Neural Interfaces

NX-422

Review of part 1

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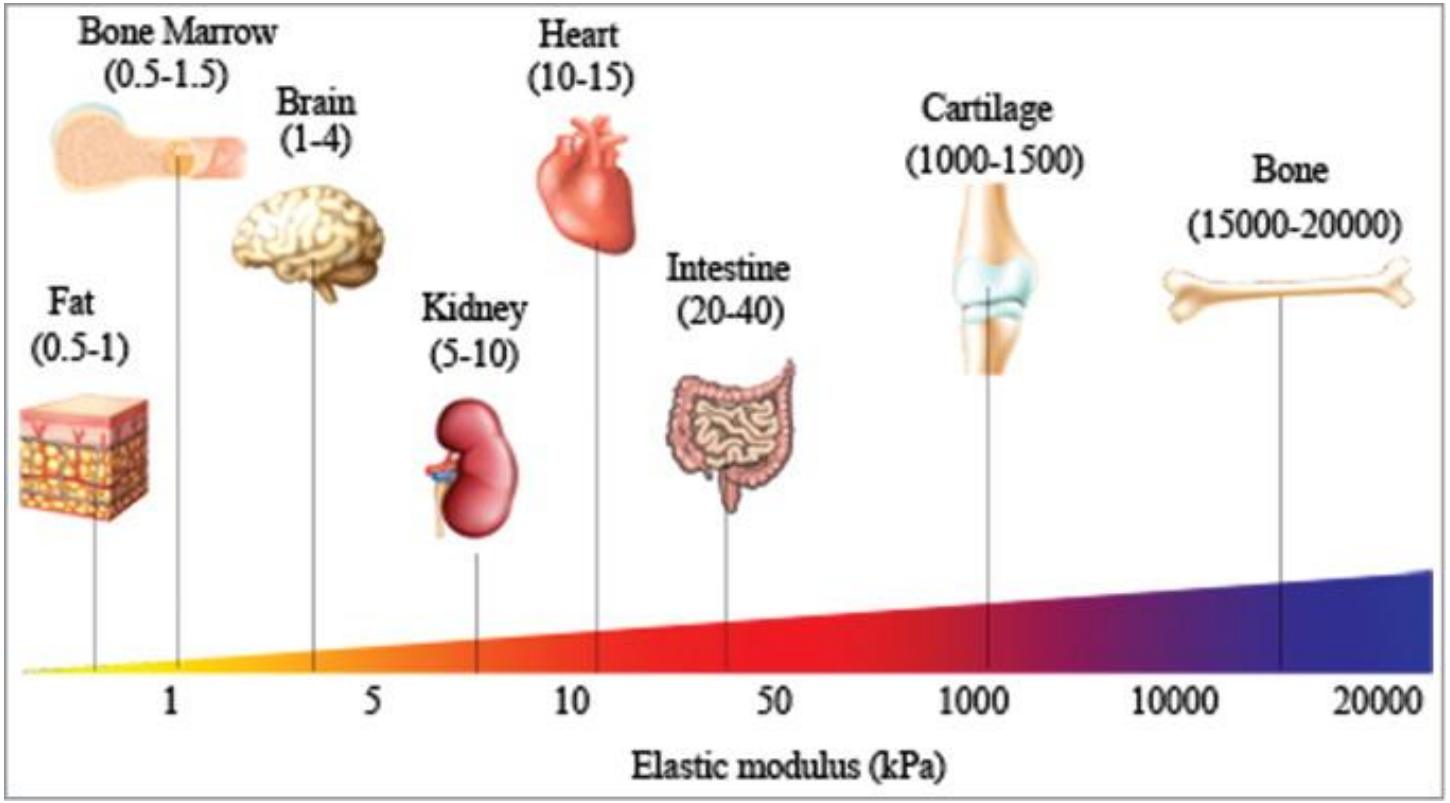
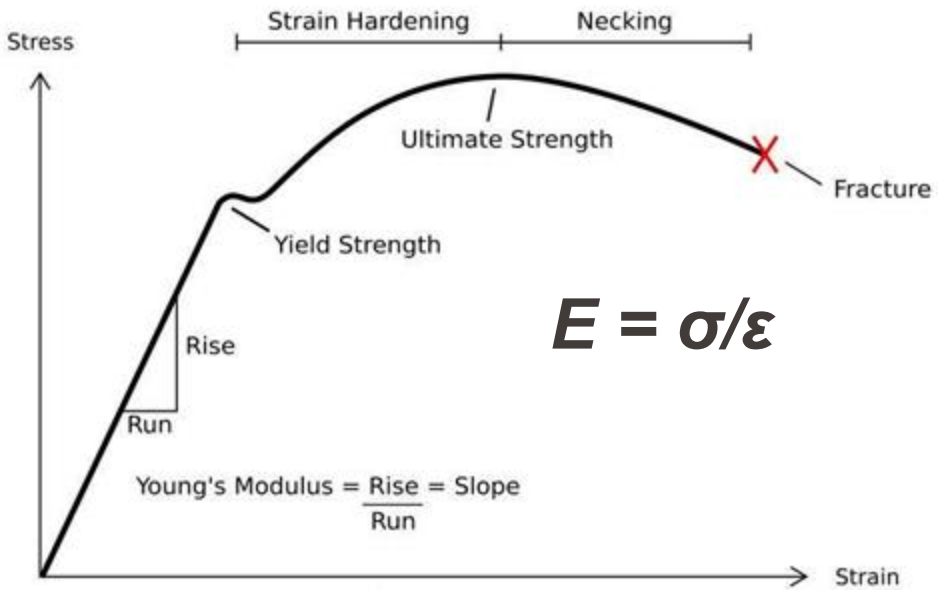
Basics: Neural tissue is soft



(Cox et al., 2011)

Basics: Stiffness, stress, strain

Stiffness (E)
Elastic modulus
Young's modulus
(Pascals (Pa))
How 'hard' is the material?



$$E = \sigma/\varepsilon$$

Stress (σ)
Force/area
(Pa, psi)
How much force is applied?

