Lecture 1 (Introduction)

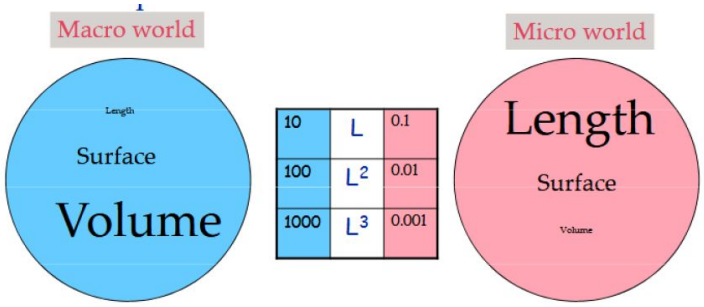
1. **List examples of commercially available neuroprosthetics and their applications.**
    - Deep brain stimulation device ("Pacemaker for the brain"): it sends electrical impulses to the brain, typically to interrupt faulty brain circuits associated with Parkinson's disease.
    - Spinal cord stimulator ("Pain pacemaker"): it is a programmable medical device that deliver electrical signals to selected areas of the spinal cord (dorsal columns) for the treatment of certain pain conditions.
    - Electrocorticography (ECoG): It is the method of recording electroencephalographic signals directly from surgically exposed cerebral cortex.
    - Cochlear implant: Provides a sense of sound to a person with moderate to profound sensorineural hearing loss. Cochlear implants bypass the normal acoustic hearing process, instead replacing it with electric hearing.
    - Subretinal implant: Subretinal implant is used to substitute the lost retinal pigment epithelial cells with the ones of artificial basis to restore the vision.
    - Brain-computer interface (BCI): It could help people with neurological diseases, injuries or limb losses to move and communicate again. BCI technology works in two ways. Electrodes implanted in the brain record the activity of individual neurons while algorithms “decode” them in real time to find out which are active when a person makes different body movements, whether clenching a fist or raising an arm. Then a system of electrical pulses, known as functional electrical stimulation, translates that information into command signals for a robotic or paralysed limb.
2. **What are the spatial dimensions of neuronal structures and what is temporal scale of electric and chemical communication in the extracellular space?**
    - Spatial factors:
        - Number of neurons: 100 billion
        - Soma of neurons: 4-100 microns
        - Dendrites & axons: 1-2 micron thick
        - Number synapses: 100 trillion
    - Temporal factors:
        - Action potentials: 1-2 ms
        - Chemical signals: > 50 ms
3. **List stimulation methods used to interact with neurons.**

    Recording:
    - Electrical and chemical signals
    - Optical signals through molecular transducers

    Stimulate (inhibitory/excitatory):
    - Electrical pathways (delivery of stimuli)
    - Chemical communication (delivery of drugs)
    - Genetic methods (transducers to deliver both)
    - Thermal (heat) and mechanical (ultrasound)

4. **Explain what is MEMS and how is this field influenced by the progress in the semiconductor industry.**
   MEMS (Micro-Electro-Mechanical Systems), is a technology that in its most general form can be defined as miniaturized mechanical and electro-mechanical elements (i.e., devices and structures) that are made using the techniques of microfabrication. The evolution of MEMS is closely related to advances of semiconductor industry, in many process steps are similar, or identical, and adapted to the requirements. The principal features of the MEMS manufacturing processes are:
   - Miniaturization. The reduction in the size to be smaller and lighter with shorter response times.
   - Multiplicity. The capacity to produce tens, hundreds or even thousands of products in parallel, being inherited characteristic of the semiconductor production processes.
   - Microelectronics. The intelligence of MEMS which allows control implemented as closed systems with integrated microsensors and microactuators.

   Theses advantages show the great influence of the manufacturing processes of the electronics integrated circuits. However, it is important to note that not all microdevices have a benefit of miniaturization. One of the major limitations of the techniques inherit from semiconductor processes, is the works in planar scale, difficult the design of devices in three dimensions.
5. **Explain why physical phenomena are different in the microscale!**
   At the microscale, different forces become dominant over those experienced in everyday life. Because of scaling, shrinking existing large devices and expecting them to function well at the microscale is often counterproductive.



Volume	V ~ L^3
Mass	M ~ L^3
Surface	SA ~ L^2
Strength	S ~ L^2
Force	F ~ L^2
Acceleration	A ~ 1/L
Frequency	f ~ 1/L
Power	P ~ L^2
Power density	P ~ 1/L

* Assumes constant mass density

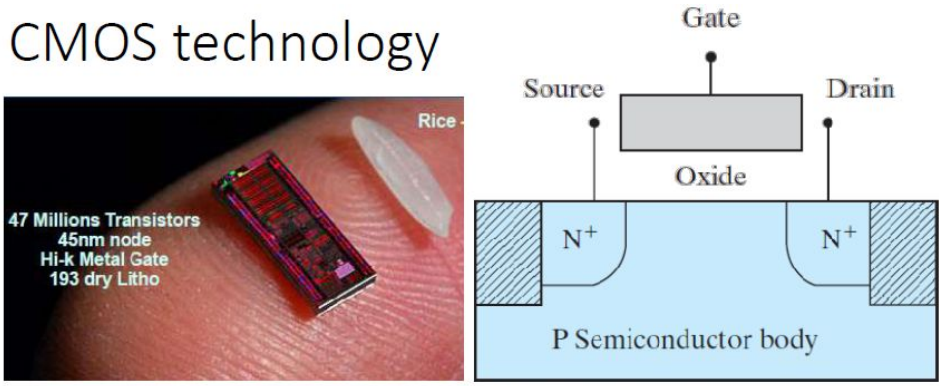
Voltage	V ~ constant
E Field	E ~ 1/L
Resistance	R ~ 1/L
Capacitance	C ~ L
Current	I ~ L
Magnetic wire	B ~ constant
Heat capacity	C_v ~ L^3
Heat flow	dT/dt ~ $1/L^2$
Turbulence	Re ~ L

* Assumes constant voltage

6. **What is the advantage of MEMS based neural probes?**
    - Low unit cost of fabrication
    - High reproducibility
    - Low variability
    - High spatial resolution and density

Lecture 2 (Technology)

1. **Explain CMOS technology briefly.**
   The term CMOS stands for “Complementary Metal Oxide Semiconductor”. CMOS technology is one of the most popular technology in the computer chip design industry and broadly used today to form integrated circuits in numerous and varied applications. The complementary of the Commodore Semiconductor Group (CSG) or Metal Oxide Semiconductor (MOS) is called as CMOS technology. This technology is used in developing the microprocessors, microcontrollers, digital logic circuits and many other integrated circuits. It facilitates low- power dissipation and high-packing density with very less noise margin. It is mostly used to build digital circuitry.
   CMOS
   MOSFET
   CMOS vs NMOS



Planar transistors are basic building block of digital, analog, and memory circuits

MOSFET - Metal-Oxide-Semiconductor Field Effect Transistor

CMOS – using complementary and symmetrical pairs of p-type and n-type MOSFETs for logic functions

IC – Integrated Circuit (large number of transistors on one piece of silicon, cheaper)

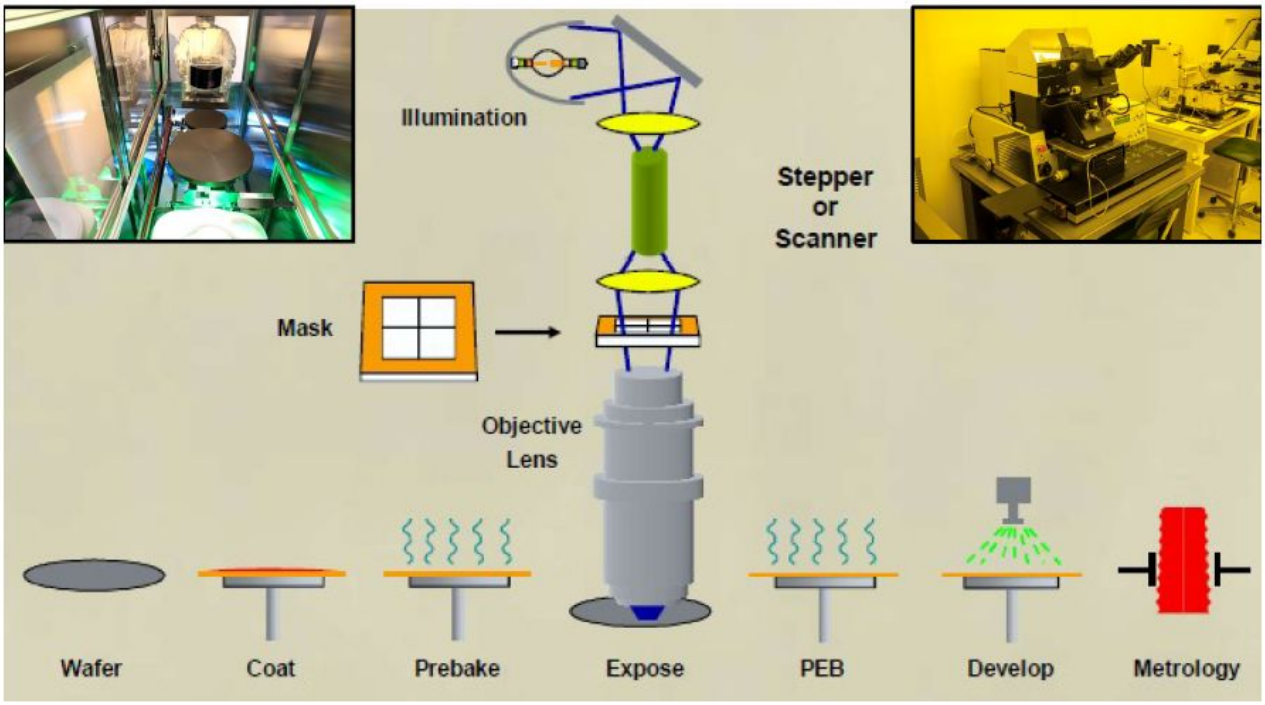
CMOS Technology – planar technology for CMOS IC fabrication

2. **List basic semiconductor processes that are used fabricate silicon chips.**
   1. Patterning-Photolihtography
   2. Doping-Ion implantation, Diffusion
   3. Thin film growth/deposition-Oxidation, CVD, PVD, ALD, Electroplating

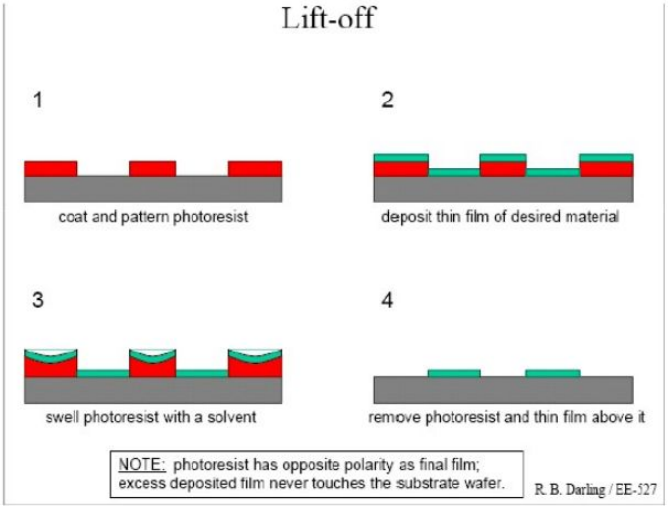
4. Thin film removing-wet etch, dry etch, strip, CMP
5. Wafer bonding
6. Packaging

3. **Why is the clean environment crucial in the semiconductor industry?**
   It is important in the prevention from unwanted impurities.
   Three tiered approach:
   1. clean factories(clean room)
   2. wafer cleaning
   3. Gettering

4. **Describe the process flow for photolitography.**
   https://static1.squarespace.com/static/57b26cc76b8f5b7524bf9ed2/t/57f97113725e25a7b5dd0907/1475965203340/Photolithography_Lessons_0.pdf



5. **Describe the „lift-off" process.**
   Lift-off consists of forming an inverse image of the pattern desired on the wafer using a stencil (sablon) layer, which covers certain areas on the wafer and exposes the rest. The layer to be 'patterned' is then deposited over the 'stenciled' wafer. In the exposed areas of the stencil, the layer material gets deposited directly on the wafer substrate, while in the covered areas, the material gets deposited on top of the stencil film.



After the layer material has been deposited, the wafer is immersed in a liquid that can dissolve the stencil layer. Once the stencil is dissolved by the liquid, the layer material over it gets 'lifted off' (hence the term 'lift-off'), leaving behind the layer material that were deposited over the wafer substrate itself, which forms the final pattern on the wafer.

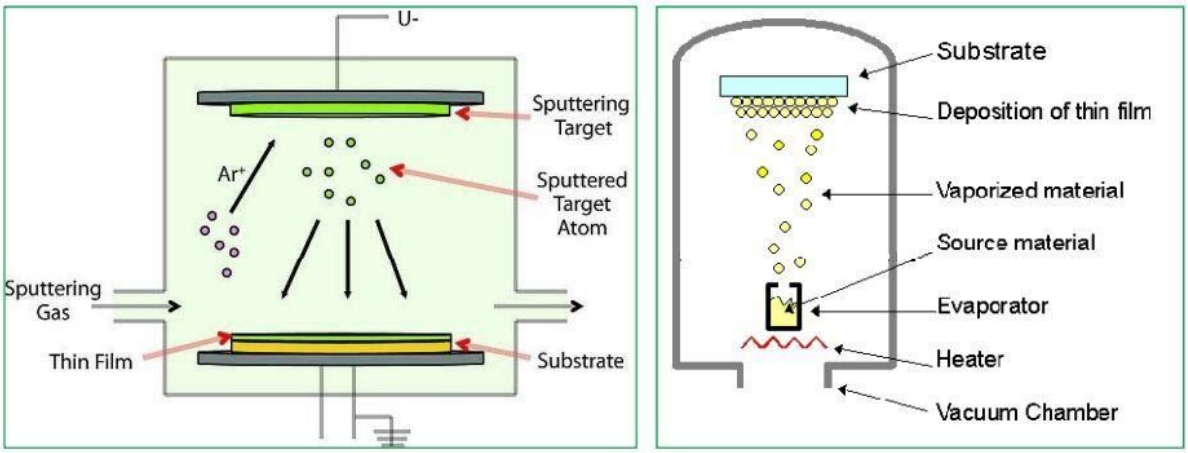
6. **Compare CVD and PVD processes in terms of process temperature, step coverage and film purity.**
   PVD (Physical Vapour Deposition): sputtering (freccsentés), evaporation (kipárolgás)
   CVD (Chemical Vapour Deposition): gaseous precursors react to form a solid coating on a heated substrate

	CVD	PVD
Flexibility	Poor	Good
Deposition temperature	High	Low
Deposition pressure	High	Low
Step coverage (conformality)	Good	Poor
Thickness uniformity	Good	Good
Composition control	Good	Poor
Film purity	High	Low
Dielectric	Preferred	-
Metal	-	Preferred

7. **Describe the processes of sputtering and evaporation.**
   Sputtering: The sputtering method of thin film deposition involves introducing a controlled gas, usually chemically inert argon, into a vacuum chamber, and electrically energizing a cathode to establish a self sustaining plasma. The exposed surface of the cathode, called the target, is a slab of the material to be coated onto the substrates. The gas atoms lose electrons inside the plasma to become positively charged ions, which are then accelerated into the target and strike with sufficient kinetic energy to dislodge atoms or molecules of the target material. It can be thought of as a sort of atomic scale bead blasting. This sputtered material now constitutes a vapor stream, which traverses the chamber and hits the substrate, sticking to it as a coating or "thin film".

   Evaporation: Thermal Evaporation involves heating a solid material inside a high vacuum chamber, taking it to a temperature which produces some vapor pressure. Inside the vacuum, even a relatively low vapor pressure is sufficient to raise a vapor cloud inside the chamber. This evaporated material now constitutes a vapor stream, which traverses the chamber and hits the substrate, sticking to it as a coating or film. Since, in most instances of Thermal Evaporation processes the material is heated to its melting point and is liquid, it is usually located in the bottom of the chamber, often in

some sort of upright crucible. The vapor then rises above this bottom source, and the substrates are held inverted in appropriate fixtures at the top of the chamber. The surfaces intended to be coated are thus facing down toward the heated source material to receive their coating.



