Drug delivery neural probes

Applications in Neural Microsystems
Lecture 9

Zoltan Fekete

Outline

1. Goal of local drug delivery
2. Active drug delivery principles
    A. Convection enhanced
    B. Electrophoresis
3. Technology of passive devices
4. Integrated active solutions
5. Exampes of microelectrodes with integrated fluidics

Applications

Microneedles:

- Transdermal injection of drugs
- Microdialysis tests

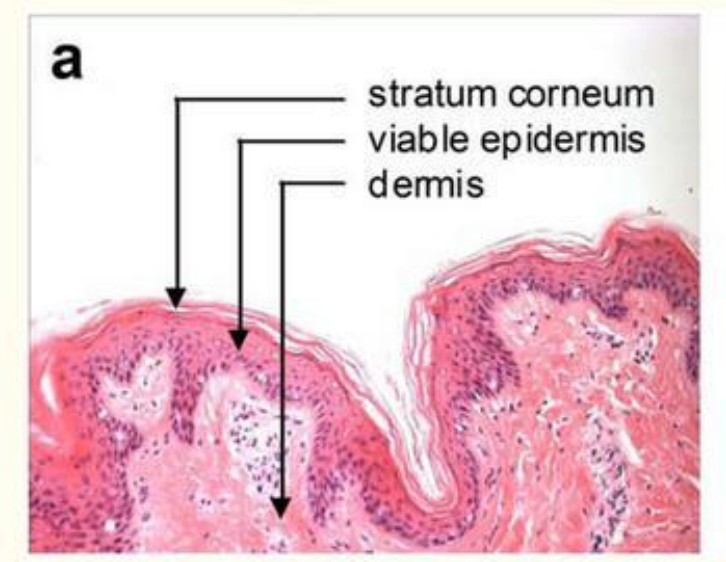
Microelectrodes:

- 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

Basic configurations:

Microfluidics + MEMS = Multipurpose implants

Transdermal delivery



Prausnitz, 2009

Applications already approved:
Dementia (Rivastigmine, 2007)
Rotigotine (Parkinson's disease, 2006)
Selegiline (Depression, 2006)

Under clinical development:
Influenza vaccine
Sufentanil (chronic pain)
Parathyroid hormone (Osteoporosis)

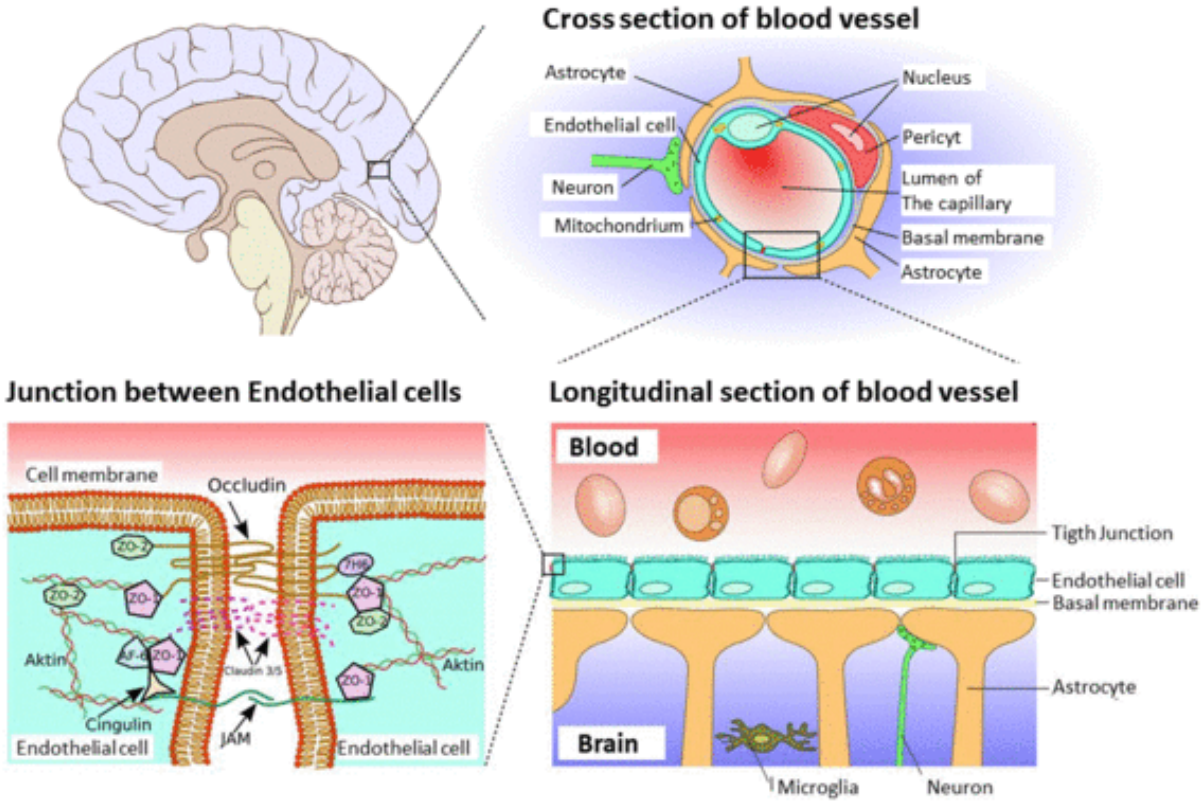
Specific delivery technologies:

- Passive
- Chemical enhancer
- Iontophoresis
- Heat enhancement

Drug delivery through the blood brain barrier (BBB)

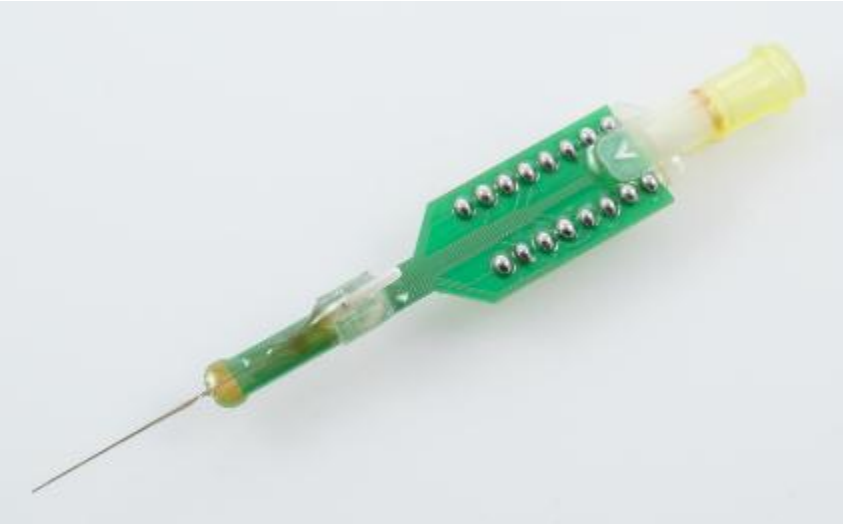
BBB: separates circulating blood from extracellular fluid in the CNS

- Nearly all neurotheraputics and small molecule drugs are excluded
- Nanoparticles embedded in liposomes & peptides are able to cross BBB
- Alternative diagnostics:
- Disruption of BBB by local injection of drugs



Strategies to administer drugs in the brain

- Convection enhanced delivery
- Iontophoresis aided delivery
- Polymer coatings with tunable drug release

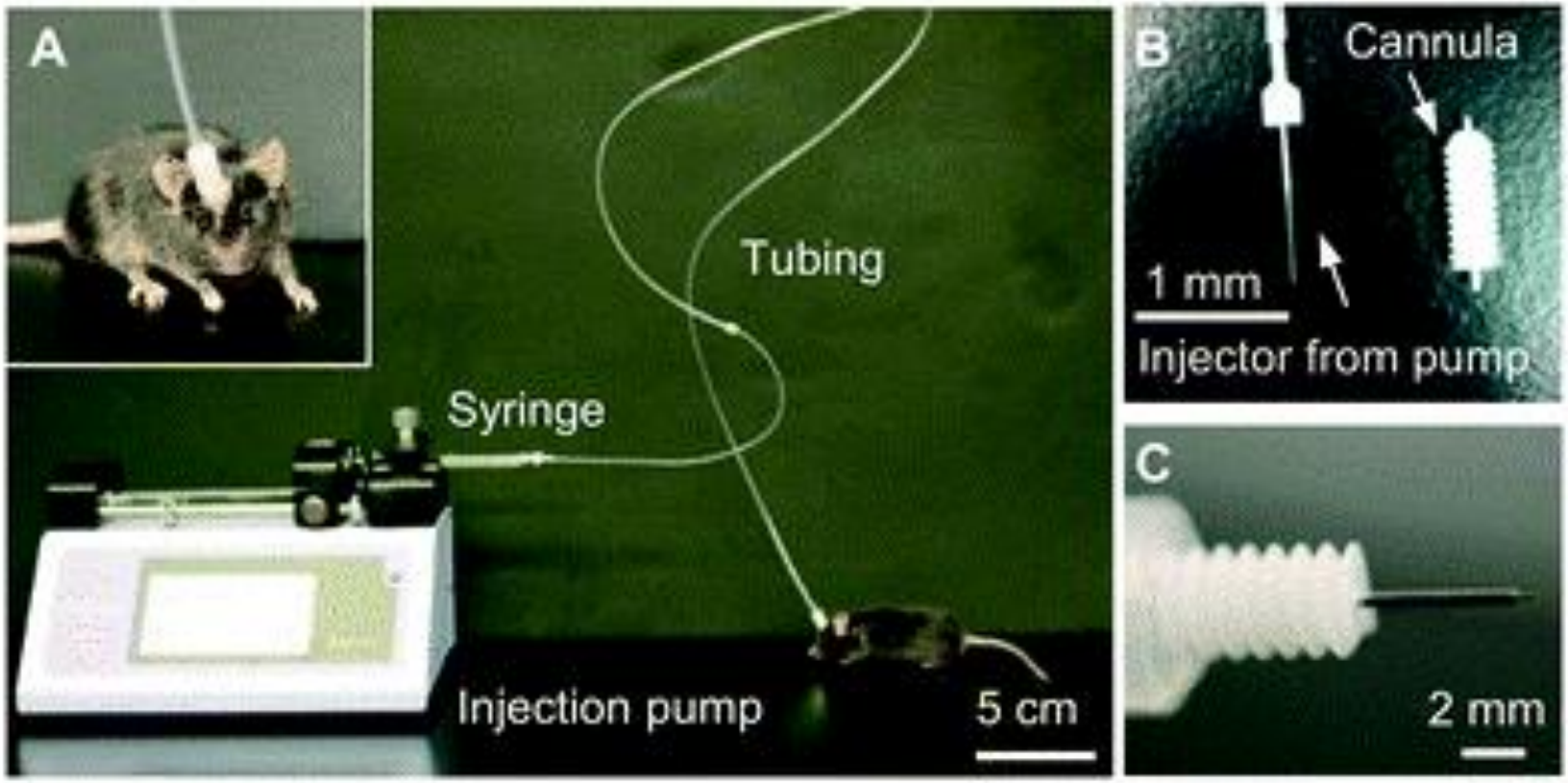


Usually pressure based solutions are available on the market.

Convection enhanced delivery (CED)

Conventional solutions:

- Bulky (250-500 micron in diameter)
- Rigid (E ~200GPa)



Sim, 2017

Fundamentals in hydrodynamics

Governing equation (Navier-Stokes):

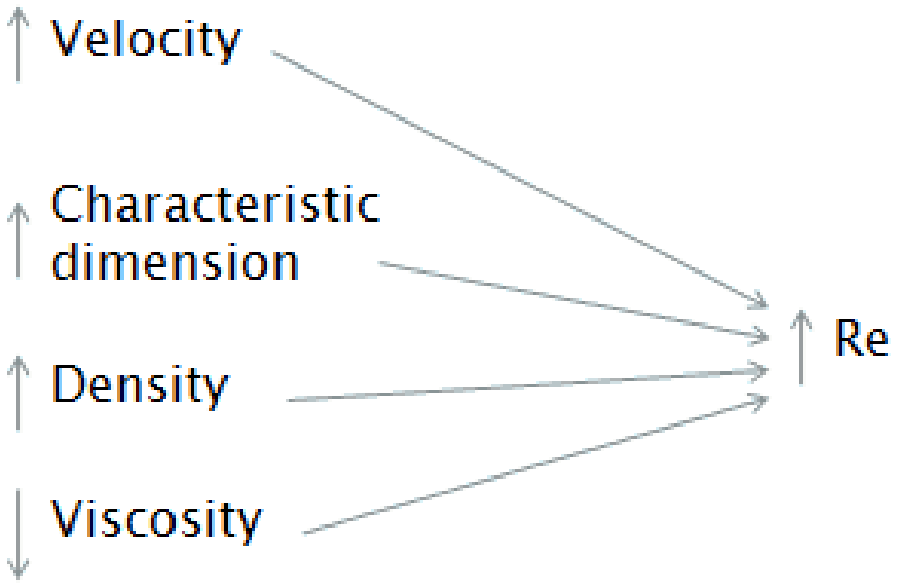
$$\rho \frac{\delta \boldsymbol{u}}{\delta t} = -\nabla P + \mu \nabla^2 \boldsymbol{u} + \mathrm{g}$$

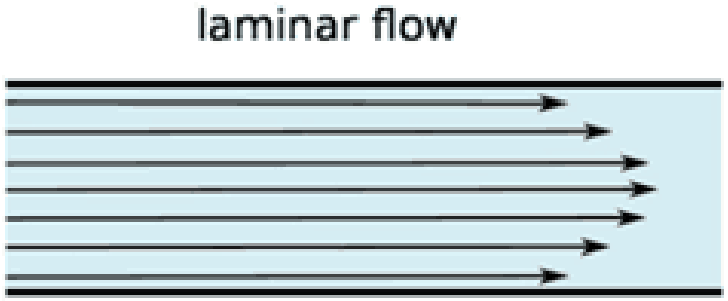
Driving forces:

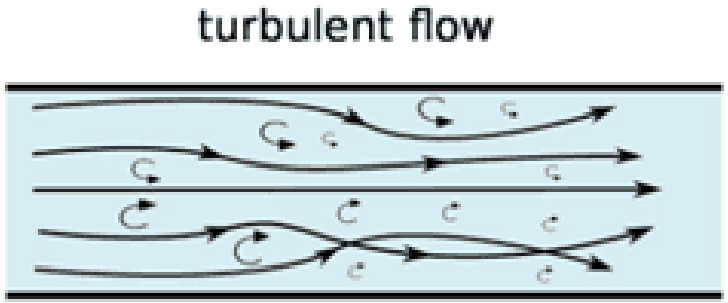
pressure gradient, viscous forces, gravity

Flow at the microscale in CED

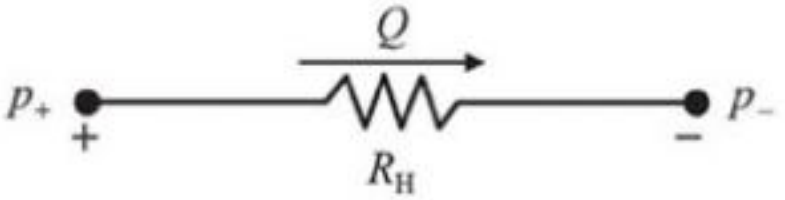
$$Re = \frac{\text{inertia forces}}{\text{viscous forces}} = \frac{\rho \cdot V \cdot D}{\mu}$$



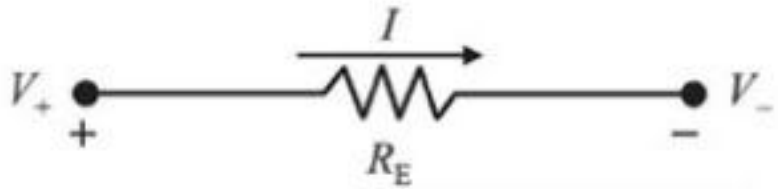




Typical circuit models in microfluidics



Hagen-Poiseuille's law: $\Delta p = p_+ - p_- = Q R_H$



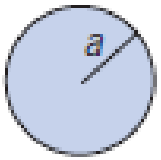
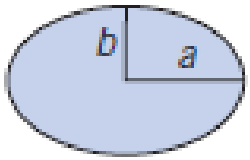
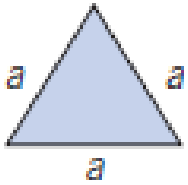
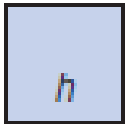
Ohm's law: $V = V_+ - V_- = I R_E$

Series: $$R_{total} = R_1 + R_2 + \ldots + R_N$$

Parallel: $$\frac{1}{R_{total}} = \frac{1}{R_1} + \frac{1}{R_2} + \ldots + \frac{1}{R_N}$$

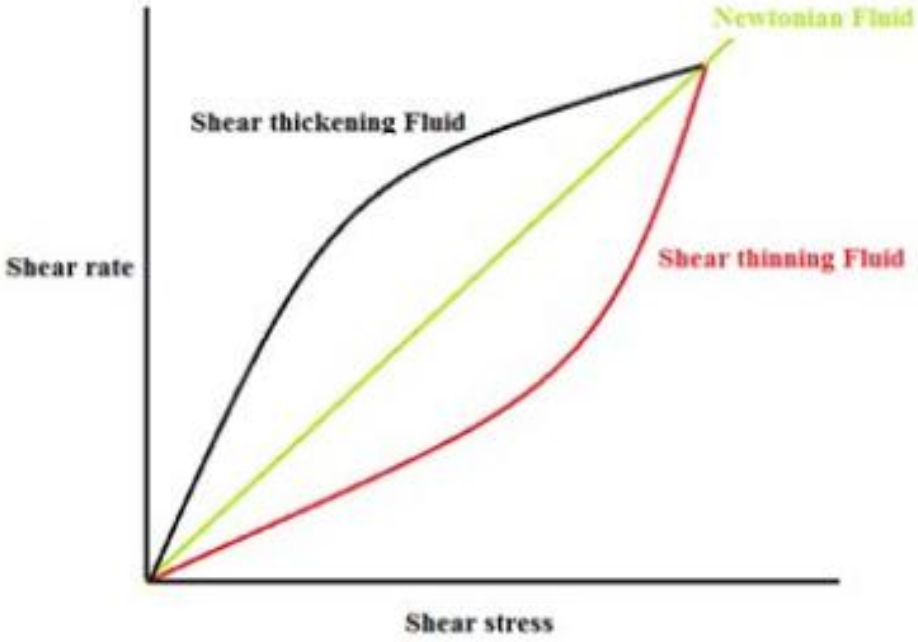
P – pressure, Q – flow rate, R_H – hydraulic resistance

Hydraulic resistance

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 	$\frac{12\mu L}{0.37h^4}$

- Cross-section dominantly influences
- Typically inherently limited by production technology used

Viscosity



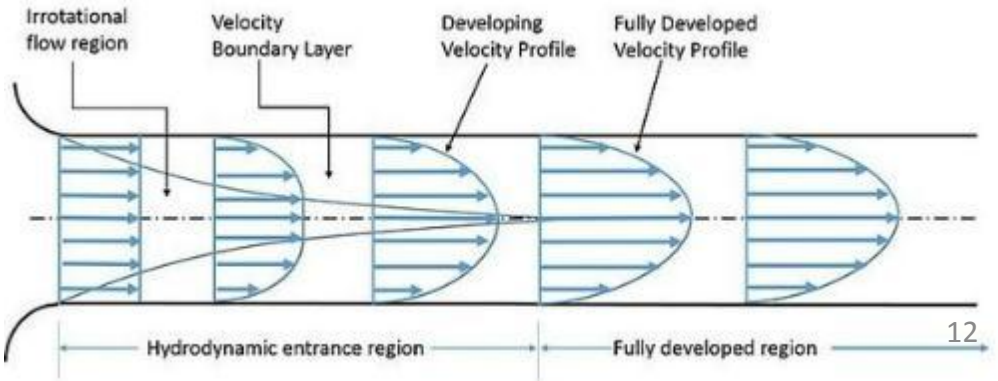
Water viscosity

Temperature - t - ($^{\circ}C$)	Dynamic Viscosity - μ - (Pa s, N s/m^2) x 10^{-3}	Kinematic Viscosity - ν - (m^2/s) x 10^{-6}
0	1.787	1.787
5	1.519	1.519
10	1.307	1.307
20	1.002	1.004
30	0.798	0.801
40	0.653	0.658
50	0.547	0.553
60	0.467	0.475
70	0.404	0.413
80	0.355	0.365
90	0.315	0.326
100	0.282	0.29

Shear rate: change of velocity at which one layer of fluid passes over an adjacent layer

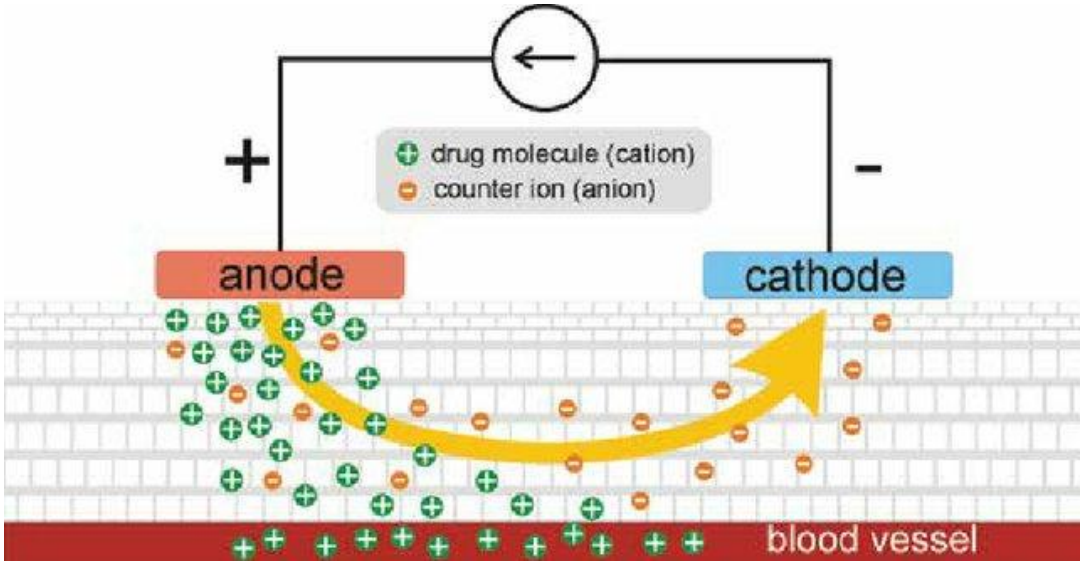
Shear stress $\tau = \mu \frac{du}{dy}$

Typically, Newtonian fluids are administered.