Strain (ε)
Distance/distance
(%, unitless)
How much is the material deforming?

- *Source: Instructables*

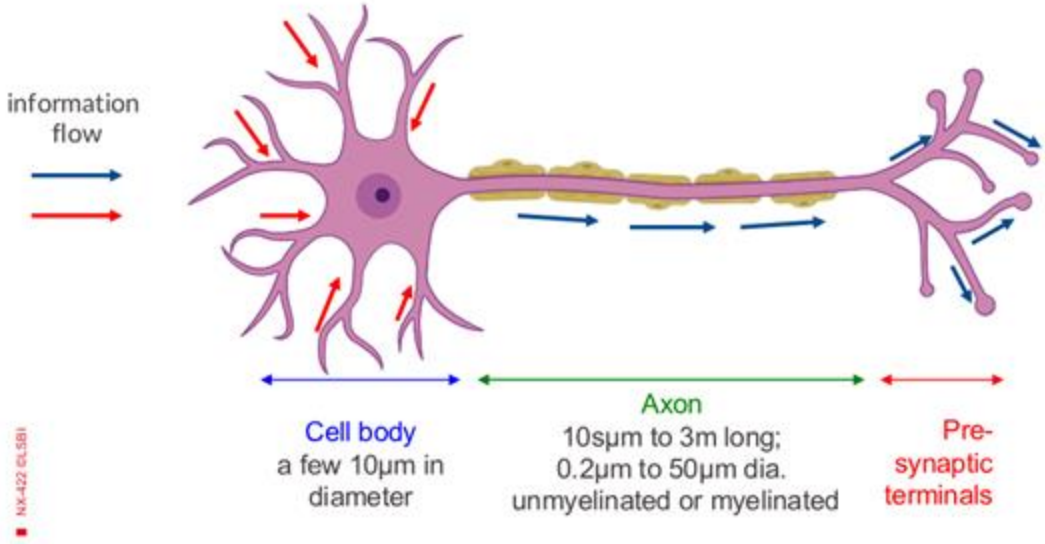
Basics: Neural cells

Neuron = cell body, axon, dendrites, myelin

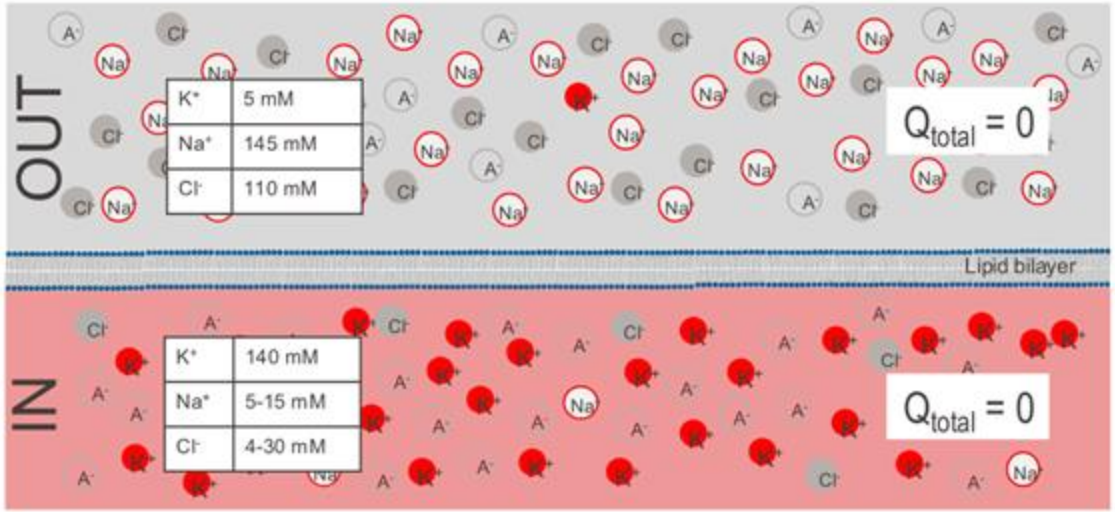
Dendrites receive; axon sends

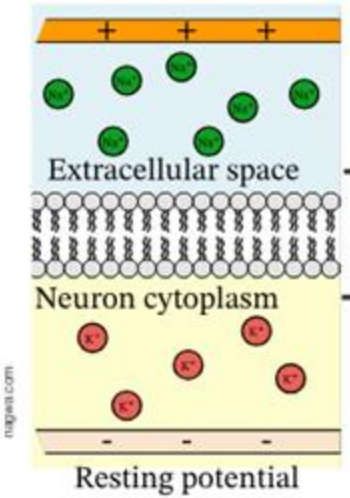
Glial cells (glia) = support cells
- Astrocytes
- Oligodendrocytes (CNS)/Schwann cells (PNS)
- Microglia (immune)

Endothelial cells



Neuronal membrane





$V_m < 0$

Inside w.r.t. outside

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)