Sputtering Evaporation

8. **Define etch rate and selectivity.**
   Etch rate is defined as etched depth per unit time(speed at which etching occurs). Typical unit: r [nm/min] Common desired etch rates are between 100 to 1000 angstroms per minute. If the etch rate is too high, the process will be difficult to control. However, in some cases, high etch rates are preferable for deep hole etching (i.e., anisotropic etch process which creates deep penetrating holes and trenches in wafers) or substrate removal.

   Selectivity is the ratio of the etch rates of one materials over the other. For example, the selectivity is ratio of the etch rate of the layer being etched to the etch rate of the mask or the layer under the layer being etched. Etching with high selectivity is supposed to remove the selected layer entirely without harming the substrate and mask. For example, KOH etches polysilicon over oxide, with selectivity 1000 to 1, which shows that the polysilicon can etch 1000 times faster than oxide.

9. **How an isotropic and anisotropic etch profile looks like and why?**
   Isotropic etching: removes material equally in all directions-->undercut of the mask
   Anisotropic etching: removes material only perpendicular to the surface-->accurate transfer of he mask pattern

10. **Explain how anisotropic etching is influenced by crystallographic orientation of the substrate.**
    Anisotropic etchants etch desired structures in crystalline materials when carried out properly. Anisotropic etching results in geometric shapes bounded by perfectly define crystallographic planes since the rate of etching is direction dependent. The etchants etch crystalline materials at very different rates depending upon which crystal face is exposed. Due to the strong dependence of the etch rate on crystal direction and on etchant concentration, a large variety of silicon structures can be fabricated in a highly controllable and reproducible manner.

11. **Explain the mechanism of dry etching in general.**
    Dry etching, also called plasma etching, sputters or dissolves the materials using reactive ions in a gas phase. It utilizes plasma instead of liquid etchants to remove the materials, which is more precise, controllable and repeatable compared to wet etching, but a more expensive vacuum system is required. For instance, plasmas are easier to start and stop, and less sensitive to temperature; moreover, they are capable of defining feature sizes smaller than 100nm. It is capable of defining feature sizes smaller than 100 nm, and produces highly anisotropic etching. It may remove the materials by chemical reactions (using chemical reactive gases or plasma, isotropic, selective), by purely physical methods (e.g., sputtering and ion beam-induced etching, anisotropic, less selective), or with a combination of both chemical reaction and physical bombardment (e.g., reactive ion etching, anisotropic, selective).

12. **Explain how chemical and physical processes take part in the mechanism of deep reactive ion etching.**
    Deep reactive ion etching combines physical and chemicals effect to remove material from the wafer surface. The Bosch process alternates repeatedly between two modes to achieve nearly vertical structures:
    1. A standard, nearly isotropic plasma etch . The plasma contains some ions, which attack the wafer from a nearly vertical direction. Sulfur hexafluoride [SF6] is often used for silicon.
    2. Deposition of a chemically inert passivation layer.

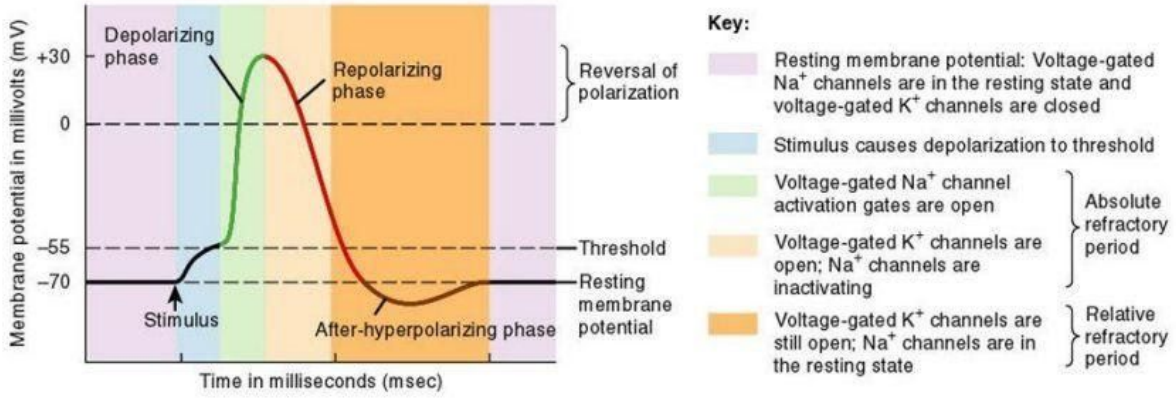
    Each phase lasts for several seconds. The passivation layer protects the entire substrate

from further chemical attack and prevents further etching. However, during the etching phase, the directional ions that bombard the substrate attack the passivation layer at the bottom of the trench (but not along the sides). They collide with it and sputter it off, exposing the substrate to the chemical etchant.

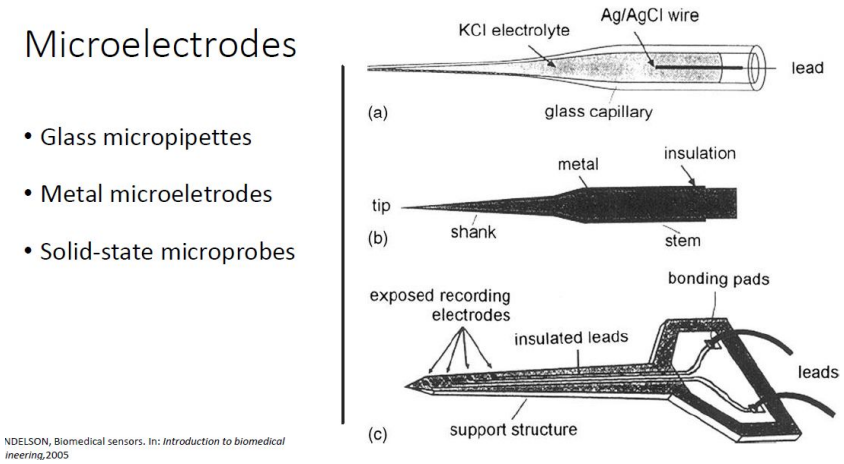
These etch/deposit steps are repeated many times over resulting in a large number of very small isotropic etch steps taking place only at the bottom of the etched pits.

Lecture 3 (Neuronal recordings)

1. **Draw the waveform of an action potential denoting the relevant phases, time- and voltage scales.**



2. **Define signal-to-noise ratio. Mention some of the typical sources of noise during neuronal recordings.**
   Signal-to-noise ratio is a dimensionless ratio of signal power to noise power.
   Noise sources:
   - Neuronal noise: random intrinsic electrical fluctuation within a neural network
   - Movement: blinking, speaking in EEG signals
   - Activation patterns to a sound
3. **What type of microelectrodes/probes are used to measure extracellular potentials?**



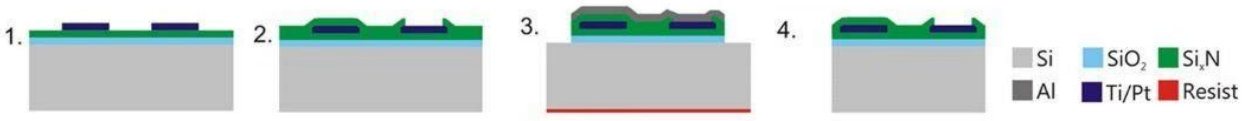
NDELSON, Biomedical sensors. In: *Introduction to biomedical ineering*,2005

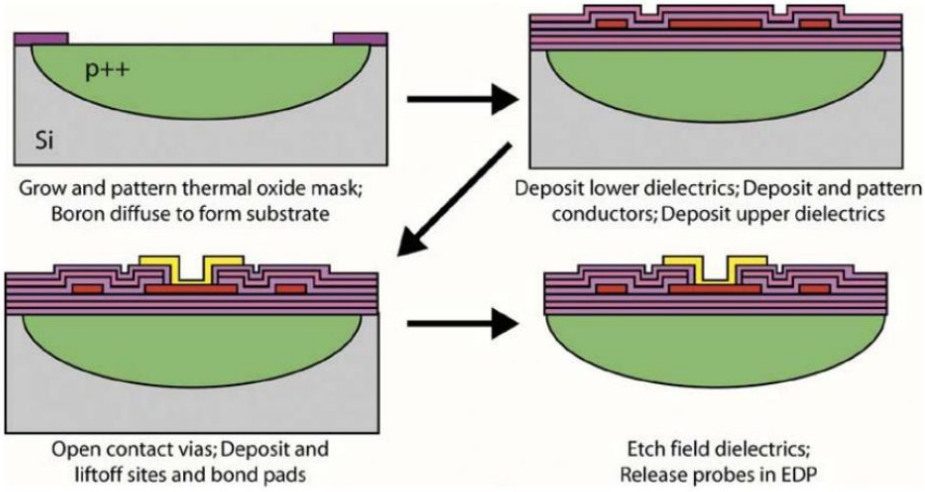
4. **What is the difference between EEG and ECoG recordings?**
   ECoG provides better signal quality (cortex surface vs EEG's scalp surface), but requires the implantation of subdural electrodes. (Plus see next question)

5. **Characterize neural signals like action potentials, LFP, EEG and ECoG in terms of signal amplitude and frequency domain.**

AP	LFP	ECoG	EEG
= Spikes • Single unit • Close to the neuron • 500 µV, 20 kHz	= Local Field Potential • Summation of activity from a population • Microelectrodes / low impedance electrodes • 1 mV, 200 Hz	= Electro-cortico-gram • Collective activity throughout cortex • Surface electrodes • 5 mV, 200 Hz	= Electro-encephalo-gram • Coherent collective neural activity through the scalp • Surface electrodes • 300 µV , 100 Hz

6. **What are the major differences between microwire arrays and planar silicon probes?**
   For silicon-based electrodes, they use micromachining techniques to generate more rigid structure.
   Si arrays are smaller than microwire electrodes → more sites in different layers of cortex.
   Overcome of inflammation, tissue damage, low flexibility
   Si can be coated with conductive metal
7. **Draw a schematic showing the major steps of the fabrication scheme of commercially available Michigan-type probes.**

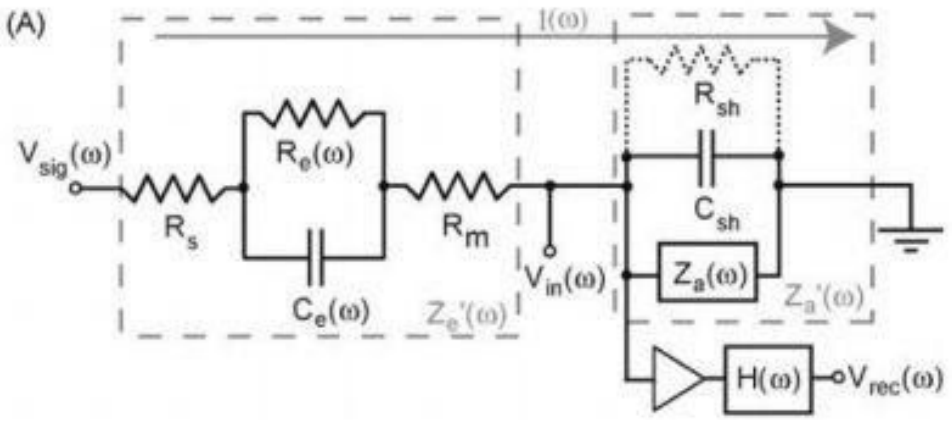




Basic process flow for a passive silicon micromachined electrode array.

8. **What are the advantages and disadvantages of Utah arrays compared to Michigan-type probes?**
   In contrast to Michigan arrays, Utah arrays are 3D, consisting of 100 conductive silicon needles. However, in a Utah array signals are only received from the tips of each electrode, which limits the amount of information that can be obtained at one time. Furthermore, Utah arrays are manufactured with set dimensions and parameters while the Michigan array allows for more design freedom.
   Michigans are shank with Si substrate, Utah are polymers up to the tips for biocompatibility. Utah: deep insertion, recording from individual neurons with high locative resolution

9. **List the components of an equivalent circuit model of a recording setup.**
   Z'_e: effective impedance of electrode
   R_s: resistance of electrolyte
   $R_{e'}$, C_e: resistance and capacitance at the double layer interface
   R_m: metal electrode resistance
   Z'_a: effective input impedance of the amplifier
   Z_a: head-stage amplifier impedance
   R_{sh},C_{sh}: shunt resistance and capacitance



Lecture 4 (Probes with active electronics)

1. **Describe the typical detection range of single neurons when using depth recording electrodes.**
   Detection range of electrodes is around 140 μm

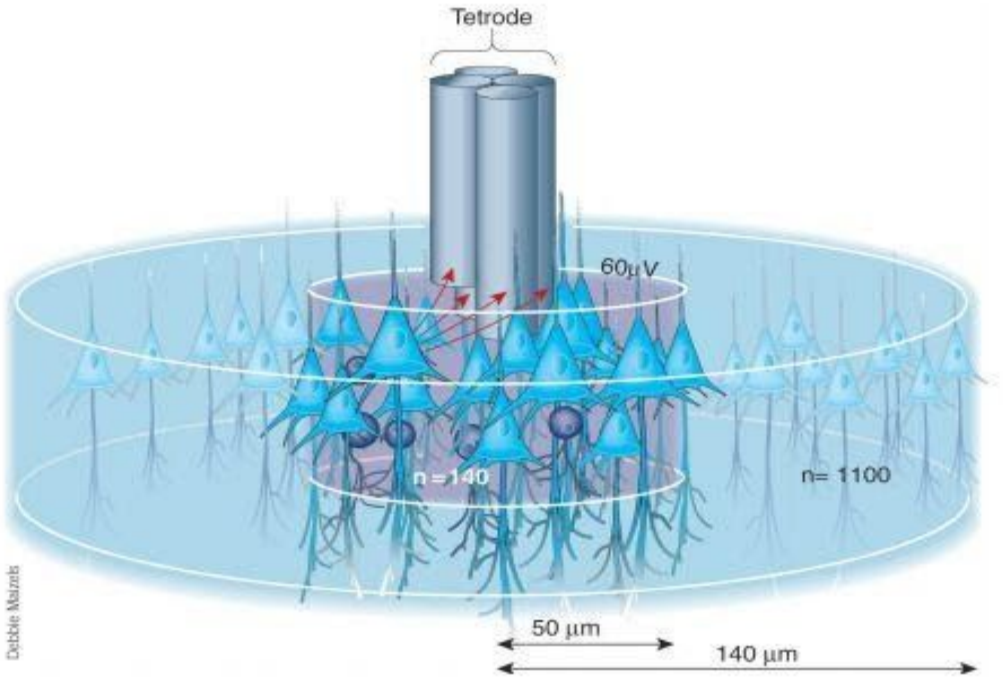
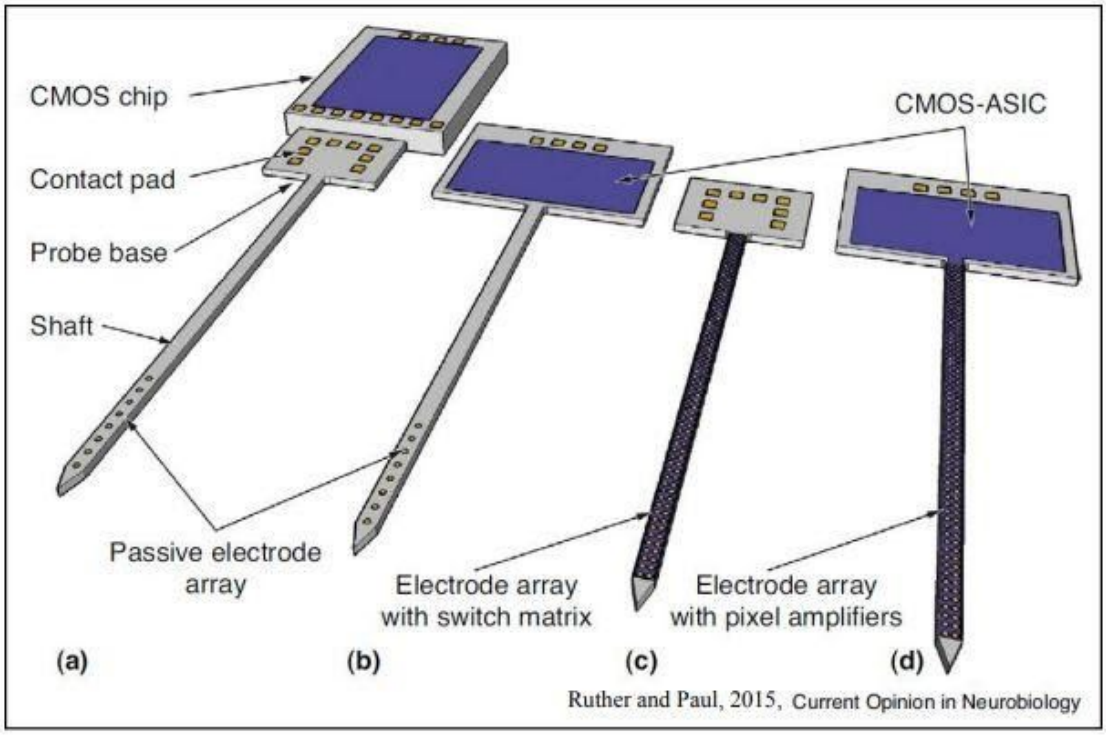


Figure 1 Unit isolation quality varies as a function of distance from the electrode. Multisite electrodes (a wire tetrode, for example) can estimate the position of the recorded neurons by triangulation. Distance of the visible electrode tips from a single pyramidal cell (triangles) is indicated by arrows. The spike amplitude of neurons (>60 μV) within the gray cylinder (50 μm radius), containing ~100 neurons, is large enough for separation by currently available clustering methods. Although the extracellularly recorded spike amplitude decreases rapidly with distance, neurons within a radius of 140 μm, containing ~1,000 neurons in the rat cortex[19,21], can be detected. Improved recording and clustering methods are therefore expected to record from larger number of neurons in the future.

