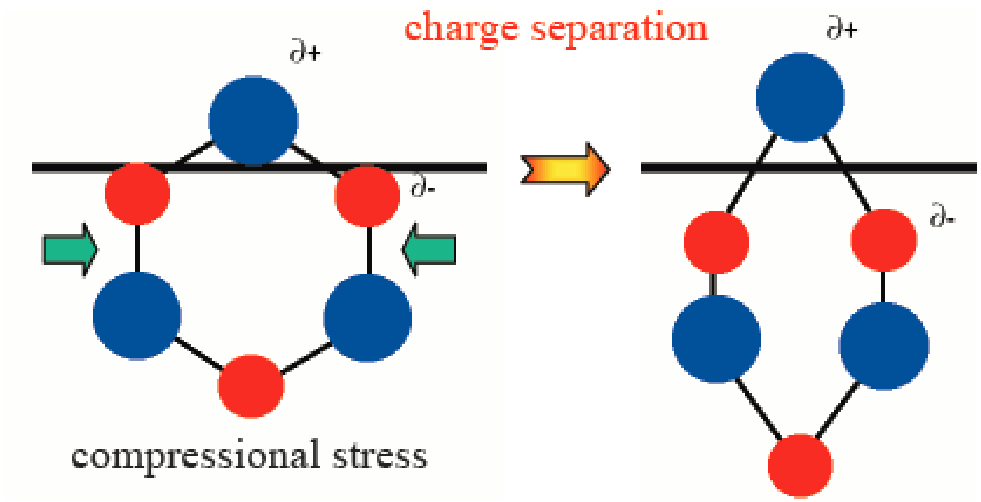
→ Thin conducting layer with biomaterial on the other side. A small change in refractive index of the biomaterial causes a large shift of θ.

[12]

Surface Plasmon Resonance



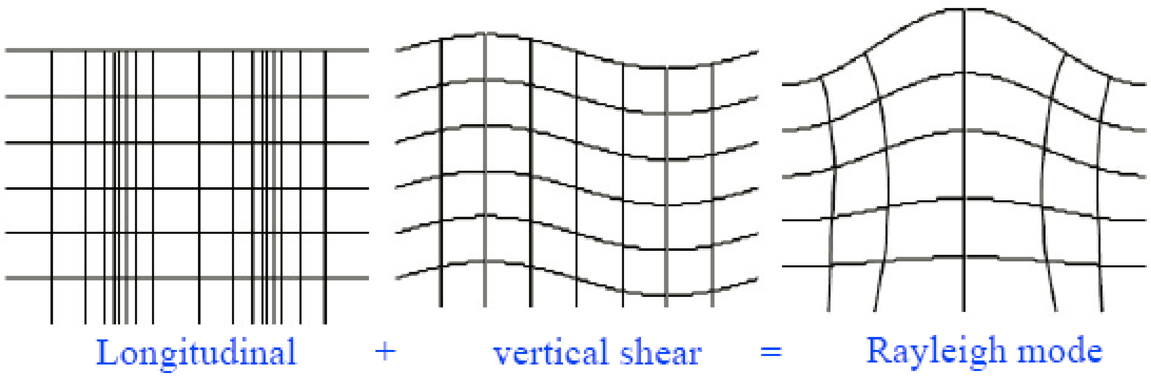
Piezoelectricity

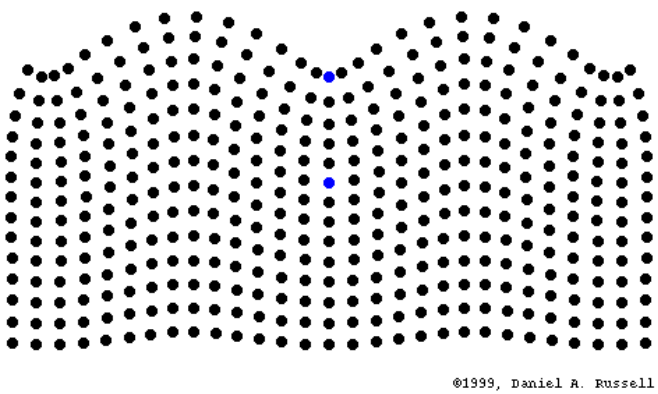


- Applied stress: $T = cS - e^{T}E$
- Electric displacement (polarization): $D = eS + \varepsilon E$

