SUMMARY
in master's programme Biomedical Engineering
Course 362.118 Biomedical Microsystems

Summary of the course

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Vienna, December 19, 2022

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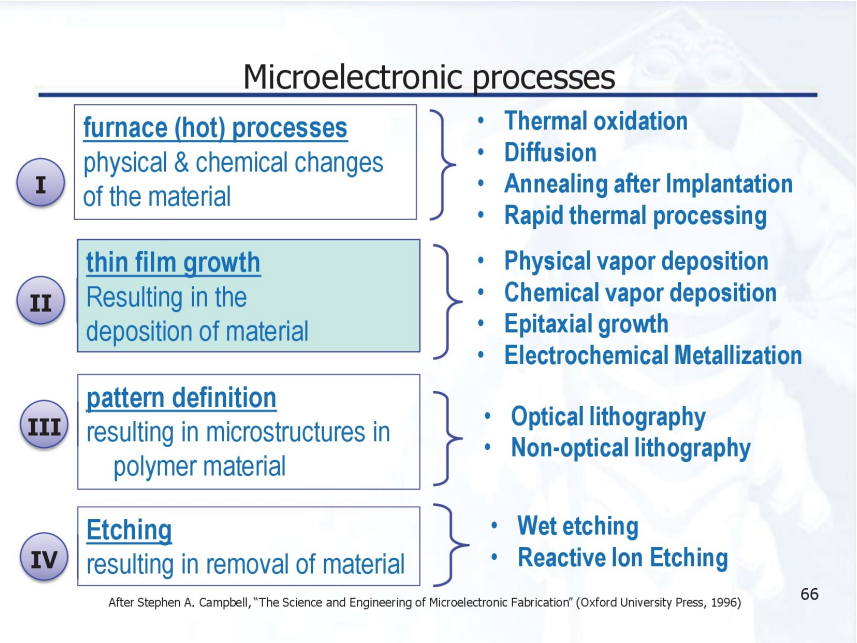
1 Fabrication of Micro- and Nanostructures



1.1 Furnace Process

Thermal oxidation:

- Dry oxidation: $Si + O_2 \rightarrow SiO_2$
- Wet oxidation: $Si + 2\ H_2O \rightarrow SiO_2 + 2\ H_2$

1.2 Thin film growth = Deposition

A single atom appearers, then a second one, they attached to each other. More atoms go to this and it grows by attaching together.

	Physical	Chemical
Dry (= vacuum)	Physical vapor deposi-ton (PVD), Molecular Beam Epitaxy (MBE), Sputter depo-sition	Chemical vapor deposi-tion (CVD), Atomic layer depositon (ALD)
Wet (= liquid)	Spin coating	Electro plating, Electro less plating

PVD process is done by melting metal and steam it on the surface.
Sputter deposition use a High-frequency plasma.
Spin coating have we done in the laboratory exercise.

CVD Chemical reactive gases are used to synthesize thin solid films. Can be classified by

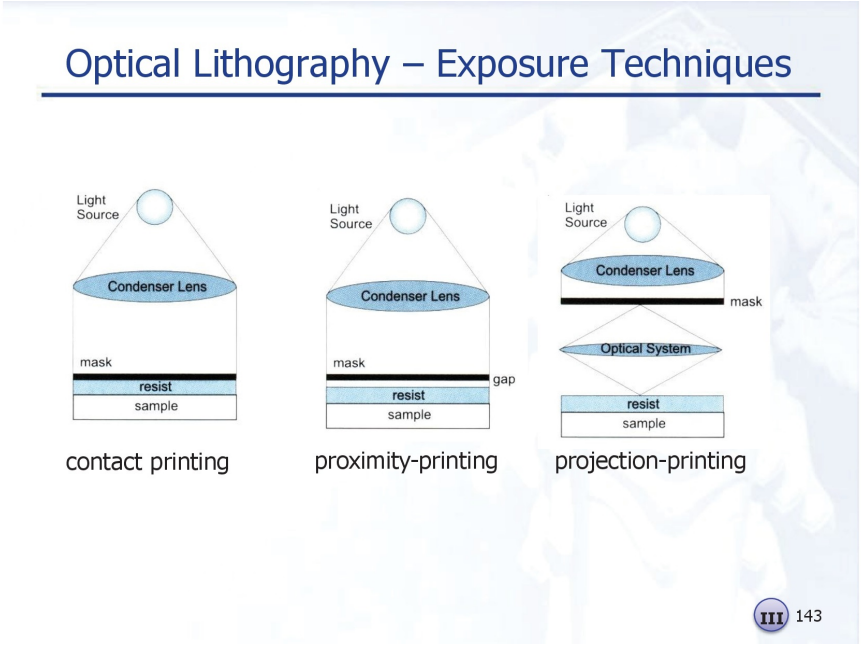
the operating pressure (atmospheric pressure, low-pressure, ultra-high vacuum).
ALD Two gases are sequentially supplied.
Electron plating/Less plating is a RedOX reaction. Non-galvanic type ot plating. Use of electrical current to reduce cation of a desired material form a solution and coat a conductive object with a thin layer of the material.