Iontophoretic drug delivery (IDD)

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

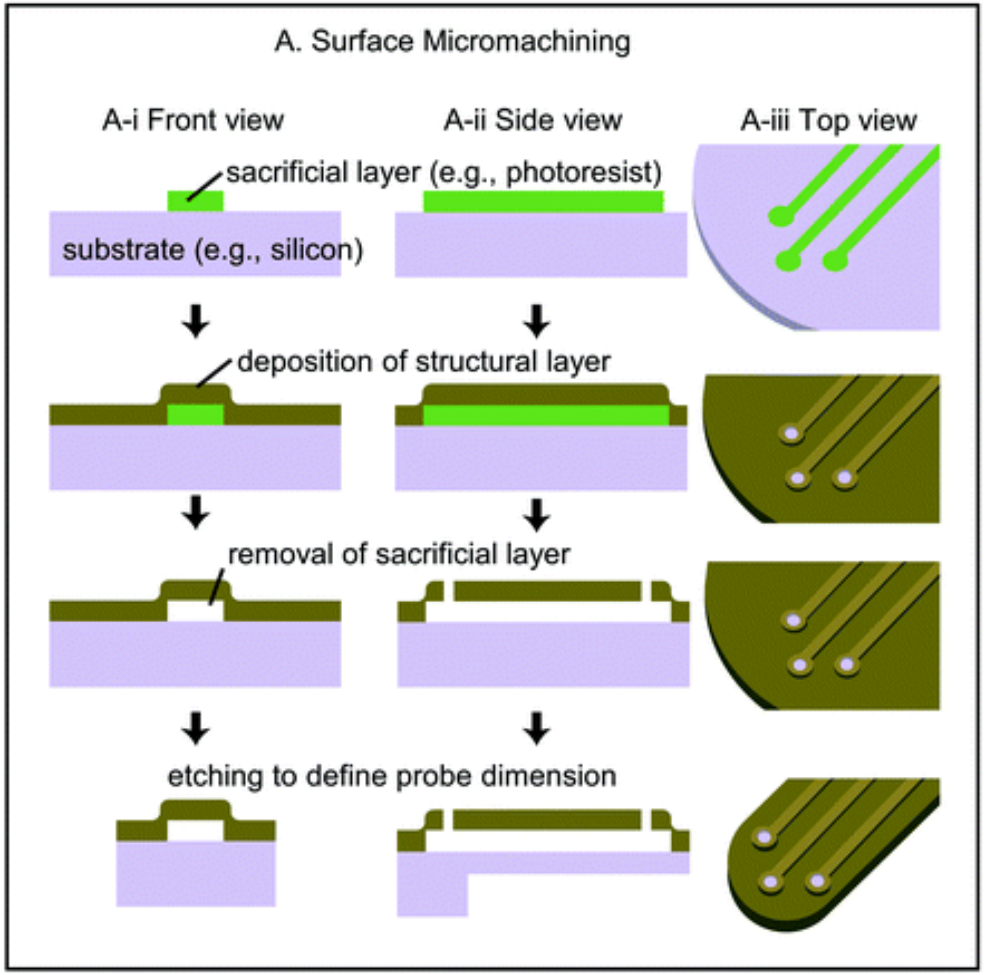


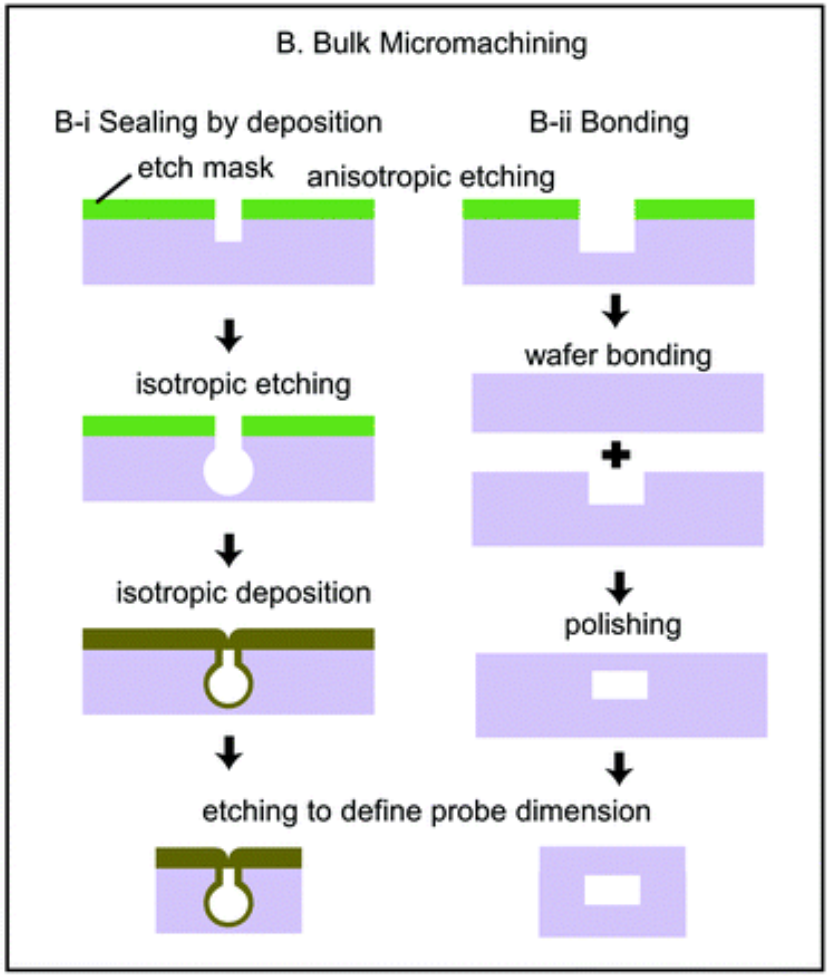
$$N_e = \frac{I}{F}$$

$$Q = M_w * N_e$$

N_e – mol number of electrons which pass through the external circuit per second,
F – Faraday constant (96487 C/mol)
Q – drug delivery rate
M_w – molecular weight

Integrated solutions (silicon)

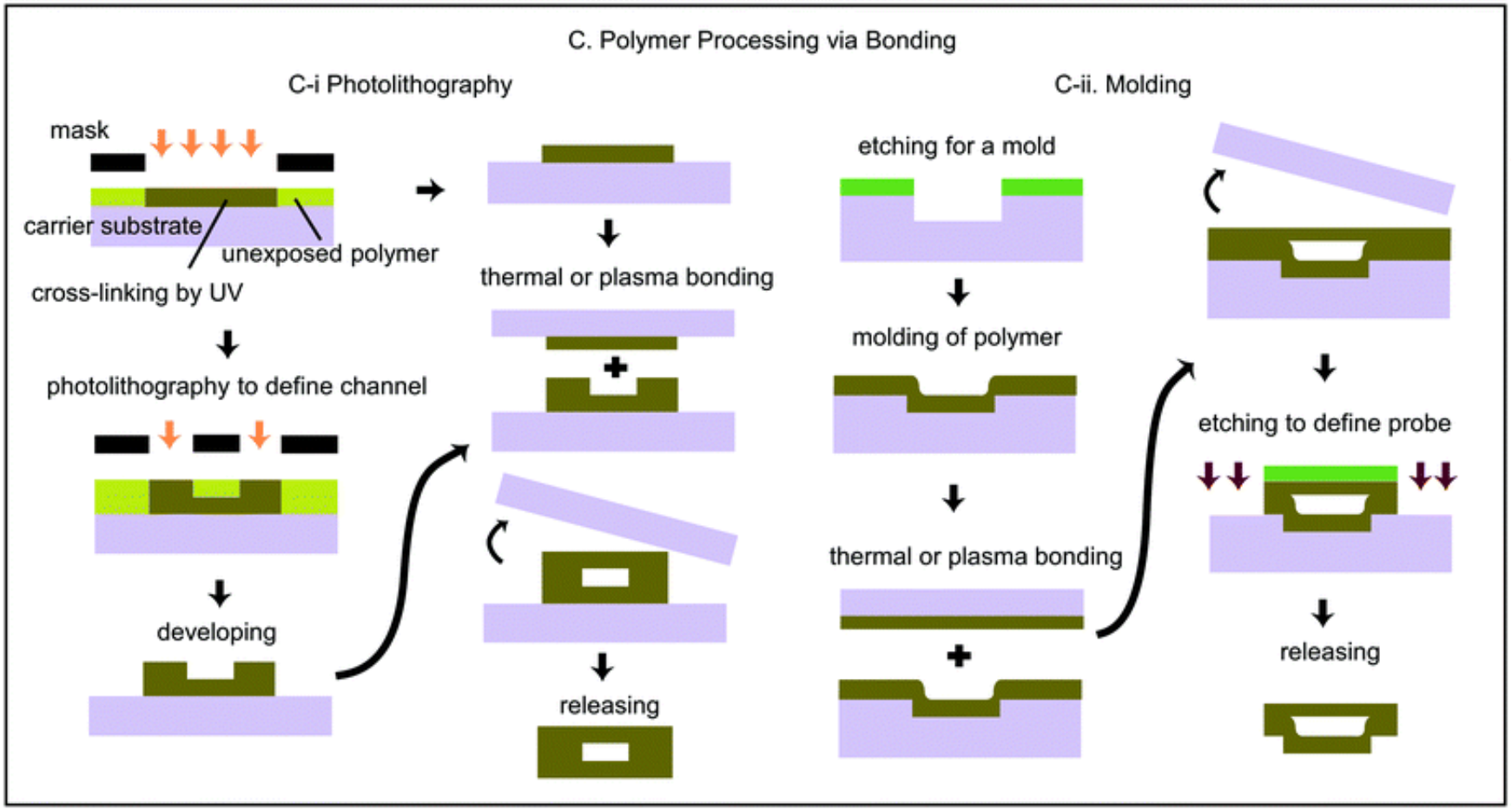




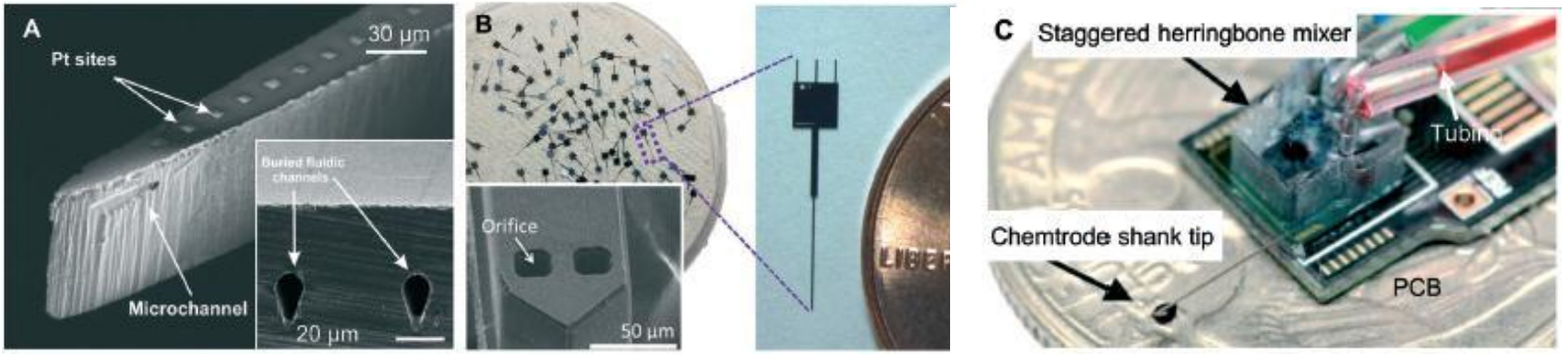
Small volume of fluids

Large volume of fluids

Integrated solutions (polymers)

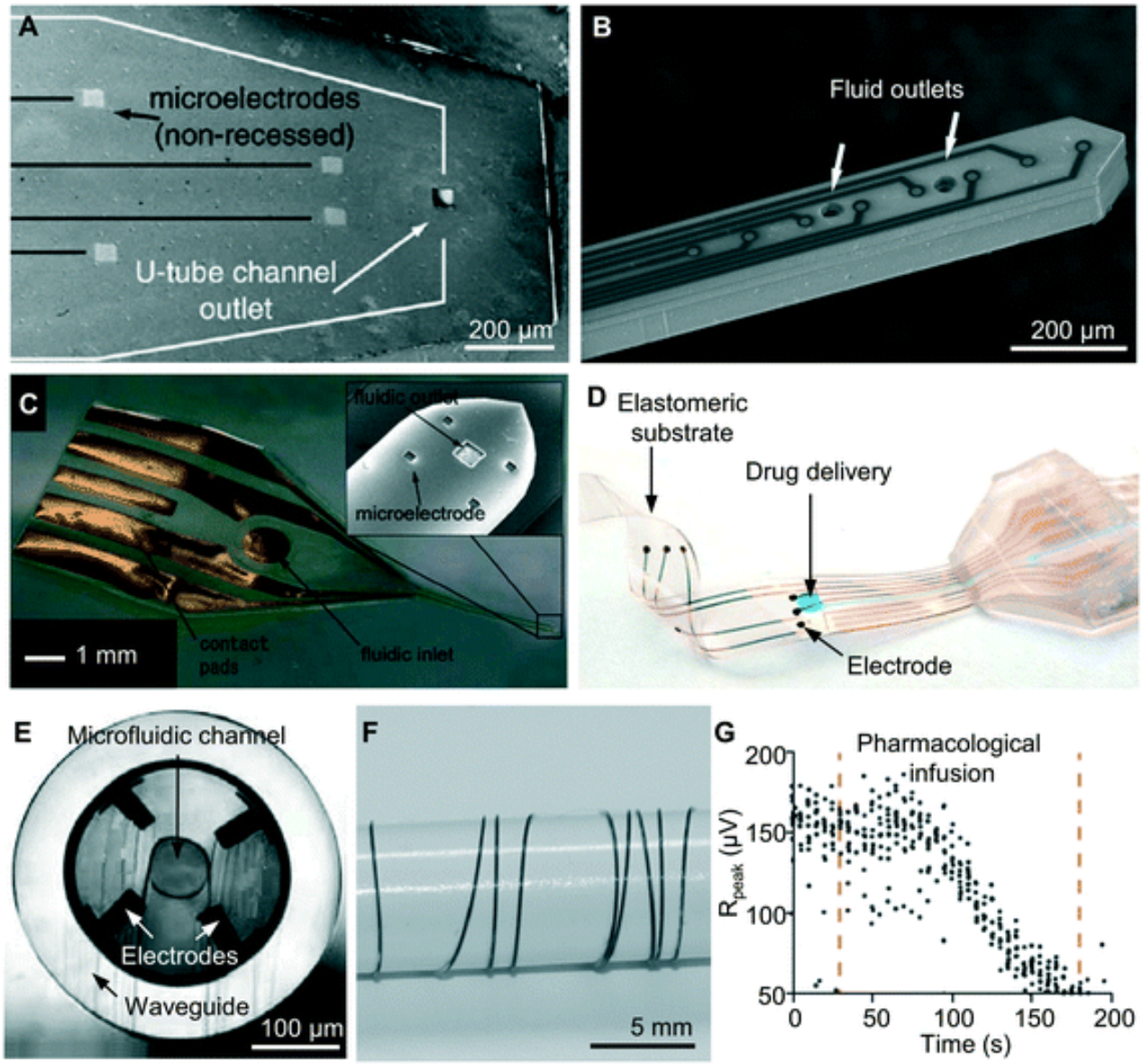


Silicon electrodes

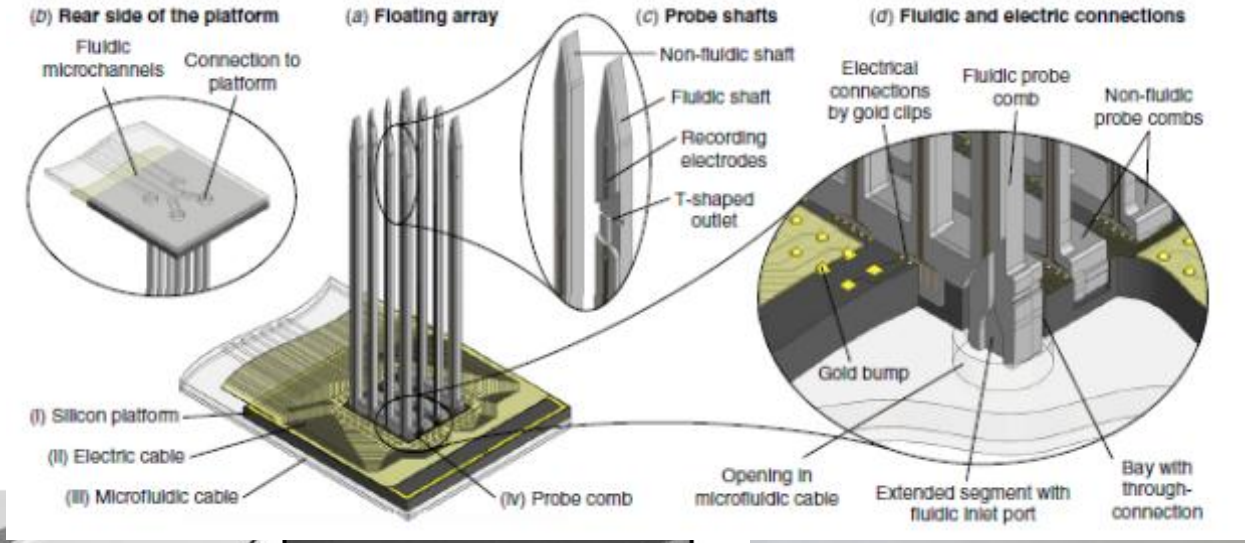


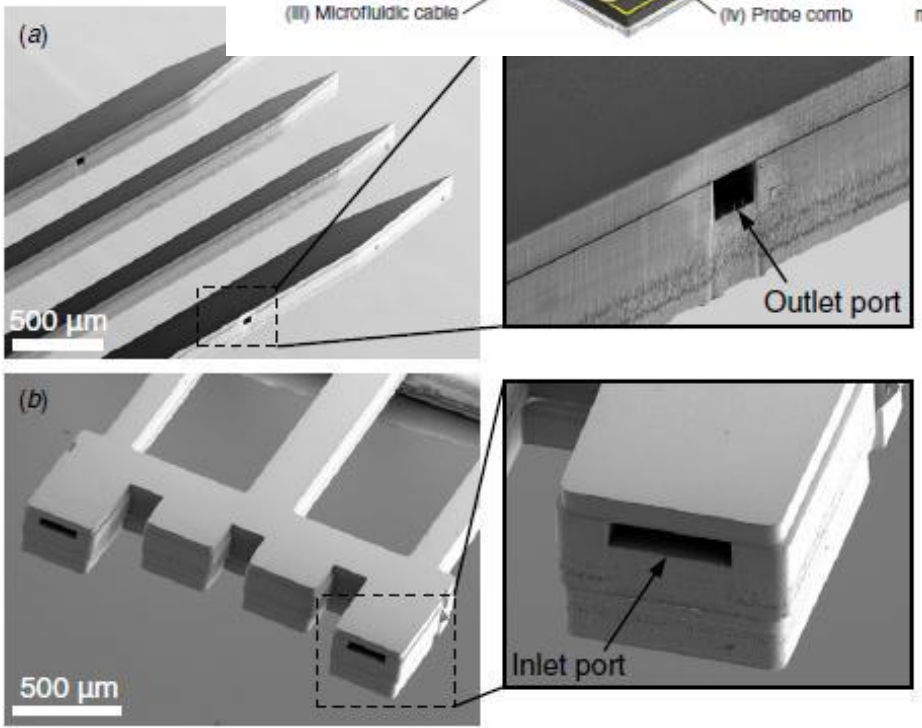
Sim, 2017

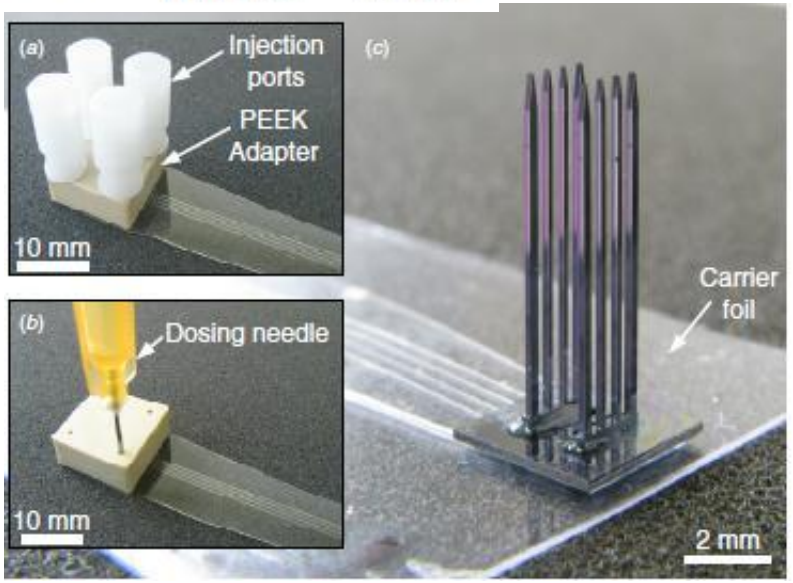
Flexible microfluidic probes on polymers