2. **Explain the technological challenge of developing high-density recording probes.**
   In traditionally used silicon probes each recording site/electrode has a direct connection (metal line) with the contact pads on the probe base. These metal lines, buried in the silicon shaft, have a significant thickness (~µm), which means more recording sites mean more wires and that implicate a larger probe shaft. However, shafts of silicon probes should be thin to decrease the damage done to the brain tissue during insertion (thickness < 50 µm, width < 100 µm)
   Possible solutions: CMOS technology (wire thickness in the nm range), selection of a subset of recording sites, multiplexing. These solutions need integrated electronics/circuits. Probes without IC are called passive probes, and with IC they are called active probes.

3. **Draw schematics showing the typical architecture of active probes.**



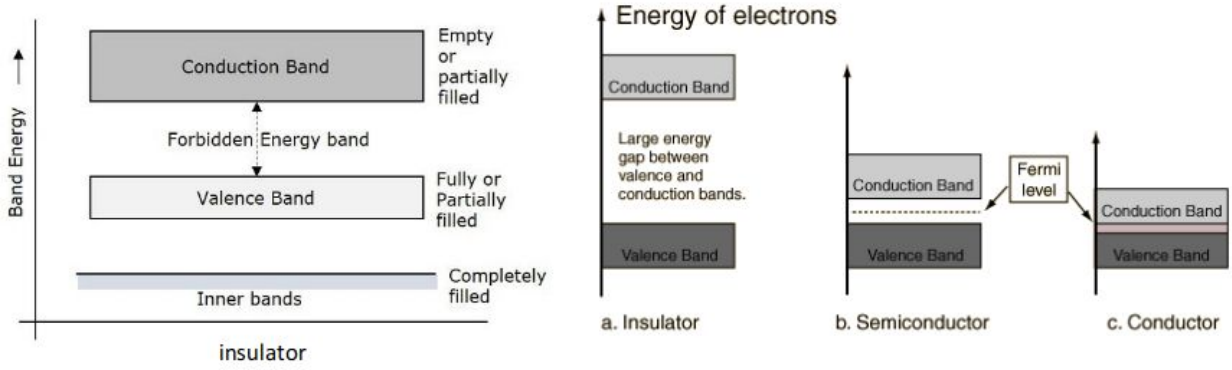
(a) passive silicon probe with CMOS chip in hybrid assembly
(b) silicon probe with CMOS circuitry on the probe base
(c) EDC probes with a CMOS switch matrix integrated on the probe shaft
(d) fully CMOS enhanced probe array with integrated circuitry on probe shaft and base

4. **List typical signal processing functionalities typically implemented integrated circuits on the probe backbone.**
   - Passive electrode array
   - Electrode array with switch matrix
   - Electrode array with pixel amplifiers

5. **Describe a biological event which can be efficiently observed with high-density recording probes.**
   Neuropixels probes are next-generation electrodes that record the activity of hundreds of neurons in the brain. Until recently, recording methods could either resolve the activity of individual neurons or monitor multiple brain regions. Neuropixels overcome this difficulty by distributing close to 1,000 sites over a one-centimeter shank. In the rodent brain, these sites record from hundreds of neurons distributed across different brain regions. For instance, two Neuropixels probes can record simultaneously from over 500 neurons in 5 regions of the mouse brain. For example: visual/whisker sensory stimulus + movement reaction can be observed together.

Lecture 5 (Material properties)

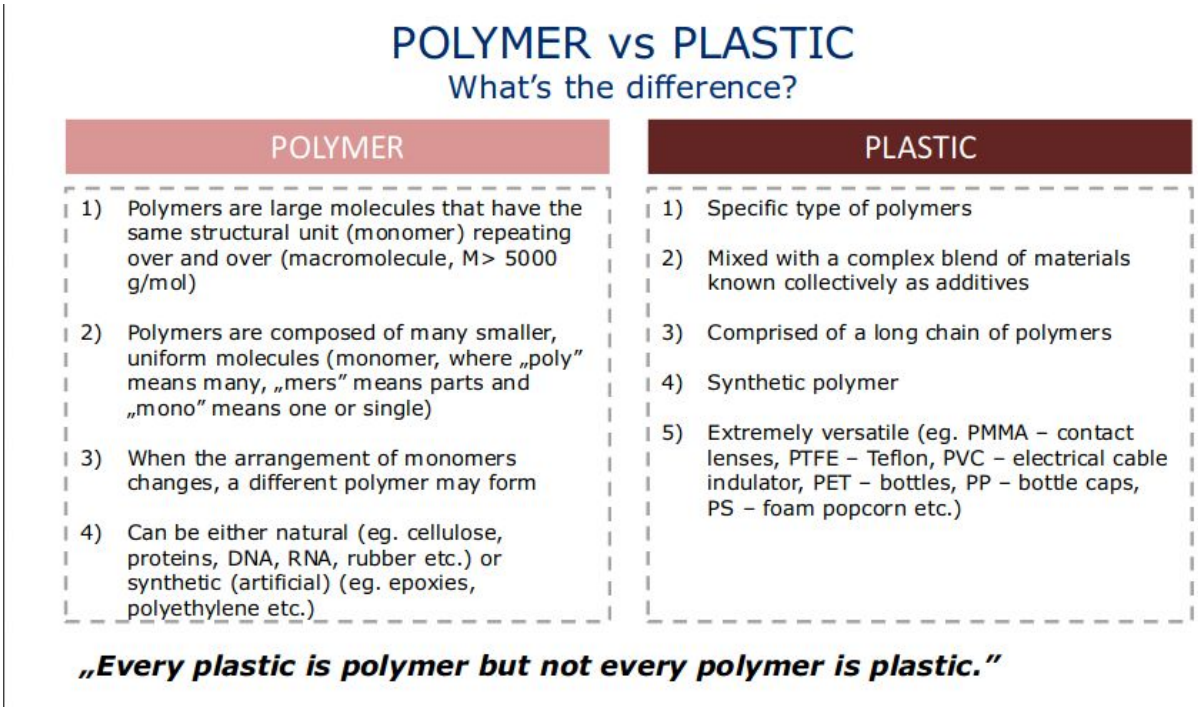
1. **What is the main difference between an insulator and a conductor (e- energy band theory)? What is role of the substrate and the encapsulation materials (including 1-1 specific examples)?**



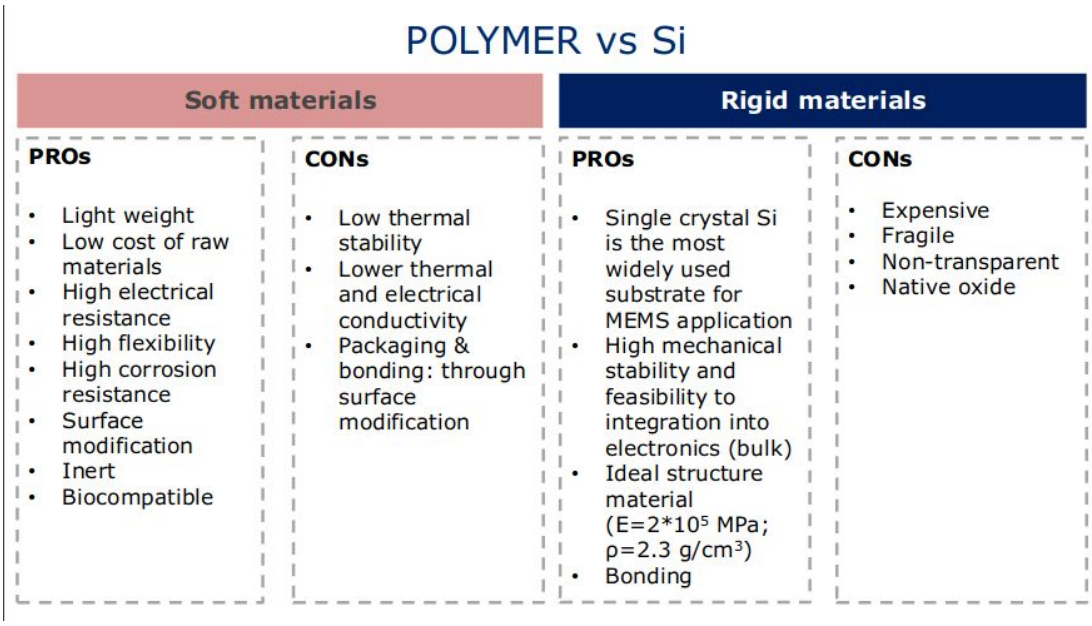
The schema consists of two energy bands (valence and conduction band) and the band gap. The valence electrons - which serve as charge carriers - are located in the valence band, in the ground state the conduction band is occupied with no electrons. Between the two energy bands there is the band gap, its width affects the conductivity of materials.
In insulators the valence band is fully occupied with electrons due to the covalent bonds. The electrons can not move because they're "locked up" between the atoms. To achieve a conductivity, electrons from the valence band have to move into the conduction band. This prevents the band gap, which lies in-between the valence band and conduction band.
Only with considerable energy expenditure (if at all possible) the band gap can be overcome; thus leading to a negligible conductivity.
In conductors, the valence band is either not fully occupied with electrons, or the filled valence band overlaps with the empty conduction band. In general, both states occur at the same time, the electrons can therefore move inside the partially filled valence band

or inside the two overlapping bands. In conductors there is no band gap between the valence band and conduction band.
In semiconductors, there is a smaller band gap, meaning that they generally act as insulators, but expending energy (e.g. heat, doping of impurities) can result in conductivity.
I think substrate materials have to be semi?conductors (Si, polymers), while encapsulation materials have to be insulators (Si-oxide, Si-nitride, polymers).

2. **What is the difference between polymers and plastics?**



3. **Compare soft and rigid interface substrates. Highlight advantages and disadvantages of their applications.**



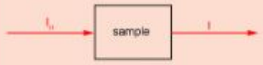
4. **List the relevant thermal, mechanical and electrical properties that are usually used to characterize substrates of neural interfaces.**

Material characterization – Insulating materials

Mechanical properties	Method
Young's modulus (GPa)	Stress (Pa)–Strain (%) (in the **linear elasticity regime** of a uniaxial def.)
Tensile strength (MPa)	Stress (Pa)–Strain (%) (**maximum** stress the material withstands)
Bending strength (MPa)	3-point flexure test Load (N)-Deflection (mm)

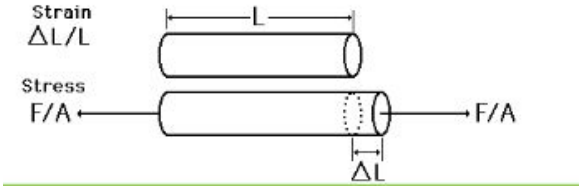
Electrical properties	Method
Dielectric strength (V/mil)	Test specimen placed between two electrodes in air or oil (**max. V** required to produce a dielectric breakdown)
Dielectric constant / Relative permittivity(F/m)	1) Polaization 2) Cole-Cole diagram 3) Microwave measurement
Volume resistivity (Ω·cm)	4-point probe

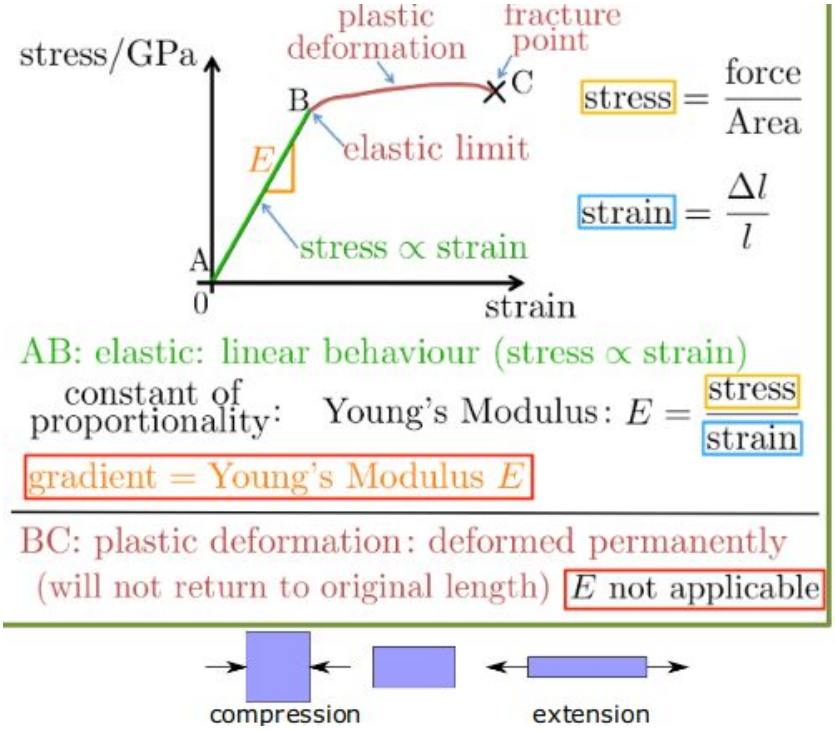
Thermal properties	Method
Glass transition T (°C)	Deformation (%)-Temp. (°C)
Thermal conductivity (W/m·K)	Steady state or transient
Melting temperature (°C)	Differential Scanning Calorimetry
Thermal stability (°C)	Thermogravimetric analysis

Optical properties	Method
Transmittance (%)	
Autofluorescence	Fluorescence emission (on different wavelength than the excitation) observed when certain molecules are excited by UV or visible radiation.

5. **What does mechanical mismatch between the device and the tissue mean?**
   If the tissue's Young's modulus is much smaller than the devices Young's modulus, the insertion will cause a high amount of stress in the probe-tissue interface. It causes improved foreign body reaction, electrical and spatial insulation, failure of long-term neural recording performance. The obvious way to reduce this is to choose more flexible substrates. As their Young's modulus approaches the brain tissue's, the mechanical mismatch will be reduced significantly.

6. **Define Young's modulus.**
   Strain: length change relative to absolute length
   Stress: force on an object per area
   Strain: $\varepsilon = \Delta L/L$
   Stress: $\sigma(\varepsilon) = F/A$
   Young's modulus: $E = \sigma(\varepsilon)/\varepsilon$





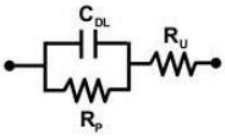
Different material types react differently to stress (brittle material: little strain to high stress, steel: stretch very little and then break suddenly, ductile material: after elastic region permanent deformation, plastic: very small elastic region)

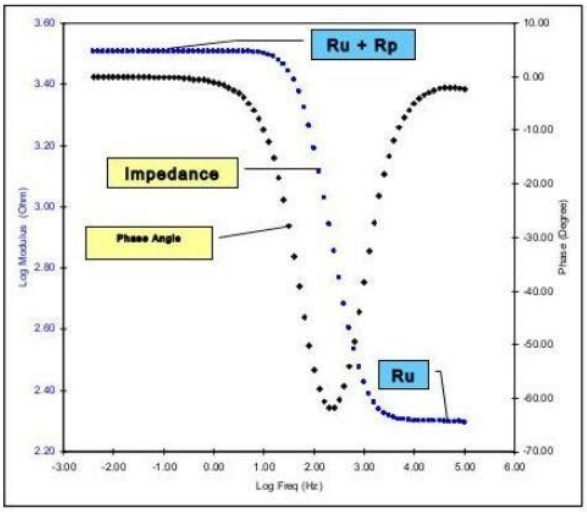
7. **What is the relationship between the thermal noise and the electrode impedance?**
   Thermal noise is the electronic noise generated by the thermal agitation of the charge carriers (usually the electrons) inside an electrical conductor at equilibrium, which happens regardless of any applied voltage. Thermal noise is present in all electrical circuits and increases with temperature. Because of the fluctuating thermal noise, the impedance is also changing in time.
   https://www.physics.queensu.ca/~phys352/lect04.pdf

8. **Explain electrochemical impedance spectroscopy. Describe the representation of related data in a Bode-plot.**
   Electrochemical impedance spectroscopy (EIS) is a powerful analysis technique to detect the changes of the interfacial properties of the electrode after the interaction of analytes with their probing molecules immobilized on electrode surfaces. Electrochemical Impedance Spectroscopy (**EIS**) is a well-established quantitative method for the accelerated evaluation of the anti-corrosion performance of protective coatings. The result of **EIS** is the impedance of the electrochemical system as a function of frequency.