1.3 Pattering

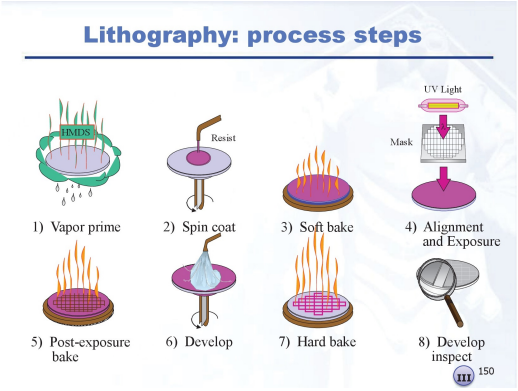
Lift-off	Etch-bak
1) Pattern Photoresist 2) Material deposition 3) Lift of (= Striping)	1) Material deposition 2) Pattern Photoresist 3) Etching 4) Striping of Photoresist with a ionic solvent

Define a pattern $\rightarrow$ Lithography
Transfer the pattern $\rightarrow$ Etching

Positive lithography is when this part, who stays during exposure in the shadow, get insoluble.



Below of 157 nm light is absorbed by all materials. UV-light changes Diazonaphtochion in Carboxyl acid.



STEP	goal
1.Vapor prime	Adhesion layer
2.Spin coat	resist
3.Soft bake	Resist drying
4. Alignment and exposure	Resist exposure
5.Post-exposure bake (PEB)	Resist hardening
6.Develop	Removal of exposed
7.Hard bake	Resist hardening
8.Develop inspect	control

1.4 Etching

Methods of Etching:

- Wet etching $\rightarrow$ Isotropic
- Plasma etching
- Ion beam etching/Ion milling

2 Principles of Microelectronic Devices

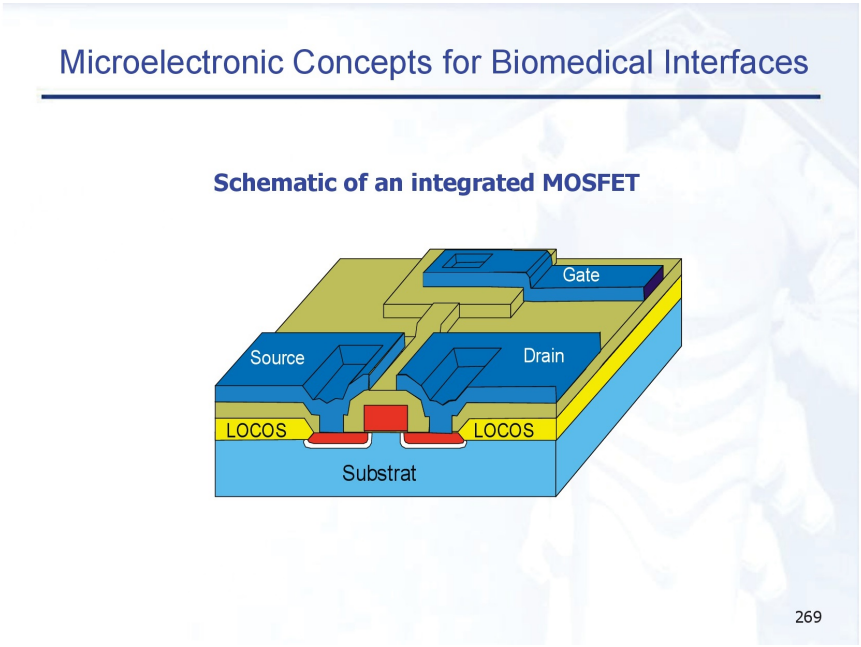
Elements of a network:

- Independent sources
- Resistors
- Capacitors
- Switches

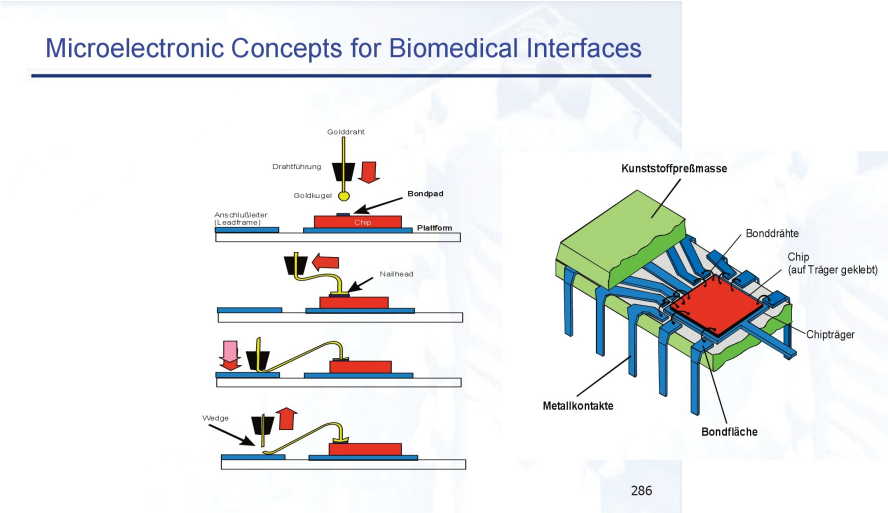
Superposition-theorem: Each single source contributes to the overall response independently form each other source. Superposition works for voltage and currents but not for power.
$\rightarrow$ Überlagerungsverfahren nach Helmholz
Spannungsquelle wird zu einem Kurzschluss
Stromquelle zu einer Unterbrechung

Microelectronic arrays (MEA) can be used for stimulation of cells and electrophysiologic recordings.

Metal-oxide-semiconductor field-effect transistor (MOSFET) are used to amplify or switch electronic signals.



Bonding of a chip:



pMOSFET have a source and drain part which is a p^+ region. The body is a n-region, as result an pnp-MOSFET. If a voltage (+) is applied by the gate the electrons (e^-) of the body are went to the gate. A brig between the source and drain appears where the e^- can travel from the source to the drain.

3 Metal-Liquid-Interfaces: inorganic and organic electrolytes

Biomedical micro devices often define a new interface between:

- metallic phase, charge carriers are electrons

- conductive solution/electrolyte, charge carriers are ions

Electrochemistry is the study of reactions in which charged particles cross the interface between two phases of matter.

Interfacial potentials can exist between any two phases in contact, even in the absence of chemical reactions. They are the result of absorption or ordered aligment of ions or molecules on the surface of a second phase.

For measuring a potential difference two contact leads of a voltmeter must be bring in contact with the object.

Water is capable to undergo oxidation and reduction. Pure water is an isolator.

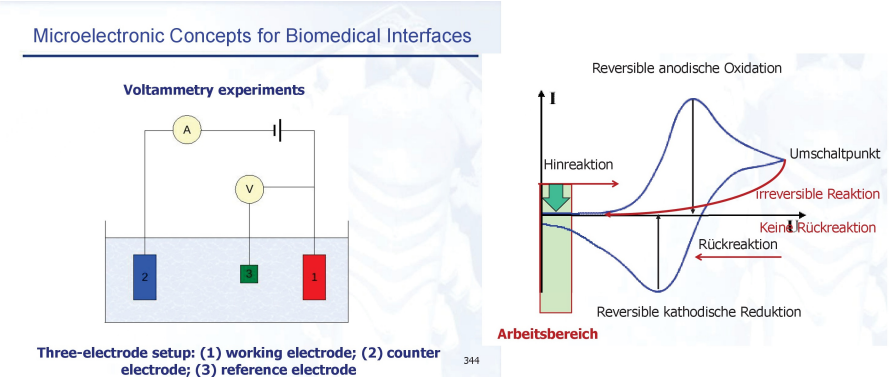
Electromotive/activity series $\rightarrow$ Similar comparison of metals mad it possible to arrange them in the order of their increasing electron-donating power.