Out-of-plane Si structures with wafer bonding

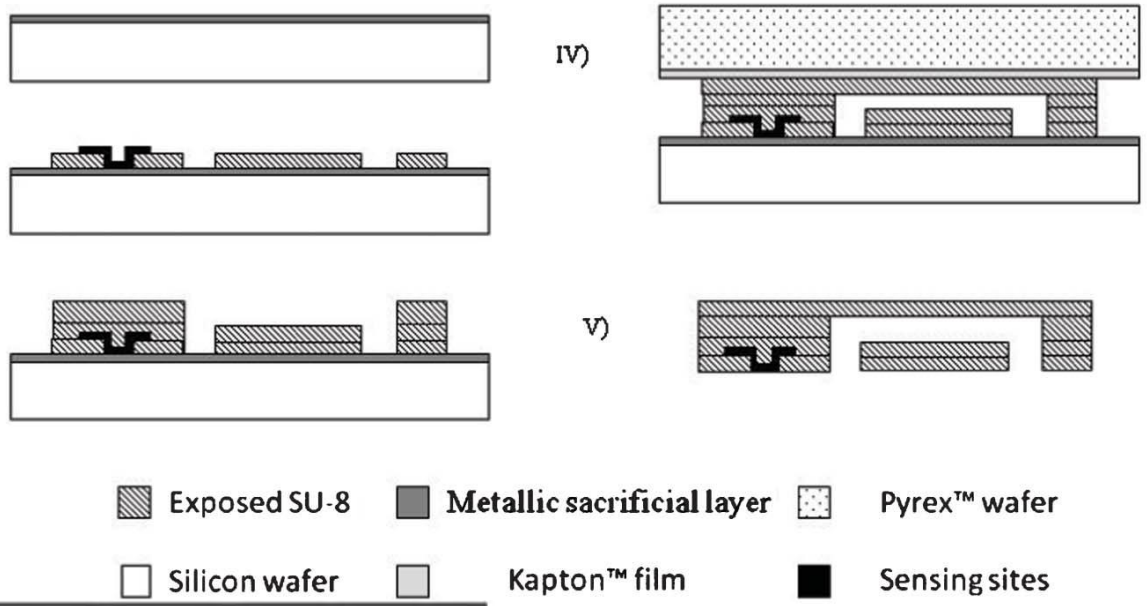


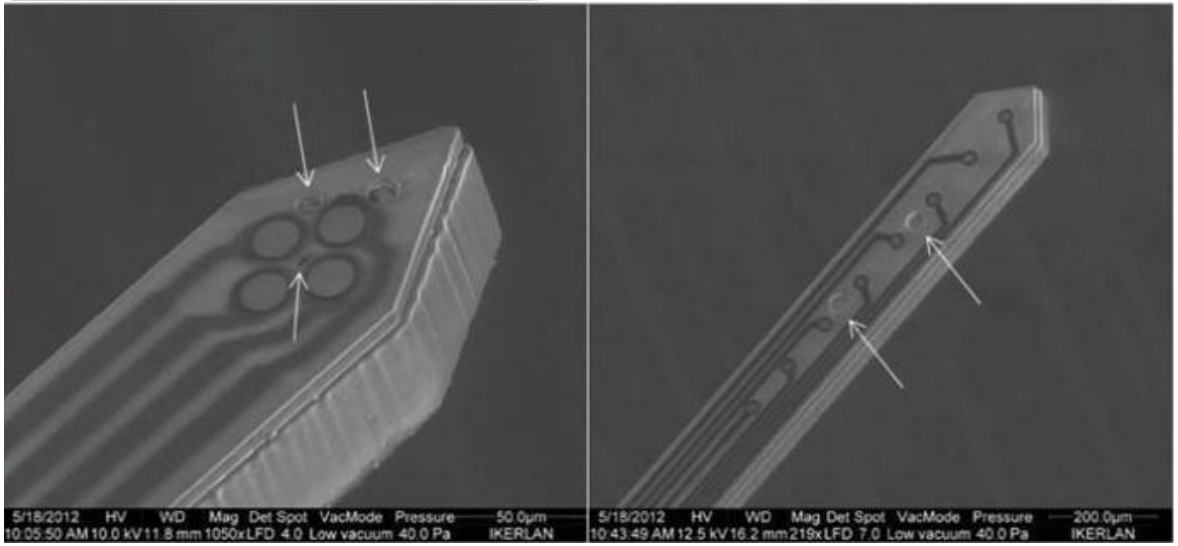


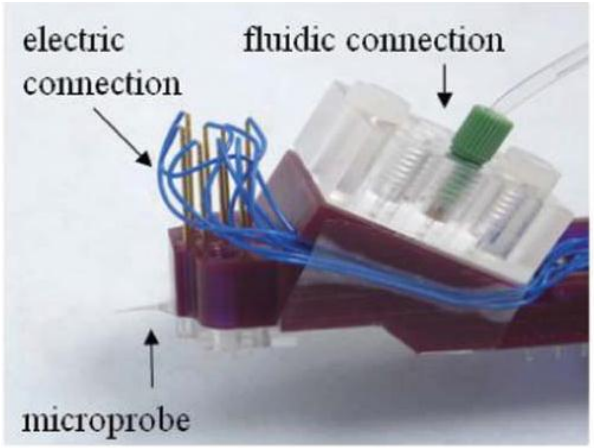


Spieth, 2011

Hollow microelectrodes in SU-8 double layer

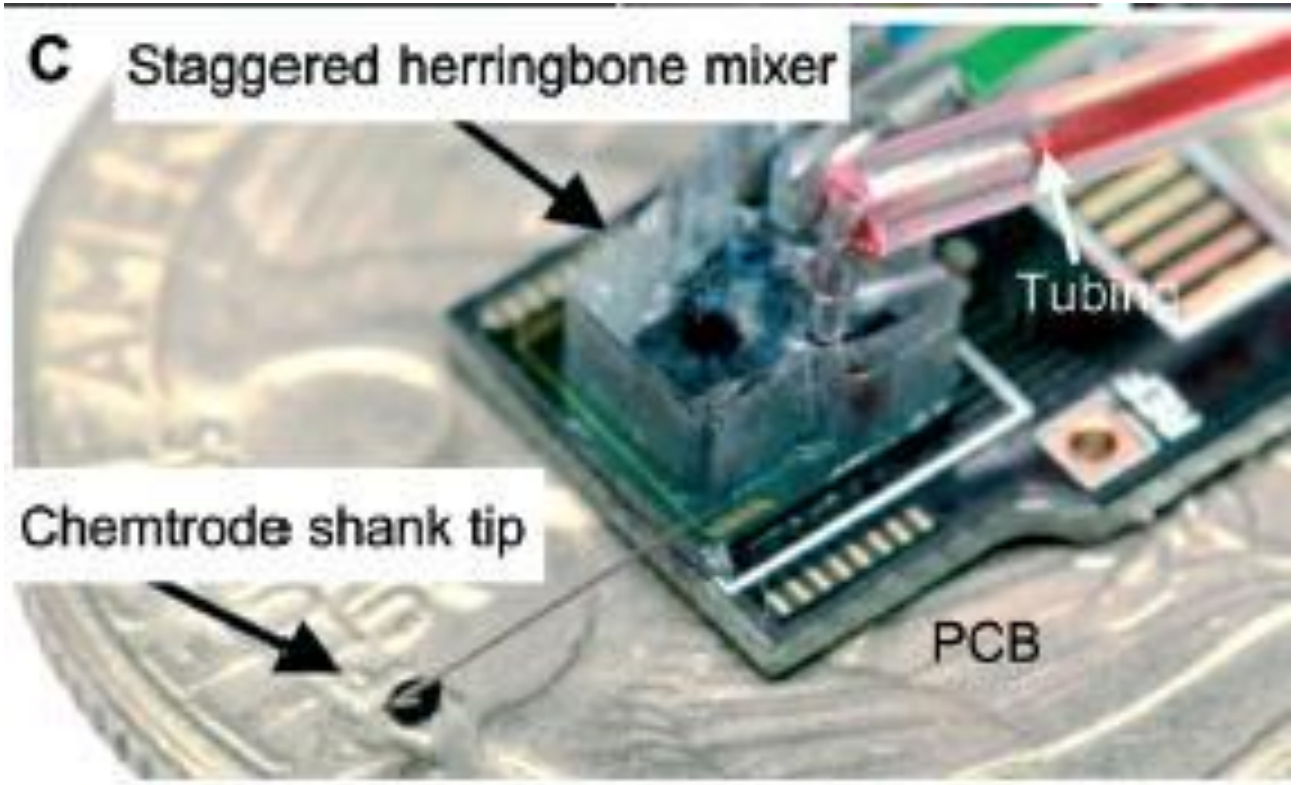






Altuna, 2013

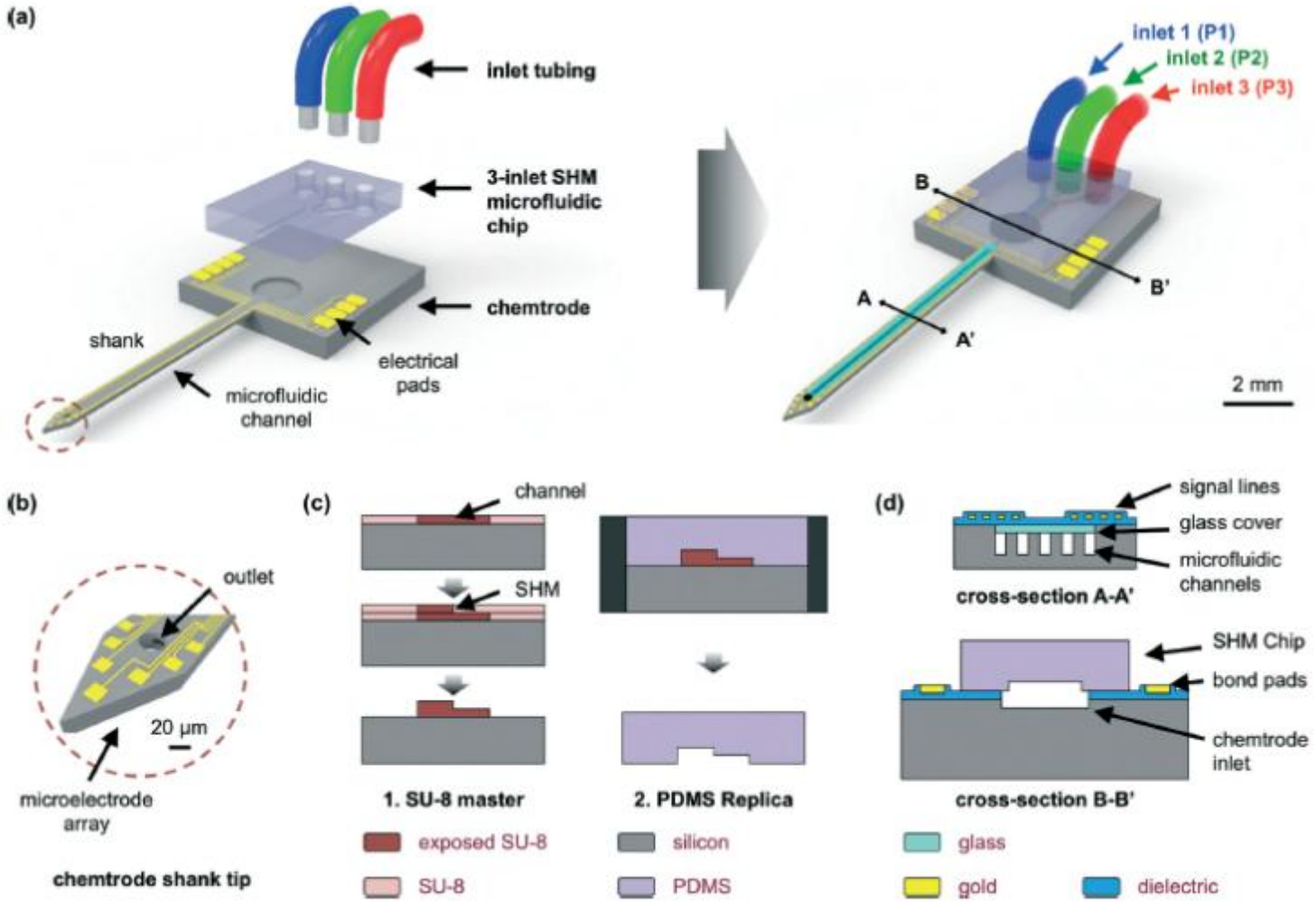
Miniaturization of complete systems



Shin, 2015

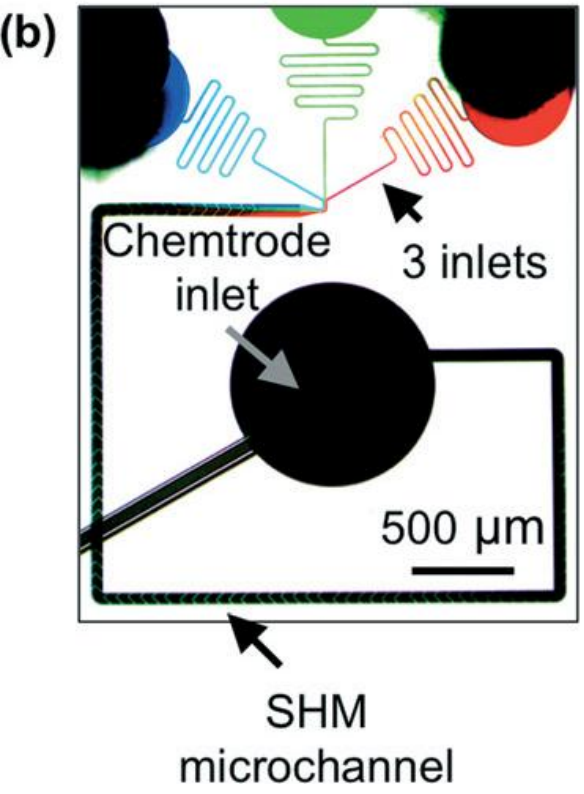
„Micro meets macro”: overall device dimensions are typically limited by external interfaces (tubing, connectors, pumps etc)

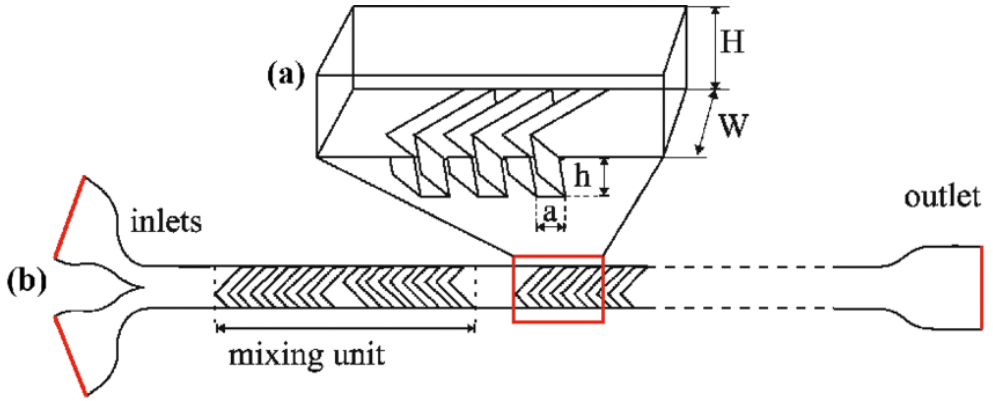
Integration of passive components (mixing)

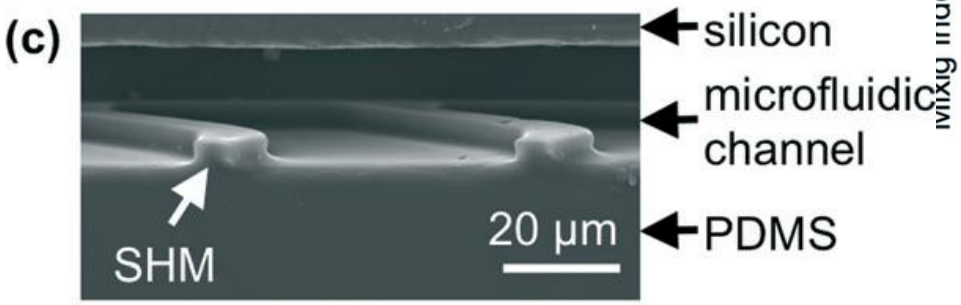


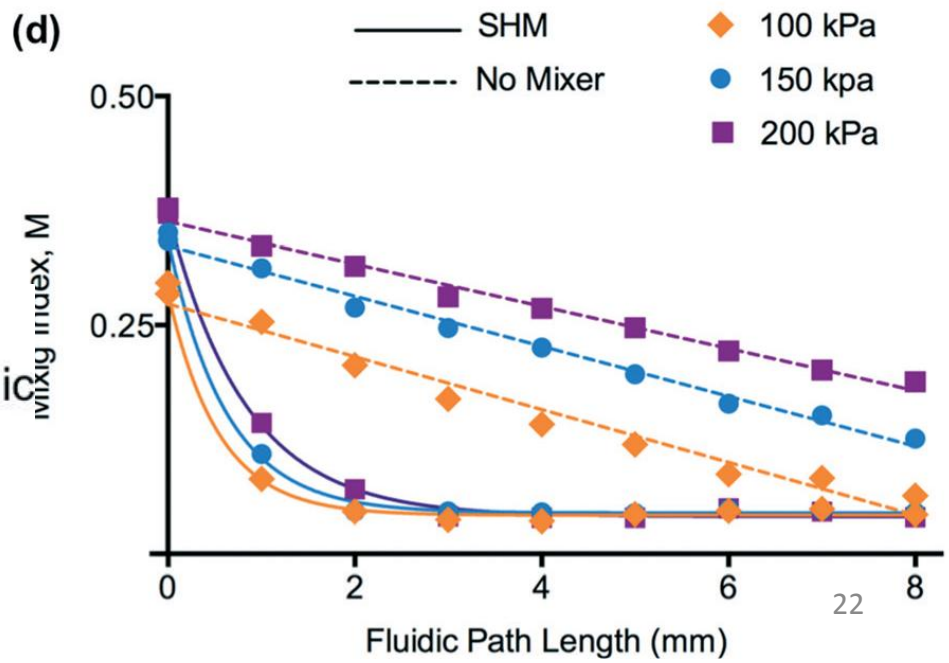
Shin, 2015

Integration of passive components (mixing)



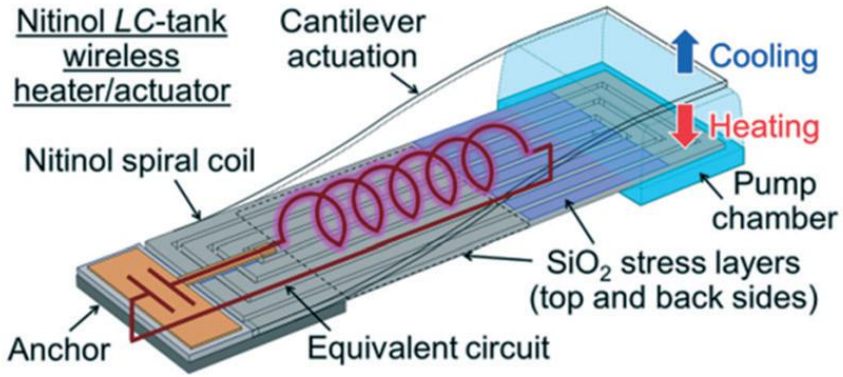




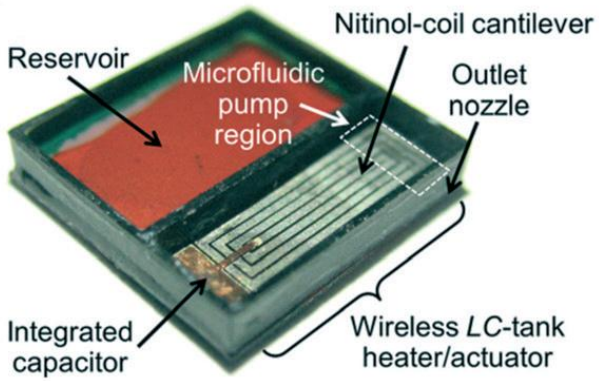


Compact pumping solutions (thermal actuation)

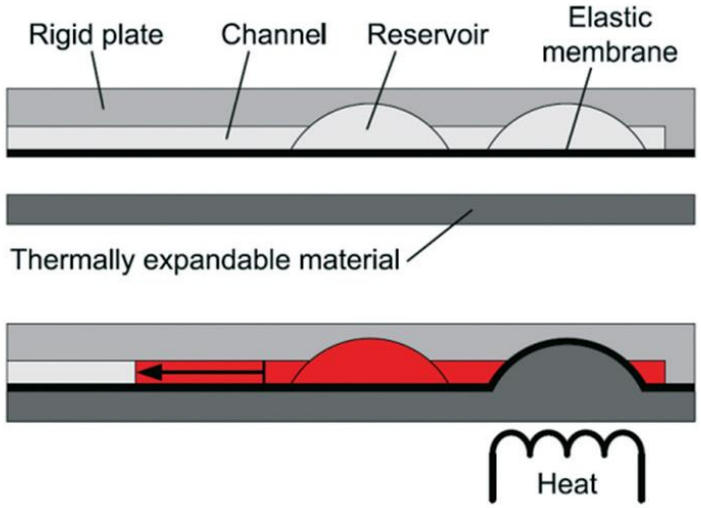
C-i



C-ii

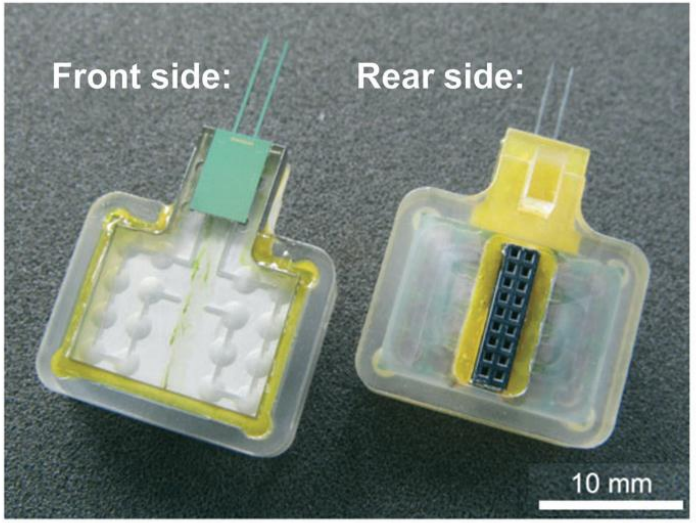


D-i



Fong, 2015

D-ii



Spieth, 2012

Requirements of pumping solutions

- Low power consumption
- Long term stability of drug release
- Fast response time
- Leak-free and clog free operation
- Small device footprint
- Multichannel actuation
  (administration of multiple drug components/reagents)

Multipurpose silicon drug delivery probes

Table 3
Realized silicon microelectrodes and concepts providing simultaneous recording and drug delivery functionalities.

Reference	Basic fabrication process	Design				Bench-top tests			Overall performance		
		Fluidic outlet/ shaft	Probe length (mm)	Configuration	Actuation	Fluidic	Electrical	Mechanical	Flow rate (μL/min)	Pressure (kPa)	Test on simultaneous functions
[68]	Wet etching	1	6	Single-shaft	Ext. spyringe pump	Yes	Yes	–	10–90	2.5–300	–
[69]	Wet etching + fused silica catheter	1	–	Single-shaft	Ext. syringe pump	Yes	–	–	0.5–1	–	Acute in vivo
[5]	Dry etching + wafer bonding	1–3	6–8	Dual-shaft	Ext. syringe pump	Yes	Yes	Yes	0.75–3.75	0.5–2.5	–
[55]	Dry etching + Parylene sealing	2	2.8	3D array	Ext. syringe pump	Yes	Yes	–	2–10	2.7–16	–
[33]	Dry etching + wafer bonding	1–2	8	3D array	Ext. syringe pump	Yes	–	–	0.75–3.75	0.5–2.5	–
[20]	Dry etching + wafer bonding	1	8	Dual-shaft	Thermal actuator	–	–	–	0.75–3.75	0.5–2.5	Chronic in vivo
[21]	Dry etching + poly-Si sealing	1–2	15–70	Single-shaft	Ext. syringe pump	Yes	Yes	–	0.1–1.6	40–200	Acute in vivo

Fekete, 2015, Sensors & Actuators B:Chemical

„The more complicated, the more likely users will be not able to use”

Multipurpose polymer drug delivery electrodes

Table 4
Flexible neural interfaces with integrated microfluidic functionality.

Authors	Interface type	Substrate materials	Channel dimensions (μm x μm)	Flow rate (μL/min)	Release rate (nmol/days)	In vivo animal model	In vitro study	Test duration	Extra features
[103]	penetrating	Polyimide	up to 20× 200	up to 1200	–	–	yes	–	electrical recording
[107]	penetrating	Parylene C	up to 10× 200	N/A	–	rat	–	acute	electrical recording
[100]	penetrating	Parylene C	11.4 × 50	0.09	–	–	yes	27 days	–
[10]	penetrating	Polyimide/SU-8	50 × 45	240	–	mouse	–	acute	electrical recording, waveguides for optogenetics
[44]	surface	Polyimide/PDMS	50 × 200	–	0.1–0.5	–	yes	–	electrical recording
[8]	penetrating	SU-8	40 × 20	40	–	rat	–	acute	electrical recording
[20]	surface	PDMS	50 × 100	120–360	–	rat/mouse	–	6 weeks	electrical stimulation
[101]	surface	PDMS/Parylene/PET	10 × 10	5.2	–	mouse	–	6 weeks	wireless, μLEDs for optogenetics

Fekete, 2017, Sensors & Actuators B:Chemical

„Thickness requirements limits the range of materials”

Polymer coatings for drug delivery

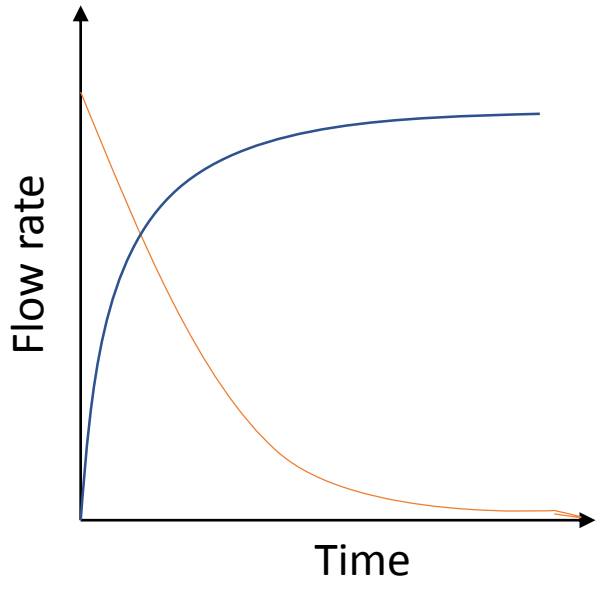
- Solvent activated

  (swelling- or osmotically-controlled devices)
- Chemically controlled

  (biodegradable polymers)
- Externally-triggered systems

  (Temperature, pH)
- *Electrically activated*

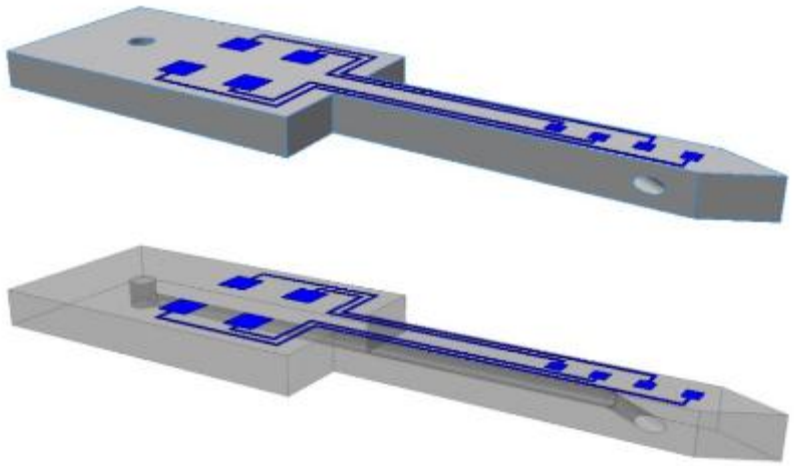
  (conductive polymers)

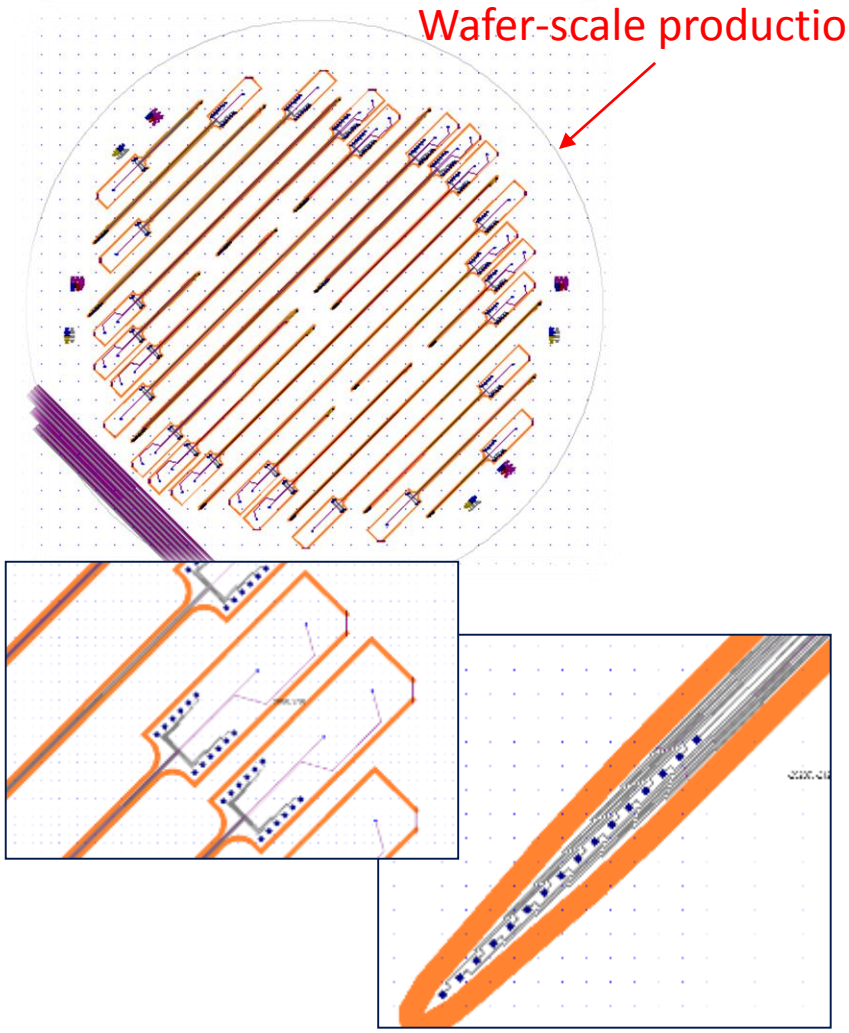


Case study 1

Fabrication & characterization of silicon microelectrode for CED

Concept & design
How to integrated drug delivery channels?





