SENSORS
LECTURE 8

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TalTech Lab-on-a-Chip

01.02.2022

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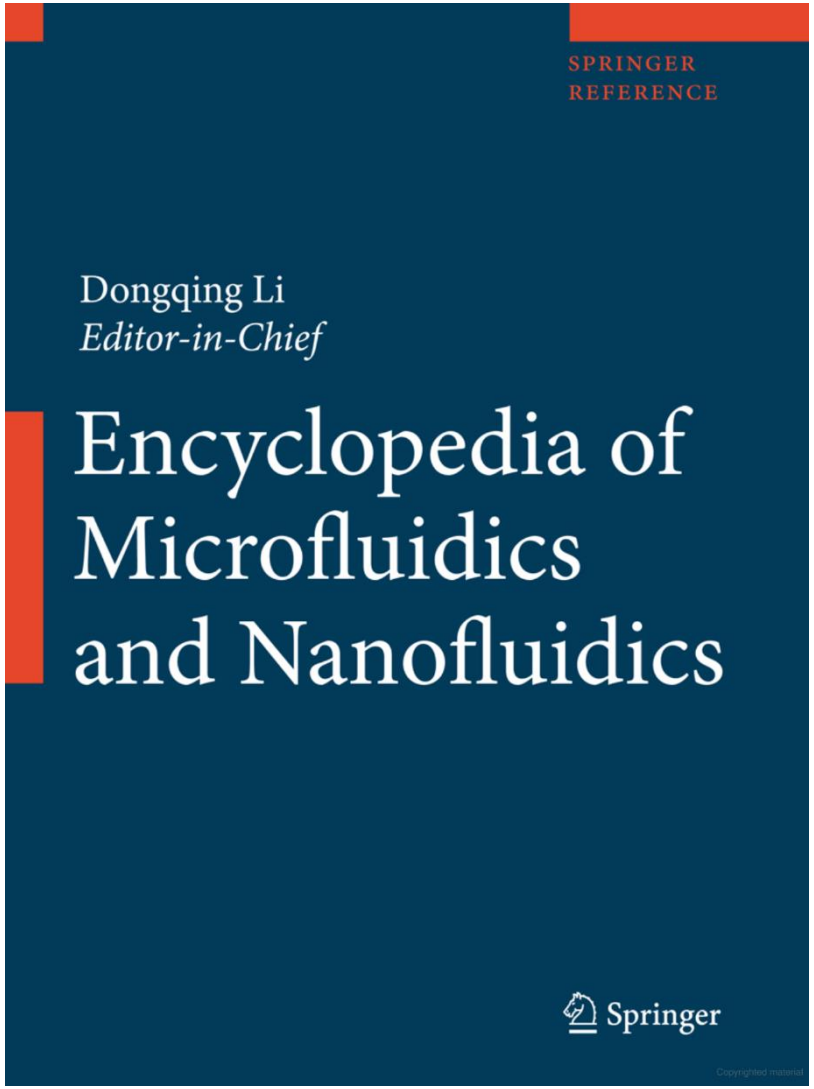
BEFORE WE BEGIN…

- Encyclopedia of Microfluidics and Nanofluidics
- Dongqing Li
- ISBN: 9780387324685

- Slides based on originals from IEE1720 lecture 1 by Natalja Sleptšuk
- BioMEMS course, Peter Pazmany Catholic University, Budapest, Hungary (by: Kristof Ivan)
- **Additional materials:**
  - https://www.sciencedirect.com/science/article/pii/S095656631530329 8



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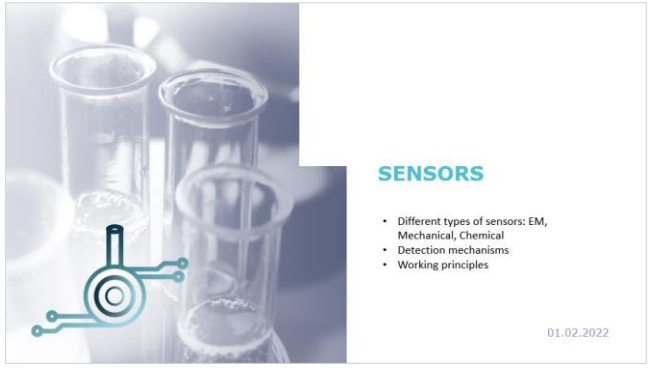
OVERVIEW



INTRODUCTION

- What are sensors?
- How do biosensors work?
- Human biomarkers

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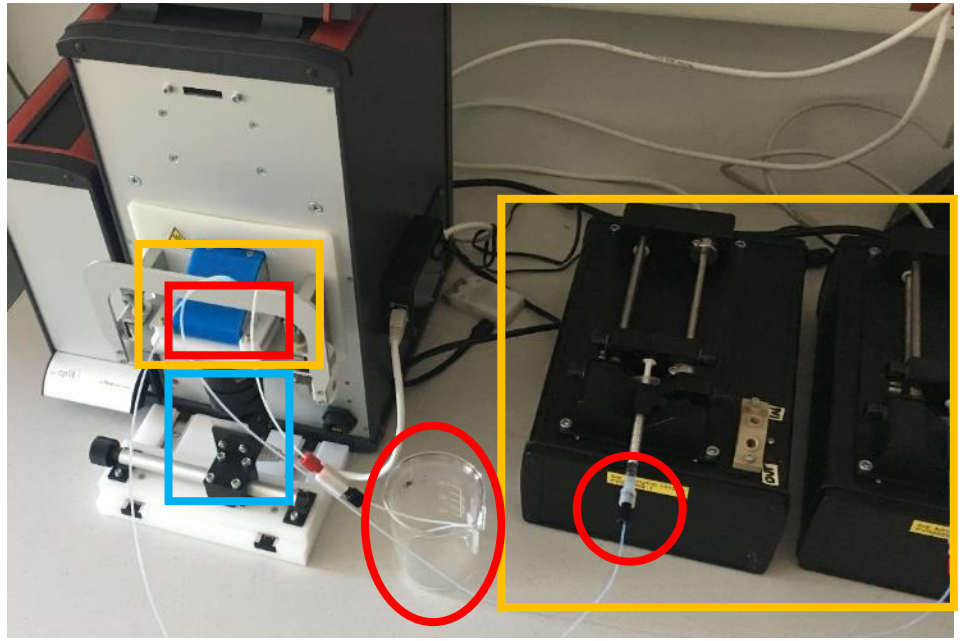
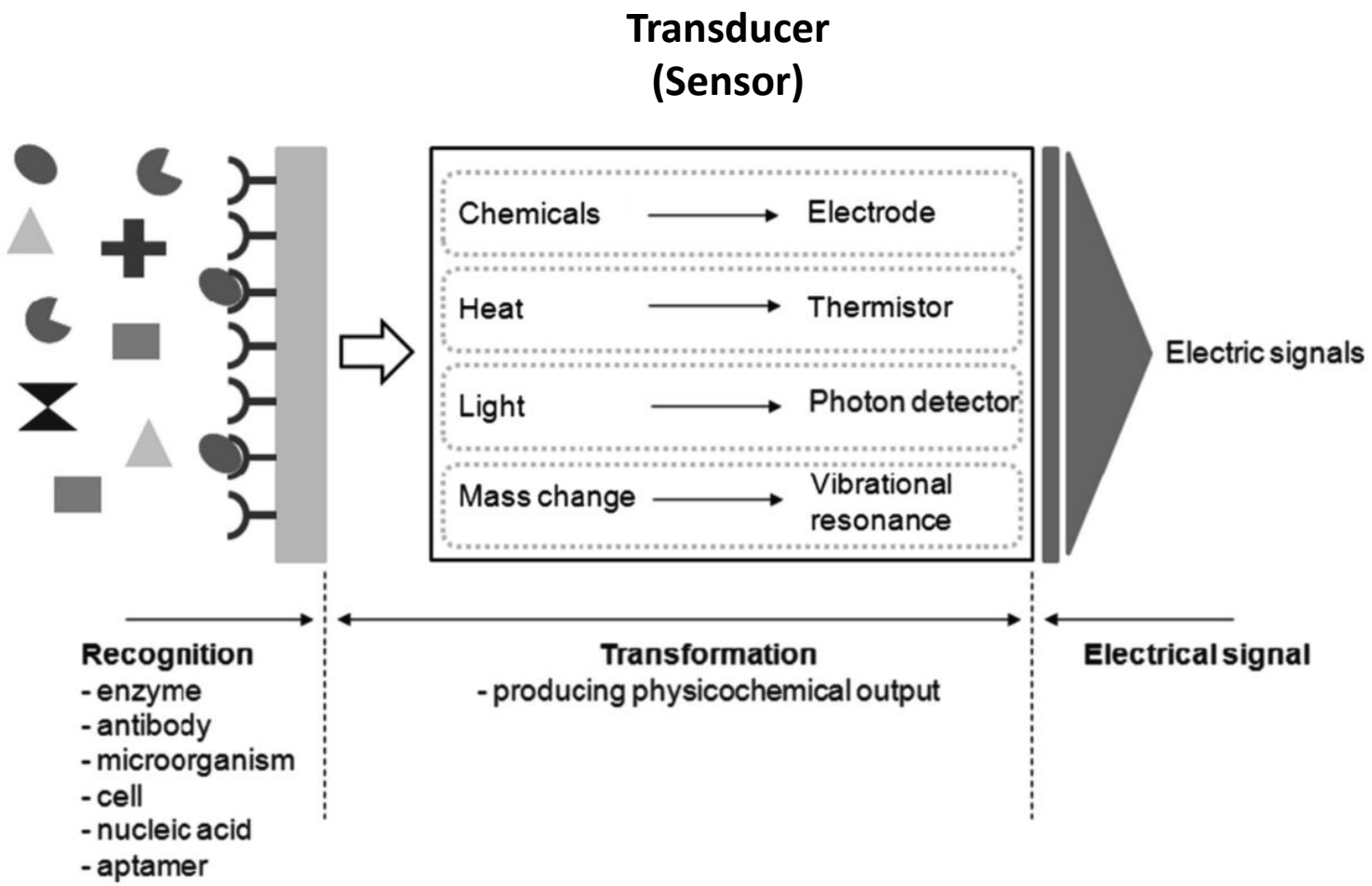
EXTERNAL SYSTEM COMPONENTS

- 1. **Liquid path:** → Lecture 3
  - Liquid reservoir
  - Tubing, fittings, chip holder, connector
  - **Microfluidic chip (reactor)**
  - Product/waste collector
- 2. **Actuators (internal/external):** → Lecture 9
  - Pump, valve, flow regulator
  - Thermal regulation (thermostat, heater etc.)
- 3. **Sensors (internal/external):**
  - Optical: camera, fluorometer etc.
  - Electrical: impedimetric sensors
  - Flow control: pressure sensor, flow meter
- Plus, power supply, control board, network interface, user I/O interfaces etc.