Active metals are all "attached" by acids.

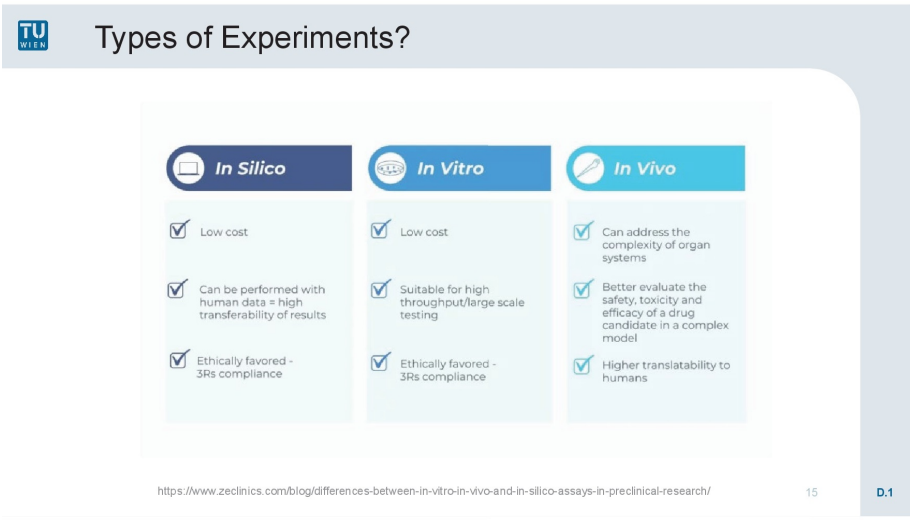
Challenges for Biomedical Micro devices:

- Charge particles may accumulate at the electrode surface
- Charged particles in the electrolyte may transfer electrons form or to the electrode surface

Voltammetry is a category of electroanalytical methods. Information about an analyte is obtained bay measuring the current as the potential is varied.



4 Micro- and Nanostructured Interfaces & Microfluidics

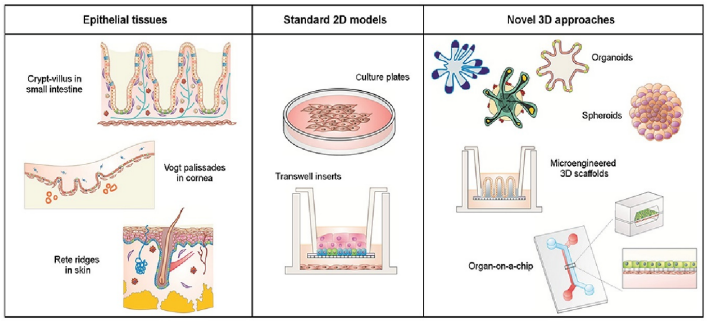


In Silico studies are biological experiments carried out entirely in a computer or via simulations.
In vitro assays take place in a controlled environment, outside a living organism.

	In-vivo	In-vitro
Advantage	Complex interactions can be studied, well defined test animals, cells in natural environment	Reduce use of animals, ease of cultur handling, cheap, less ethical problems
Disadvantages	ethic problems, high effort, costs	some questions need a complex test system, behaviour studies need living animals

Primary cultures = cells cultured directly
Immortalired cell line = cells proliferate indefinitely
Immortal cells maintain telomere length with the aid of an enzyme telomerase.

2D vs 3D cell cultures as in-vitro models



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Liquid in which cells are grown contains factors like:

- physiologic, ph
- supraphysiologic, hormones
- nonphysiologic, antibiotics

Cell types:

- active; neuronal, heart
- passive; skin

Materials of the microchip which is interfacing with living cells have to be:

- aviable with microelectronic fabrication
- Non-corrosive
- Biocompatible

Structural Patterning

- Topography forces cells into non-natural growth shapes

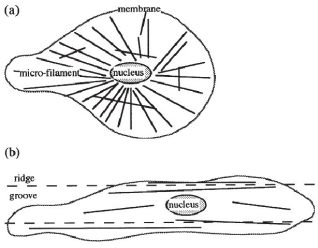

Fig. 2. Schematic of cytoskeleton. (a) shows a cell on a flat surface while (b) shows the reorganisation of the micro-filaments that occurs on a grooved surface—the dashed lines show the line of closest contact between the ridges and grooves.