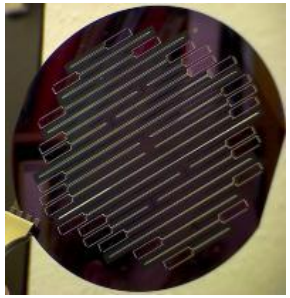
Probe designs	MFA	DBS Kit	Neuro Nexus	Neuro Probe
Length [mm]	70	> 100	70	8
Diameter [µm]	200 400	1270	Appx 150	150-250
Nr of the Pt electrical sites	4 - 16	4	32	4
Fluidic channel	+	-	-	+

Fabrication (Monolithic integration of fluidic channel in neural probes)

I. Fluidic channel

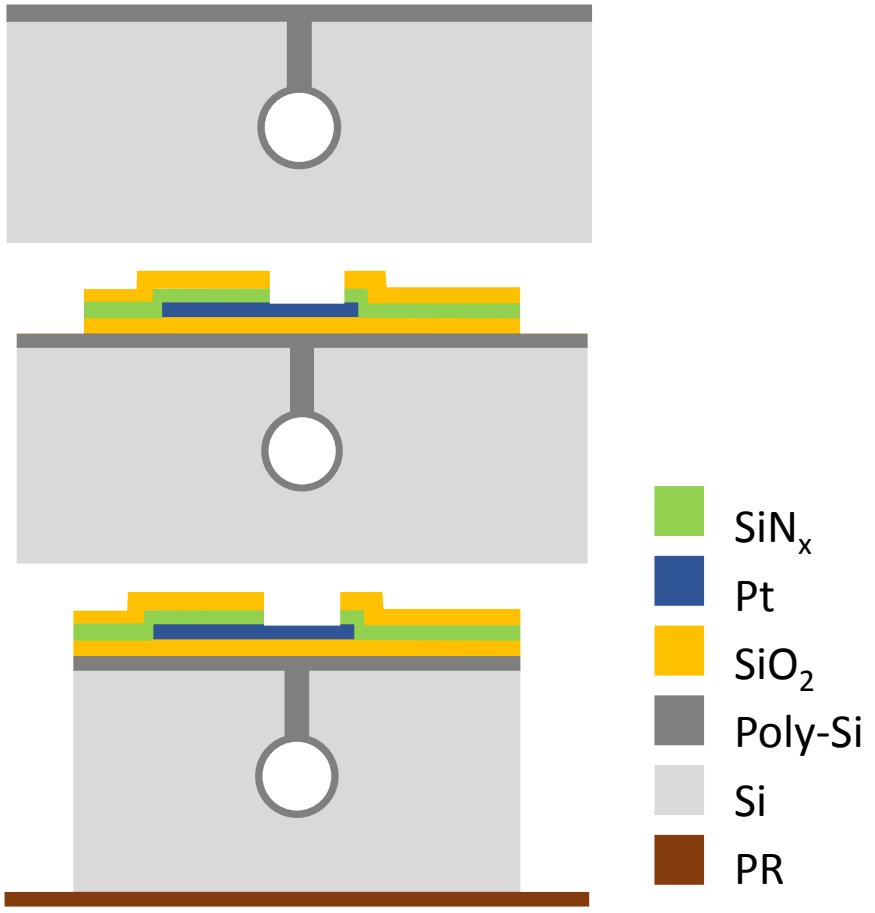
II. Electrical wiring

III. Probe body

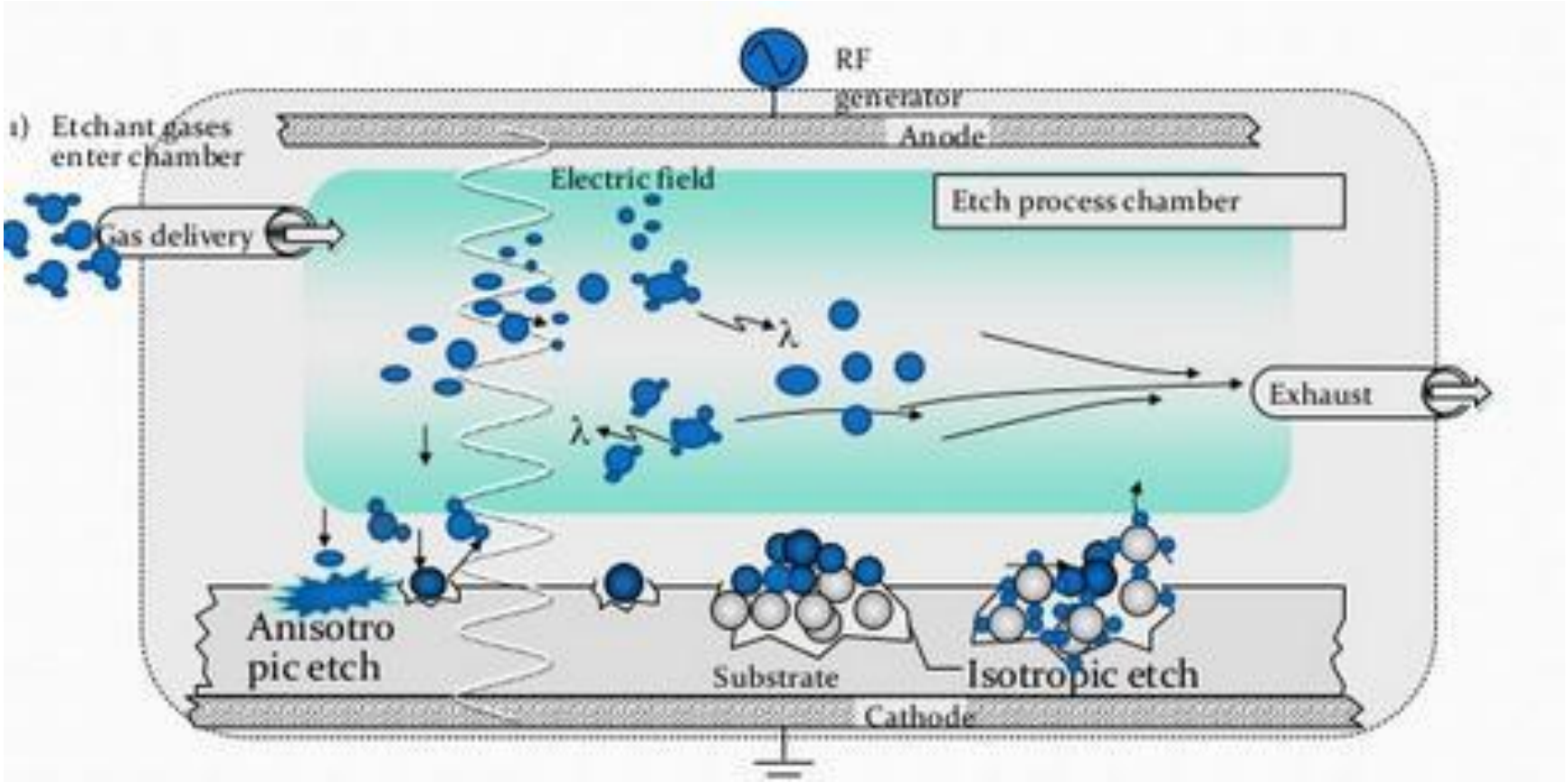


Process steps included:

- *4 photolithography steps*
- *Lift-off (platinum wiring & sites)*
- *Low-pressure chemical vapour deposition of dielectrics*
- *Deep reactive ion etching of channel & device contour*



Dry etching - fundamentals



Why dry etching?

Dry etching advantages

- Eliminates handling of dangerous acids and solvents
- Uses small amounts of chemicals
- Isotropic or anisotropic/vertical etch profiles
- Directional etching without using the crystal orientation of Si
- Faithful pattern transfer into underlying layers (little feature size loss)
- High resolution and cleanliness
- Less undercutting
- Better process control

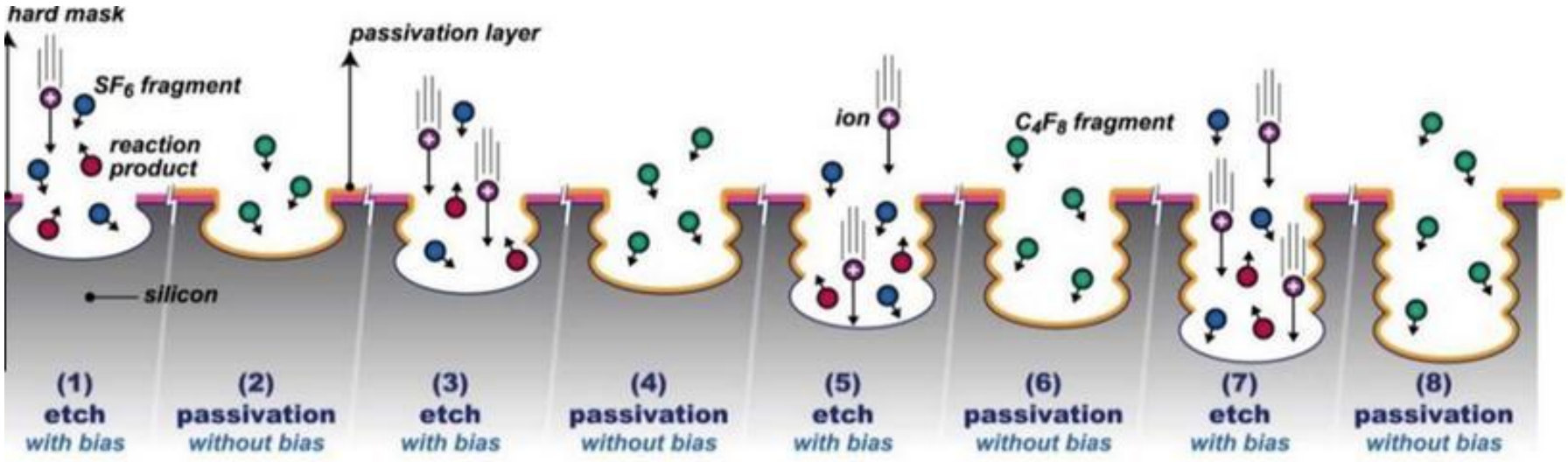
Dry etching disadvantages:

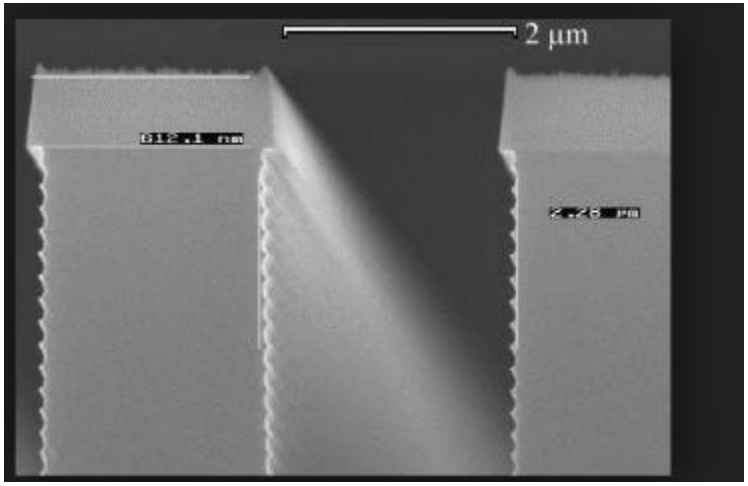
- Some gases are quite toxic and corrosive.
- Re-deposition of non-volatile compound on wafers.
- Expensive equipment ($200-500K for R&D, few million for industrial tools).

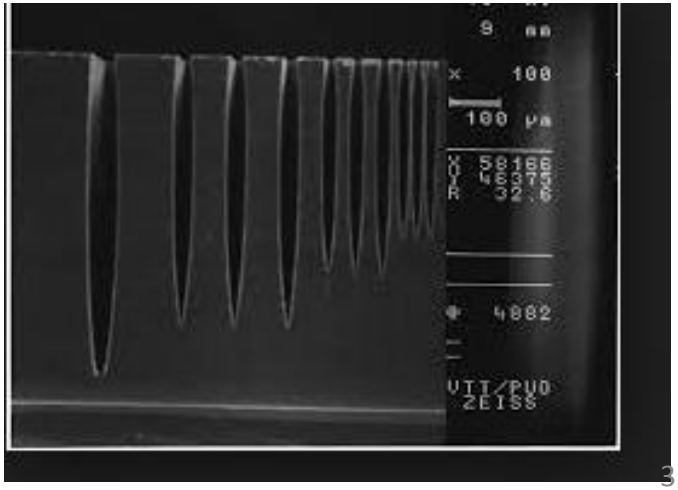
Types of dry etching:

- Non-plasma based - uses spontaneous reaction of appropriate reactive gas mixture.
- Plasma based - uses radio frequency (RF) power to drive chemical reaction.

Bosch process (used to define channel depth and device contour)





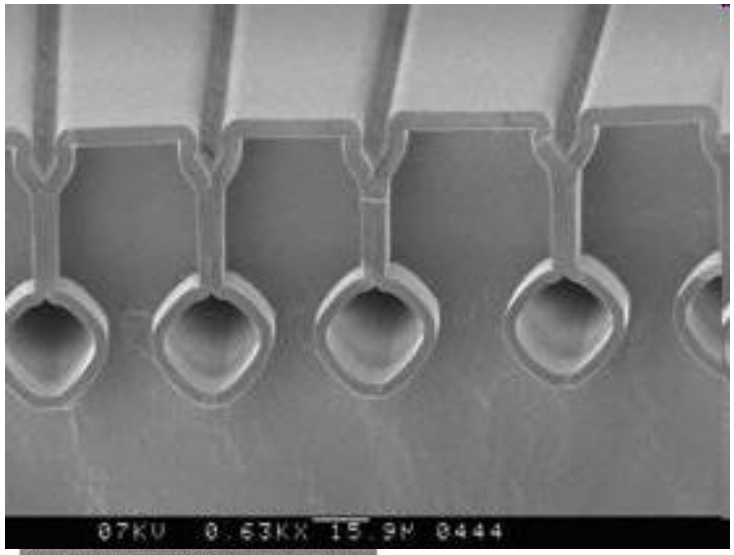


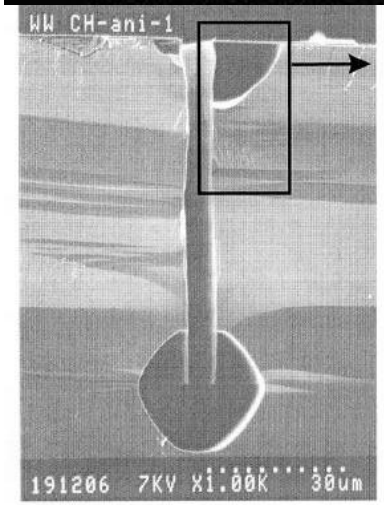
Versatility of DRIE process

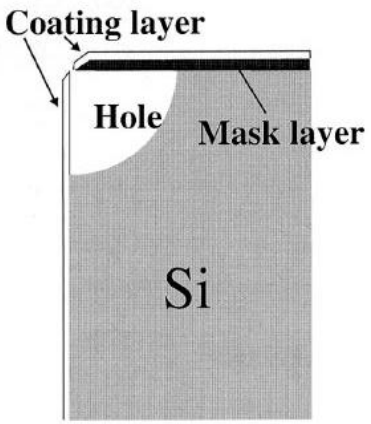
Two materials, four etching procedure, one machine

	SiO_2 etch	Deep Si etch—Bosch process (passivation/etch)	Highly anisotropic SiO_2 etch	Isotropic Si etch
Process step	Step 3	Step 4	Step 7	Step 8
Pressure (mTorr)	8	30/40	30	40
ICP power (W)	2,000	–/750	–	750
LF power (350 kHz)	–	1/8 W	–	8 W
RF power (W)	100	–	200	
C_4F_8 flow rate (sccm)	36	100/–	–	
O_2 flow rate (sccm)	4	–	–	
SF_6 flow rate (sccm)	–	–/150	–	150
Ar flow rate (sccm)	–	–	20	
CHF_3 flow rate (sccm)	–	–	30	
Time	–	4/9 s (cycle time)	5 min	5 min

Original process flow

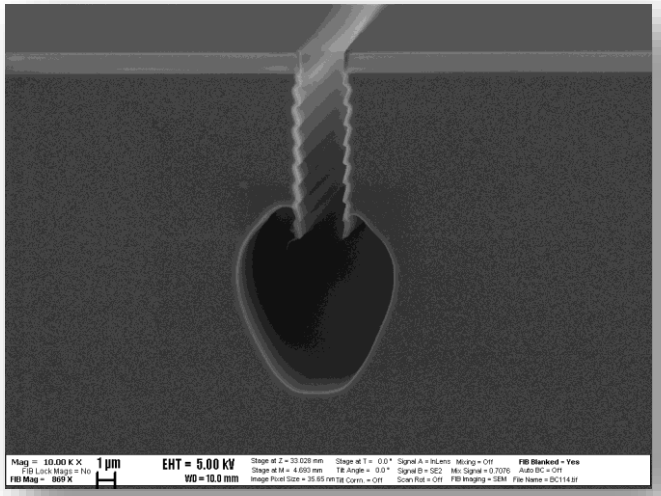


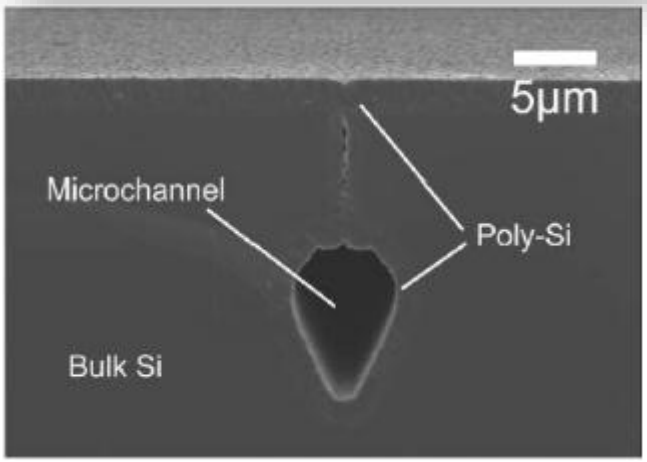




De Boer et al, 2000

Improved process flow



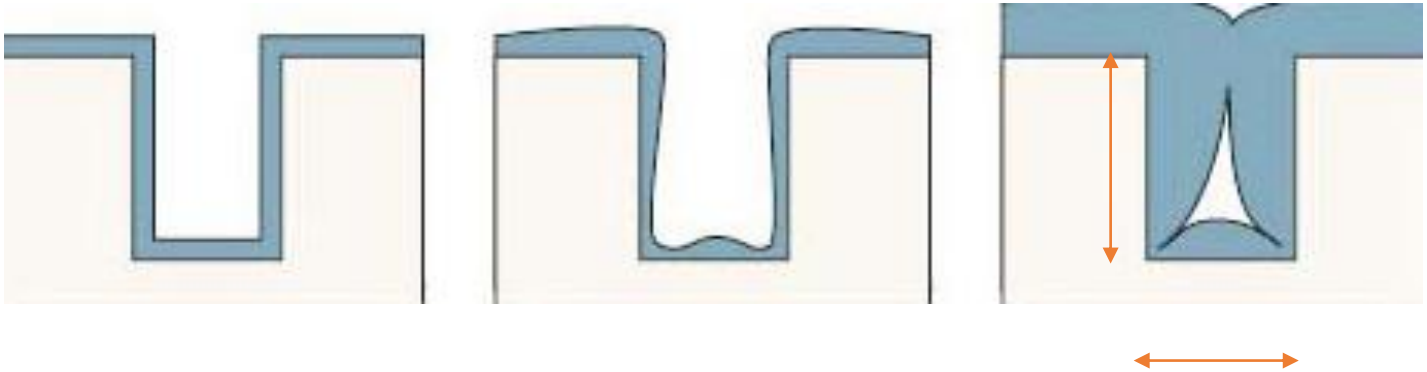


Fekete et al, 2012

Improved version: probe surface can be exploited to add further functional components

Step coverage

- Tailors the quality of forming buried/embedded components in the substrate

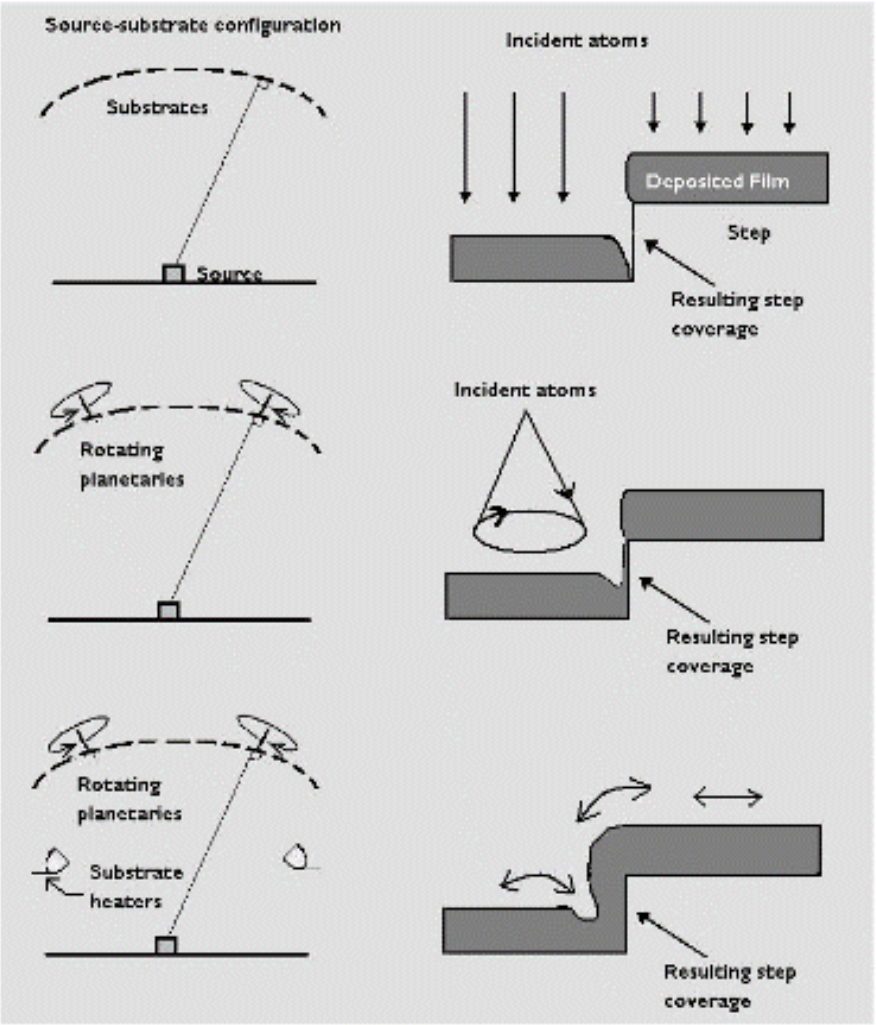


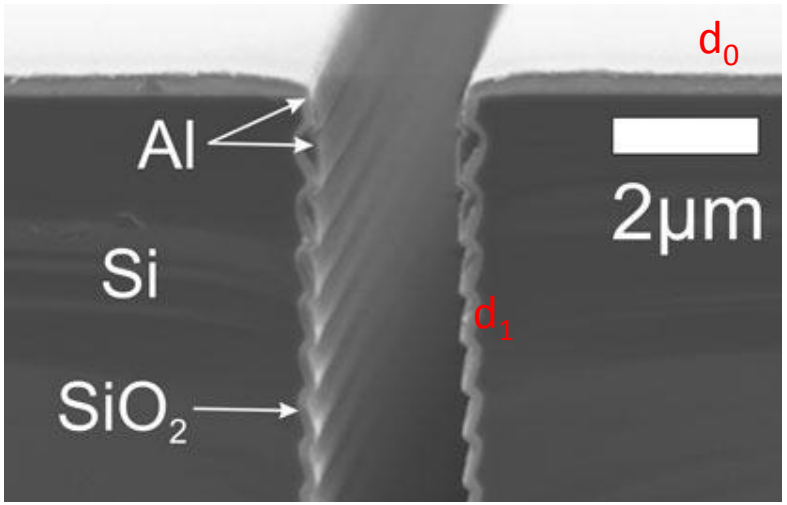
Uniform Non-uniform Aspect ratio = x / y

