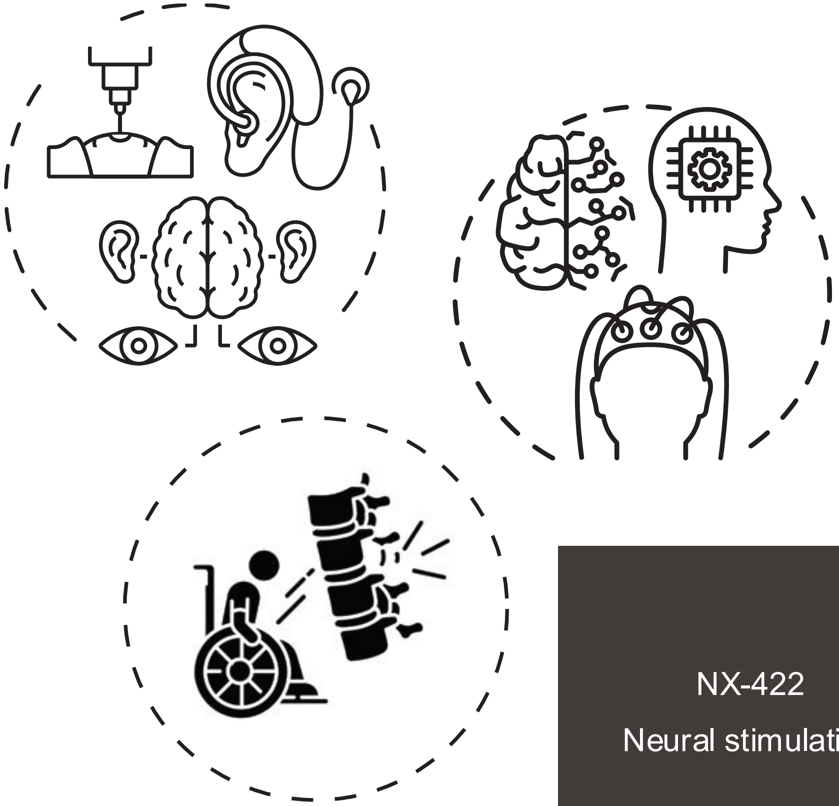


Neural Interfaces

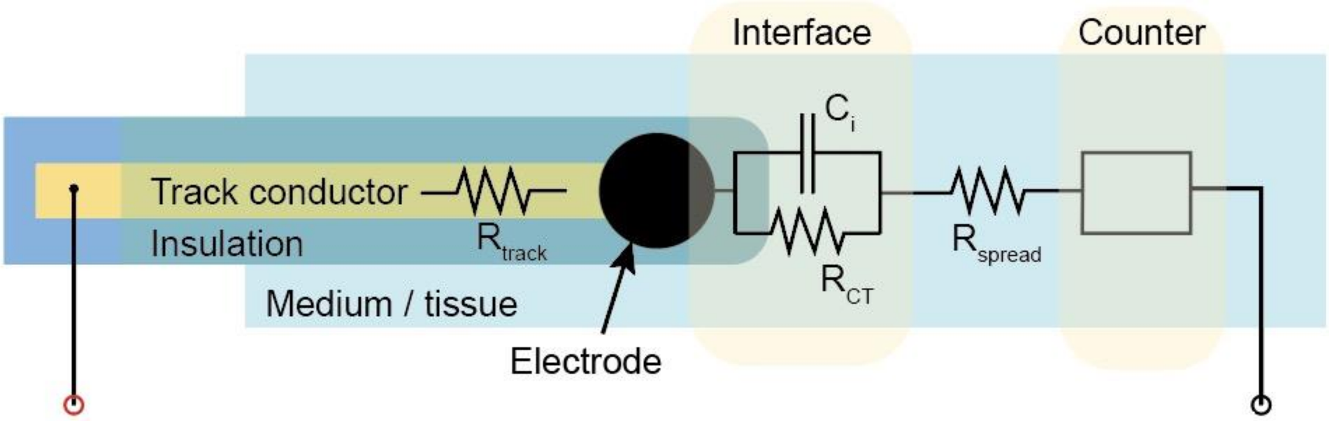
NX-422

Neural stimulation

Giuseppe Schiavone

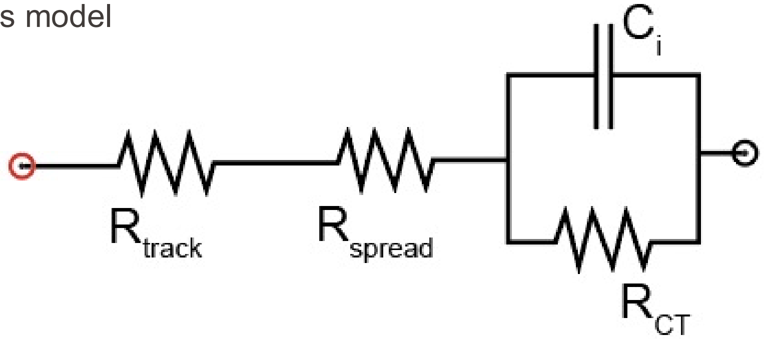
Neuro-X Institute

Equivalent electrical model of an electrode

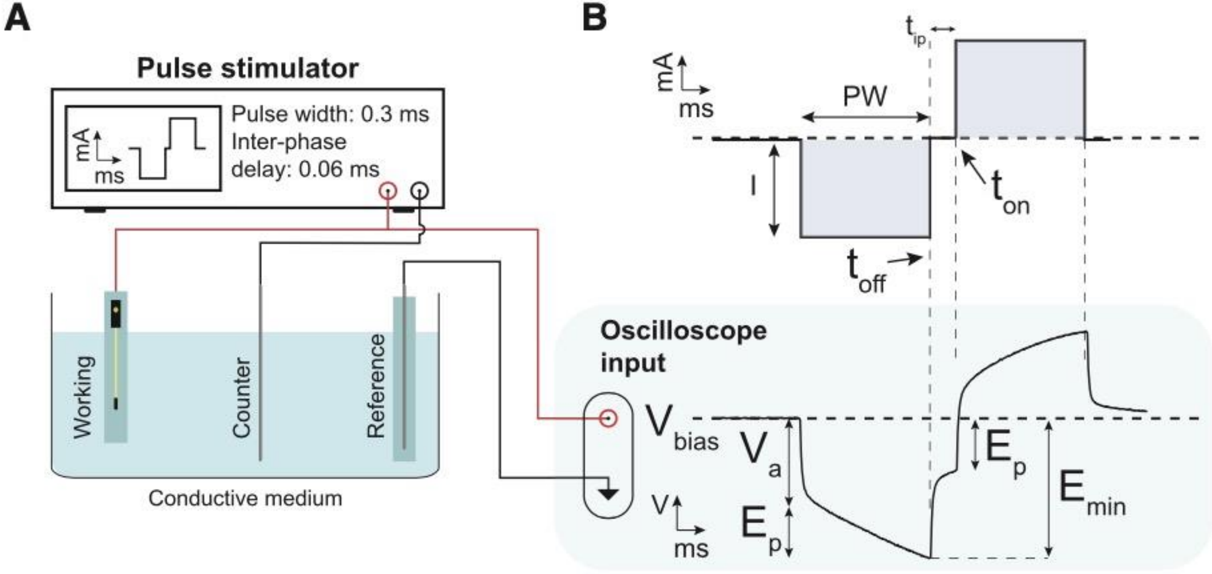


G. Schiavone et al, Neuron 2020

Randles model



Voltage transient measurements

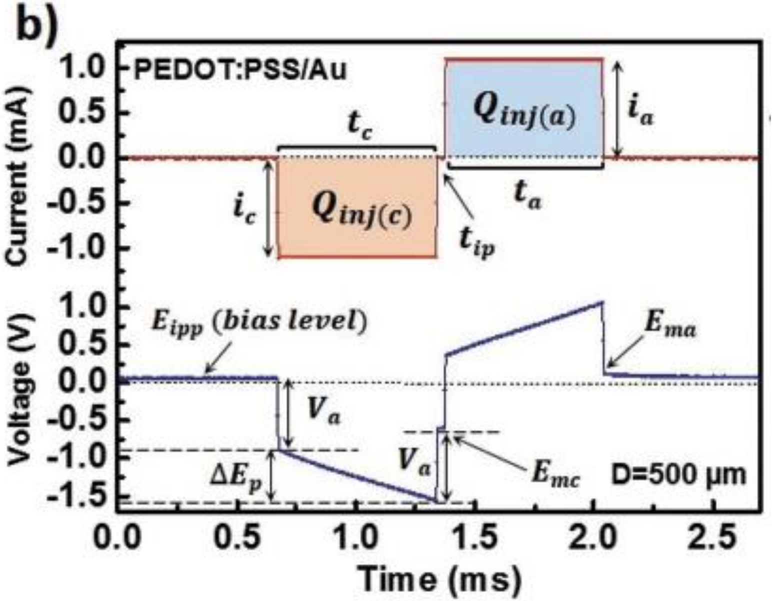


G. Schiavone et al, Neuron 2020

Charge Injection Capacity CIC

- E_{mc}:
  - maximum cathodal electrochemical potential excursions calculated by subtracting V_a from the maximum negative voltage transients or the electrode potential immediately, (when V_a is zero)
- E_{ma}:
  - maximum anodic electrochemical potential excursions
- Injected charges: $\mathbf{Q_{inj} = Q_{inj(b)} + Q_{inj(a)}}$
- **CIC**:
  - total charge density at which either E_{mc} reaches water reduction potential (cathodal limit) and/or E_{ma} reaches water oxidation potential (anodal limit).

$CIC = Q_{inj,c} / GSA$



Measurement of the CIC limit

1. Define the stimulation waveform (PW)
2. Set the injected cathodic charge: $Q_{inj,C} = I_C \times t$
3. Measure the cathodic interface polarisation potential E_{mc}
4. Ramp the charge until E_{mc} reaches the « water window » limit

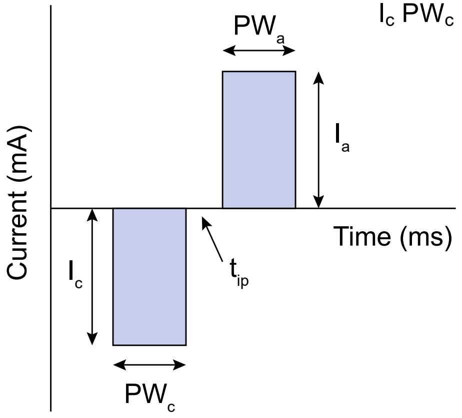
5. Calculate the corresponding CIC: $CIC = Q_{inj,C,max} / GSA$

