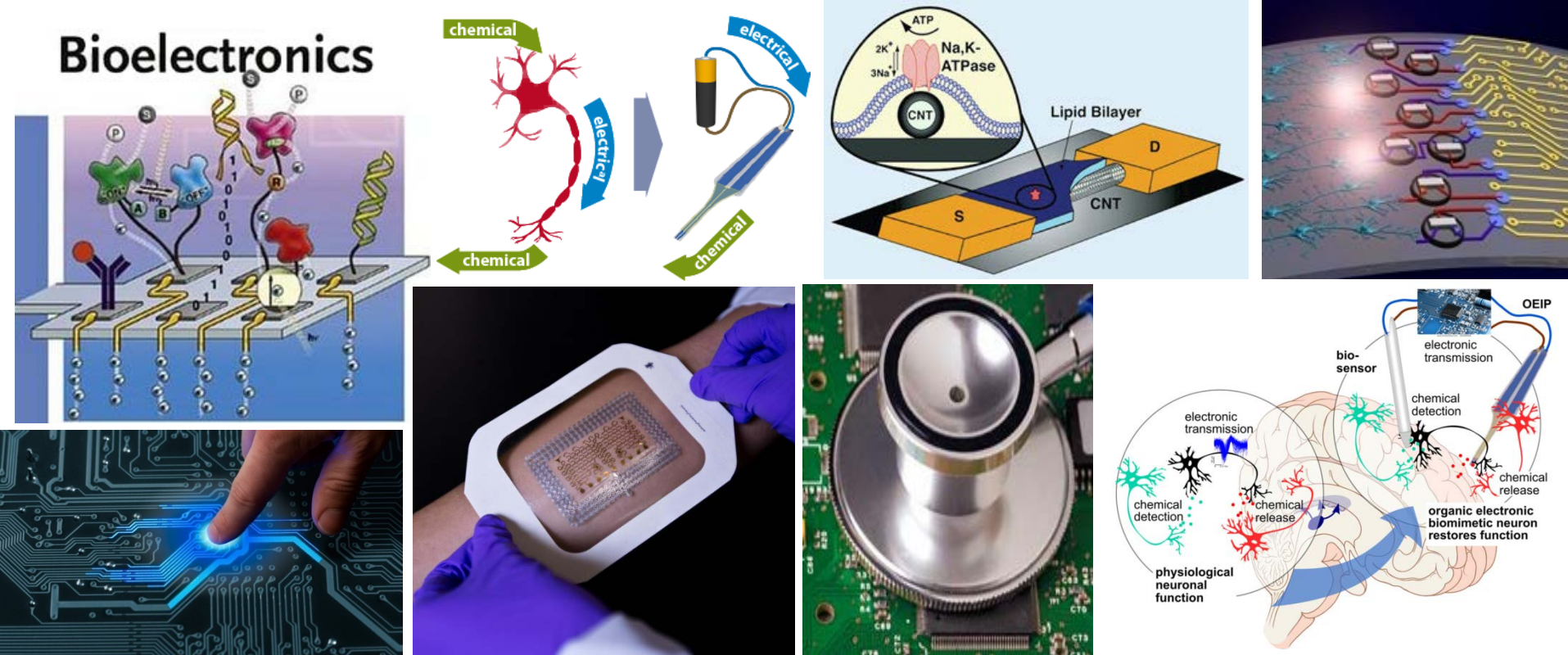


# Bioelectronics



## Bioelectronics: Interfacing Electronics with Biology



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Research Center for Applied Sciences (RCAS), Academia Sinica, Taiwan

2016/04/28

# What is Bioelectronics?

- **Biology + Electronics**
- The application of electronic devices to living organisms for clinical testing, diagnosis and therapy.
- The interactions of increased computing power, advances in prosthetic devices, artificial implants, and systems that blend electronic and biological components.

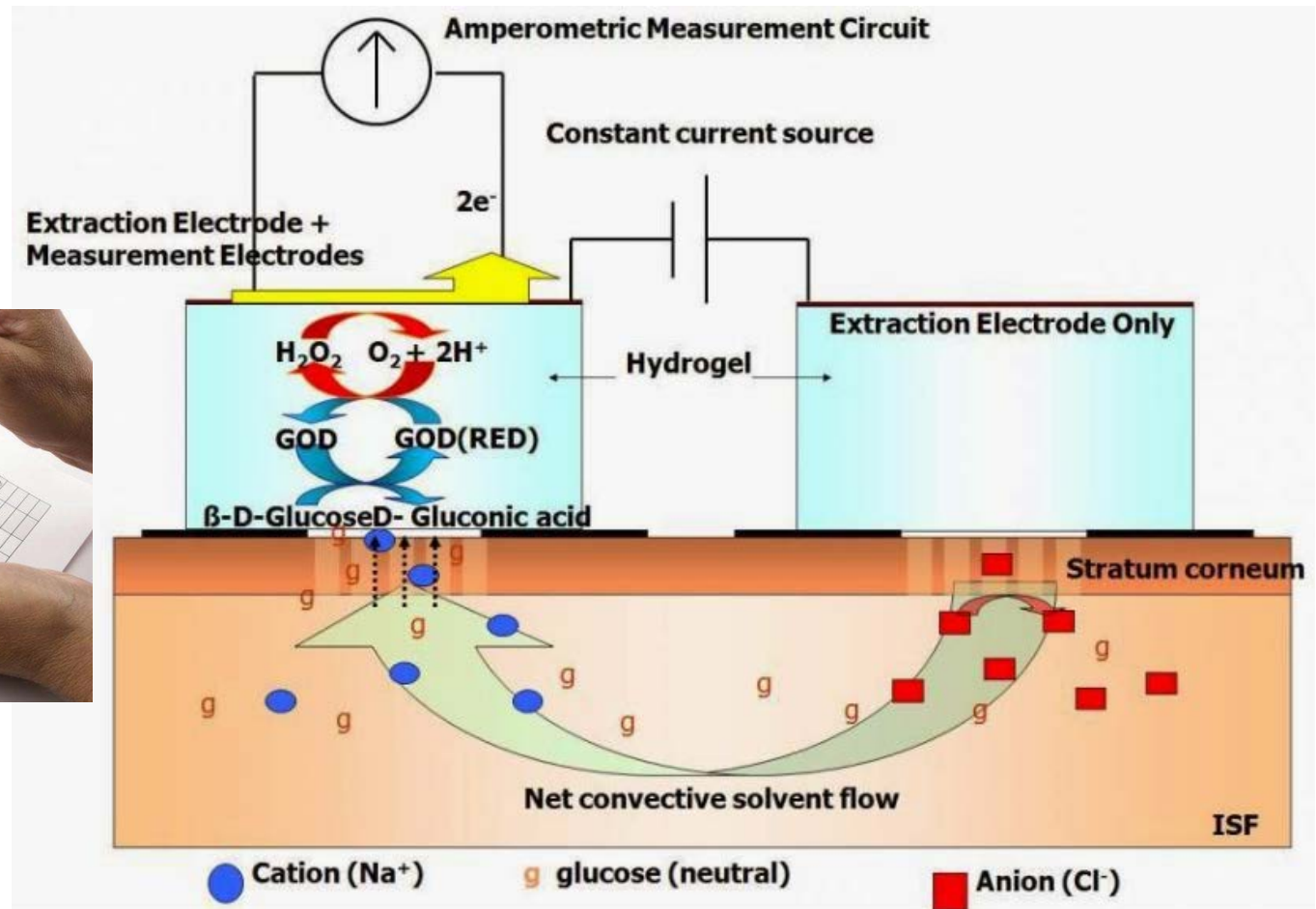
Sources: <http://dictionary.reference.com/browse/bioelectronics>  
<http://www.svegritet.se/ethics-bioethics/bioelectronics-and-implanted-devices/>

## Do CYBORGS exist?

- The earlier and more strict definition of **Cyborg** was almost always considered as increasing or enhancing normal capabilities, whereas now the term can also be applied to those organisms which use technology to repair or overcome their physical and mental constraints.
- Examples are artificial limbs and hands.



# Blood Glucose Meters

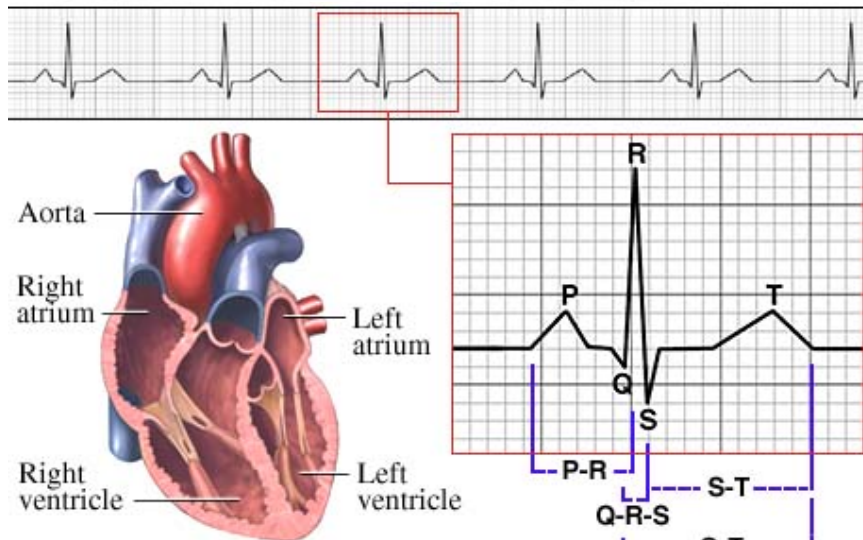


Glucose undergoes a chemical reaction in the presence of enzymes and electrons are produced during the chemical reaction. These electrons (i.e., the charge passing through the electrode) are measured and this is proportional to the concentration of glucose in the solution.



# Electrocardiography (ECG) Measurement Technology

## First Electrocardiograph (ECG) by William Einthoven in 1903



## Patient Monitors



## Portable ECG system



## ECG Holter



## Embedded ECG

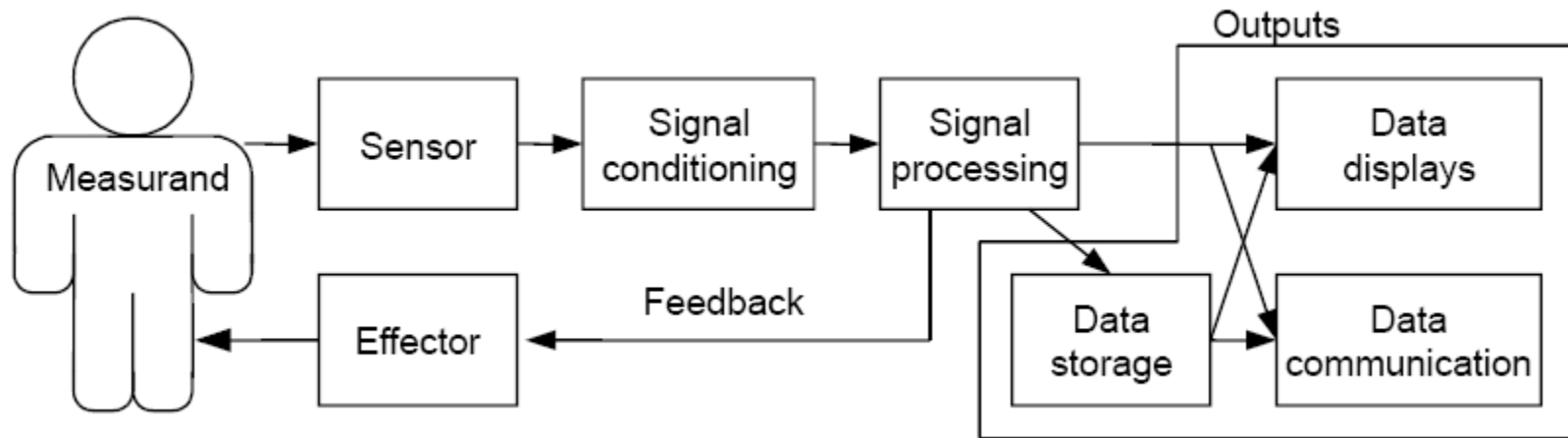


## ECG chip

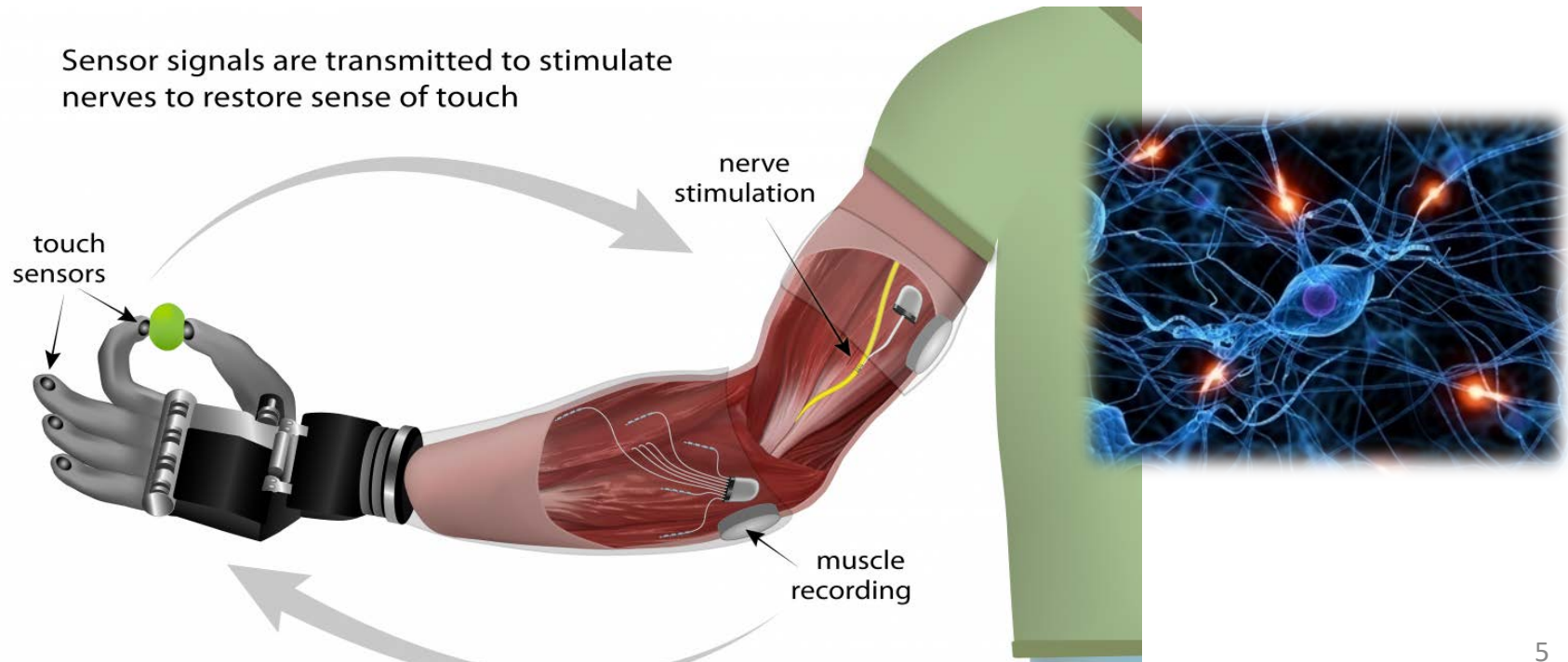




# Bioinstrumentation



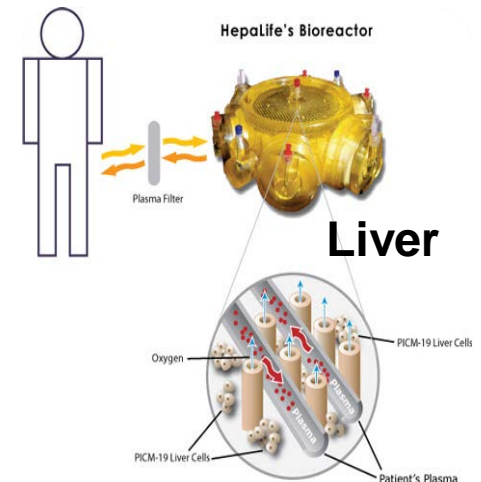
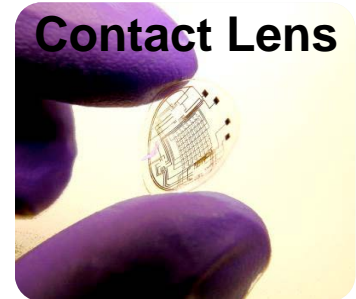
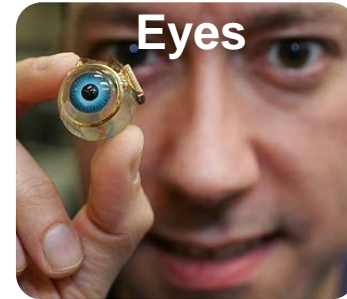
John G. Webster, *Bioinstrumentation*, John Wiley & Sons, 2003.



# Bioelectronics and Implanted Devices



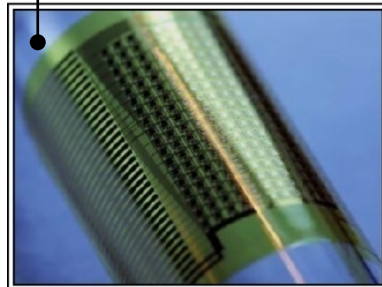
- Eyes
- Ears
- Heart
- Lung
- Liver
- Kidney
- Hands
- Feet



# Bioelectronics for Smart Skin or Smart Textiles

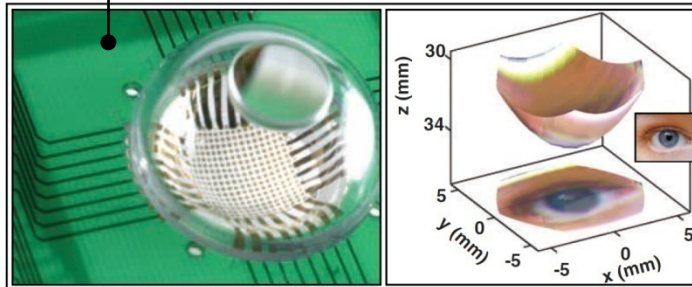
Implantable device for measuring the heart's electrical output with a vast improvement over conventional devices [Science Transl. Med. 2, 24ra22 (2010)].

Heart implant



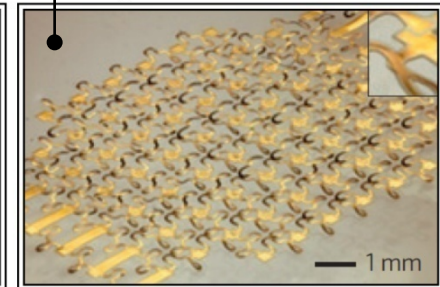
Electronic eyeball camera that uses a hemispherically curved array of silicon photodetectors and picture collected with a similar camera that uses a paraboloid design [Rogers et al., Science 327, 1603 (2010)].

Artificial retina

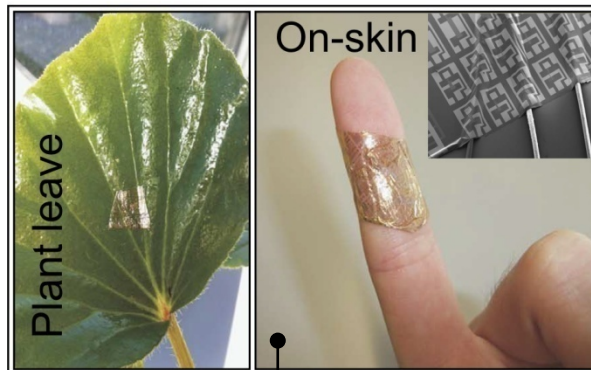


Stretchable array of light emitting diodes (LEDs) [Kim et al., Nature Mater. 10, 316 (2011)].

Optoelectronics

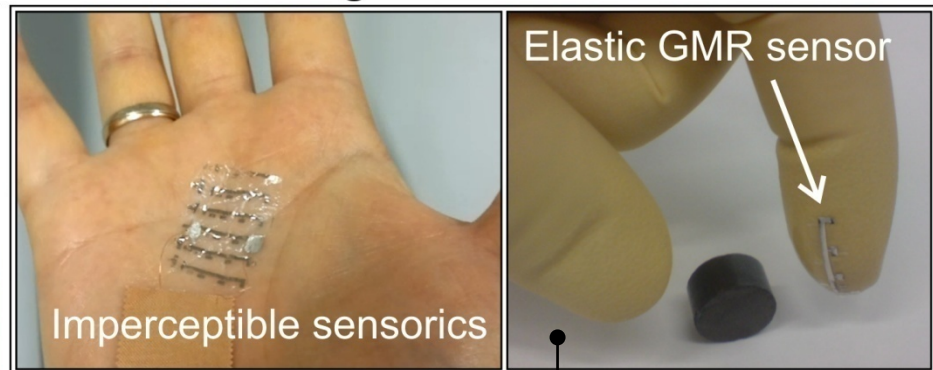


Active electronics



Flexible InGaZnO-Based active electronics [Salvatore et al., Nature Comm. 5, 2982 (2014)].

Magnetoelectronics



Flexible and stretchable inorganic magnetosensorics [Melzer et al., Nano Letters 11, 2522 (2011)].

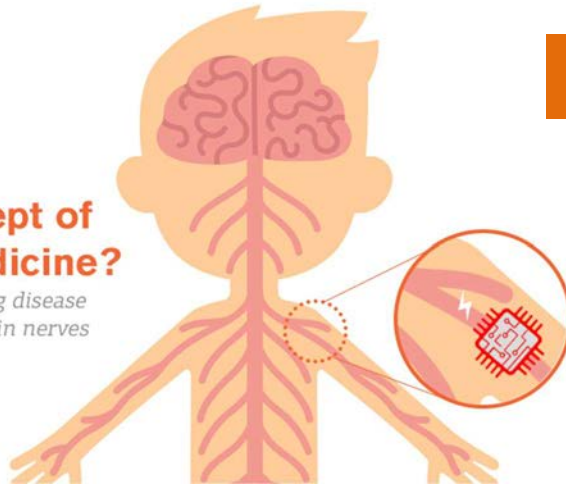


# Bioelectronics and Medicine's Future

1

## What is the concept of bioelectronic medicine?

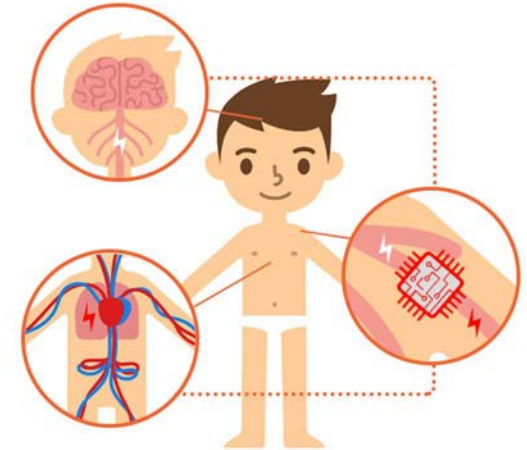
A tiny implanted device treating disease by changing the electric pulses in nerves to and from specific organs.



2

## How does bioelectronics work?

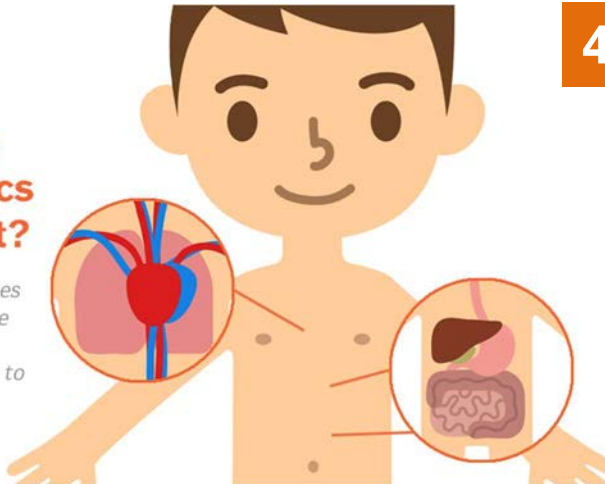
A tiny device attached to a nerve that would adjust the electrical signals between the brain and the organs in the body.



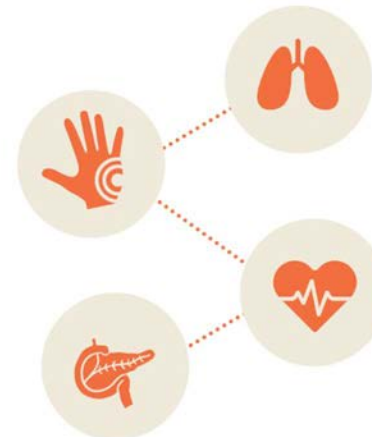
3

## What body parts can bioelectronics potentially affect?

We believe bioelectronic devices have the potential to modulate nerve signals that control the lungs, stomach and intestines to mention just a few.



4



## What diseases could bioelectronics potentially treat?

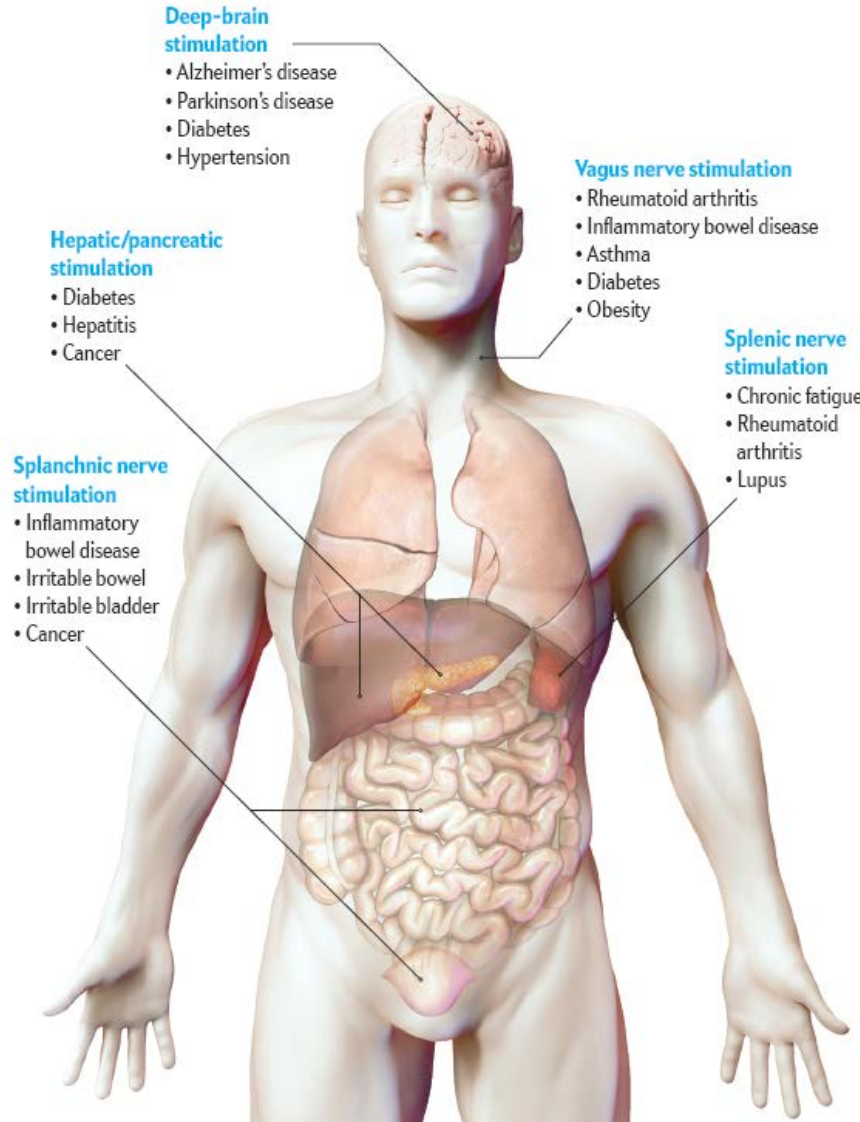
We anticipate it has the potential to treat asthma, arthritis, hypertension and diabetes to mention just a few.

**Bioelectronics will be commonly used by 2025**

<https://www.youtube.com/watch?v=AX4Yr02-olo>



# Personalized Bioelectronic Medicines : Targets and Diseases



**Bioelectronic medicine** holds promise for using electrical stimulation technologies to treat a variety of diseases—and may become an alternative to some pharmaceuticals. Vagus nerve stimulation—the topic of this article—is only one of these techniques. Deep-brain stimulation is already helping patients with Parkinson's disease. Other therapies, such as splenic nerve stimulation, are being investigated but have not reached clinical trials.

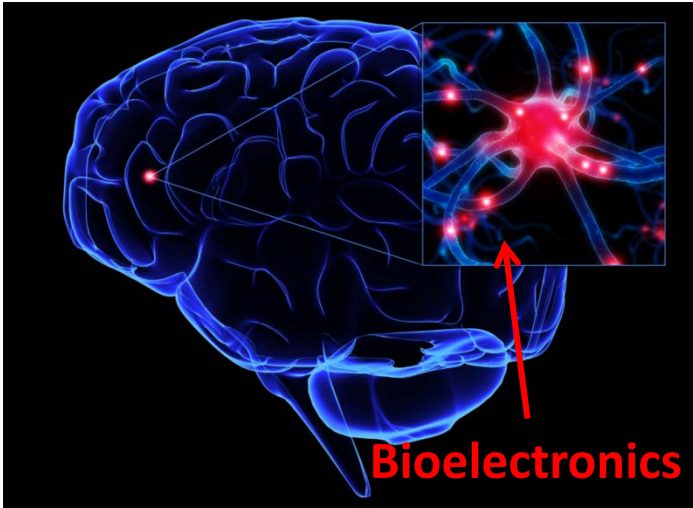
# Outline

- **Personalized Bioelectronic Medicines**
- **Why Organics? What is the Organic Electronic?**
- **Organic Bioelectronic Interfaces (OBEIs) and Pi materials**
- **Micro/Nanofabrication Technologies for Organic electronics**
- **Neuroscience**
  - Introduction to neural interfacing
  - Recording single neurons without penetrating the brain
  - Recording brain activity with high signal-to-noise ratio
  - Stopping seizures (in vitro) with localized drug delivery
  - Ion transport in conducting polymers
- **Stem Cell Therapies**
- **Cancer Treatment and Diagnostic**□

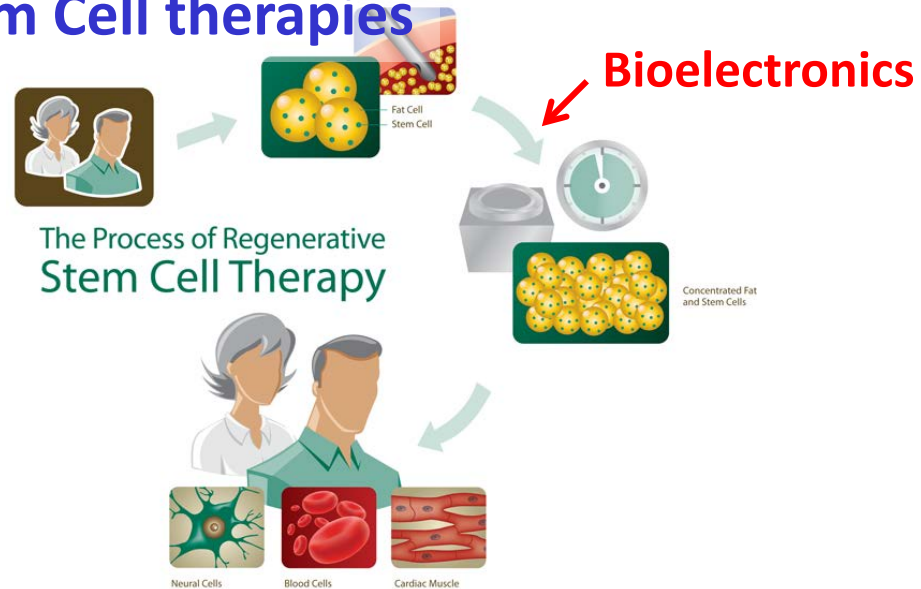


# Personalized Bioelectronic Medicines

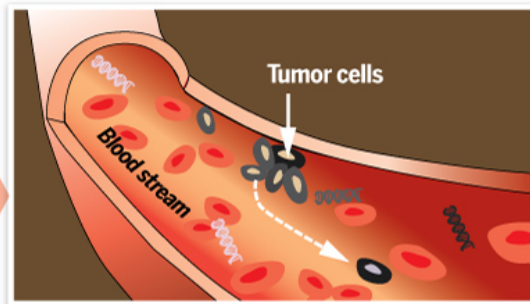
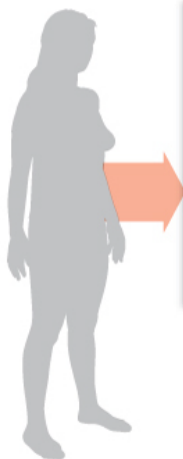
## 1) Neuroscience



## 2) Stem Cell therapies

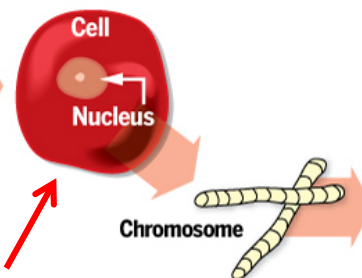


## 3) Cancer Treatment and Diagnostic



### Detecting tumor cells

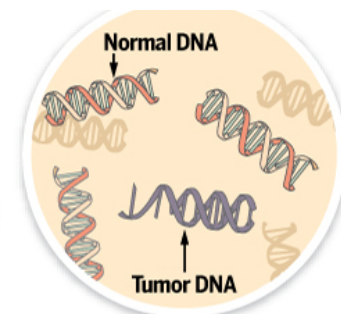
Tumor cells die routinely just like other cells, and when they do, they shed DNA into a person's bloodstream. This means the bloodstream will contain DNA from all over the tumor, not just one section.



### Bioelectronics

#### Blood is drawn

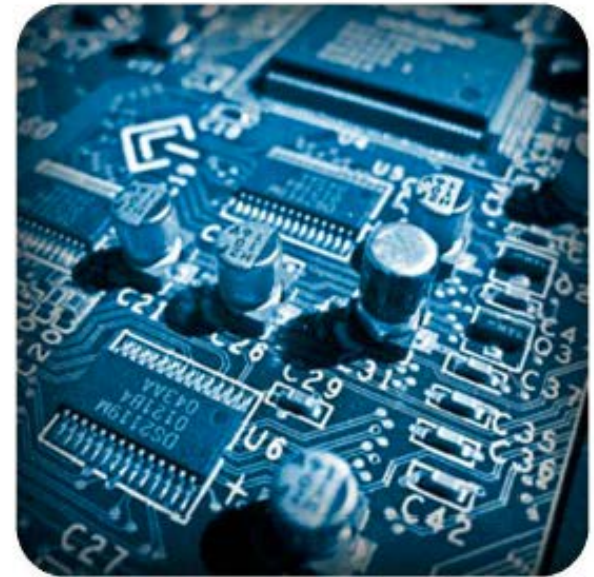
Once a patient's blood sample is taken, technicians isolate the DNA by removing red blood cells, platelets and plasma. Technicians get the DNA from the nuclei of white blood cells.



#### DNA tumor

The DNA is then read searching for markers of cancer. These are areas of the genetic script in which cancer cells differ markedly from normal cells.