SENSORS



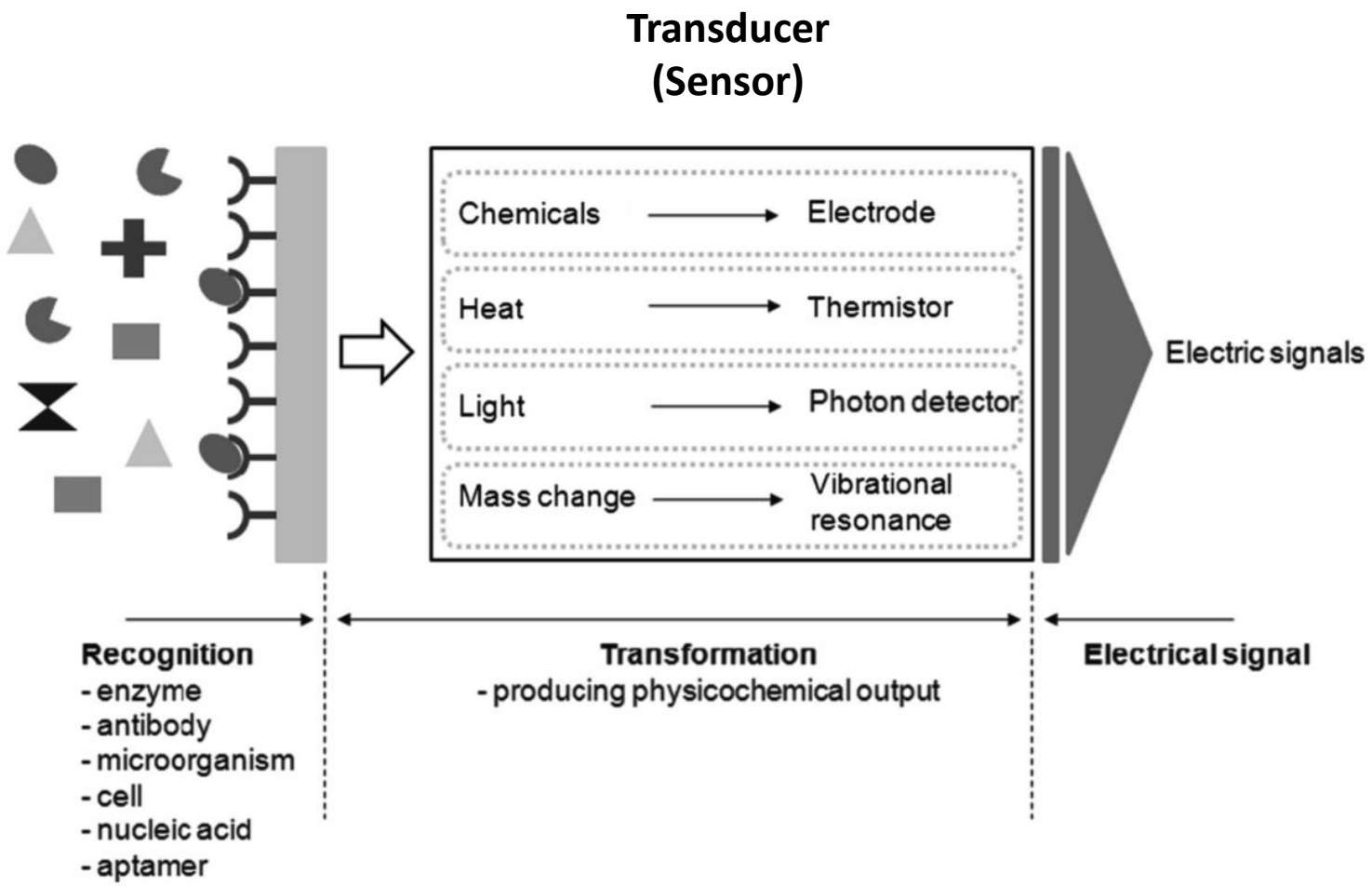
Sensor:

"**converts** one form of **energy** to another, and in so doing detects and conveys information about some physical, chemical or biological phenomena"

Sensor, as **transducer**:

converts the **measurand** (a quantity or a parameter) into a signal that carries information

SENSORS



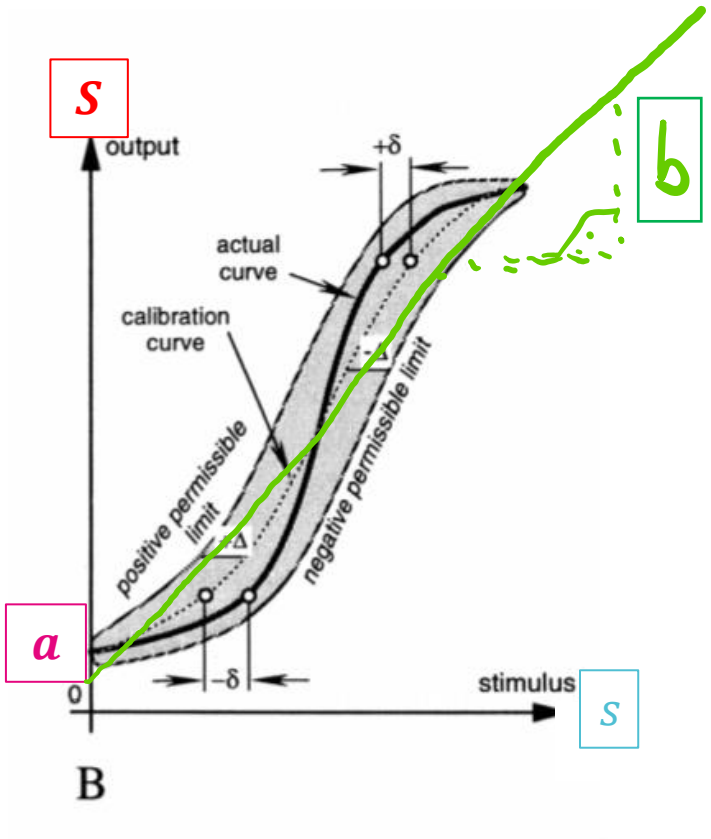
Ideal sensor

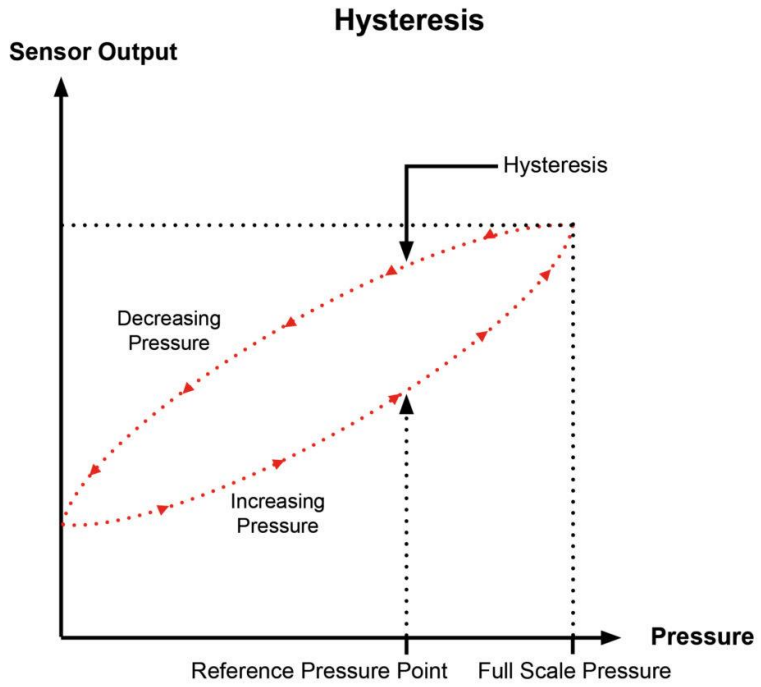
- Measures continuously
- Is sensitive and selective
- Has fast and predictable response
- Has reversible behavior
- High SNR
- Compact
- Immune to environmental interference
- Is easy to calibrate