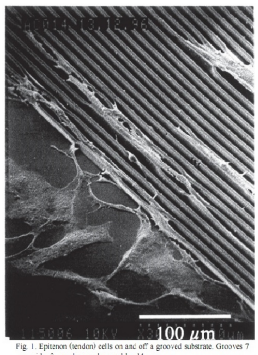

Fig. 1. Epitenon (tendon) cells on and off a grooved substrate. Grooves 7 μm wide, 3 μm deep and spaced by 14 μm.

2002_Wilkinson-C.D.W_Curtis-A.S.G._The-use-of-materials-patterned-on-a-nano--and-micro-metric-scale-in-cellular-engineering_Mater.-Sci.-Eng.-C_19_1-2

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D.3

Patterning of surface effects cell adhesion.
The different types of cell junctions:

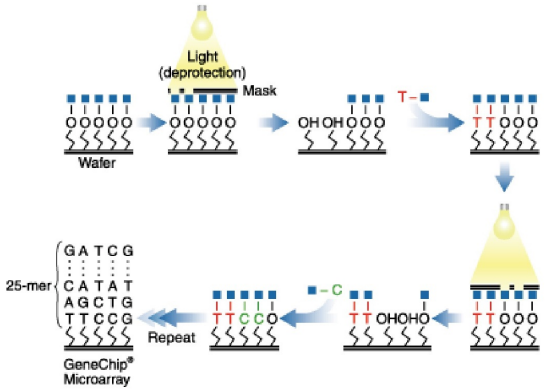
- Tight junctions, plasma membrane
- Adherens, actin filaments
- Desmosomes, intermediate filament
- Hemidesmosomes, intermediate filament to basal lamina
- Gyp junctions, tunnels between cells

$Reynoldsnumber = \frac{Interialflow}{Viscousforces}$ low Re = laminar flow
intermediate Re = transitional flow
high Re = turbulent flow

2 structuring approaches of DNA chips:

- Lithographic patterning of surface (Affymetrix)
- Drop dispersion with a micronozzle (egInkJet)

Photolithography (Affymetrix)



https://pubs.acs.org/doi/10.1021/cr0684467
www.cs.tau.ac.il © Zohar Yakhini

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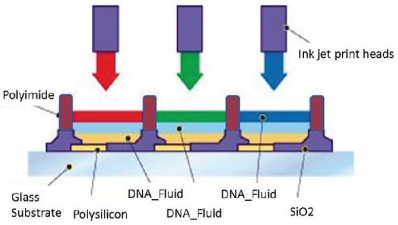
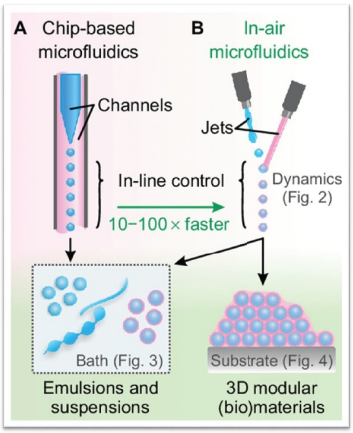
The so produces wafer is flooded with a solution that contains DNA. If the strands are complementary they fits together. The fluorescence target, that was attached to the sample, starts than to glow.

Inkjet Printed Microarrays





https://www.researchgate.net/figure/Agilent-oligonucleotide-microarray-A-Noncontact-inkjet-printing-technology-delivers-a_fig5_26888549

Acid's (Adenin, Guanin, Thymin, Cytosin) are printing to a tower whit this technics. They use light of different wavelengths to look if the DNA have fit.