   Electrochemical impedance is the response of a cell to an applied potential (the frequency dependence of this impedance can reveal underlying chemical processes).

Electrochemical impedance is usually measured by applying an AC potential to an electrochemical cell and then measuring the current through the cell. Assume that we apply a sinusoidal potential excitation (fixed freq. - repeat for a lot of different frequencies and analyze).

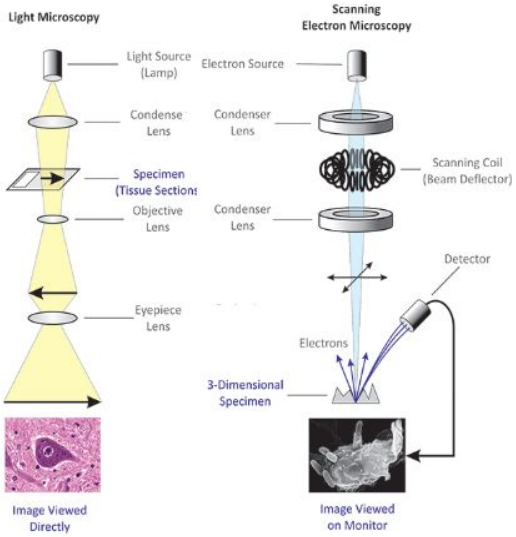




9. What are the advantages of SEM compared to light microscopy?

SCANNING ELECTRON MICROSCOPY VS LIGHT MICROSCOPY

Feature	Light or Optical Microscope	Electron Microscope
Radiation/ Illumination source	Light rays	Beam of electrons
Magnification	X 2000	X 500,000 (1,000,000)
Max. resolution	200-300 nm	0.5 nm (0.2 nm)
Image focused by	Glass objective lenses	Electromagnetic objective lenses
Image seen by	Eyes through glass ocular lens	received in $ZnSO_4$ Fluorescent Screen or Photographic Plate
Vacuum	Not required	Essential
Cooling system	No	Yes (to take out heat generated by high electric cur.)
Specimen preparation	Few min-hours	Few days
Coloured images	Yes	No
Live or dead specimen	Both	Only dead or died



- SEM display enhanced depth to map the surface of objects in 3D
- SEM has a much higher range of magnification and much higher resolution

Lecture 6 (Soft polymer implants)

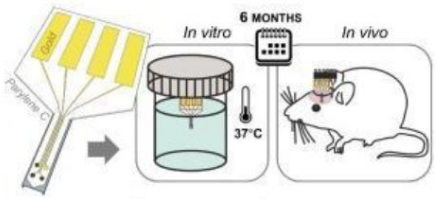
1. **How can derive the expected lifetime of a device using accelerated ageing tests?**

$$T_{sim} = T_{exp} * Q_{10}^{\Delta T/10}$$

The rate of chemical reactions increase exponentially with the temperature. Accelerated Aging is an artificial procedure for determining the lifespan or shelf life of a product. It uses the Arrhenius equation. Temperature, pH, p elevated, but constant.

Accelerated ageing

1. Polymer life-time prediction; biostability assessment
2. Prediction for polymer material degradation characteristics
3. Standard test methods:
   - **ISO 10993-18**
   - **ISO 11607** (Accelerated aging)
   - **ASTM F1980-16** (Standard Guide for Acc. A. of Sterile Barrier Syst. for Med. Devices)



Aziliz Lecomte et al., *Sens.Act. B*, 2017

4. Maintain constant **elevated** T, p, pH, c etc.
5. Characterization on the final structure
6. **Arrhenius law** (empirical):
   rates of chemical reactions increase exponentially with T

$$T_{sim} = T_{exp} \cdot Q_{10}^{\Delta T/10}$$

, where Q_{10} = 2, for polymer materials

2. **Describe the equivalent circuit model of an electrode-electrolyte interface. What does each component mean?**

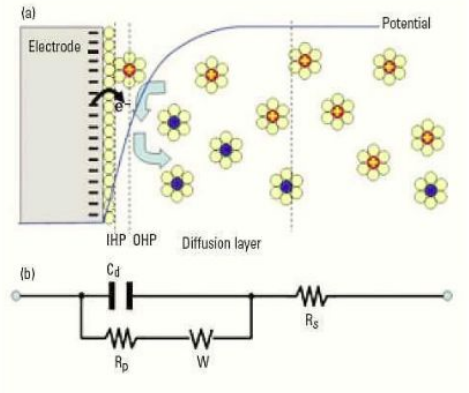
IMPEDANCE & EQUIVALENT CIRCUIT ANALYSIS – MODEL ELEMENTS

Double Layer Capacitance (C_{DL}):
- occuring the interface between solid and ionic solution due to charge separation

Charge Transfer Resistance (R_P or R_{CT}):
- resistance to the polarization or to the charge transfer

Uncompensated (Electrolyte) Resistance (R_S):
- bulk electrolyte combined with the internal resistance of the electrode

Warburg diffusion element:
- Diffusion (mass transport) of ions into the electrode surface



- For recording electrodes, the metal-tissue interface has a linear current-voltage relationship
- Capacitive mechanism of charge transfer dominates

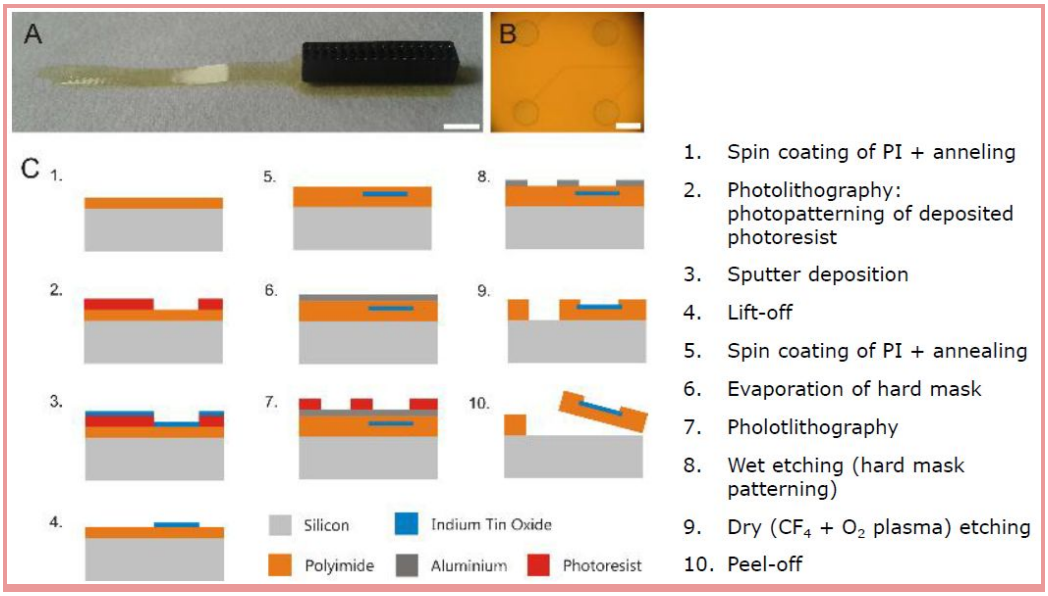
- Ionic currents in the extracellular medium cause an electric current in the metal electrode
- No charge carriers passing through the phase boundary
- No electrochemical reactions should occur in this low voltage and current regime

3. **List polymer substrates (at least five) usually used to fabricate microscale neural interfaces.**
    - Polyimide (PI)
    - Poly(para-xylylene) (PPX)
    - Liquid Crystal Polymer (LCP)
    - Poly-dimethyl-siloxane (PDMS)
    - SU-8
    - Shape-memory polymer (SMP)
    - Nanocomposites

4. **Characterize polyimide in terms of material properties and processing.**
   Material properties
    - Thermally stable
    - Resistant to most solvents
    - Mechanically durable
    - Non-cytotoxic
    - Absorbs water (-)
    - High optical transmittance (80% above 550 nm)
    - High autofluorescence (not usable in laser microscopy)
    - Good insulator (highly compatible with electronics)

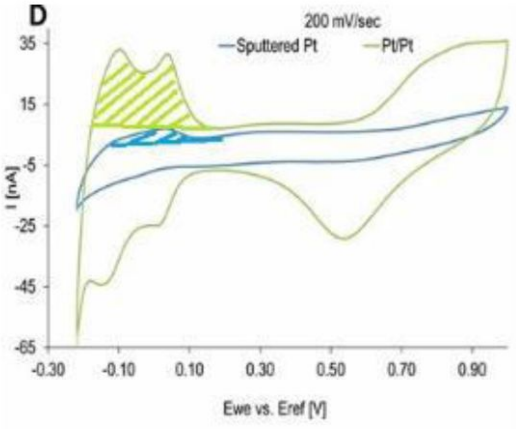
   Fabrication
    - Need clean room environment
    - Planar micromachining techniques
    - Spin-coating
    - Photo-definable and non-photo-definable options
    - Dry etching using CF4 + O2 plasma
    - Easy to process, cheap

5. **Draw the fabrication scheme of a typical polymer ECoG.**
Polyimide



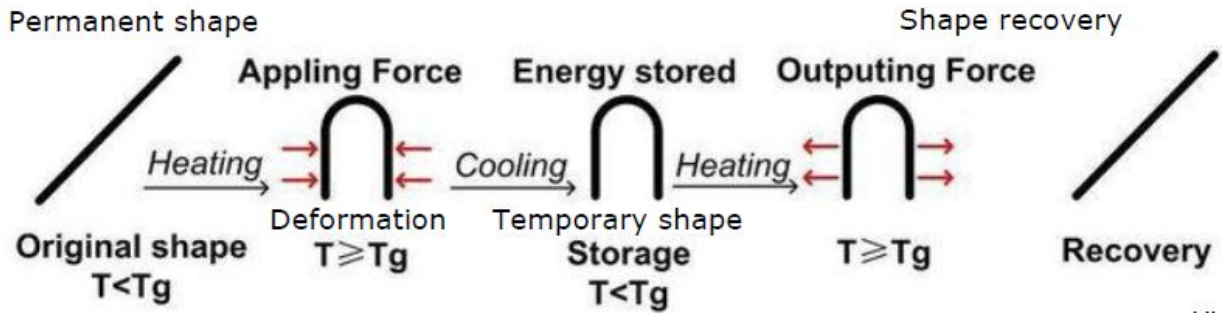
6. **Describe the significance of electroplating in the technology of neural interfaces. How can we measure the improvement in electroactive surface area?**
Electroplating uses electric current to reduce dissolved metal cations, so that they don't form a thin coherent metal coating on an electrode, enhancing its conductivity by improving its stability. This method is especially useful on smaller diameter, densely packed recording sites, where accurate fabrication is difficult and the small size decreases SNR and recording quality, but accurate realization would achieve much better spatial resolution.

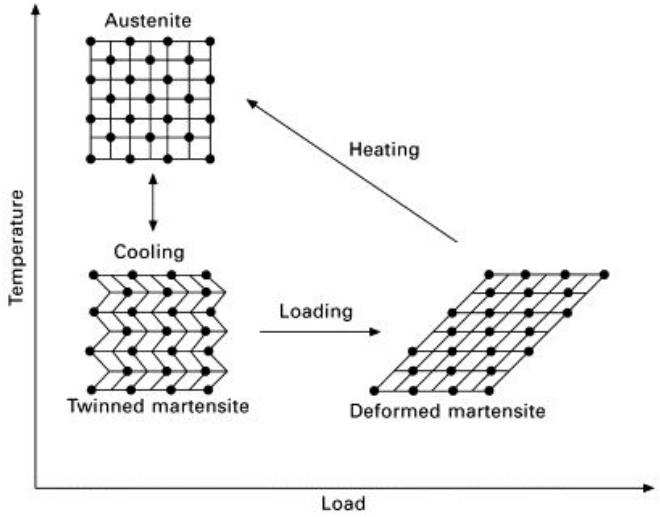
Methods for measuring:
We can analyze the CV (cyclic voltage - capacitance-voltage) curves (of Hydrogen desorption?) to observe improved stability (of current):
RF (rate of forward reaction) = electrochemically active surface area / whole geometric surface area. RF will improve



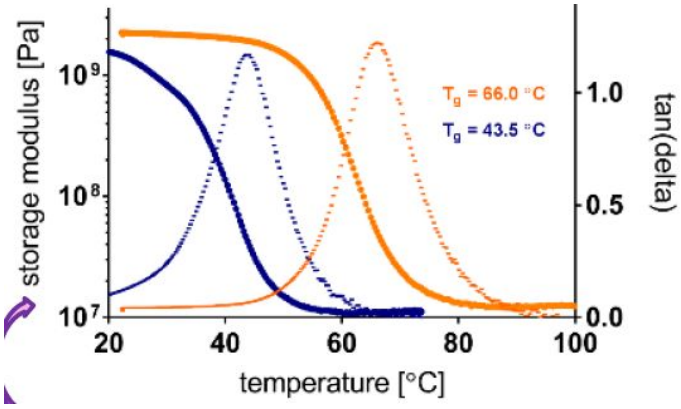
We can also observe the 400 nm thick, homogeneous, robust porous Pt (platinum) using Scanning Electron Microscopy (crack formation, soak in distilled water before implanting to reduce).
We can validate in vivo, 3.5x improvement of SNR on electroplated Pt after 72 hours

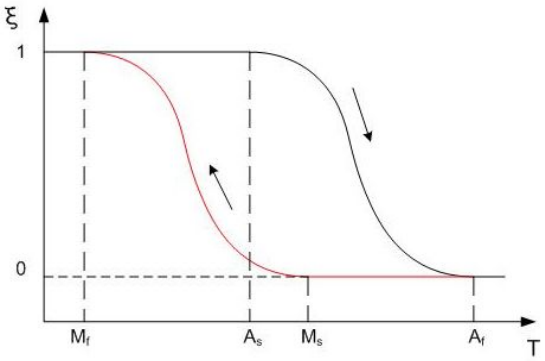
7. **Explain the shape-memory effect. Draw a characteristic relationship between temperature and Young's modulus of a shape-memory material.**

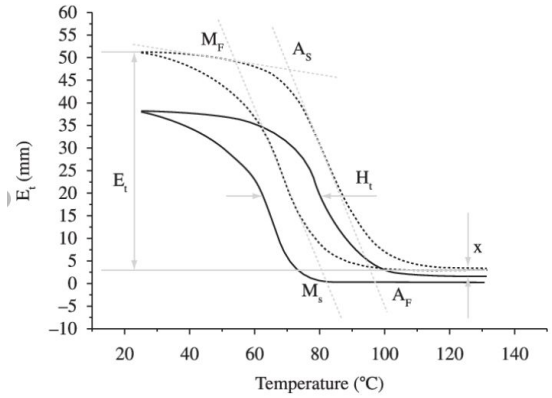




If we deform a SMP after heating it up, then cool it down (or deform when it is cold), it will keep its new form (store the deformation energy) until it is heated again, at which point it will output this energy as force and return to its original form.