- $$E_{ion} = \frac{R\,T}{z\,F} \cdot \ln \frac{[ion]_{out}}{[ion]_{in}}$$

Membrane potential V_m and Nernst potential

- $V_m = V_{in} - V_{out}$ by definition: voltage difference across the inside and the outside
- For a given ion species i in a mixture:
- Electrochemical potential E_i is $E_i = \mu_i + z_i F V_i$
- z_i is the ion valence, F is Faraday's constant, μ_i is the chemical potential
- μ_i is by definition the molar partial derivative of Gibbs free energy G: $\mu_i = \left.\frac{\partial G}{\partial n_i}\right|_{T,P,n_{j\neq i}} = \mu_i^0 + RT \ln a_i$
- μ^0 is the equilibrium potential, a_i is the activity (proportional to concentration c_i)
- For an ion species inside and outside the membrane, at equilibrium: $E_{in} = E_{out}$

$$E_{in} = \mu_{in} + z F V_{in} = \mu^0 + RT \ln a_{in} + z F V_{in}$$

- →

$$E_{out} = \mu_{out} + z F V_{out} = \mu^0 + RT \ln a_{out} + z F V_{out}$$

$$E_{in} = E_{out} \Leftrightarrow \mu^0 + RT \ln a_{in} + z F V_{in} = \mu^0 + RT \ln a_{out} + z F V_{out}$$

$$\Leftrightarrow z F (V_{in} - V_{out}) = RT \ln \frac{a_{out}}{a_{in}} = RT \ln \frac{c_{out}}{c_{in}}$$

- $$\Leftrightarrow (V_{in} - V_{out}) = V_m = \frac{RT}{zF} \ln \frac{c_{out}}{c_{in}}$$

Membrane potential V_m and Nernst potential

$$\Leftrightarrow (V_{in} - V_{out}) = V_m = \frac{RT}{zF} \ln \frac{c_{out}}{c_{in}}$$

Sign convention: $V_m = V_{in} - V_{out}$

$$E_{ion} = \frac{R\,T}{z\,F} \cdot \ln \frac{[ion]_{out}}{[ion]_{in}}$$

If a **cation like K^+** has $c_{in} > c_{out}$ (e.g. mammalian neurons)→ ln < 0 → E < 0. (~ membrane potential)

OUT

K^+	5 mM
Na^+	145 mM
Cl^-	110 mM

IN

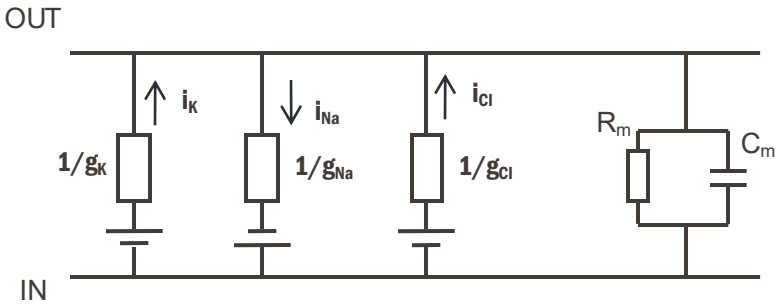
K^+	140 mM
Na^+	5-15 mM
Cl^-	4-30 mM

Note: If you define the opposite convention (i.e. $V'_m = V_{out} - V_{in}$)
→ Do the derivation and you will get

$$E'_{ion} = \frac{R\,T}{z\,F} \cdot \ln \frac{[ion]_{in}}{[ion]_{out}}$$

i.e. the sign of your potentials are relative to the specific convention.

Electrical model for the neuronal membrane

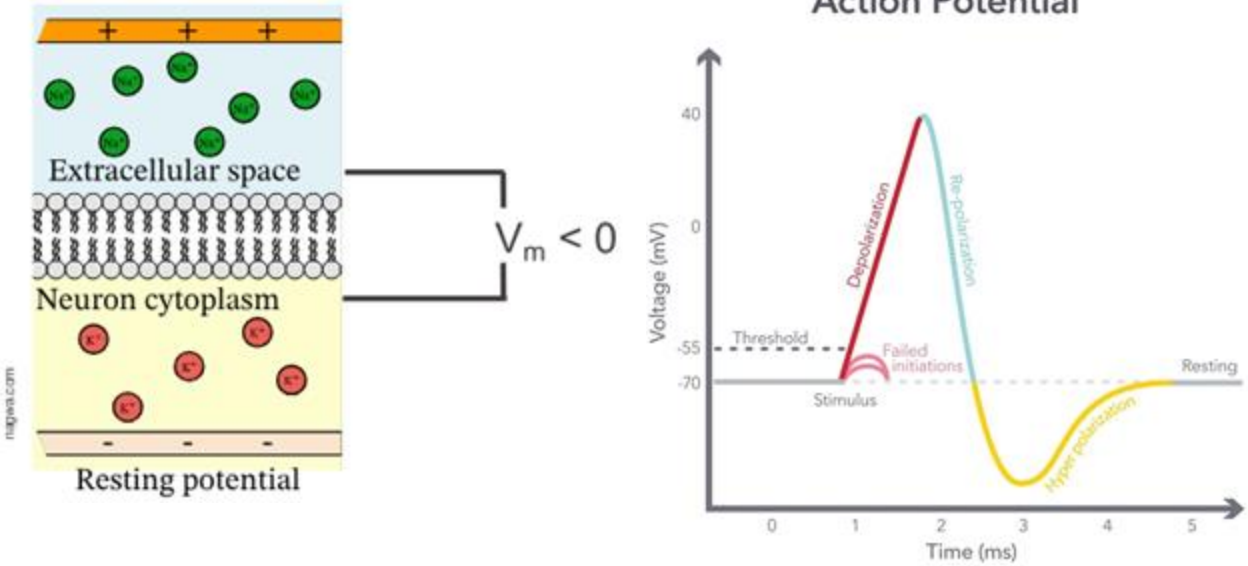


g_x = ion conductance
E_x = Nernst potential
I_x = ion current
P_x = Permeability (Diff coeff. / thickness)