The Rayleigh Surface Wave

- Amplitude ~ 10Å





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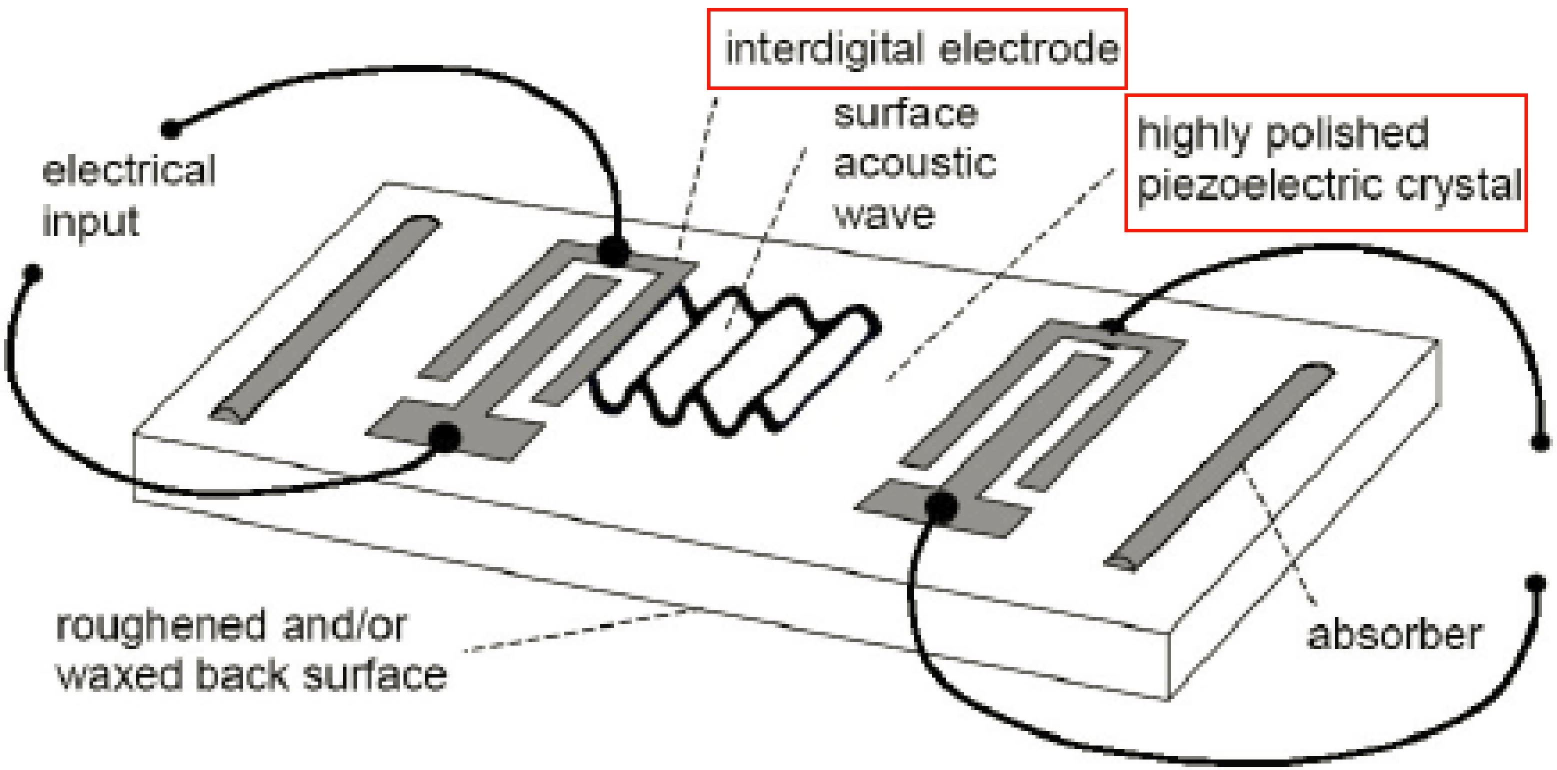
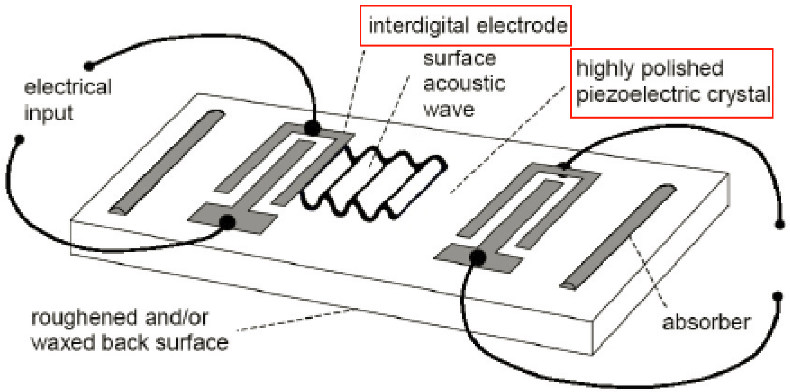
Surface Acoustic Wave Transducer