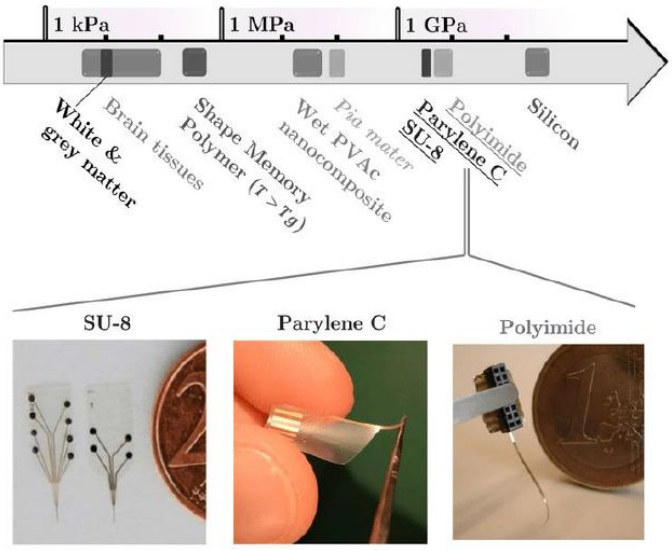




8. **Describe how chemoresponsive polymers are changing their softness to external conditions.**
   Chemoresponsive polymers change between hard and soft states when exposed to a liquid.
   Rapid water uptake: predominant factor
   PVAc-CNC: stiff cellulose fibrin nanofibers encased in PVAc
   Dry state: fibers percolate with hydrogen bonds into a rigid network
   Wet state: inter-nanocrystal hydrogen bonds are displaced with water molecule-nanocrystal bonds -> this reduces PVAs glass transition point to 20°C, overall reduces the storage modulus

9. **Compare typical polymers with silicon and brain tissue by characterizing their Young's modulus.**

		PI	Pary C	Pary HT	LCP	PDMS	SU-8	SMP	Silicon
Moisture absorption	**%**	0.5	< 0.1	< 0.01	0.04	0.5	0.55	n/a	-
Glass transition T (Tg)	**°C**	360	80-100	n/a	>280	n/a	200	variable	-
Thermal conductivity@RT	**W/(m*K)**	0.105	0.084	0.096	0.2	0.2	0.2	0.15-0.30	130
Linear coefficient of thermal expansion@25°C	**ppm**	3	35	36	3-50	310	52	n/a	2.6
Melting temperature (T_m)	**°C**	none	290	>500	275-330	226-232	n/a	variable	1414
Thermal stability (@ 5% wt.loss)	**°C**	620	100	450	320	200	300	<200, low pressure	-
Tensile strength	**MPa**	350	68.95	51.71	52.8 - 185 (230)	2.24-6.2	73	155-323	7000
Young's modulus	**GPa**	8.50	2.76	2.55	8.5 - 17.2 (40.0)	$1.32\text{-}2.97*10^{-3}$	2.00	0.04-0.30	130.0-180.0
Elongation at break	**%**	100	200	200	1.2-7.0	600	4.80	Up to 800	-
Bulk/Volume resistivity	**Ω*cm**	$>10^6$	$8.8*10^{16}$	$2.0*10^{17}$	10^{19}-10^{20}	$6.0x10^{18}$	$7.8x10^{14}$	n/a	-

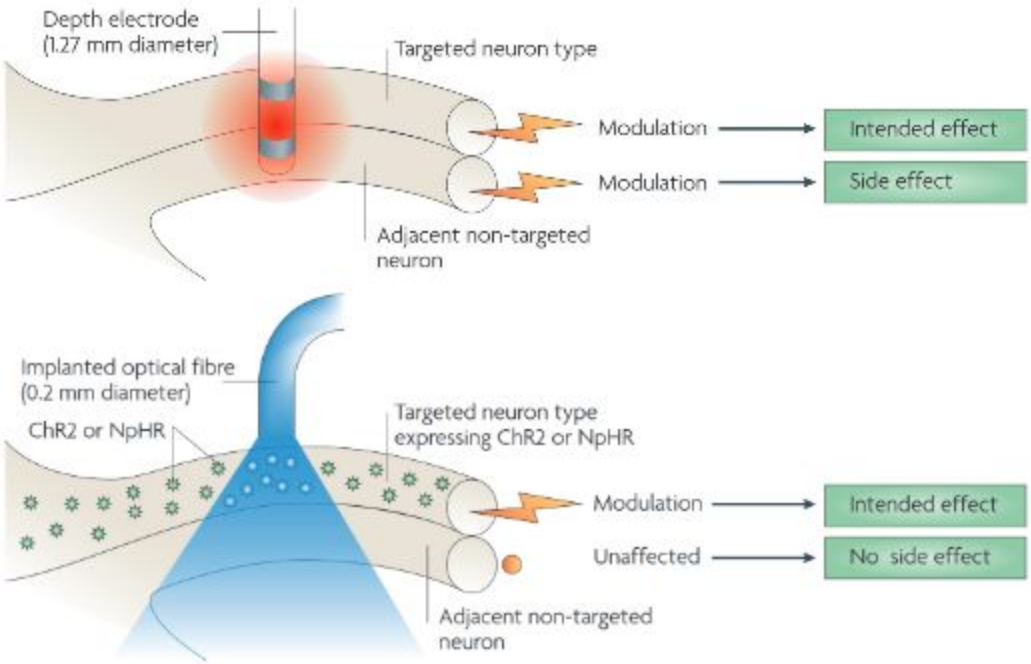

1 kPa
1 MPa
1 GPa
White & grey matter
Brain tissues
Shape Memory Polymer (T > Tg)
Wet PVAc nanocomposite
Pia mater
SU-8
Parylene C
Polyimide
Silicon
SU-8
Parylene C
Polyimide

Lecture 7 (Optogenetic probes)

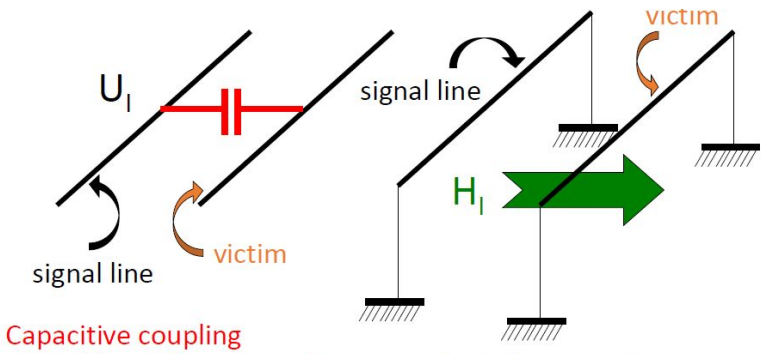
1. **Explain the basics of optogenetics.**
   Opsin is a light-sensitive protein → if we integrate it in the cell membrane, it generates light-sensitive ion channels. This way we can switch on/off specified neurons by specified light. There are Type I and Type II opsins. The peak wavelengths are 473, 532, 561, 594 and 638 nm. Opsin is carried into the cells by viruses.

2. **Compare electrical stimulation and optogenetics.**
   Optogenetics:
   + Temporal, spatial precision (fast, local and selective)
   - Genetic modification → obstacle of application in humans

   Electrical:
   + Temporal and spatial precision (fast and local, but NOT selective)
   - General, non-selective effect
   - Noise artefact in electrical recording



3. **Why is the relative position of signal and supply lines is important in the case of active optrodes?**
   Because we need to avoid cross-talk between them. Capacitive (displacement current) or inductive (inducing voltage change in each other) coupling can occur between micro-wires/conductive loops (respectively) that are too close to each other, generated by the electric field around them. We can avoid or attenuate these artefacts by increasing the distance between the wires, or decrease the amount or the overall area of facing conductive surfaces.



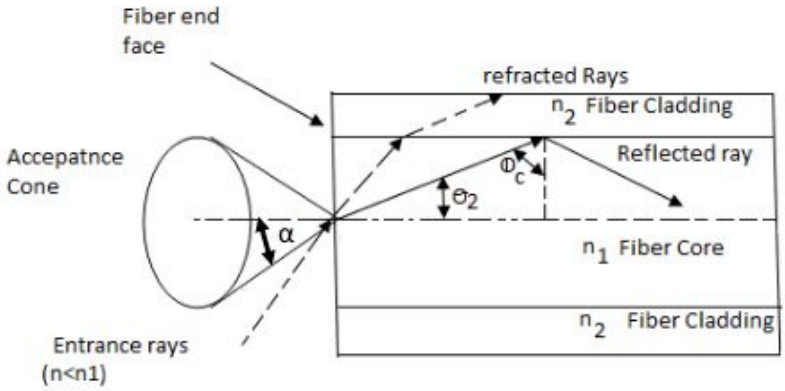
4. **How we can mitigate the extent of photoelectric artefacts in our recordings when using visible light optrodes?**
   Physical avoidance:
   - Avoid direct illumination of the recording sites
   - Place the light source far from the recording sites
   - Use incoherent light
   - Use longer wavelength light
   - Use conductive materials with a high band gap (ITO, graphene)

   Numerical (data processing) avoidance
   - Use two identical probes simultaneously and compare results
   - Pre-calibrating the present photoelectric effect and subtract it from results

5. **Compare the optical properties of LASER and LED sources in general.**

LASER	LED
Advantages	**Advantages**
• Appropriate intensity • Low beam divergence • Tight spectral bandwidth	• Reliability • Small size • Stability • Incoherent light source
Disadvantages	**Disadvantages**
• Fragility • Bulky size • Power stability • Long warm-up time • Coherent light source	• Low efficiency waveguide coupling → difficult to achieve appropriate intensity • Broader spectral tuning

6. **Explain the theory of total internal reflection.**
   - TIR occurs when the angle of incidence is greater than the critical angle of the particular medium boundary (and light enters an optically denser material)
   - Core: optically denser, cladding: optically rarer (n1>n2)
   - Numerical aperture: $NA = sin(\alpha) = \sqrt{(n1^2 + n2^2)}$
   - Angle of acceptance cone = full acceptance angle = 2α
   - It is wavelength and temperature dependent



7. **Explain the photoelectric artefact.**
   Photo-generated electrons act as electric signal and impact the electrophysiological registration.

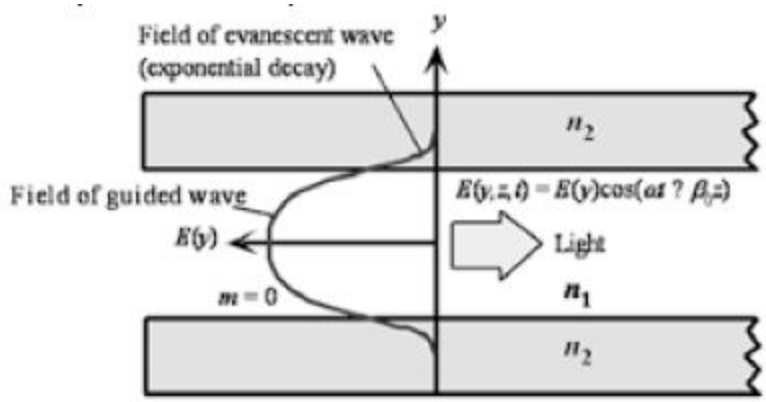
8. **List pair of thin film materials that are used to form integrated waveguides.**

Material	n	Material	n
SiO_2	1.47	Parylene-C	1.6
Si_3N_4	2.05	SU-8	1.58
SiON	1.52	Polyimide	1.5
ZnO	2	Water	1.33
Al_2O_3	1.77	Brain	1.41
Air	1	Gray matter	1.36

$n_{core} > n_{cladding}$

9. **Describe the evanescent field of a waveguide. What is the significance of that in the case of designing the cladding layer of a waveguide?**
   Evanescent field is an oscillating electric and/or magnetic field that doesn't propagate, but whose energy is spatially concentrated in the vicinity of the source. Its Poynting vector is therefore zero.
   Coupling is the main source of loss. Beam splitters facilitate coupling from one source to multiple waveguides, and we can reduce bending loss using large bending radius (>1mm)

Glass cladding layer (3.2 um thickness) reduces attenuation (csillapítás) due to the presence of the evanescent field's concentrated energy.

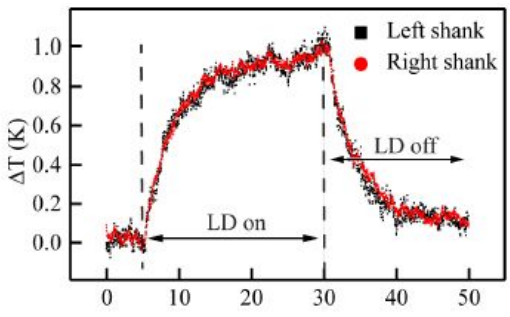


10. List pro and contra for passive and active devices for optogenetics stimulation.

Passive optrodes	Active optrodes
Advantages	**Advantages**
• Lower tissue heating onsite • No electrical cross-talk	• Possibility of wireless stim.&rec. • Stimulation at multiple sites
Disadvantages	**Disadvantages**
• Stray light (propagation loss) • High area on device layer • Coupled to external optical fiber: limits freely moving experiments • Coupling efficiency is critical	• Tissue heating onsite • Light source's feeding current causes electrical cross-talk • Inherent requirements (size, biocompatibility)

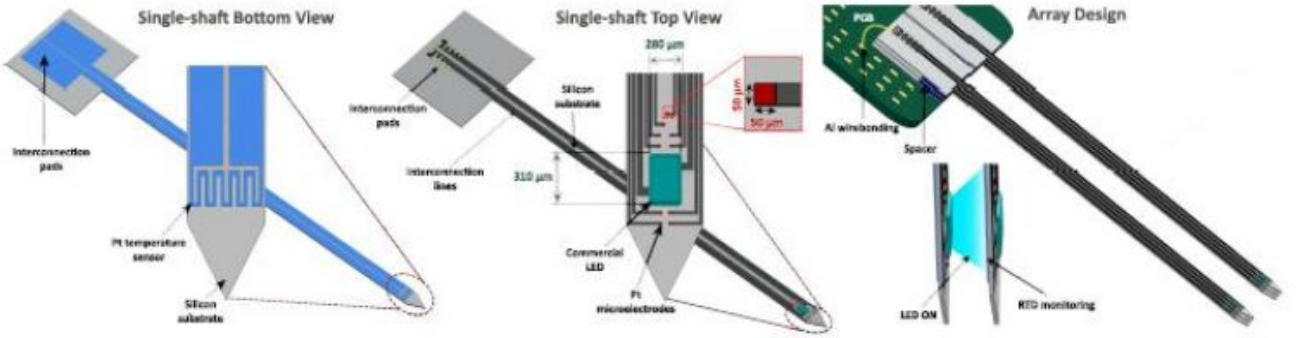
11. Explain the issue of self-heating of integrated light sources. What temperature increase is acceptable and why?

Small, tightly packed electric light sources -> self heating during operation, which can damage surrounding tissue if it is much hotter than the normal body temperature



"In the absence of external influence, no outer surface of an implantable part of the active implantable medical device not intended to supply heat to the patient shall be greater than ***2 °C*** above the normal surrounding body temperature of 37 °C when implanted, and when the active implantable medical device is in normal operation or in any single component failure"

12. Describe an integrated solution for on-chip temperature sensing.

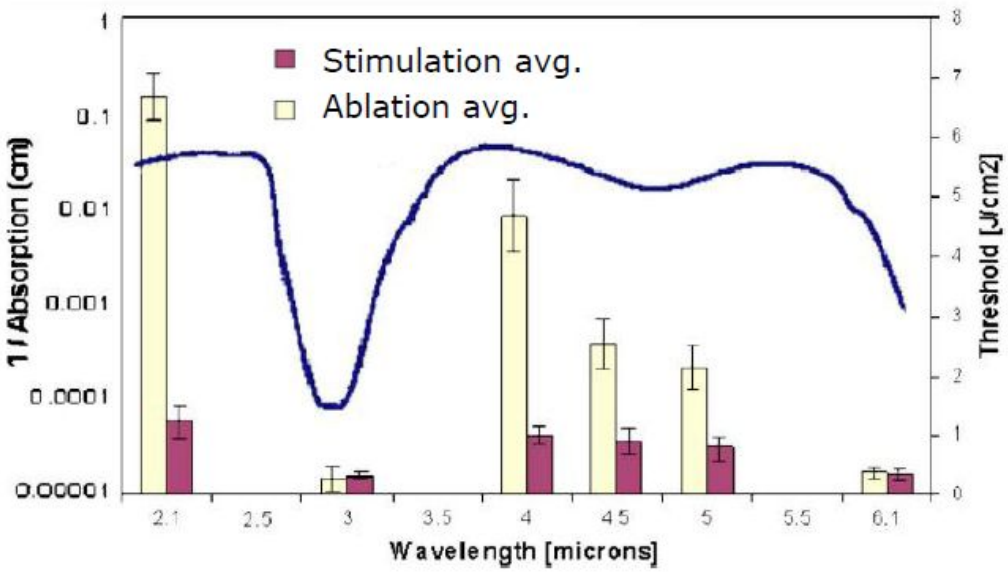


Goncalves, 2018

- Resistance thermometer integrated on optrode arrays
- High sensitivity (above 1500 ppm) and high precision (better than 0.1 K)

Lecture 8 (Infrared neural stimulation)

1. **Compare optogenetics with infrared neural stimulation.**
   Optogenetics: switching specified neurons on/off by specified light. Based on Opsin, a light sensitive protein, which generates light-sensitive ion channels after being integrated into the cell membrane.
   Typical power density: 1-10 mW/mm^2 (1-5 required for opsin-expressing cells), up-to 75 for short pulses is safe in vivo
   Light: only invasive signal acquisition
   Thermogenetics (IRS): Selective neuro-activation by temperature (Transient Receptor Potential cation channels), conductances change dramatically with temperature, may be non-invasive, 1-2°C temperature shifts can switch on/off neurons (larger would be unsafe for other physiological processes).
   Weak promoters can be used
   Neuron activation by IR instead of simple electric signals (PNS, now CNS today)
2. **Most of the studies on Infrared Neural Stimulation work with excitation wavelength of around 1800-2000 nm. Why?**
   Because that is the only wavelength domain where the ablation average crosses the threshold of action potential generation/inhibition. Induction of a temperature gradient induces capacitive currents -> membrane depolarization (ion channel conductance change). Absorption is the largest here, as well as the possible stimulation (from the graph). Talán még ez a legjobb.
   Probably. Couldn't find an intelligent answer.