Goldman-Hodgkin–Katz voltage equation:

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

Stimulating the neuronal membrane

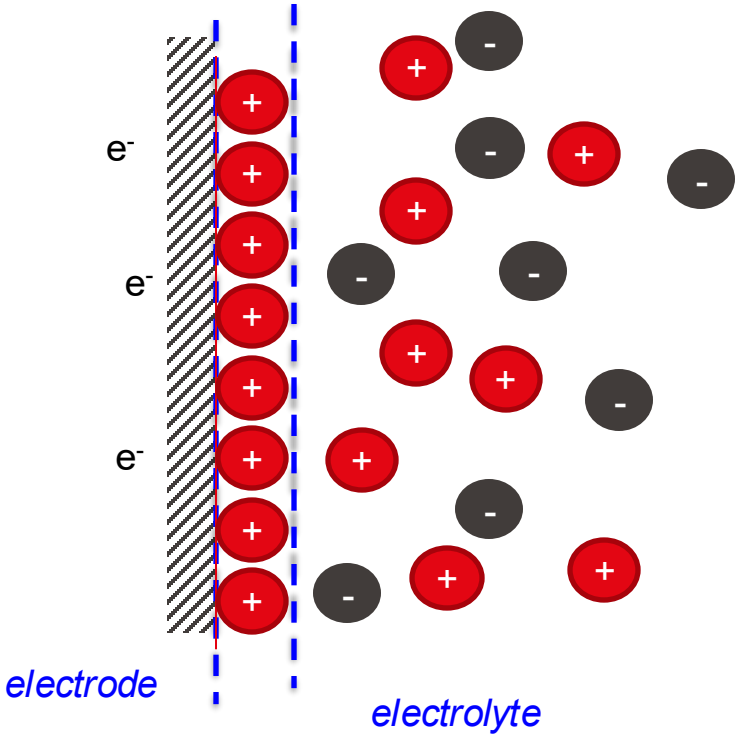


Local depolarization → voltage-gated Na+ channels open → action potential

Electrode stimulation = Artificial local depolarization

Cathodic-first stim (w.r.t. Ref) → neg. electrode takes (+)-ions from ECM → more negative ECM (depolarization)

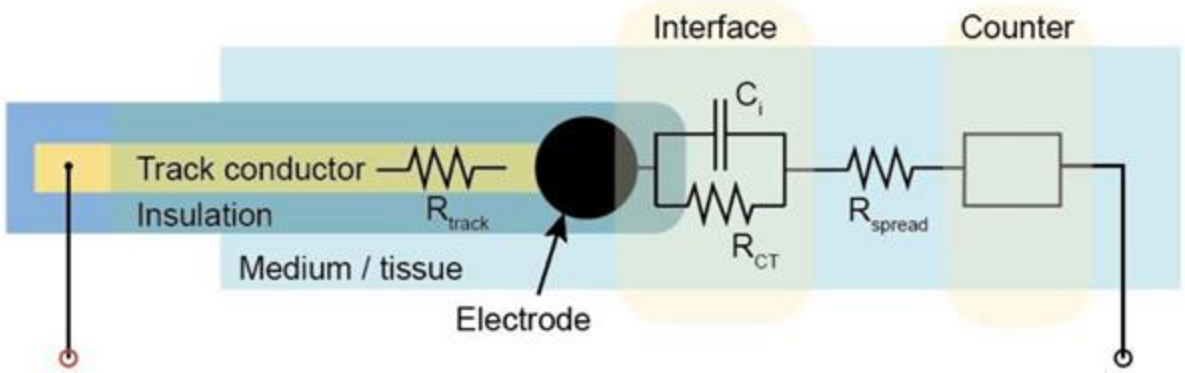
Electrode interface



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

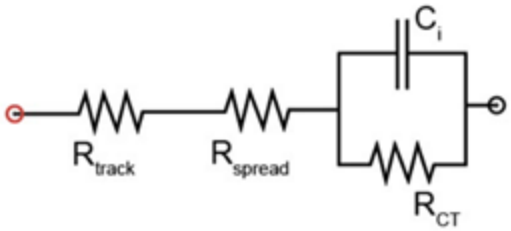
Equivalent Electrical Model of an Electrode

