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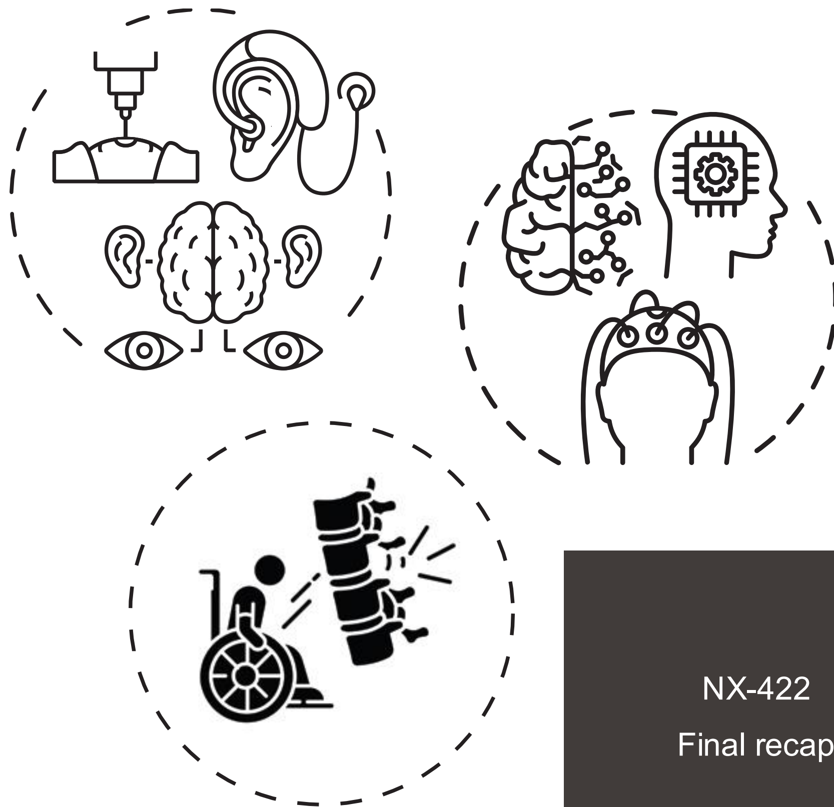


Neural Interfaces

NX-422

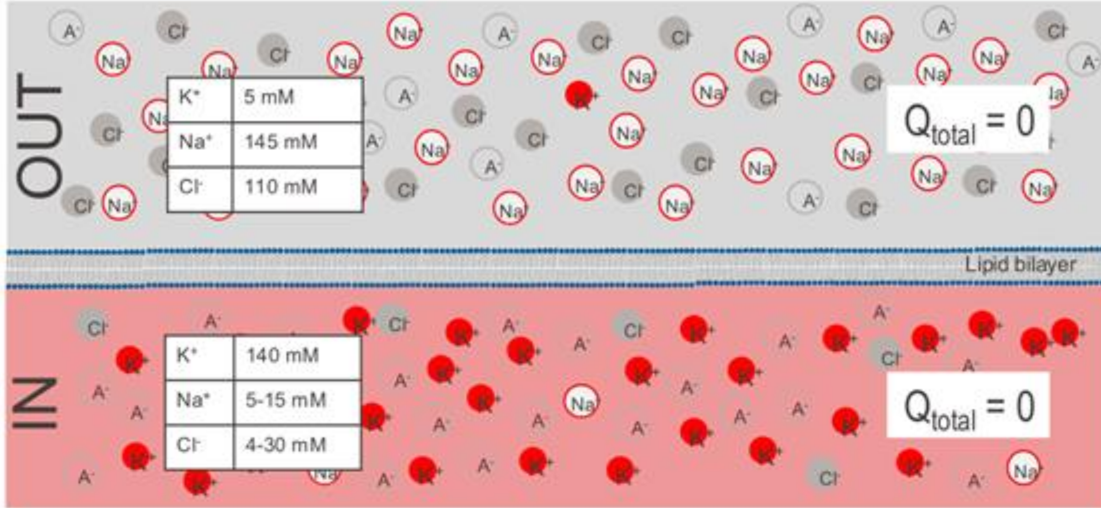
Final recap

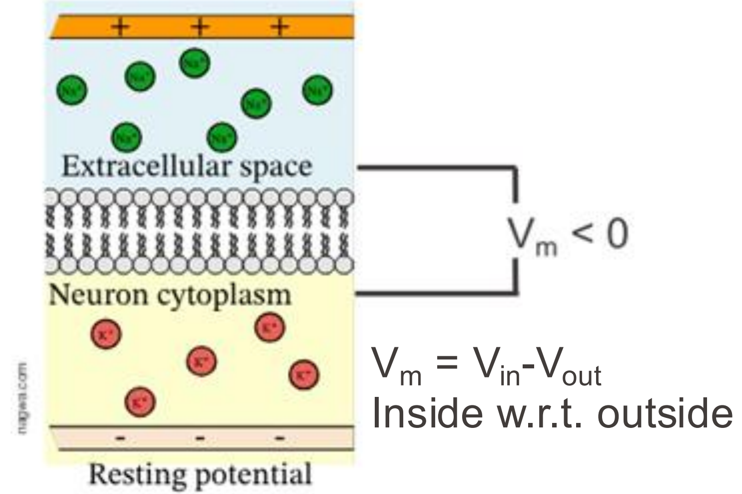
Giuseppe Schiavone

Neuro-X Institute

EPFL

Membrane potential





Na/K pump moves **3 Na+ outside** for each **2 K+ inside** = **negative inside**

More K+ leakage than Na+ = **positive charges exit the cell**

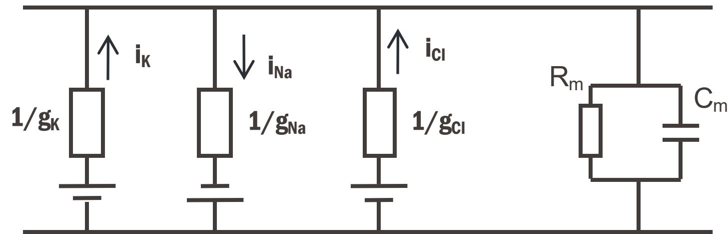
→ Resting membrane potential similar to the Nernst potential of K+ (-90 mV)

$$E_{ion} = \frac{RT}{zF} \cdot \ln \frac{[ion]_{out}}{[ion]_{in}}$$

NX-422 ©LSBI

Electrical model for the neuronal membrane

g_x = ion conductance
E_x = Nernst potential
I_x = ion current
P_x = Permeability (Diff coeff. / thickness)