Categories

- Biosensor
- Smart sensor
- Passive/active
- Array type
- Multimodal…

SENSORS





Transfer function:
(Relation between output signal and measurand)

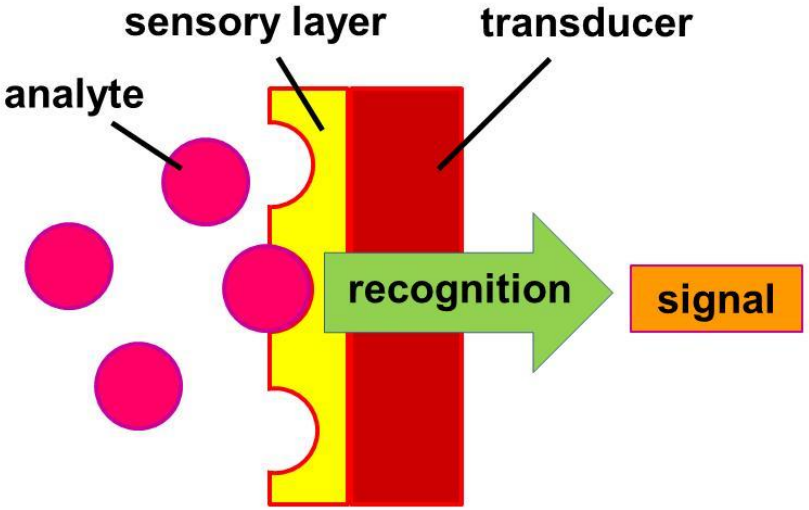
$$S = a + bs$$

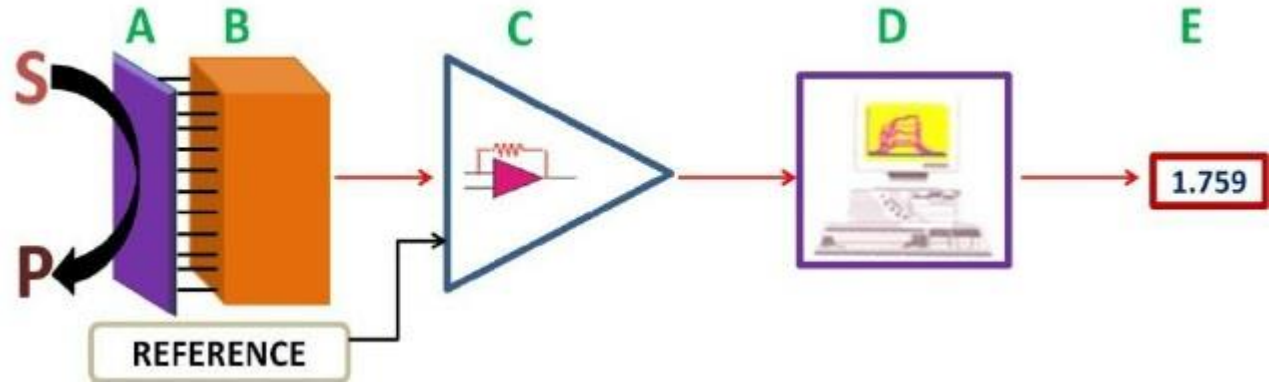
S: output electric signal
a: intercept (output at zero input signal)
b: slope/sensitivity
s: input stimulus

Hysteresis (error)**:**
Maximum difference between outputs at a specific point of input stimulus when approached first increasing then decreasing stimulus
(e.g.: inflating and deflating a balloon while measuring pressure)

WHAT IS A BIOSENSOR?

- **Goal**: to tell how much of something you have in a solution
- Something = target/analyte, measured in **concentration** (e.g. molarity in mol/m^3 or mol/L
- **Principle**
  - A: Reaction, produces product P in a specific concentration
  - B: transducer converts concentration to electric signal
  - C: signal is amplified
  - D: signal is processed
  - E: processed, amplified signal is visualized in human-readable form





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https://www.elprocus.com/what-is-a-biosensor-types-of-biosensors-and-applications/

HUMAN BIOMARKERS

- **Biomarker**=*"chemical, its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measured in the human body" (WHO definition)*

Biomarker concentration ⇔ physiological state of organism

- Example:
  - hCG as indicator of pregnancy
  - Released by placenta after implantation of fertilized egg
  - Rapid tests available since 60's, today <1€/test

Category	Detection target	Bodily fluid	Biomarker or substance
Cancer detection	prostate cancer	blood	PSA (prostate specific antigen)
	liver cancer	blood	AFP (tumor marker alpha-fetoprotein)
Other commonly used	pregnancy	urine	hCG (human chorionic gonadotropin)
Cardiac markers	myocardial damage (infarction)	blood	troponin
	myocardial infarction (no skeletal muscle damage)	blood	creatine kinase (CK-MB)
	myocardial infarction	blood	lactate dehydrogenase (LDH-1)
Exposure to toxic substance (biomonitoring)	lead	blood	blood lead
	arsenic	urine	urinary arsenic
	nitrates	blood	methemoglobin
	phtalates	urine	phtalate metabolites

Source: (own work) course work report, IEM9040, by Tamas Pardy, 2014

INTRODUCTION

- What are sensors?
- How do biosensors work?
- Human biomarkers

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SENSORS

- Different types of sensors: EM, Mechanical, Chemical
- Detection mechanisms
- Working principles

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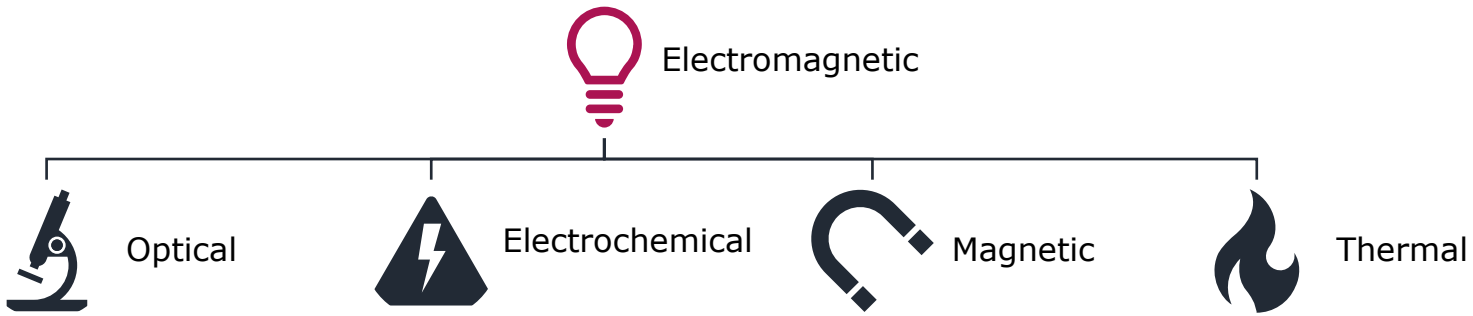
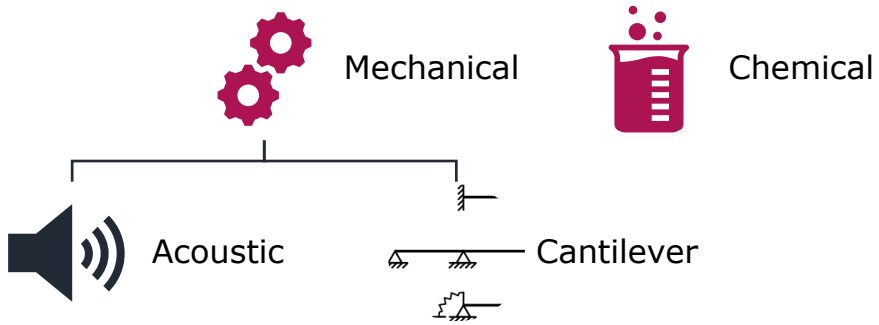
DETECTION METHODS

Technology





Labeling
- Labeled
- Label-free

Amplification
- Signal amplification
- Target amplification

State of organism
- In vivo
- In vitro
- *Ex vivo (e.g. cell cultures)*

SPECTROPHOTOMETRY

- Beer-Lambert Law:

  attenuation of light ⇔ properties of material being lit

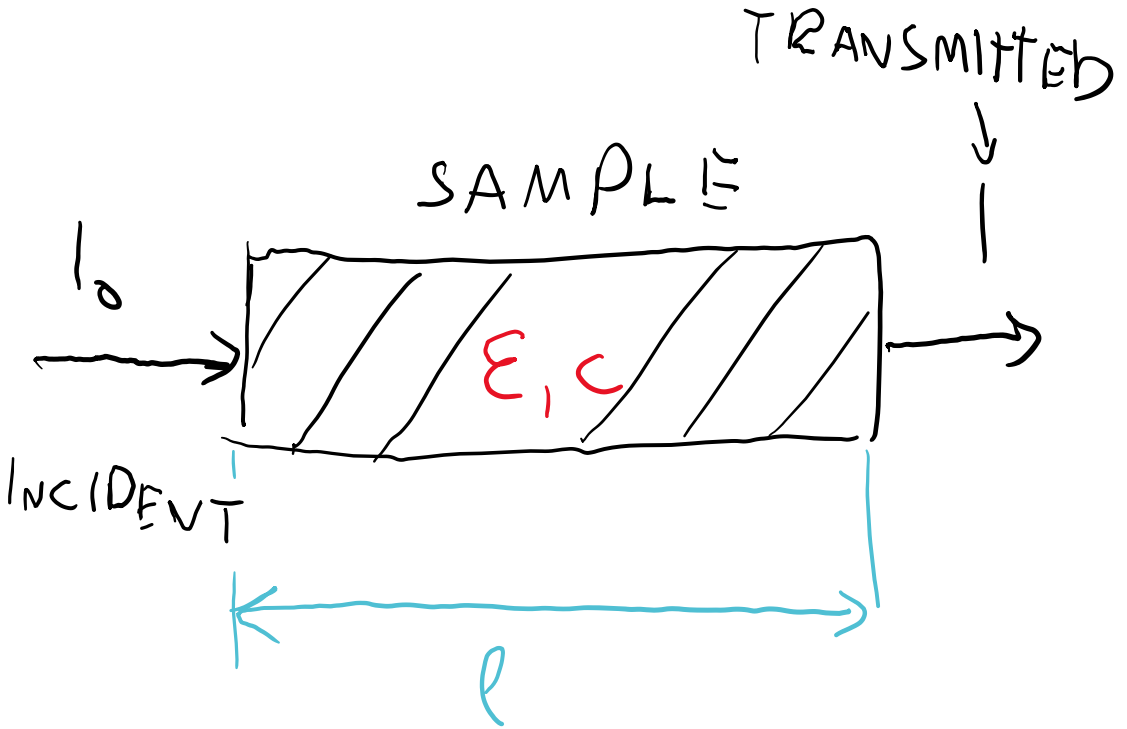
$$A = \varepsilon l \boldsymbol{c}\ [a.u.]$$

- Measurement modes:
  - Absorbance

$$A = \frac{I_0}{I}$$

  - Transmittance

$$T = \frac{I}{I_0}$$



A: *absorptivity* $[a.u.]$

ε: *molal attenuation coefficient* $\left[\frac{m^2}{mol}\right]$

l: *optical path length* $[m]$

$\boldsymbol{c}$: ***concentration of species*** $\left[\frac{\boldsymbol{mol}}{\boldsymbol{m^3}}\right]$

Optical

SPECTROPHOTOMETRY

- Beer-Lambert Law:

  attenuation of light ⇔ properties of material being lit

$$A = \varepsilon l c \; [a.u.]$$

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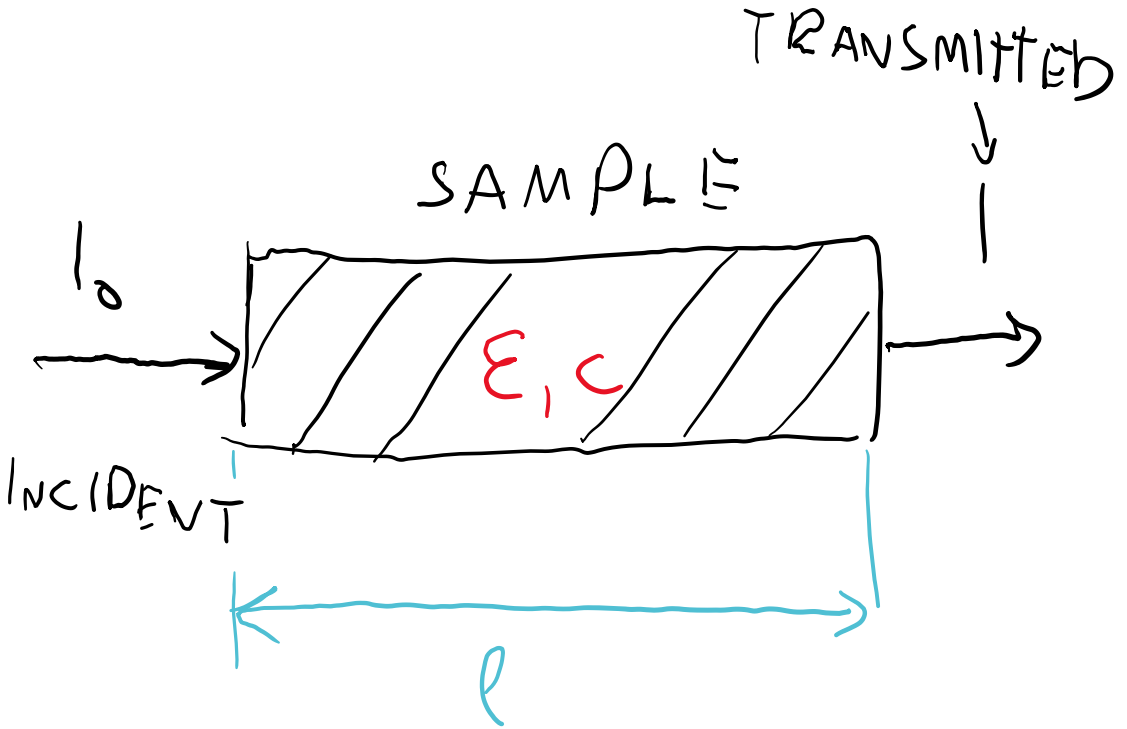

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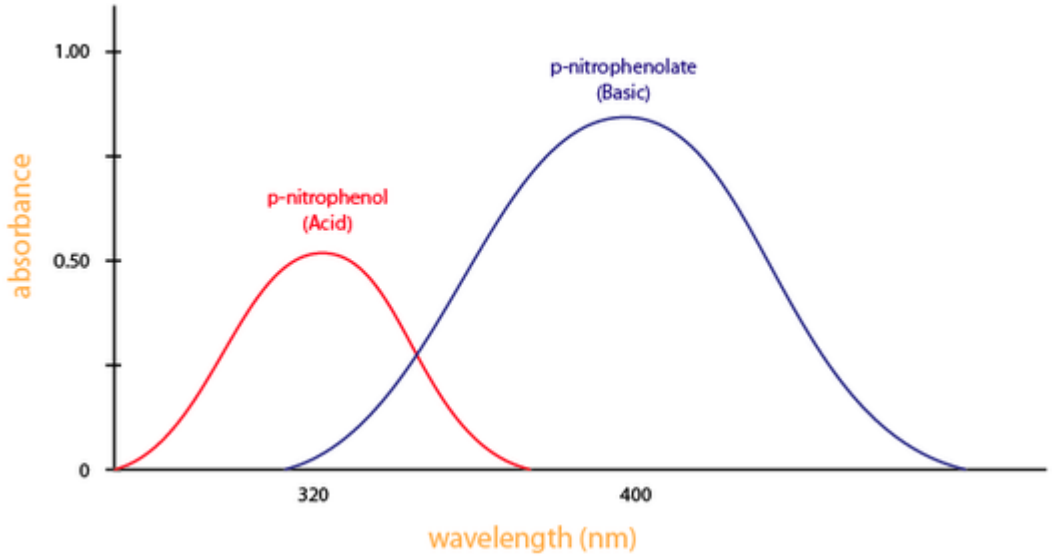
Optical

SPECTROPHOTOMETRY

- Beer-Lambert Law:

  attenuation of light ⇔ properties of material being lit

$$A = \log_{10}\left(\frac{I_0}{I}\right) = \varepsilon l c$$



- Measurement modes:
  - **Absorbance**

$$A \approx \frac{I_0}{I}$$

  - Transmittance

$$T = \frac{1}{A} \approx \frac{I}{I_0}$$

Transparent:

$I = I_0$

$T \approx 100\%$

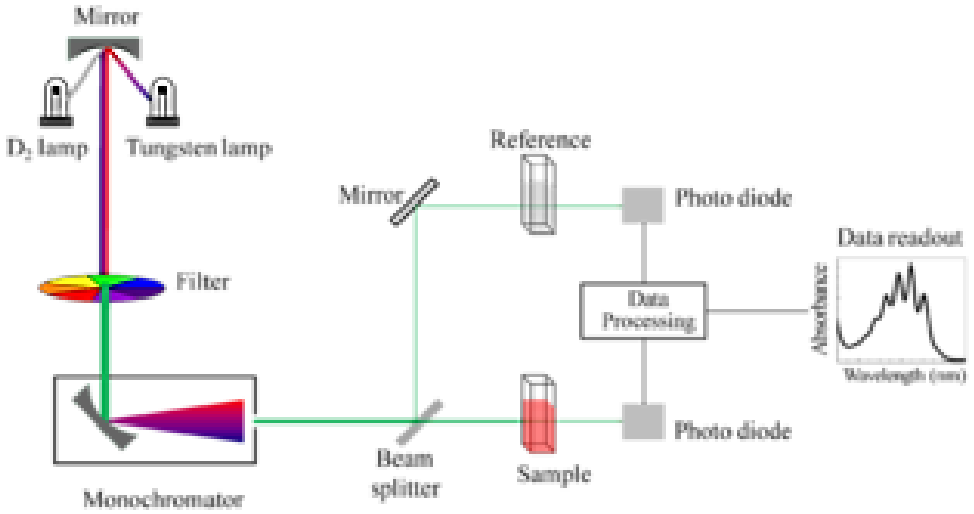
$A \approx 0\%$

Opaque:

$I \to 0$

$T \to 0\%$

$A \to 100\%$



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Optical

FLUOROMETRY

- Fluorochrome/fluorophore: molecule that absorbs energy from incoming light and emits another light