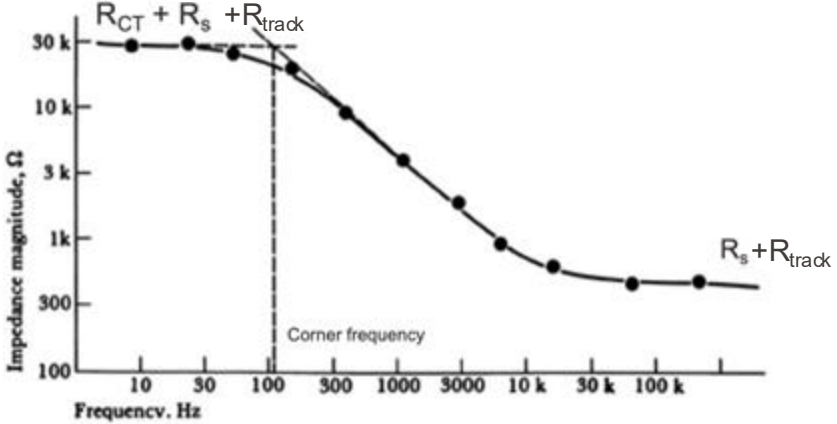


Impedance element	Equation	Technology	Design
Track resistance	$R_{track} = R_s \frac{L}{w}$	R_s: sheet resistance of the track conductor (material and process dependent)	L: length of track w: width of track
Spreading resistance	$R_{spread} = \frac{\rho}{4r}$	—	ρ: resistivity of the medium r: radius of 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*

Electrochemical Impedance Spectroscopy (EIS)

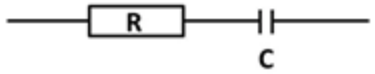


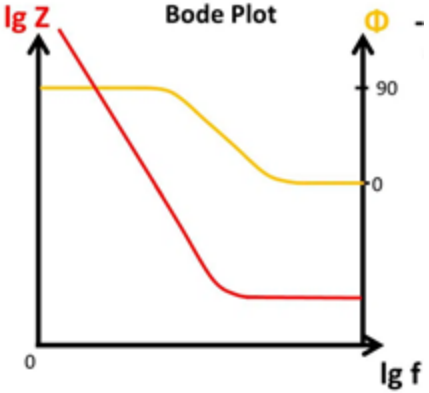


- Broad range of frequencies (typically <1Hz to 10^5 Hz)
- Electrical impedance measured through sinusoidal voltage/current excitation of the electrode

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

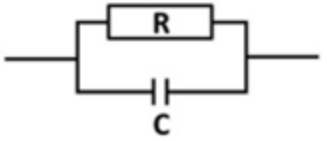
Bode plots

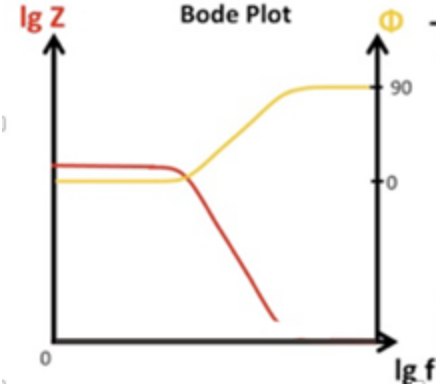




$$|Z(j\omega)| = \sqrt{R^2 + \left(\frac{1}{\omega C}\right)^2}$$

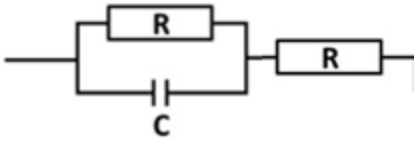
$$\phi(\omega) = -\arctan\left(\frac{1}{\omega RC}\right)$$





$$|Z(j\omega)| = \frac{R}{\sqrt{1 + (\omega RC)^2}}$$

$$\phi(\omega) = -\arctan(\omega RC)$$



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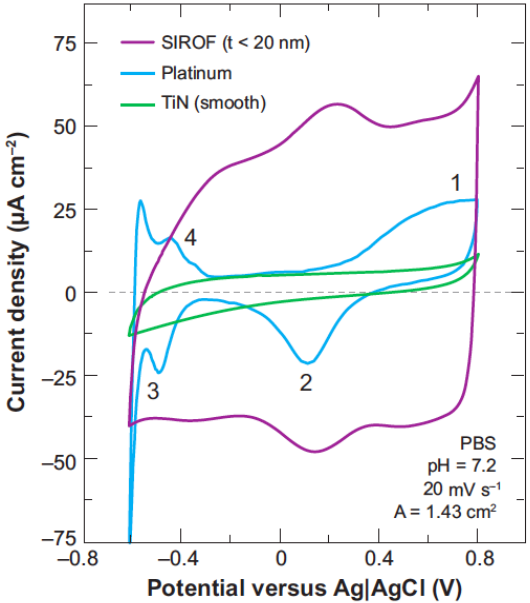
Cyclic voltammetry and CSC

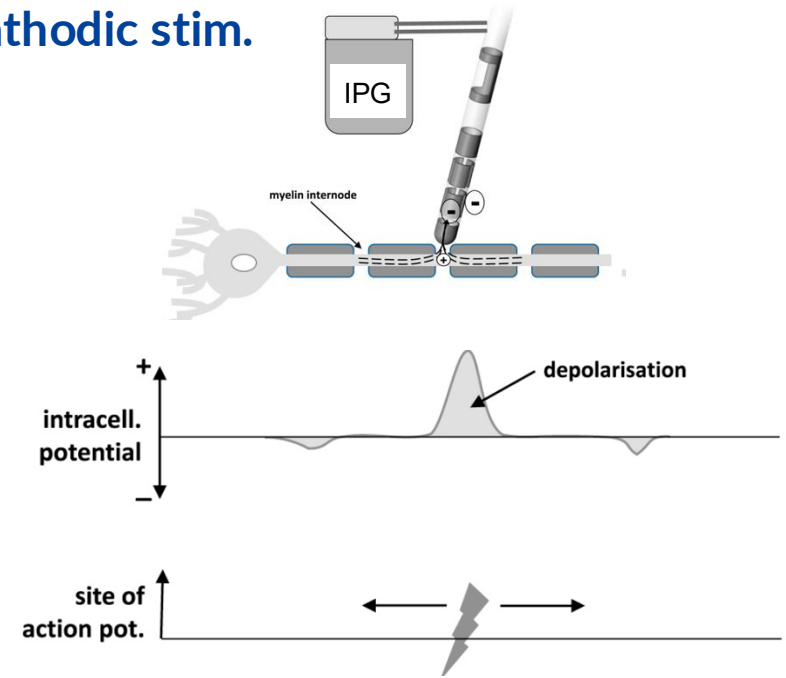
- 3-electrode setup:
  - Sweep the potential of WE applied against CE and measured against RE
  - Measure the current at WE