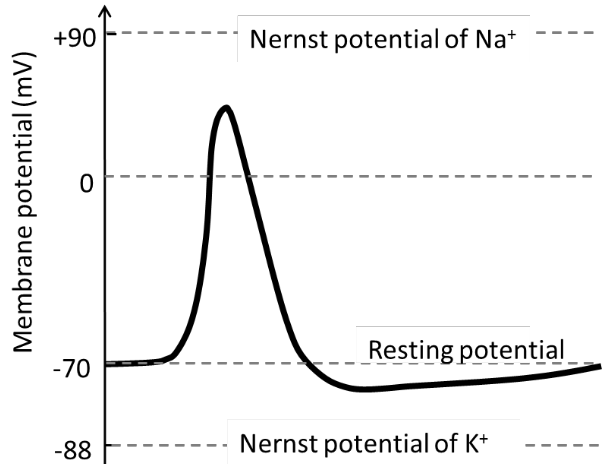


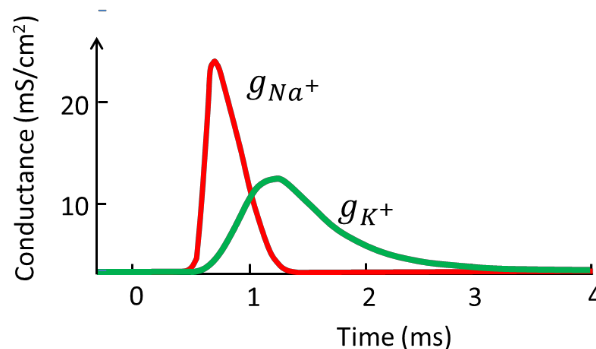
Goldman-Hodgkin–Katz voltage equation:

$$V_m = \frac{RT}{F} \ln \left(\frac{P_K[K^+]_{\text{out}} + P_{Na}[Na^+]_{\text{out}} + P_{Cl}[Cl^-]_{\text{in}}}{P_K[K^+]_{\text{in}} + P_{Na}[Na^+]_{\text{in}} + P_{Cl}[Cl^-]_{\text{out}}} \right).$$

NX-422 ©LSBI

Time evolution of the Action Potential

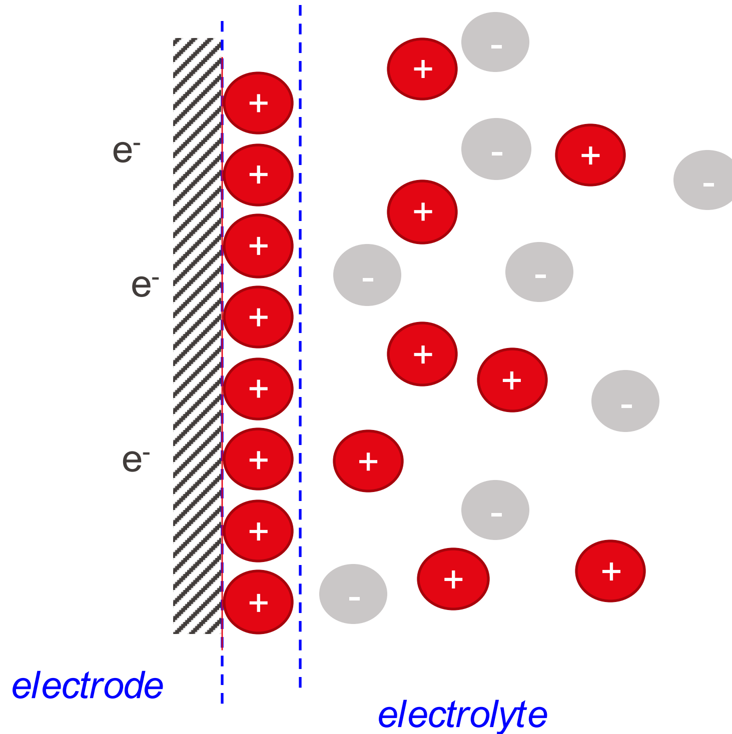




1. Local depolarization of the neuron membrane is triggered.
2. Na^+ rushes into the cell (down concentration gradient). This is called the 'fast sodium current'.
3. Voltage sensitive K^+ channel open causing K^+ to flow out of the cell. This is called the 'delayed rectifier potassium current'.
4. The membrane potential first swings to the Na^+ Nernst potential but as the Na^+ conductance decreases and K^+ conductance increases, the cell membrane is repolarized.

The AP lasts approximately 1ms.

Electrode interface



Charge transduction mechanisms

- **Capacitive:** accumulation of charges of opposite signs at the interface (drift current charging the double layer)
- **Faradaic:** chemical reactions involving transfer of charge across the interface, preferably in a reversible manner (charge carriers can cross back and forth)
- **Pseudocapacitive:** Same as Faradaic, but confined to the surface

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Neural signals

Electrocorticography **ECoG**

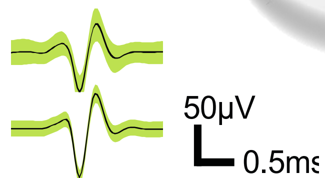
0.01 – 5 mV, < 200 Hz

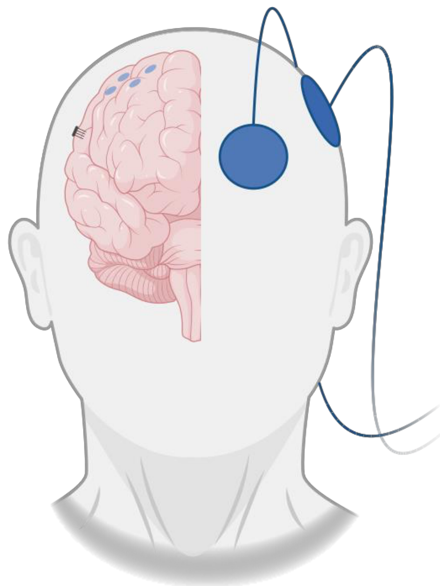
Local field potentials **LFP**

<1 mV, < 200 Hz

Action potentials **Spikes**

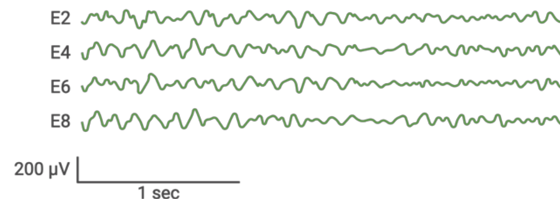
- ~ 500 µV, 0.5 – 5 kHz





Electroencephalography **EEG**

5 – 300 µV, < 100 Hz



Created with BioRender

GSA vs ESA

The real active surface of an electrode is not always equal to its visible geometrical surface (GSA): roughness and structure (ESA) strongly affect electrochemical activity.