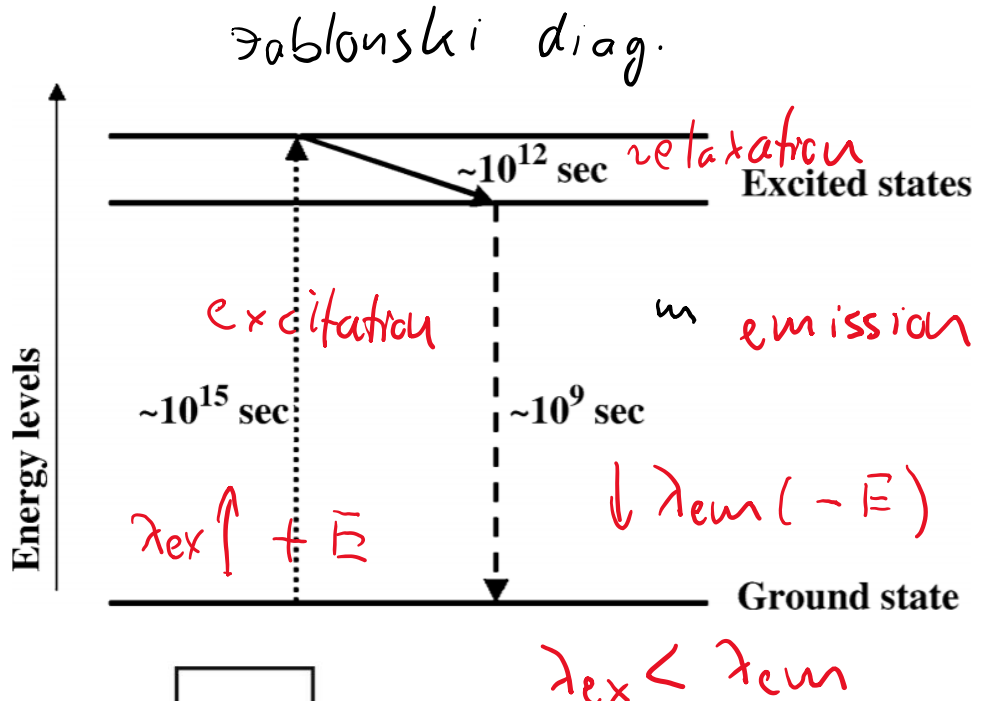
$$E = h\frac{c}{\lambda}\ [J]$$

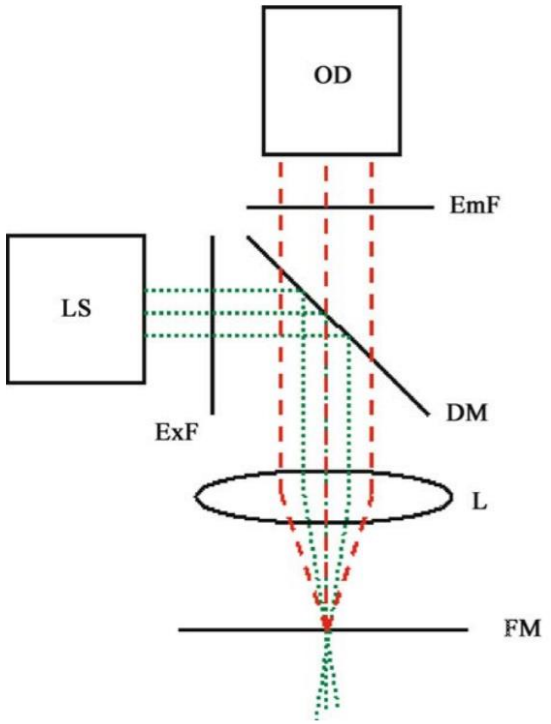
  - Where h: Planck's constant, c: speed of light [m/s], λ: light wavelength [m]

- Fluorescent intensity ⇔ lifetime

$$I(t) = I_0 e^{\left(-\frac{t}{\tau}\right)}$$

τ: $fluorescent\ lifetime$





LS = light source,
OD = optical detector,
ExF = excitation filter,
EmF = emission filter,
DM = dichroic mirror,
L = lens,
FM = position of fluorochrome molecules

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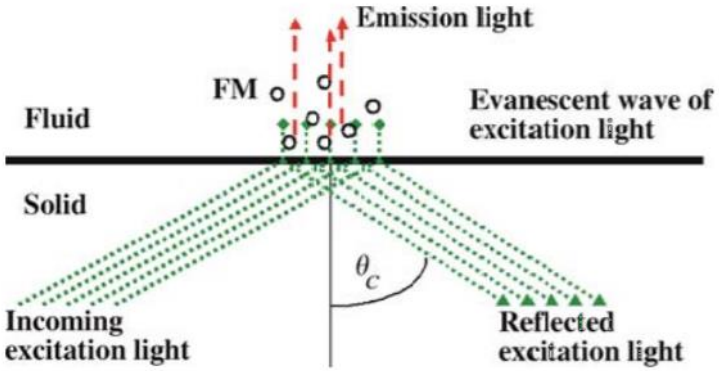
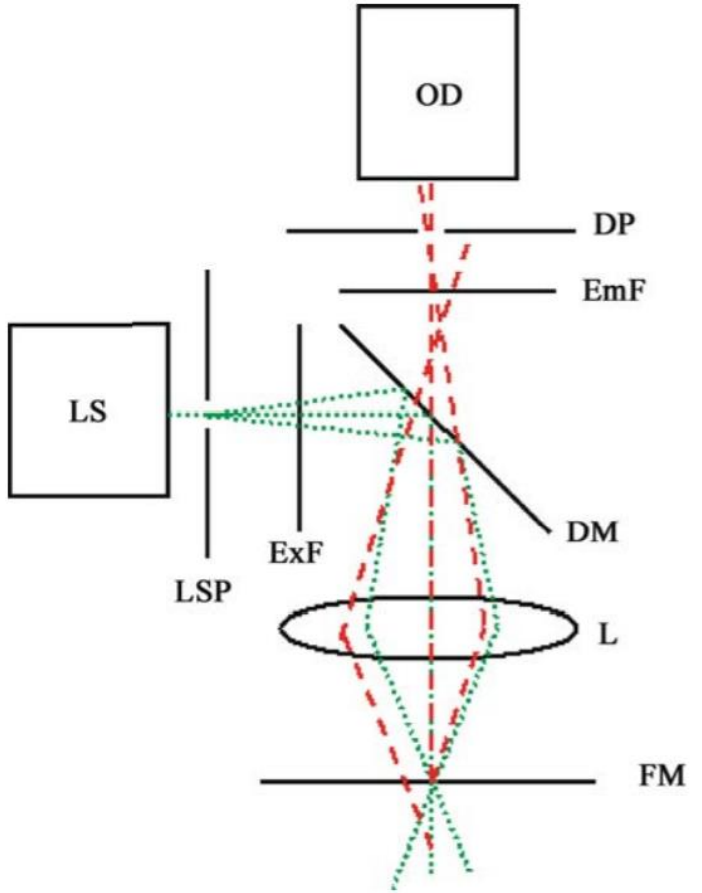
Optical

FLUOROMETRY

- Special cases



Fluorescence Measurements, Figure 4 *The* schematic concept of TIRF. FM = fluorochrome molecules. Note that only fluorochrome molecules that reside very close to the solid–fluid interface is illuminated by the excitation light and generates the emission light; the other fluorochrome molecules are not involved in the measurement



Fluorescence Measurements, Figure 3 The schematic concept of a confocal fluorescence microscope configuration. LS = light source, OD = optical detector, ExF = excitation filter, EmF = emission filter, DM = dichroic mirror, L = lens, FM = position of fluorochrome molecules, LSP = Light-source pinhole, and DP = detector pinhole. Note that the emission light coming from out-of-focus fluorochrome molecules is blocked away by the detector pinhole

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Optical

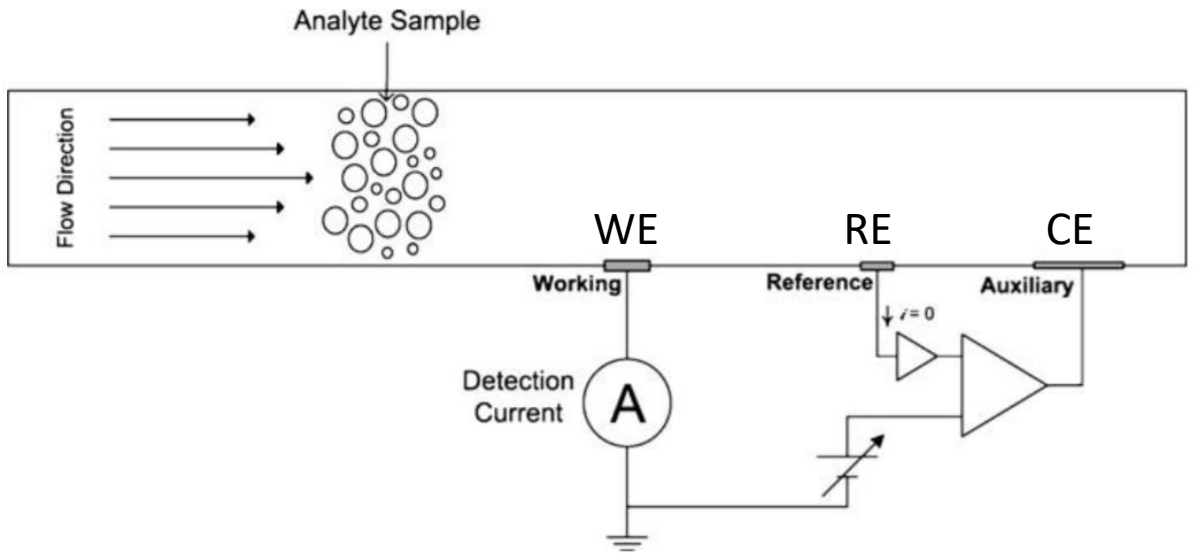
AMPEROMETRY

- Faraday's first law of electrolysis:
  "*the amount of chemical change produced by current at an electrode-electrolyte boundary is proportional to the quantity of electricity used*"
- Reaction: reduction-oxidation (redox)
- **Electrodes**:
  - **Working** (where the reaction e.g. oxidation happens, material e.g. C, Au)
  - **Auxiliary** (counter, where the reaction goes in the opposite direction, e.g. reduction, material e.g. Pt)
  - **Reference** (Ag/AgCl)
- **Amperometry**:
  - Voltage applied to working electrode
  - Current measured from working to counter electrode