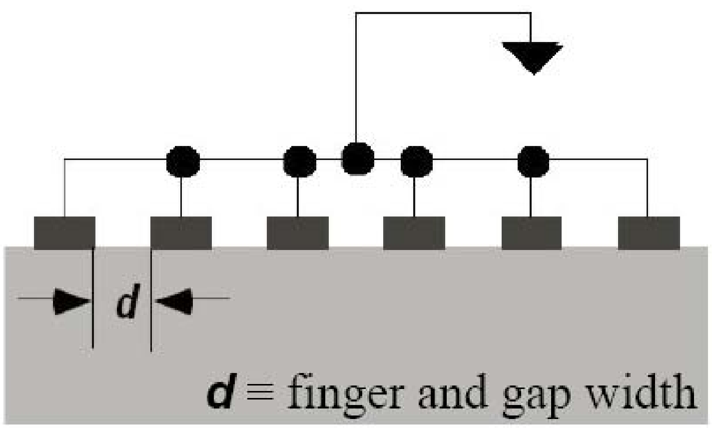


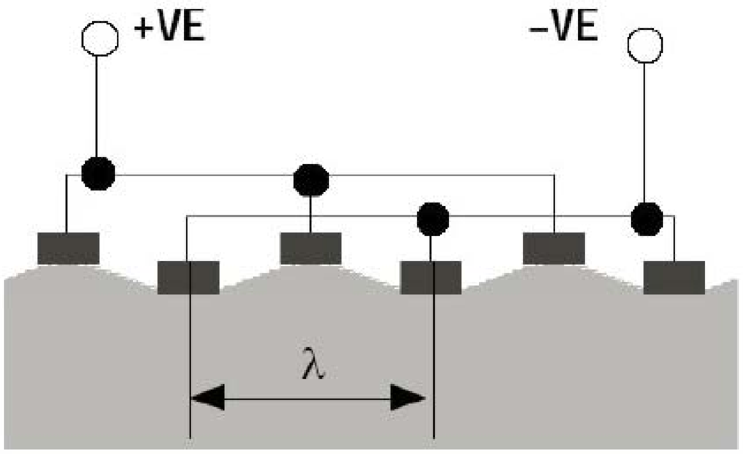
Surface Acoustic Wave Transducer

- Resonance frequency:

$$F_0 = V_R/\lambda = V_R / 4d$$







[1]

Overview

- What is a biosensor?
- The biological component
    - Immobilization
- Some transducer principles
    - Electrochemical
    - Optical
    - Acoustic-Piezoelectric
- Some application areas
    - Diabetes
    - Marine observation
- Conclusion

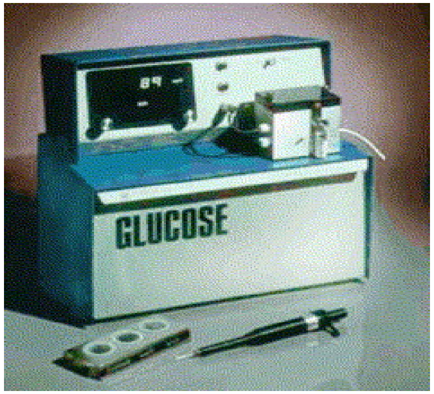
Application areas

- Health industry
    - Blood glucose sensors for diabetes patients
- Food industry
  - Determination of the composition
  - Degree of contamination:
    - Pathogens, pesticides, microorganisms, toxins
  - *On line* control of the fermentation process
- Natural environment
    - Water quality control

History of the biosensor

Leland C. Clark Jr. (1918-2005)

- Invented by Clark in 1962
- Commercialized in 1974
- World market in 2004: $5 billion



First commercial glucose biosensor

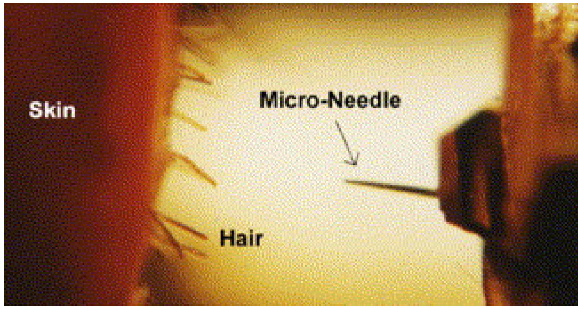
Diabetes

- Medical disorder, where the hormone that regulates uptake of sugars fails

  → high blood glucose level
- Type 1: lack of insulin

  Type 2: lack of insulin sensitivity
- 2006: 171 million people, 2030: twice as much
- #6 of the leading causes of death in the US