	GSA	ESA
Definition	“Macroscopic” area of the electrode, calculated from its shape and dimensions.	“Active” area effectively participating in electrochemical processes.
Depends on	Electrode size and geometry.	Roughness, porosity, surface treatments, coatings.
Relevance in bioelectronics	Theoretical reference, useful for data normalization.	Determines real charge-transfer efficiency with biological systems.

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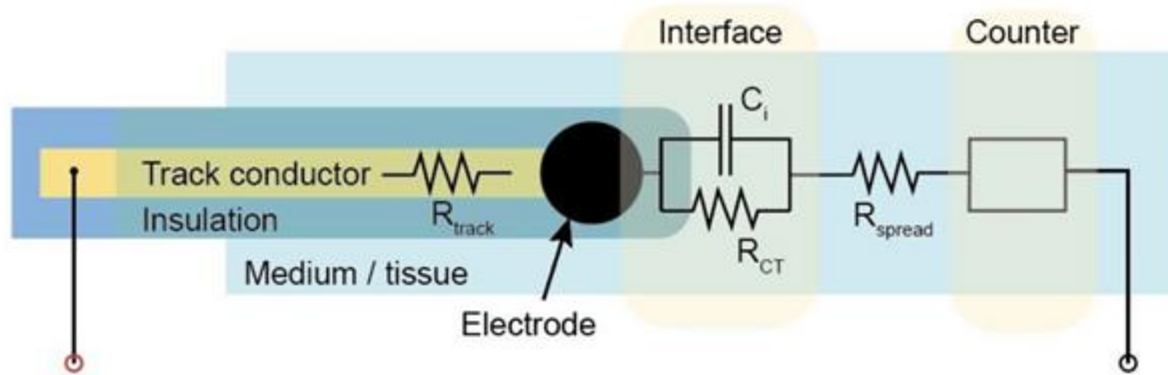
Equivalent circuit model



Impedance element	Equation	Technology	Design
Track resistance	$R_{track} = R_s \frac{L}{w}$	R_s: sheet resistance of the track conductor (material and process dependent)	L: length of track w: width of track
Spreading resistance	$R_{spread} = \frac{\rho}{4r}$	—	ρ: resistivity of the medium r: radius of electrode
Interface capacitance (C_i)	$\lvert Z_{Ci} \rvert \propto \frac{1}{2\pi f \cdot \mathrm{ESA}}$	f: frequency ESA: electrochemical surface area of the electrode (process, coating roughness, and electrode radius dependent)	
Charge transfer resistance (R_{CT})	$\lvert Z_{CT} \rvert = R_{CT}$	R_{CT}: charge transfer resistance (electrode area and coating material dependent; the material affects the voltage onset of electrochemical reactions)	

Schiavone, G., et al. (2021). Dimensional scaling of thin-film stimulation electrode systems in translational research. *Journal of Neural Engineering*

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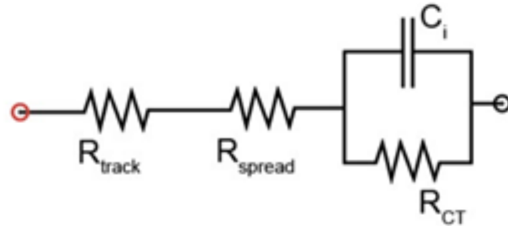
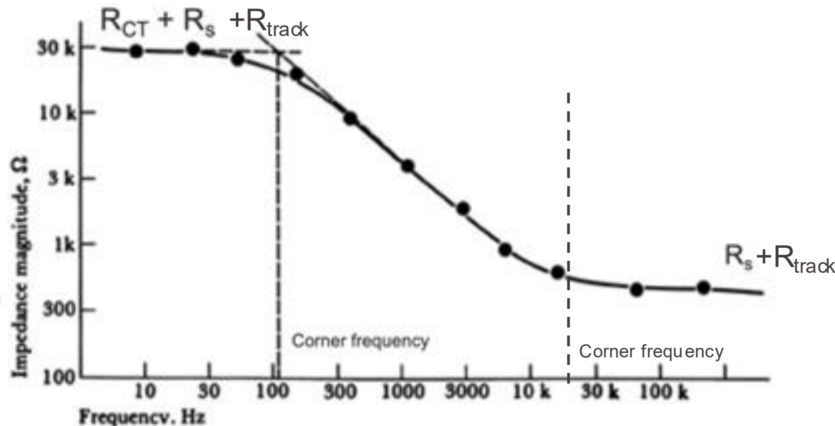
EIS



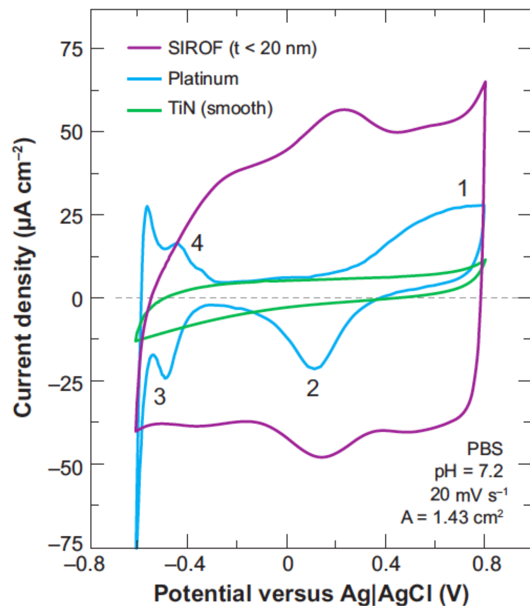


- Broad range of frequencies (typically <1Hz to 10^5 Hz)
- Electrical impedance measured through sinusoidal voltage/current excitation of the electrode

- High frequencies: resistive contribution of tissue conductivity
- Low-frequencies: non negligible charge transfer at the electrode-tissue interface

Cyclic voltammetry and CSC

- 3-electrode setup:
  - Sweep the potential of WE applied against CE and measured against RE
  - Measure the current at WE