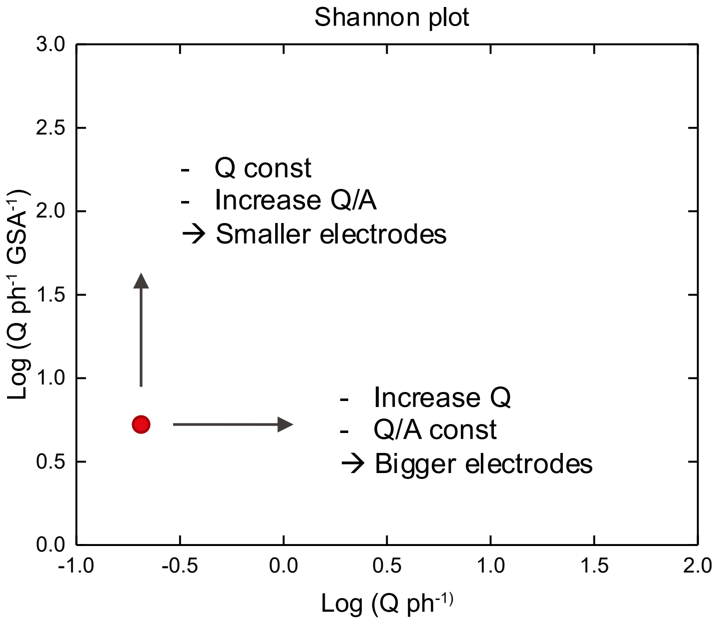
Shannon Plot

Biphasic, cathodic leading, charge balanced, symmetric pulses

$I_c = I_a$

$I_c\,PW_c = I_a\,PW_a$





- Q const
- Increase Q/A

→ Smaller electrodes

- Increase Q
- Q/A const

→ Bigger electrodes

When discussing safety and often for ease of comparison:

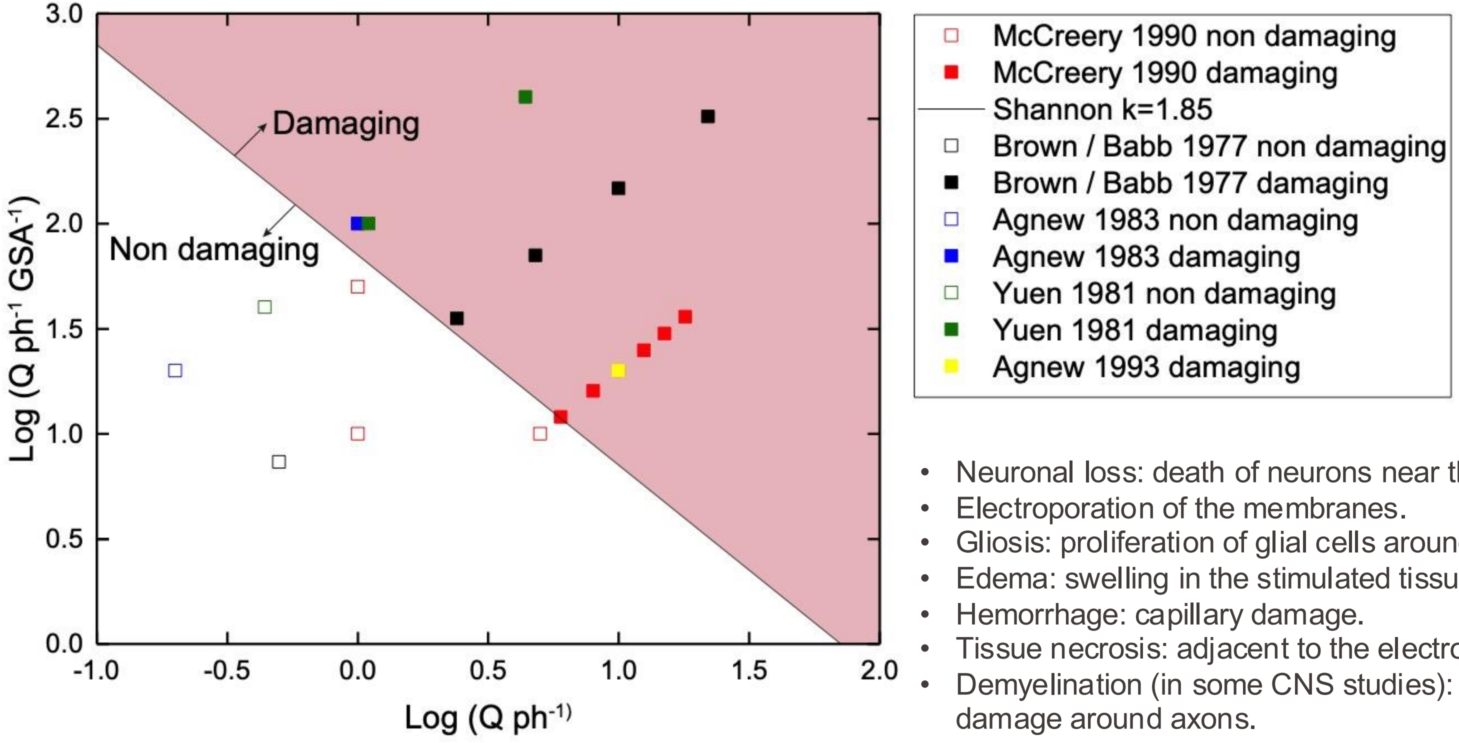
- Q/ph. = $I_c\,PW_c$ — [$\mu C\ ph^{-1}$]
- Q/GSA = Q/ph./GSA — [$\mu C\ ph^{-1}\ cm^{-2}$]

(All plots in these units, log scale)

→ We can map stimulation protocols on this plot

The Shannon limit

Planar macroelectrodes using the specified waveform



- Neuronal loss: death of neurons near the electrode.
- Electroporation of the membranes.
- Gliosis: proliferation of glial cells around the electrode (response).
- Edema: swelling in the stimulated tissue region.
- Hemorrhage: capillary damage.
- Tissue necrosis: adjacent to the electrode.
- Demyelination (in some CNS studies): local myelin sheath damage around axons.

“the Shannon limit”
$1.5<k<2$

$$\log\left(\frac{Q}{A}\right) = k - \log(Q)$$

Fits the data

The Shannon limit and GSA

What does this law imply in terms of current? Can you derive a limit for safe current?