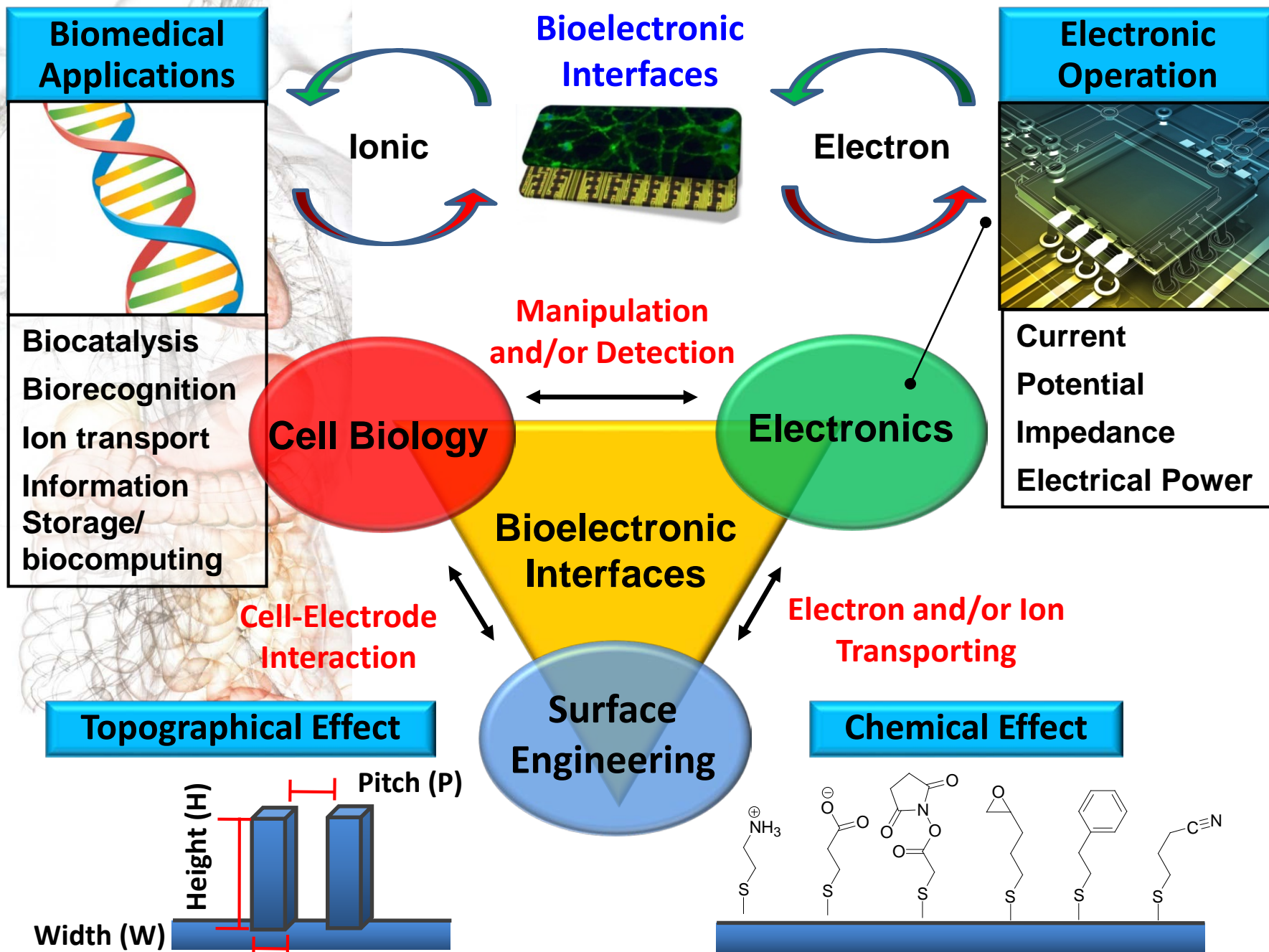
# Bioelectronics: Coupling biology and electronics



Mostly soft  
Complex signaling  
Dynamic

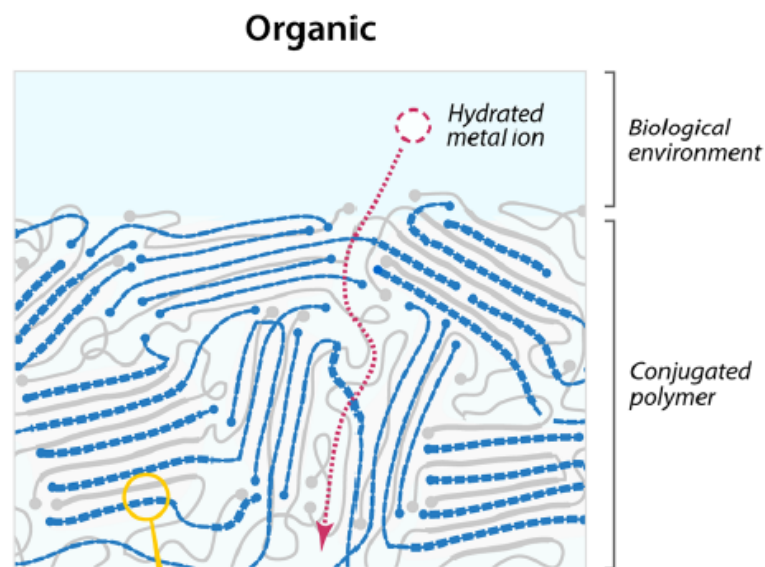
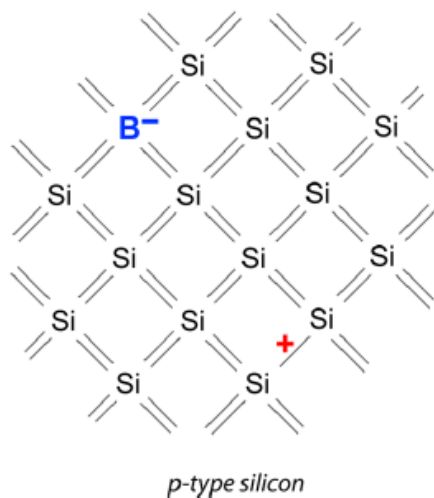
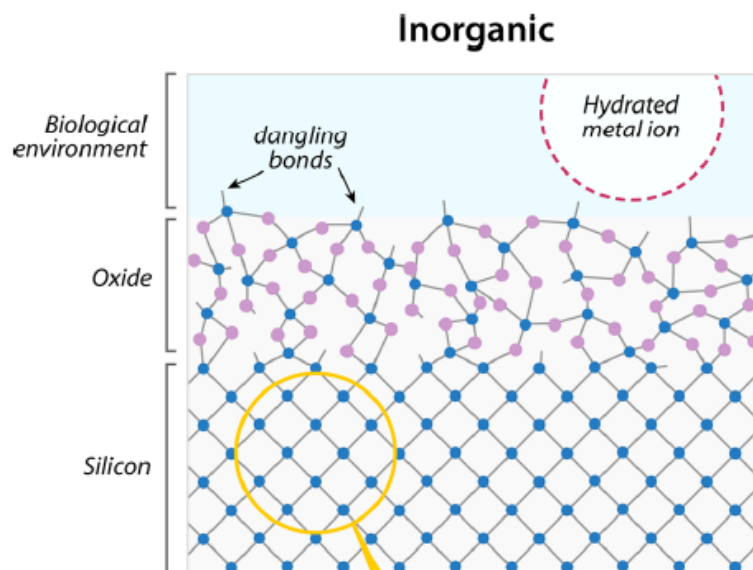


Hard  
Electrons/holes  
Static

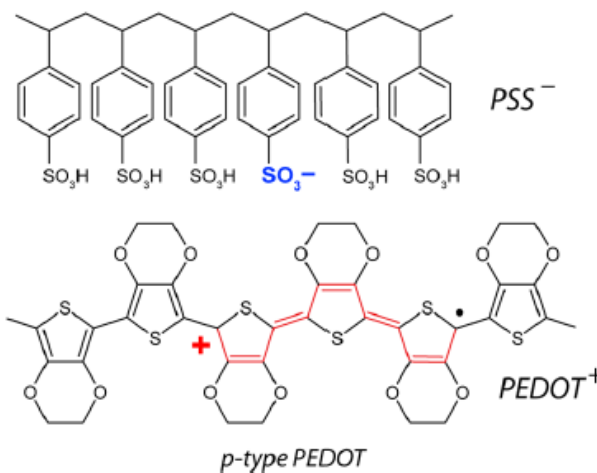




# Why Organic? Bioelectronic Interfaces (BEIs)



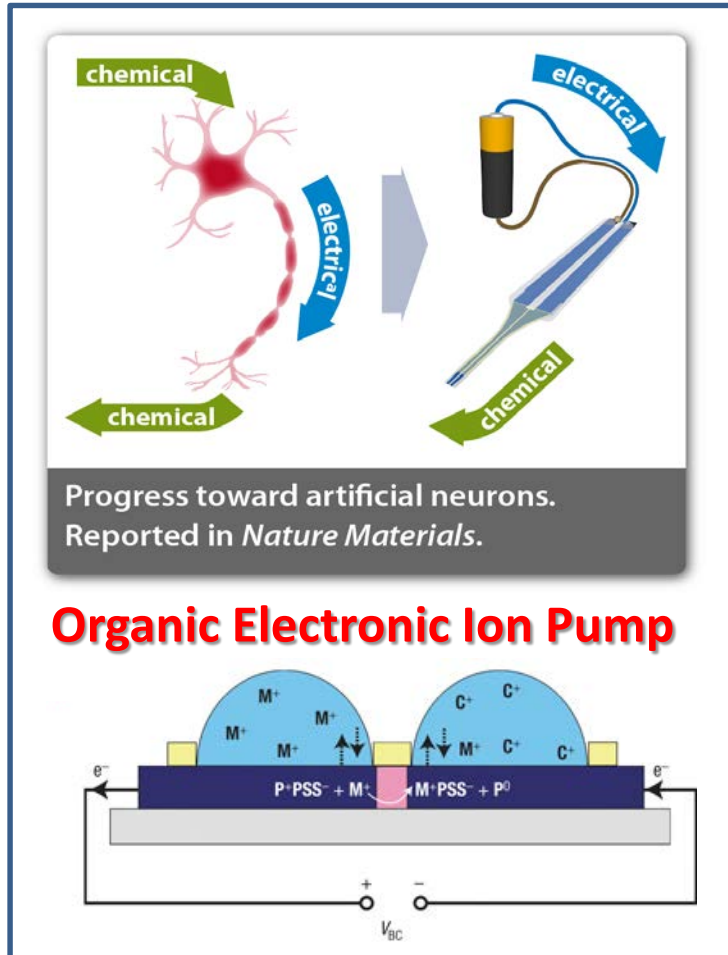
**Conducting polymers show mixed conductivity**



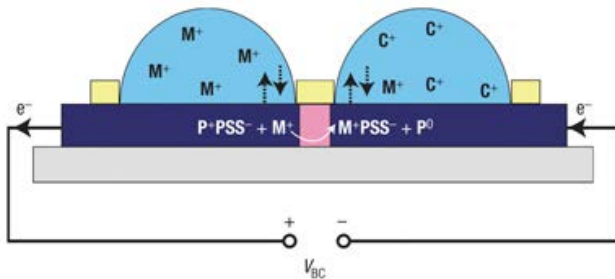
# Organic Electronics meets Biology

**Organic electronics** provide the future application demand  
– the “silicon” based devices are unable to provide!!

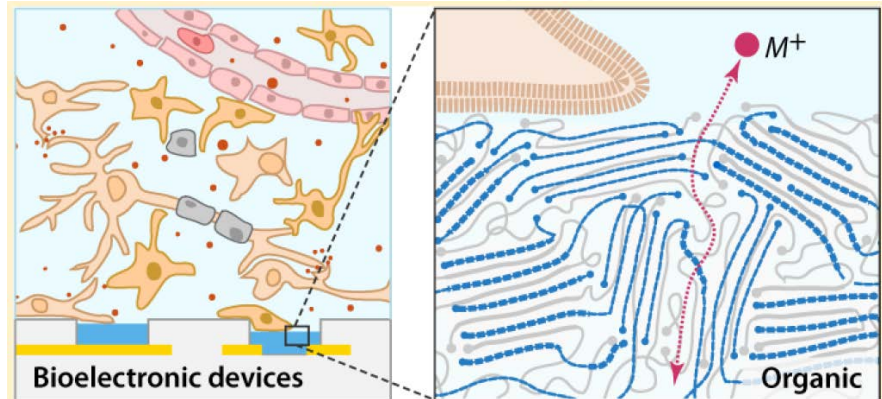
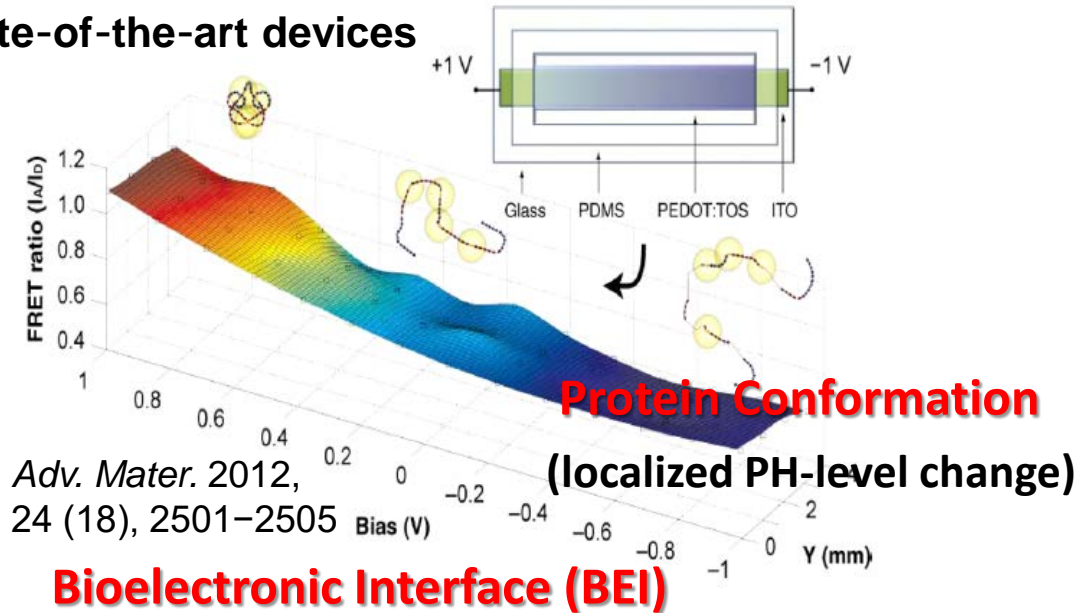
Mixed conductivity leads to novel/state-of-the-art devices



## Organic Electronic Ion Pump



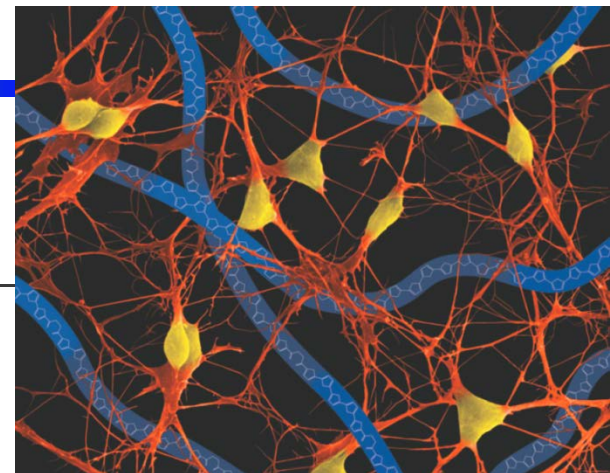
*Nature Materials* 2007, 6, 673-679



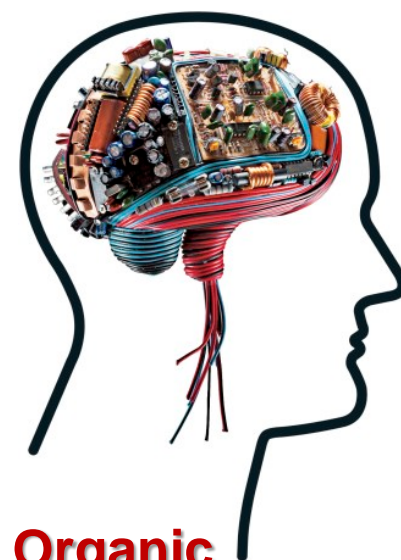
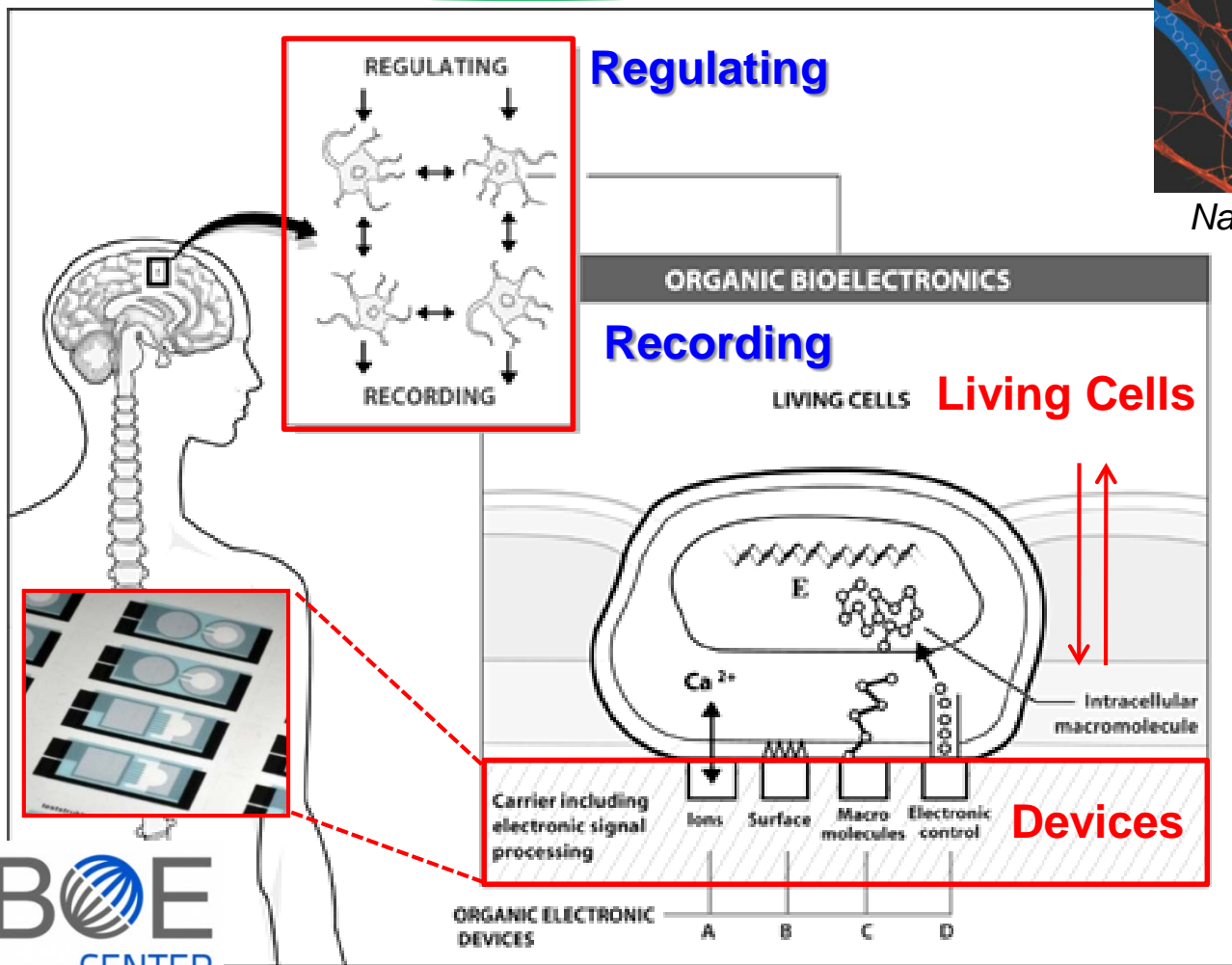
*Chem. Mater.* 2014, 26, 679-685

# Organic Bioelectronics

**Bioelectronic Medicines:** Based on the knowledge obtained from biology, electronics and surface engineering, it will help bring a new class of **precision medicines** to patients.



*Nature Materials*, 13 (2014), 775.

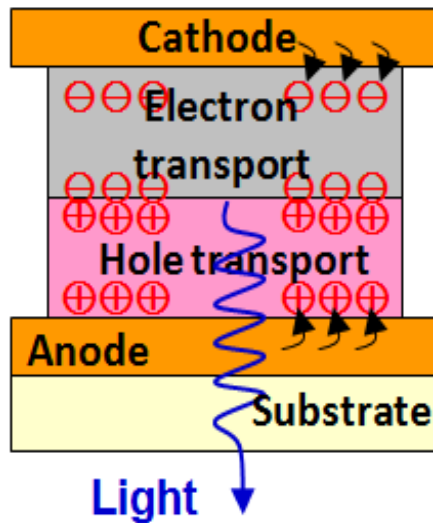


**Organic Bioelectronic Medicines**



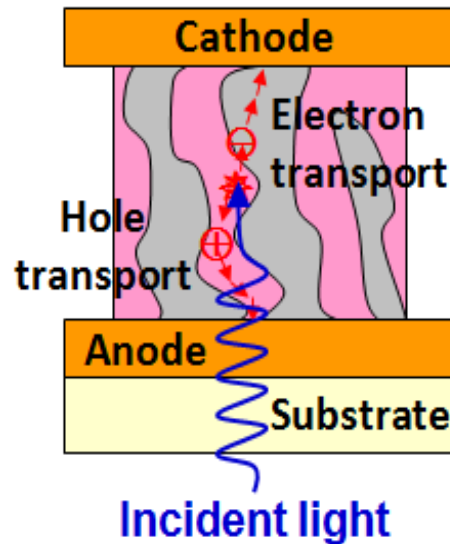
# Organic Electronics and Pi Materials

## Organic Light Emitting Diode (OLED)



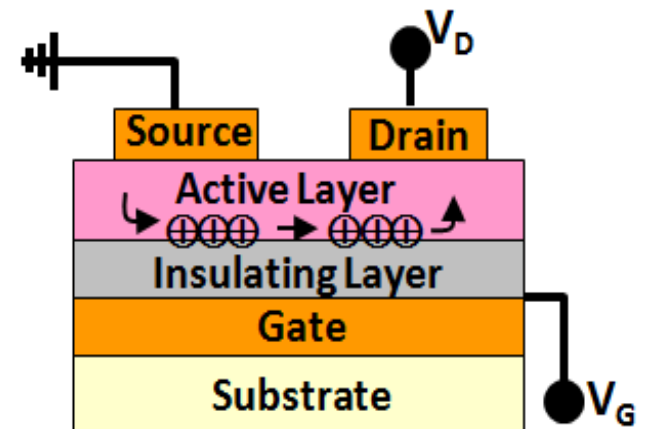
(a) Electron/Hole injection

## Organic Photovoltaic (OPV)



(b) Photoexcitation

## Organic Thin film Transistor (OTFT)



(c) Electroactive operation for dynamic doping



OLED

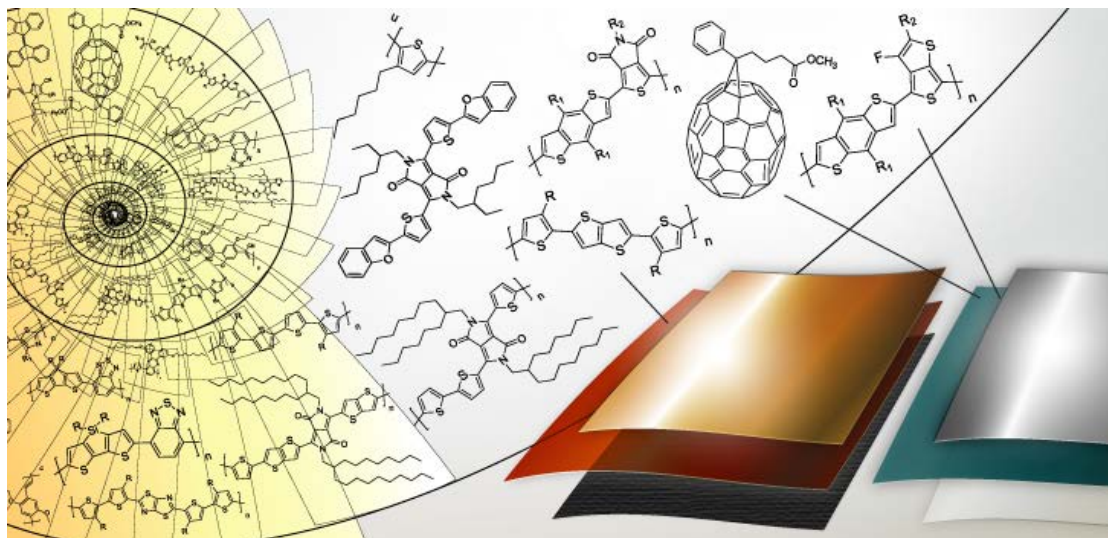


OPV

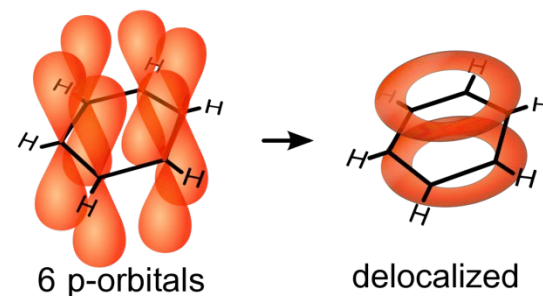


OTFT

# Fundamental knowledge of Pi Materials



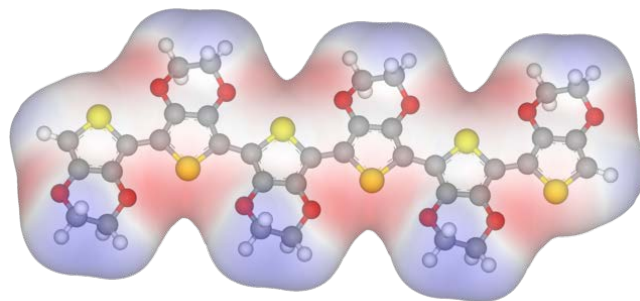
## Pi-conjugated materials



**Hybridization:  $sp^2$  and  $p_z$**

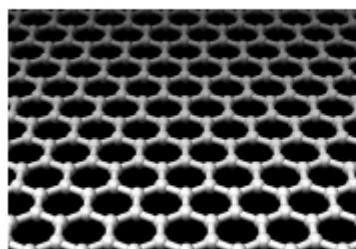
**Pi-conjugated materials** are carbon-based macromolecules which have extended chains of **alternating single and double bonds**. As a result, the macromolecule has **pi-electrons** that reside above and below the molecular plane of the chains.

## Conducting Polymers



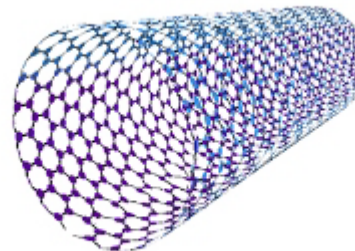
## Carbon Materials

2-D



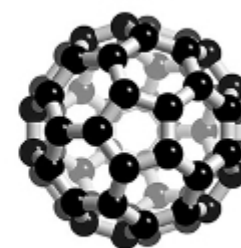
Graphene

1-D



Carbon nanotube

0-D

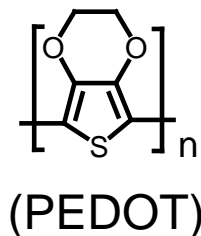
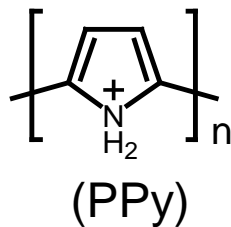
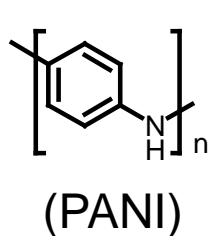


Fullerene (C<sub>60</sub>)

# Organic BEI Materials

External Stimulation

## 1. Conducting polymeric materials

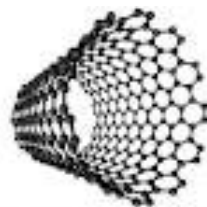


Electrical conductivity

~ 40 S/cm    ~ 40 S/cm    ~4000 S/cm

External Stimulation

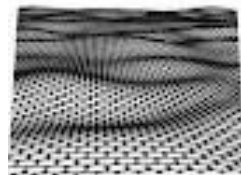
## 2. Carbon materials



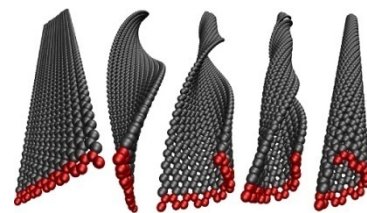
(CNT)



(C<sub>60</sub>)



(Graphene)



(CNR)

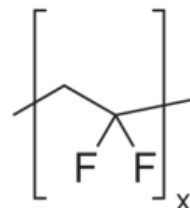
Localize Stimulation

Biology

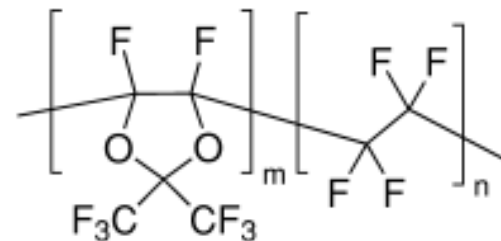
Bioelectronic Interface  
(BEI)

Electronics

## 3. Piezoelectric polymeric materials



(PVDF)



(Teflon AF)

piezoelectric coefficient

20~350 pC/N

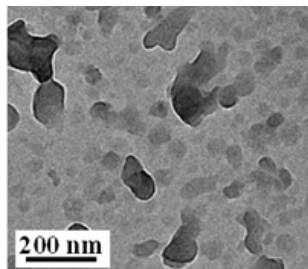
~600 pC/N



# Organic BEI Materials

## PEDOT

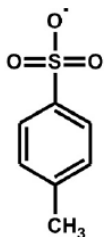
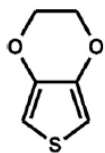
### (1) Prepare by polymer solution



(PEDOT:PSS)

### (2) Chemical polymerization

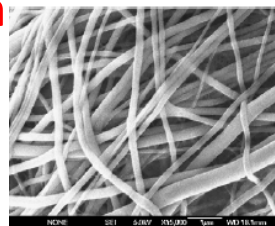
EDOT



(Fe<sup>3+</sup>)

Oxidizer:

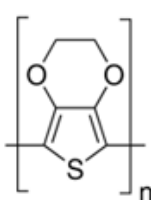
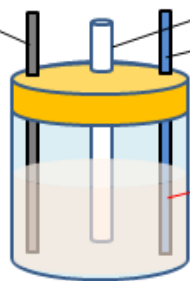
iron(III) tosylate (TOS)



### (3) Electropolymerization

Counter Electrode (C): Pt      Reference Electrode (R): Ag/AgCl

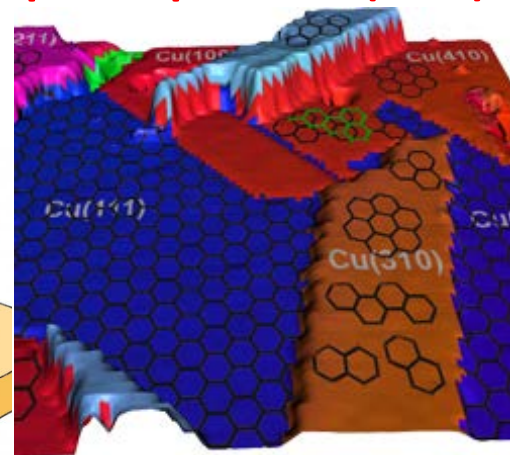
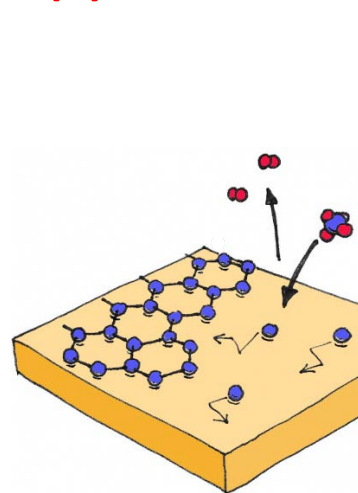
Working Electrode (W): ITO



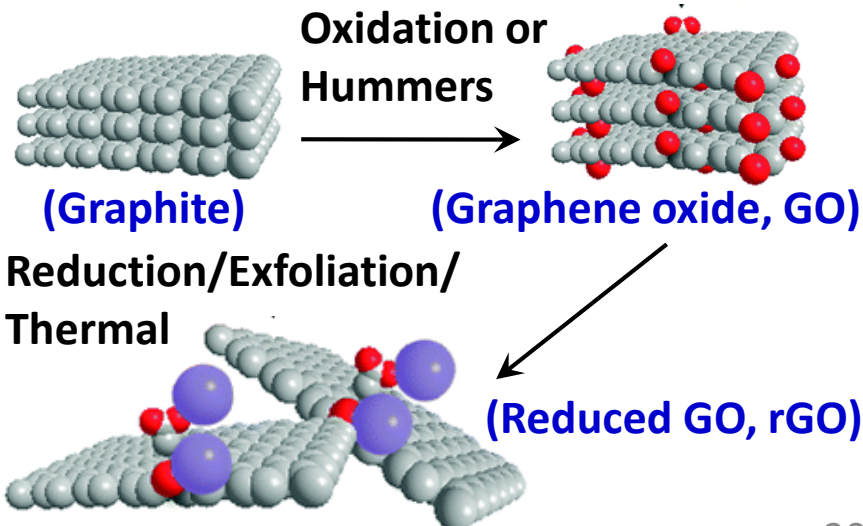
microemulsion  
polymerization

## Graphene

### (1) Chemical vapor deposition (CVD)

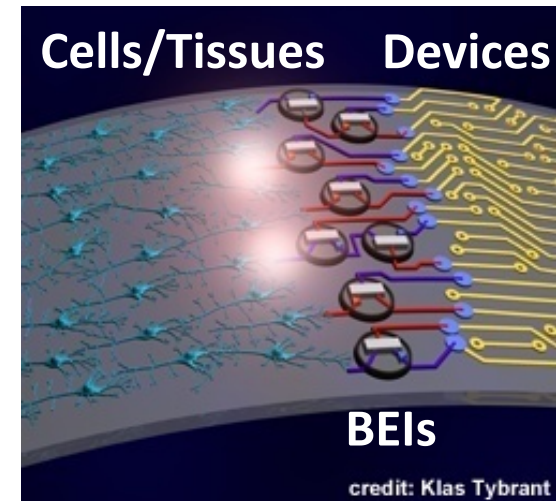
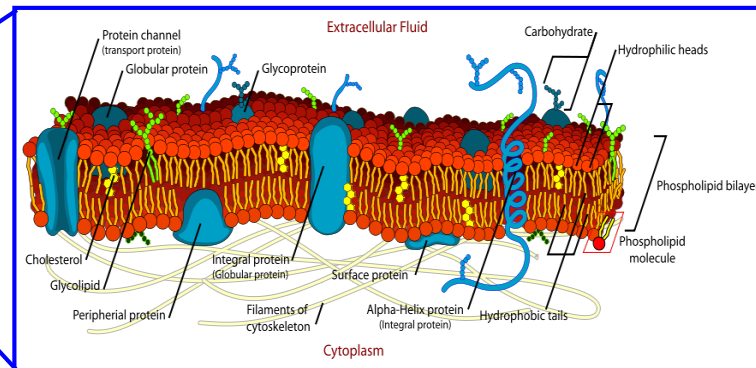
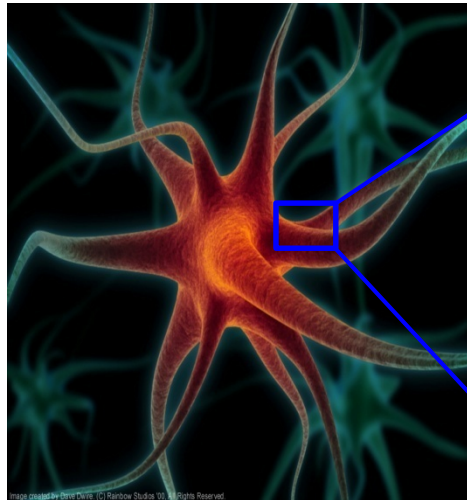