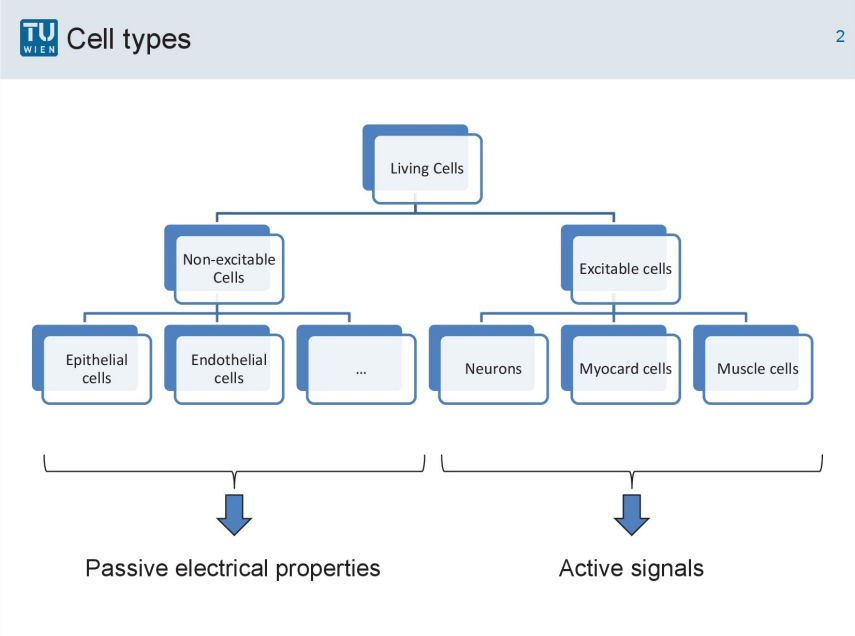
5 Cell-Monitoring and Sensing: electrically inactive cells

Communication:

- Nerve cells → ions flows through their membranes
- Electronic → electrons flows through solid metals; faster flow between silicon and metal

ISSUE: Active microelectronic in a wet environment!

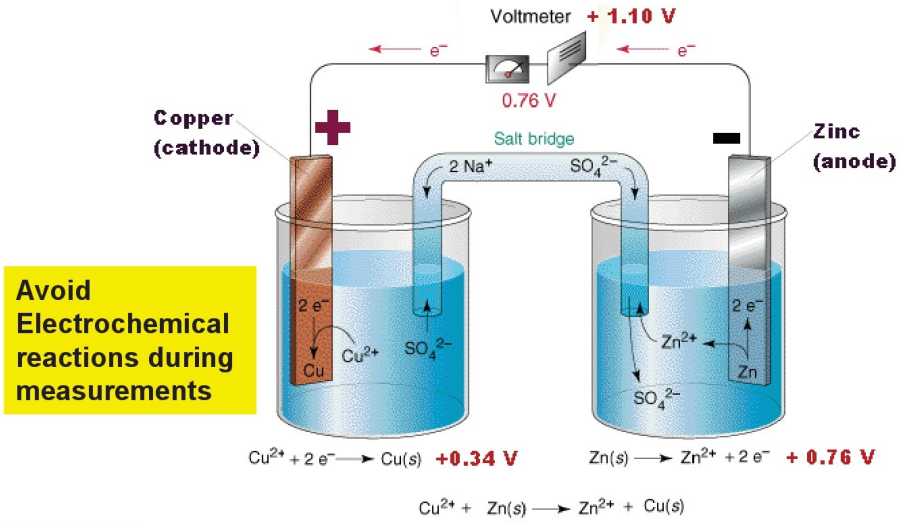
Excitable cells	Non-excitable cells
generate action potential cardiac cells drive or control electrical components	no own electrical signal; external signal applying endothelial cells changes due to metabolic processes ban be detect by electrical co



Living cells only survive in cell medium. Which is a solution with many ionic components. The measurements are performed in a electrolyte.

Basic setup of an electrochemical cell consist of:

- electron conductor
- ion conductor



The charge transfer takes place on both plates and acts as a capacitor.

Electrical inactive cells → Bioimpedance

Optimum setup for electrochemical cells:

- AC current
- < 2 V
- electrodes with rough surface

Optimum setup for biochemical samples:

- AC current
- < 50 mV
- inert electrodes

Interdigitated electrodes are ideal for research and development. It can use for wet chemical applications. It makes gas detections possible. It is cheap, ultra clean and extremely efficient.