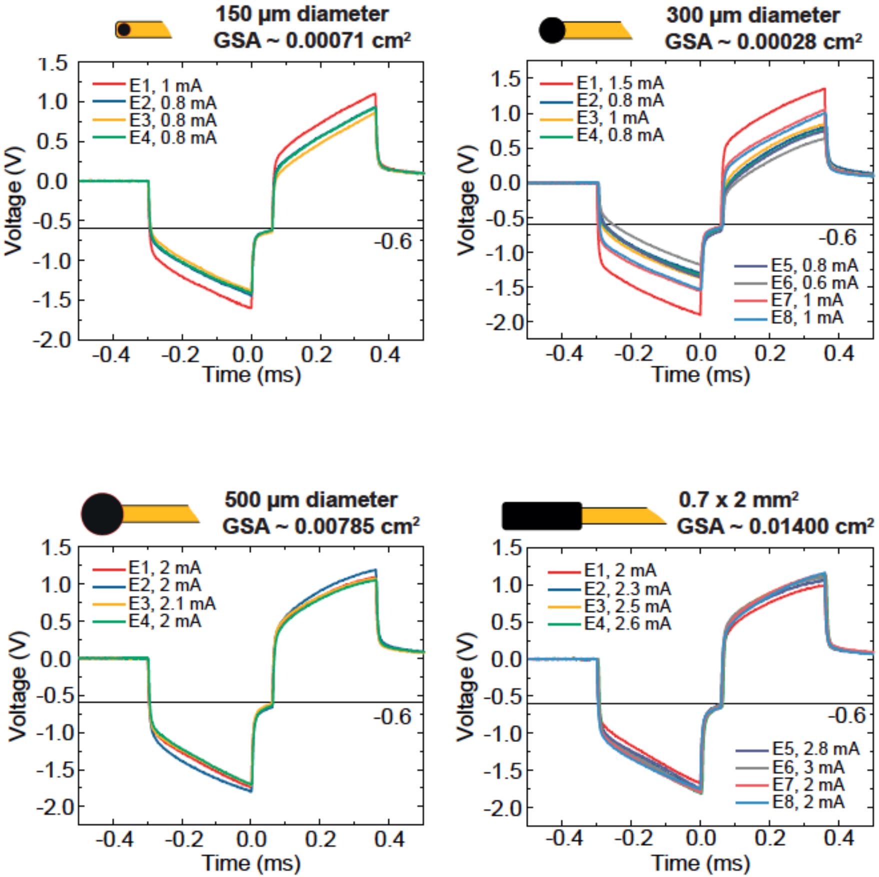
$$\log\frac{Q}{A} > k - \log Q \qquad \Leftrightarrow I > ?$$

Electrochemical limits follow a similar trend

GSA: 150μm ⌀ → 1.4mm²

Four electrodes are characterised (identical material but different GSA).

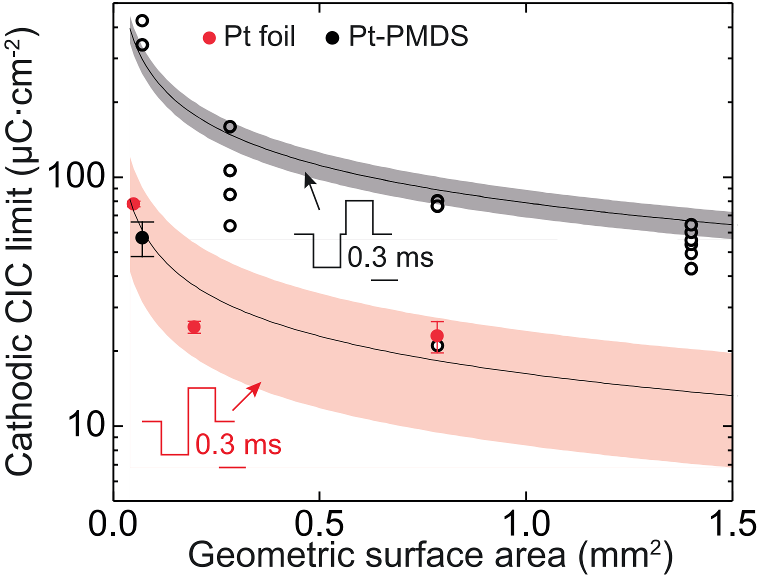
How does the CIC evolve with GSA?



G. Schiavone et al, Adv. Mater. 2020

Electrochemical limits follow a similar trend

G. Schiavone et al, Adv. Mater. 2020



CIC limits measured by VT in saline also follow a GSA^{-1} trend

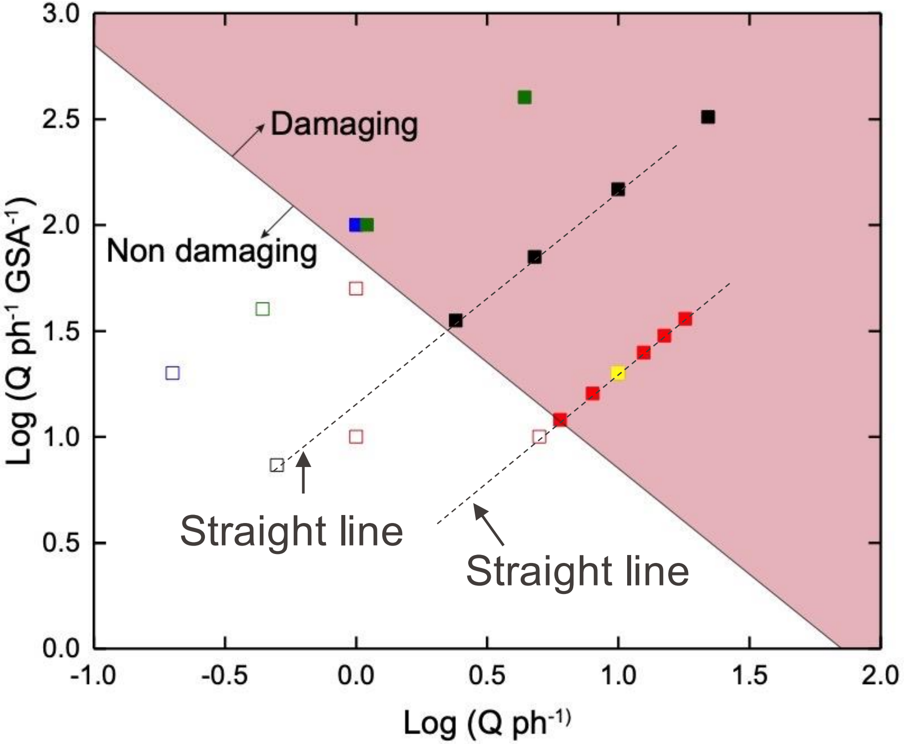
Datapoints show comparison between two electrode materials (plain platinum and platinum-silicone composite).