3. **Explain strategies to form IR light delivery functions on implantable microelectrodes.**
   (100) c-Si: substrate and waveguide's core
   Conventional Si deep-brain passive electrode array formation methods:

- Dicing of the initial Si chip

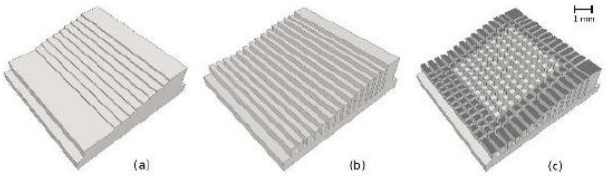
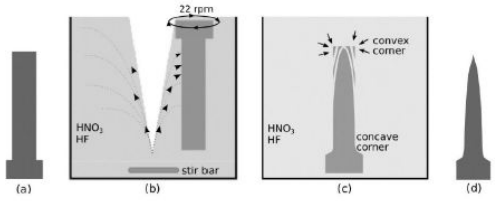


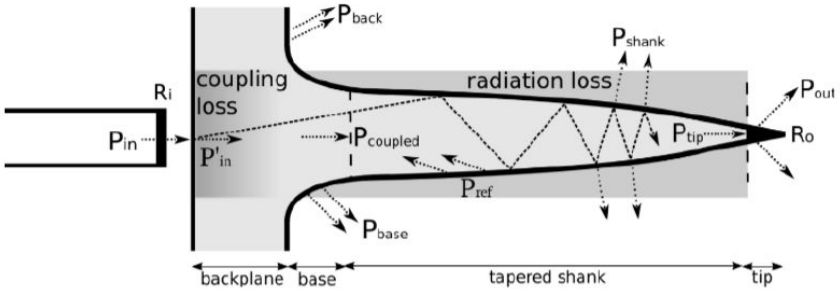
Fig. 5. Array dicing steps. Darker shanks constitute sacrificial regions.

- Wet chemical etching
  - Dynamic etching for isotropic thinning
  - Static etching for tip sharpening



4. Describe loss mechanisms along the integrated waveguide of an optrode device.

$$P_{in} \times (1 - R_i) = P'_{in} = P_{back} + P_{base} + P_{shank} + P_{out} + P_{ref}.$$



T. V. F. Abaya *et al.*, 2012 *Biomed. Opt. Express* 3

- The primary loss mechanisms are expected to be:
  - Fresnel reflections (R): fiber-to-Si and Si-to-tissue interfaces (with air gaps or index matching material)
  - mode coupling,
  - radiation,
  - loss due to reflection towards the source

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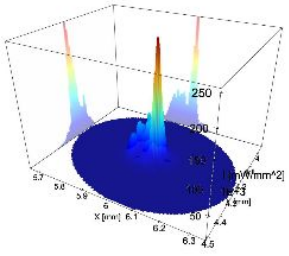
Optrode width only influences the beam width.
Tip taper angle only modifies the divergence of the beam exiting the tips.
In tissue, the beam divergence is expected to be smaller according to Snell's law, because the refractive index on the output side increases.
Scattering is considered insignificant because light travels at a grazing incidence along a relatively smooth shank.
With an input fiber smaller than the optrode shank, the majority of system loss is determined to come from the tips, where total internal reflection towards the source dominates over Fresnel loss and scattering.

5. Draw a schematic on how the beam shape exiting a waveguide can be characterized. Denote each component with captions. ??

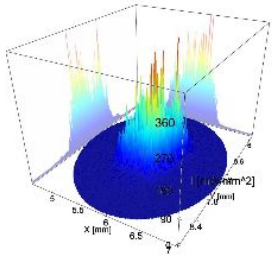
Beam profile

- Remember: LASER has Gaussian spatial beam profile

Profile emitting from fiber end



Profile emitting the Si shaft



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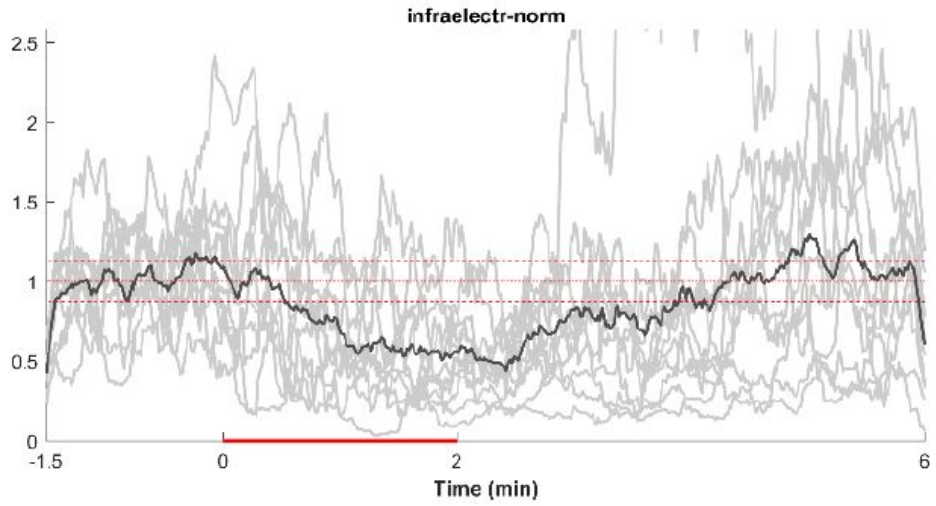
6. **How the spike of cortical cells change in the case of infrared neural inhibition?**

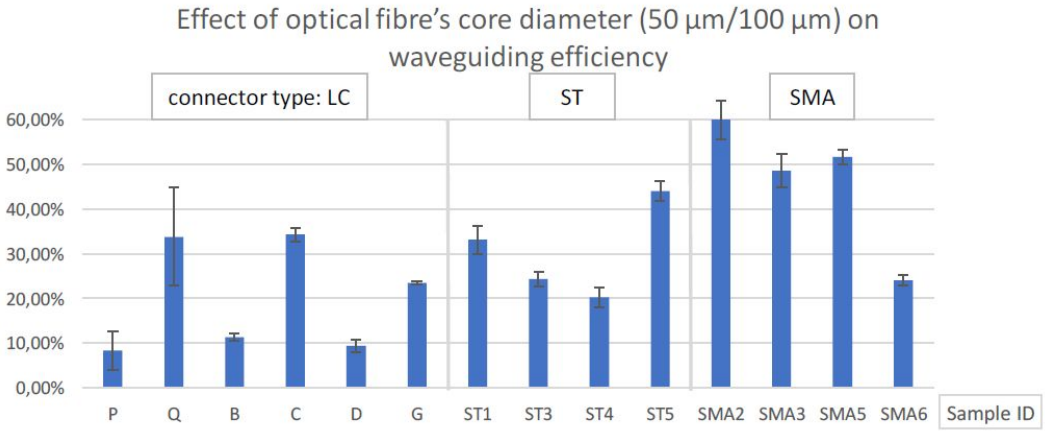
AP signal shapes do not change significantly, so the effects are harmless. SR~ 50% decrease during inhibition



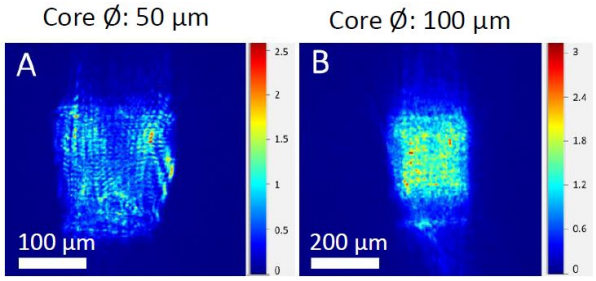
7. **Explain why silicon is appropriate to act as both mechanical carrier and a waveguide for INS?**

Insulator -> prevents short-circuit during soaking, impedance stable in long-term, Young's modulus appropriate for durable but not brittle structure, refractive index of Si composites is appropriate for waveguides. ??? Mentioned exactly no-fucking-where

8. **How the coupling efficiency from an optical fiber to an optrode will change if the core diameter of the fiber increases?**



A larger diameter focuses the light better, increasing efficiency.

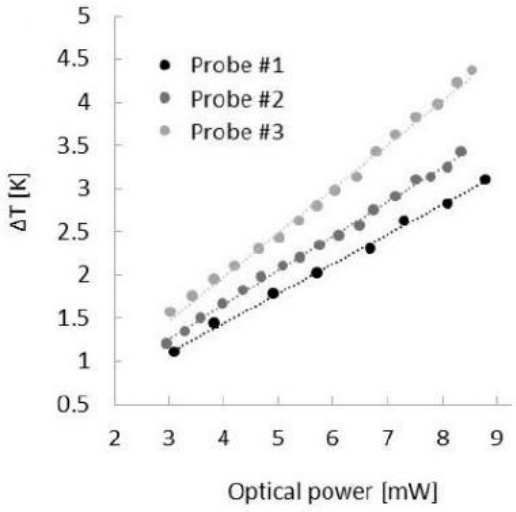


9. How the spot size is defined?

In micrometers. WTF?

The area upon which the stimulation exerts its effects. Affects the number of activated neurons. No idea, didn't even mention this

10. Draw a figure showing the relationship of optical power and temperature when using INS.



11. What are the limitations of Utah type IR optrode compared to Michigan-type IR optrode?

Michigan is multimodal, Utah is not. Michigan's modalities:

Optical stimulation and measurements: Bulk Si: mechanical carrier and IR waveguide (2 in 1). Waveguiding efficiency, optical power, beam size, optical heating

Monitoring heat accumulation via thermosensor: Pt thinfilm thermometer (100x100um^2) at tip

Electrophysiology: 900 um^2 Pt recording sites with 100 um spacing, recording sites' impedance measured by electrochemical impedance spectroscopy, SiO2 layer prevents short-circuit during soaking

Lecture 9 (Drug delivery probes)

1. **List five medical applications of microscale drug delivery.**

   Microneedles:

   - Transdermal injection of drugs
   - Microdialysis tests

   Microelectrodes:

   - Administration of pharmacuticals through the blood-brain barrier (therapy, diagnostics)
   - Injection of anti-inflammatory agents during implantation
   - Injection of anatomic tracers
   - Release of neurotransmitters to investigate neurodegenrative diseases

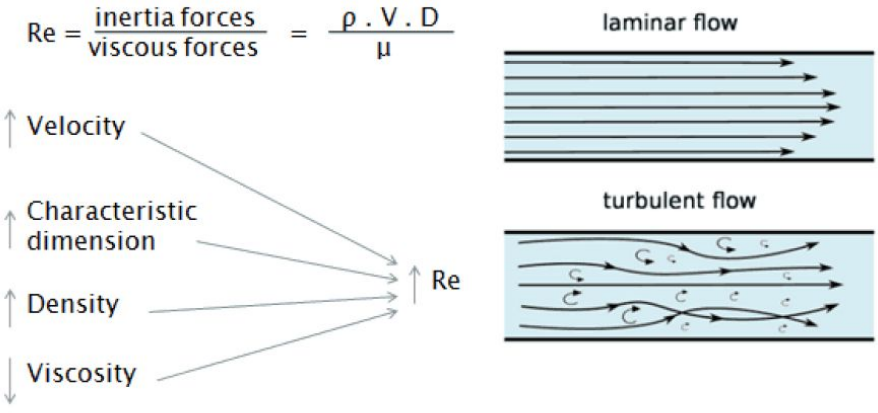
2. **What parameters determine the flow rate in the case of iontophoretic injection of charged particles?**

   Governing equation (Navier-Stokes):

$$\rho \frac{\delta \boldsymbol{u}}{\delta t} = -\nabla P + \mu \nabla^2 \boldsymbol{u} + \mathrm{g}$$

   Driving forces:

   pressure gradient, viscous forces, gravity

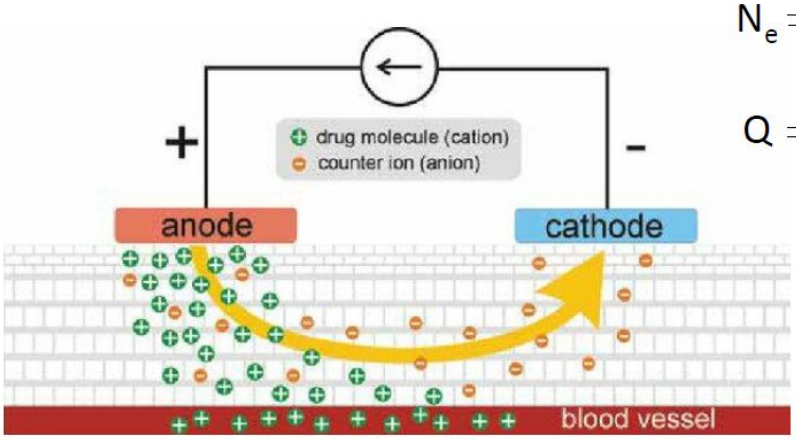


Az előző két ábra csak általános, a konkrét megoldás:

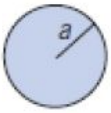
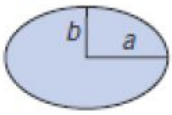
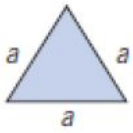
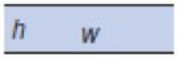
- Administration of solutions containing charged particles
- Governing equations: Faraday's law

$$N_e = \frac{I}{F}$$

$$Q = M_w * N_e$$

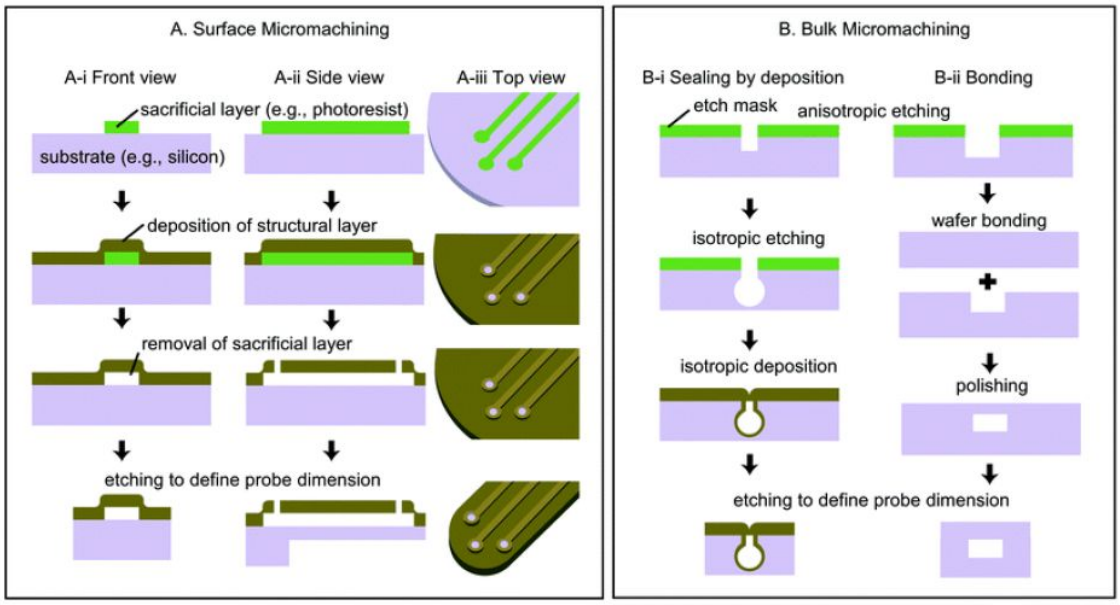


3. What parameters determine hydrodynamic resistance in a microchannel?

Shape	Formula for R_{hyd}
Circle 	$\frac{8\mu L}{\pi a^4}$
Ellipse 	$\frac{4\mu L[1+(b/a)^2]}{\pi a b^3}$
Triangle 	$\frac{320\mu L}{\sqrt{3}a^4}$
Two plates 	$\frac{12\mu L}{h^3 w}$
Rectangle 	$\frac{12\mu L}{h^3 w[1-0.63(h/w)]}$
Square 	$\frac{12\mu L}{0.37h^4}$

Determining parameters: channel length (L), fluid viscosity (u), radius, height, width, etc.