Faraday's law of electrolysis:

$$i_t = \frac{\partial Q}{\partial t} = \eta F \frac{\partial N}{\partial t}$$

i_t: *current generated at time t* $[A]$
Q: *charge* $[C]$
η: *valency*
N: *moles of analyte* $[mol]$
F: *Faraday constant*



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Electrochemical

AMPEROMETRY

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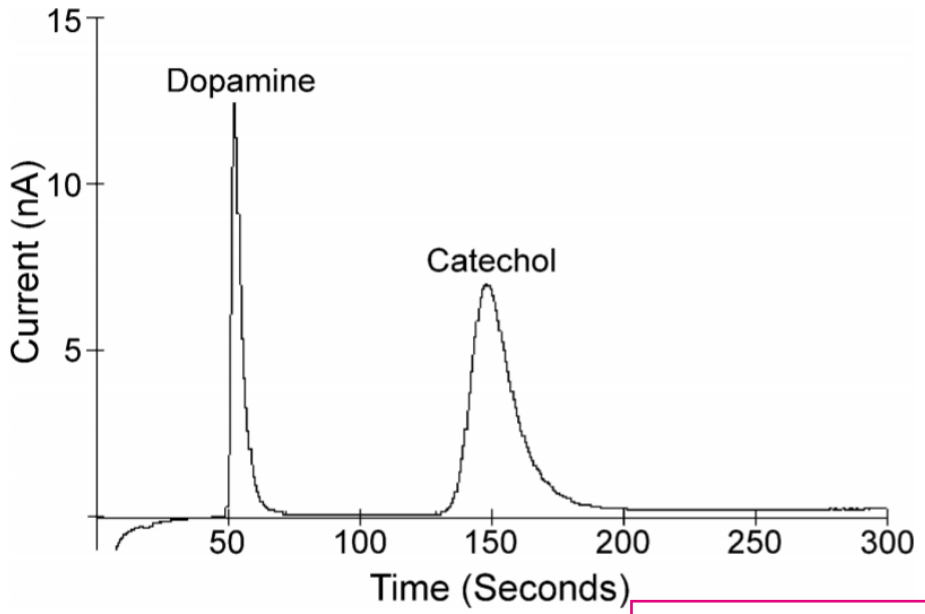

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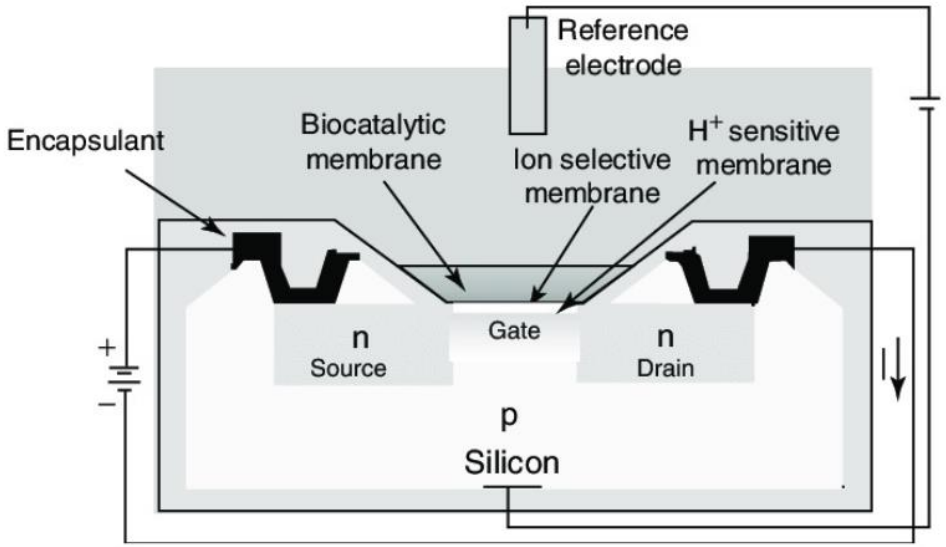
Electrochemical

POTENTIOMETRY

- Setup similar to amperometry, but
  - Electrode impedance high ➔ minimal current flow
  - Charge accumulation on electrode ➔ Nernst potential measured



reactant product

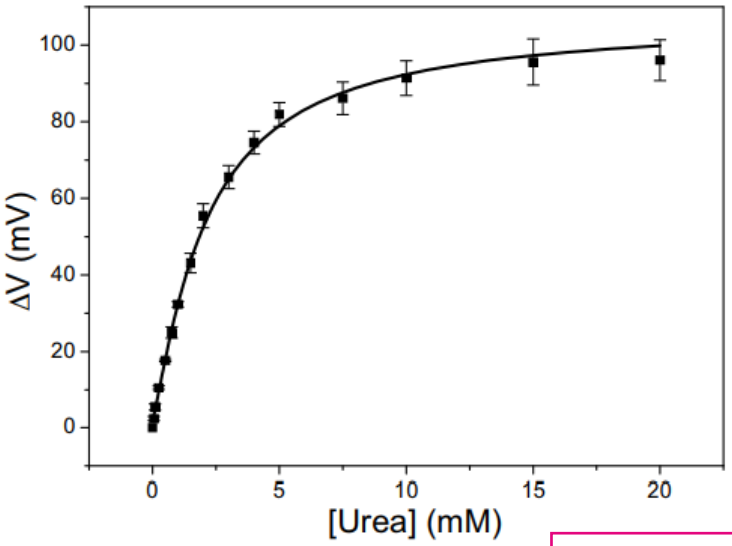
$$\alpha A \rightarrow \chi C + ne^- \quad \text{(anode)} \quad \text{(oxidation)}$$

$$\beta B + ne^- \rightarrow \delta D \quad \text{(cathode)} \quad \text{(reduction)}$$

(=redox)

$$E = E^0 - \frac{0.059}{|n|} \log\left(\frac{a_C^{\chi} a_D^{\delta}}{a_A^{\alpha} a_B^{\beta}}\right)$$

$E: working\ electrode\ potential\ [V]$
$E^0: standard\ electrode\ potential$
$n: number\ of\ e^-$
$a: activity\ of\ A - D$



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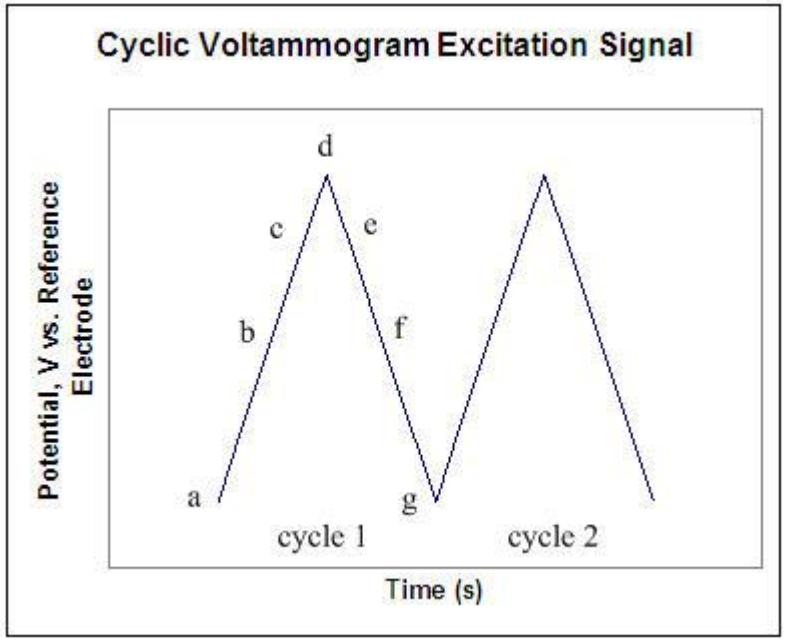
http://cdmf.org.br/2019/05/27/potentiometric-detection-of-chemical-species-by-spin-assisted-assembly-of-vanadium-pentoxide-nanorods/

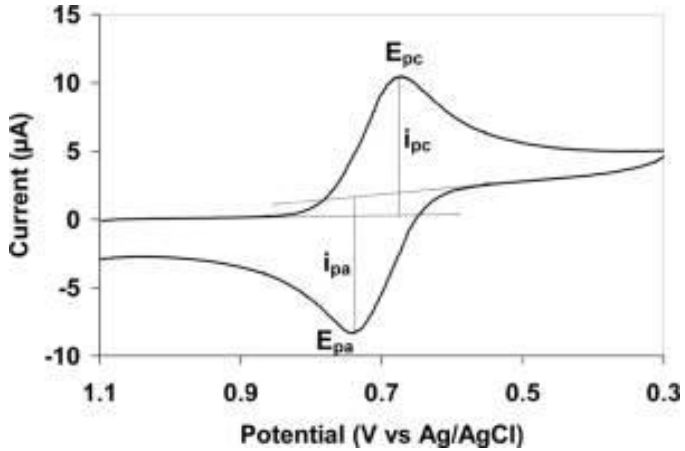
Electrochemical

CYCLIC VOLTAMMETRY

- Working electrode potential linearly and cyclically ramped in time
- Electrode potential: $E = E_i + vt$
  - E_i: $initial\ potential\ [V]$
  - v: $sweep\ rate\ \left[\frac{V}{s}\right]$
  - t: $time\ [s]$