Electrode material	CSC (μC/cm^2)
Gold	20
Stainless steel	50
Platinum	75
Titanium nitride	250
Iridium oxide	Up to 3,000

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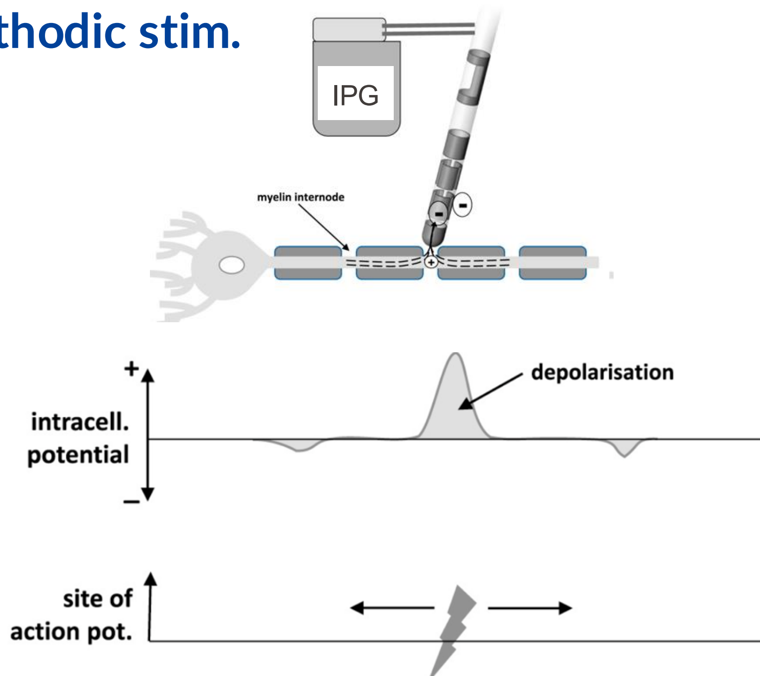
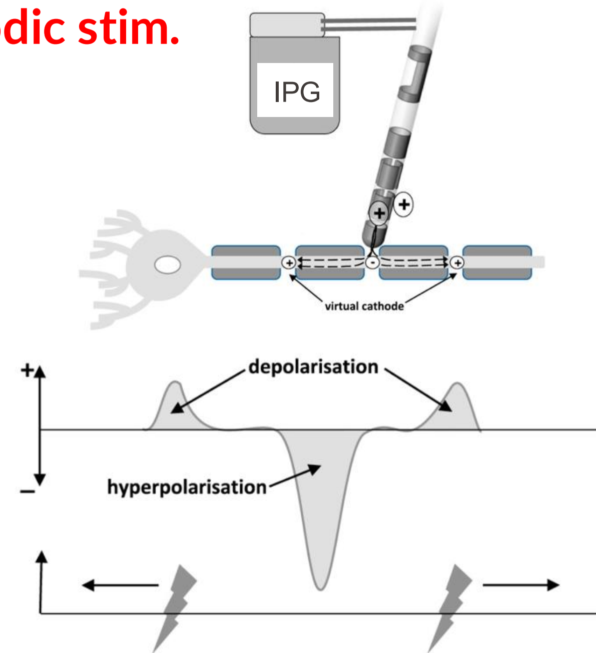
Cathodic vs anodic stimulation

Cathodic stim.



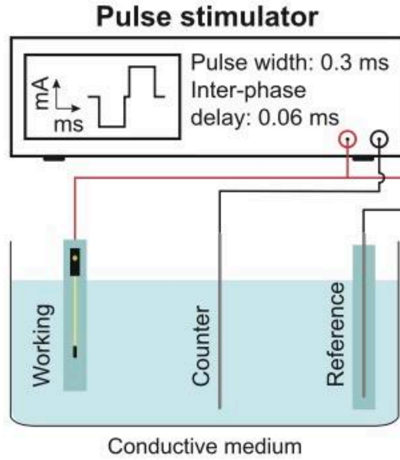
Anodic stim.