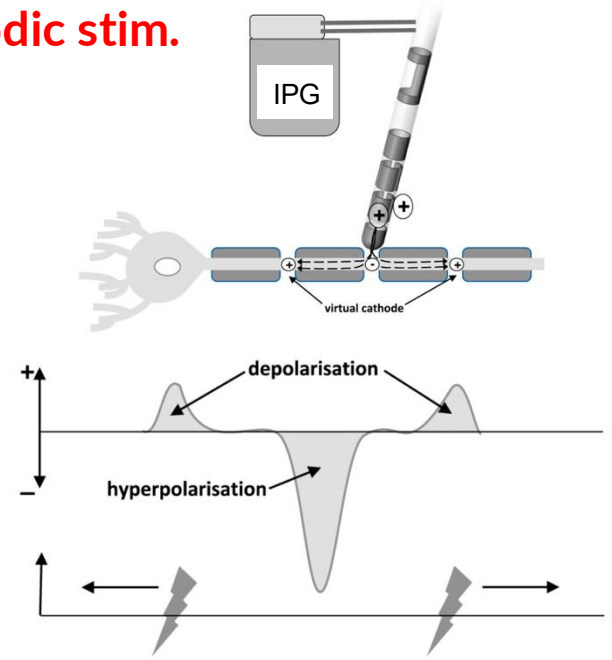
Electrode material	CSC (μC/cm²)
Gold	20
Stainless steel	50
Platinum	75
Titanium nitride	250
Iridium oxide	Up to 3,000

Cathodic vs anodic stimulation

Cathodic stim.

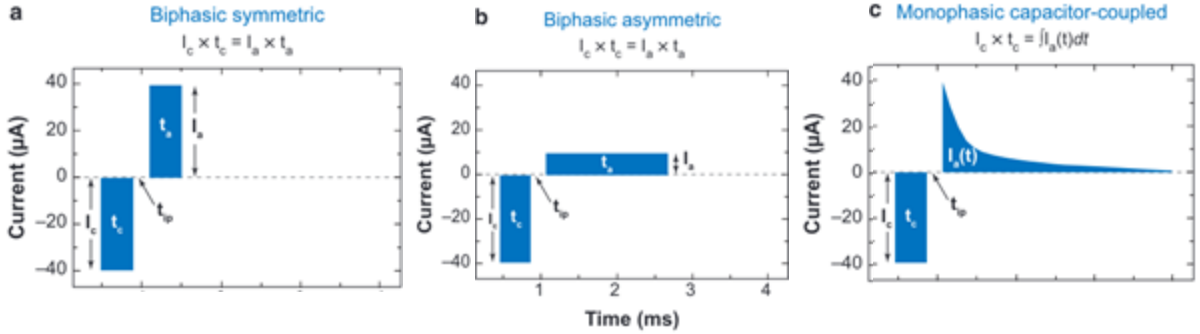


Anodic stim.