- Concentration (Fick's 2nd law):
  - $\frac{\partial \boldsymbol{c}}{\partial t} = D\frac{\partial^2 \boldsymbol{c}}{\partial x^2}$
  - **Concentration change <-> diffusion** (to electrode surface)





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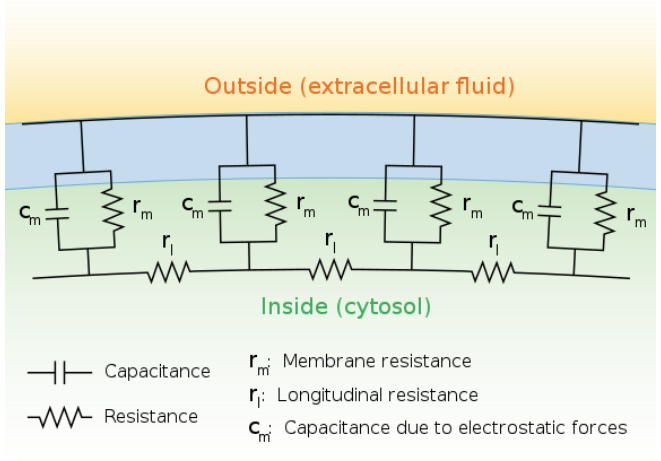
https://chem.libretexts.org/Bookshelves/Analytical_Chemistry/Supplemental_Modules_(Analytical_Chemistry)/Instrumental_Analysis/Cyclic_Voltammetry

IMPEDANCE SPECTROSCOPY

- Tissue ~ resistor(s) + capacitor(s)
- If we use A.C. excitation, e.g. sinusoidal, complex impedance will change according to the excitation frequency
- Cells:



Resistor:

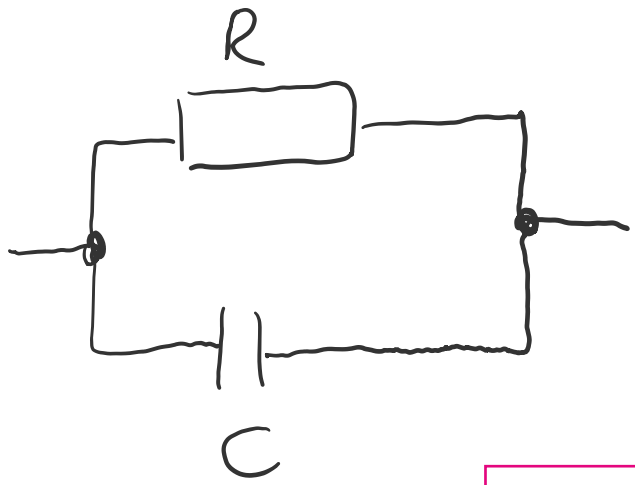
$$Z_R = \frac{V(t)}{I(t)} = Re(Z) - j \cdot Im(Z)$$

Capacitor:

$$Z_C = \frac{1}{j\omega C}$$

$$\omega: angular\ freq.$$

$$\omega = 2\pi f \ where\ f: excitation\ freq.$$



IMPEDANCE SPECTROSCOPY

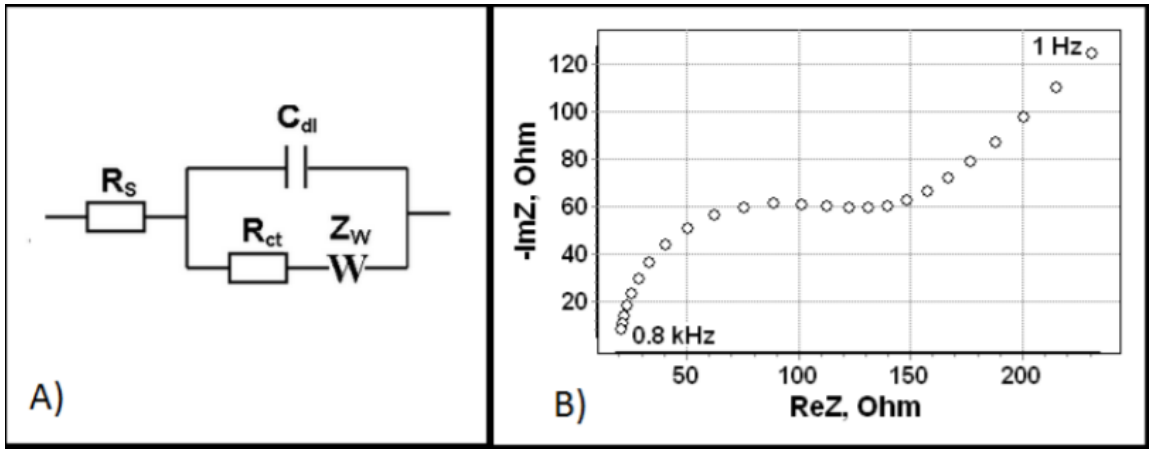
- Tissue ~ impedance(s) + capacitance(s)
- We measure varying impedance in response to voltage change

- Setup:
  - working + counter electrode + max. 2 reference electrodes
  - Randles equivalent circuit
  - Bode or Nyquist plot used for visualization
  - At high frequency: $I = V/R_S$
  - At mid to low frequency: $I = V/(R_S + R_{CT})$

$$Z^* = \frac{V(t)}{I(t)} = Re(Z) - j \cdot Im(Z)$$

$$I(t) = V(t)\frac{1 + (\omega RC)^2}{R - j\omega R^2 C}$$

$$\omega = 2\pi f \; where \; f: excitation \; freq.$$



$R_S: electrolyte \; resistance$
$C_{dl}: double - layer \; capacitance$
$R_{ct}: charge - transfer \; resistance$
$Z_W: Warburg \; element$

R_S = 20 Ω, C_{dl} = 25 µF, R_{ct} = 100 Ω, A_W = 300 Ω•$s^{-0.5}$

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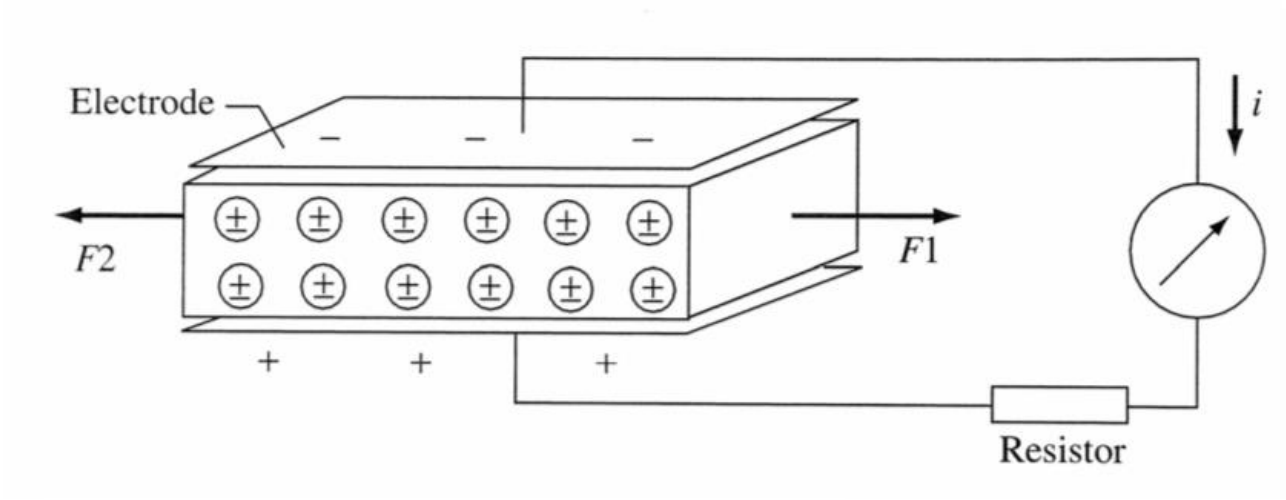
Electrochemical

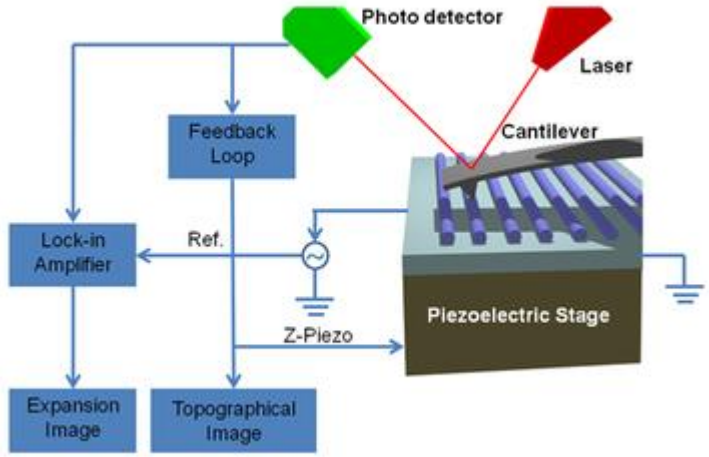
PIEZOELECTRIC SENSORS

- Electromechanical sensors
- Piezoelectric effect:
  - deformation ⇔ electric field

$$S = \mathrm{d}E$$
$$D = \mathrm{d}T$$

- Where:
  - S: $strain$
  - d: $piezoelectric\ coeff.$
  - E: $electric\ field\ \left[\frac{V}{m}\right]$
  - D: $linear\ displacement\ [m]$
  - T: $stress\ [N/m^2]$