### (2) Spin-coating of GO or rGO solution

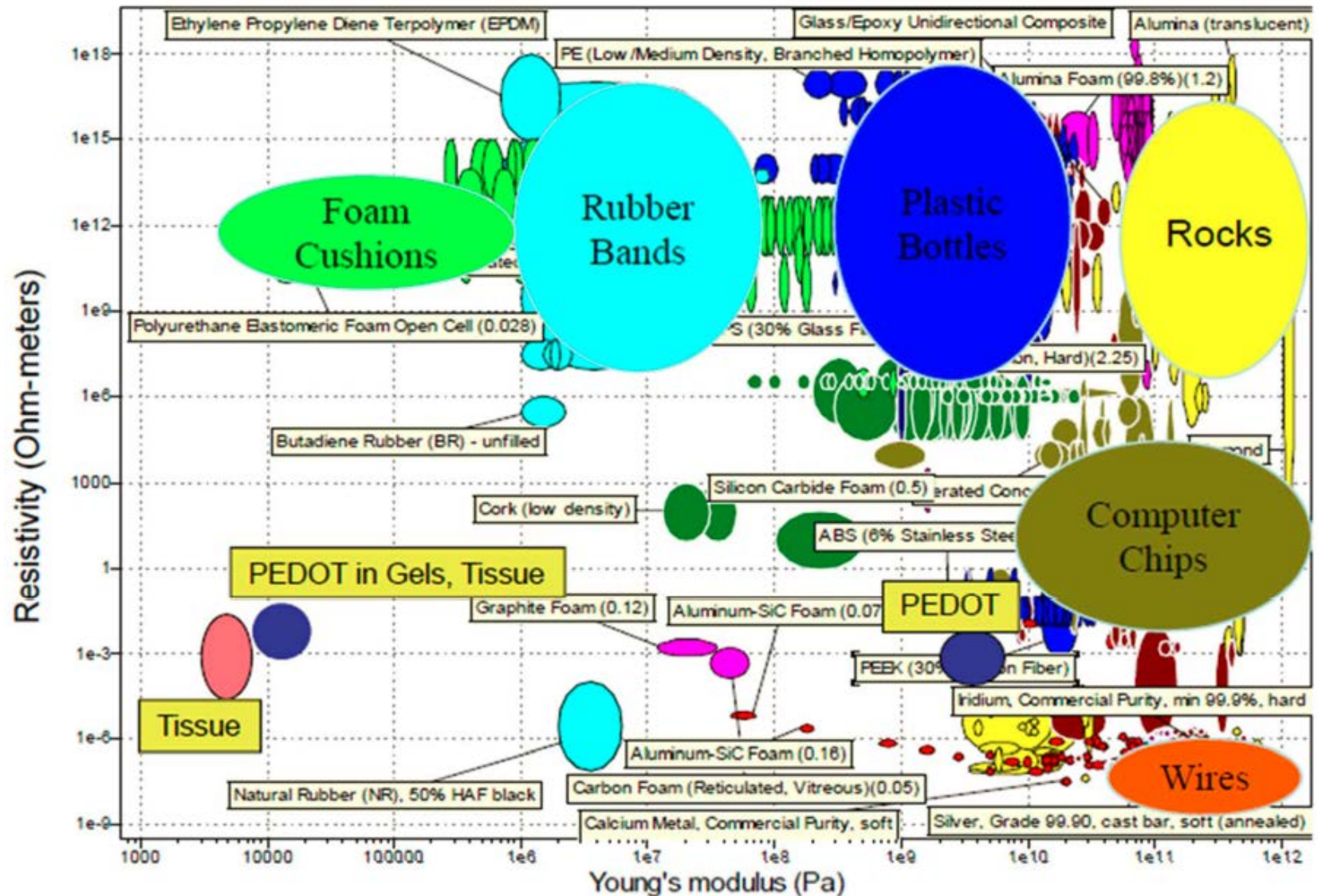


# Critical Properties of Organic BEIs

- **Biocompatible and biodegradable** (surface engineering; stiffness)
- **Easily doped or conjugated with functional materials** (high functionality)
- **High integration to OM systems** (high transparency)
- **Solution process** (low cost; mass production; compatibility with fabrication)
- **Responsive actions** (temp.; PH; pressure; light; electrical etc.)
- **Cell-electrode interface** (charge-electron transporting; low Impedance)
- **Signal transduction** (biomolecules; ionic transporting; action potential)



# Conducting polymers match properties of tissue



Slide courtesy of Dave Martin (U. Delaware)

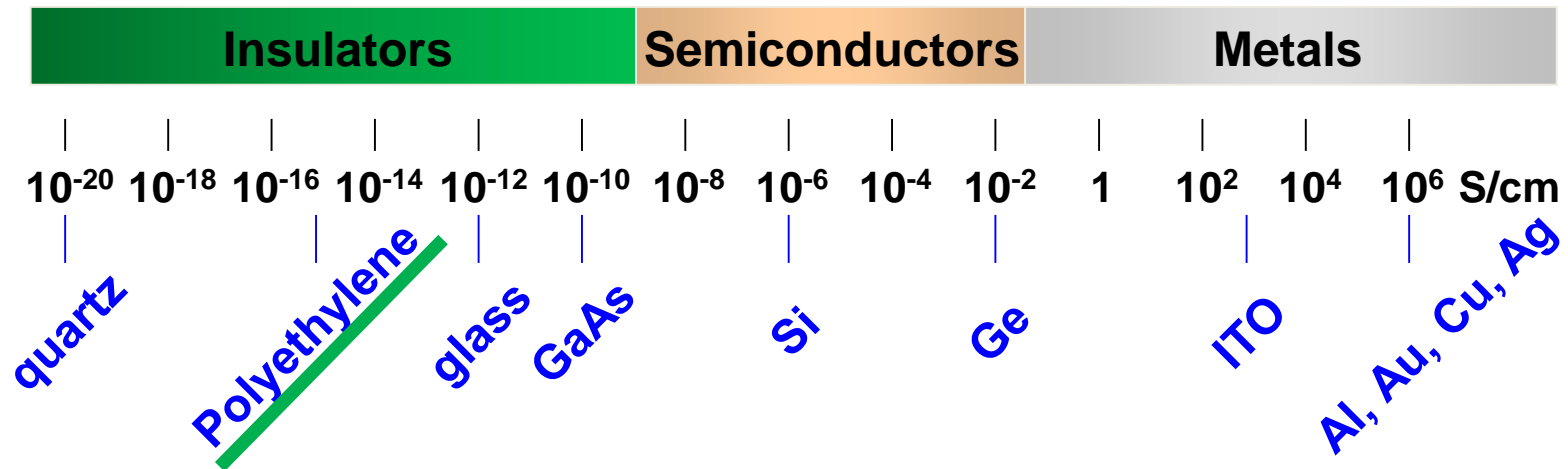


# Fundamental knowledge of Polymeric Materials

- **Polymers** are macro molecules formed of many identical units (called repeated units) bound to each other like pearls in a necklace.
- Flexibility & Lightweight.
- Cheap cost of production.
- Good electrical insulation.



**Applications:**  
Plastics  
Rubbers  
Fibers  
Coatings

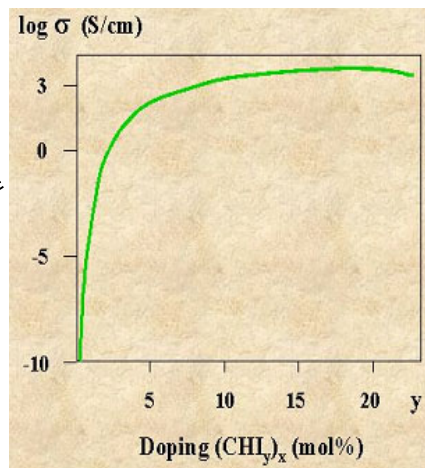
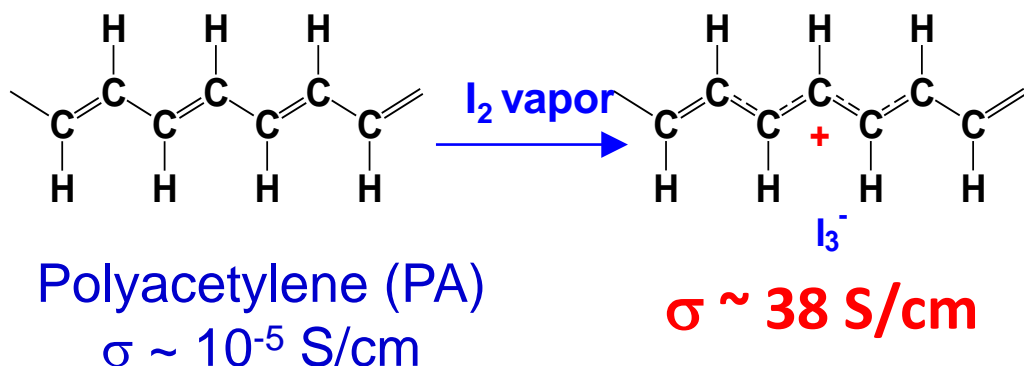


**Plastics can be electrically conductive?!**

# The first conjugated conductive polymer established

1977, H. Shirakawa, A. G. MacDiarmid & A. J. Heeger

## Doping of Polyacetylene



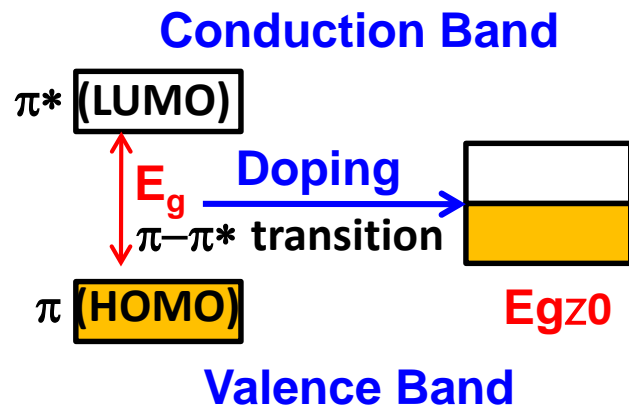
Discovery of **doping phenomena** and resulting **10 order of magnitude increase** in the conductivity of polyacetylene

***Oxidation with iodine*** causes the electrons to be jerked out of the polymer, leaving "**holes**" in the form of **positive charges** that can move along the chain.

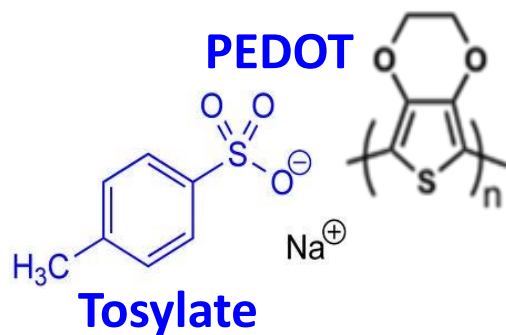
1977  $\sigma = 38 \text{ S/cm}$   
2000  $\sigma = 30\,000 \text{ S/cm}$   
2000  $\sigma_{\text{max}} = 10^5 \text{ S/cm}$   
 $\sigma_{\text{Cu,Ag}} = 10^6 \text{ S/cm}$

Discovery of conducting polymers and the ability to dope these polymers over the full range from **insulator to metal**

# Chemical, Optical and Electrical Properties of Organic Semiconducting Materials



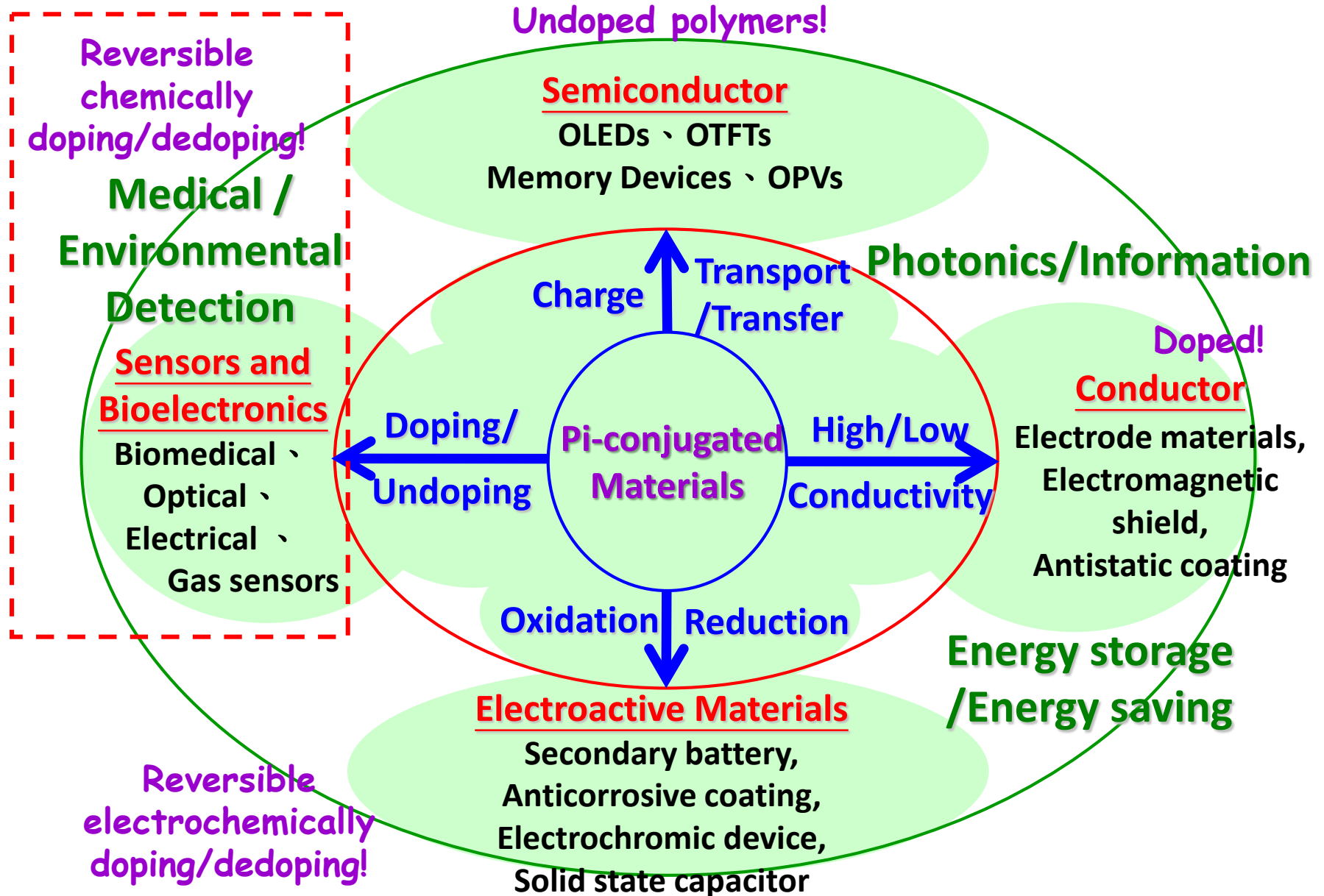
## 聚3,4-乙撑二氧噻吩(PEDOT)



Polymer	Structure	Doping Materials	Conductivity (S/cm)
Polyacetylene <b>PA</b>	$(\text{CH})_n$	$\text{I}_2, \text{Br}_2, \text{Li}, \text{Na}, \text{AsF}_2$	$10,000^a$
Polypyrrole <b>PPy</b>		$\text{BF}_4^-, \text{ClO}_2^-, \text{tosylate}^b$	500-7500
Polythiophene <b>PTh</b>		$\text{BF}_4^-, \text{ClO}_2^-, \text{tosylate}^b, \text{FeCl}_3$	1000
Poly(3-alkylthiophene) <b>PTh</b>		$\text{BF}_4^-, \text{ClO}_2^-, \text{FeCl}_2^+$	$1000-10,000^a$
Polyphenylene sulfide <b>PPS</b>		$\text{AsF}_2$	500
Polyphenylene-vinylene <b>PPV</b>		$\text{AsF}_2$	$10,000^a$
Polythienylene-vinylene		$\text{AsF}_2$	$2700^a$
Polyphenylene <b>PPP</b>		$\text{AsF}_2, \text{Li}, \text{K}$	1000
Polyisothianaphthene		$\text{BF}_4^-, \text{ClO}_4^-$	50
Polyfuran		$\text{BF}_4^-, \text{ClO}_4^-$	100
Polyaniline <b>PANI</b>		$\text{HCl}$	$200^a$

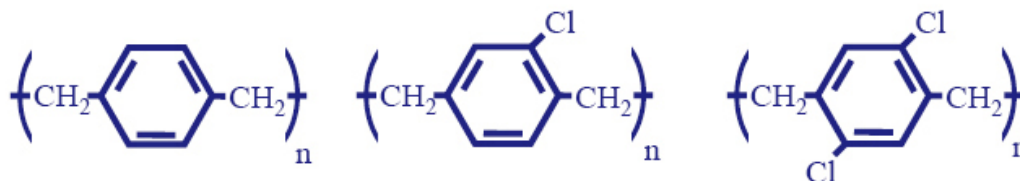
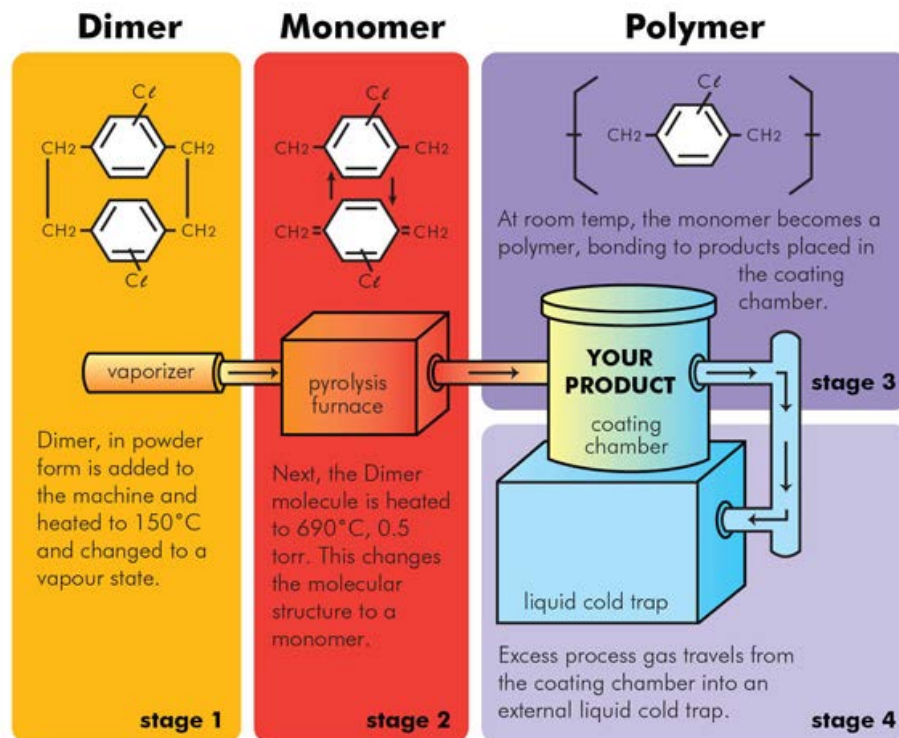
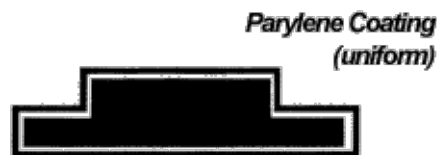
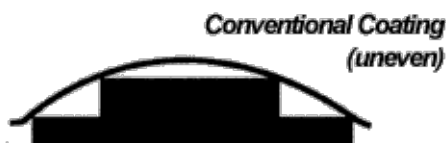
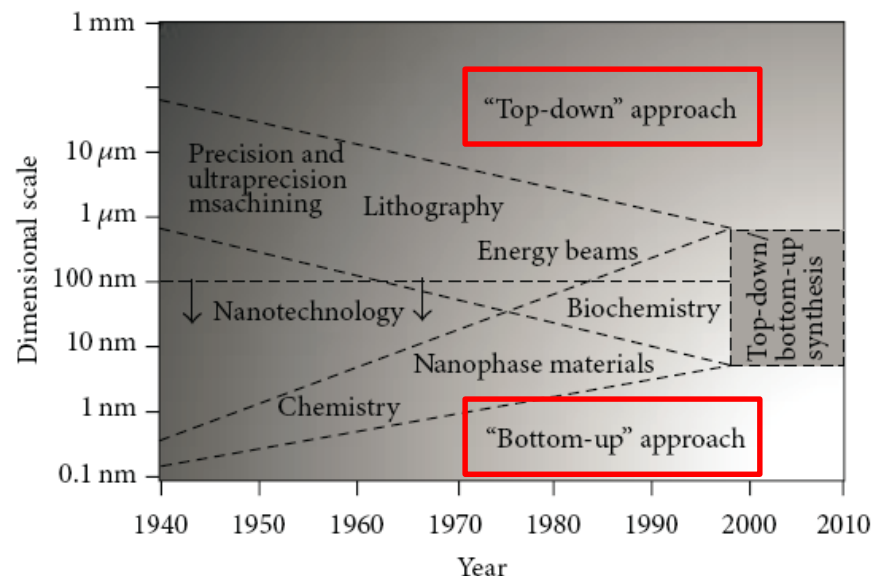


# Pi-conjugated Materials and their Applications

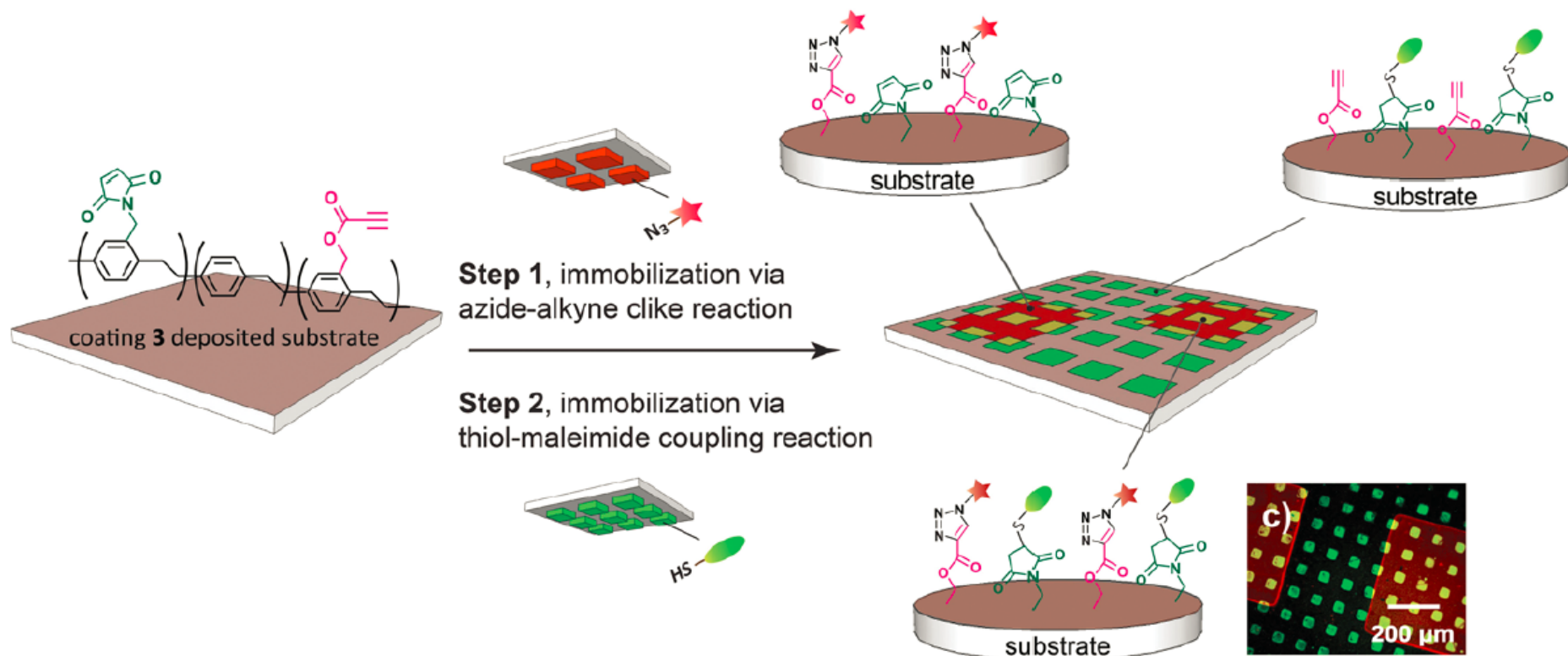
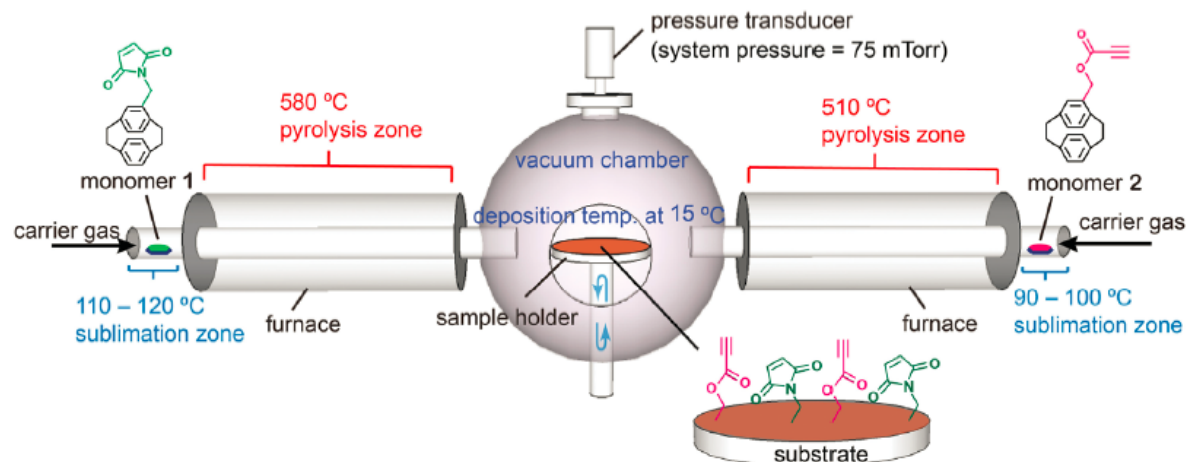


# Micro/Nanofabrication Technologies

## • Chemical Vapor Deposition (CVD)



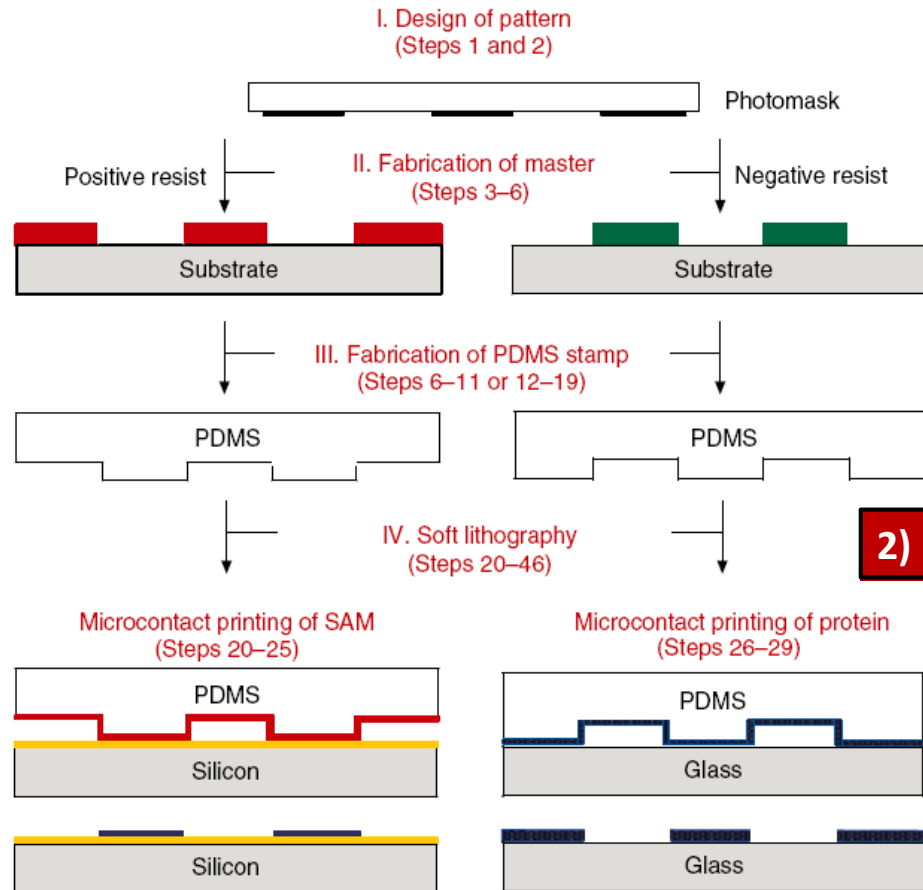
# Vapor-Based Multicomponent Coatings for Antifouling and Biofunctional Synergic Modifications





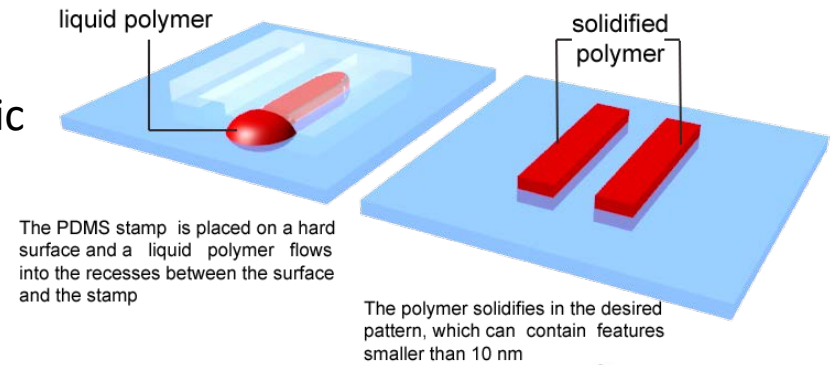
# • Soft Lithography

They are essentially based on **printing, molding, embossing, and transferring** with an elastomeric stamp.

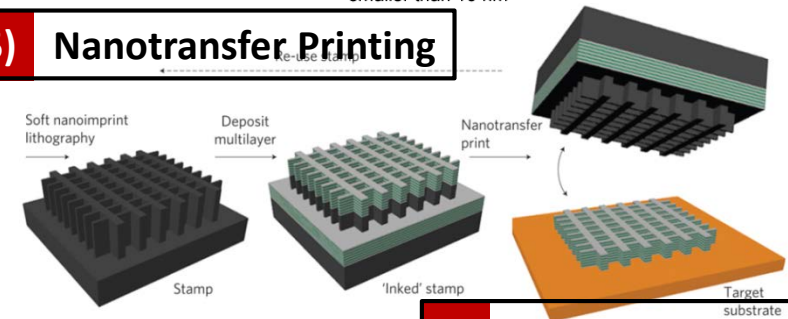


## 1) Microcontact Printing ( $\mu$ CP)

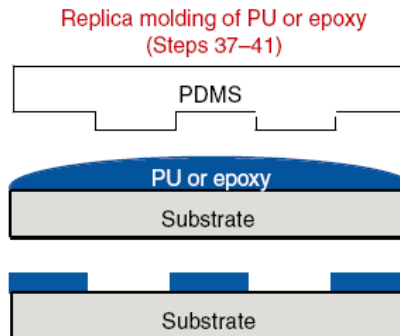
## 4) Micro-molding in Capillaries (MIMIC)



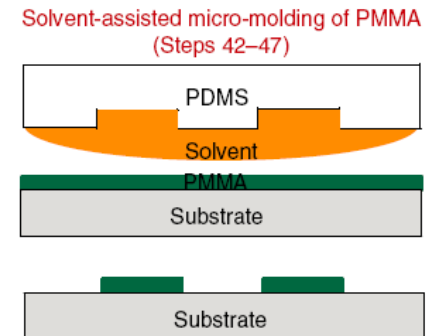
## 5) Nanotransfer Printing



## 2) Replica Molding (REM)

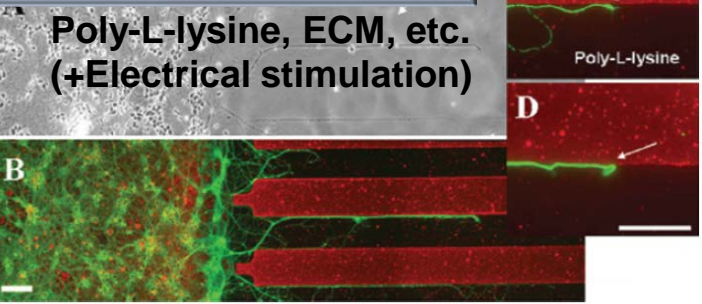


## 3) Solvent-assisted Micromolding (SAMIM)

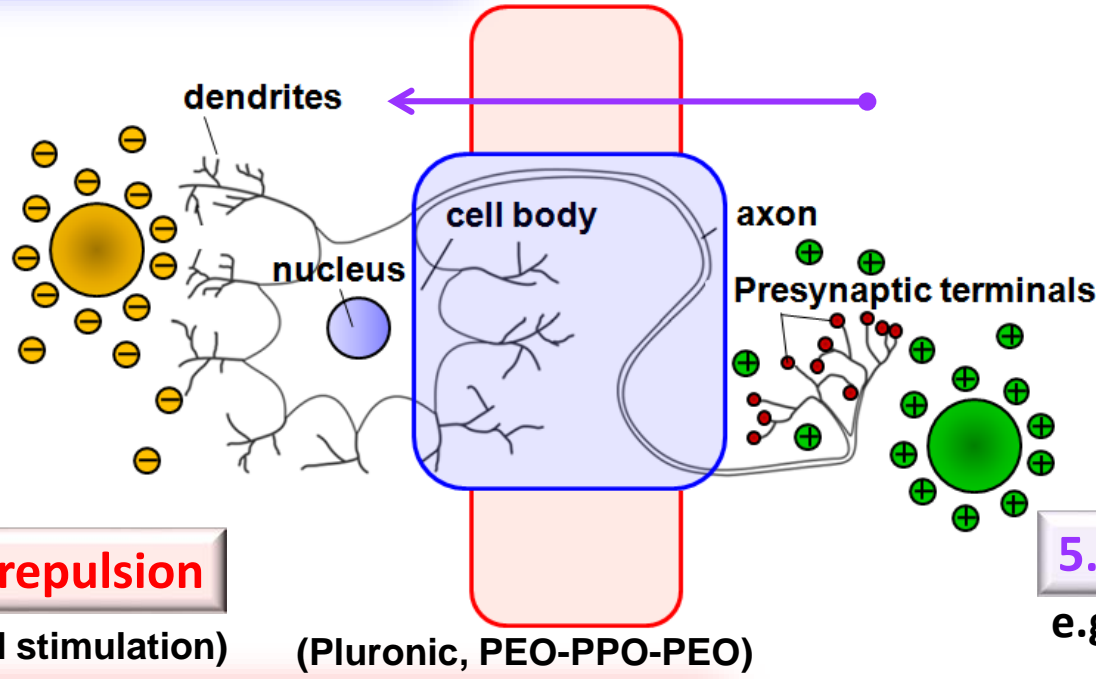


**Figure 1** | Schematic illustration of the four major steps involved in soft lithography and three major soft lithographic techniques.