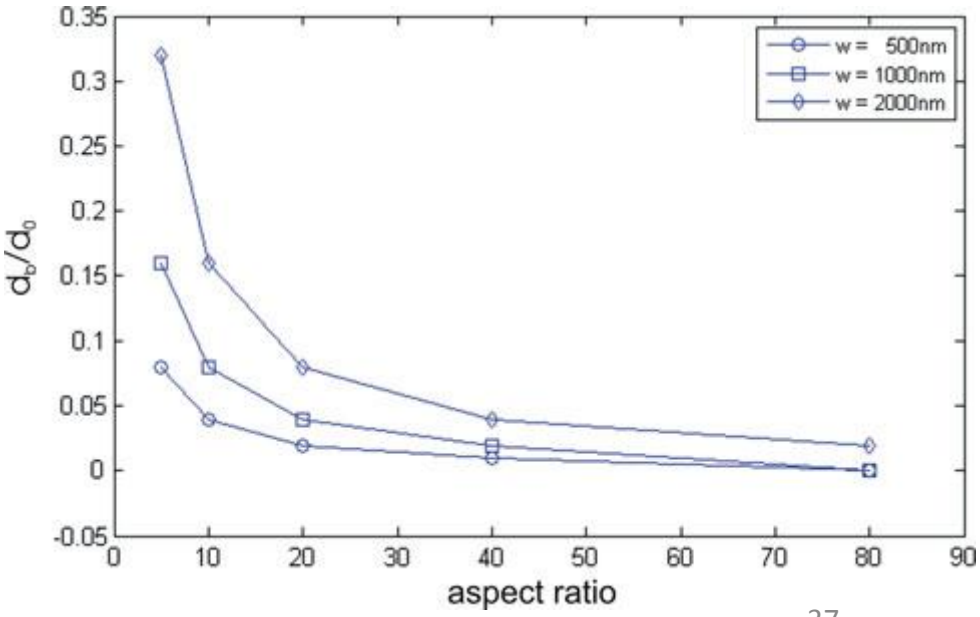
Uniform: typically CVD; Non-uniform: typically PVD

- Chemical vapour deposition(CVD): PECVD, LPCVD, ALD
- Physical vapour deposition (PVD): evaporation, sputtering

Modelling of step coverage (evaporation)

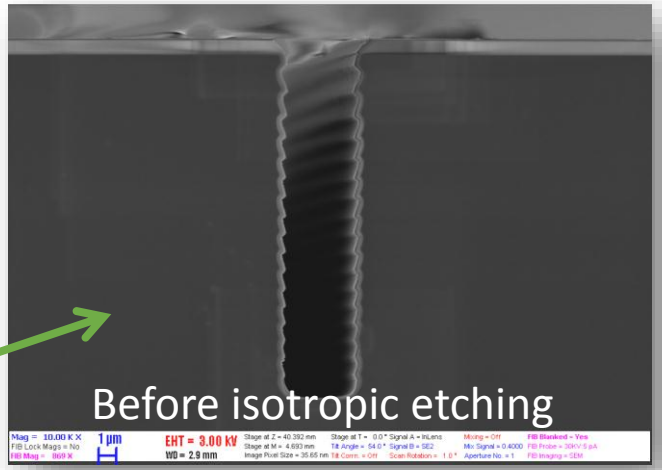


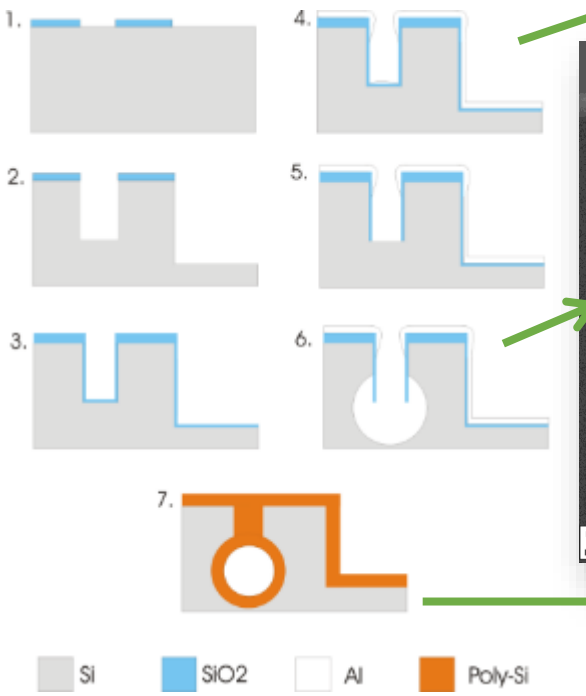


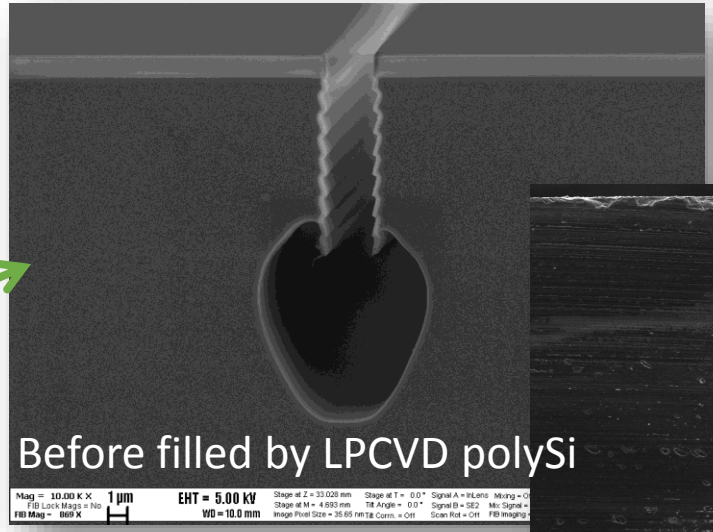


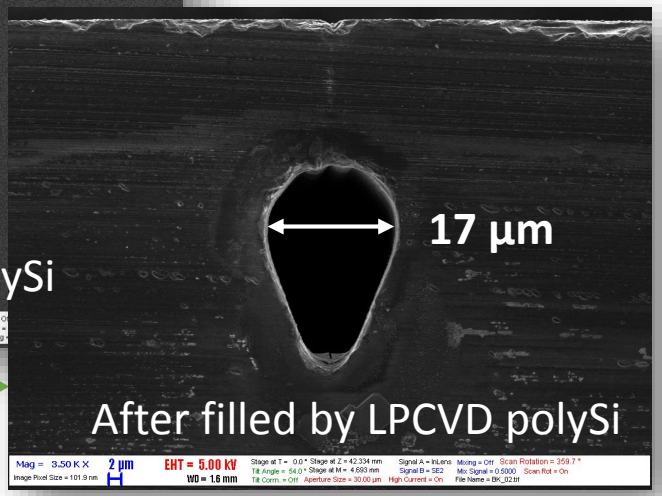
Fabrication – Fluidic channel

Poly-crystalline silicon (polySi) is deposited inLPCVD chamber to fill up the trench







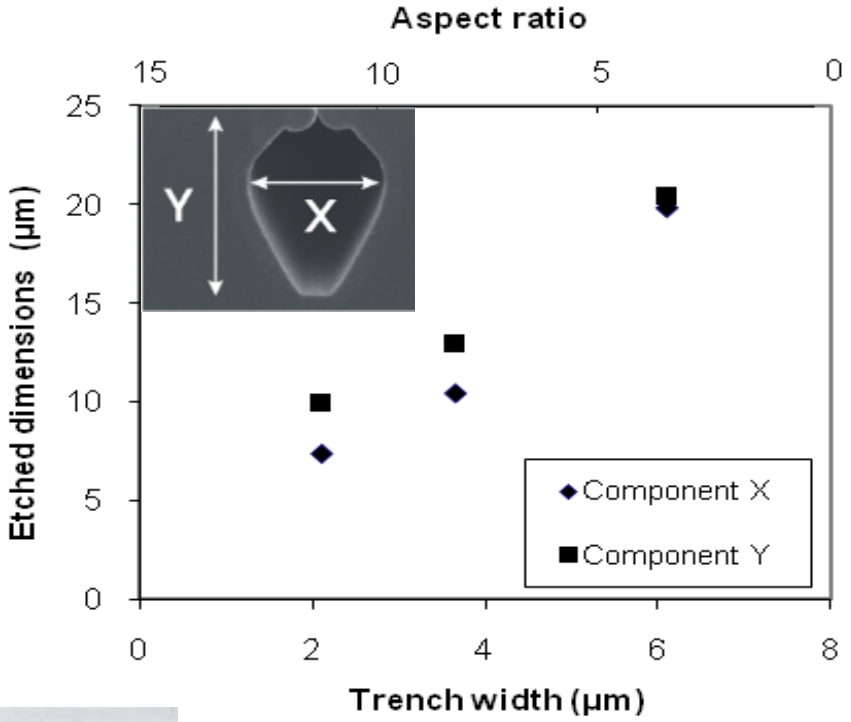


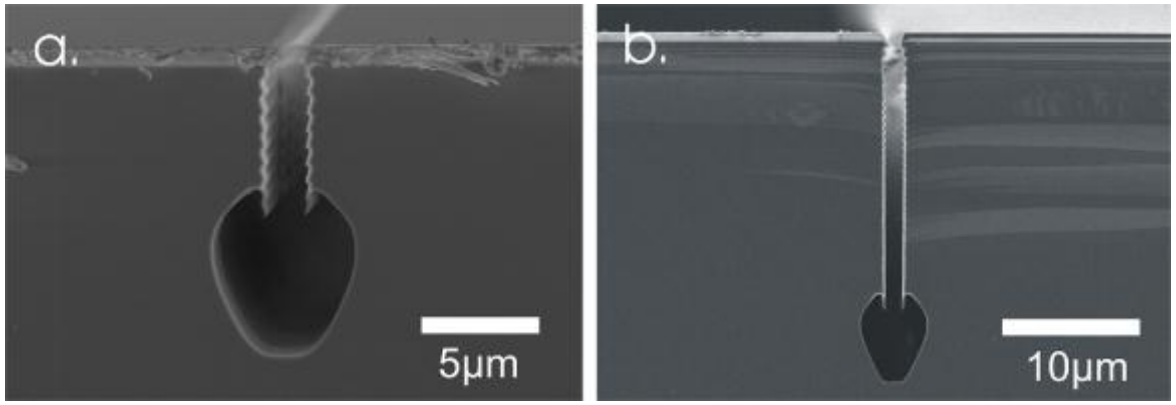
Fekete et al., 2012

Effect of dry etching fabrication parameters on channel location and profile

Investigated relationships:

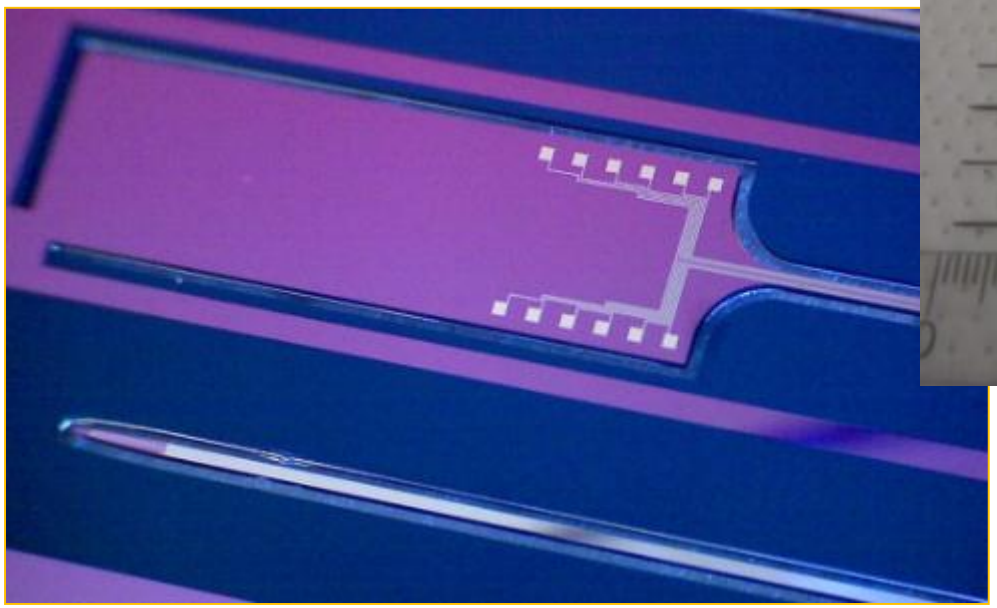
- Trench width vs. Deep Si etching
- Aspect ratio vs Si etch in SF_6 plasma
- Trench width vs profile assymetry