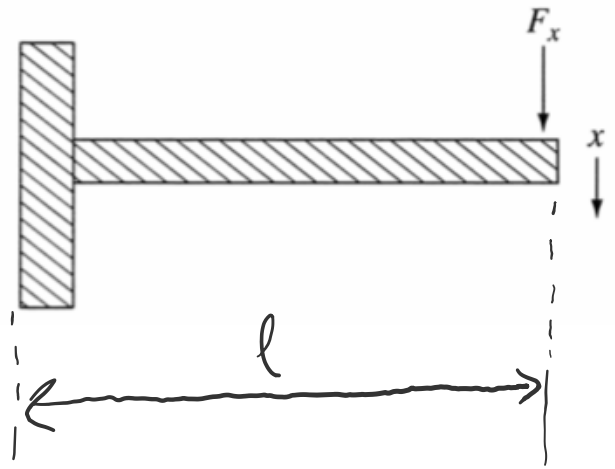
CANTILEVERS

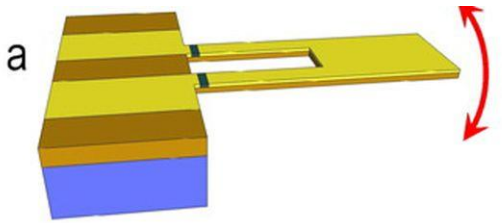
- Typically microcantilevers
- Beam displacement x <-> Applied force F_x and beam length l

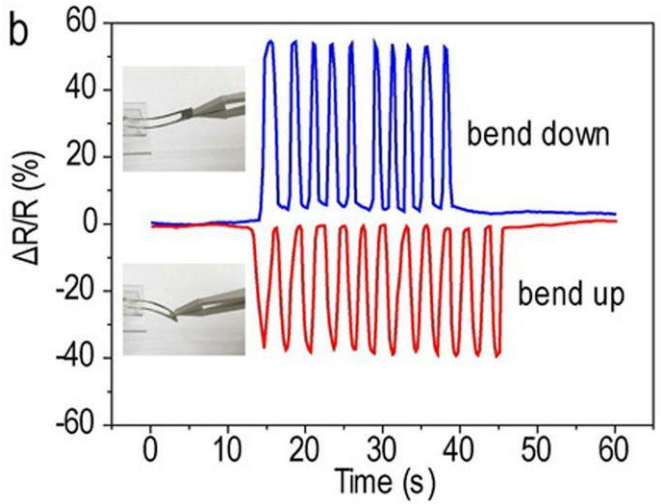
$$\Delta x = \frac{l^3}{3E_m I_m} F_x$$

$$F_x = k_m \Delta x$$

- Where:
  - E_m: $Young's\ modulus\ \left[\frac{N}{m^2}\right]$
  - I_m: $second\ moment\ of\ inertia\ [kg/m^2]$
  - F_x: $Force\ [N]$
  - l: $length\ [m]$
  - k_m: $spring\ constant\ \left[\frac{N}{m}\right]$







Mechanical

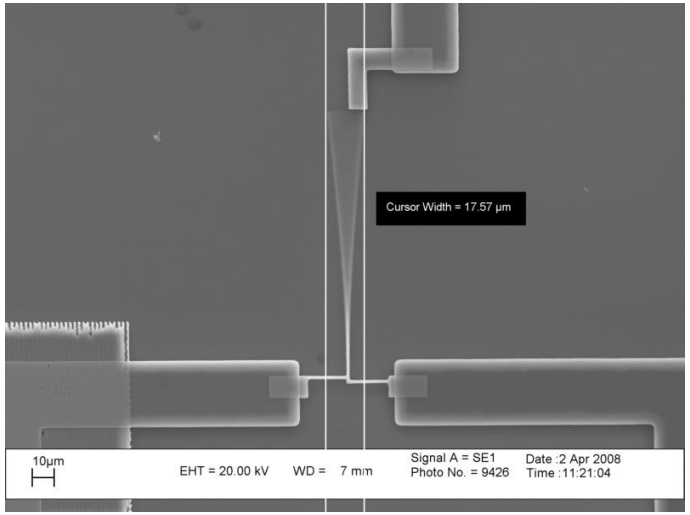
CANTILEVERS

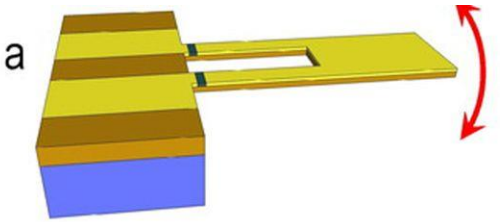
- Typically microcantilevers
- Beam displacement x <-> Applied force F_x and beam length l

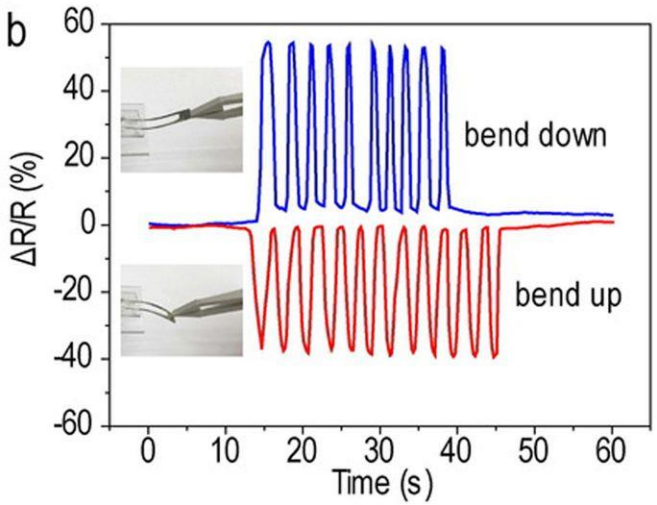
$$\Delta x = \frac{l^3}{3E_m I_m} F_x$$

$$F_x = k_m \Delta x$$

- Means to convert mechanical to electrical:
  - Strain gauge (resistance <-> force)
  - Optical (diffraction <-> force)
  - Piezoelectric







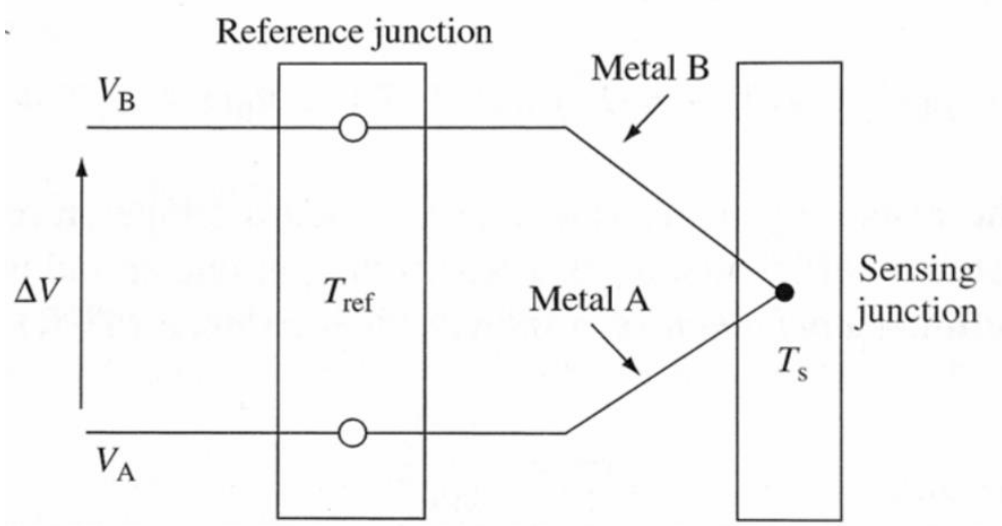
Mechanical

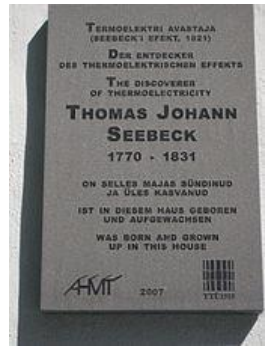
THERMOCOUPLE

- Based on the Seebeck effect:
- Temperature difference at a junction of dissimilar conductors creates an electric potential difference:

$$\Delta V = \alpha_S \Delta T$$

- ΔV: $electrical\ voltage\ [V]$
- α_S: $Seebeck\ coefficient\ \left[\frac{V}{K}\right]$
- ΔT: $temperature\ difference$





WHAT WE'VE COVERED IN THIS LECTURE

Detection method	Example	Measured response to analyte concentration	Pros	Cons
Optical	Spectrophotometry	Optical intensity change	No electrical interference, contactless	Slow response, complex instrumentation
Electrical	Cyclic voltammetry	Current change in response to voltage input	Highly sensitive and compact, simple fabrication	Sensitive to noise
Mechanical	Cantilevers	Beam deflection (analyte mass is detected)	Highly sensitive and compact	Complex fabrication, sensitive to vibrations

SENSORS

- Different types of sensors: EM, Mechanical, Chemical
- Detection mechanisms
- Working principles

01.02.2022

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self diagnostics

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