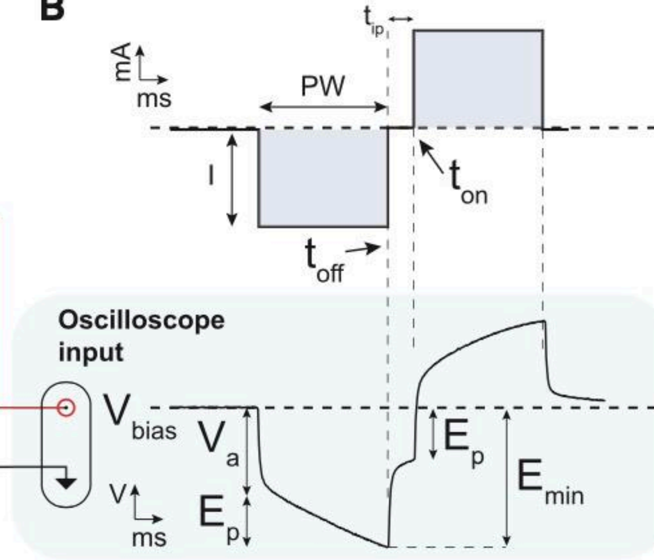


Parkinsonism & Related Disorders (2018) 55 pp 61-67

Voltage transient measurements

G. Schiavone et al, Neuron 2020





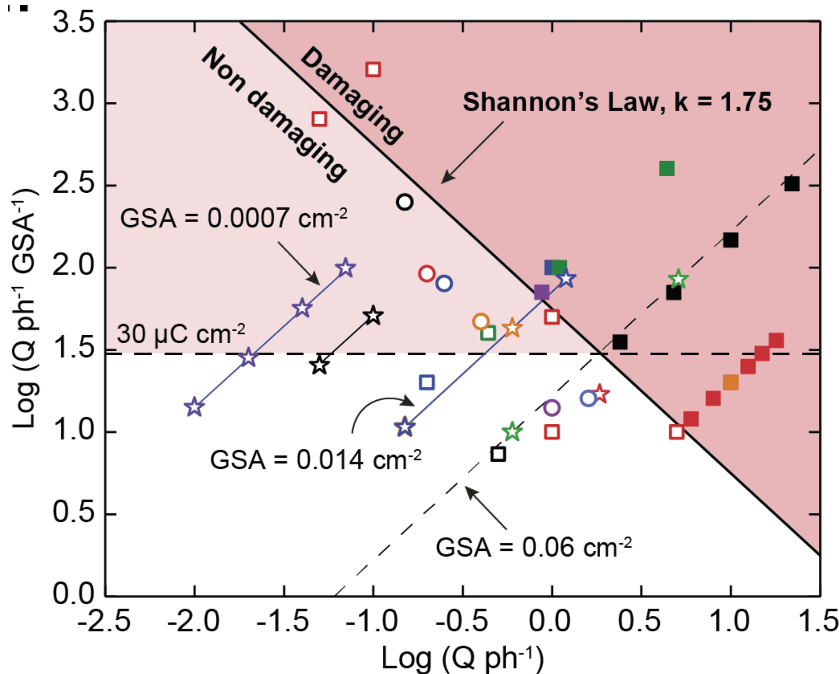
- V_{bias}: equilibrium potential (half-cell potential)
- V_a: Access voltage (ohmic drops)
  - IR drop in the interconnect
  - IR drop in the tissue/electrolyte
  - Concentration overpotential η_c
- E_p: Electrode polarisation at the interface
  - Activation overpotential η_a
  - Potential equilibrium shift E_0

- **E_{min}: Minimum cathodic excursion = $V_a + E_p$**

Charge vs charge density for safe stimulation
Shannon plot

"the Shannon limit" $\log\left(\frac{Q}{A}\right) = k - \log(Q)$

$1.5<k<2$



- Brown 1977, Cerebellum NHP
- Yuen 1981, Cortex feline
- Agnew 1983, Cortex feline
- McCreery 1988, Cortex feline
- McCreery 1990, Cortex feline
- Agnew 1993, Cortex feline

- Minev 2015, SCS rat
- Garcia-Sandoval 2018, SCS rat
- Schiavone 2018, SCS minipig
- Schiavone 2020, SCS NHP

- Salinsky 1996, VNS human
- Mahadevappa 2005, Retina human
- Schrader 2006, ECoG human
- Shepherd 2006, Cochlea human
- Abejon 2007, SCS human
- Balthasar 2008, Retina human
- Fujikado 2011, Retina human
- Wagner 2018, SCS human

UNSAFE: irreversible electrochemical reaction
tissue damage
neuronal hyperactivity

G. Schiavone et al. Neuron (2020) 108, pp. 238-258

Microfabrication in a Cleanroom a highly controlled environment

- **Classification ISO**
  - ISO class 1: 10 particles per m^3 (particles > 0.1µm)
  - ISO class 5: 100’000 particles per m^3 (particles > 0.1µm)

- **Air filtration**

- **Temperature and humidity control**

- **Surface cleanliness**

Class	≥0.1 µm	FED STD 209E equivalent
ISO 1	10[b]	
ISO 2	100	
ISO 3	1,000	Class 1
ISO 4	10,000	Class 10
ISO 5	100,000	Class 100
ISO 6	1,000,000	Class 1,000
ISO 7	[c]	Class 10,000
ISO 8	[c]	Class 100,000
ISO 9	[c]	Room air

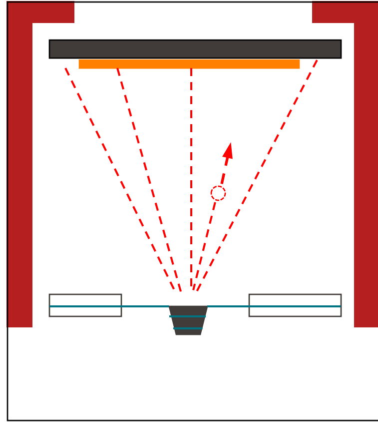
https://en.wikipedia.org/wiki/Cleanroom#ISO_14644-1_and_ISO_14698

Metallization

Process parameters:

Pressure
Temperature
Deposition rate

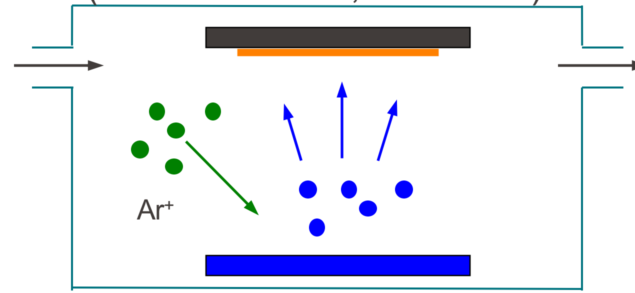
Evaporation



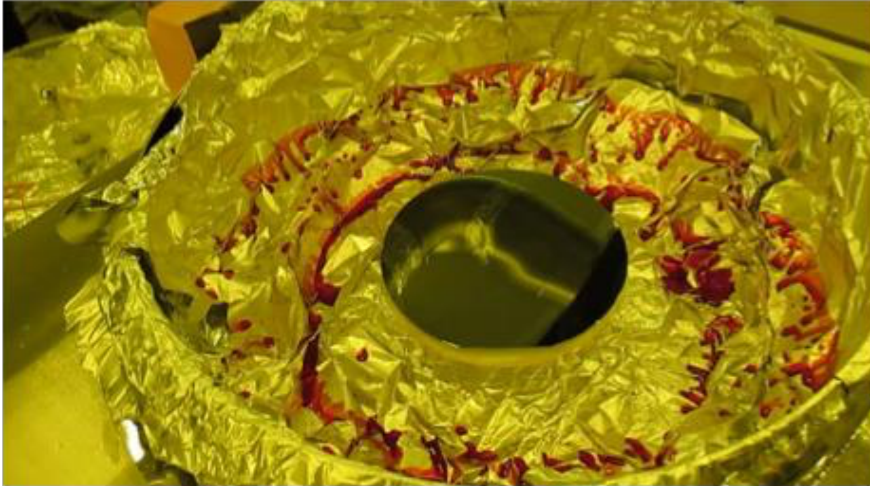
www.lesker.com

Sputtering

Also used for a wide range of inorganic materials (semiconductors, dielectrics)