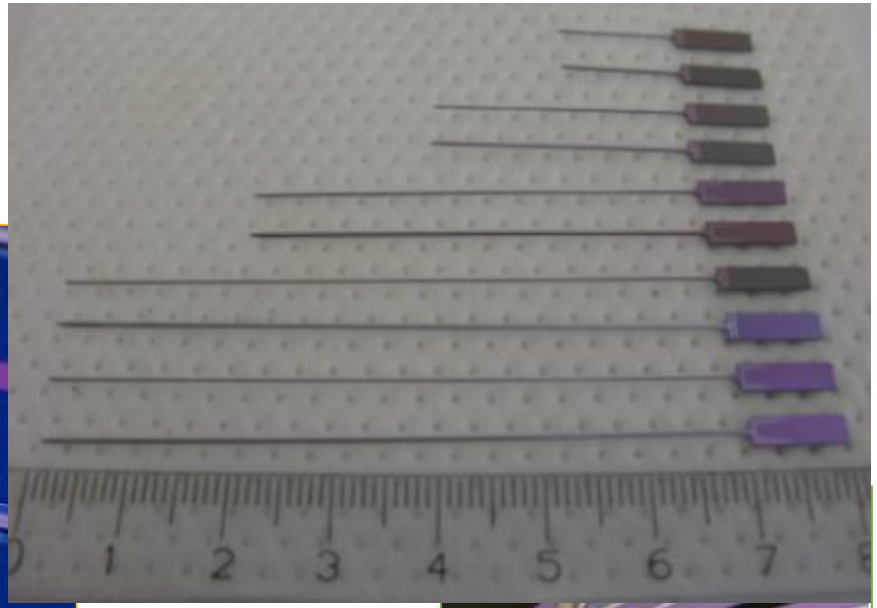


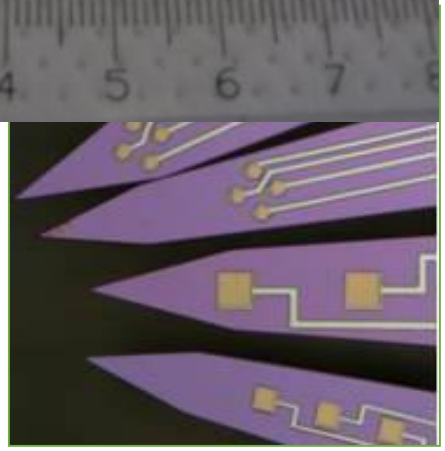


Fekete et al., 2013

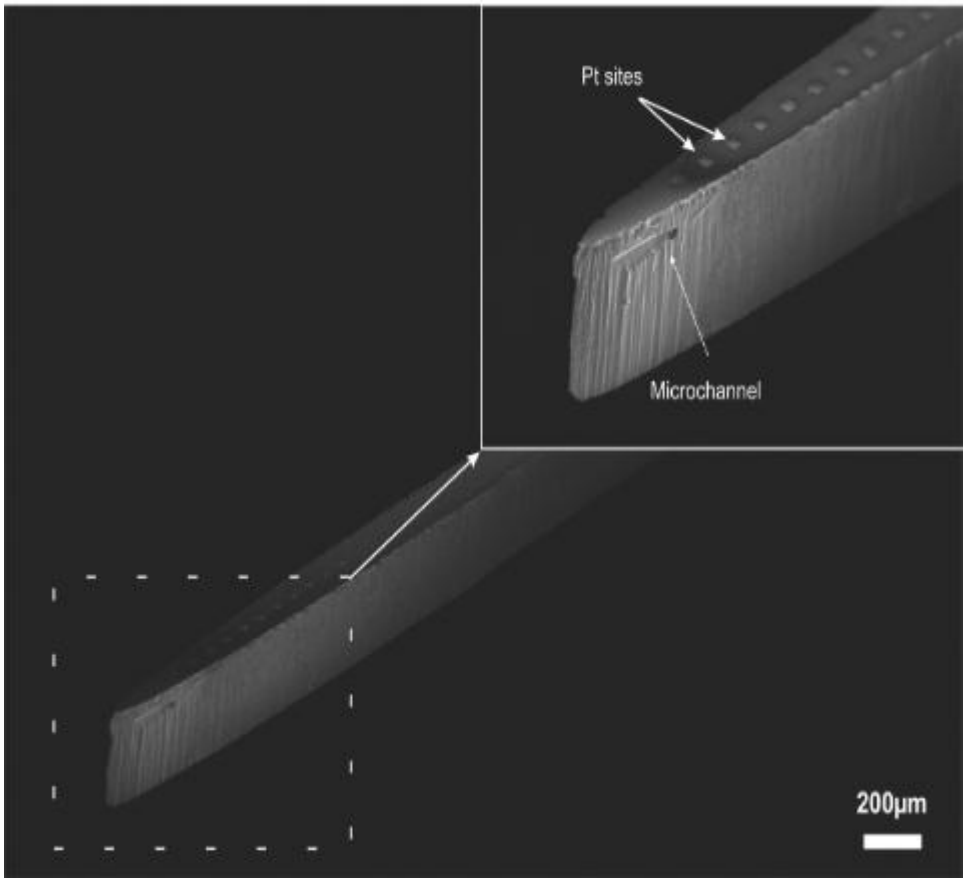
Chips ready for packaging

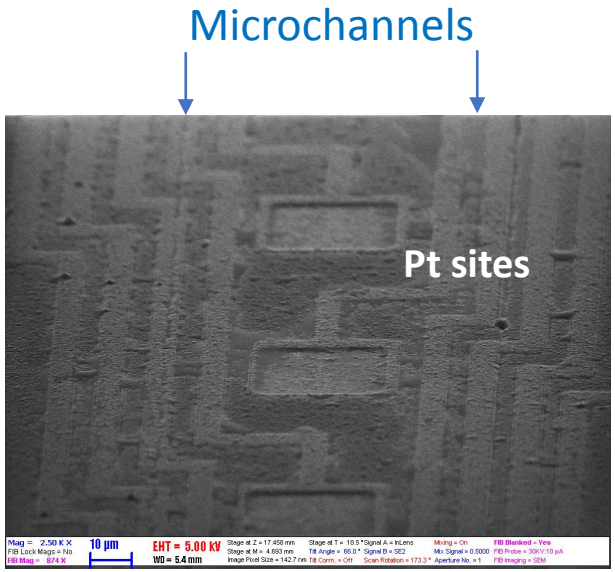


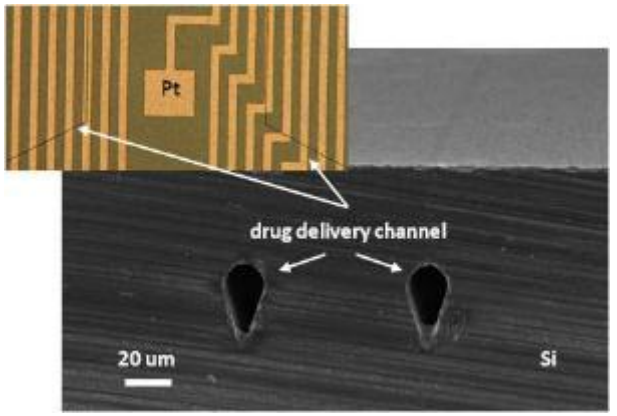




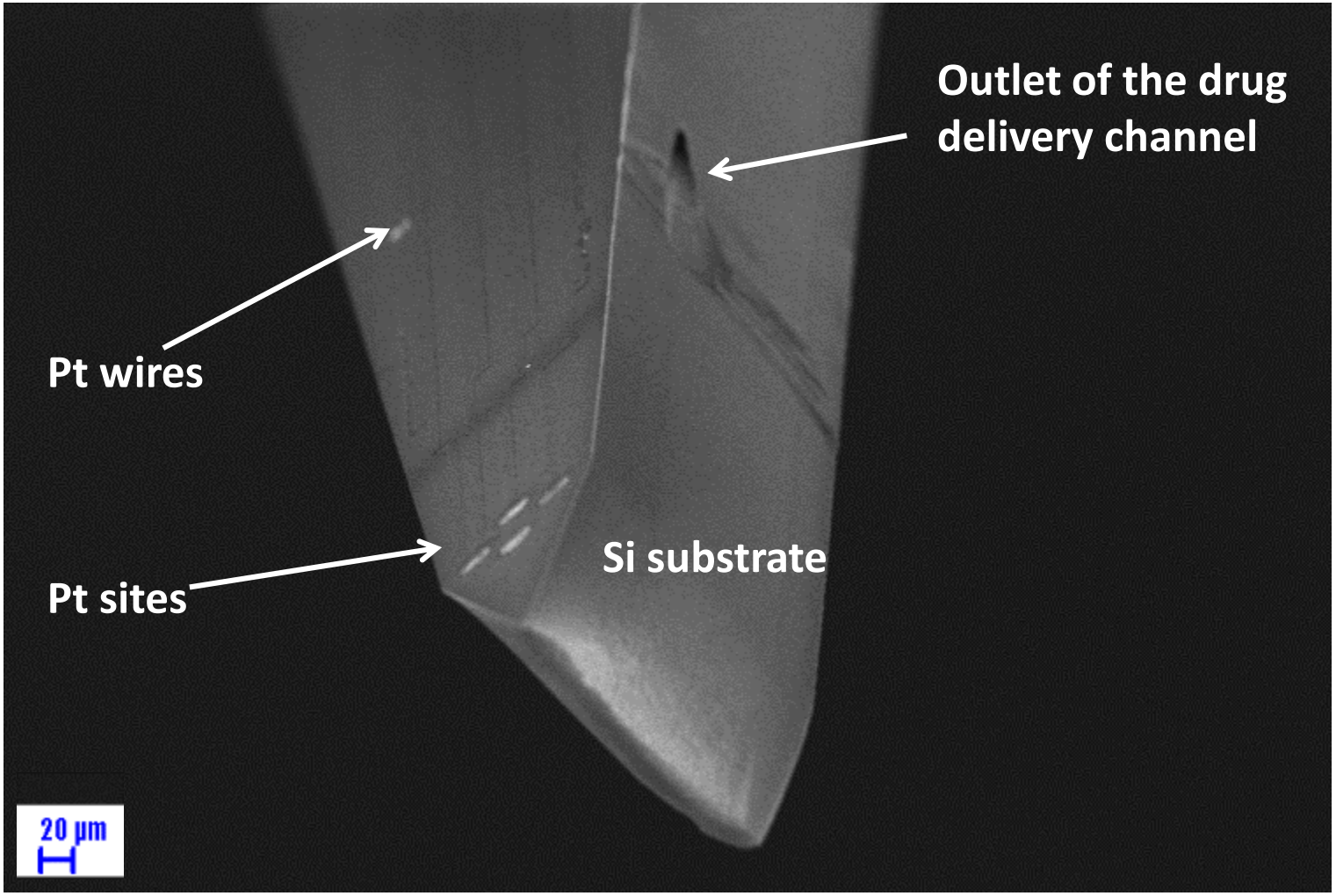
Optical inspections

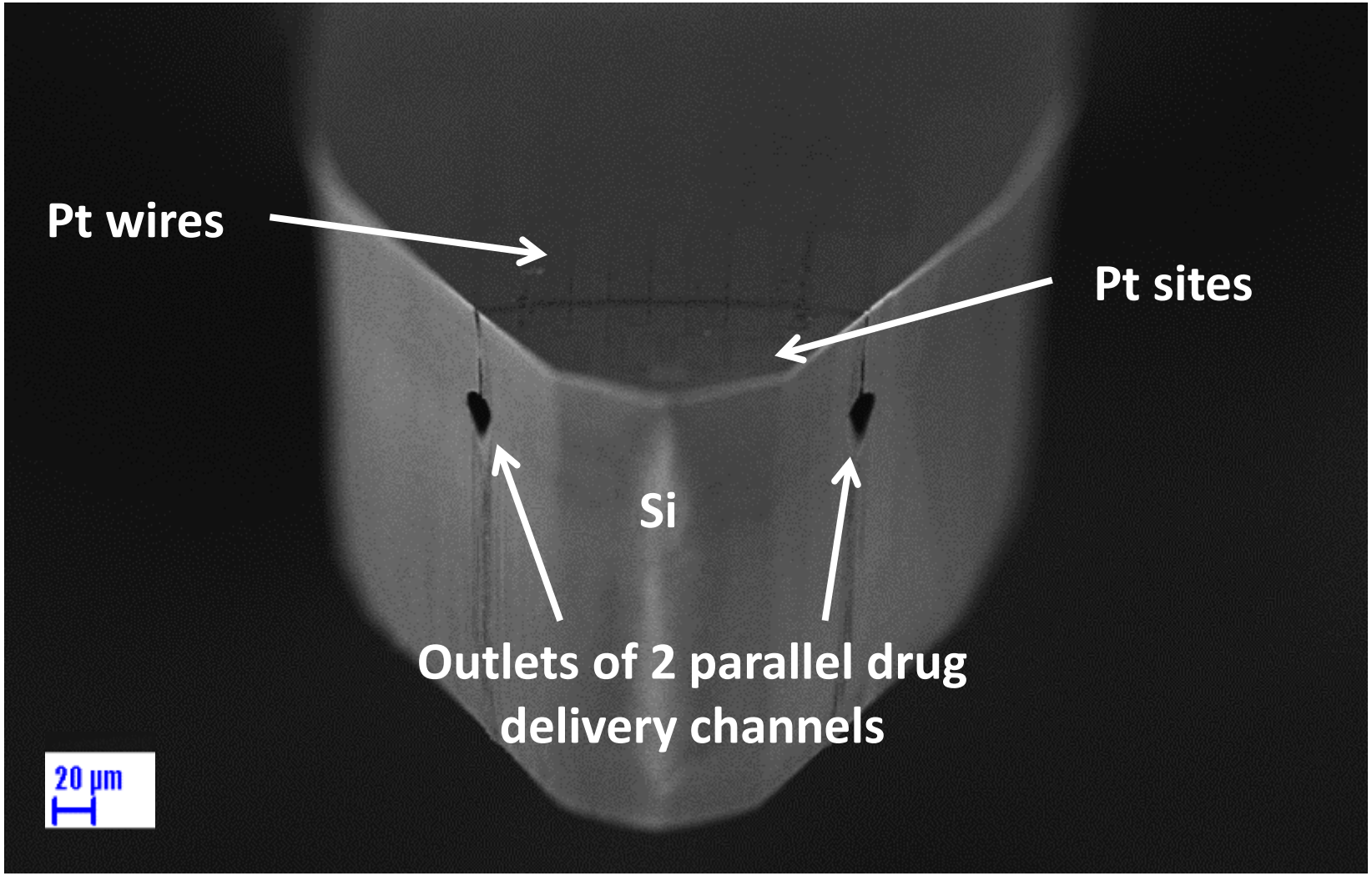






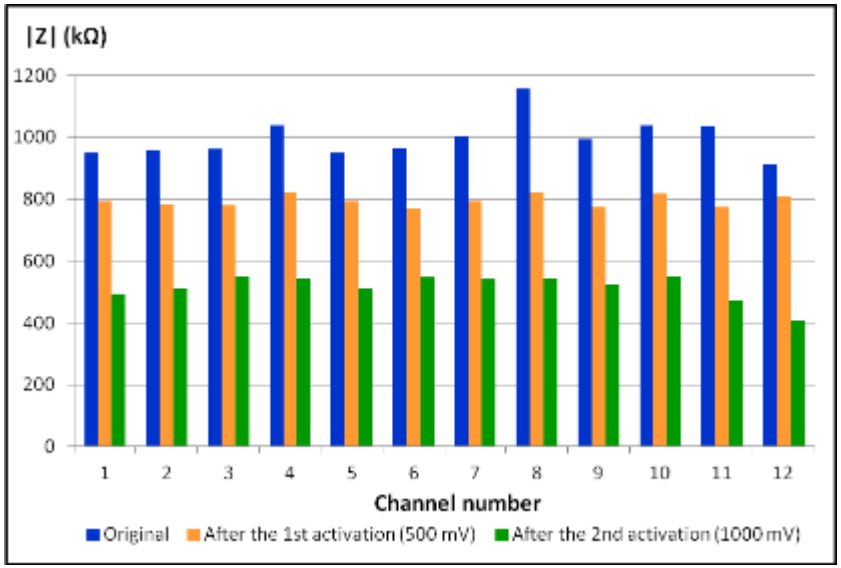
Pongrácz, 2013


Outlet of the drug delivery channel
Pt wires
Pt sites
Si substrate
20 µm

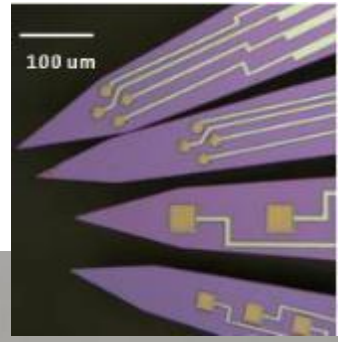

Pt wires
Pt sites
Si
Outlets of 2 parallel drug delivery channels
20 µm

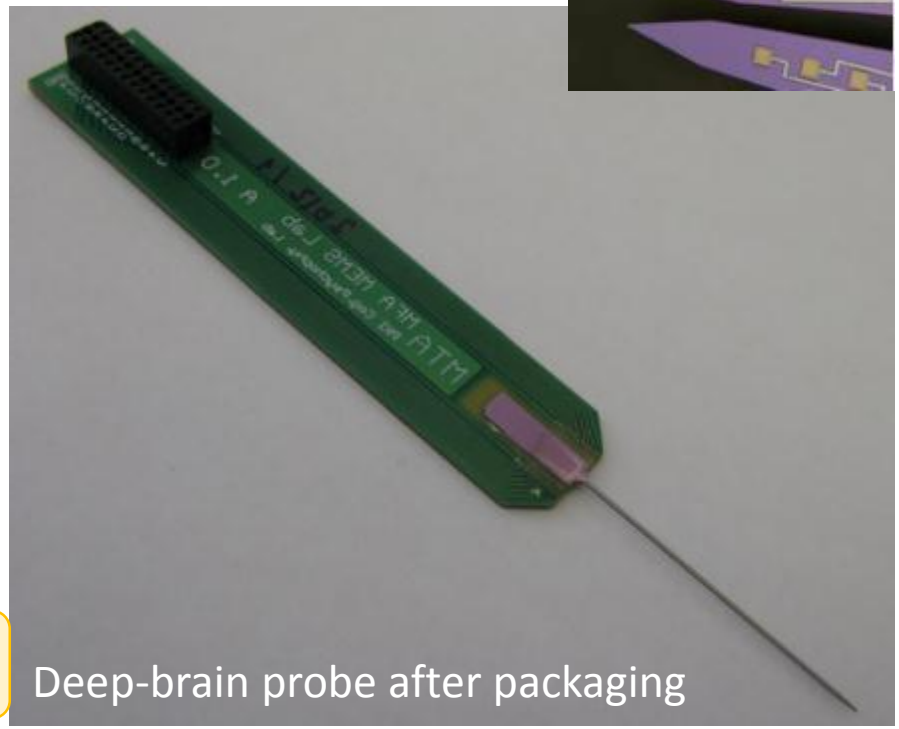
Characterization – Electrical properties

Results of impedance spectroscopy



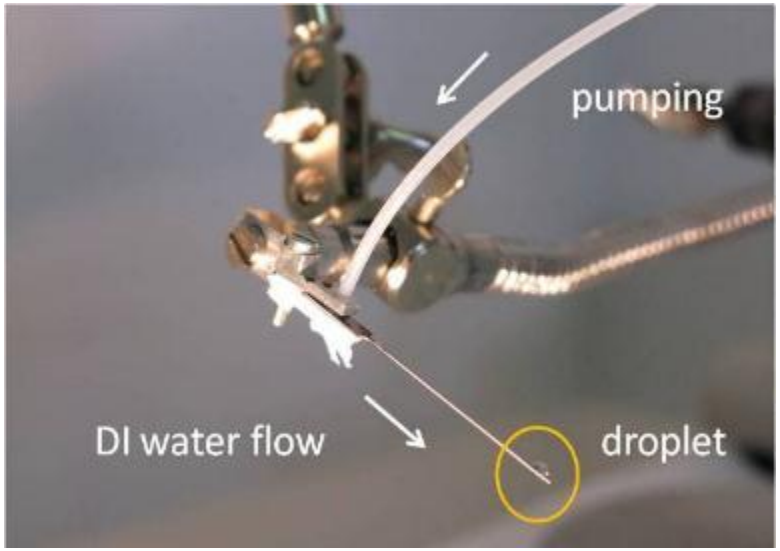
Final impedance values at 1 kHz: 517 ± 43 kΩ.



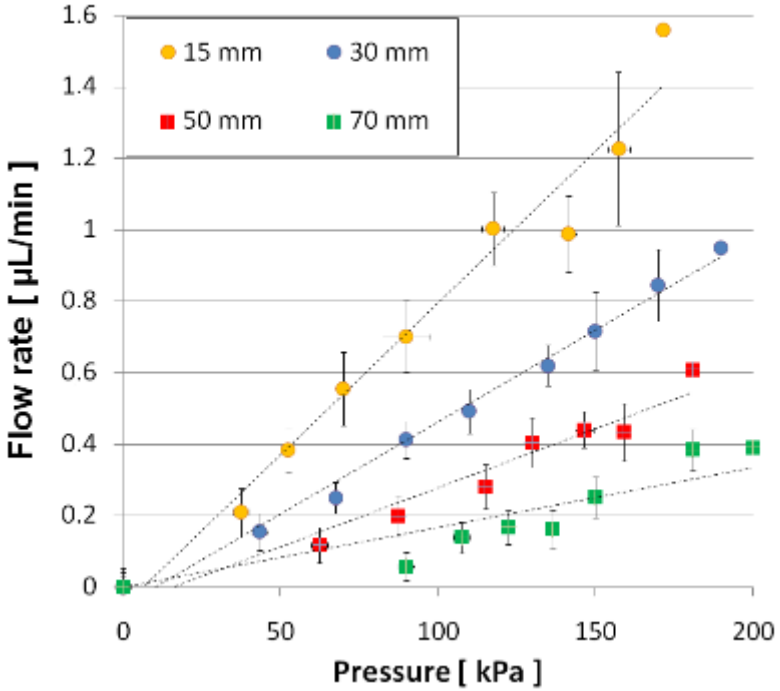


Deep-brain probe after packaging

Hydrodynamic characterization (chip-scale)



Setup: Pumping DI water through the integrated drug delivery channel of a single chip.



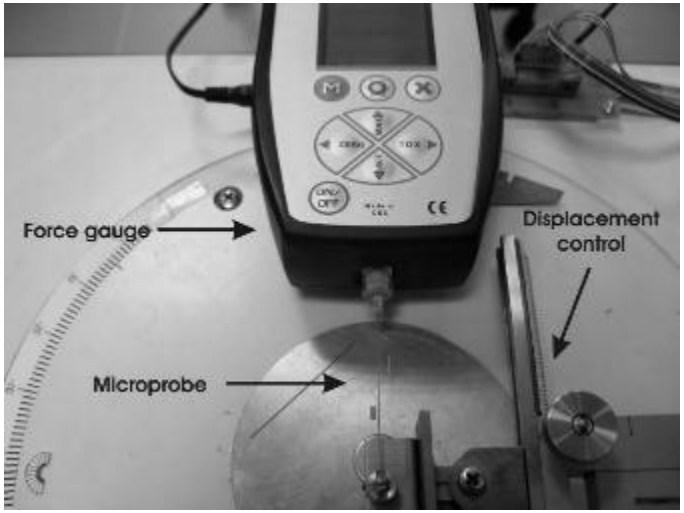
Pressure vs flow rate

Hydrodynamic resistance is increasing with increasing fluidic channel length

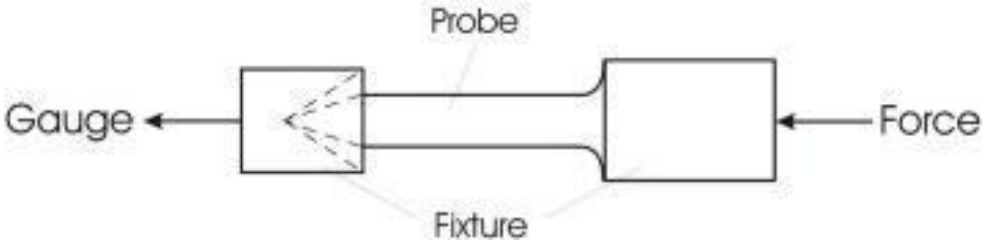
Flow rate is in the range 0.5 - 1.5 µl/min

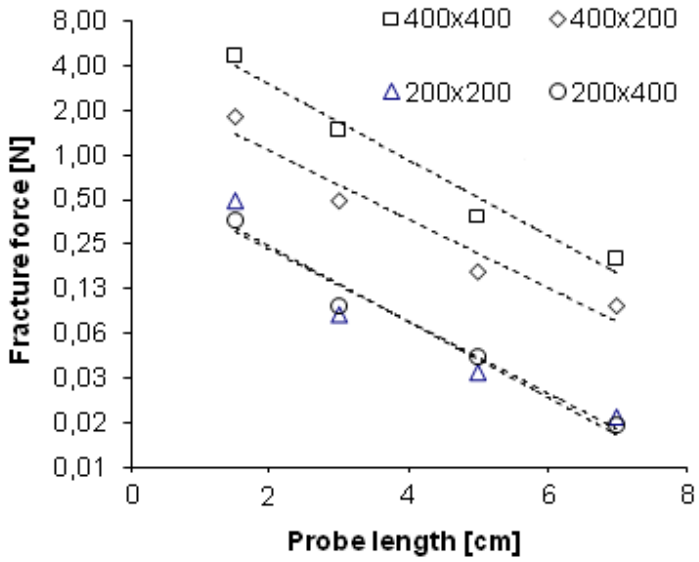
Fracture mechanics

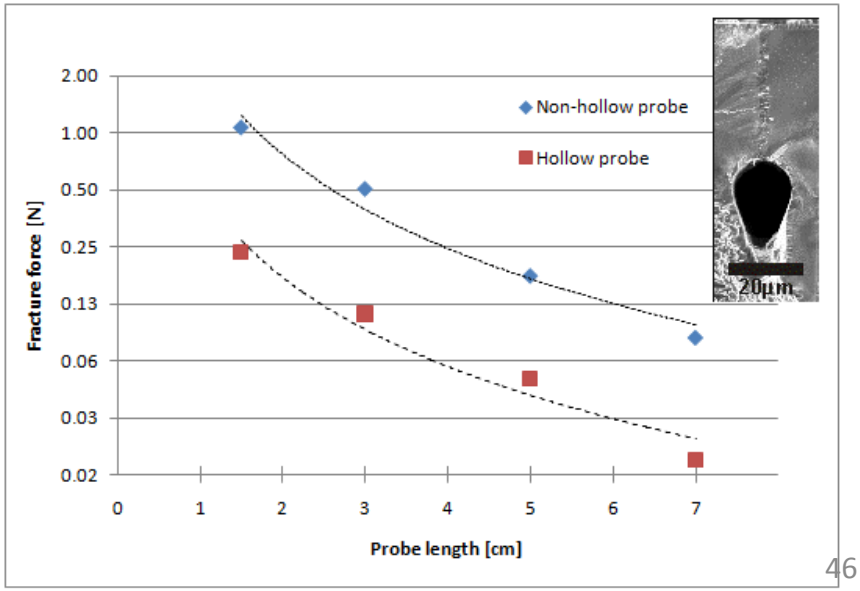
Role of second moment of inertia! Lower in case of a hollow structure than for solid structure of the same cross-section



Constraints:





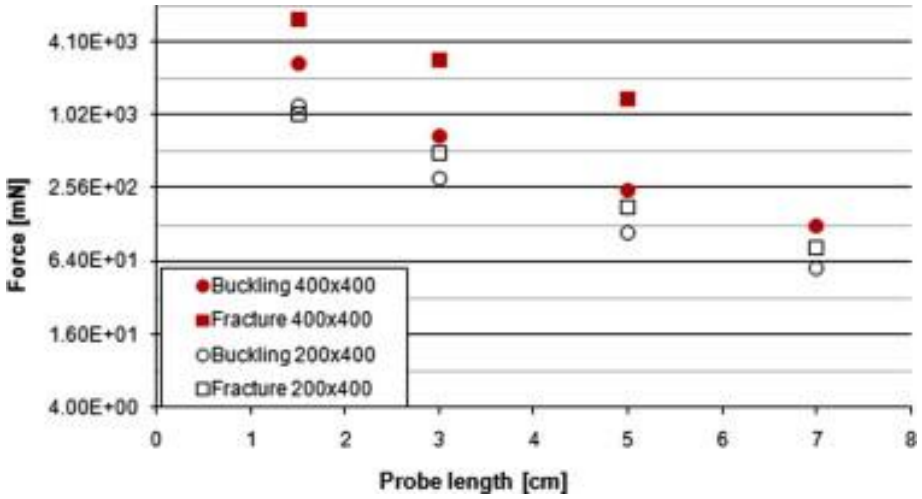


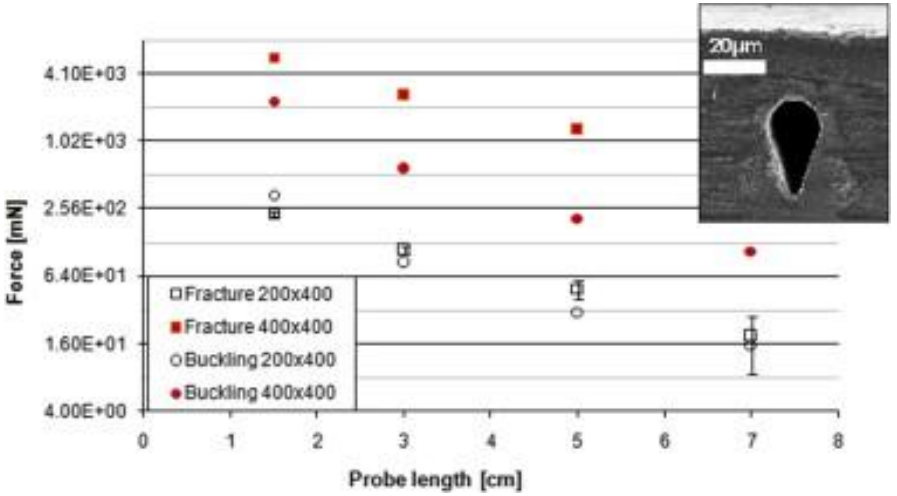
Buckling analysis

Critical buckling force in Euler beam theory:

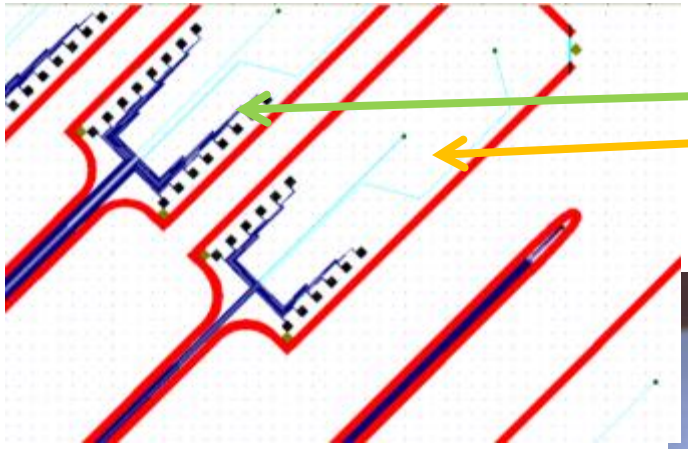
$$F_b = \frac{\pi^2 \cdot E \cdot I}{4 \cdot L^2}$$

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

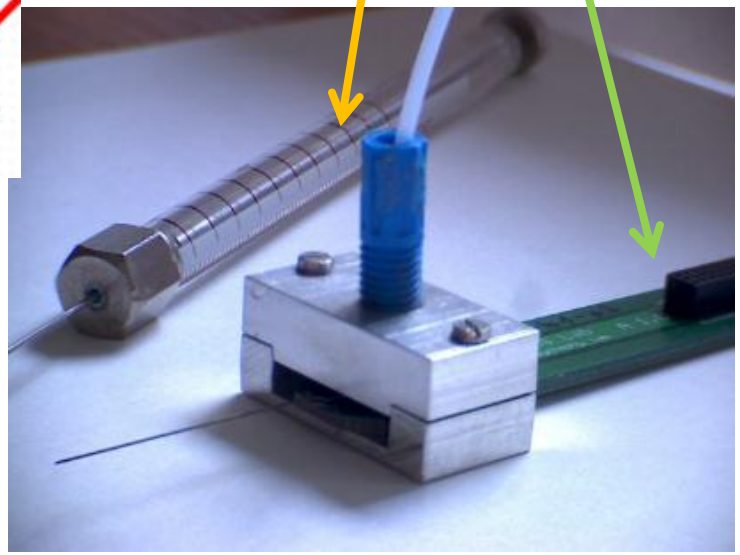




In vivo testing – External fluidic interface



Electrical connections
Fluidic ports



https://www.omnifit.com
Omni-Lok Inverted Cone

Features of the final device:

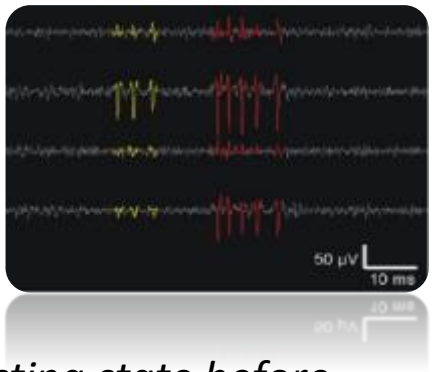
- Probe length: 30 mm
- Probe cross-section:
  400 µm × 400 µm
- Configuration of recording sites:
  tetrode (#4)
- Number of integrated fluidic components:
  2 buried channels

http://www.precidip.com
Preci Dip PCB socket connector

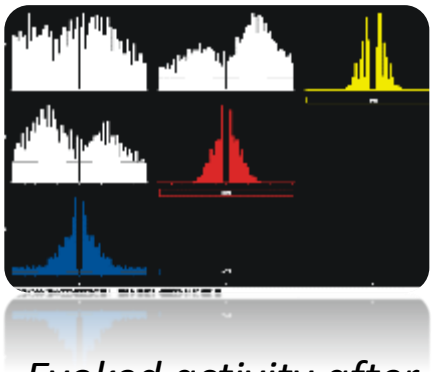
In vivo validation

Pongrácz, 2013

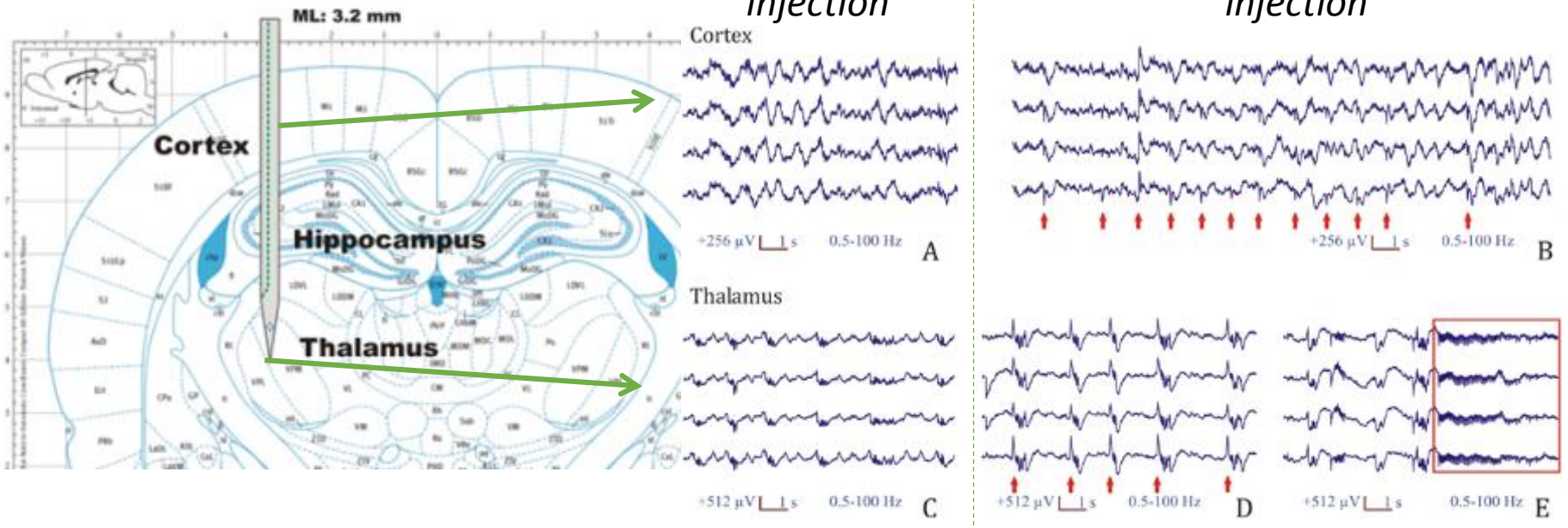
Acute animal experiment demonstrated simultaneous drug injection and neural signal recording (LFP, MUA, SUA)