Interdigitated Electrodes

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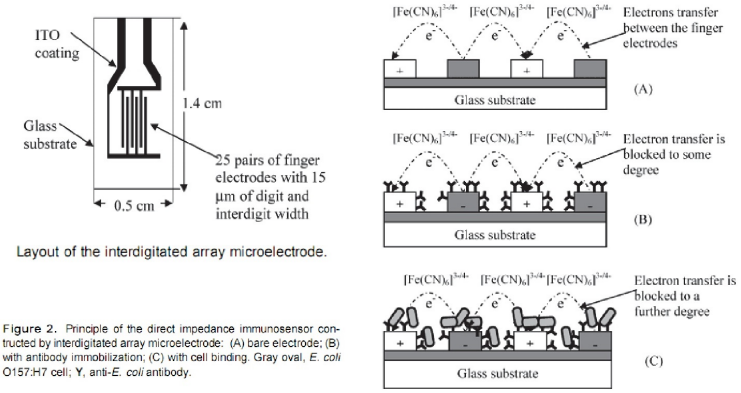

Figure 2. Principle of the direct impedance immunosensor constructed by interdigitated array microelectrode: (A) bare electrode; (B) with antibody immobilization; (C) with cell binding. Gray oval, *E. coli* O157:H7 cell; Y, anti-*E. coli* antibody.

2004_Yang-L._Erf-G.F._Interdigitated-Array-Microelectrode-Based-Electrochemical-Impedance-Immunosensor-for-Detection-of-Escherichia-coli-O157-H7_Anal.-Chem._76_4_

Transepithelial Electrical Resistance (TEER) is used to measure the confluence of cell layers.

Non-excitable cells have a permittivity, which can be measured via impedance. Biompedance allows to measure the presence, amount and junction of cells!

6 Cell-Monitoring and sensing: electrically active cells

Electrogenic Cells

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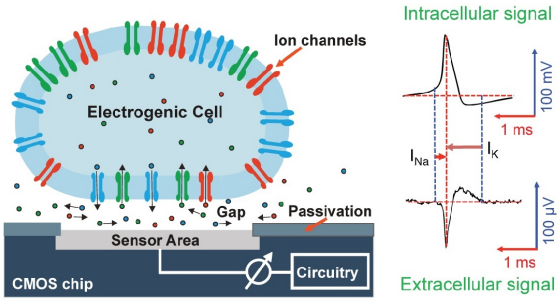
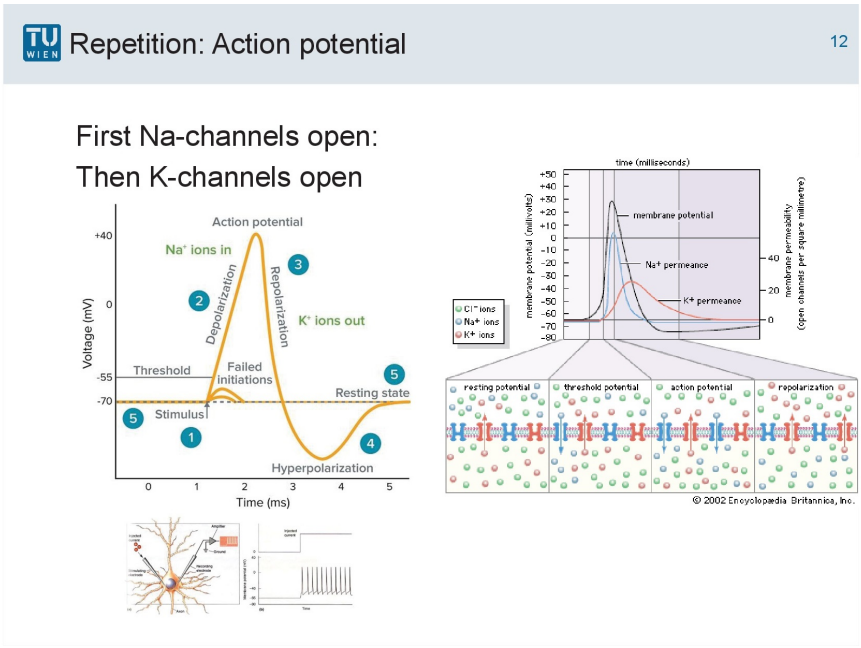
- Electrogenic Cells on Chips:
  Ions pass through the cells ion channels
  The moving charges create an electric field that is picked up by noble-metal electrode



The membrane potential is calculated from total ion permeability of the membrane for all ions using the Goldman equation. $U = \frac{R \cdot T}{F} \ln\left(\frac{p_x[y]^e + ...}{p_x[y]^i + ...}\right)$