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

Charge-balanced current waveforms in neural stimulation

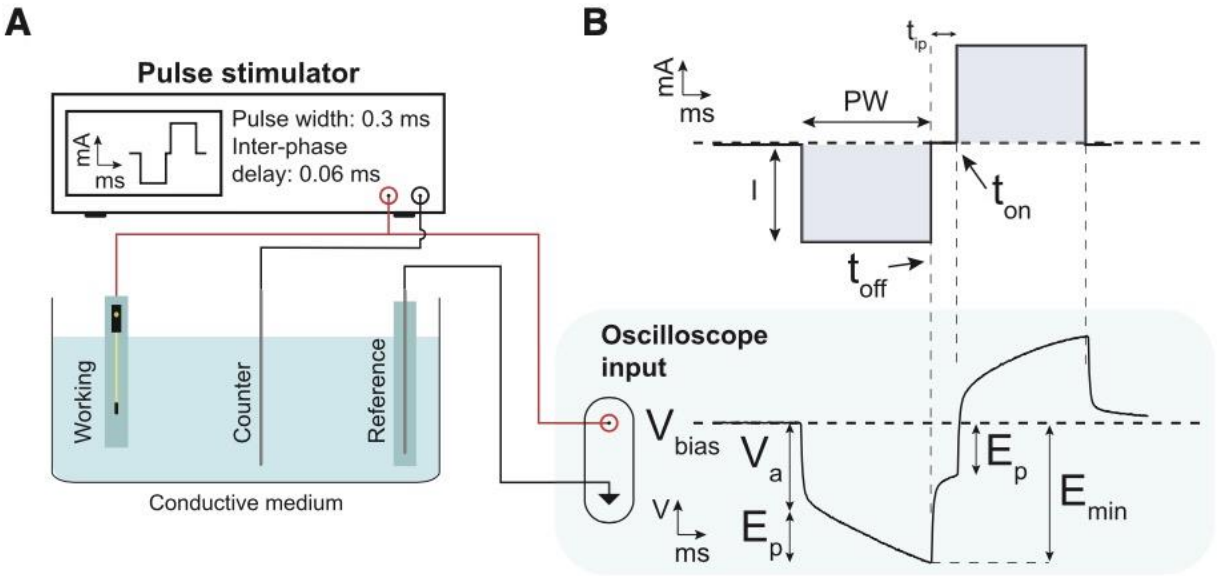


Application	Placement	Species	Type	Threshold charge/phase (nC ph^{-1})	Threshold charge density (μC cm^{-2})	Pulse Width (μs)
Vision	Epi-retinal	Human	Surface	6–1120	5–570	1000
Vision	Epi-retinal	Human	Surface	24–100	80–306	2000
Vision	Optic nerve	Human	Surface	7–124	4–62	25–400
Vision	Intracortical	Human	Penetrating	0.4–4.6	190–2300	200
Vision	Cortical	Human	Surface	200,000	11	200
Hearing	VCN	Cat	Penetrating	0.75–1.5	60–90	40–150
Hearing	AB	Human	Surface[a]	10–200	2.6–52	300
Micturition	Intraspinal	Cat	Penetrating	9	4000	100
DBS	STN	Human	Penetrating[b]	135–400	2.3–6.7	60–200
Motor	Intrafascicular	Cat	Penetrating	4[c]	0.5	50
Motor	Sciatic nerve	Cat	Penetrating	5[c]	96	200
Motor	Sciatic nerve	Cat	Surface	46	0.35	200

The geometric surface area (GSA) is used to define the charge density

The parameters vary widely depending on the application and size of the electrode.

Voltage transient measurements



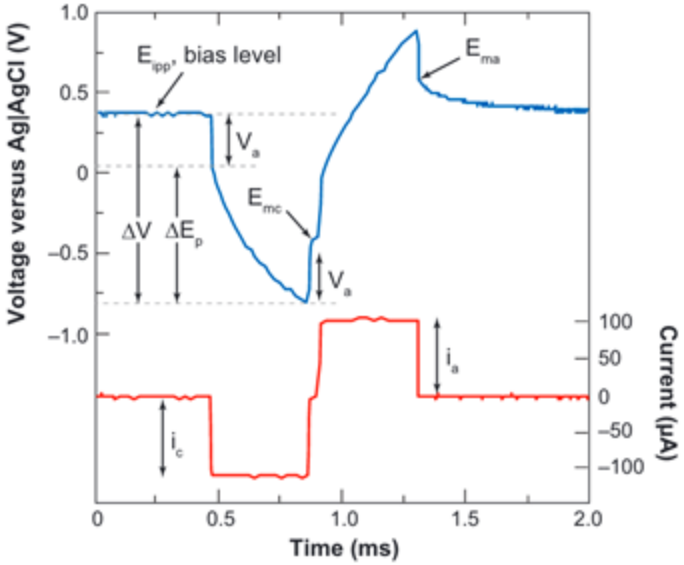
- **E_{min}: Minimum cathodic excursion = V_a + E_p**

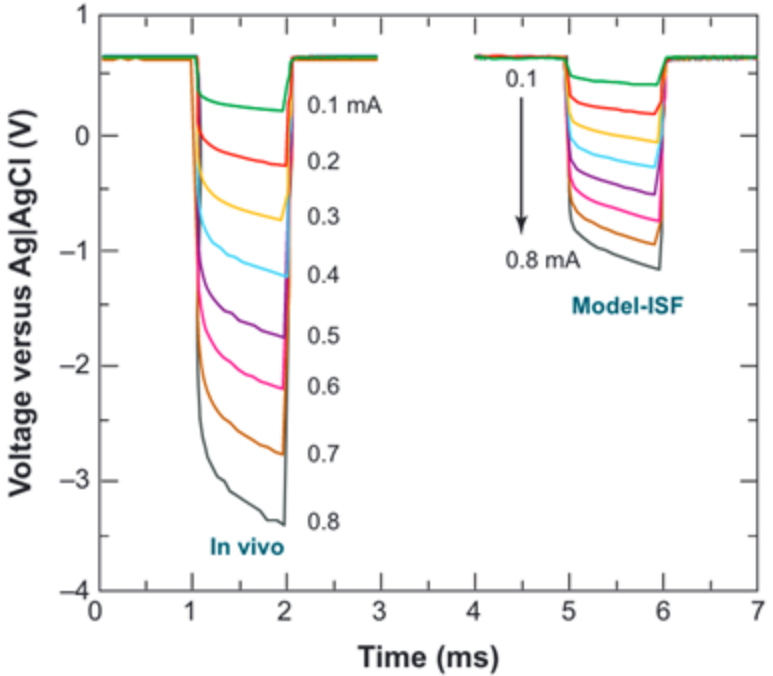
E_{min} = $IR + \eta_c$ + $E_o + \eta_a$

V_a E_p

Voltage Transient

Frequently used to estimate the maximum charge that can be injected in a current-controlled stimulation pulse.





In vivo ≠ In vitro !!