**1. Contact attraction**

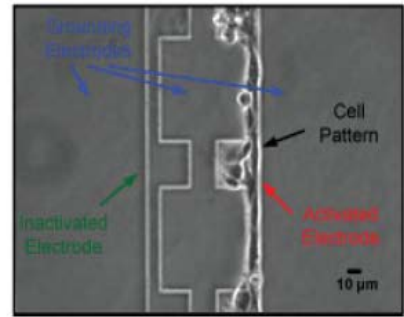
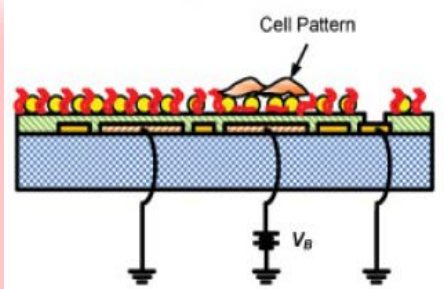


**(1) Artificial Designs for Cell Manipulation : (e. g., Neuron Cells) (1-5)**  
**(Extracellular Environments)**

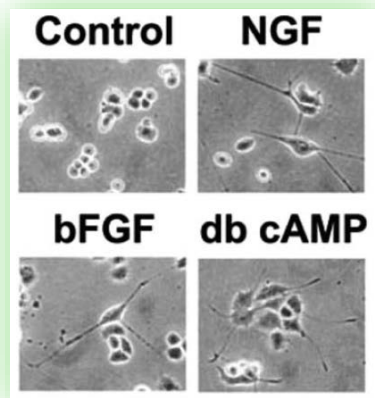


**2. Contact repulsion**

(+Electrical stimulation)



**3. Chemoattraction**



**4. Chemorepulsion**

**5. Electrical Field**

e.g., Dielectrophoresis (DEP)

**Electrical response:**

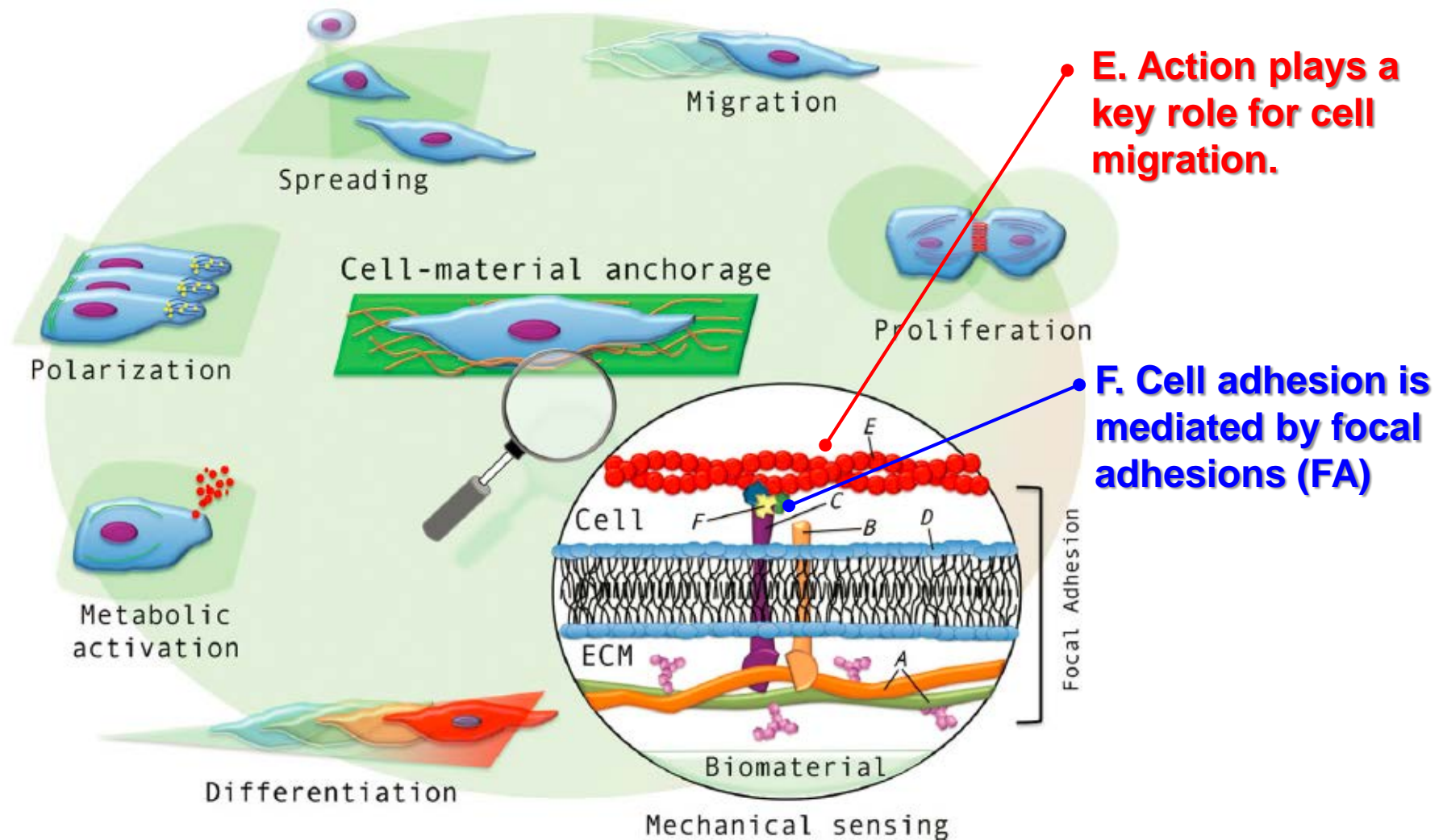
- Signaling
- Stimulation

**Photo response:**

- Stimulation

Neuron cell.  
Osteoblast.  
Myoblast.  
Fibroblast.

# Cell–Substrate Anchorage Driving Key Cellular Processes

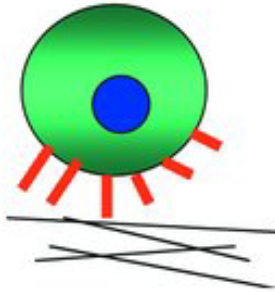




# Cell Adhesion

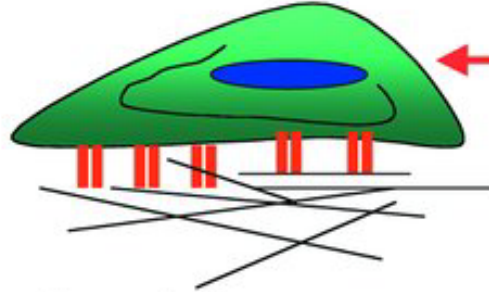
## Cell-Substrate Interaction:

**Weak Adhesion**  
(attachment)



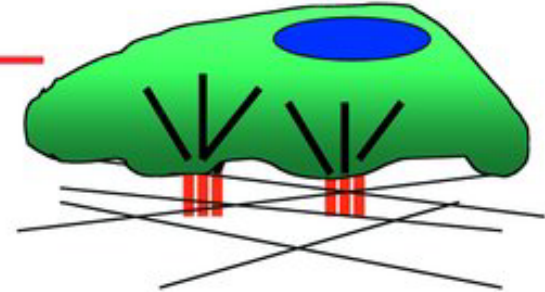
Cell death  
beyond  
apoptosis

**Intermediate Adhesion**  
(Cell shape and spreading)

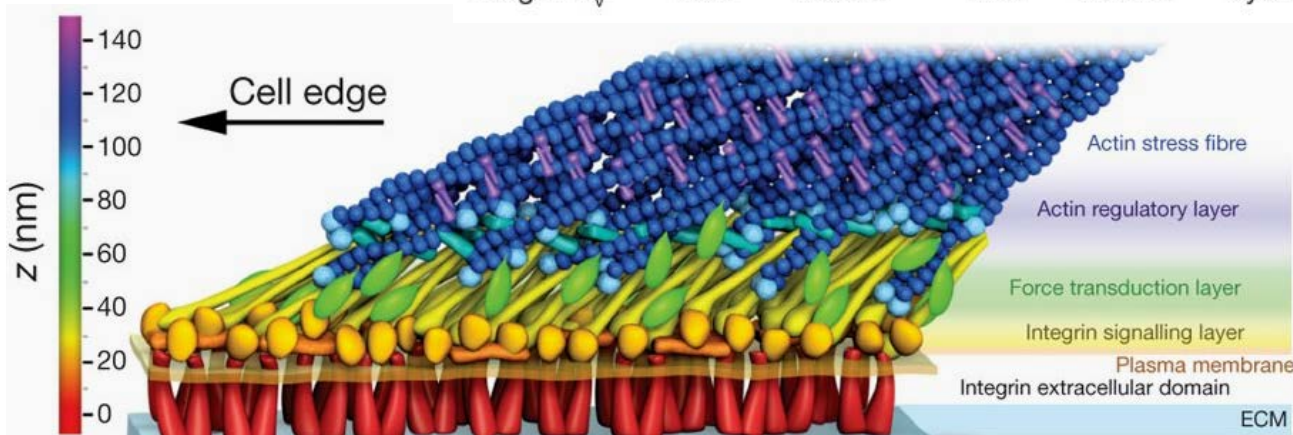


cell survival  
differential gene expression  
motility?

**Strong Adhesion**  
(Focal adhesion and stress fibers)

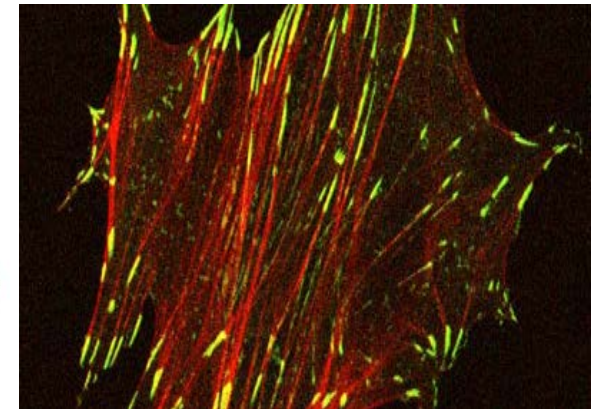
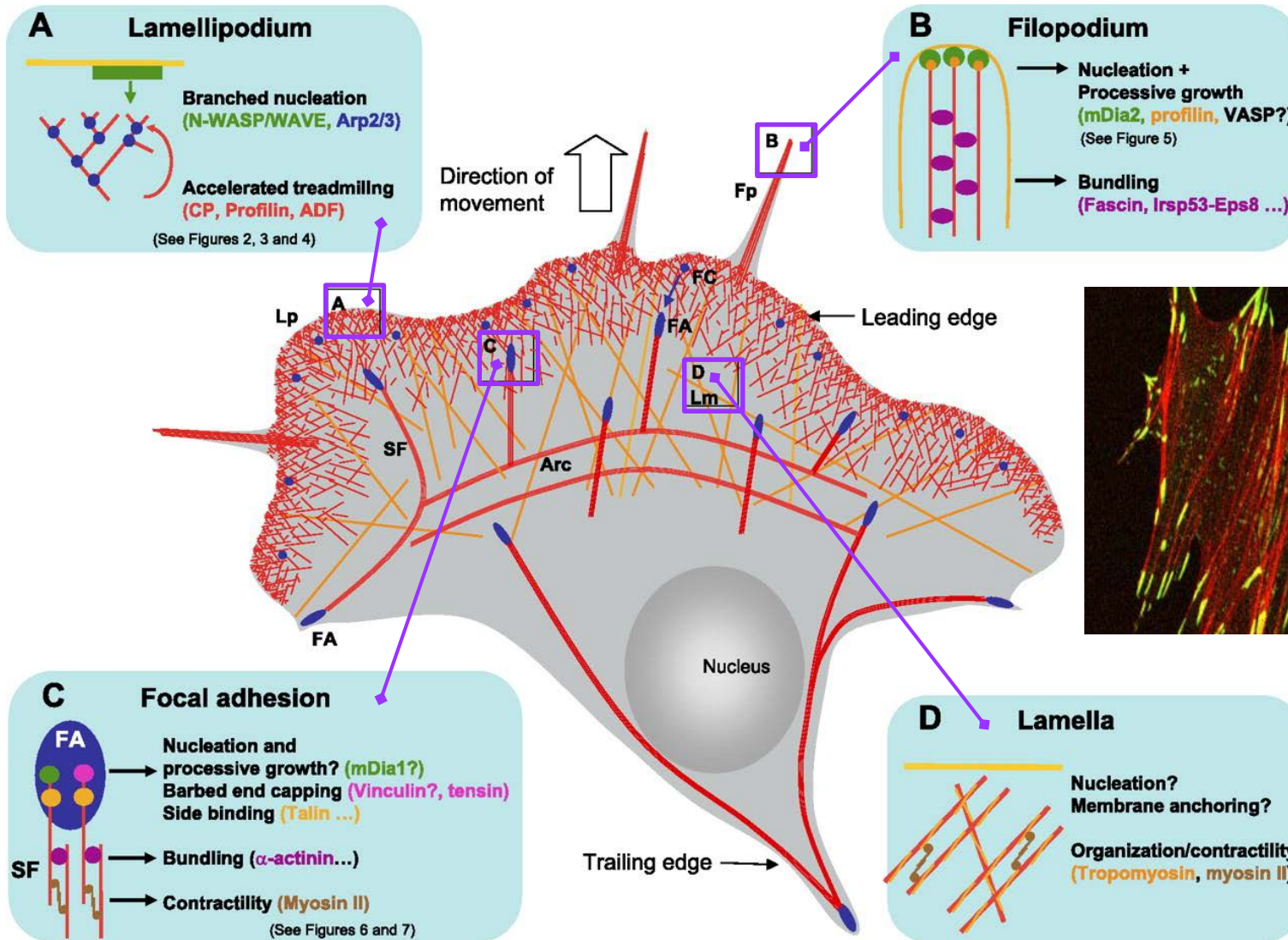


cell growth  
cell differentiation  
stationary cells



**Focal adhesion proteins**

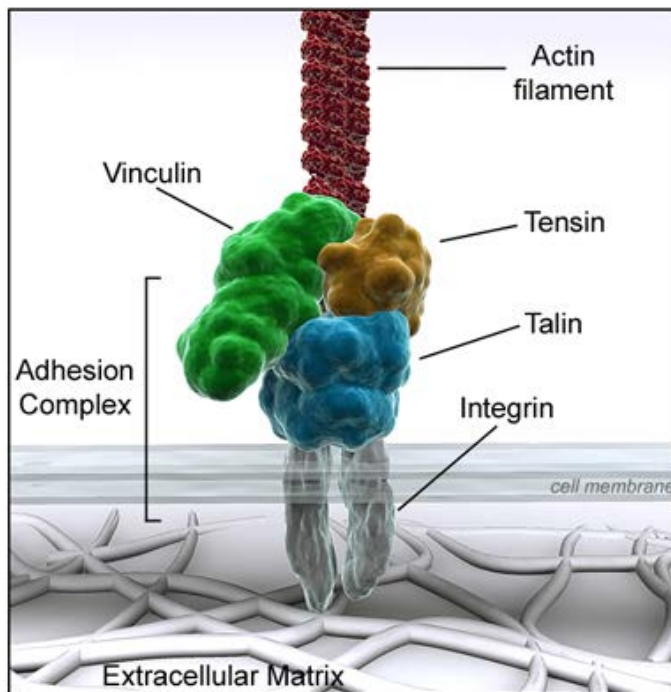
# Actin Cytoskeleton in a Migrating Cell





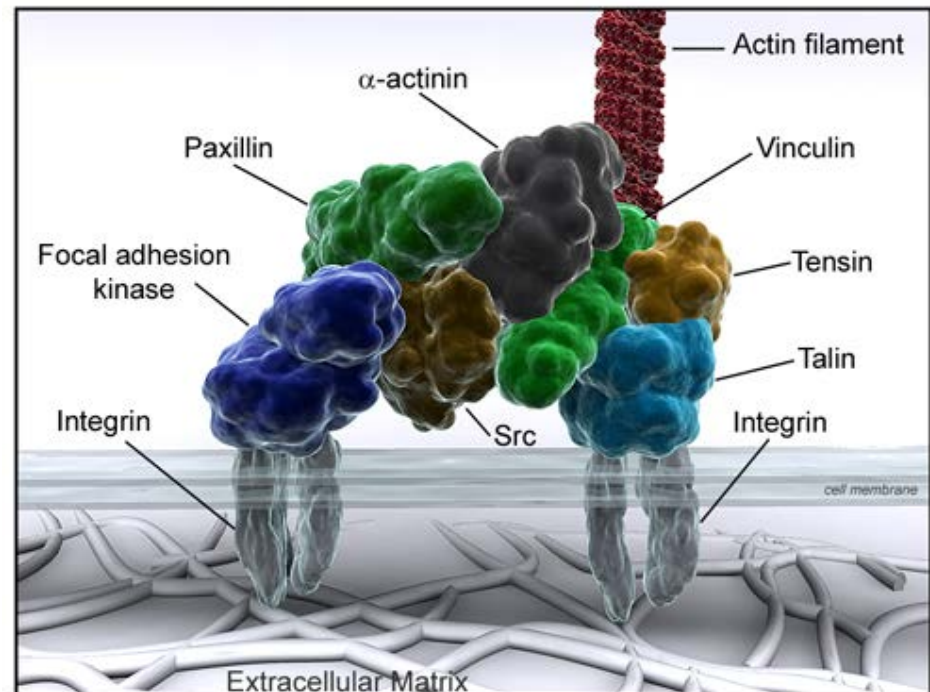
Once the **lamellipodium** has formed, **adhesion complexes** assemble and attach it to the surface allowing the **cell to generate traction**. Adhesion complexes are dynamic structures and are constantly being assembled and disassembled in actively migrating cells. These adhesion sites are composed of complexes of **more than 50 different proteins**. When the cell comes to a stop the **focal adhesion complexes (FC)** can mature into more stable focal adhesions (FA).

### Structure of an adhesion complex in migrating cells



**The dynamic assembly and disassembly of focal adhesions plays a central role in cell migration.**

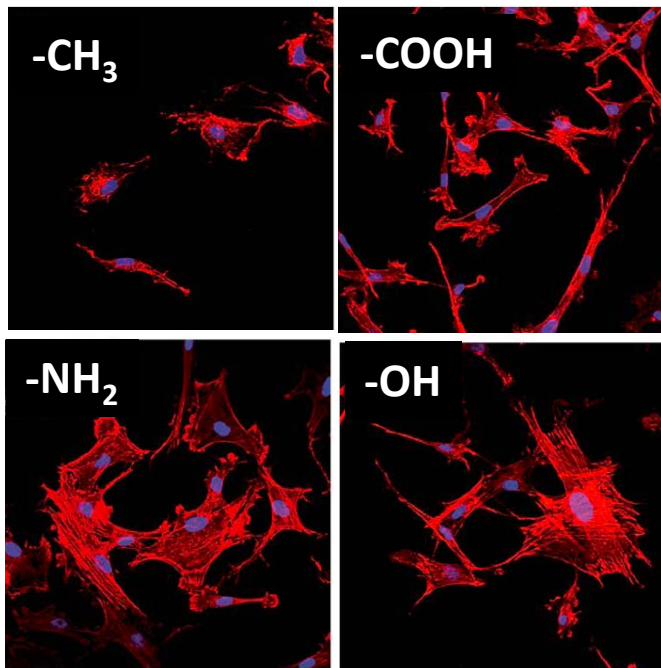
### Composition of a focal adhesion



**Mechanical force and regulatory signals are transmitted**

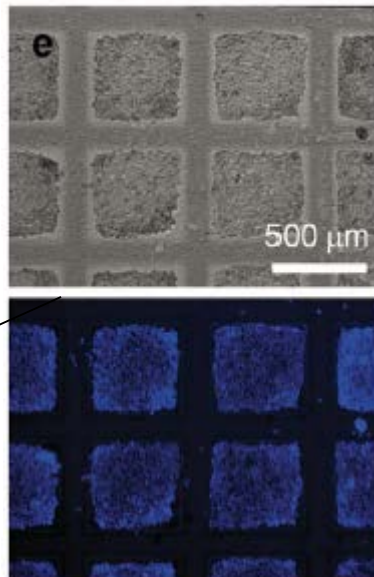
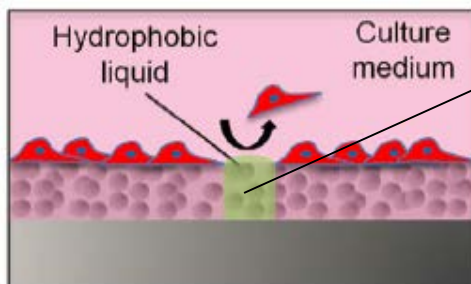


## Surface Potential



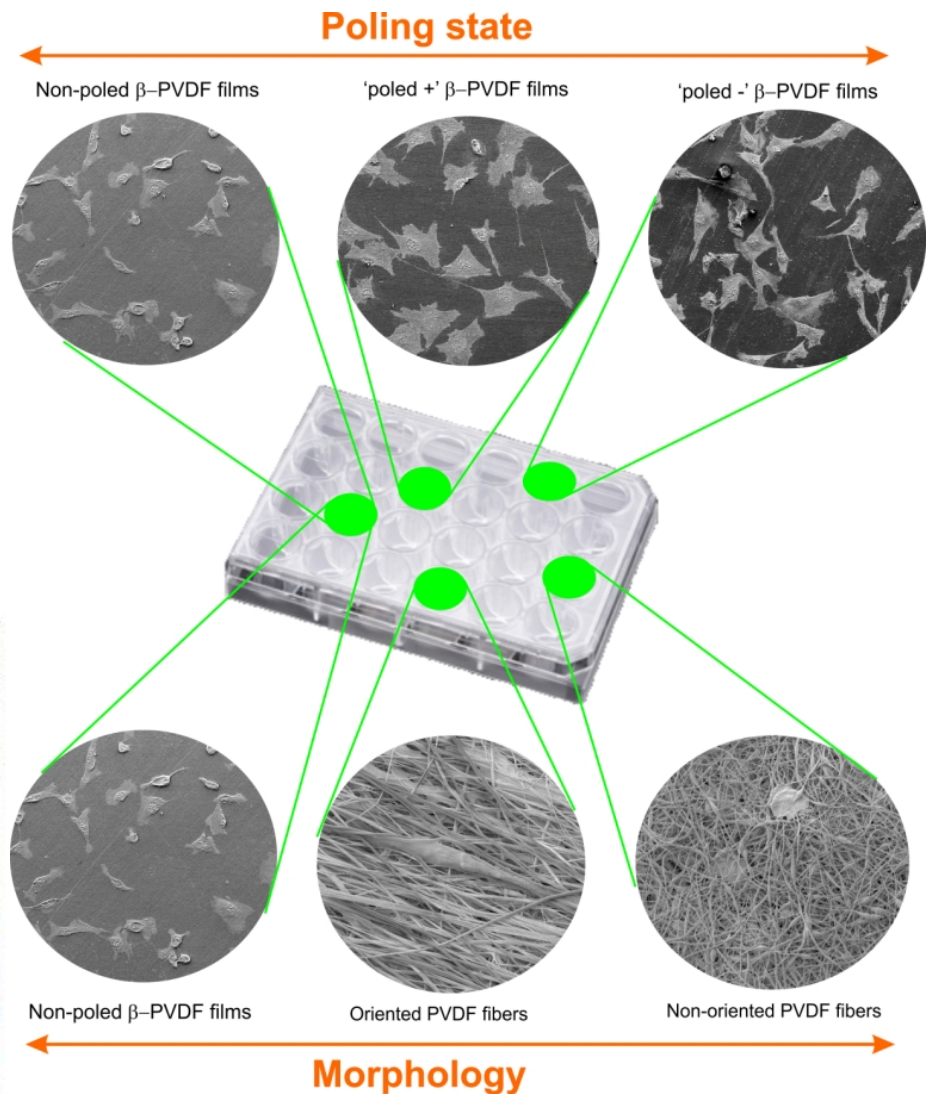
*Soft Matter*, 2011, 7, 3808

## Hydrophobic Barrier



*Adv. Healthcare Mater.* 2013, 2, 1425.

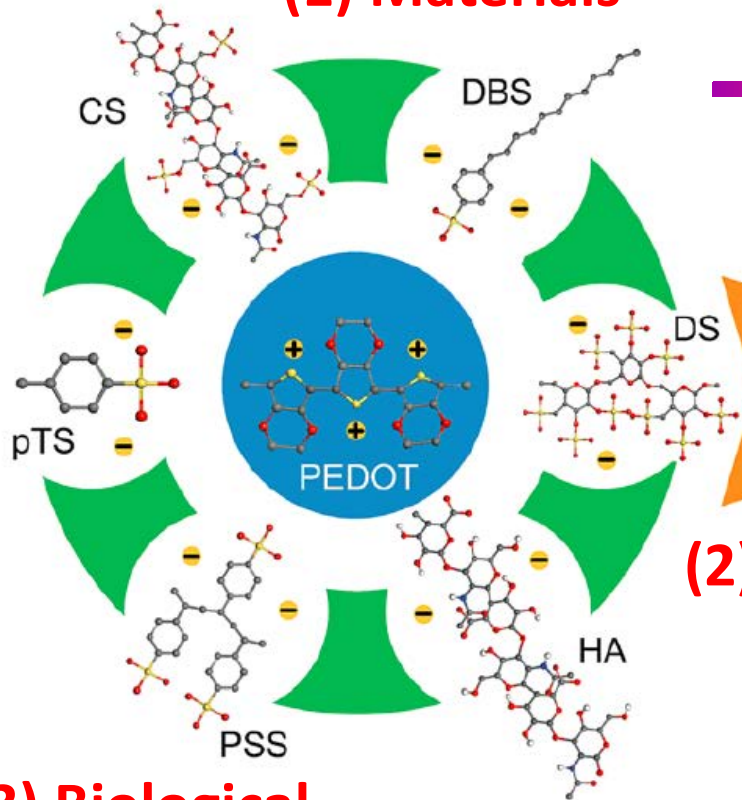
## Surface Morphology & Wettability



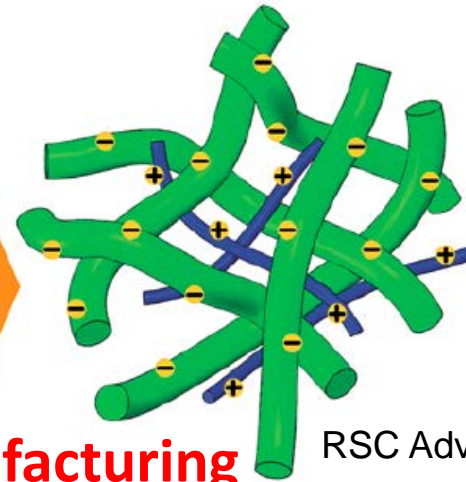
*RSC Adv.*, 2013, 3, 17938.

# Organic Bioelectronic Interfaces

## (1) Materials



*Electro-chemical Synthesis*

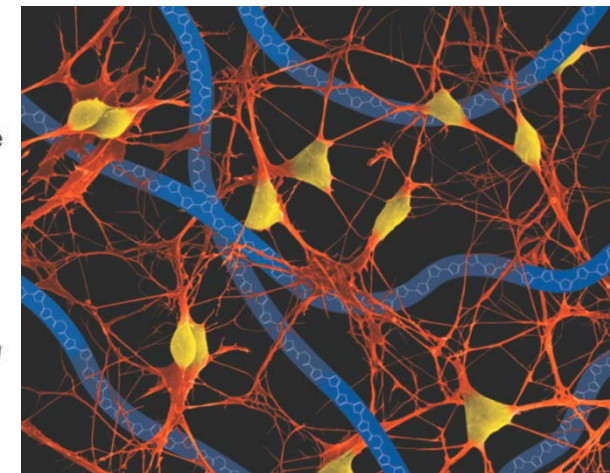
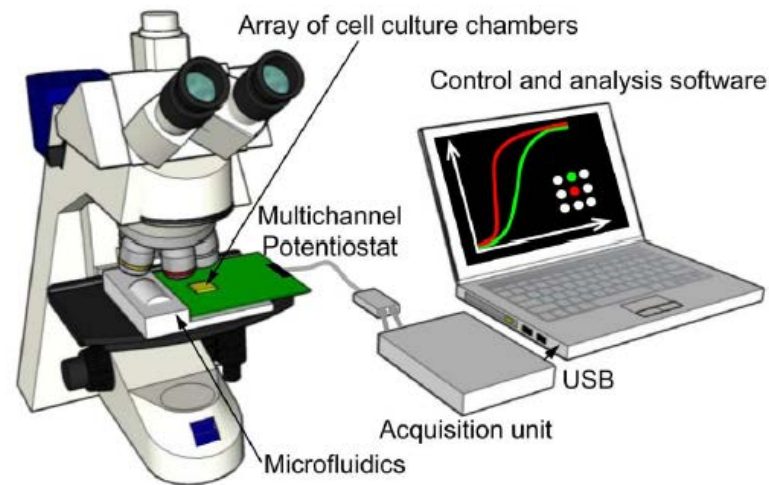


RSC Adv., 2014, 4, 47461–47471.

## (2) Manufacturing

 PEDOT  
 Dopants

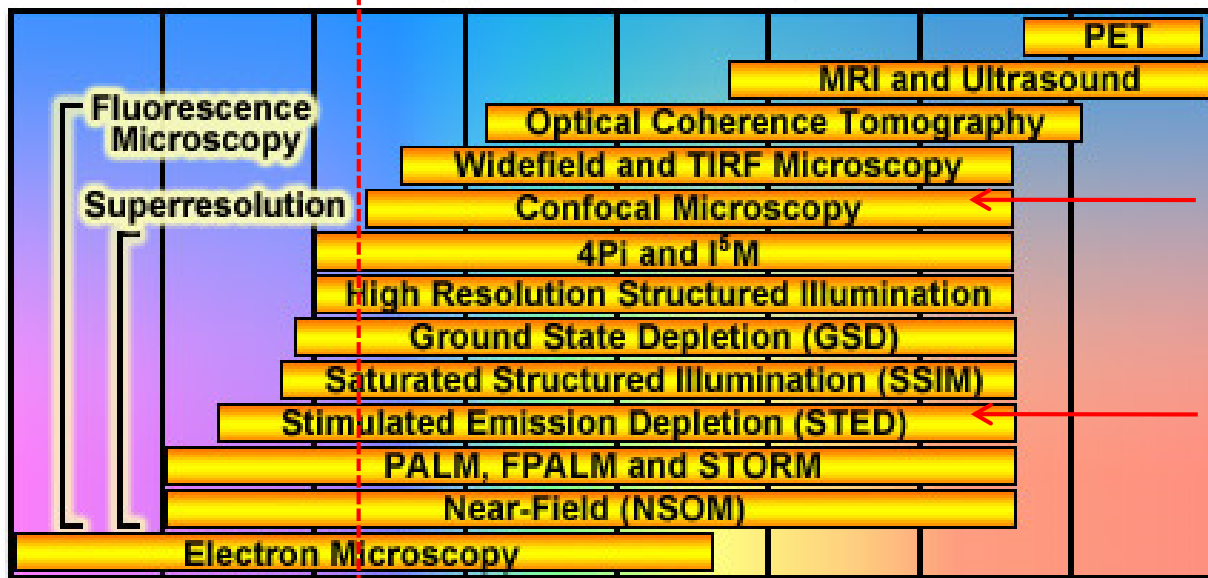
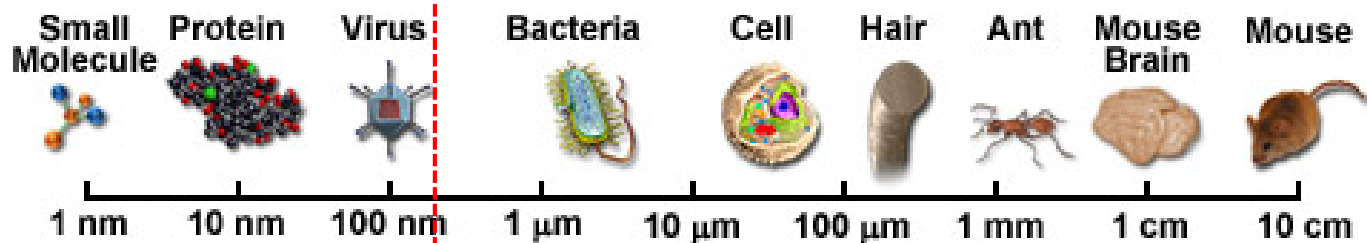
## (3) Biological Applications



*Nature Materials*, 2014,13, 775.

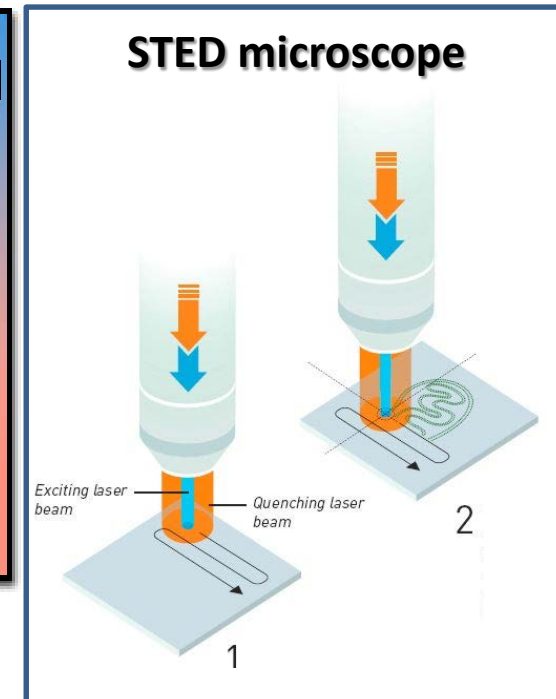
# Spatial Resolution of Biological Imaging Techniques

Abbe's Diffraction Limit ( $0.2\mu\text{m}$ )



Limit of resolution:

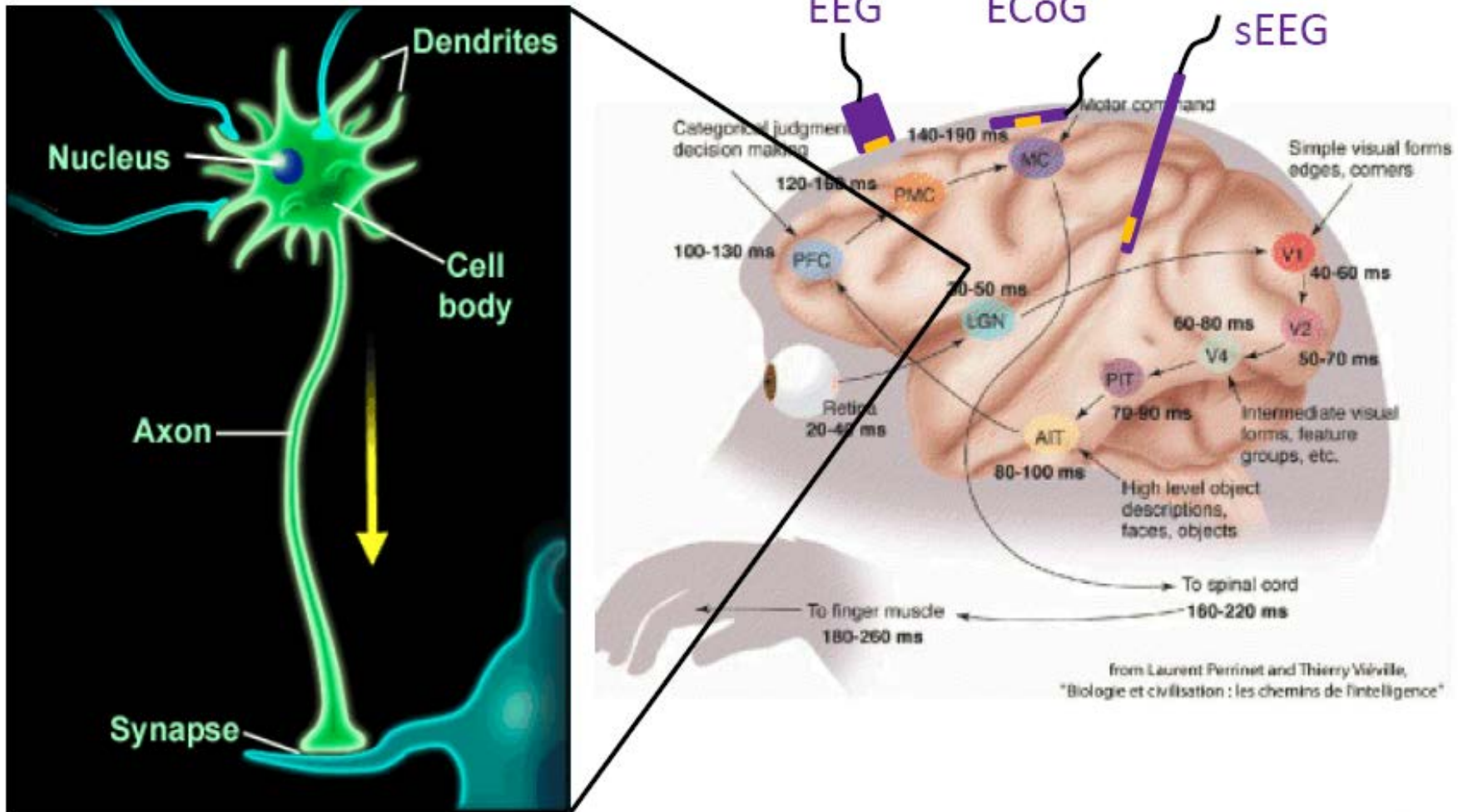
- Human eye: 0.1 mm.
- Optical microscope: 60-200 nm.
- Scanning electron microscope (SEM): 5-10 nm.
- Transmission electron microscope (TEM): 0.5 nm.