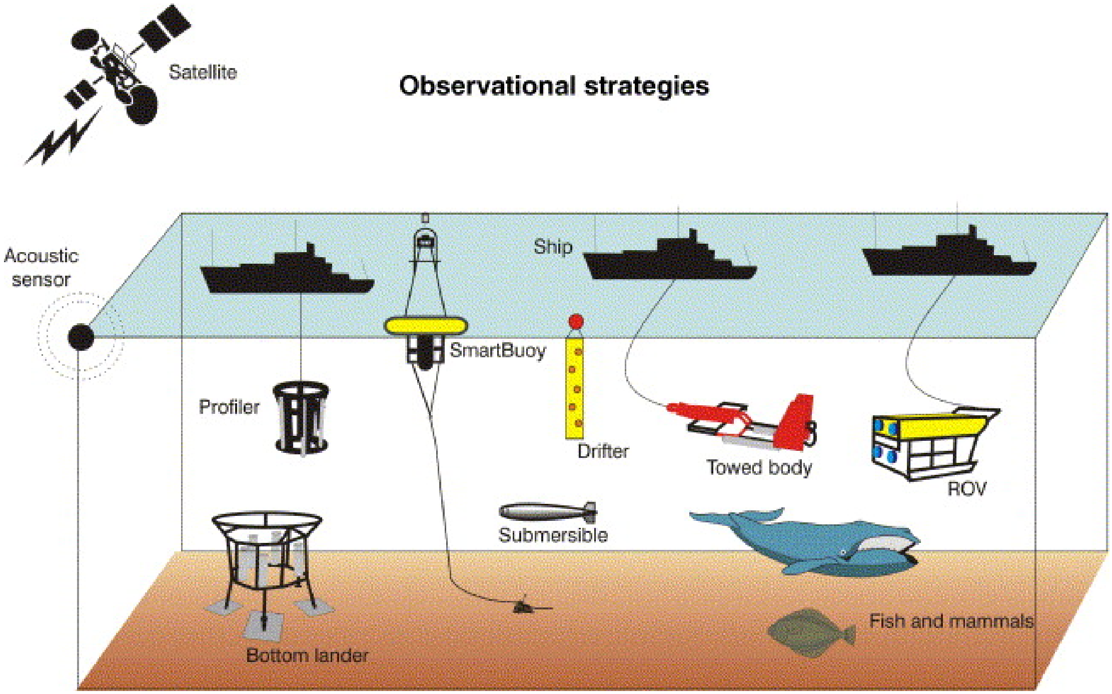
Blood glucose biosensors

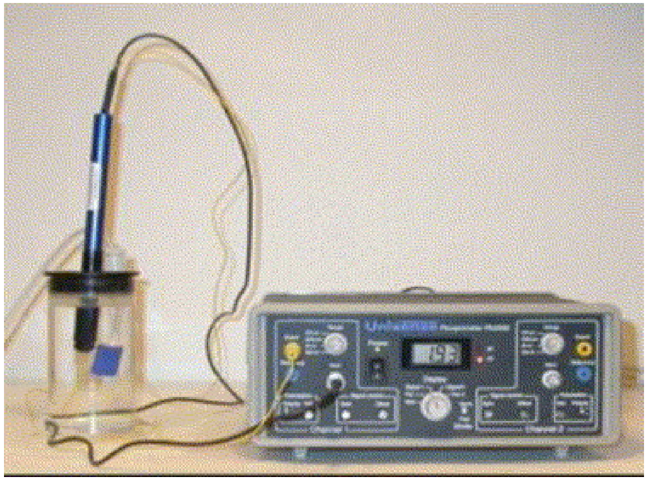


- Replaced the reflectance meters
- Now: 85% of the world market for biosensors

[4]

Marine observation





Nitrate biosensor

- Nutrient concentrations, algal biomass, species composition, water quality (oxygen, toxins etc.)

Commercial success & expectations

Commercial succes due to popularity in:

- Academic research (cheap equipment, broad learning field)
- Politics (improvement of human health / environment; defence against biochemical terrorism)

Sensor type	Advantages	Disadvantages
Single use	high accuracy and sensitivity, modest costs	
Intermittent use	fast	not precise, very expensive
Continuous use		cannot hold calibration yet

[3]

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E-Mail: n.munnikes@mytum.de