Geometrical surface area (GSA) vs electrochemical surface area (ESA)

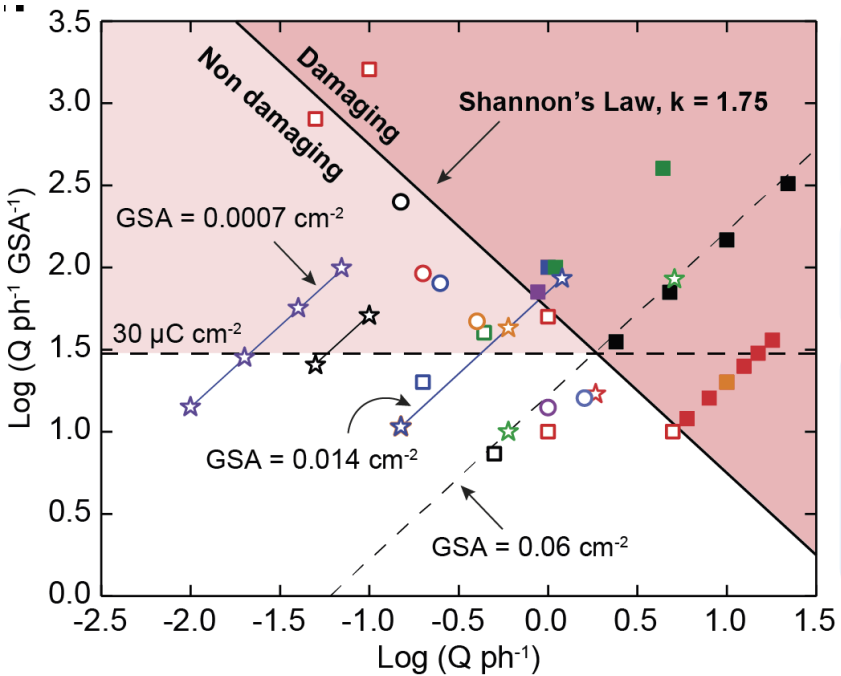
The real active surface of an electrode is not always equal to its visible geometrical surface (GSA): roughness and structure (ESA) strongly affect electrochemical activity.

	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.

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

Histological (empirical) vs e-chem safety limits

MACRO/CLINICAL electrodes

- High Q/ph. up to ~ 3 μC ph.$^{-1}$
- Low Q/GSA up to 30 μC cm^{-2}

- Functional thresholds ~ 0.6 μC ph.$^{-1}$, ~ 10 μC cm^{-2}

→ Wide [Q/ph, Q/GSA] therapeutic window

Penetrating microelectrodes

- Low Q/ph. up to ~ 4 nC ph.$^{-1}$
- High Q/GSA up to ~ 3000 μC cm^{-2}

- Functional thresholds ~ 1 nC ph.$^{-1}$

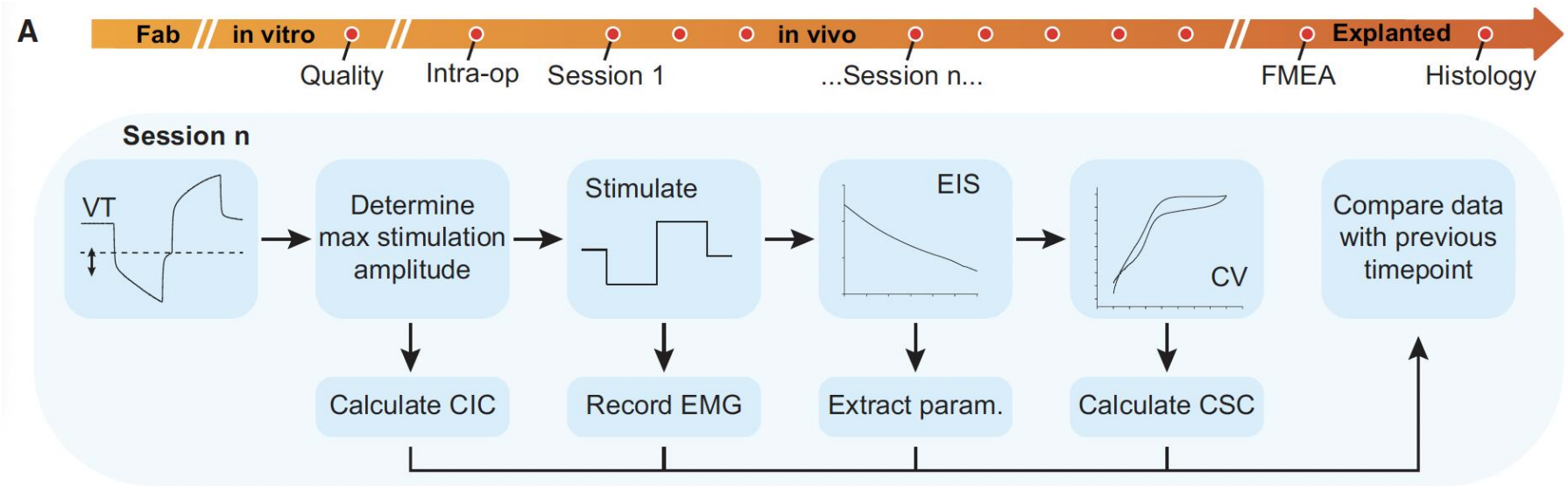
→ Narrow Q/ph therapeutic window

Electrochemistry

Safe polarisation limits:
Based on H_2O electrolysis

$2H_20 + 2e^- \rightarrow 2OH^- + H_2$
(reduction, alkaline shift)
$2H_20 \rightarrow 4H^+ + O_2 + 4e^-$
(oxidation, acidic shift)

Series of electrode characterisation: from fab to in vivo



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