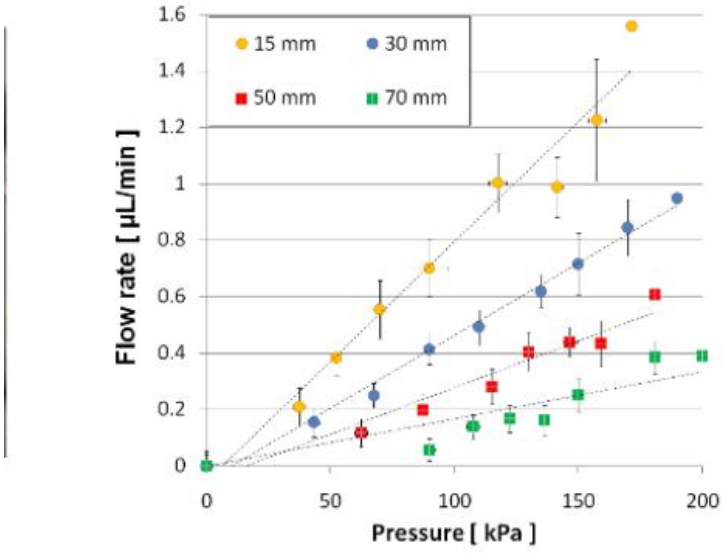
4. **Draw the schematic process flow of surface-, bulk micromachining approaches to fabricate microfluidic channels.**



Small volume of fluids

Large volume of fluids

5. **What is the relationship between pressure and flow rate in a laminar flow?**



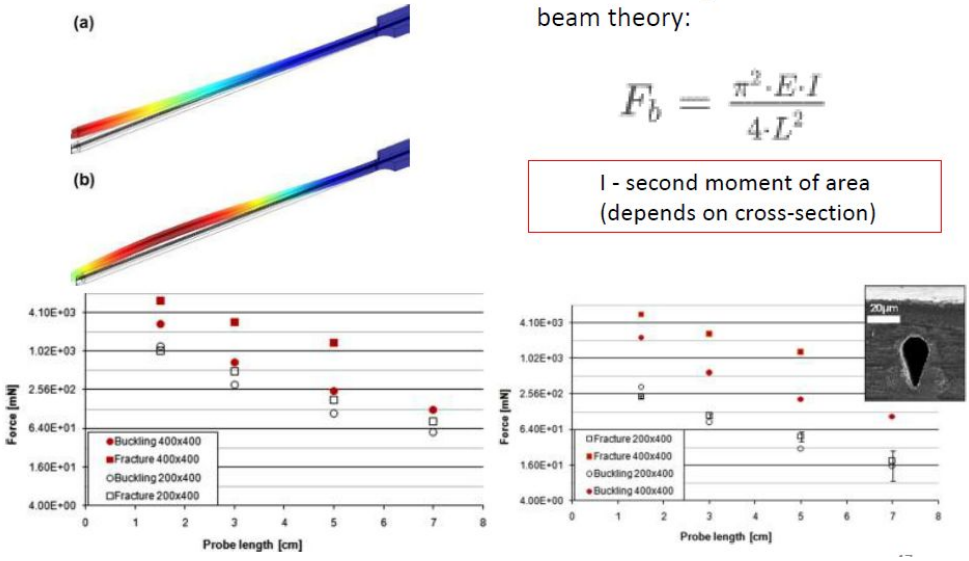
Pressure vs flow rate

R_{hyd} is increasing with increasing fluidic channel length

Flow rate is in the range 0.5 - 1.5 µl/min

Erm, I think this plot is valid here, it is an approximately linear relationship, and they remain constant.

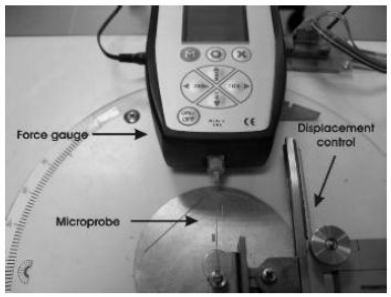
6. What dimensional and material parameters determine the buckling force of a hollow needle?



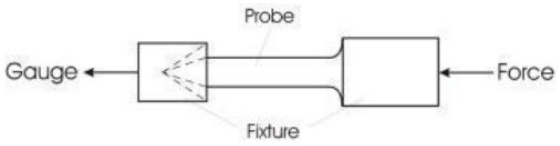
Critical buckling force in Euler beam theory:

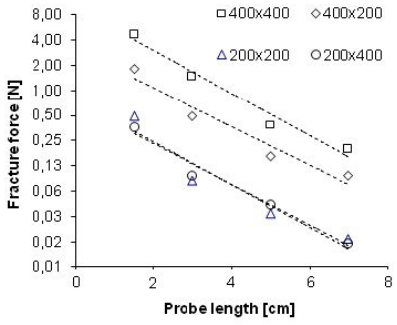
$$F_b = \frac{\pi^2 \cdot E \cdot I}{4 \cdot L^2}$$

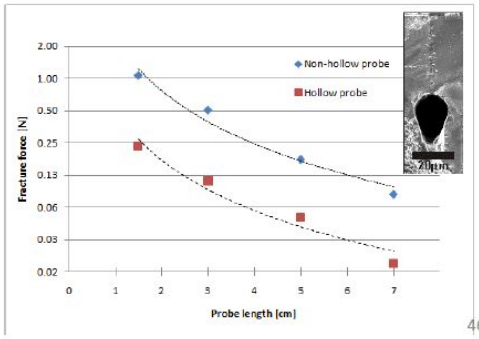
I - second moment of area (depends on cross-section)



Constraints:

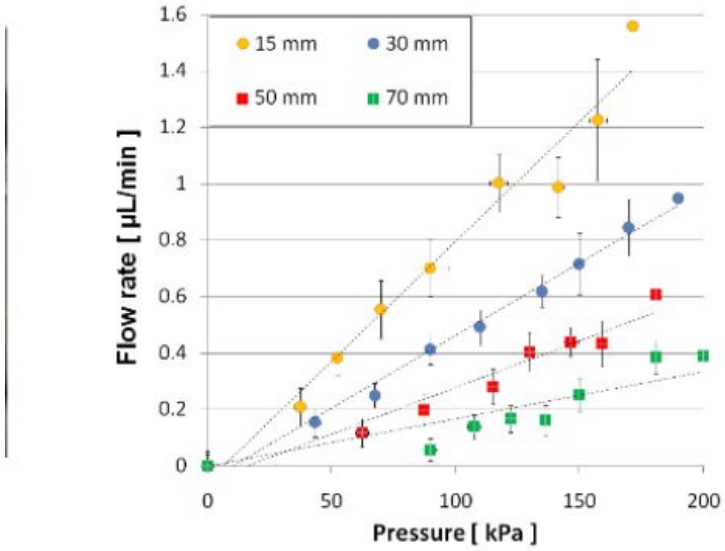






I guess this would require further explanation. I'll try tomorrow.

7. **How does the steepness of pressure flow rate curve changes if the length of the microchannel increased?**



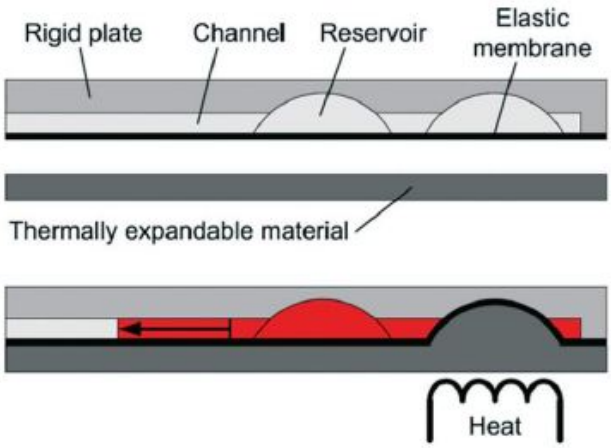
Pressure vs flow rate

R_{hyd} is increasing with increasing fluidic channel length

Flow rate is in the range 0.5 - 1.5 µl/min

Its steepness (meredekség) decreases, due to the increasing R_{hyd}.

8. **What is the operation principle of thermally actuated integrated micropump?**

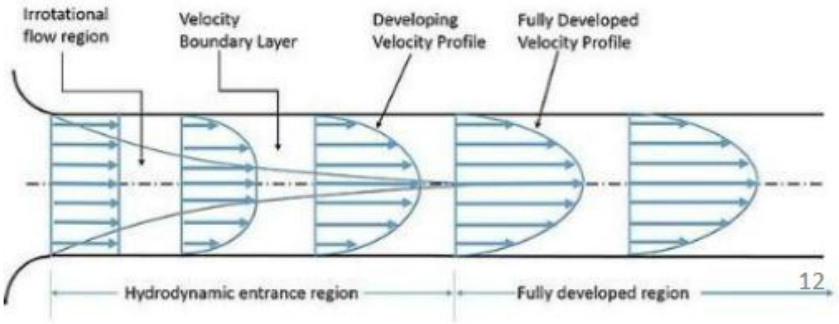


There is a “bubble” of reservoir fluid inside the channel, which is covered by an elastic membrane. On the other side, there is a layer of thermally expandable material. If heated, this will protrude into the reservoir, pumping the fluid forward.

9. **What is the effect of elastic components on flow profile?**

Can’t find the answer for this anywhere. I guess it would be logical that flow rate is lower in the beginning, and the flow profile only develops fully after the beginning of the flowing

activity, after having pushed the elastic channel out to its boundaries determined by pressure and viscosity. It probably also influences Rhyd.



Lecture 10 (Mechanical considerations)

1. **List relevant device properties that have influence on device-tissue interactions.**

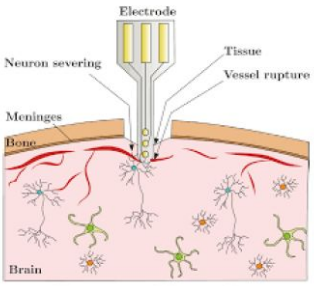
   - Sensor geometry (structural design)
   - Chemical and physical nature of boundary interfaces
   - Bulk properties (Flexibility, softness, density)
   - Packaging, interconnections

   Other important variables:

   - Implantation methods
   - Variability in biological properties of the target tissue

2. **List the main sources of mechanical interactions between device and tissue.**

   - Surgical procedure: insertion (penetration)
   - Repositioning of the device inside the tissue
   - Oscillatory motions (Micromotions)



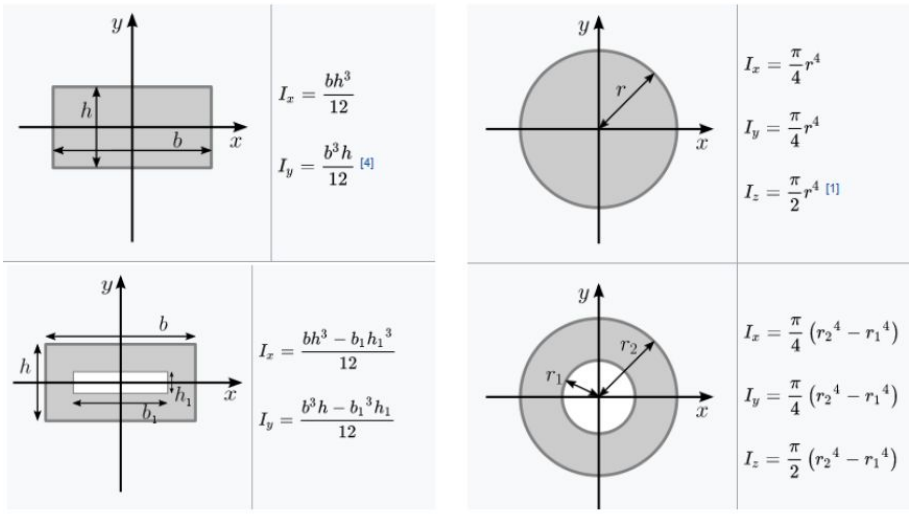
Trauma of insertion

Significance

   - Induces neuronal loss
   - Contributes to structural failures of the device

   And most probably causes significant noise

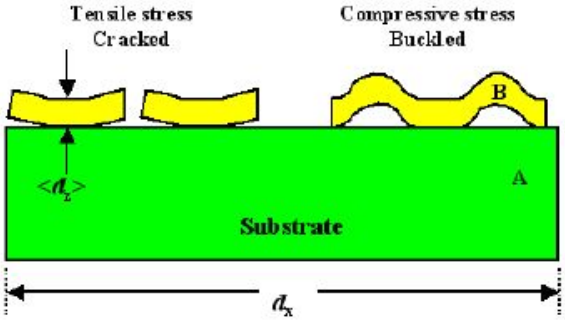
3. **How does an integrated bulk component change response of needle-like implants to bending and buckling loads?**
   Thin probes are prone to deflection without external forces



Integrated bulk components (e.g. microfluidics, waveguides etc) alters $\boldsymbol{I}$.

Second moment of inertia (deflection and calc of caused stress) is affected (reduced).

4. **What is residual stress in MEMS devices and why is it important?**
   Stresses that remain in the material after the original cause of the stress has been removed.



Reason: high-temp processes, mismatch in CTE (coefficient of thermal expansion).
The larger the Si composite ratio inside the device, and the higher the (oxidation) temperature, the lower residual stress is.
Residual stress is the reason for inherent deflection of thin probes, therefore it must be managed.

5. **What is the relationship between buckling and fracture? What is the critical buckling force of a needle?**

$$P_{CR} = \frac{\pi^2 EI}{L^2}$$ Euler's Equation

P_{CR} = critical or maximum axial load on the column just before it begins to buckle.

E = modulus of elasticity for the material

I = least moment of inertia of the column's cross-section

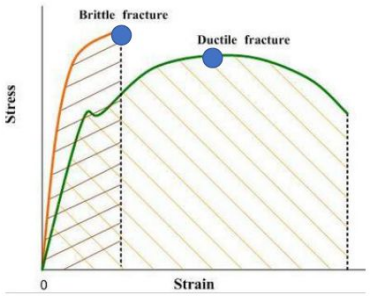
L = unsupported length of the column, whose ends are pinned

- External axial forces above the critical buckling force may lead to fracture.
- The overall stress during buckling leads to fracture when approaching the ultimate tensile strength

Ultimate tensile strength: maximum stress that a material can withstand while being stretched or pulled before breaking. (🔵)

Silicon is hard, but brittle. (7000 MPa).