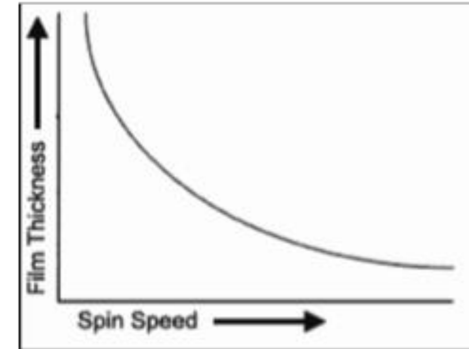
Spin coating



https://www.youtube.com/watch?v=uSalRYDq-Ng

- **Photoresists (PRs)**
- **Silicones (PDMS…)**
- **PI (Polyimide)**
- **SU-8** …

$$h_f \propto \frac{1}{\sqrt{\omega}}$$



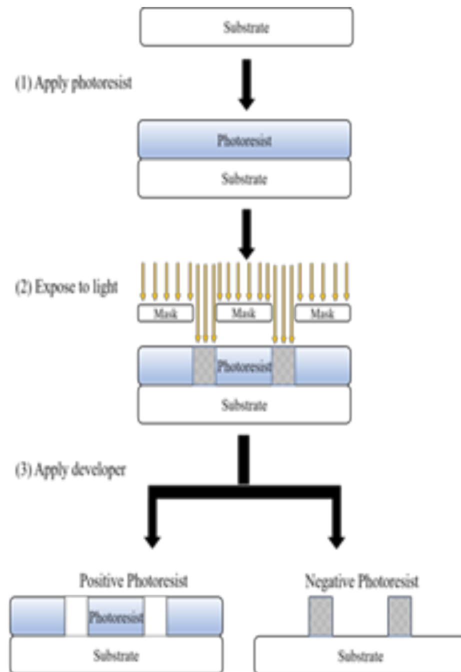
The final film thickness depends on:

- **Material concentration** in the solution
- **Solvent evaporation rate**, which is influenced by:
  - **Solvent viscosity, vapor pressure, temperature, local humidity**

spin thickness curves are typically **determined empirically**.

Photolithography

Are all the photoresist the same?
Positive vs Negative photoresists



Positive photoresist = the exposed goes

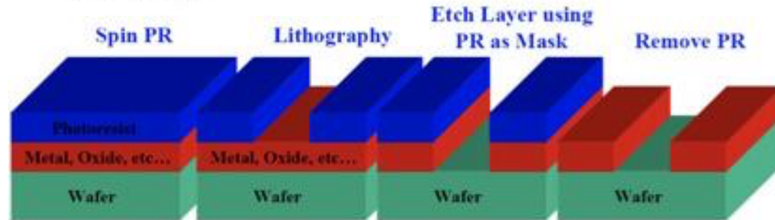
*"With **pos**itive photoresist, the ex**posed** **goes**;*

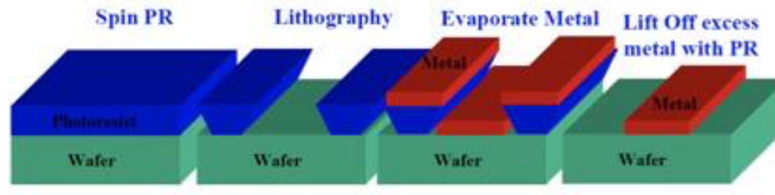
*With **nay**gative photoresist, the ex**paysed** **stays**"*

S. Erickson

Patterning

Etching vs Lift-Off

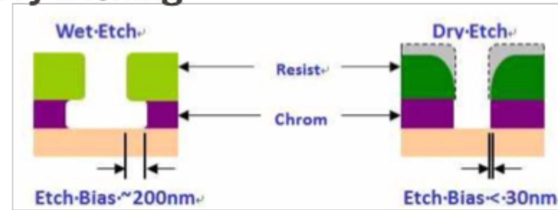




	Lift-off	Etching
Damage to substrate	Minimal	Possible, **etchant never perfectly selective**
Resolution	Limited by resist profile and mask	Limited by etchant and mask
Process complexity	**Resist profile** and deposition directionality critical	**Chemistry/plasma** must be optimized
Multi-layer structures	Easy	Different etchant per material

Patterning - Etching

Wet Etching vs Dry Etching



	Wet Etching	Dry Etching
Mechanism	Material is dissolved by **liquid chemical etchant**	Material is removed by **reactive ions or radicals in plasma**
Anisotropy	Mostly **isotropic**, etches in all directions	Highly **anisotropic**
Resolution / Feature size	Limited by **lateral etching and mask undercut**	Very high, suitable for fine patterns (<1 μm)
Surface damage	Usually gentle on surface, less physical damage	Can induce roughness, or contamination
Process control	Less precise, etch rate affected by diffusion and agitation	Can precisely control etch depth and rate **Careful sizing of PR required**
Uniformity	Very good over large areas if agitation and temperature controlled	Good over small areas, may need plasma uniformity control
Material compatibility	Limited to materials soluble or reactive with etchant	**Works for most materials**, including hard-to-etch metals and dielectrics
Cost / equipment	Simple setup, low cost, chemical baths	Requires vacuum, plasma tools → higher cost