Resting state before injection



Evoked activity after injection



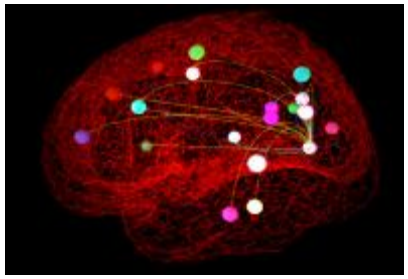
Evoked potentials by administration of biccuculine through the integrated channels

Case study 2

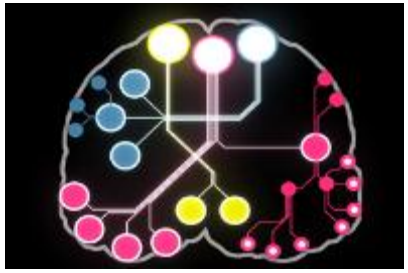
Characterization of hollow silicon microelectrode for iontophoretic administration of pathway tracers

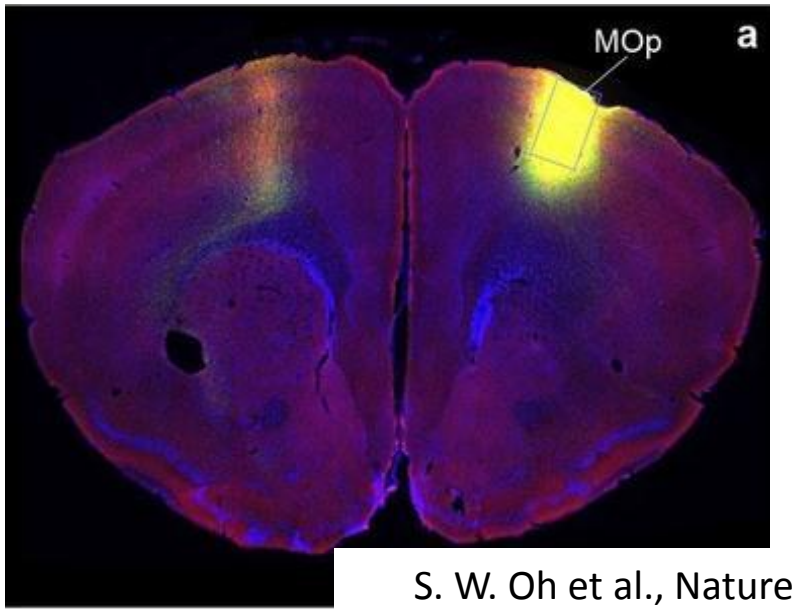
Motivation

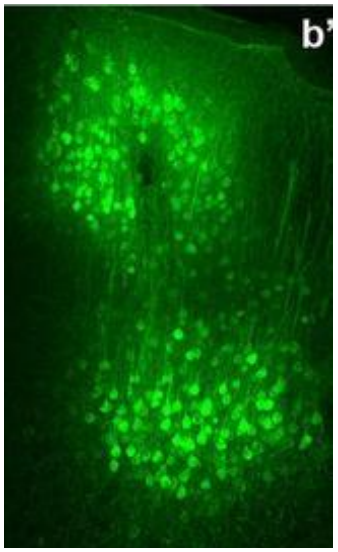
- Bridging the gap between brain structure and function
- Mapping connectome in animal studies



Human Connectome Project







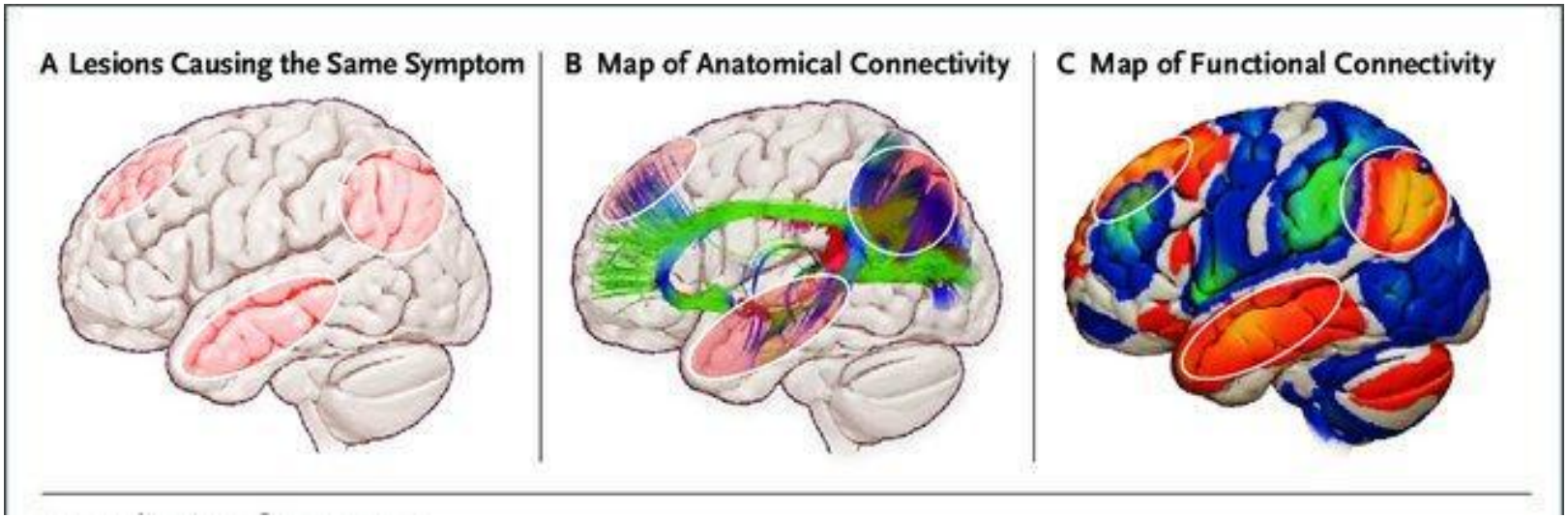
S. W. Oh et al., Nature 508, pp. 207-214, 2014.

Goal

Validation of a combined tool for in vivo electrophysiology and neuronal labeling through iontophoretic tracer injection

Connectome

Anatomical connectivity vs functional connectivity



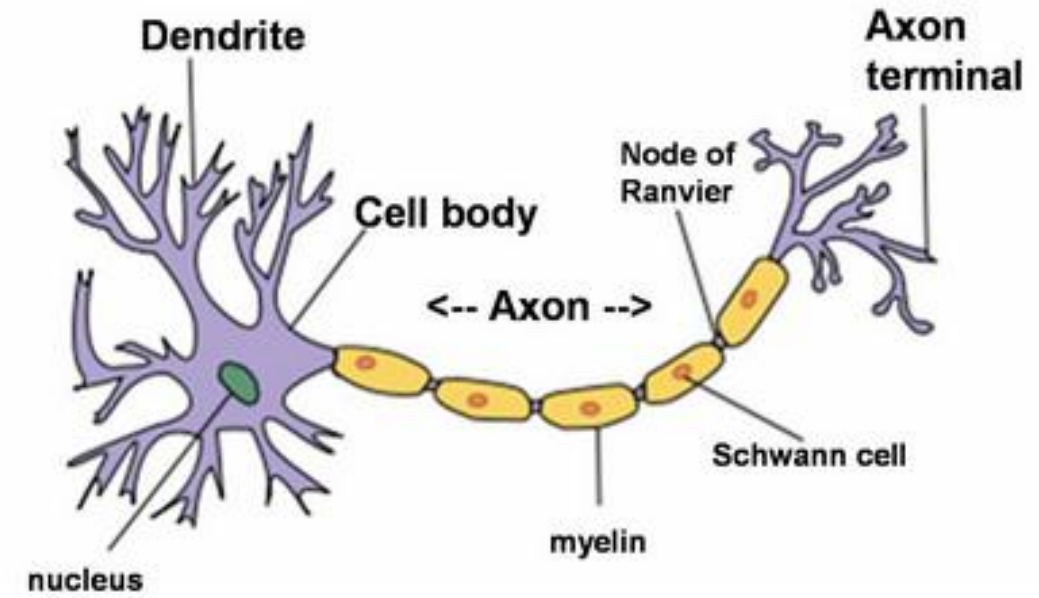
Connectome can be „rewired” → neuroplasticity

Neuronal labeling

Labeling molecules:
Biotinylated dextran amine (BDA)

Methods:
Pressure or iontophoretic ejection

into the extracellular space



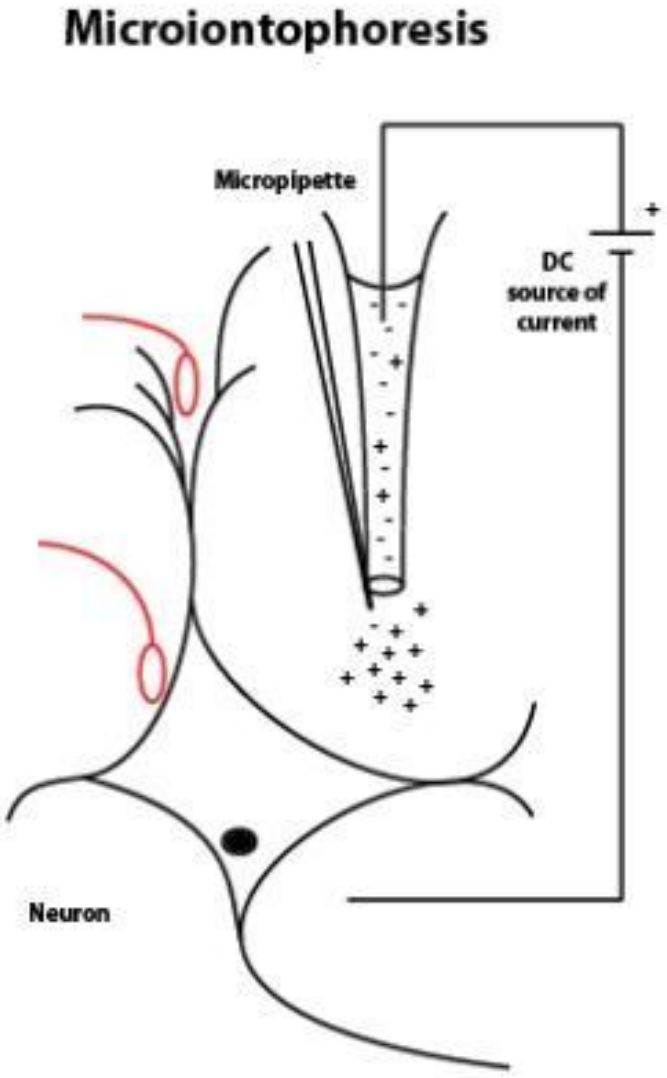
High molecular weight BDA
(10 kDa)

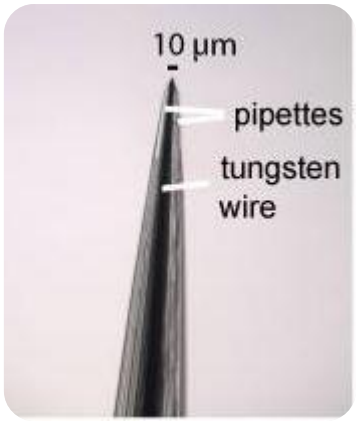
higher anterograde sensitivity
(axon & terminals)

Low molecular weight BDA
(3 kDa)

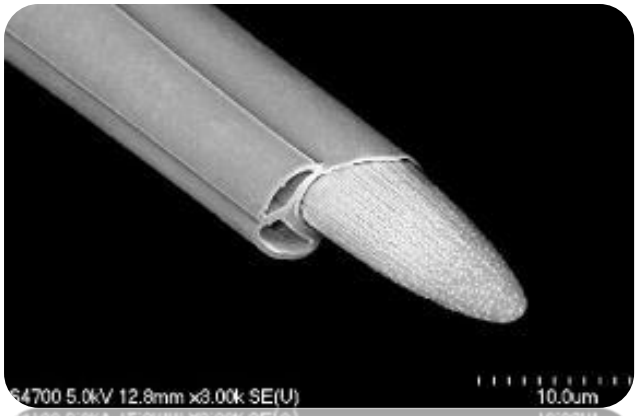
higher retrograde sensitivity
(cell bodies)

Iontophoretic tracer injection





Thiele et al., J Neurosci Methods. 2006 158 pp. 207–211.



Budai, D, Carbon Fiber-based Microelectrodes and Microbiosensors, Intelligent Biosensors, 2010

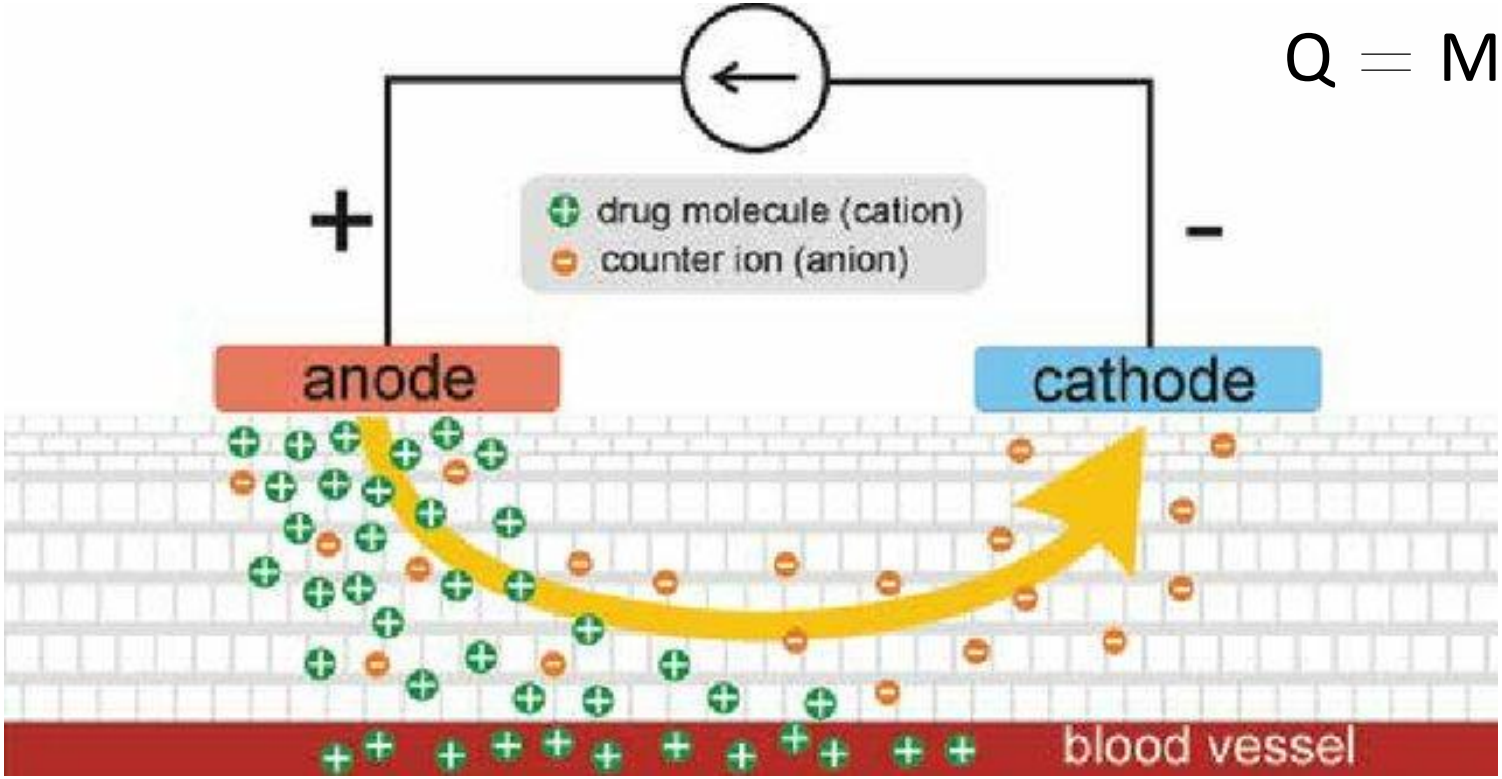
Iontophoresis	Convection enhanced drug delivery
Control	
Electric current	External pressure
Injected medium	
Ionic solution	Solution

Iontophoretic drug delivery

- Governing equations: Faraday's law

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

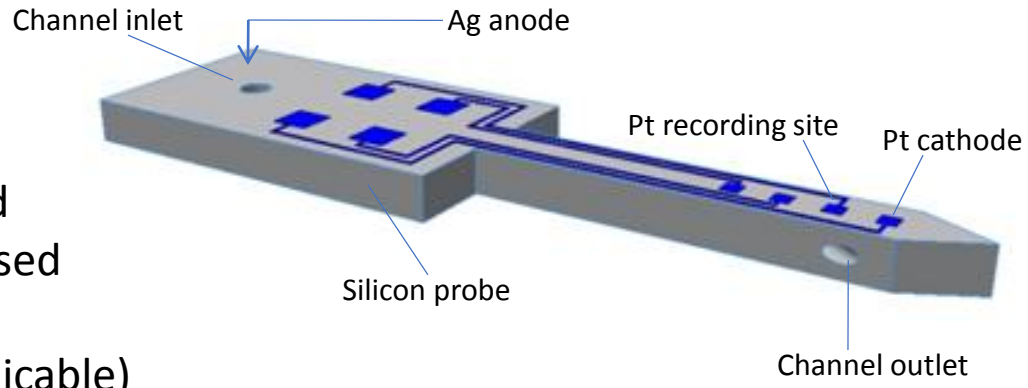
$$Q = M_w * N_e$$



Labeling protocol

Procedure:

1. Channel filling with BDA.
2. Implantation
3. Pt electrode negatively biased
   Silver electrode positively biased
4. Current injection (15 mins)
5. Electrophisiology (where applicable)
6. Histology



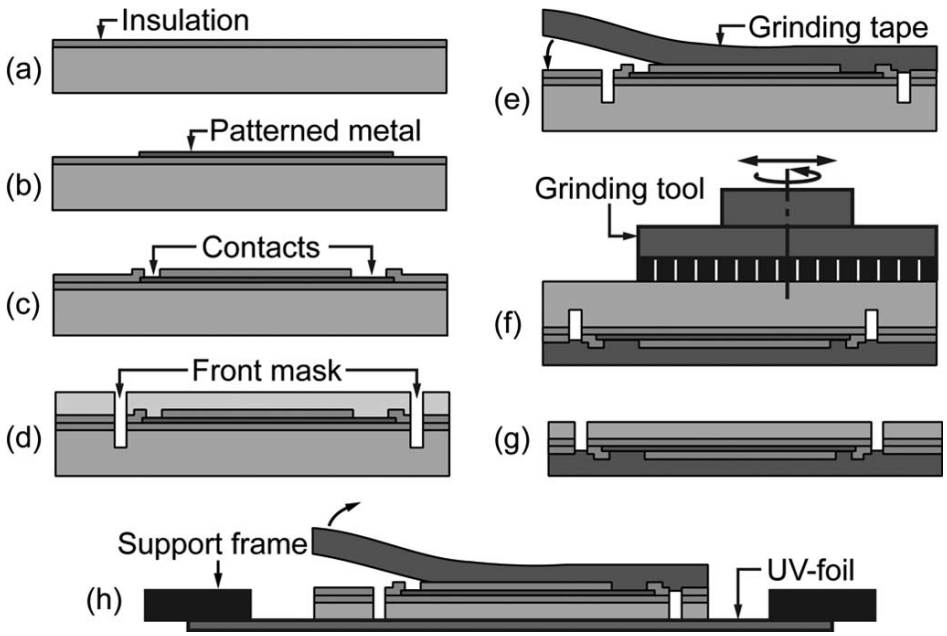
Targeted region: somatosensory cortex
Substance: 10% mixture of high & low MW BDA dissolved in 0.01M PBS (pH 7.4)
Survival time: 7 days
Histology: standard ABC protocol to visualize BDA in coronal vibratome sections

Additional control experiment: without any voltage bias

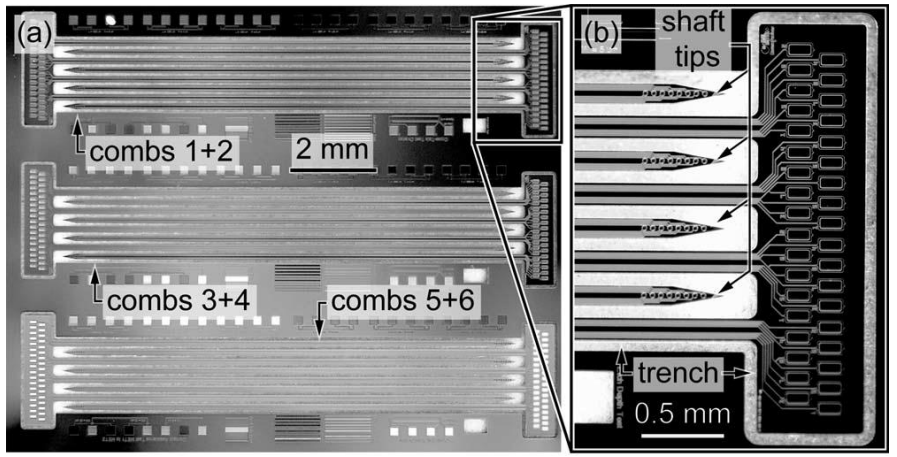
Challenge: probe dimension should be reduced to increase survivial rate of labelled neurons

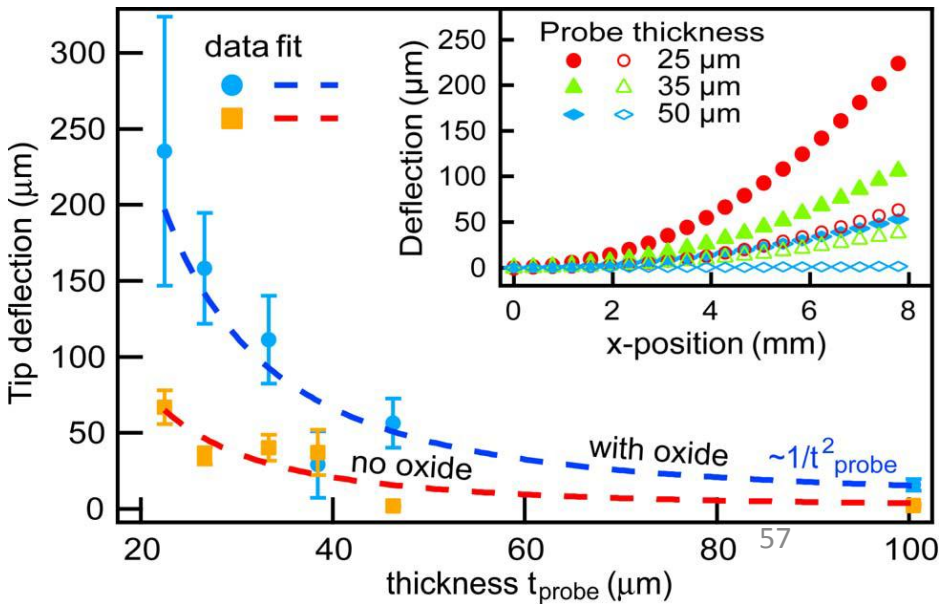
Change in probe technology for limited tissue damage?