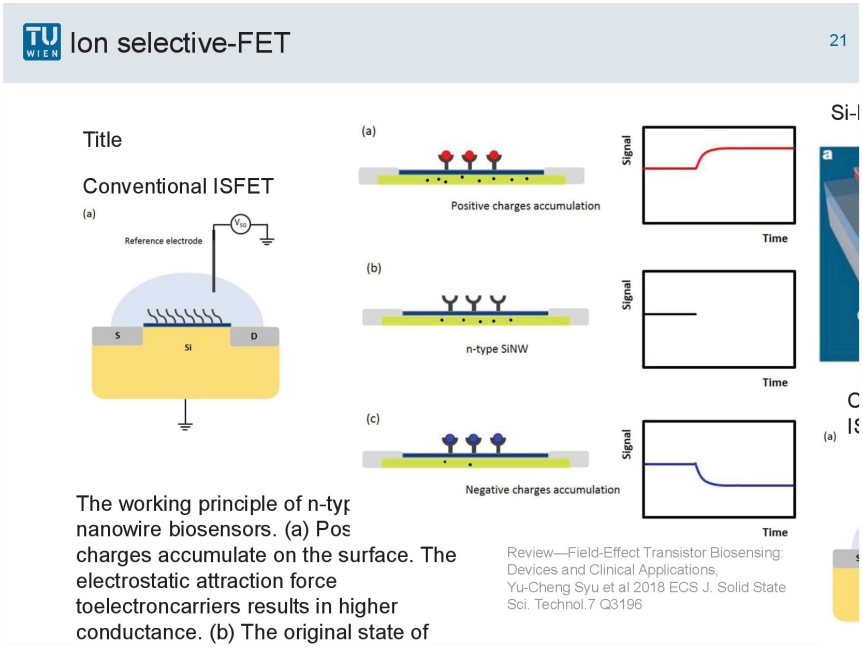
U	Voltage	[V]
R	universal gasconstant	[J/mol]
T	Temperature	[K]
F	Faradey constant	[C/mol]
p	Permeability	[ ]
$[X]$	Concentration of different Ions in/out of the cell	[ ]



Na-channels open first, later follows the K-channels.

Sodium-potassium-pump maintains the Na-K-concentration gradient. It is working independent form voltage or neurotransmitter activation but it need energy like Adenosintriphosphat (ATP).

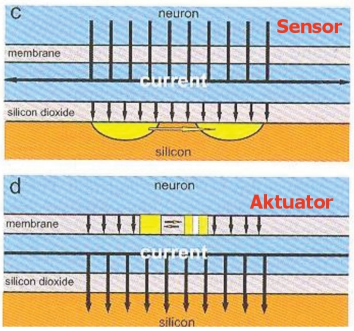
Ion selective-FET can use for DNA sequencing.



Chemical-FET, the gate is covered with a chemical selective layer that is electro-active. Drain current = f (Concentration)

In principle, a direct coupling of ionic signals in a neuron and electronic signals in the semiconductor can be attained by electrical polarization If the insulating lipid layer of the neuron is in direct contact to the insulating silicon dioxide of the chip, a compact dielectric is formed.

When nerve cells grows on a chip it does not form a compact dielectric. The cell adhesion is mediated (hält aufrecht) by protein molecules. Proteins keep the liquid membrane at a certain distance $\rightarrow$ cleft between cell an chip.



More realistic case
(c) and (d)
neuron-silicon coupling by
electrical
current.

- In (c) current through the membrane of an excited neuron leads to a Transductive Extracellular Potential in the cleft between cell and chip which polarizes the oxide and modulates the source-drain current
- In (d) capacitive current through the oxide gives rise to a Transductive Extracellular Potential, which polarizes the membrane and opens ion channels

Peter Fromherz in „Nanoelectronics and Information Technology", Wiley-VCH (2003)

List of Abbreviations

ALD Atomic layer depositon

ATP Adenosintriphosphat

CVD Chemical vapor deposition

MBE Molecular Beam Epitaxy

MEA Microelectronic arrays

MOSFET Metal-oxide-semiconductor field-effect transistor

PD Physical deposition

PECVD Plasma enhanced Chemical vapor depositon

PVD Physical vapor depositon

TEER Transepithelial Electrical Resistance