Thin films have usually lower tensile strength. (Signal quality may predict device failure)

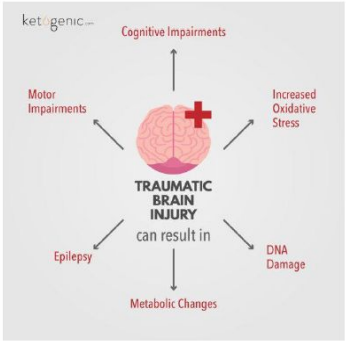


6. **What is tissue dimpling during device penetration, and why it is important to be reduced?**

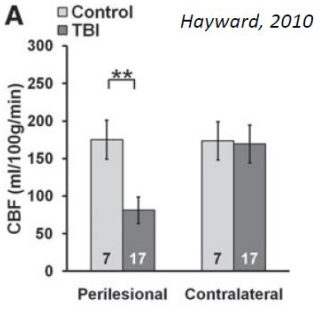
Dimpling: Indentation of superficial tissue layer before tissue rupture

Identification on force-distance curve: at maximum load

Reason to avoid: may lead to TBI (traumatic brain injury)



TBI may lead to secondary degeneration



TBI may lead to block in cerebral blood flow

7. **What is the effect of device geometry on insertion forces and dimpling measured during implantation ?**

Shank thickness x width (µm *x* µm)	Penetration force (mN)	Dimpling (mm)
200 x 200	58 ± 8	1.06 ± 0.2
200 x 400	70 ± 10	1.19 ± 0.21
400 x 200	98 ± 11	1.56 ± 0.12
400 x 400	93 ± 12	1.70 ± 0.26

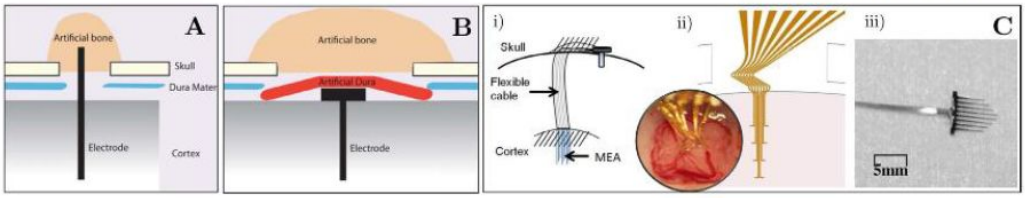
Tip angle (°)	Penetration force (mN)	Dimpling (mm)
30	27 ± 3	0.78 ± 0.08
60	72 ± 22	0.93 ± 0.11
90	112 ± 28	1.03 ± 0.08

Shank thickness generally increases the required penetration force of insertion, which in turn results in more significant dimpling. The same is true for increasing tip angle, but that results in much larger penetration force increase.

8. **What is tethered and untethered probe configuration?**

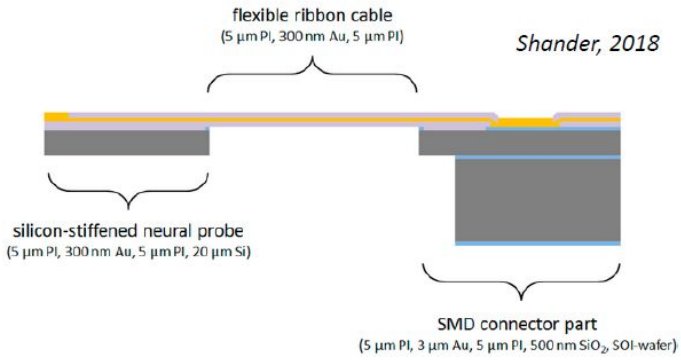
How to mitigate mechanical coupling between microdevice and connectors?

Lecomte, 2017



Shander, 2018

Concept:
Formation a hybrid stiff-flexible device configuration



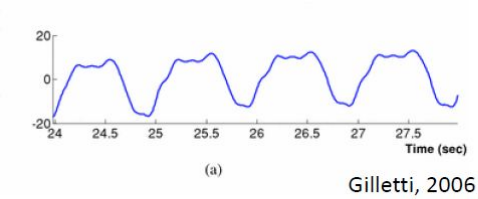
Untethered probing means that the hard probe directly connects to the microdevice, and can even be fixed to the skull. This makes it susceptible for shear stress during

micromotions or repositioning, which can damage both the implant and the surrounding tissue. This can be avoided by using a tethered configuration, which introduces a flexible cable between the electrode in the brain, and the microdevice outside the skull.

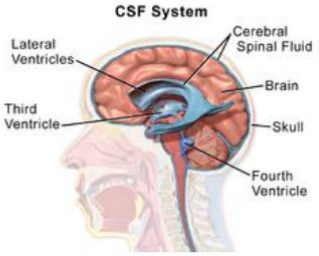
9. **Describe micromotions inside the brain. What kind of forces are induced around the implants due to micromotions?**

Micromotions

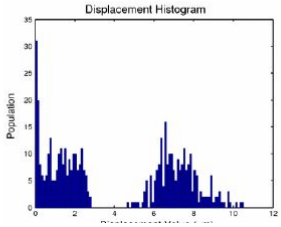
Displacements caused brain movement modulated by physiological activity



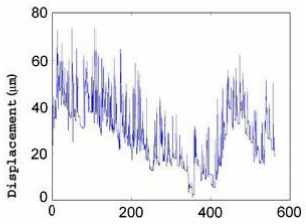
Gilletti, 2006



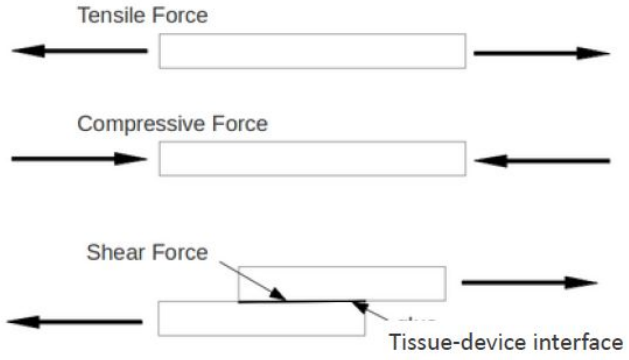
Effects of vasculature and pulmonary activity



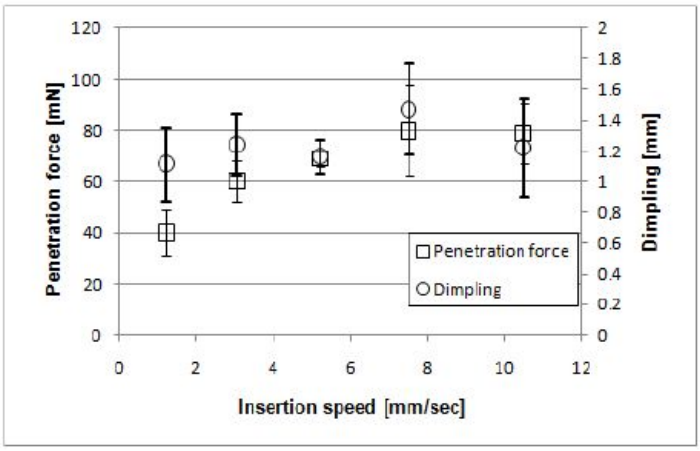
Cortical surface drift



Micromotions can cause lateral displacements and shear stress on the implants, which can be countered by using tethered configurations with a flexible cable.



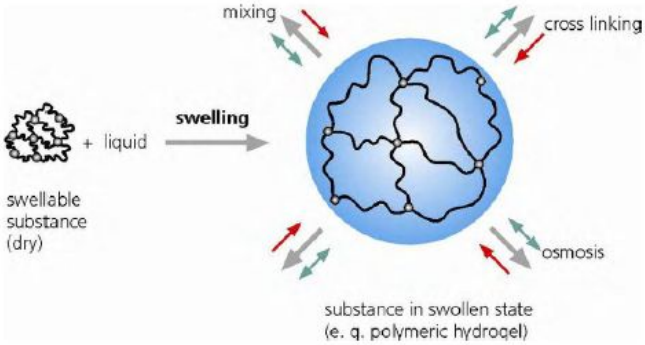
10. What is the relationship between insertion speed and penetration forces?



Low speeds result in low insertion forces, but have no effect on dimpling, which is only influenced by interfacial area. Penetration forces increase by one order of magnitude between cases of retracted and intact dura!
Slower insertion speeds result in higher SNR, less separated units and neural tissue damage. It has little to no effect on spike amplitudes, but slow speeds are safer.
Dura is getting thicker and less flexible by age.

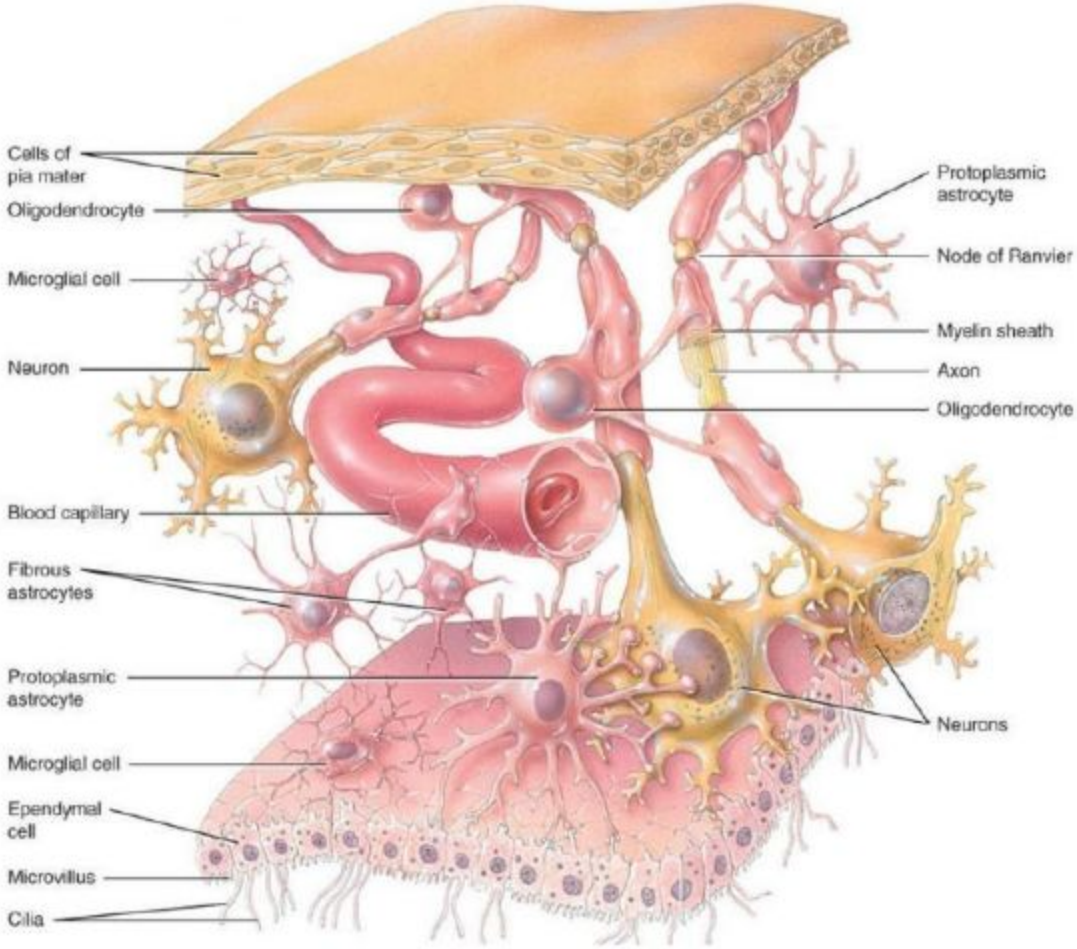
11. Describe the relevance of responsive neural implants regarding their mechanical properties.

They alter their mechanical properties at changing physiological conditions (pH, temperature, liquid. Examples are cellulose nanocomposites and shape memory polymers. Relevance: swelling example: increase device volume if exposed to liquids (water). To be considered for implants made of polymers, hydrogels, composite fibers. Huge advantage is that it reduces density mismatch between device and tissue, and it can be easier to insert.
However, it may increase strain in swollen state, which may induce injuries in blood capillaries and lead to thin film cracks.
Responsive materials must be carefully considered upon insertion for their implantation time windows, because they can induce large penetration forces due to large insertion speeds.



Lecture 11 (Long-term stability)

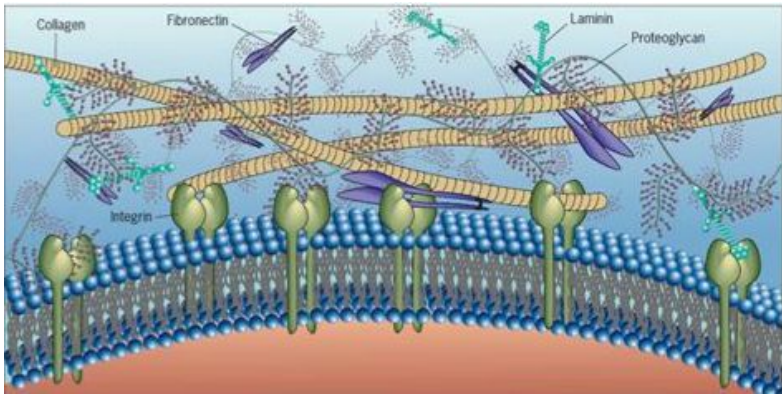
1. **What is the composition of brain tissue? (cell types, micro environment)**
   Neurons and glial cells (glia: protection, metabolism, speeding up conduction → many type, many role)



Extracellular matrix: the non-cellular component is present within all tissues and organs, it provides physical scaffolding for the cellular constituents, it initiates crucial biochemical and biomechanical cues that are needed for tissue morphogenesis, differentiation and homeostasis

Major components:

a. Viscous proteoglycans
b. Insoluble collagen fibers (strength and resilience)
c. Soluble multiadhesive extracellular matrix proteins (fibronectin, laminin) which bind proteoglycans and collagen fibers to receptors on the cell surface



2. **What is cell adhesion and why is it important?**
   Integrins attach to the extracellular matrix (ECM) and connect indirectly to the actin filaments through protein assemblies of talin-paxillin-vinculin
   - These protein assemblies stabilize the focal adhesion structure, as well as relaying signals from the ECM to the nucleus
   - Signals from the integrins are relayed to the nucleus by the bridging proteins and the actin fibers
   - These signals initiate nuclear gene expression that subsequently sends the corresponding response signal.

   Cell adhesion is the process by which cells interact and attach to neighbouring cells through specialised molecules of the cell surface. This process can occur either through direct contact between cell surfaces or indirect interaction, where cells attach to surrounding extracellular matrix, a gel-like structure containing molecules released by cells into spaces between them.Cells adhesion occurs from the interactions between cell-adhesion molecules (CAMs), transmembrane proteins located on the cell surface. Cell adhesion link cells in different ways and can be involved in signal transduction for cells to detect and respond to changes in the surroundings. Other cellular processes regulated by cell adhesion include cell migration and tissue development in multicellular organisms. Alterations in cell adhesion can disrupt important cellular processes and lead to a variety of diseases, including cancer and arthritis. Cell adhesion is also essential for infectious organisms, such as bacteria or viruses, to cause diseases.

3. **What are the main reasons for tissue damage?**
   Mechanical insertion: local injury
   Protection mechanism: foreign body response (→ gliosis: cell death, insulation)
   Mechanical mismatch: difference between the Young's modulus will affect tissue response

4. **What parameters are important to measure during stability tests?**
   Immunofluorescence staining:
   - In vitro slice from the sample
   - Anti-body based
   - Typical stains: DAPI - nuclei, GFAP - glial specific protein, NeuN: neural nuclei

   Electrochemical impedance spectroscopy
   - Early stage of gliosis: release of microglia and factor from the blood → astrocyte activation (this induces electrical changes → the impedance of ECoG is increasing for a while and remains stable after a few days)

5. **Describe the major strategies currently used to increase long-term stability of neural implants.**
   Tuning the array's surface topography with nanostructuring
   Approximate tissue's Young's modulus

Chemical composition of solid substances
Injection of anti-inflammatory agents into ECS
Coating?

6. **Describe the major consequences of nanostructuring. ??????**
   Topography and particular nanoscale features can affect cell behaviour and integrin (transmembrane receptors) -mediated cell adhesion (but we don't know the extent to which nanostructures affect cell behaviour (in vitro investigations))
   - Direct: direct result of the influence of the surface topography
   - Indirect: where the surface structure has affected the composition, orientation or conformation of the absorbed extracellular matrix components

   → surrounding surface topography affect and modifies the adhesion, migration and differentiation

7. **How can we improve longevity using specific coatings? Describe an example from literature.**
   The goal is to improve biocompatibility of the implant surfaces using bioactive coating. (Note: cellular behaviour is influenced both by chemical and physical properties of the environment)

   Polymer coating:
   - Parylene, Polyimide, Silicone are approved materials
   - Soft and flexible
   - Controlling cell-biomaterial interaction with a degree of selectivity not possible through other surface modification techniques

   Coatings can help the implantation, which reduces tissue damage and improves longevity:
   Hydro-gel: hydrophilic polymer chains:
   + resorbable , - swelling: high stress along probe track
   Silk coating:
   + temporary stiffening, - stays in the brain