Patterning - Lift-Off

Mask

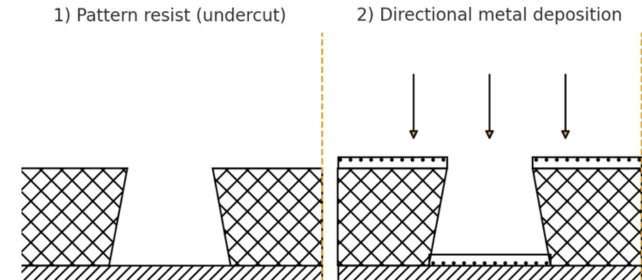
Si

PR

thin film

DOI:10.51847/7tmarkoorg

Figure 1. Lift-off process



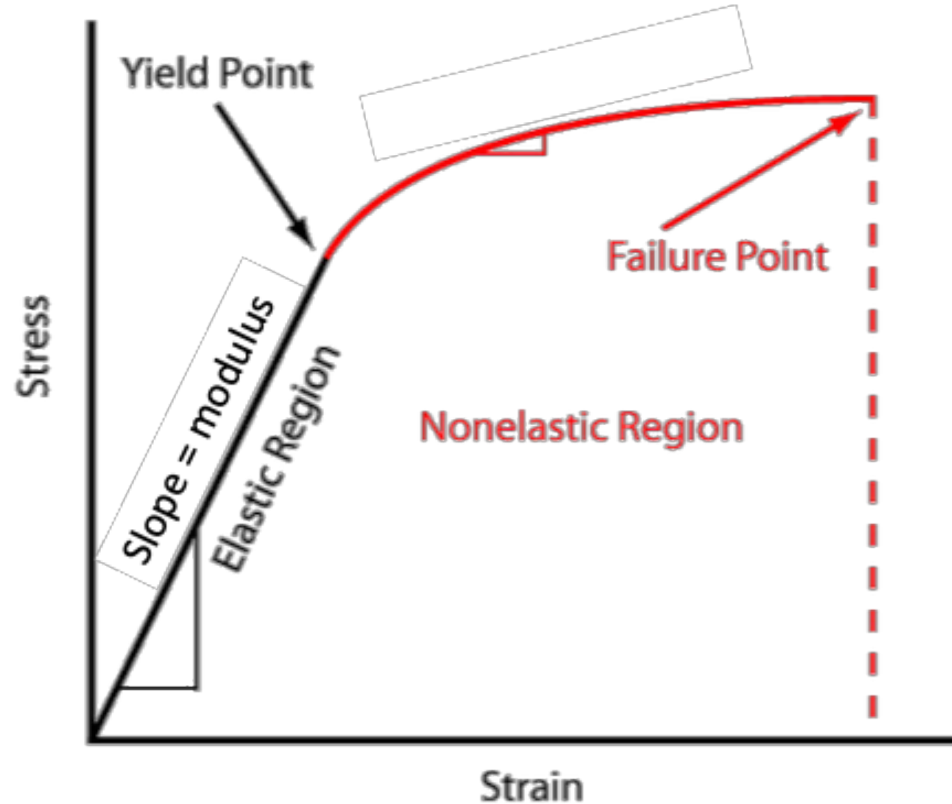
→ Avoids etching step
→ Requires careful photoresist profiling and ~directional (non-conformal) thin-film deposition

Some Typical processes

Material	Thin-film deposition	Patterning (typical)	Notes
Silicon (Si)	• **Epitaxial CVD** (SiH_4/SiH_2Cl_2 + H_2) • **LPCVD polysilicon** • **PECVD a-Si** • **Sputter/evap** (amorphous)	• **Dry:** RIE/ICP (SF_6, HBr/Cl_2), **DRIE (Bosch)** for deep high-AR • **Wet: KOH/TMAH** (anisotropic), **EDP** (legacy), **HNA** (HF–HNO_3–CH_3COOH, isotropic)	Orientation matters for wet etch (e.g., {111} slow). Use hard masks for deep Si etches.
Silicon dioxide (SiO_2)	• **Thermal oxidation** (dry/wet) • **LPCVD/PECVD/HDPCVD** • **ALD SiO_2** • **Sputter/evap**	• **Dry:** Fluorocarbon RIE (CF_4/CHF_3/C_4F_8 + O_2) • **Wet: HF**, **BOE (HF/NH_4F)**	Photoresist masks OK for short etches; for long/harsh etches use Si_3N_4 or metals as hard masks.
Gold (Au)	• **Evaporation (e-beam/thermal)** • **Sputtering** • **Electroplating** (needs seed) • **Electroless Au** (select chemistries) • (ALD exists but specialized)	• **Patterning: Lift-off (preferred)** • **Wet etch: KI/I_2** or **aqua regia** • **Dry/physical: Ion beam etch (IBE/milling)**; Cl_2/Ar RIE possible but tricky	Use **Cr or Ti adhesion** underlayers; wet etches attack Cr/Ti differently—plan the stack/removal order.
Platinum (Pt)	• **Sputtering** • **E-beam evaporation** • **ALD Pt** (e.g., $MeCpPtMe_3$ + O_2) • **Electroplating** (special baths)	• **Patterning: Lift-off** (common) • **Physical: Ion beam etch/milling** • **Dry:** Cl_2/Ar or halogen-based RIE (slow, process-sensitive) • **Wet: Hot aqua regia/oxidizing halide mixes** (slow)	Pt is hard to etch chemically; expect slower rates and more redeposition—plan for IBE or lift-off.

NX-422 ©LSBI

Mechanics of materials – tensile test



Critical strain

- For stacks:
- Strain in a layer = distance from **neutral axis/plane (NA, NP)** divided by radius.
- Where is the neutral plane? → z = distance

$$z_{\text{NA}} = \frac{\sum_k E_k t_k \, z_{k,\text{centroid}}}{\sum_k E_k t_k}$$