[http://www.nobelprize.org/nobel\\_prizes/chemistry/laureates/2014/](http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2014/)

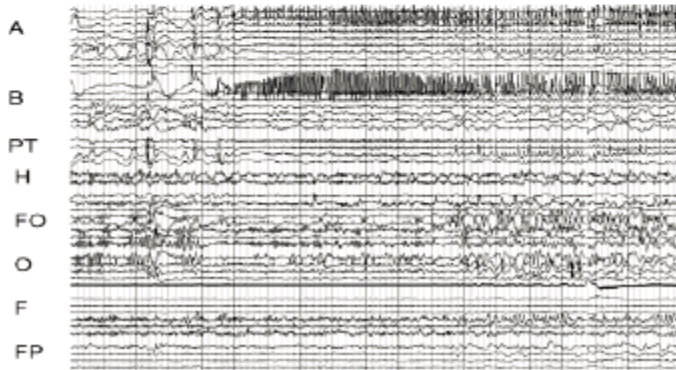


## Importance of neural interfacing



# Epilepsy

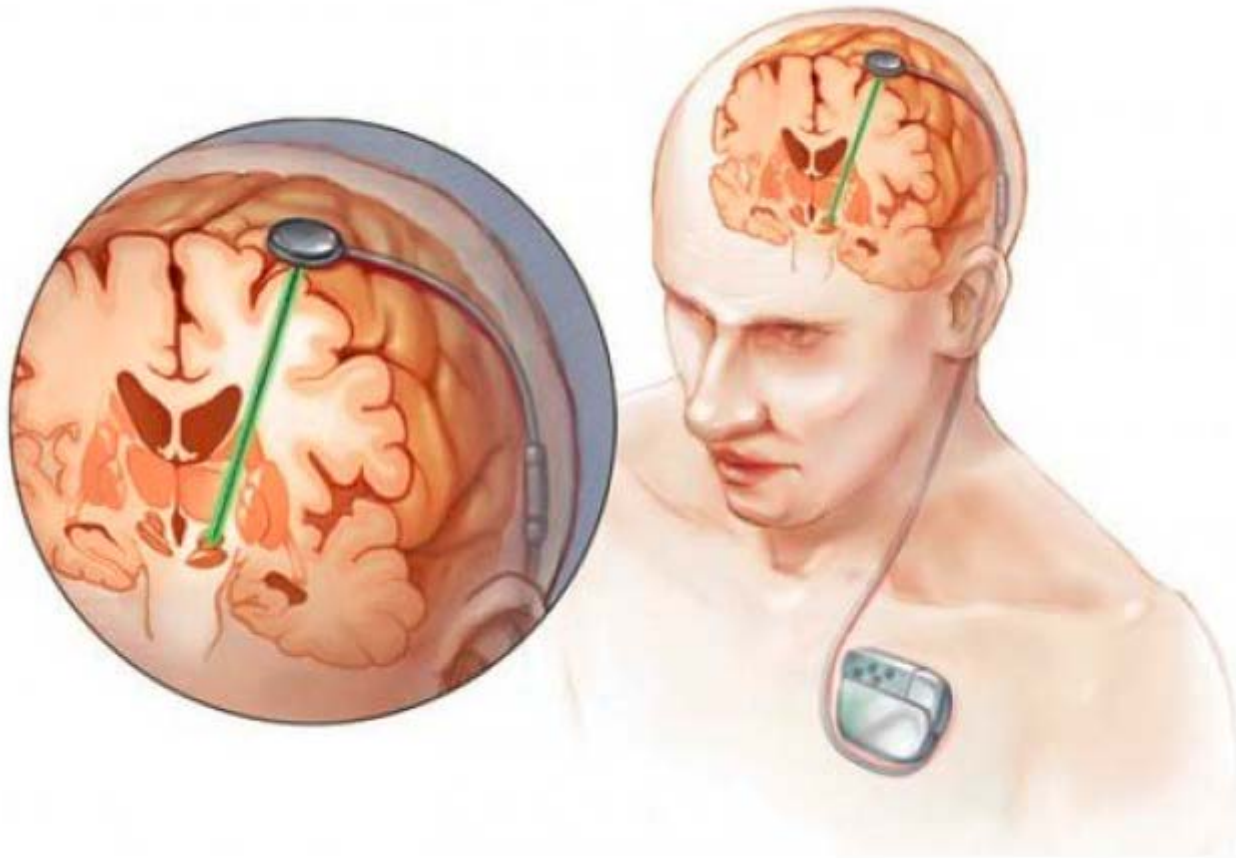
- Affects 1-2% of world population
- Temporal lobe epilepsy (TLE) is most frequent form in adults
- TLE is often drug resistant



## Key challenges:

- Improve electrode performance
- Make less invasive recordings

# Deep brain stimulation for Parkinson's





# Implantable Electronic Medical Devices

## ■ Approved devices:

- Heart pacemakers – 600,000 per year
- Cochlear implants (hearing) – 300,000 patients
- Spinal cord stimulators (pain relief) – 15,000 per year
- Deep brain stimulators (Parkinson's)
- Phrenic nerve stimulators (assisted breathing)
- Sacral nerve stimulators (bladder control)
- Vagus nerve stimulators (epilepsy)
- Retinal implants (vision)



Implantable defibrillator  
(Medtronic)



Cochlear implant  
(Cochlear)

## ■ In development:

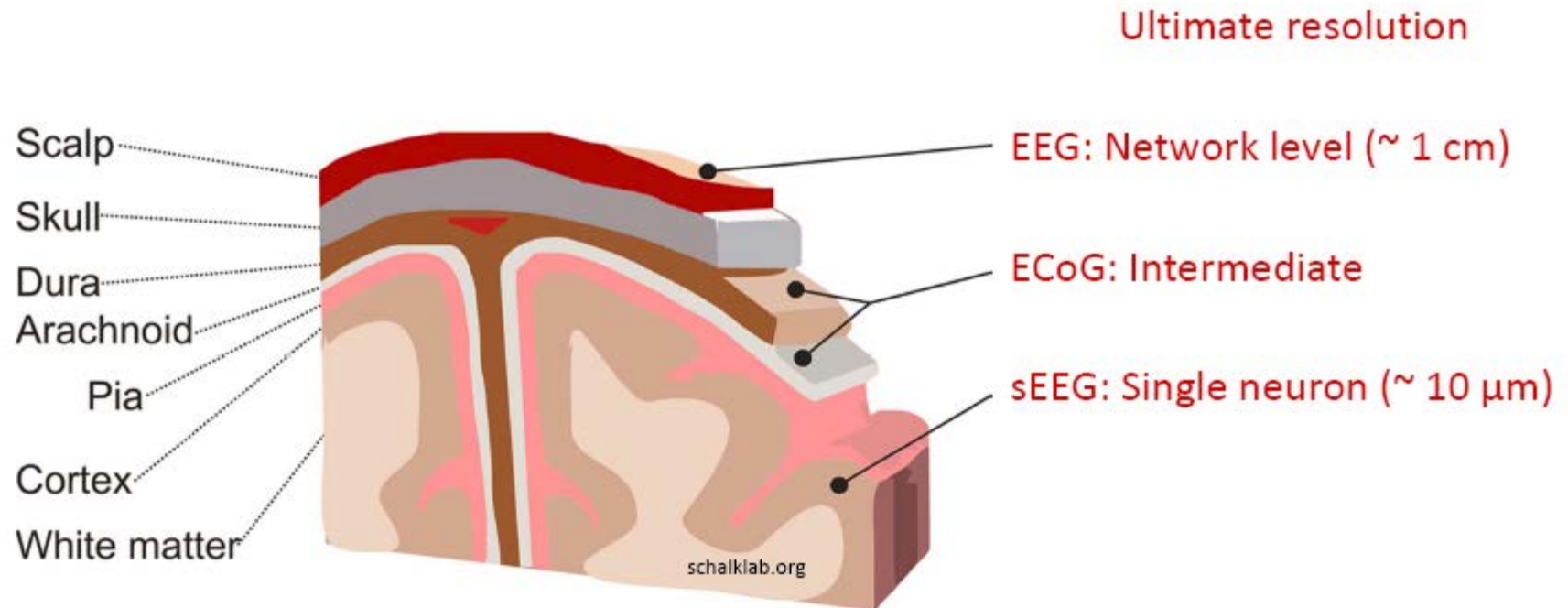
- Functional electrical stimulation (standing and gait)
- Brain Computer Interfaces (control of robotic limbs)
- DBS (severe psychiatric conditions)
- Vestibular prostheses (balance)
- Vision prostheses (vision)
- Cortical prostheses (epilepsy detection & suppression)



Artificial limbs controlled by the brain  
(Penn Center for Brain Injury and Repair)

# Conducting polymer microelectrodes record single neurons from brain surface

## Levels of neural interfacing

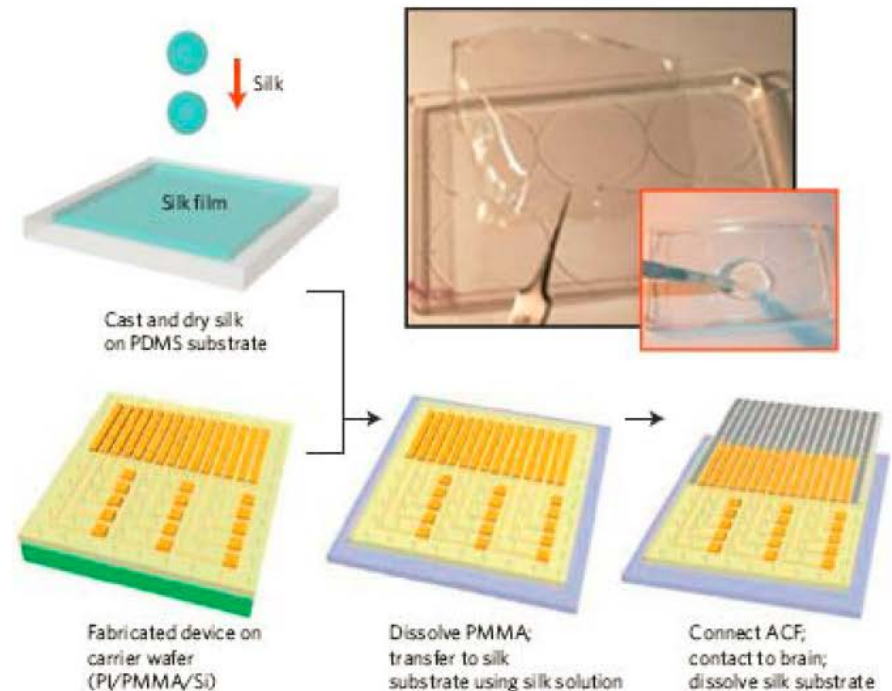
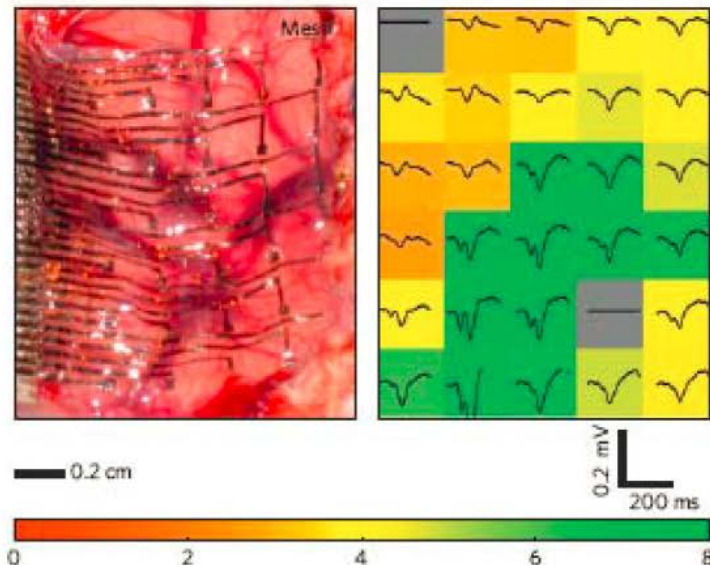


It was not considered possible to obtain single neuron recordings  
without penetrating the brain

## Dissolvable films of silk fibroin for ultrathin conformal bio-integrated electronics

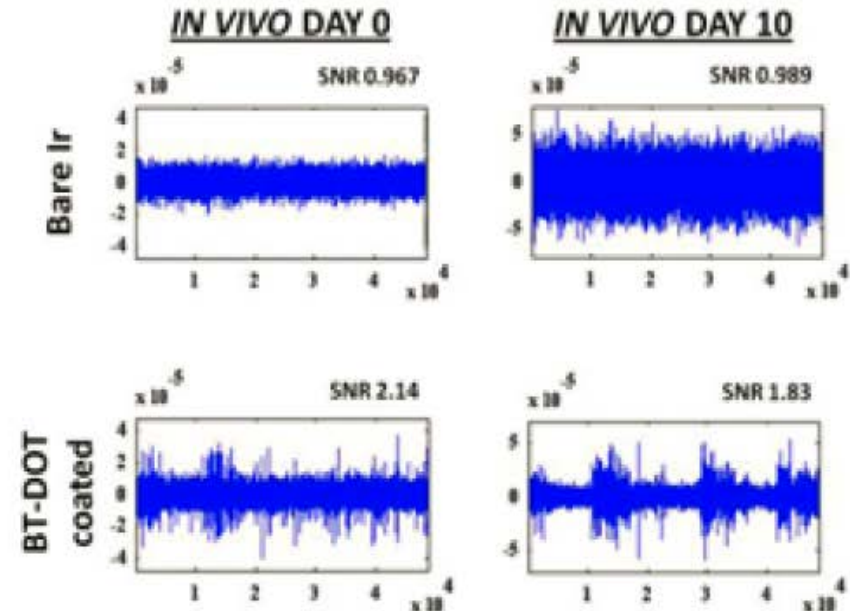
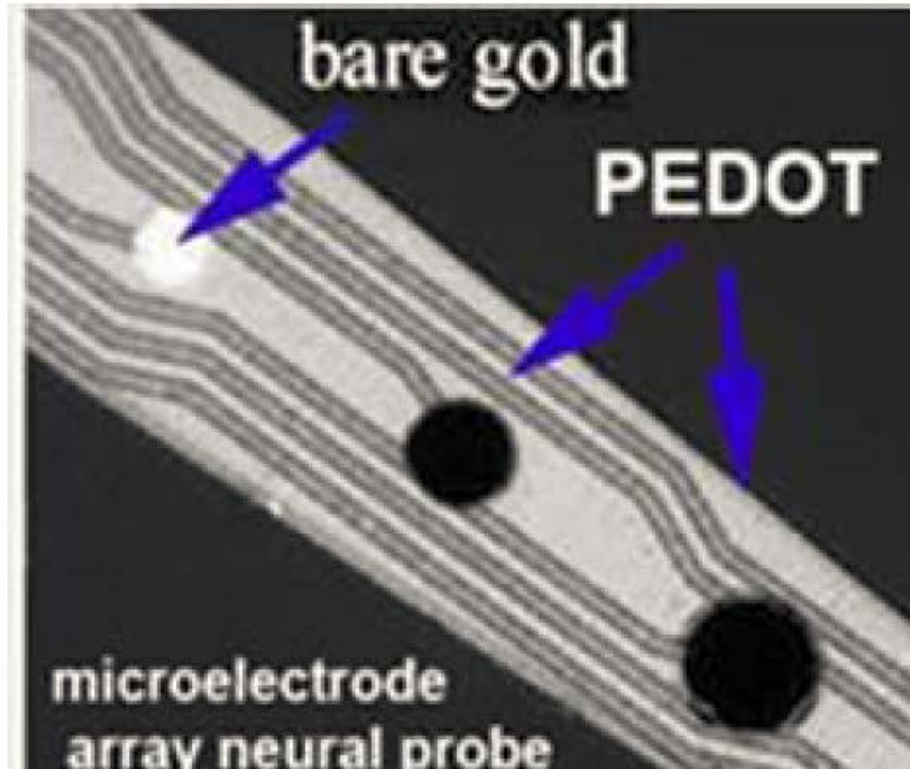
Dae-Hyeong Kim and Jonathan Viventi *et al.*\*

Rogers group (UIUC)



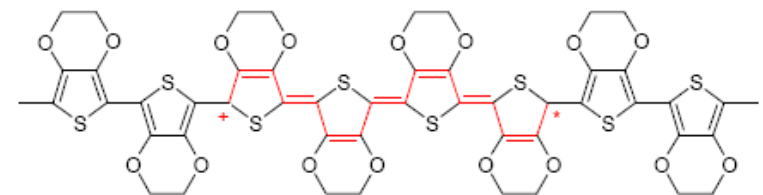
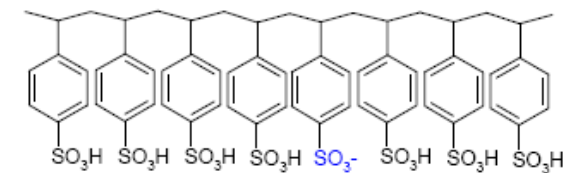
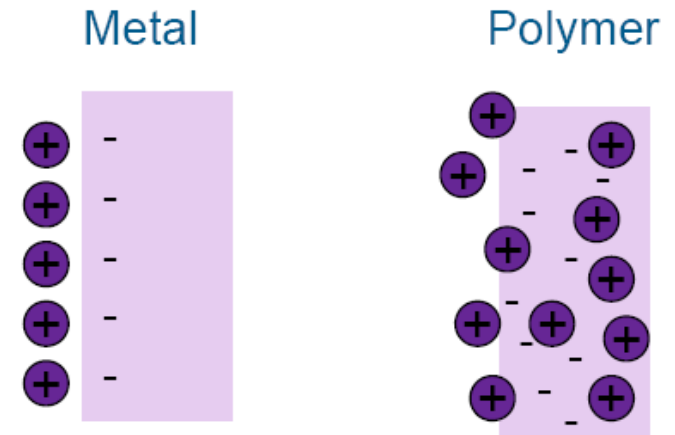
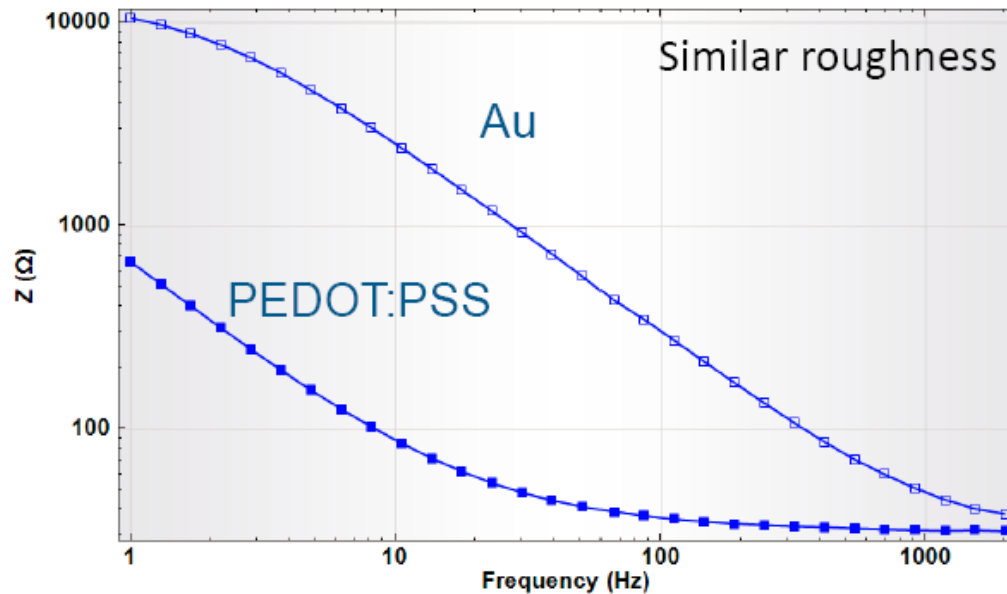


# Conducting polymers improve neural interfaces



Electrochemical growth  
on pre-patterned metal  
electrodes

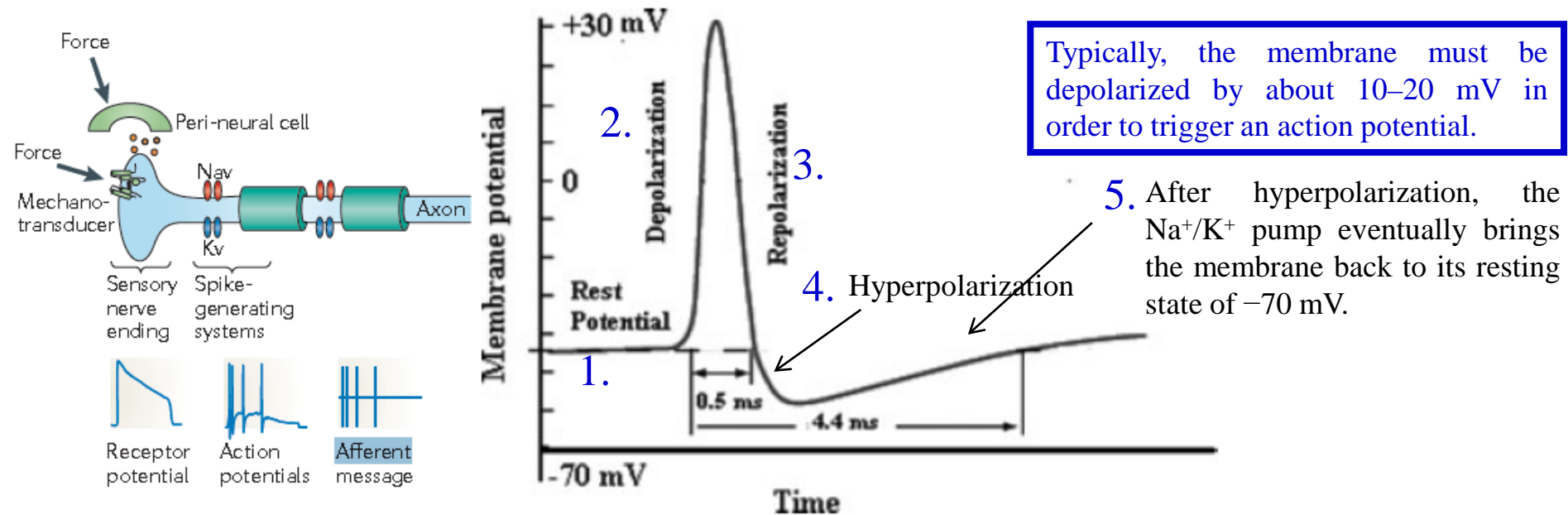
## Conducting polymers lower interfacial impedance



Different “nature” of capacitance across the electrode/electrolyte interface

# Introduction of Electrical Stimulation and Recording

Various stages (resting state, depolarization and repolarization) of nerve cells during electrical stimulation:



1. Typical value of membrane potential (resting potential):  
-60~ -100 mV

2. Depolarization:

More  $\text{Na}^+$  channels are opened and the  $\text{Na}^+$  influx drives the interior of the cell membrane up to about +30 mV.

3. Repolarization:

The membrane begins to repolarize back towards its resting potential as the  $\text{K}^+$  channels open. The repolarization typically overshoots the resting potential to about -90 mV.

4. Hyperpolarization:

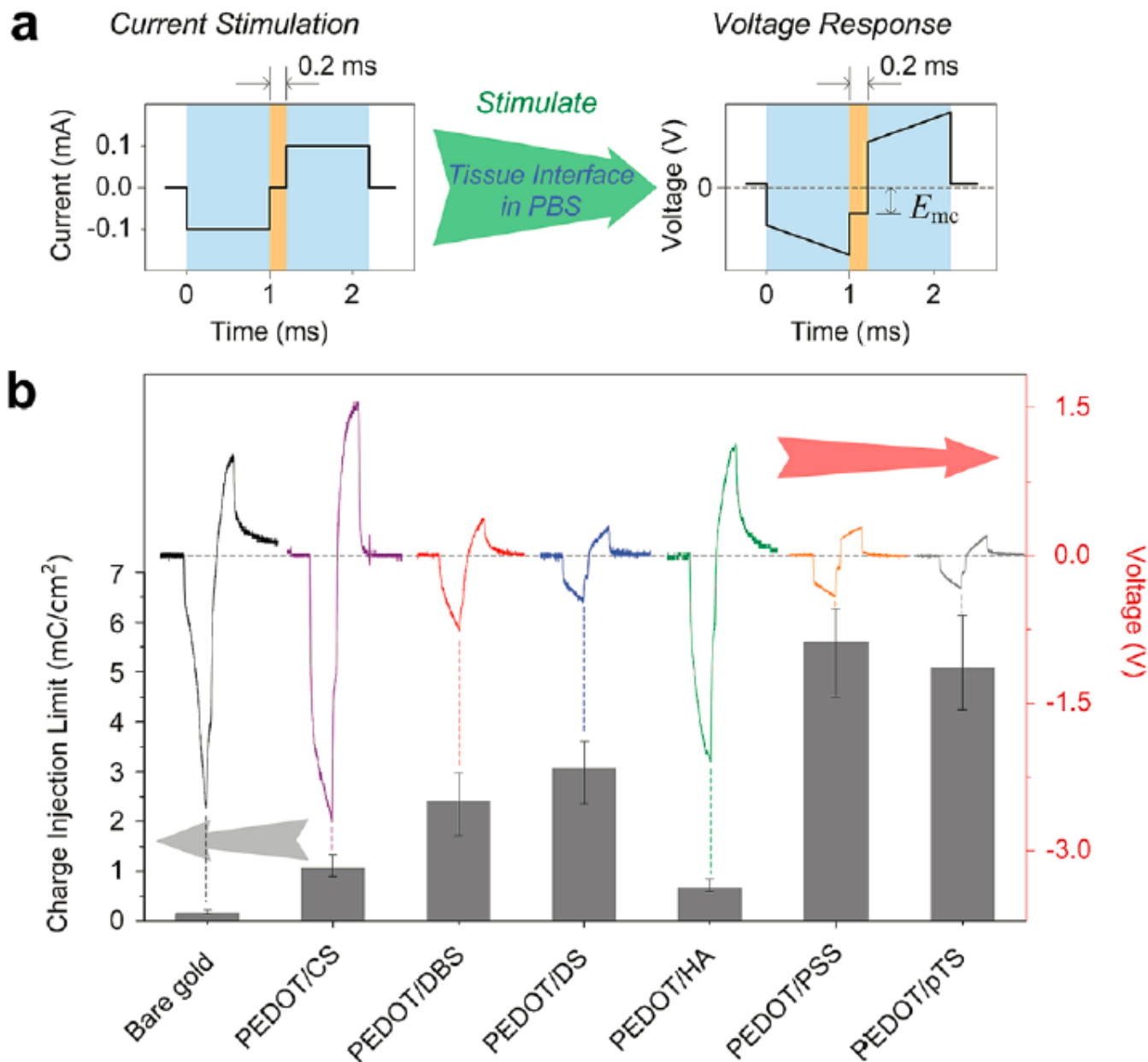
Hyperpolarization assures that the signal is always proceeding in one direction.

Nature Reviews 12 (2011) 139.

J Tissue Eng Regen Med 5 (2011) e17.

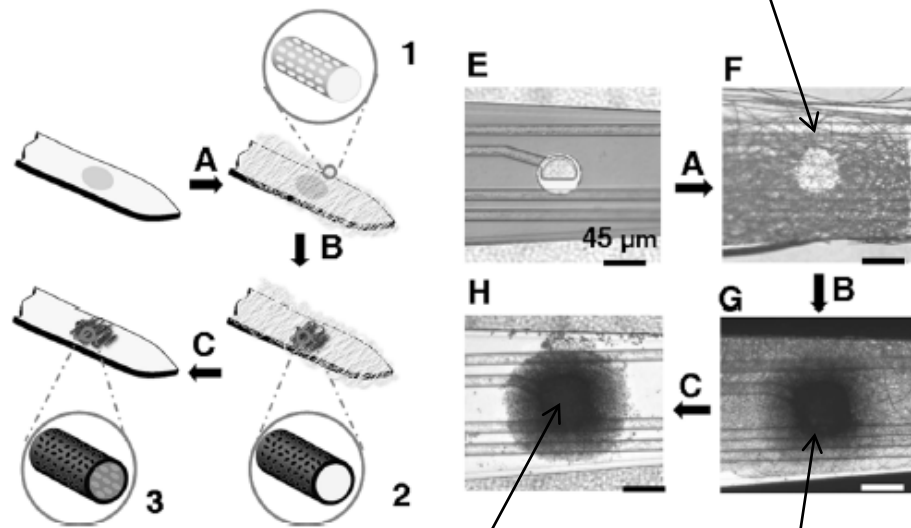


# Charge Injection Limit



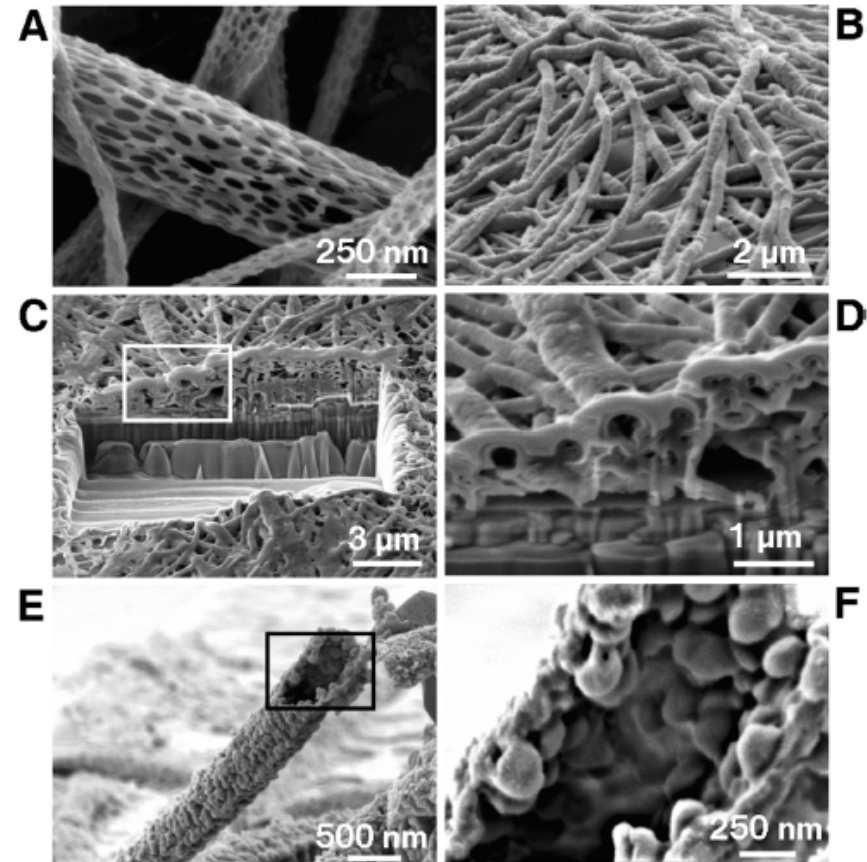
# Conducting-Polymer Nanotubes for Controlled Drug Release (DC Martin)

PLGA electrospun  
nanoscale fibers



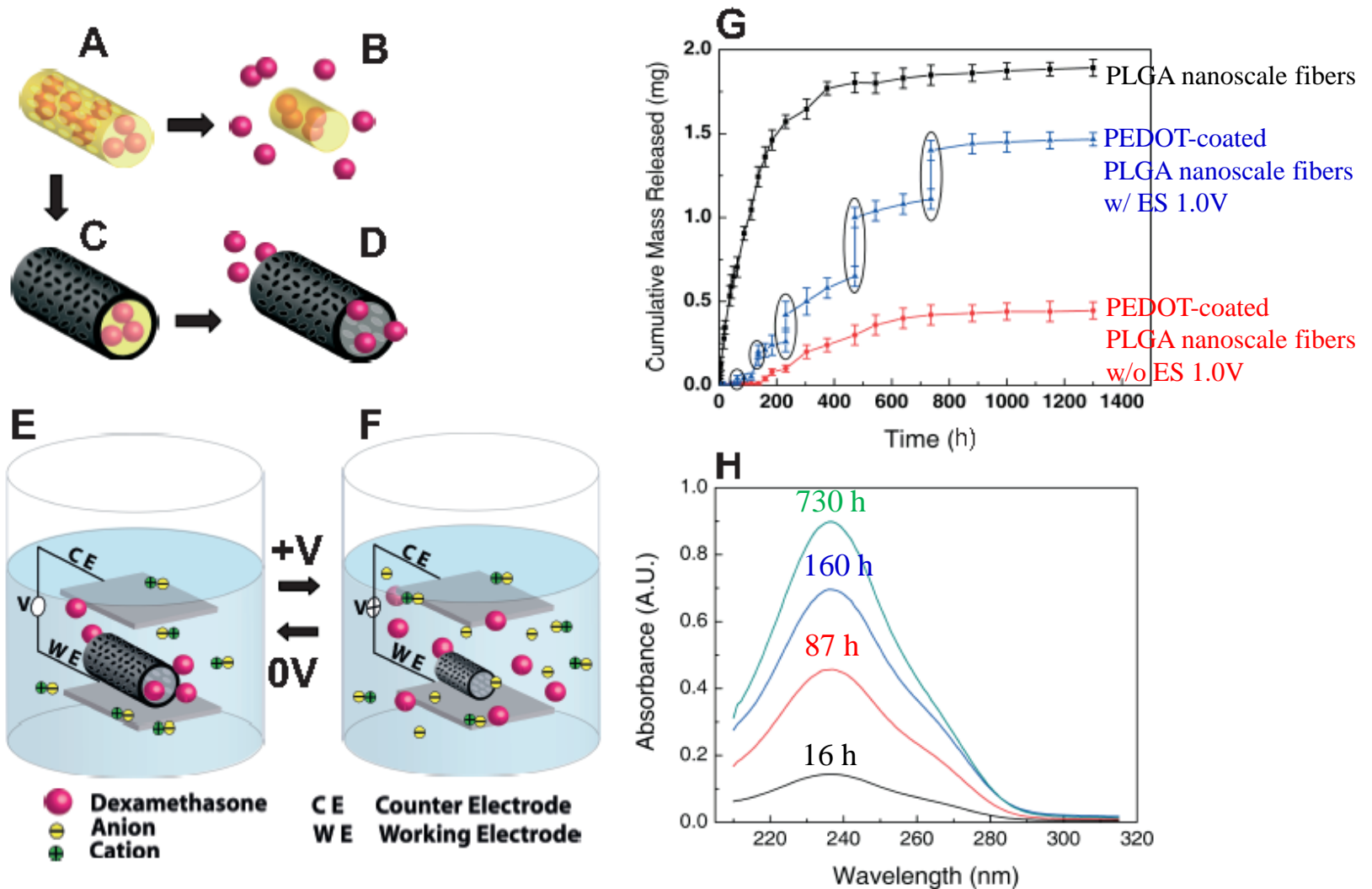
Removal of the core nanoscale  
fiber templates