Both follow a GSA^{-1} trend.

→ Increasing stimulation performance of an electrode by increasing the perimeter/GSA ratio

Geometric surface area GSA on Shannon plot

What do constant area loci look like on Shannon plot? (Hint: y = log Q/A, x = log Q)

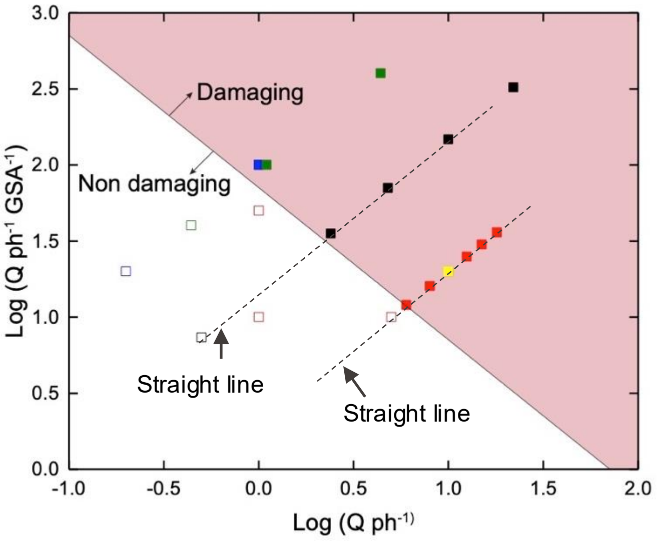


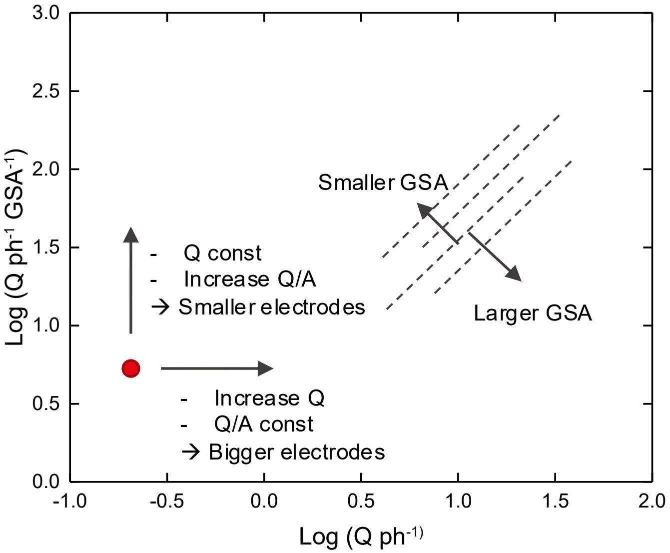
$$\log\frac{Q}{A} = k - \log Q; \qquad A = \frac{Q}{\frac{Q}{A}} = const.;$$

Geometric surface area GSA on Shannon plot

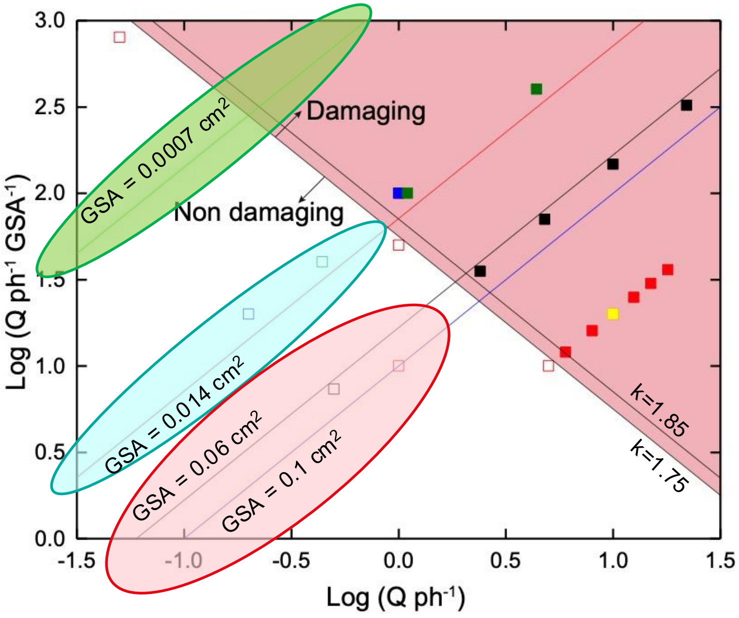
“the Shannon limit” $\log\left(\frac{Q}{A}\right) = k - \log(Q)$

“geometry” Log (Q/A) = Log (Q/ph) – Log (A);





The 30 $\mu C.cm^{-2}$ limit



🟥 MACRO / CLINICAL: e.g. SCS, DBS, VNS

🟦 MESO: e.g. e-dura (Pt composite) in minipig, NHP

Schiavone 2020

🟩 MICRO: e.g. e-dura (Pt composite) in rat

Minev 2015

For Medtronic SCS / DBS: GSA = 0.06 cm²

→Log (Q/A) = Log (Q/ph) – Log (0.06);
Log (Q/A) = k – Log (Q/ph);

For k = 1.75:

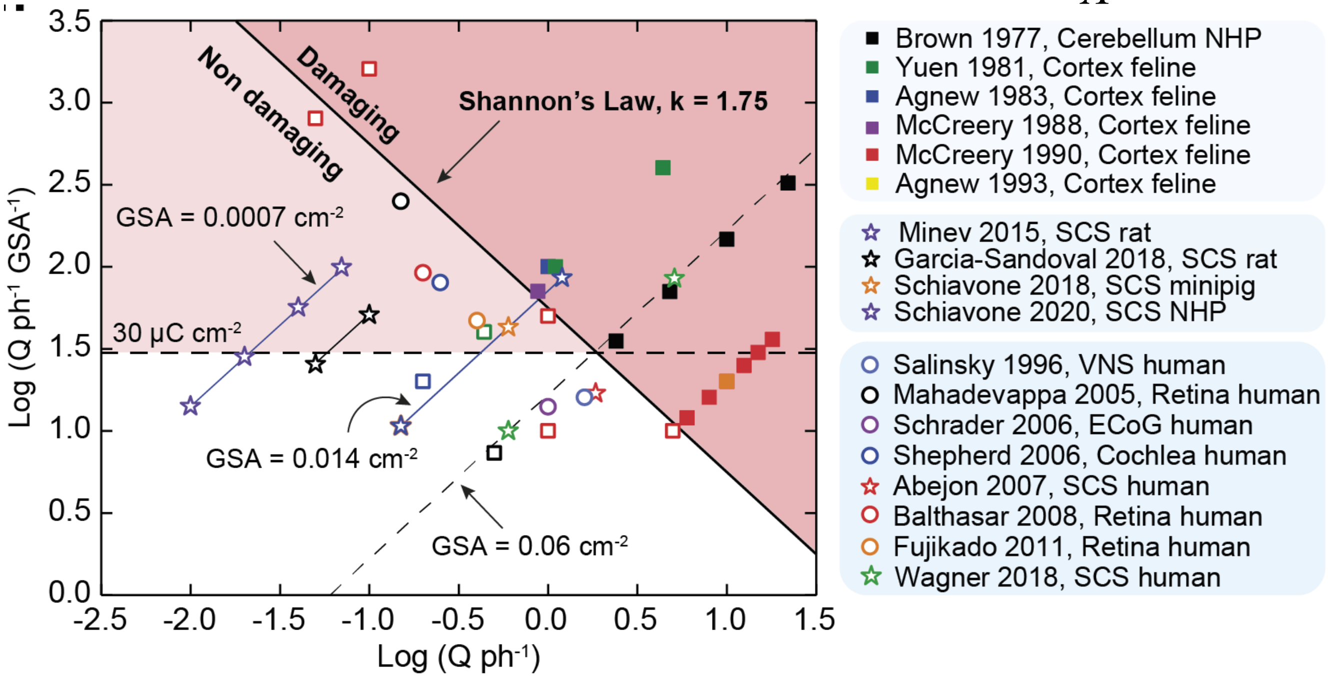
→Log (Q/A) = 0.5 (1.75 – Log (0.06)) = 1.486;

→Q/A = $10^{1.486}$ $\boxed{\sim 30\ \mu C\ cm^{-2}}$

Charge vs charge density for safe stimulation

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

$1.5<k<2$



UNSAFE: irreversible electrochemical reaction
tissue damage
neuronal hyperactivity

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

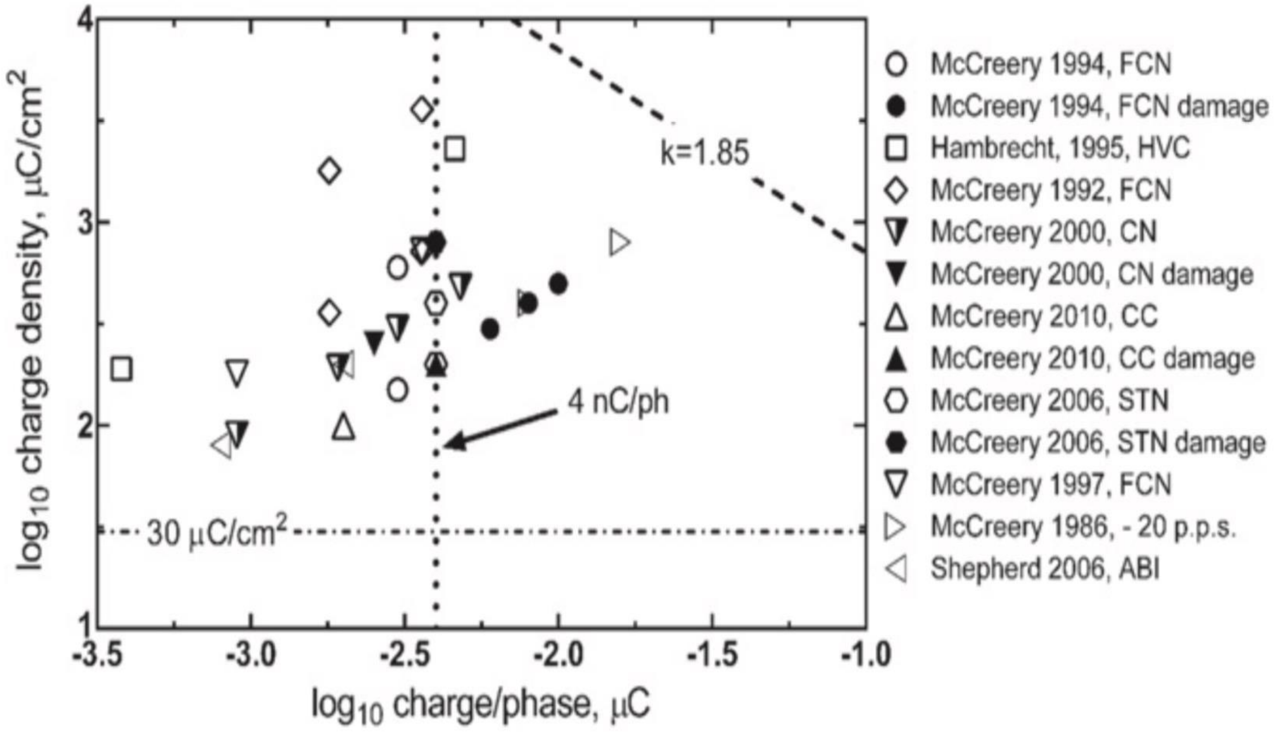
Microelectrodes behave differently

For penetrating microelectrodes tissue damage thresholds are Q/ph.-dependent.