"Centroid" = midline

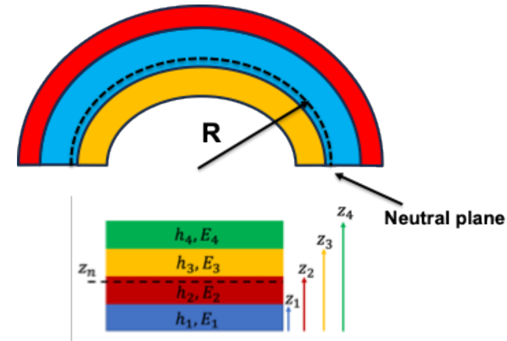
- So that distance from NA is

$$y_i = \left| z_{\text{surface},i} - z_{\text{NA}} \right|$$

- And critical strain is

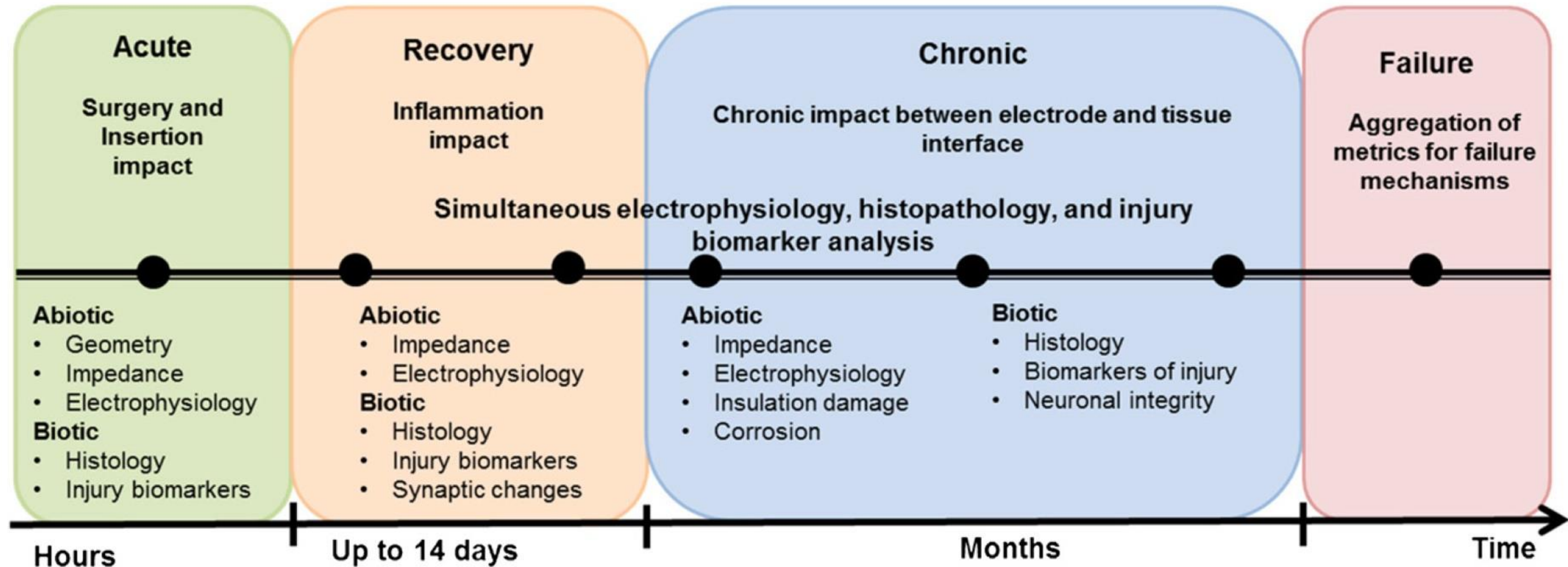
$$\varepsilon_i = \frac{y_i}{R}$$

$$R_{\text{min},i} = \frac{y_i}{\varepsilon_{\text{crit},i}}$$



Timeline of major events following chronic implantation *in vivo*

2018 *J. Neural Eng.* **15** 041004



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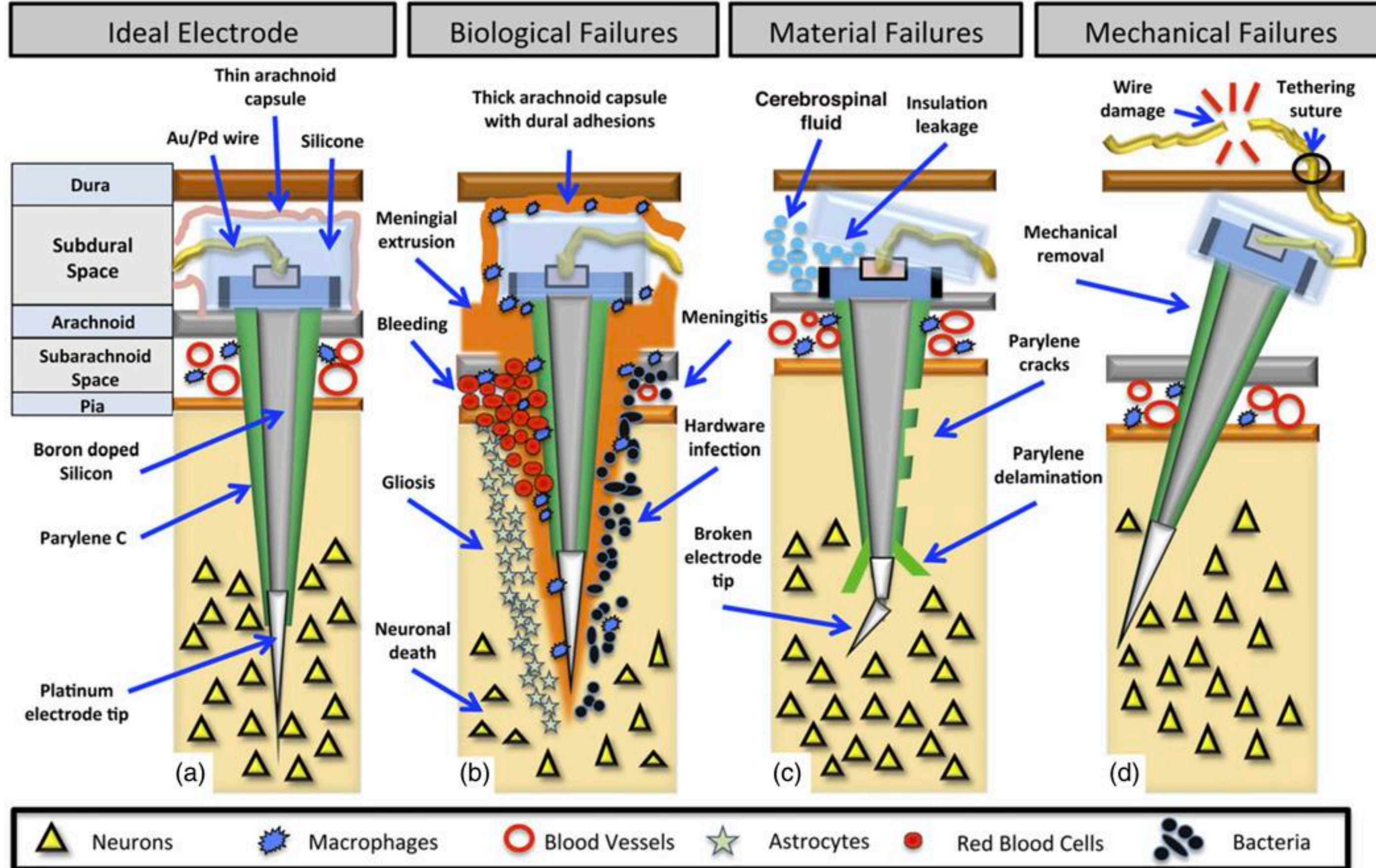
FBR and implant damage



doi: 10.1088/1741-2560/10/6/066014

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Optogenetics vs Electrical interfacing

- **Cell-type specificity:** restrict expression to desired cell population → stimulate only what you want
- **Excitation/inhibition: excite** (ChR/Chrimson) or **directly inhibit** (NpHR/Arch/GtACR) by choosing the opsins.
- **Spectral multiplexing:** leverage opsin activation spectrum to independently perform different function.
- **Low electrical artifact:** no electrical stimulation pulses → stim artifact in electrophysiology recordings.

BUT:

- **Requires gene delivery:** viruses/transgenics need time and expression needs controlling.
- **Light limits:** scattering/absorption reduce depth.
- **Hardware implants:** fibers/µLEDs more invasive than simple electrodes.
- **Heating limits efficacy:** duty cycle limited by temperature rise → limit to operation.