Electrochemical  
deposition of PEDOT



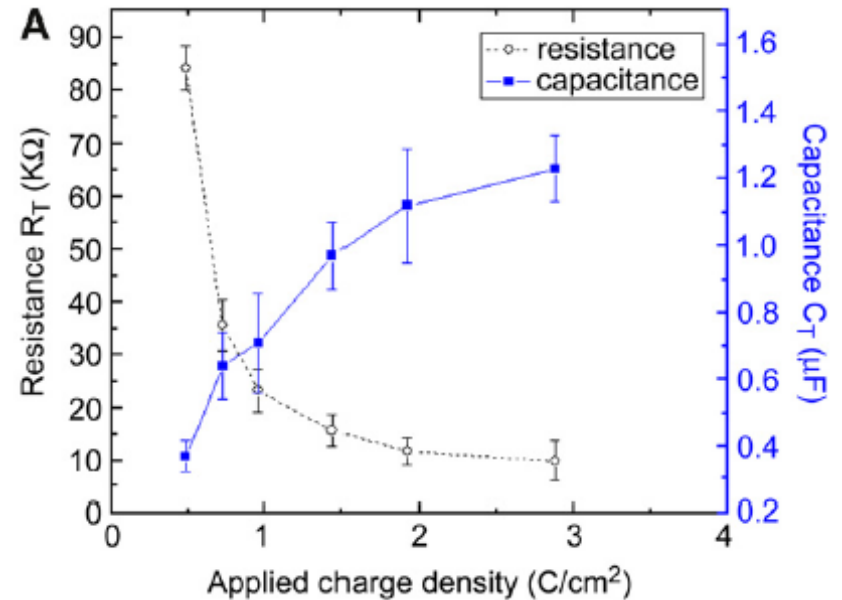
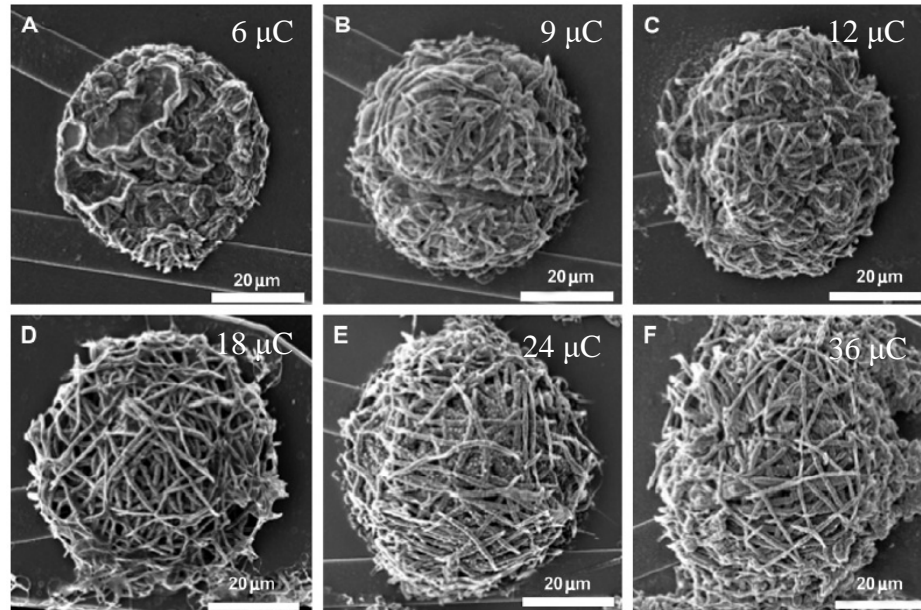
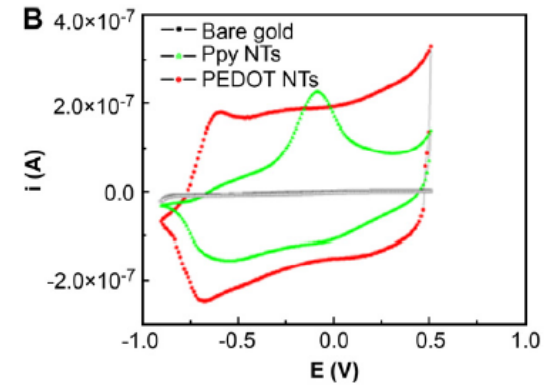
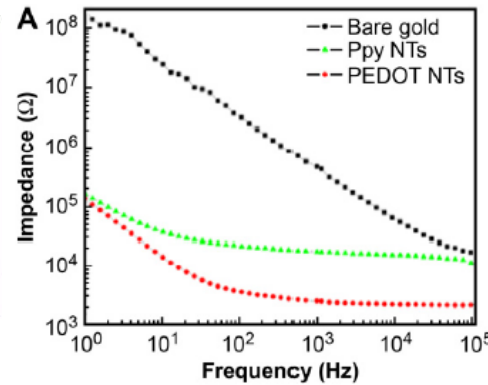
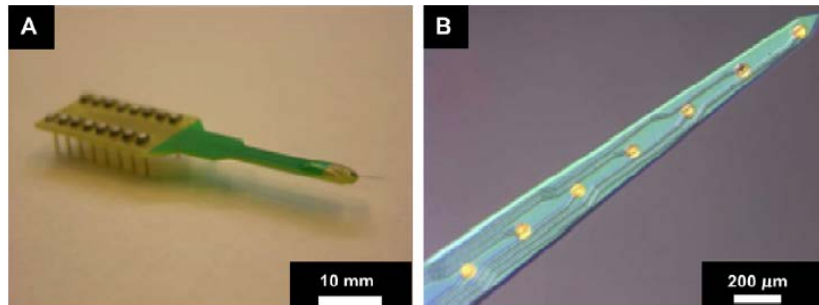
Adv. Mater. 18 (2006) 405-409.

## Cumulative Mass Release of Dexamethasone:





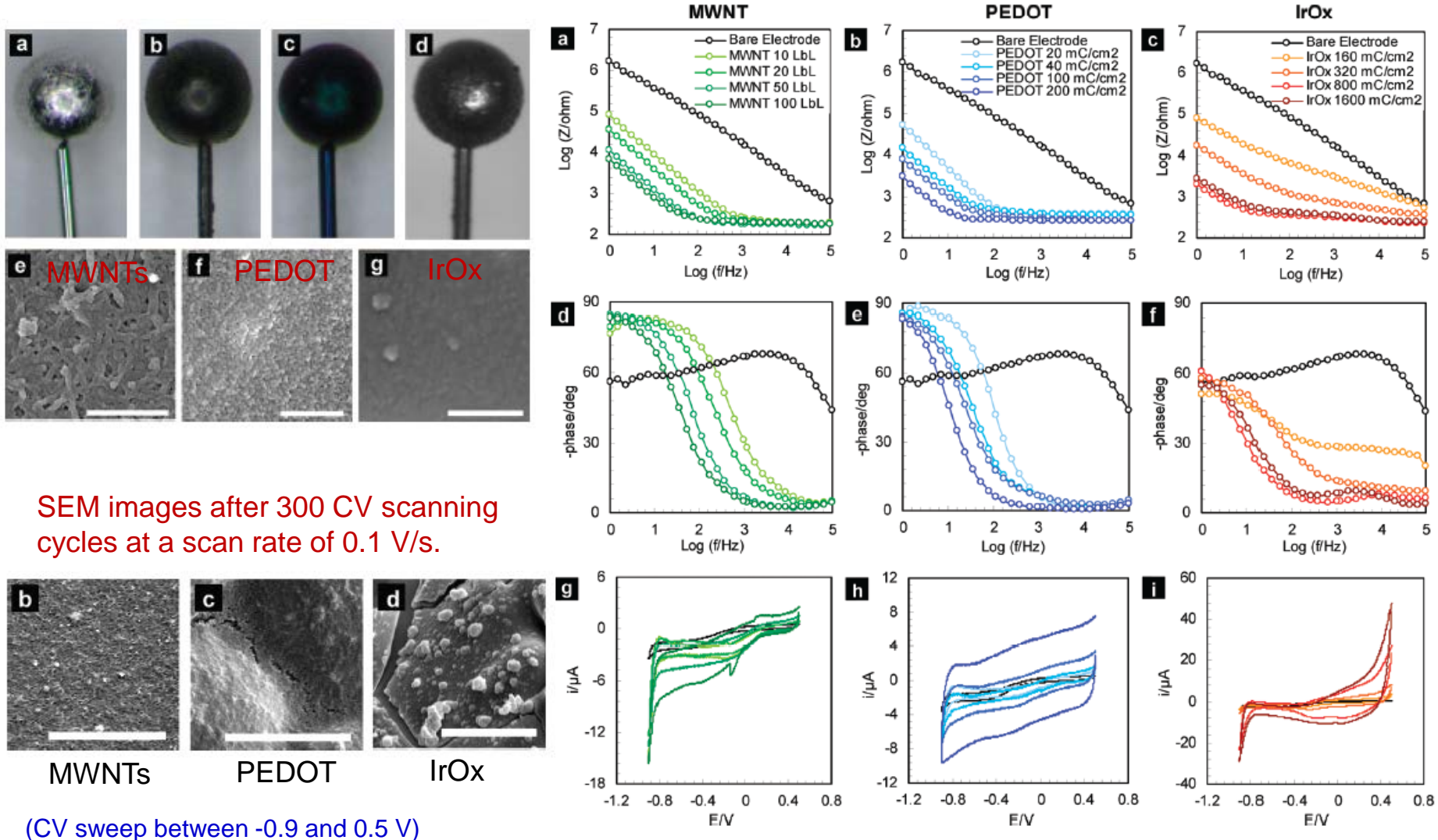
# Experimental and theoretical characterization of implantable neural microelectrodes modified with conducting polymer nanotubes



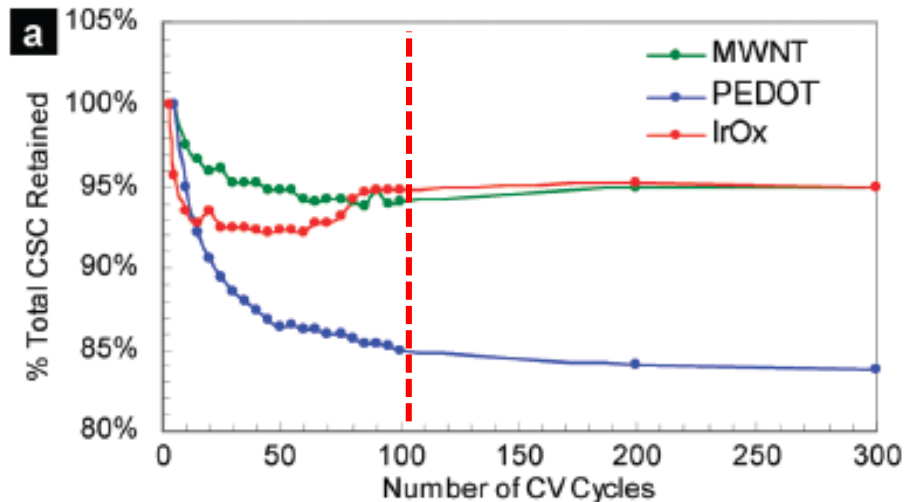
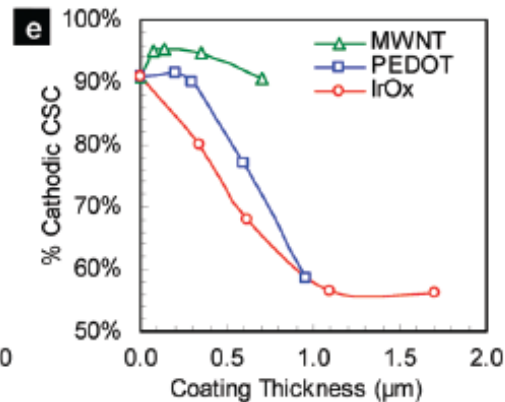
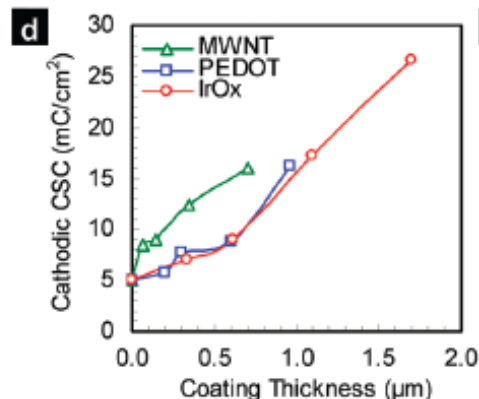
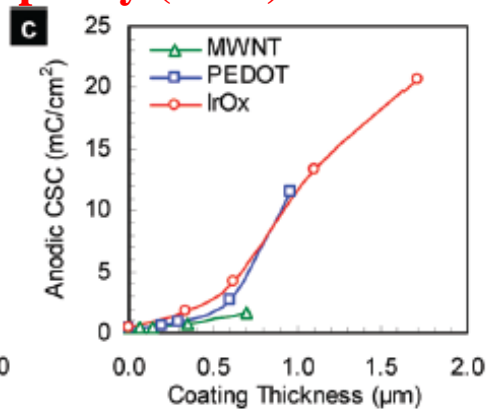
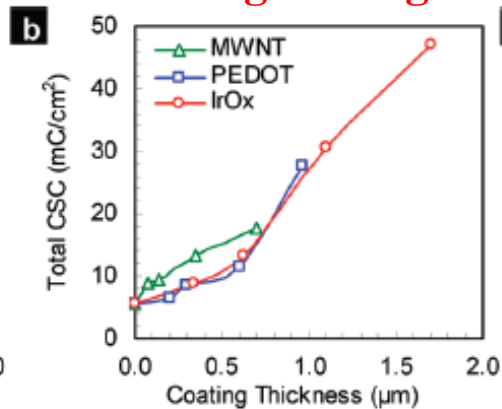
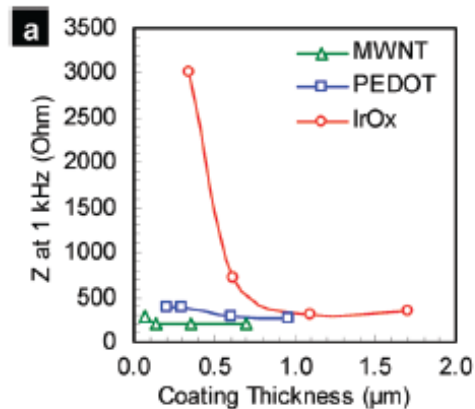
Biomaterials 29 (2008) 1273-1283.

Diffusional pseudocapacitance ( $C_T$ ) and diffusional resistance ( $R_T$ ) for PPy NTs as a function of applied charge density

# Layered Carbon Nanotube-Polyelectrolyte Electrodes Outperform Traditional Neural Interface Materials (DC Martin)



## Charge storage capacity (CSC)

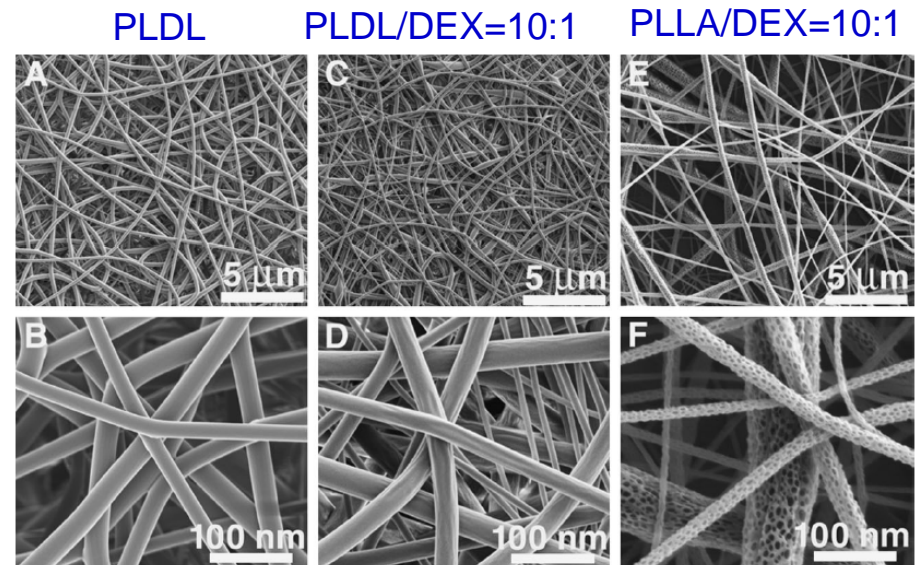
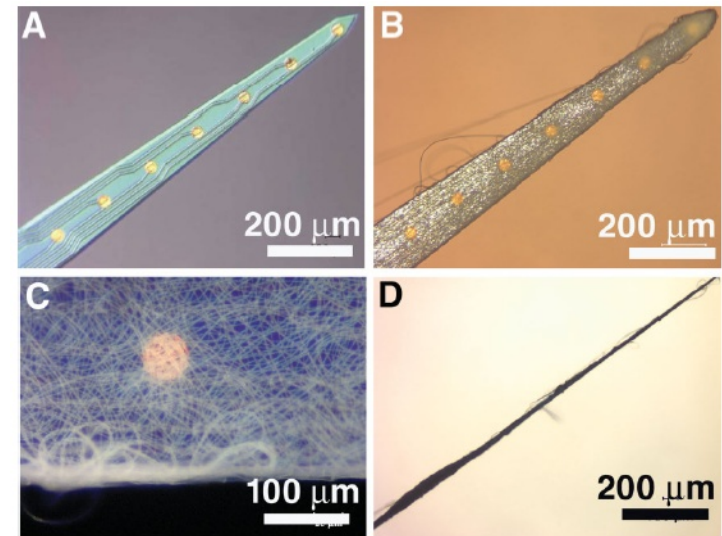
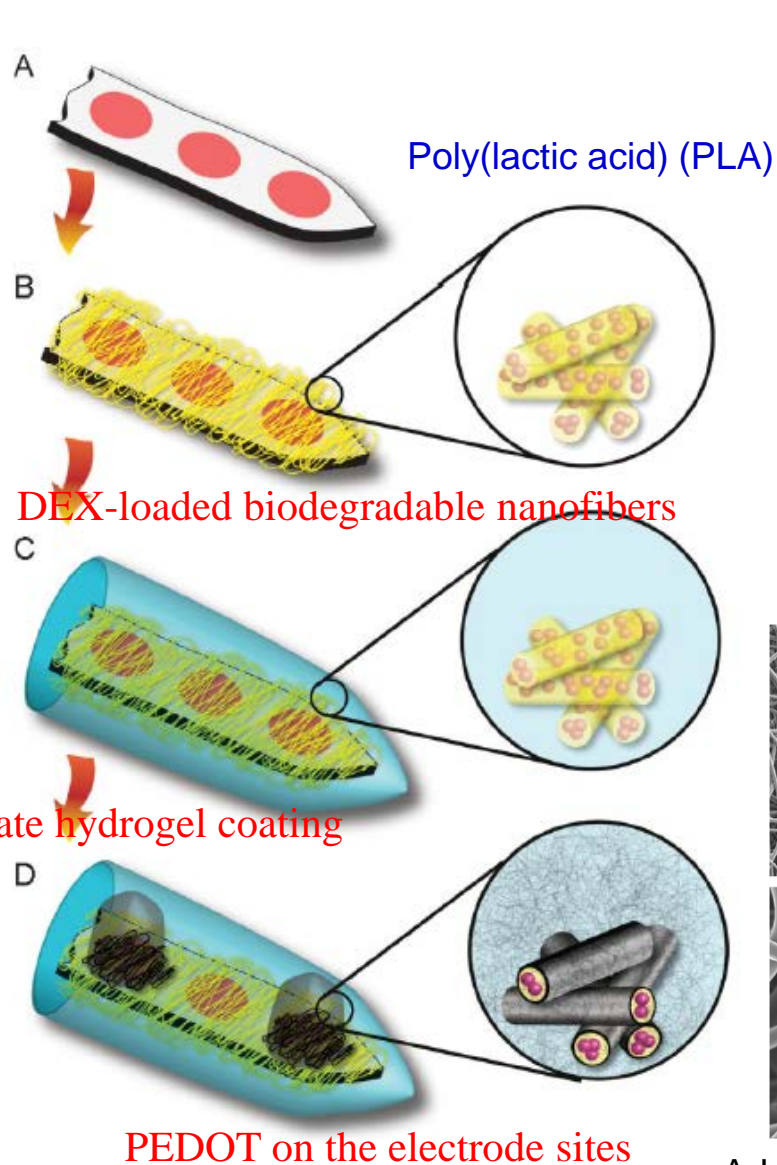


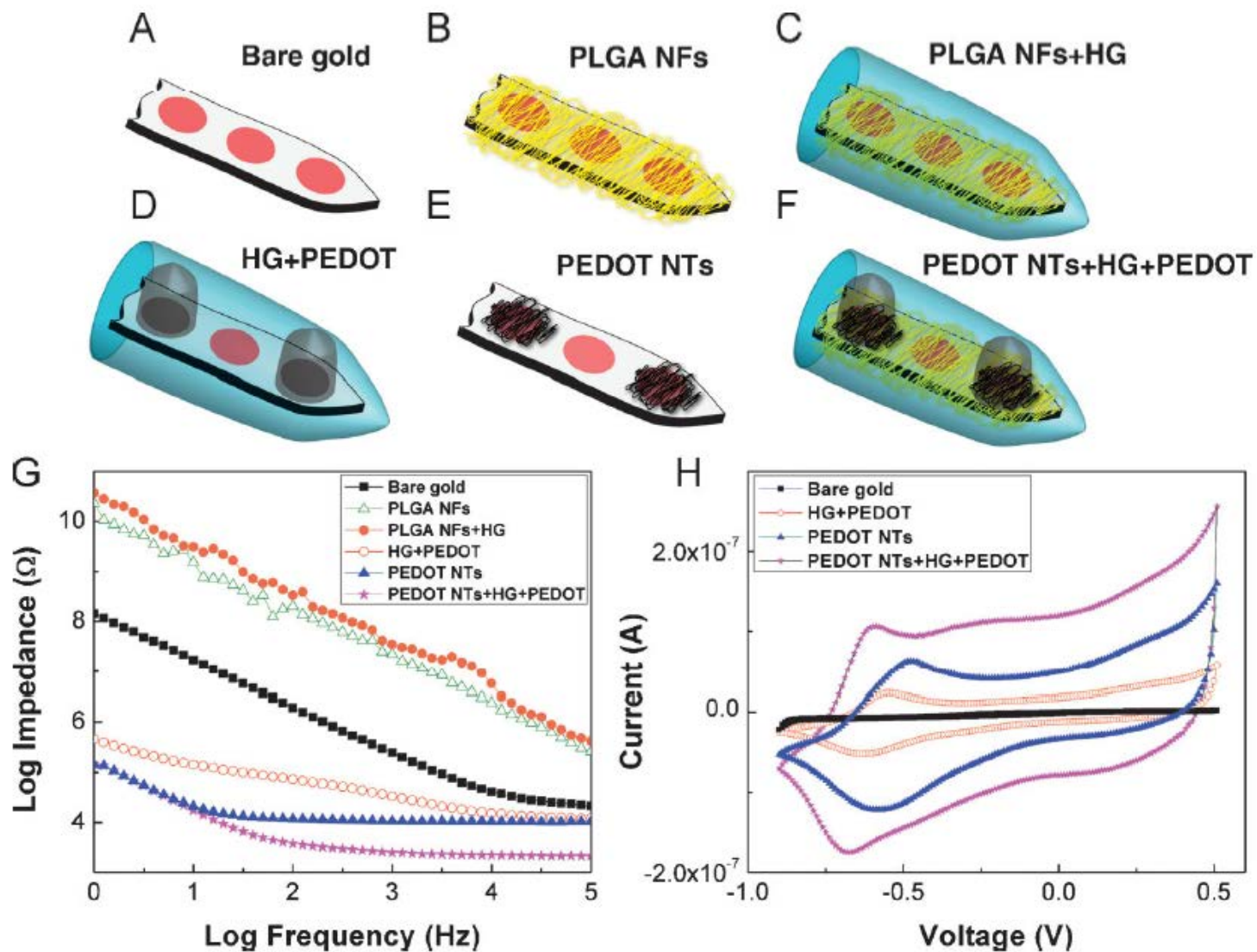
**Electrical Stimulation Stability:**

**MWNT > IrOx > PEDOT**



# Multifunctional Nanobiomaterials for Neural Interfaces (DC Martin)

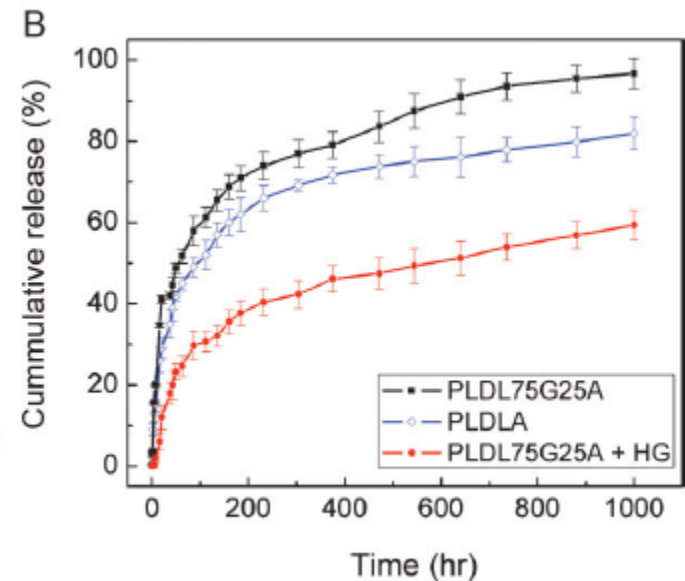
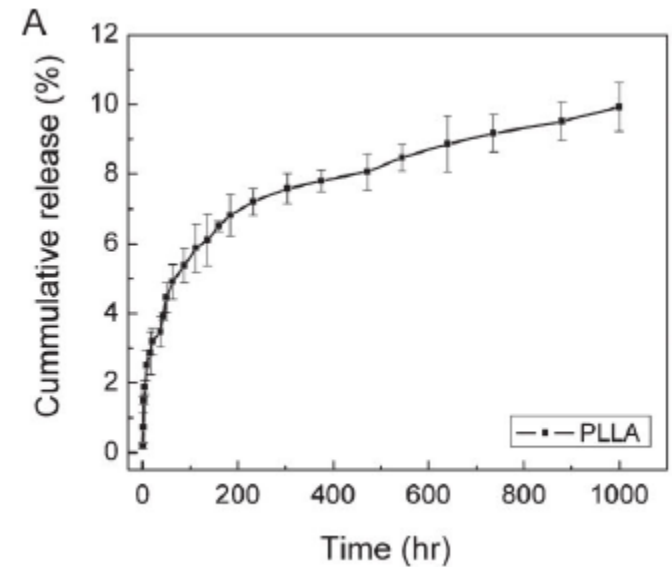
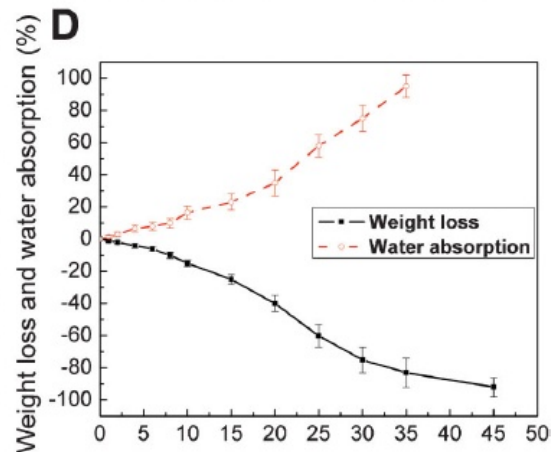
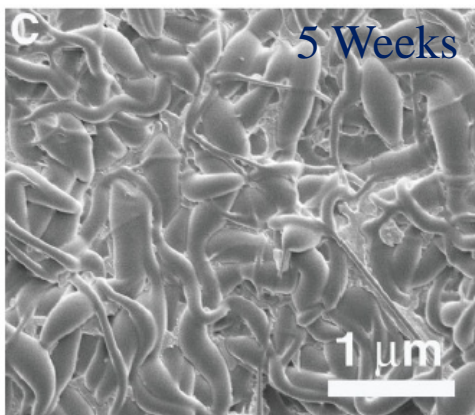
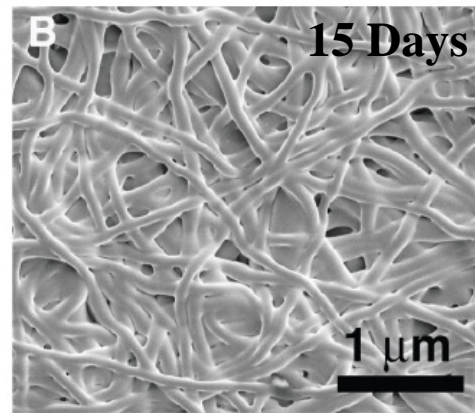
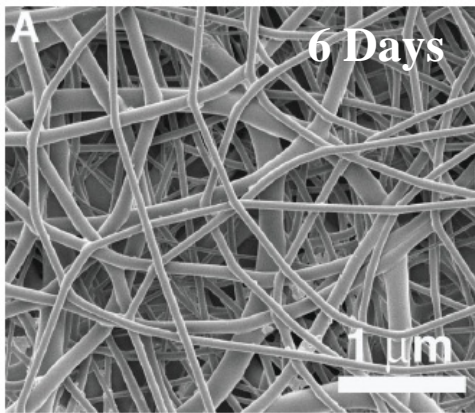






## Percentage cumulative mass release profiles of DEX-loaded polymers

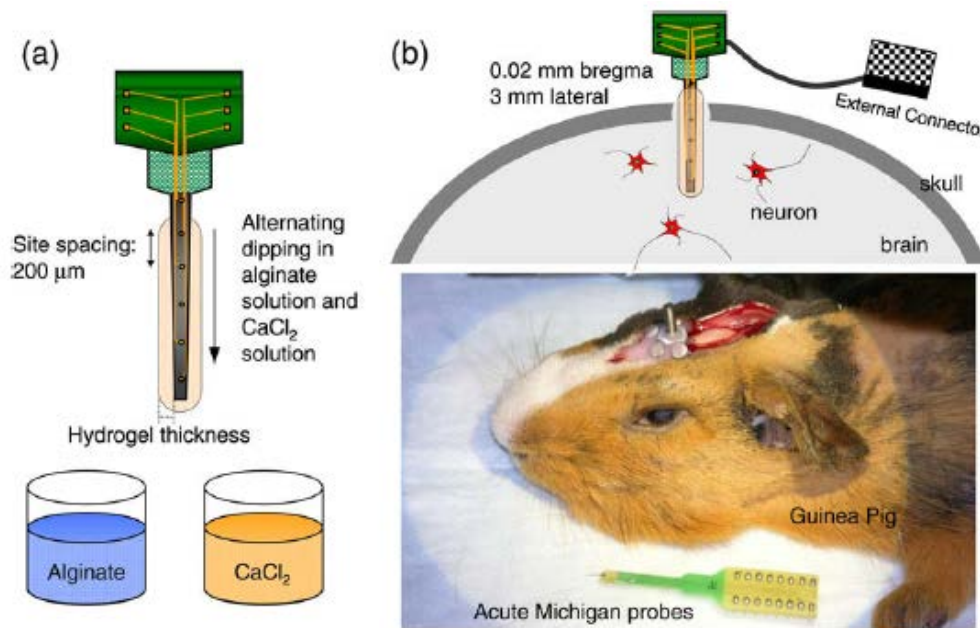
### Degradation of nanofibers in PBS solution



Adv. Funct. Mater. 19 (2009) 573-585.



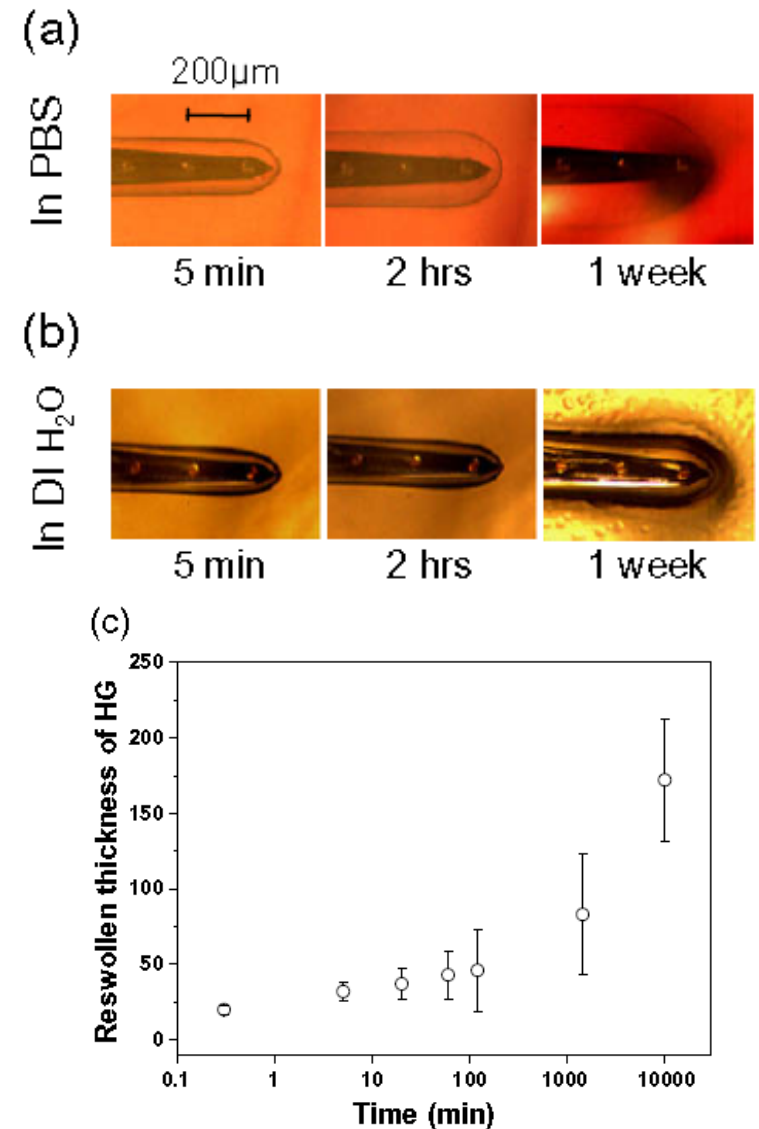
# Conducting polymers on hydrogel-coated neural electrode provide sensitive neural recordings in auditory cortex (DC Martin)



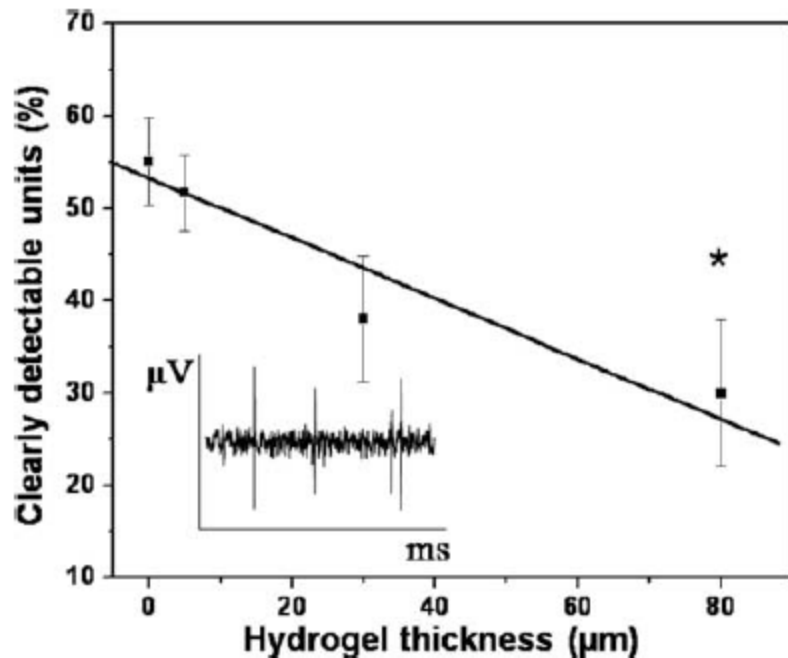
**Table 1**  
Classification of signal to noise ratios.