Point-source model

→ far-field condition, neuronal population activated not a function of the GSA

→ GSA and shape play little to no role in the observed tissue damage



Cogan 2016

Take-home messages: Electrochemical and biological safety in neurostimulation

- For different materials, geometries and pulses, the CIC limits vary widely

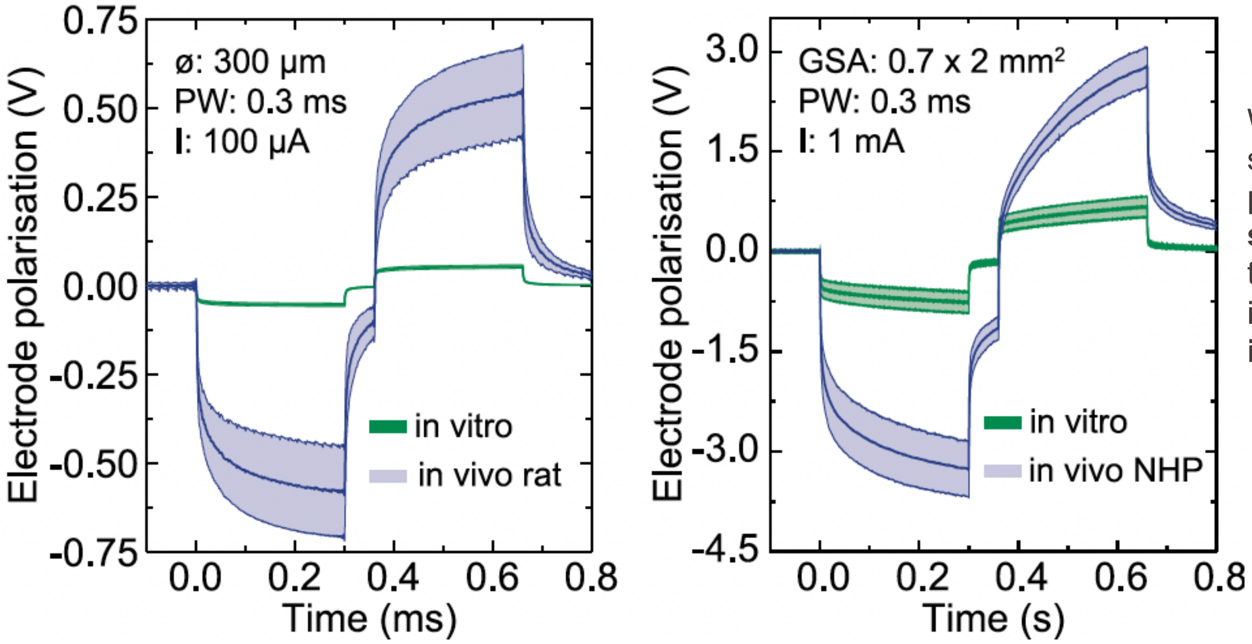
- CIC does not scale linearly with electrode area, but with electrode perimeter

- **Macroelectrodes** (GSA > ~ 1cm^2)
  - q_{inj} < ~ 30 µC / cm^2

- **Microelectrodes** (GSA << 1cm^2)
  - Q_{inj} < ~ 4 nC / ph.

Remember Shannon's law is an empirical finding derived from a confined selection of studies
Different observations may be found according to specific applications, new technologies and more tests