Thinning the probe with etching-before-grinding technology



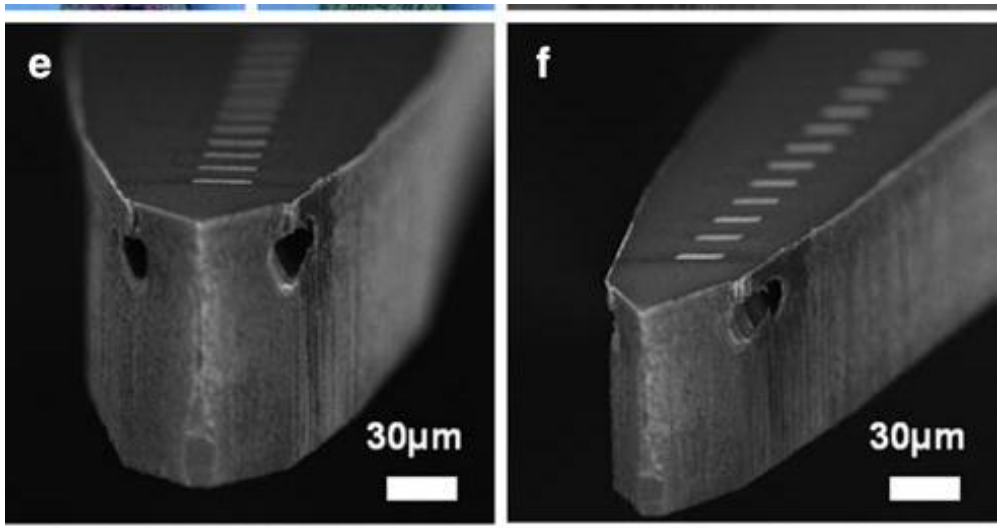
Herwik, 2011

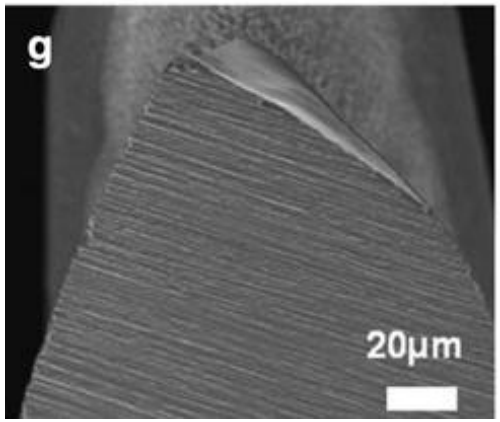




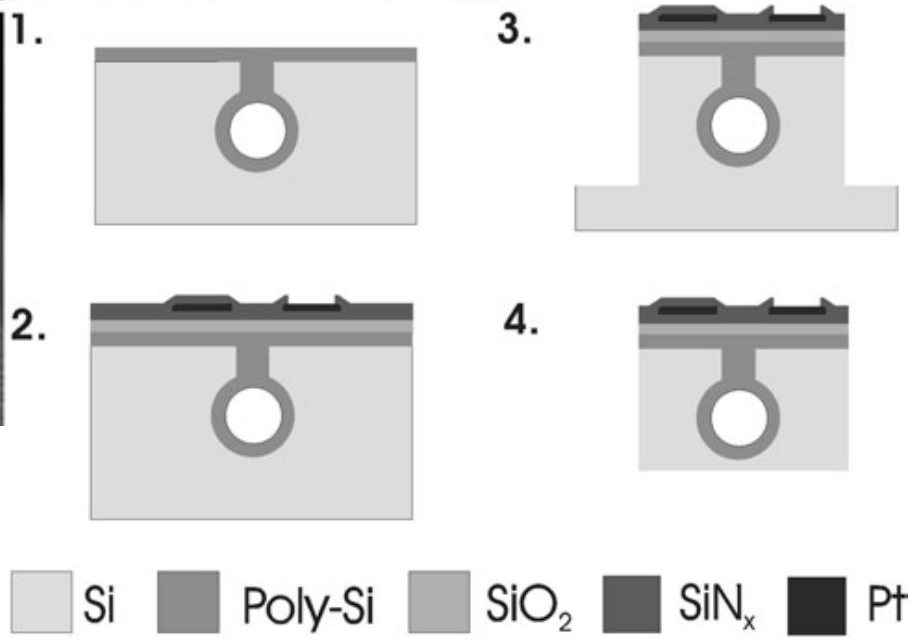
Issue: residual stress becomes dominant as substrate is getting thinner!

Grinding is compatible with the fab process?



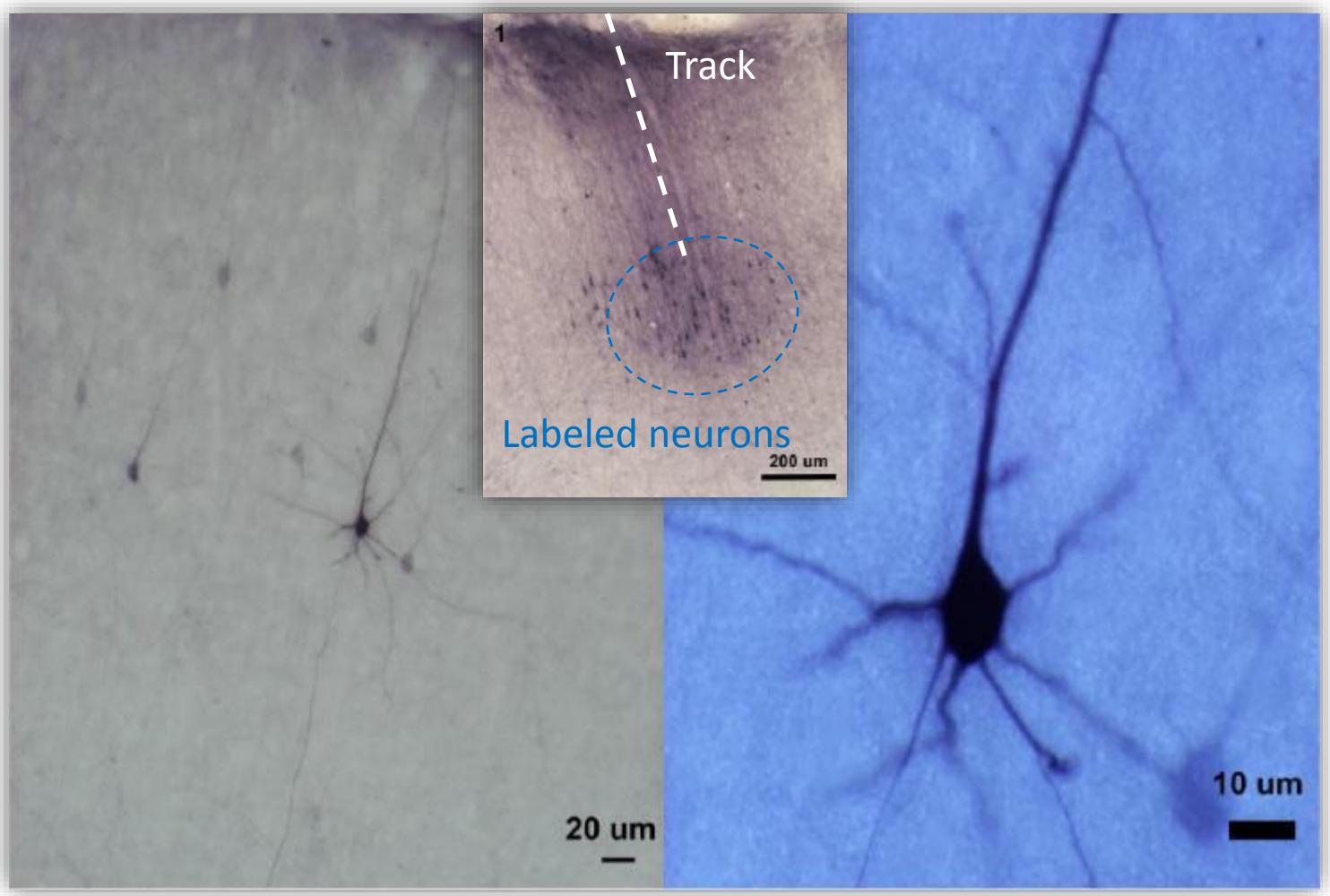


Fekete et al., 2015



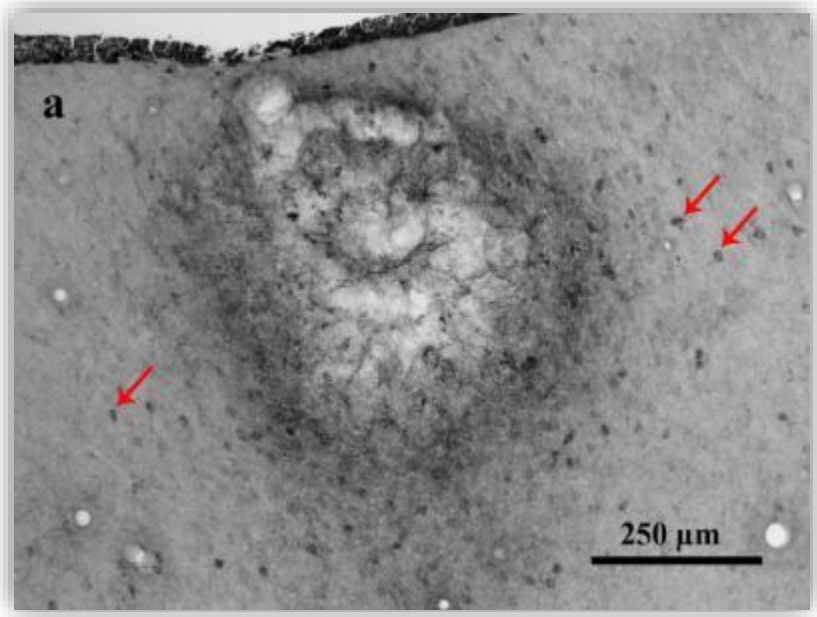
Result: microchannel outlets and surface quality was not destroyed by grinding!

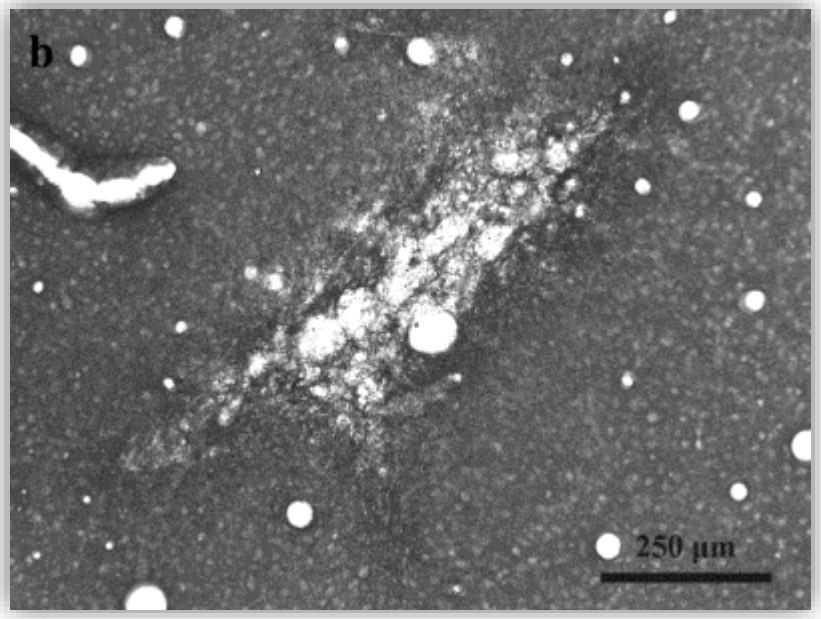
Labeled neuronal cells



Effective cross sectionof labeling: ~ 200-300 micron

Control experiment





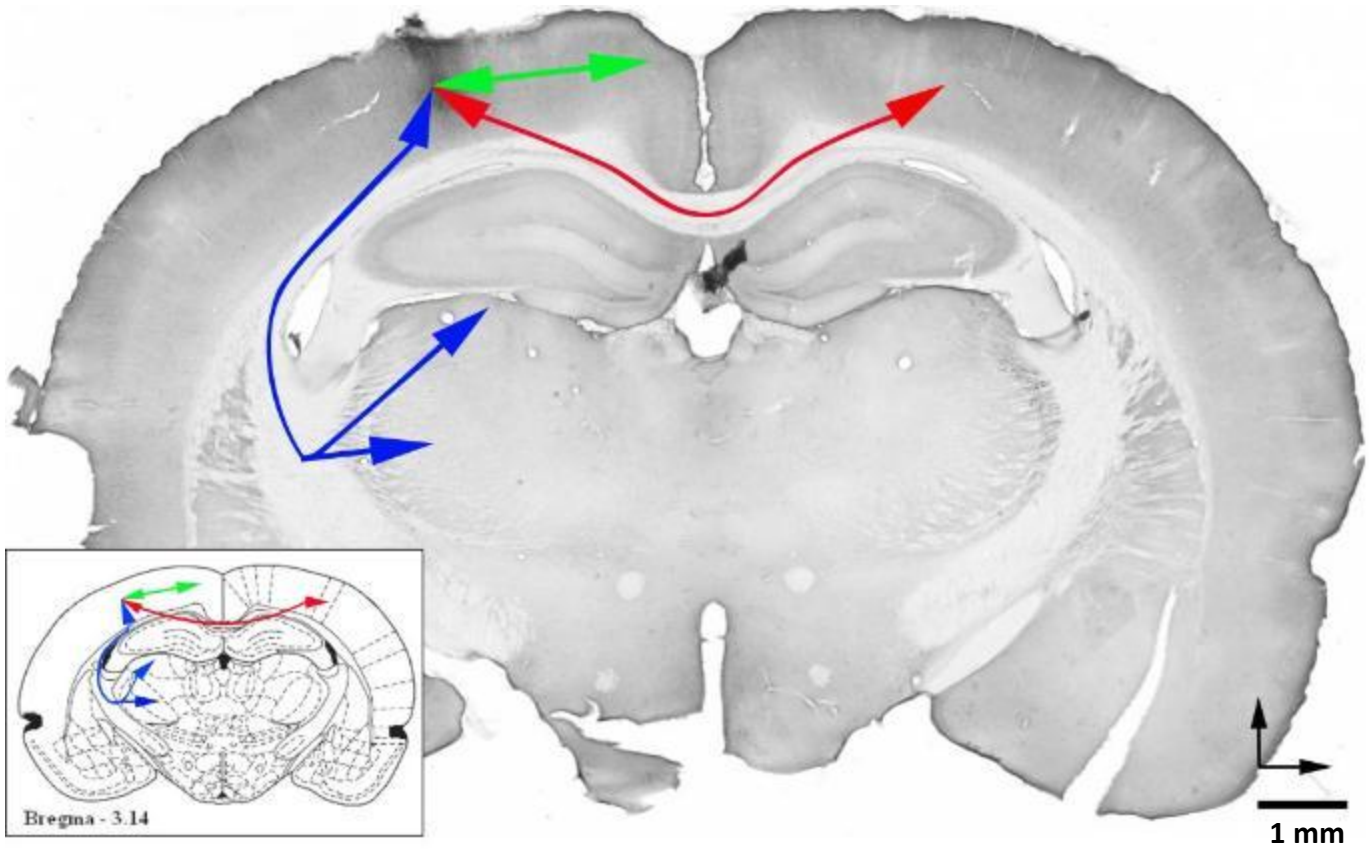
a. Labeled neuronal cell bodies (I_{inj} = 4 µA, ON/OFF cycle = 7 s /7 s)

b. Control experiment (without injection current)

Conclusion: diffusion through pre-loaded channels compared to IDD is negligible

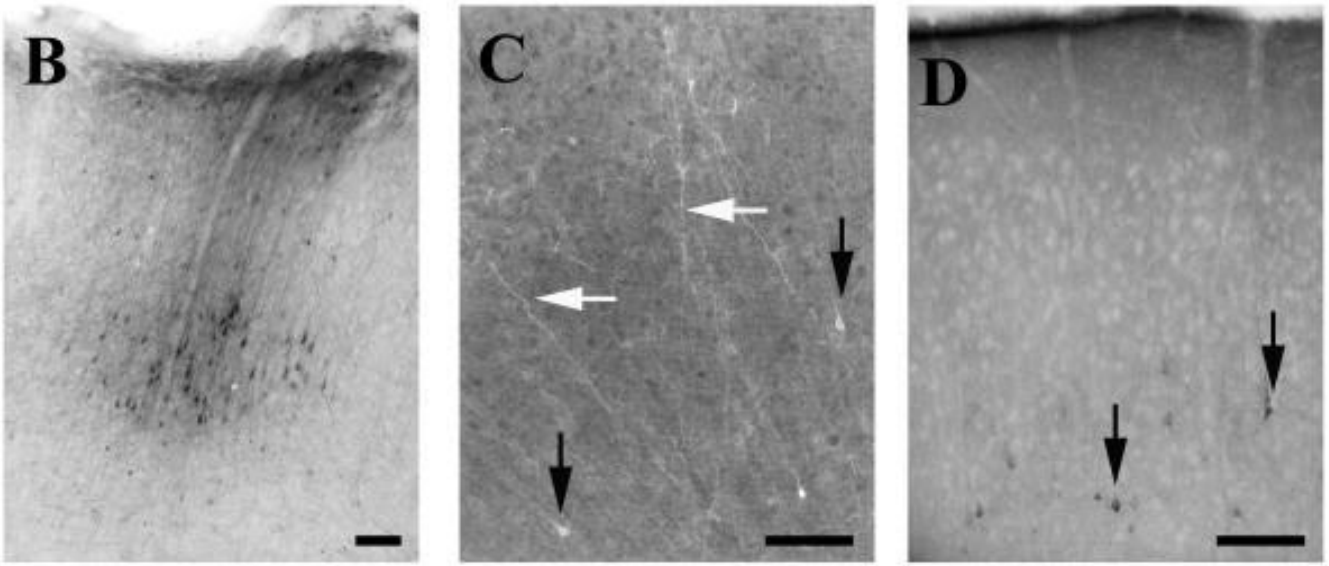
Connectome labeling

Iontophoretic injection (I = 4 µA, ON/OFF cycle = 5/5 s) & Electrophysiology



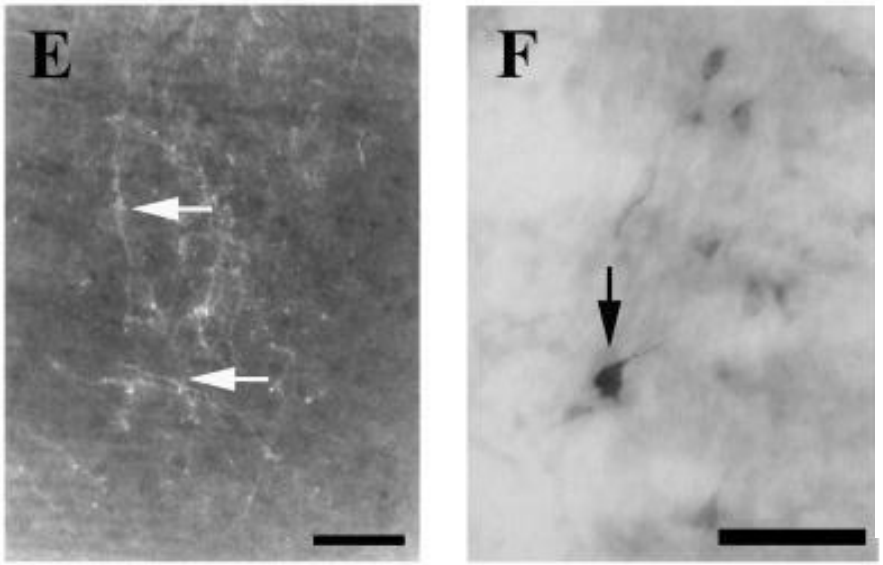
Green arrow: ipsilateral, red arrow: contralateral, blue arrow: thalamic connections.

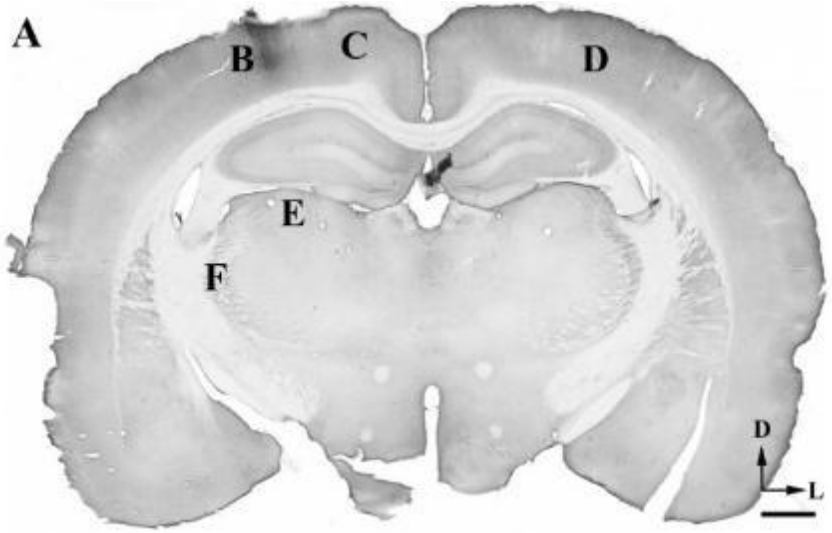
Connectome labeling



: cell bodies

: axons

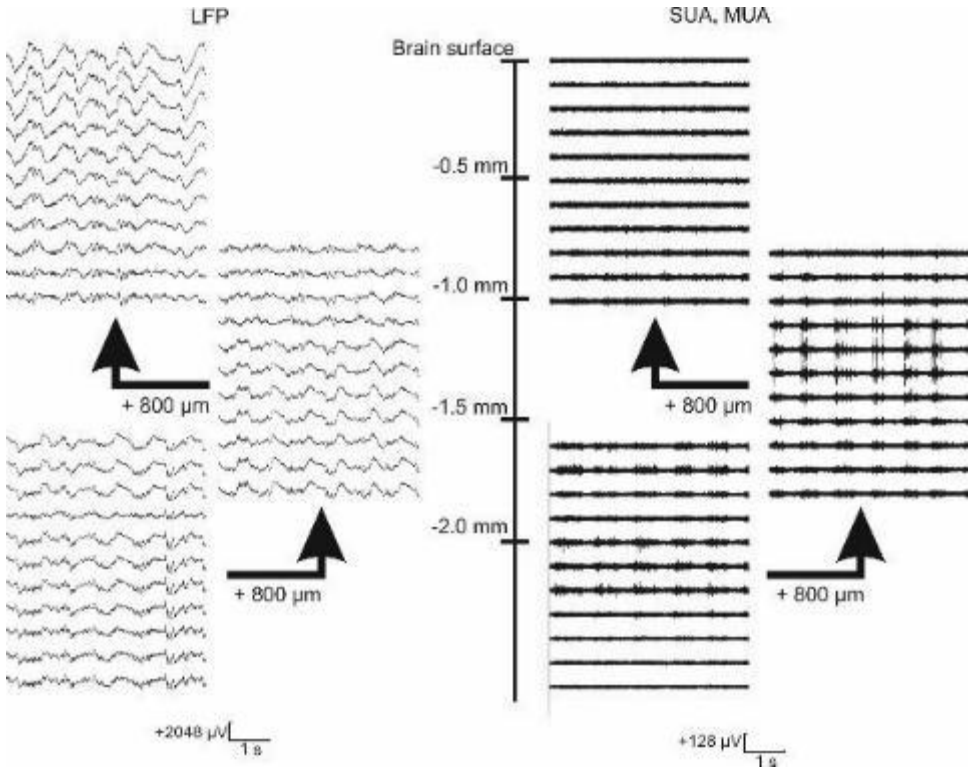




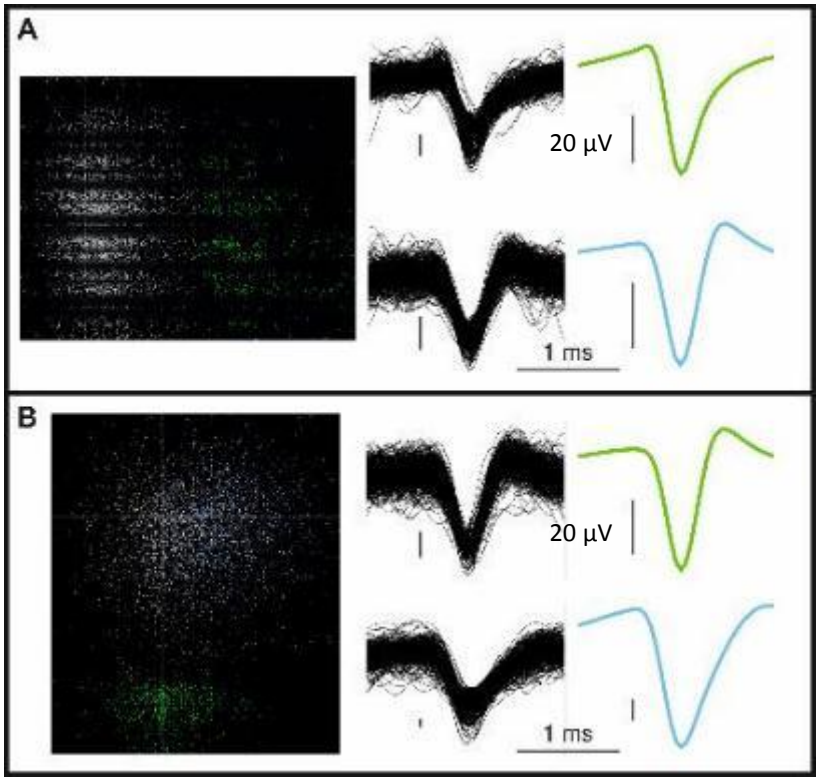
Fekete, 2016

Electrophysiology

In vivo extracellular recording after tracer injection in anaesthetized rats



Neuronal activity recorded with a linear MEA after injection



Detected unit activities at the location of iontophoresis (A) and 800 µm above (B).

Questions

1. List five medical applications of microscale drug delivery.
2. What parameters determines the flow rate in the case of iontophoretic injection of charged particles?
3. What parameters determine hydrodynamic resistance in a microchannel?
4. Draw the schematic process flow of surface-, bulk micromachining approaches to fabricate microfluidic channels.
5. What is the relationship between pressure and flow rate in a laminar flow?
6. What dimensional and material parameters determine the buckling force of a hollow needle?
7. How does the steepness of pressure flow rate curve changes if the length of the microchannel increased?
8. What is the operation principle of thermally actuated integrated micropump?
9. What is the effect of elastic components on flow profile?