Define	SNR range	Characteristics
High SNR	$\text{SNR} > 4.0$	Signals from clearly detectable units: easy to discriminated/analyzed from background noise
Medium SNR	$4.0 > \text{SNR} > 3.5$	Signals from active units: possible to be discriminated from background noise with some exceptions
Low SNR	$\text{SNR} < 3.5$	Signals from bad units: Difficult to be discriminated from background noise

Acta Biomaterialia 6 (2010) 57–62.



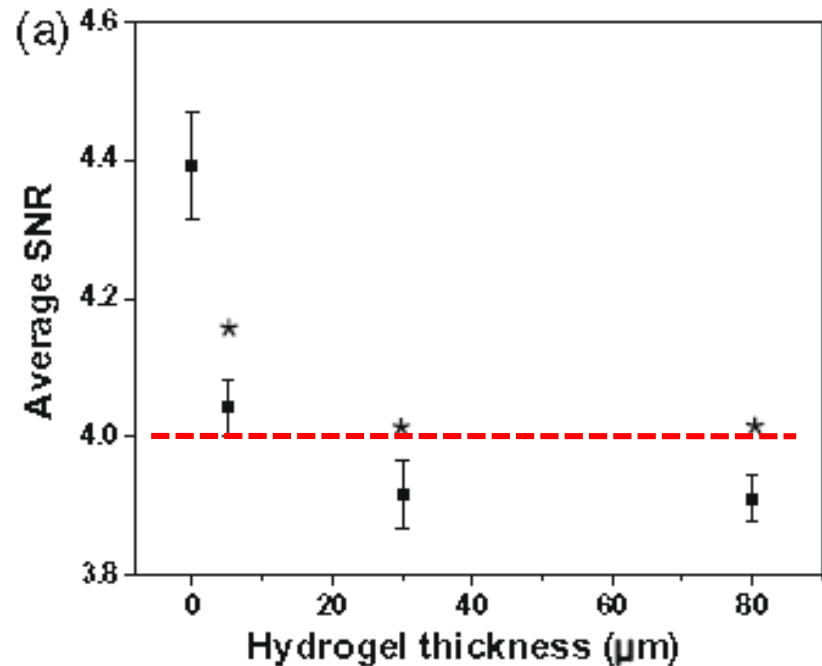
### (Sensitivity)



The average percentages of clearly detectable units as a function of the thickness of HG-coated electrodes in the auditory cortex with a 200 ms noise burst.

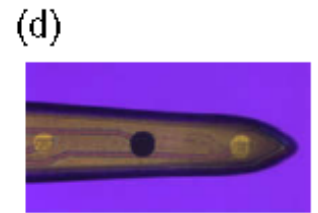
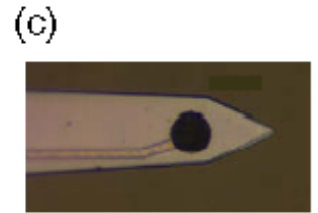
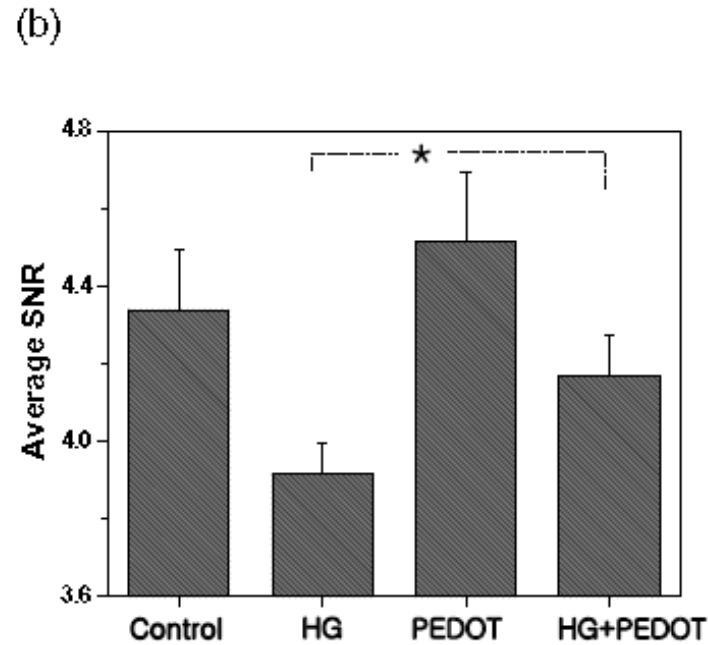
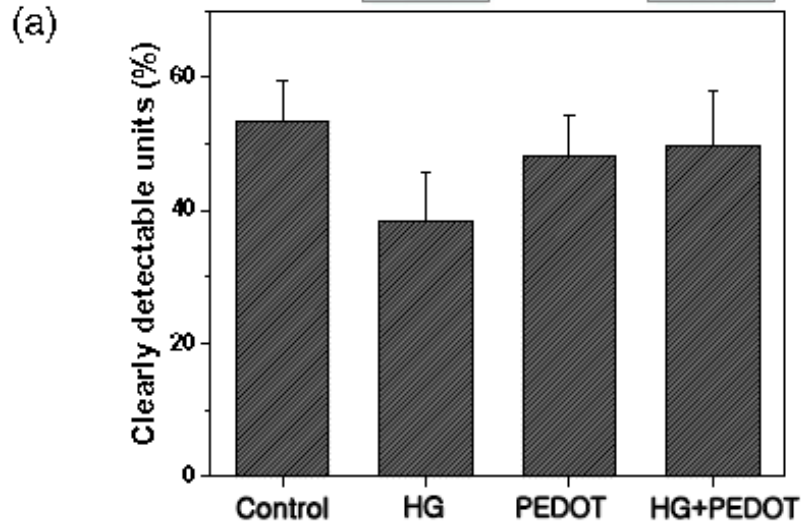
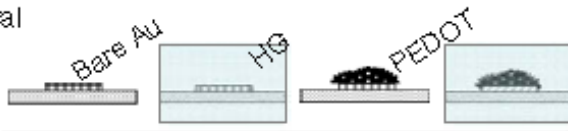
Acta Biomaterialia 6 (2010) 57–62.

### (Signal-to-noise ratio, SNR)



Average SNRs and signal quality as a function of hydrogel thickness.

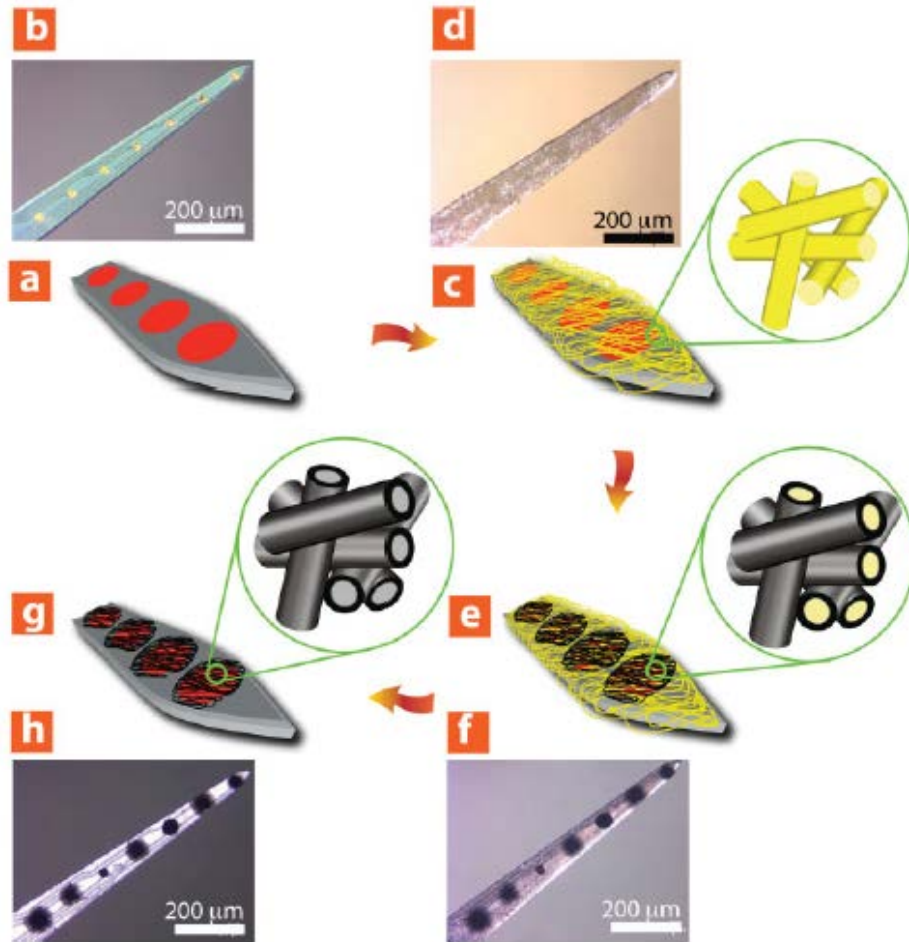
Schematic lateral view of the electrode sites



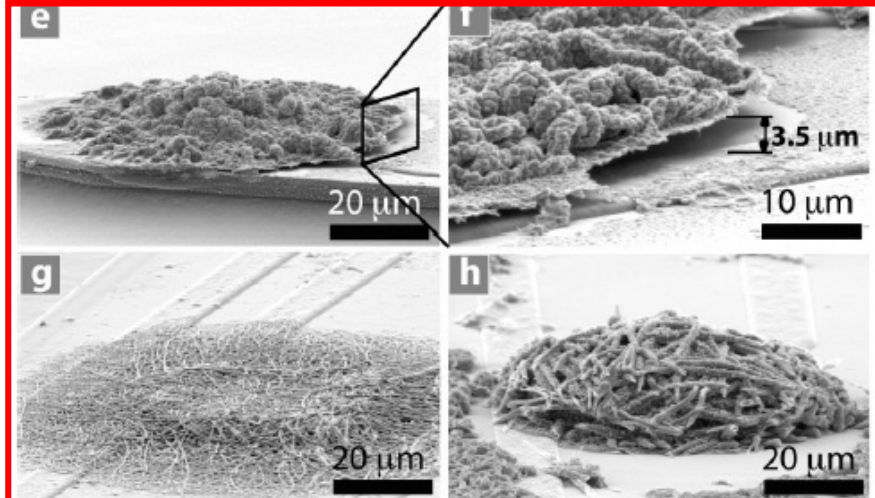
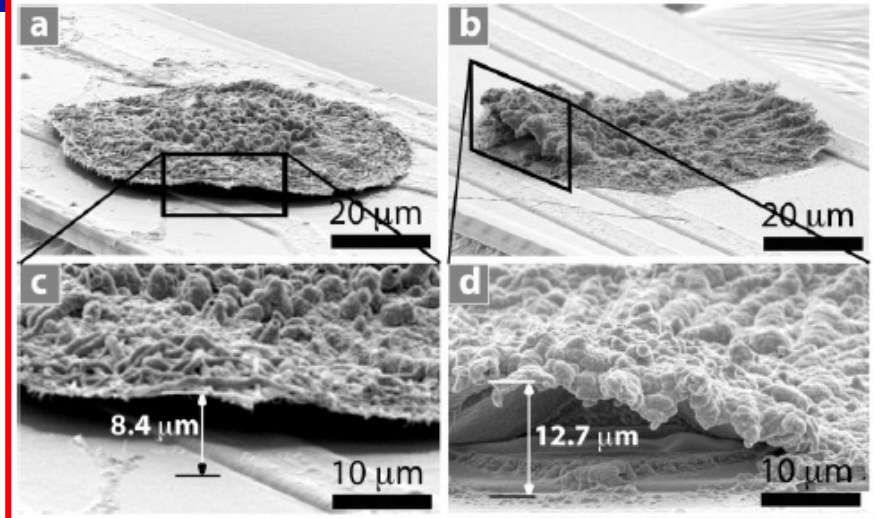
A significant loss in functionality determined by SNRs was observed with HG coatings as thin as 5  $\mu\text{m}$ , while the number of clearly detectable units gradually decreased as a function of the HG coating thickness. The loss of functionality of the electrodes is due to the lack of neurons immediately around the electrodes sites.

**PEDOT deposited** on the electrode sites **did not produce any increase in the number of clearly detectable units** as compared with the bare electrodes, the PEDOT deposition **improved** the recording functionality of the HG-coated electrodes as measured by the **SNR**.

# Conducting-Polymer Nanotubes Improve Electrical Properties, Mechanical Adhesion, Neural Attachment, and Neurite Outgrowth of Neural Electrodes (DC Martin)

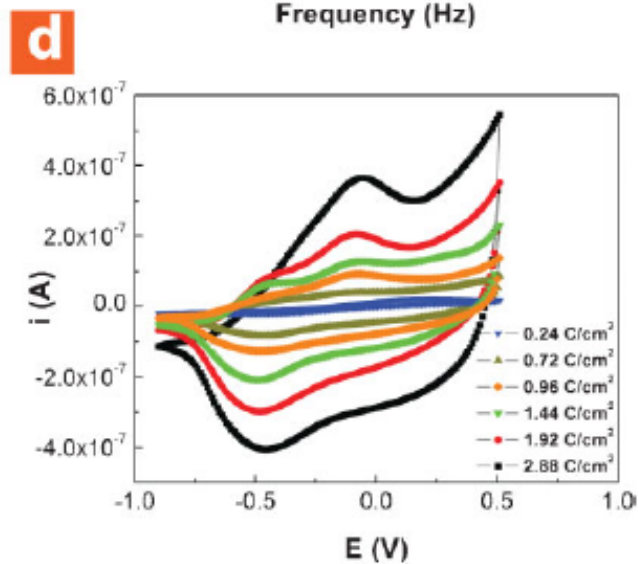
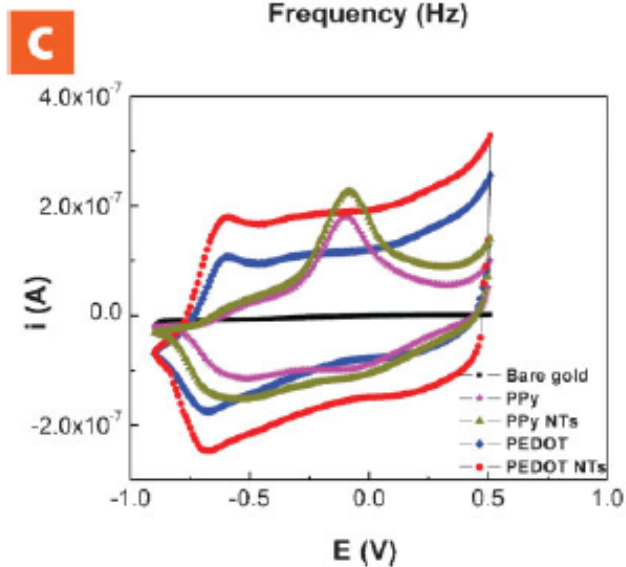
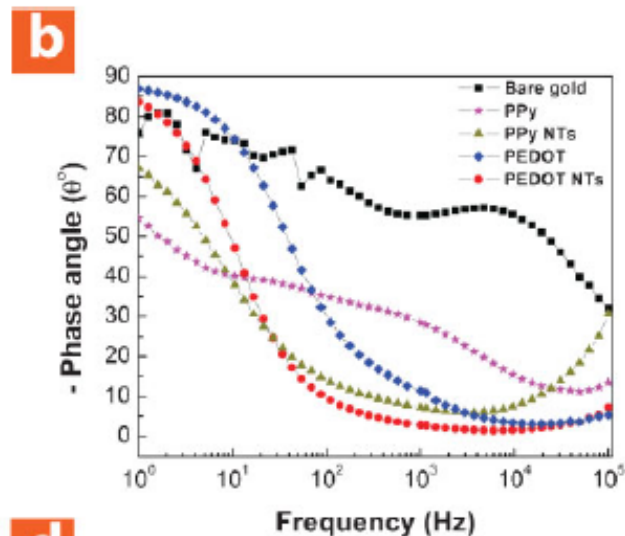
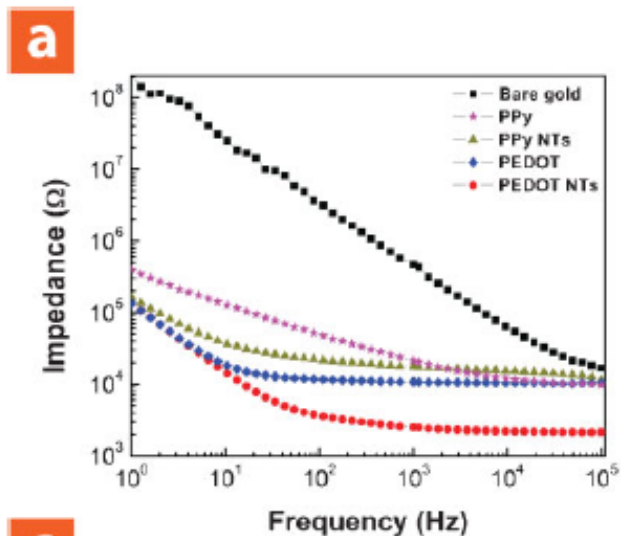


PEDOT nanotubes

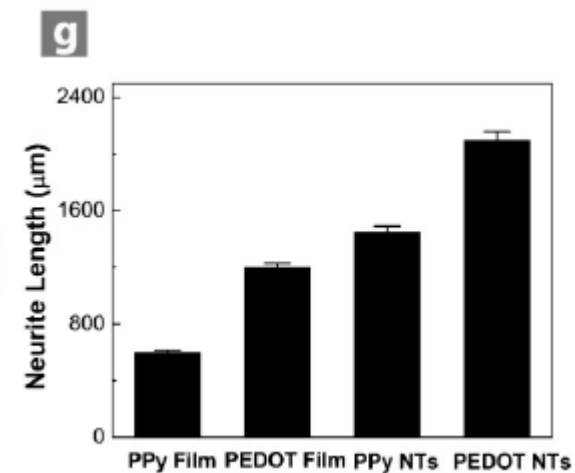
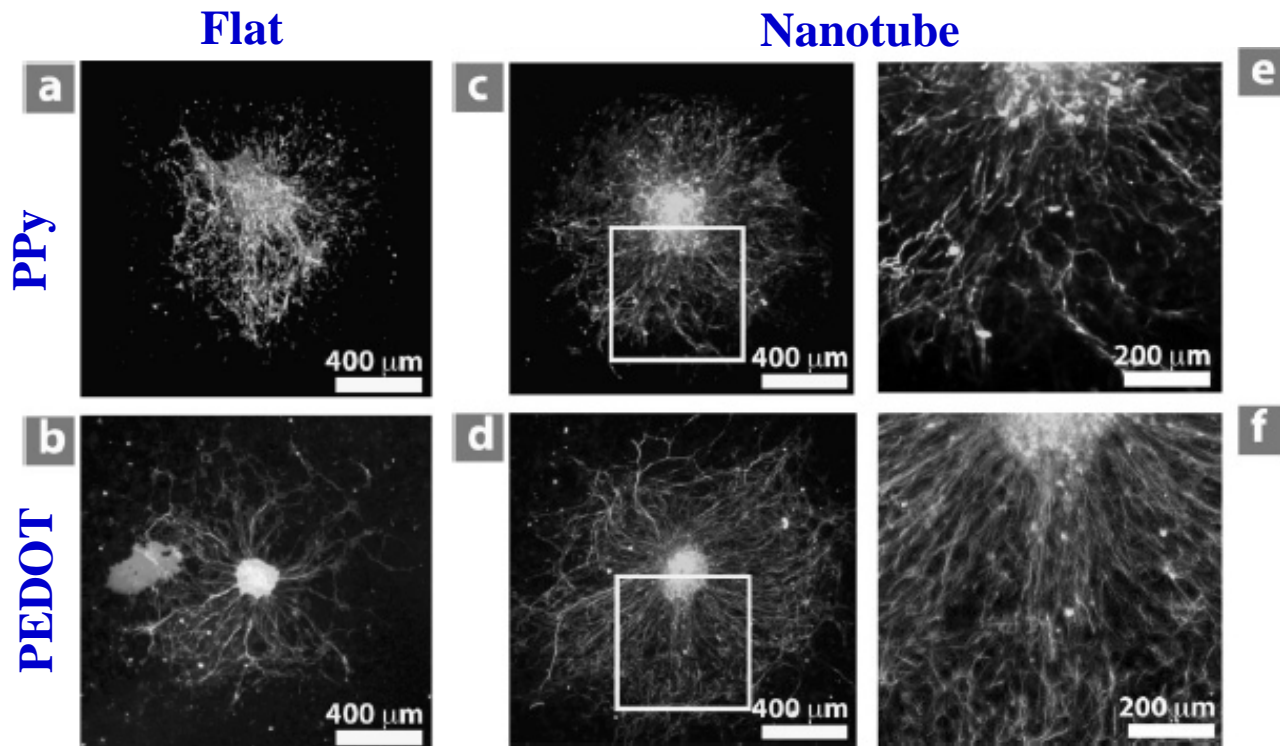


PPy nanotubes





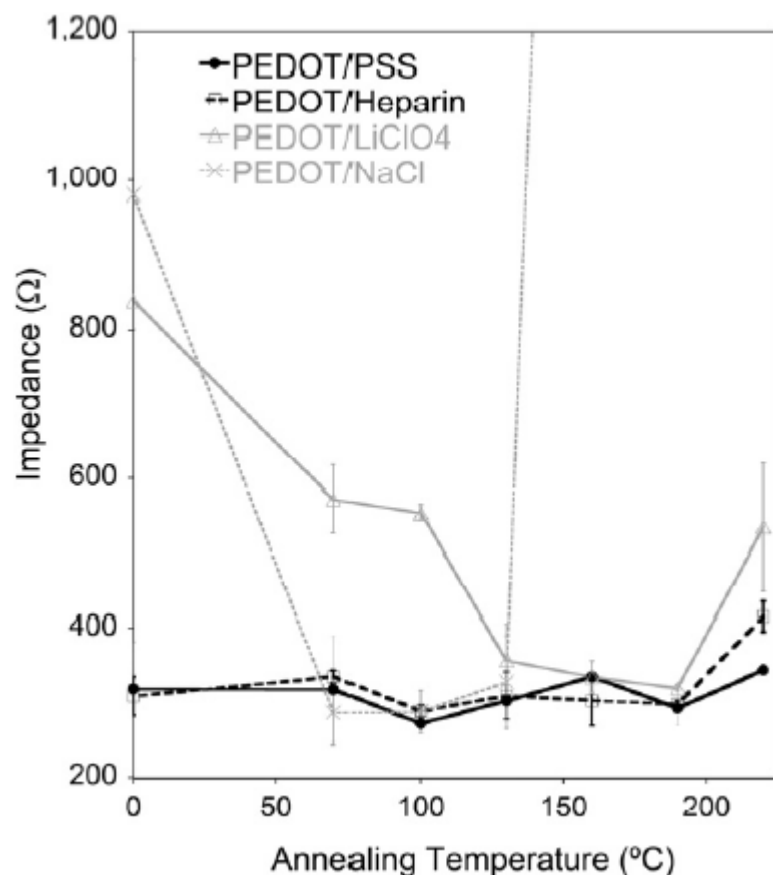
Small 6 (2010) 421–429.



DRG explants cultured on conducting polymer films and nanotubes.

Small 6 (2010) 421–429.

# Structural, chemical and electrochemical characterization of poly(3,4-Ethylenedioxythiophene) (PEDOT) prepared with various counter-ions and heat treatments (DC Martin)



**Table 1**

Comparison of PEDOT films polymerized with different counter-ions and annealed.

Counter-ion	Molecular weight	$d_{100}$ spacing	1 kHz impedance and CSC before annealing	1 kHz impedance and CSC after annealing 1 h at 160 °C
PSS	~ 70,000 Da	~1.3 nm	319 Ω 26.1 mC/cm <sup>2</sup>	335 Ω 14.7 mC/cm <sup>2</sup>
Heparin	12,000–15,000 Da		309 Ω 20.9 mC/cm <sup>2</sup>	304 Ω 11.2 mC/cm <sup>2</sup>
LiClO <sub>4</sub>	106.4 Da		839 Ω 8.6 mC/cm <sup>2</sup>	335 Ω 11.3 mC/cm <sup>2</sup>
NaCl	58.4 Da	1.27 nm	981 Ω 19.3 mC/cm <sup>2</sup>	3168 Ω 12.7 mC/cm <sup>2</sup>

**Thermal annealing**  
**→ Impedance and CSC decrease**

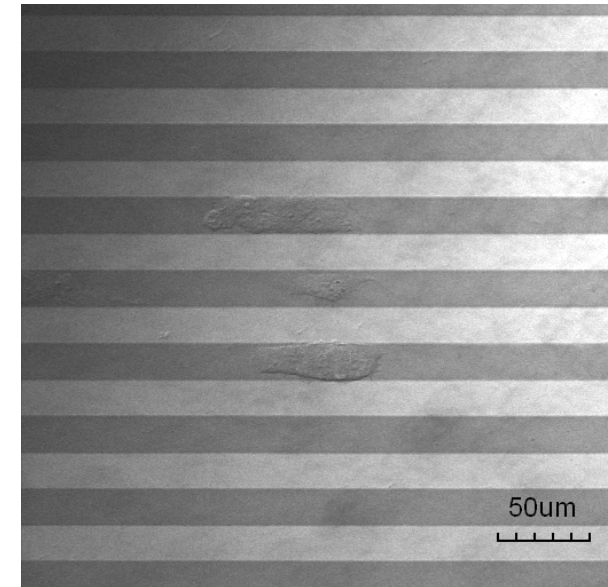
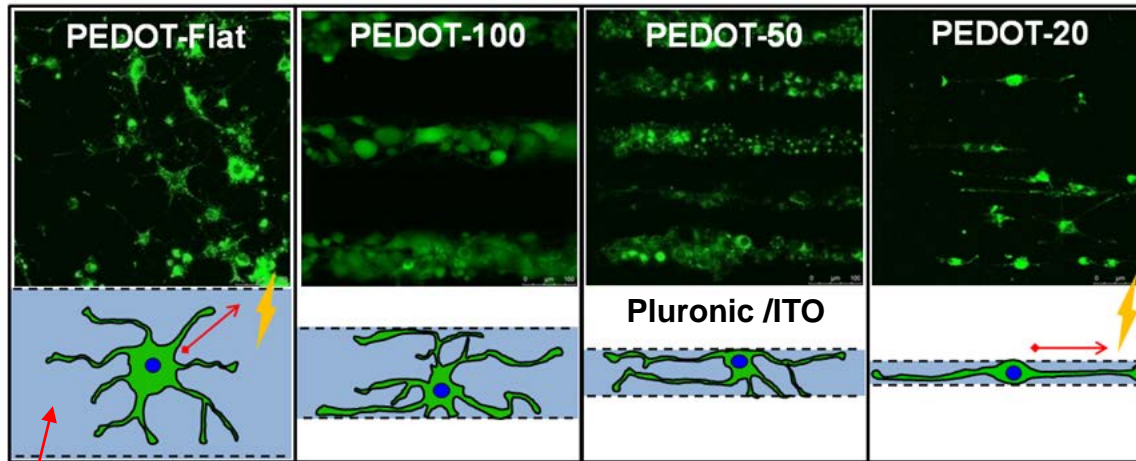
Polymer 52 (2011) 1302–1308.

# Manipulating location, polarity, and outgrowth length of neuron-like pheochromocytoma (PC-12) cells on patterned organic electrode arrays

☆ PEDOT microelectrode array system ☆

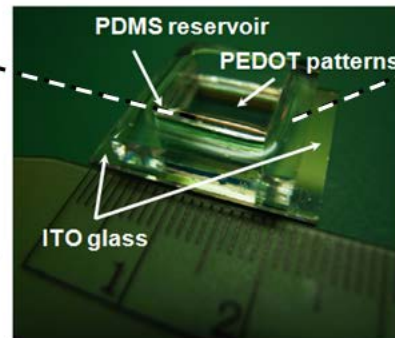
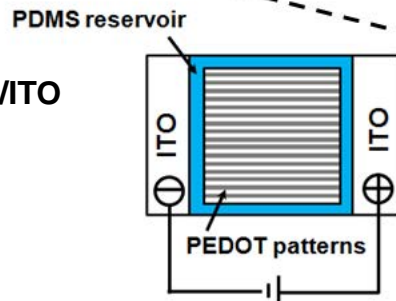
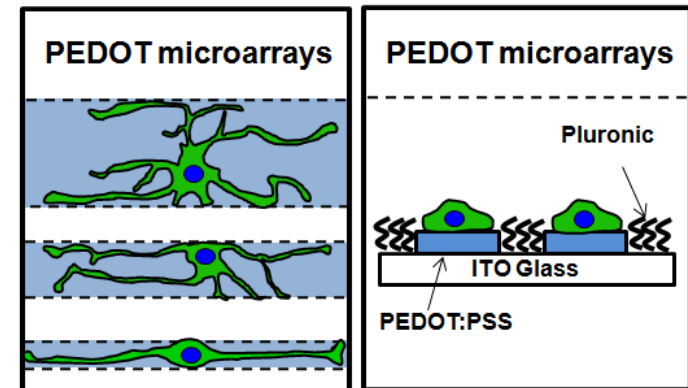
Lab Chip, 11, 3674 (2011).

Live/Dead assay: Live (green)/ Dead (Red)



Topview

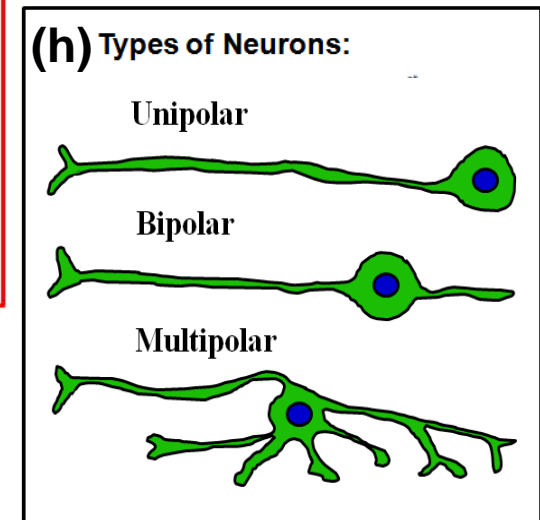
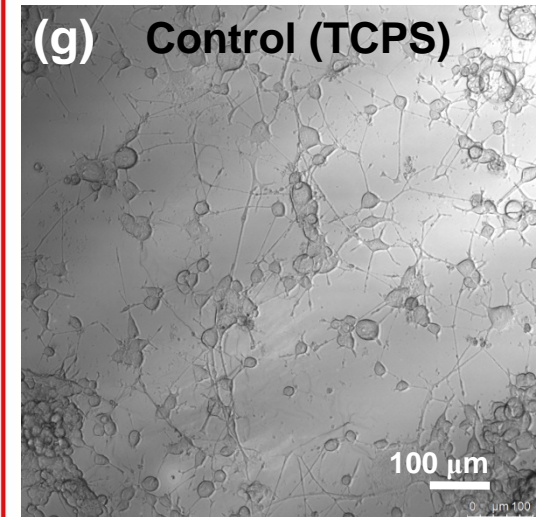
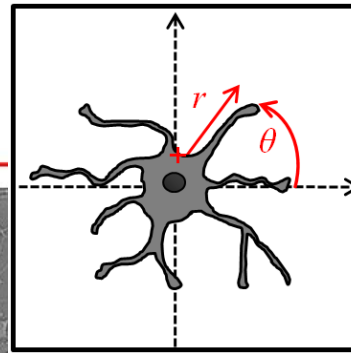
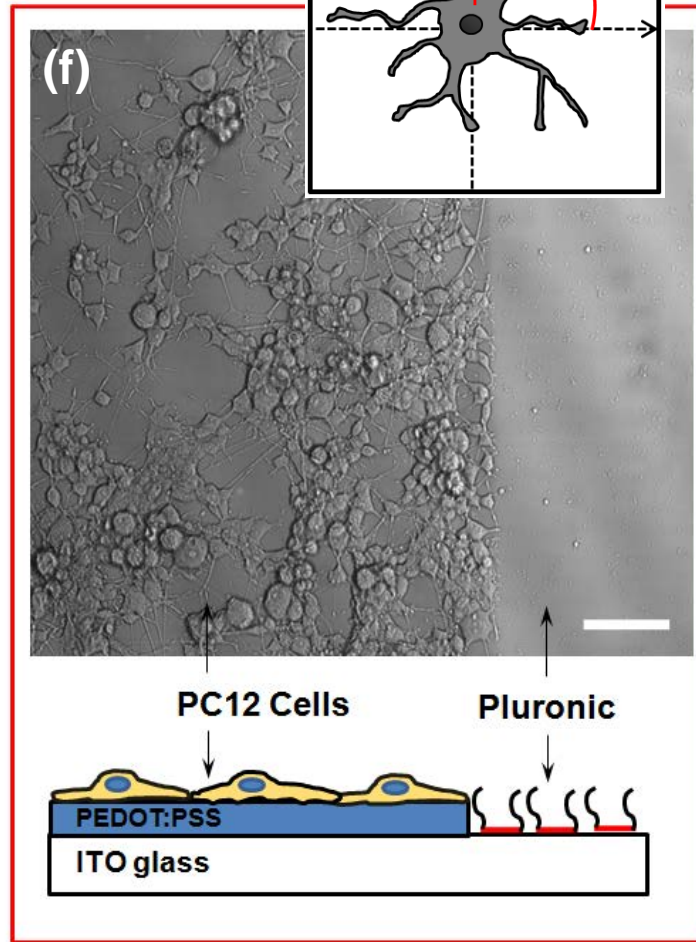
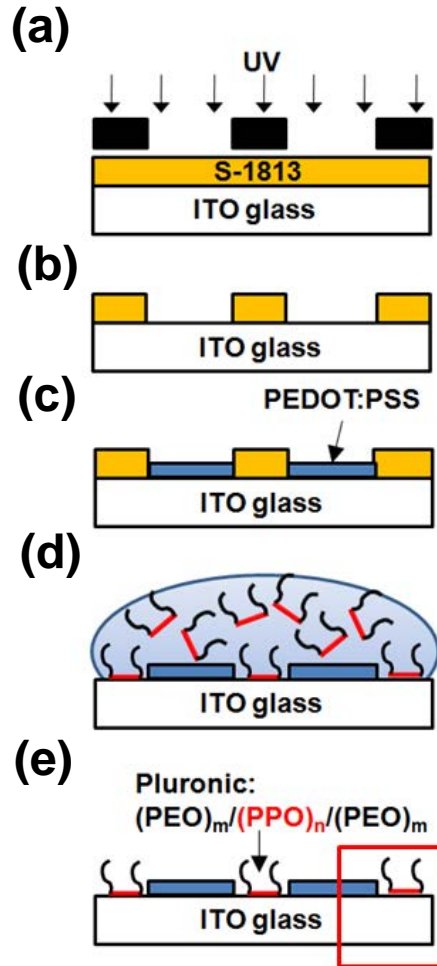
Cross-section



Pluronic

1. **Contact attraction:** PEDOT:PSS
2. **Contact repulsion:**  $(\text{PEO})_m / (\text{PPO})_n / (\text{PEO})_m$
3. **Chemoattraction.** (NGF)
4. **Electrical Stimulation**



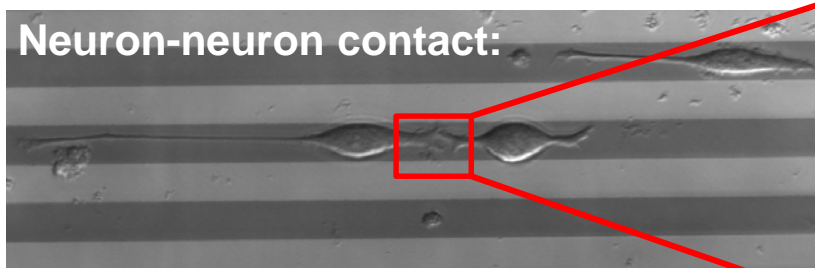
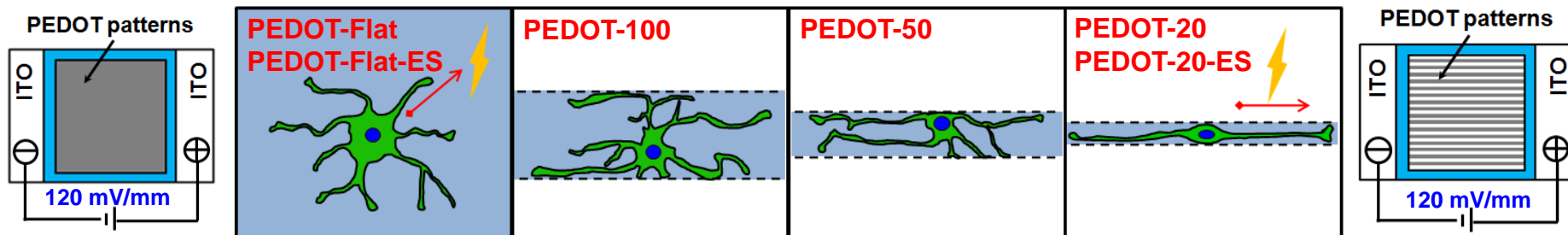


(a-e) Schematic representation of the fabrication of PEDOT microelectrode arrays with anti-adhesive Pluronic F108 coatings.