Voltage transients in vivo

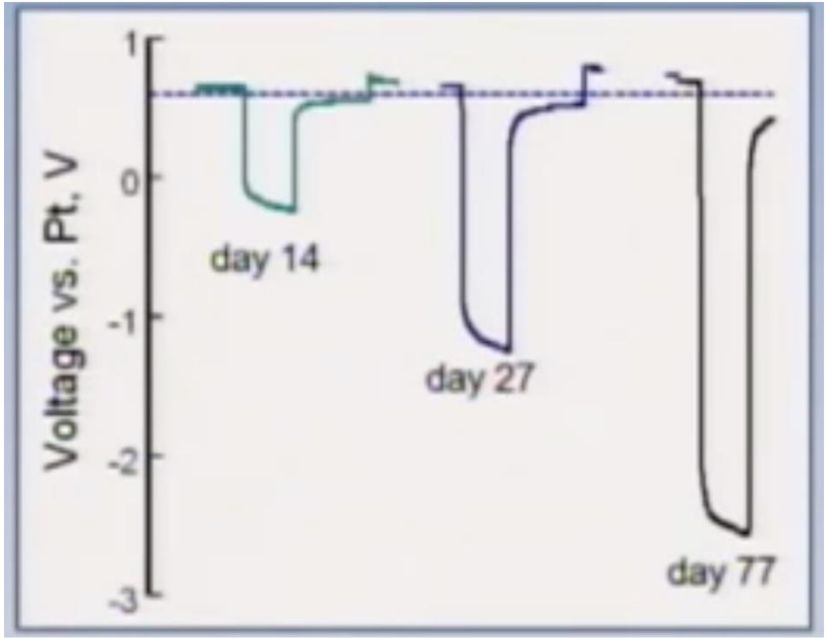


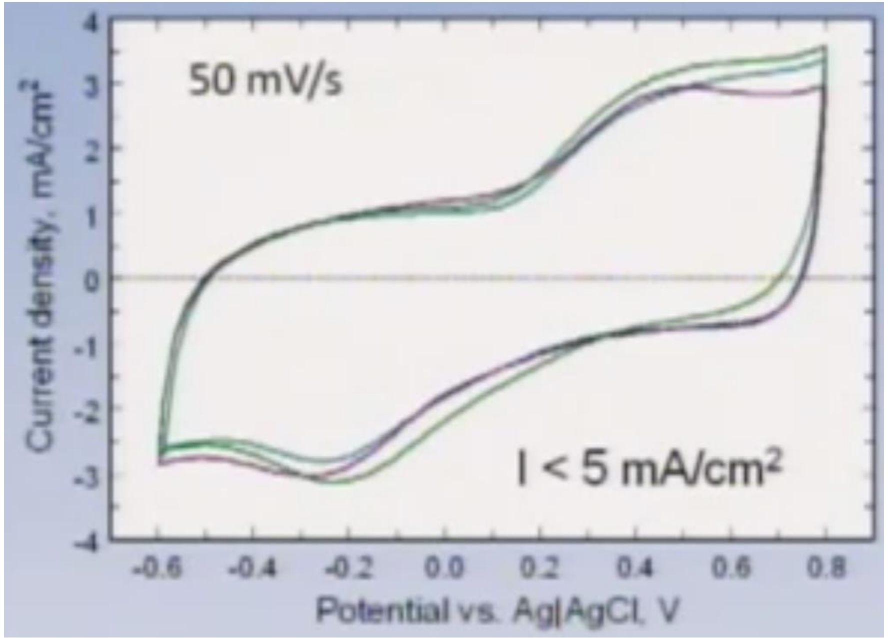
When delivering electrical stimulation in vivo, **the polarization of an electrode system is consistently larger** than what measured in vitro, both in terms of **access voltage and interface polarization.**

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

VT over time in vivo

Example: Iridium oxide electrodes on polyimide – Chronic subretinal (animal models)

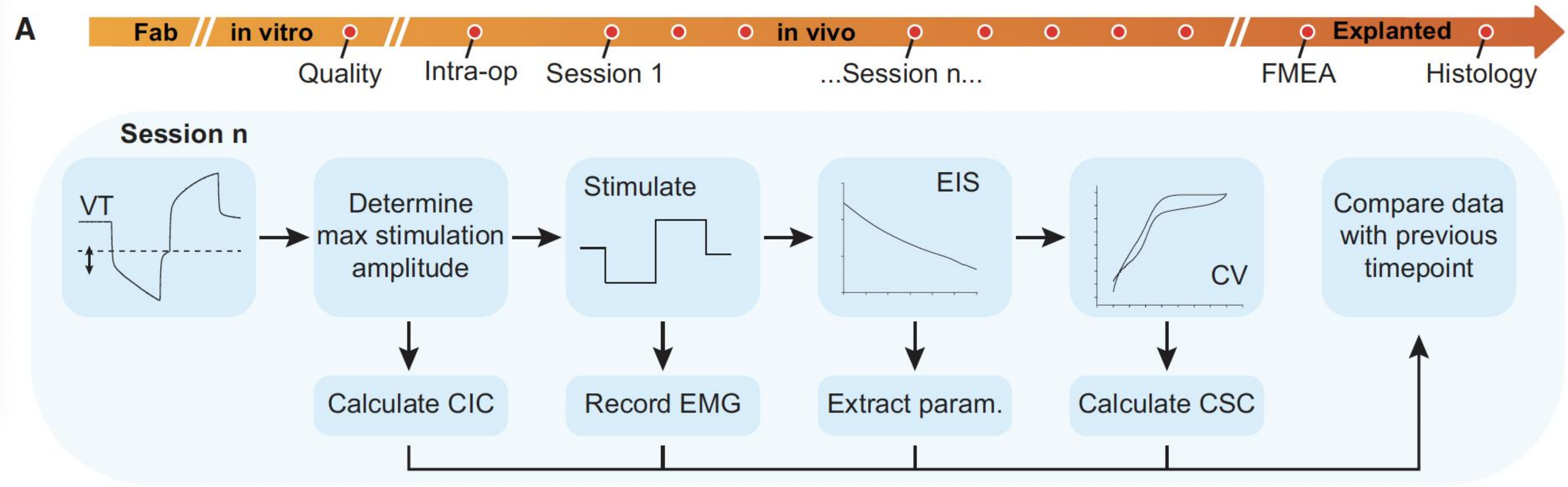




→ **If charge injection is counterion transport limited (as is the case *in vivo*), slow-scan CVs do not show change, while VT shows degraded performance.**

Instantaneous onset of current requires fast counterion current, not tested in slow-scan CV

Series of electrode characterisation: from fab to in vivo



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

Take-home messages

- **CIC limit is a good benchmarking parameter**
  - Compare the voltage-efficiency of stimulation electrodes **for a given stimulus**
  - Current-controlled measurement, easy to isolate the interface and eliminate surrounding effects
  - Measurement uses stimulus derived from application → More relevant testing compared to EIS

- ***In vitro* testing for benchmarking**
  - VT in vitro can help establish performance standards, but…
  - The real info is *in vivo.* VT increase up to 1 order of magnitude between *in vitro* and *intra-op*

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)

Correct engineering of neurostimulation interfaces

Use Shannon and GSA considerations to guide the design of neural electrodes

→ GSA selected by the *in vivo* application (but room for perimeter/area, coating improvement)

→ Identify the safe stimulation window based on the GSA (Q/ph or Q/GSA limits)

Use electrochemistry to evaluate whether safe window is larger than tissue damage thresholds

→ Use VT *in vivo* to progressively evaluate the electrode-tissue interface

→ Use EIS to model more in detail complex systems