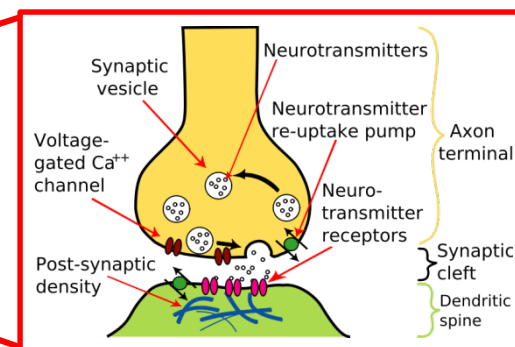
	Unipolar (% of Cells)	Bipolar (% of Cells)	Multipolar (% of Cells)	Average number of neurites per cell	Median neurite length ( $\mu\text{m}$ )	Polar order parameter (S)
Control	4	18	78	3.7	91	$-0.05 \pm 0.36$
PEDOT-Flat	6	14	$\ominus$ $\uparrow$ 80	3.2 $\uparrow$	98	$-0.08 \pm 0.36$
PEDOT-100	26	22	52	2.7	60	$0.22 \pm 0.36$
PEDOT-50	8	54	38	2.4	66	$0.68 \pm 0.24$
PEDOT-20	24	72	4 $\ominus$ $\downarrow$	1.8 $\ominus$ $\downarrow$	88	$0.97 \pm 0.07$
PEDOT-Flat-ES <sup>a</sup>	6	12	82	3.5	119	$-0.07 \pm 0.36$
PEDOT-20-ES <sup>a</sup>	20	74	6	1.8	143	$0.97 \pm 0.06$

<sup>a</sup>Electrical Stimulation (ES)

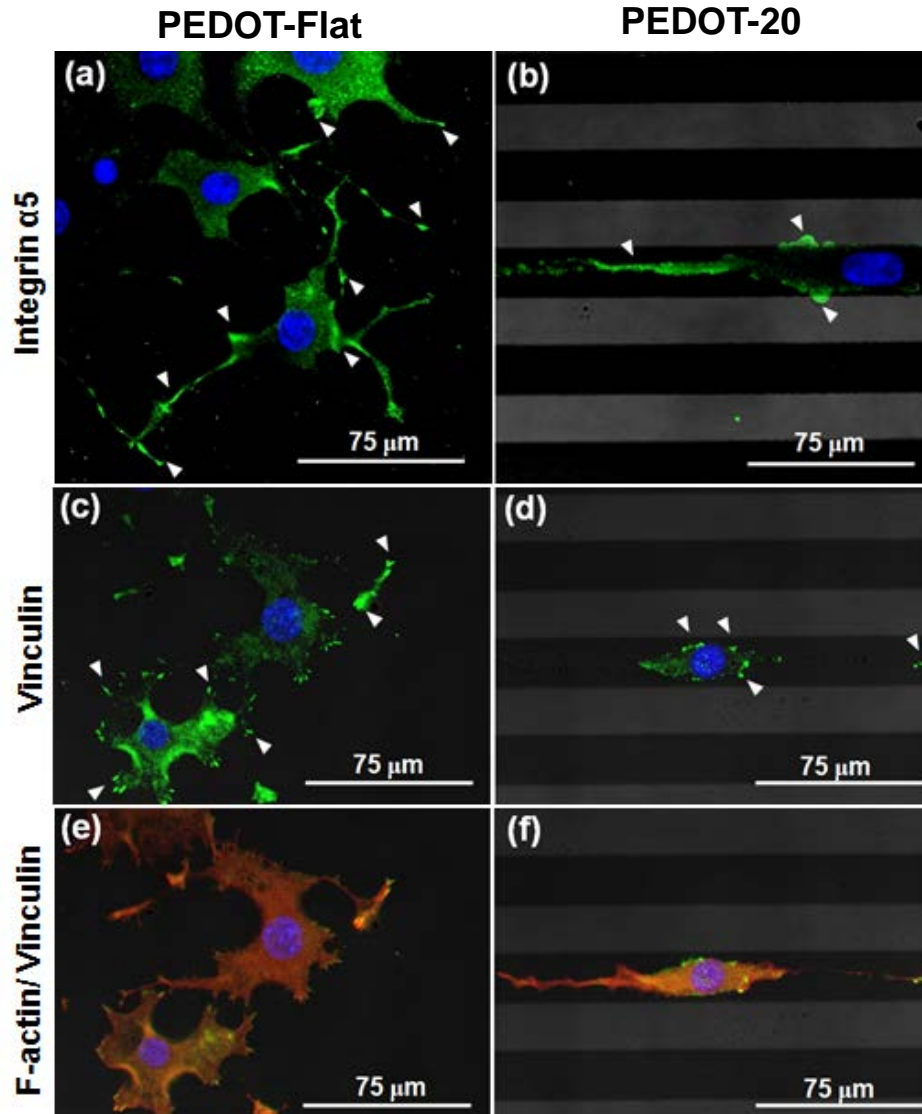
Polar order parameter (S) =  $(2\langle \cos^2\theta \rangle - 1)$



Neuron-neuron contact:



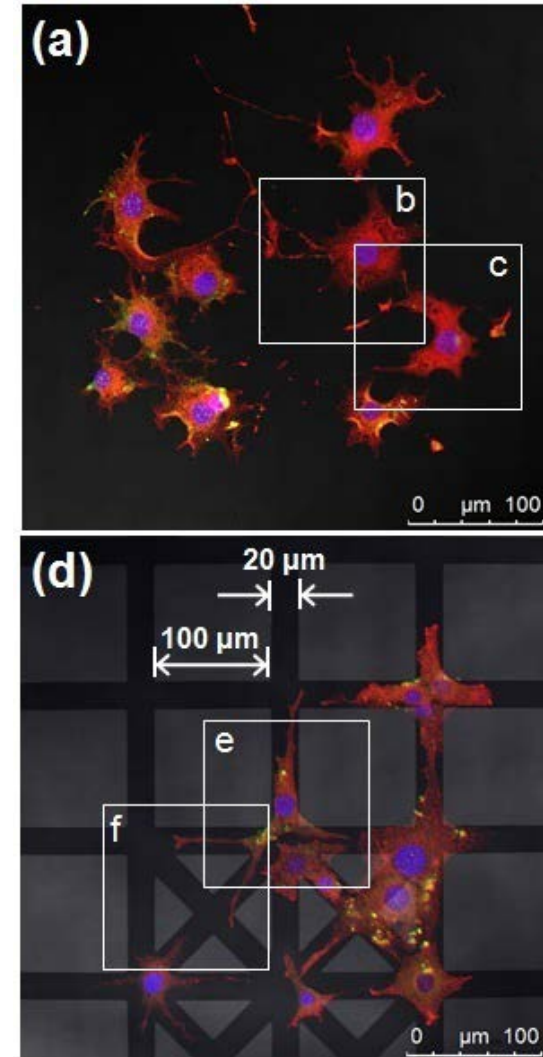
# Cytoskeleton Morphology and Focal Adhesion of PC12 cells on PEDOT-Flat and PEDOT-20 microelectrode arrays



F-actin (red)/ vinculin (green)/ nucleus (blue)

PEDOT-Flat

PEDOT-Networks



*Lab Chip*, **11**, 3674 (2011).

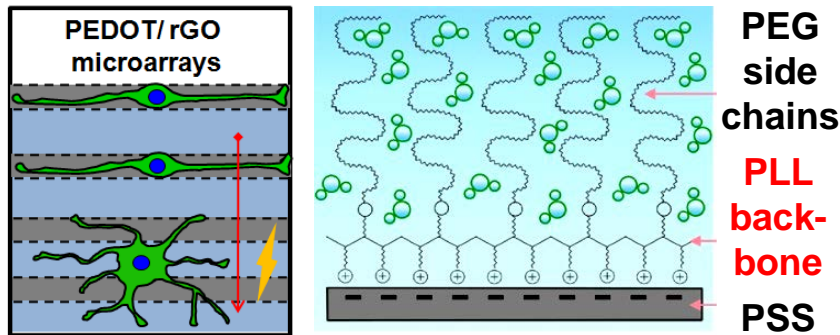


# Electrically tunable organic bioelectronics for spatial and temporal manipulation of neuron-like pheochromocytoma (PC-12) cells

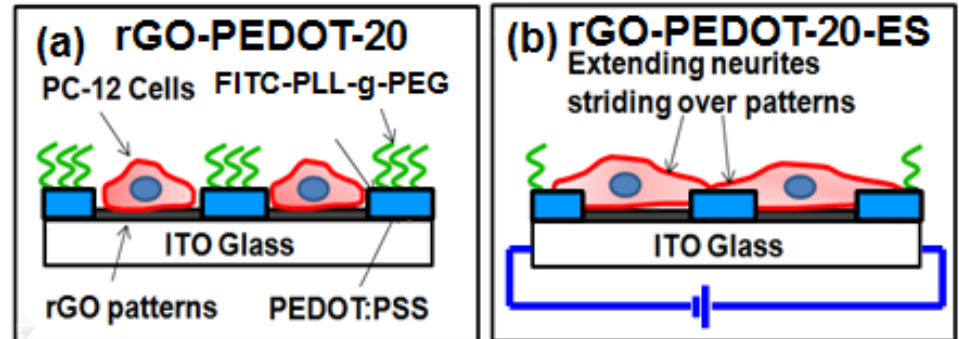
☆ **Graphene-PEDOT microelectrode array system** ☆

BBA General Subject, 1830, 4321 (2013)

## Electrical Stimulation (ES) Condition:

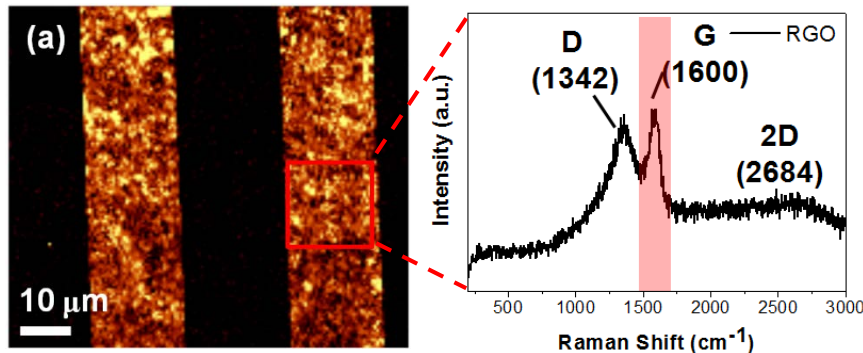


## ES for Spatiotemporal Control by DC voltage

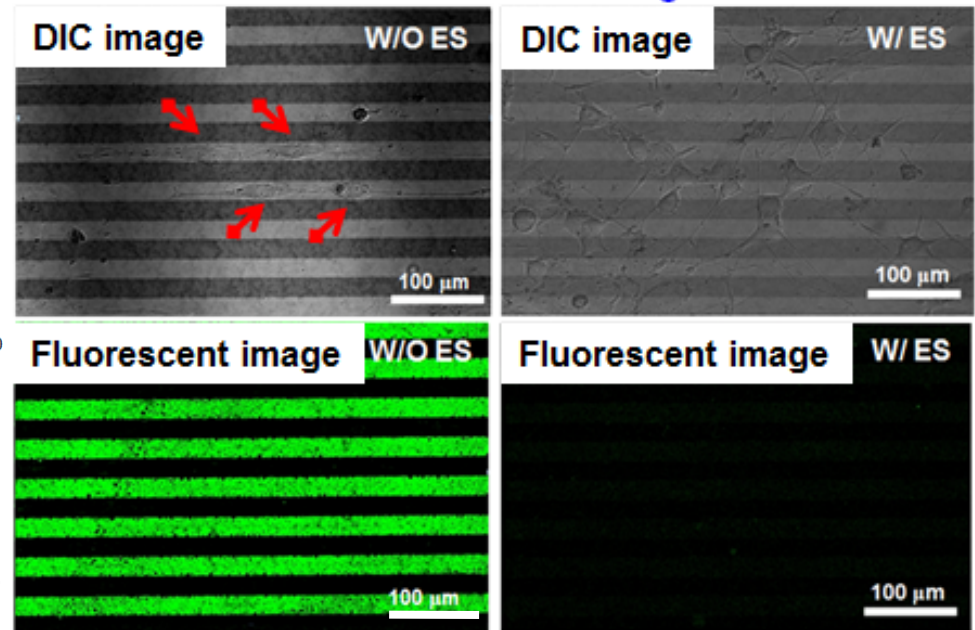


DC voltage of 120 mV mm<sup>-1</sup>

## Raman Image



Reduced graphene oxide (rGO)

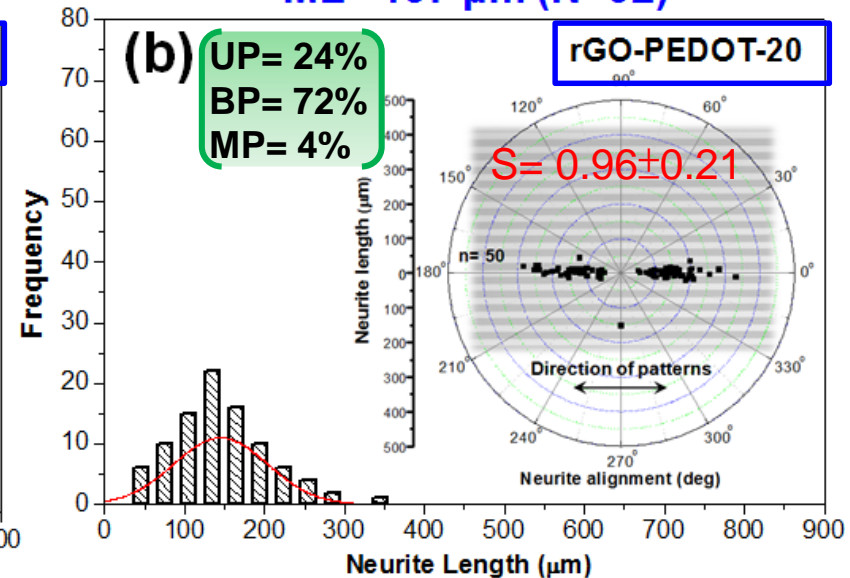
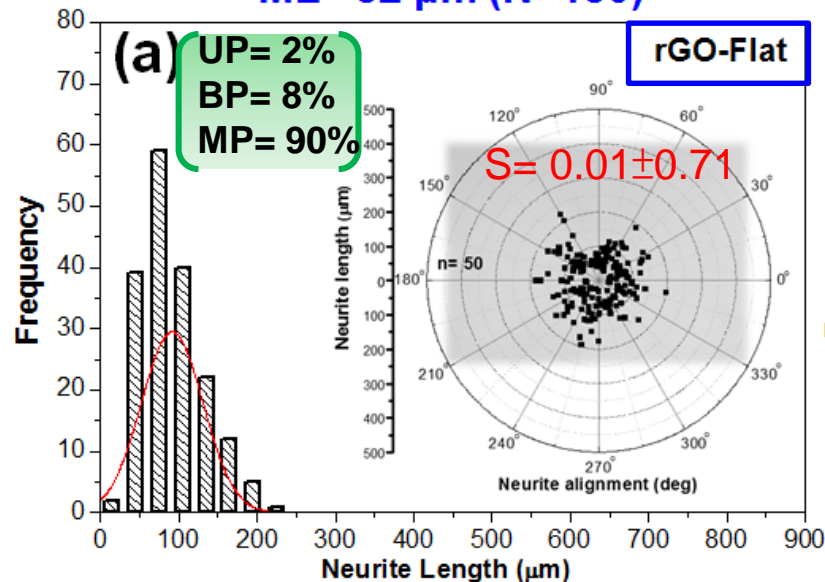


1. **Contact attraction:** rGO
2. **Contact repulsion:** PLL-g-PEG/PEDOT:PSS
3. **Chemoattraction.** NGF
4. **Electrical Stimulation**

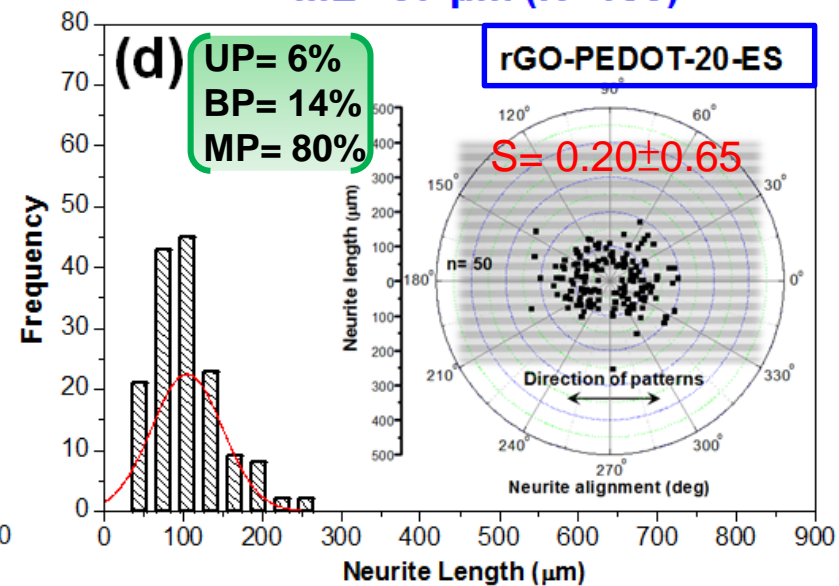
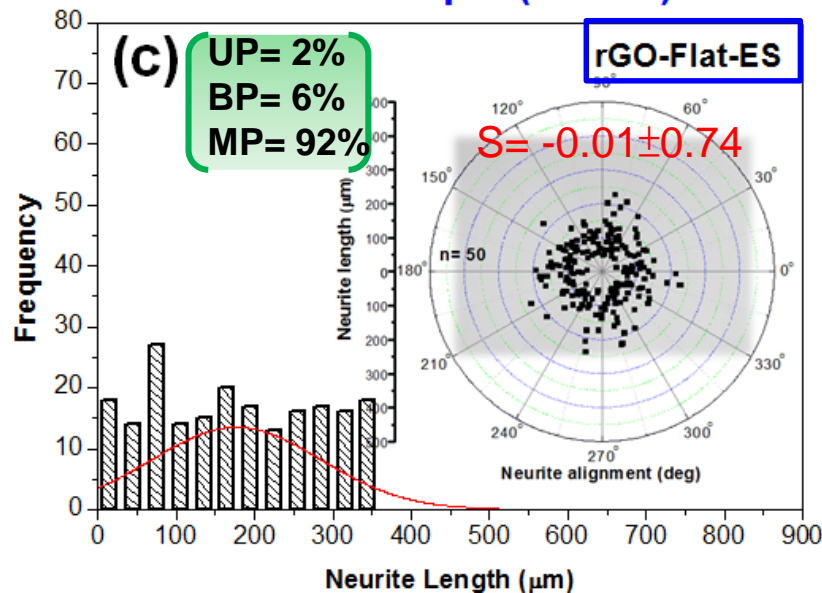


ML= 82  $\mu\text{m}$  (N=180)ML= 137  $\mu\text{m}$  (N=92)

w/o ES

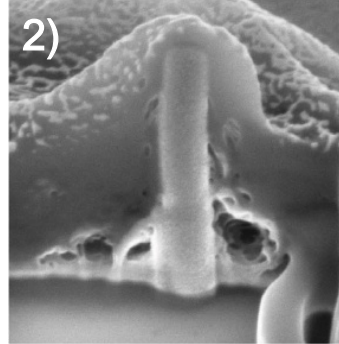
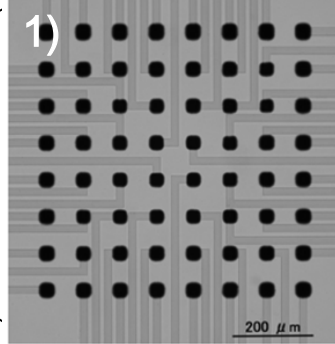
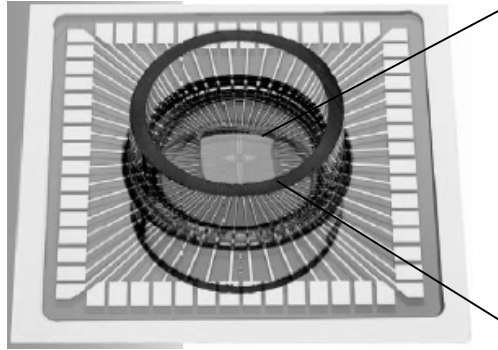
ML= 173  $\mu\text{m}$  (N=206)ML= 97  $\mu\text{m}$  (N=153)

w/ ES



PC-12 Cell type: Unipolar (UP); Bipolar (BP); Multipolar (MP)

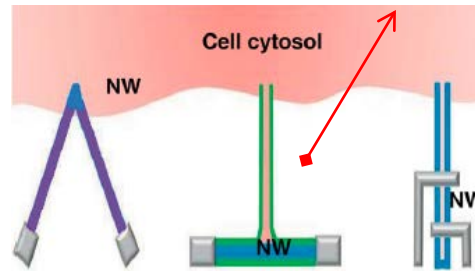
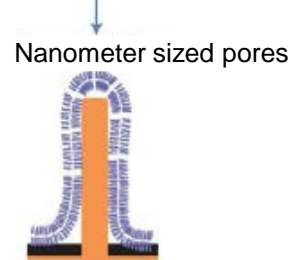
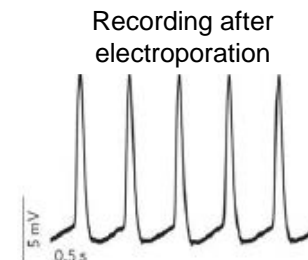
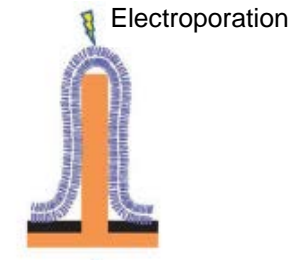
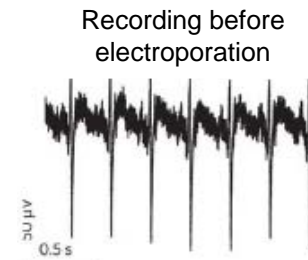
# Microelectrode Array (MEA)-System



**BI Materials**

**Vertical Nanorods**

TiN electrodes, SiN isolator, contact pads and tracks transparent (ITO), with internal reference electrode, electrode grid 8x8, 60 electrodes, electrode spacing 200μm, electrode diameter 30μm, warranty: 6 months.



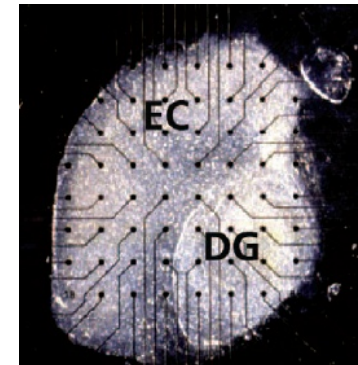
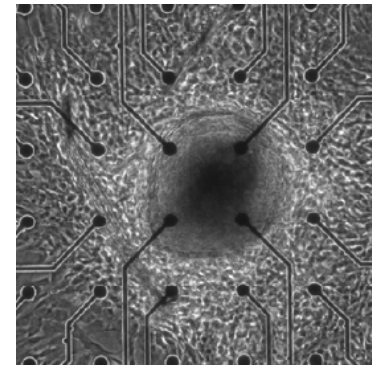
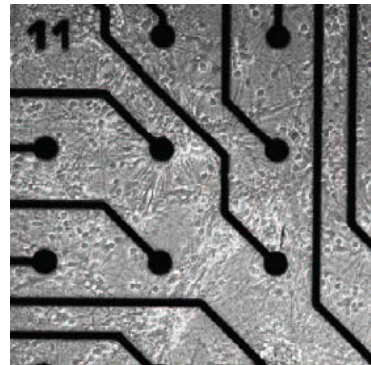
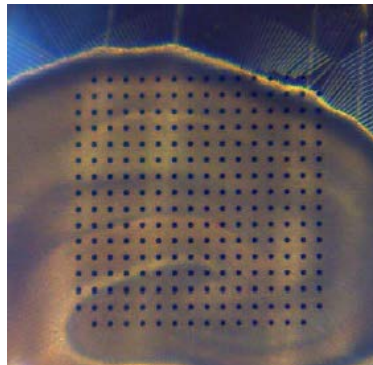
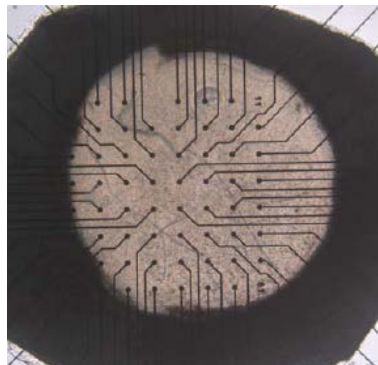
**Retina**

**Brain Mapping**

**Neuronal cells**

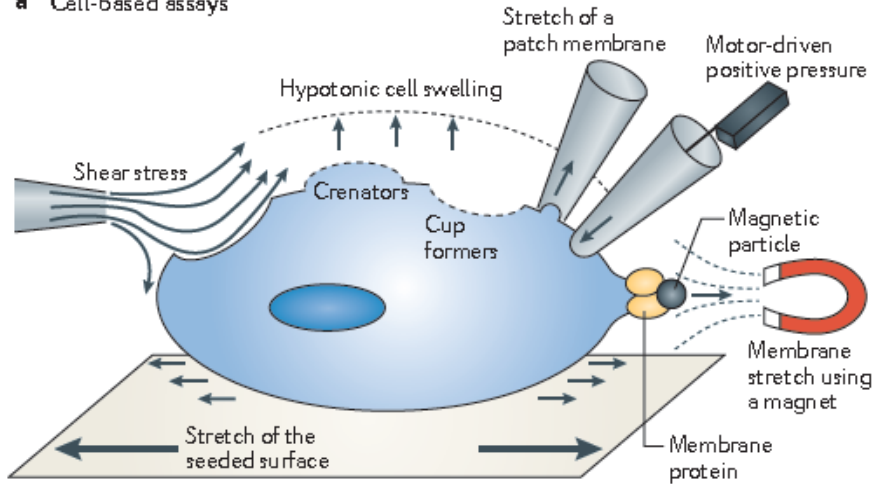
**Stem cells**

**Organotypic cultures**

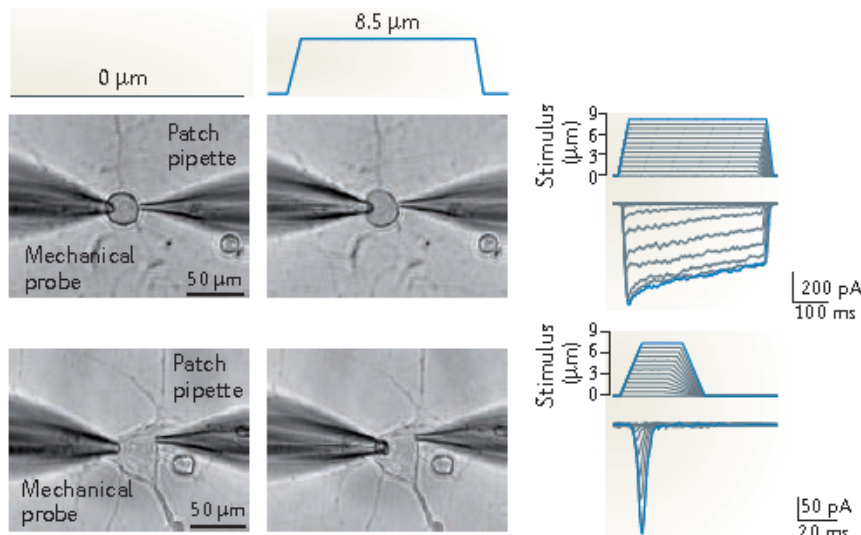


# Probe Mechanotransduction (PM)

## a Cell-based assays

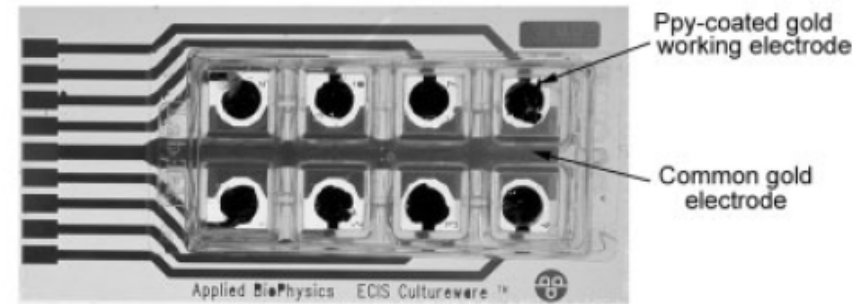


## b Whole-cell mechano-clamp

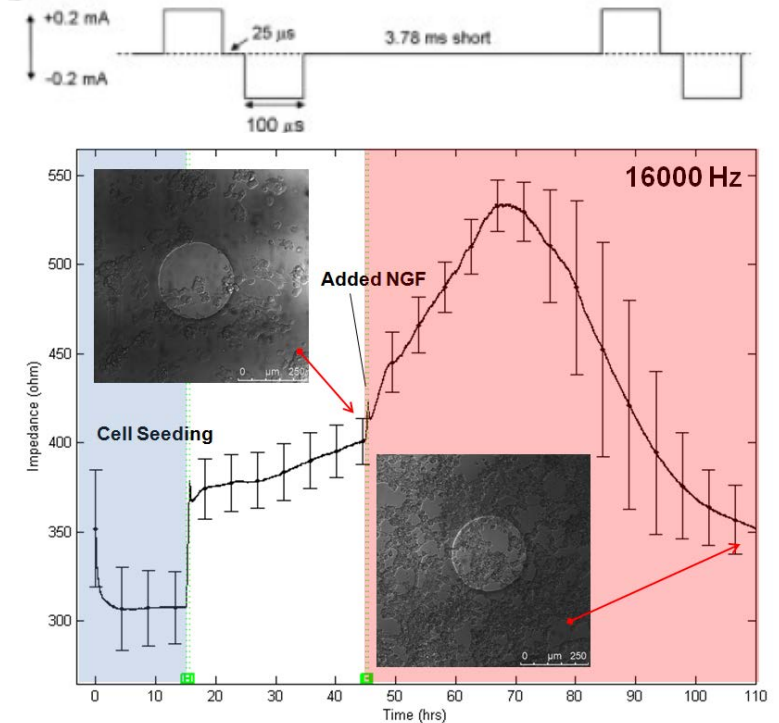


# Electric Cell-Substrate Impedance Sensing (ECIS)

## a



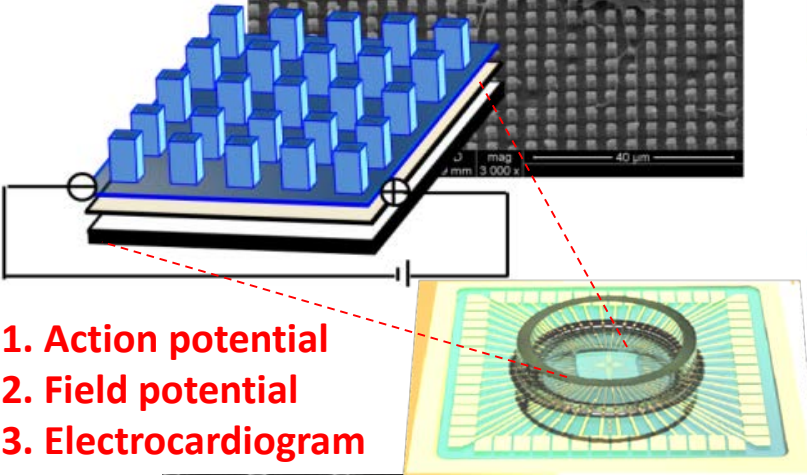
## b



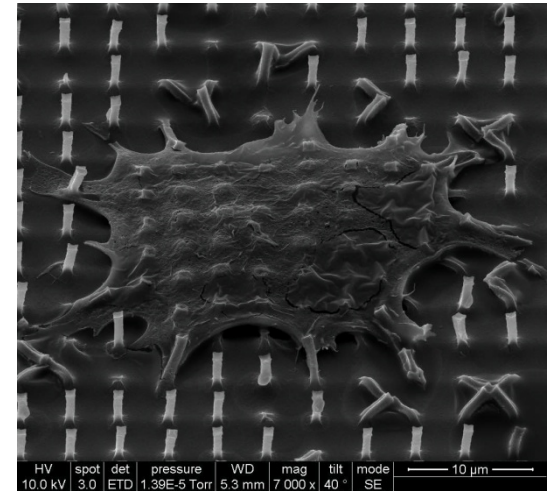
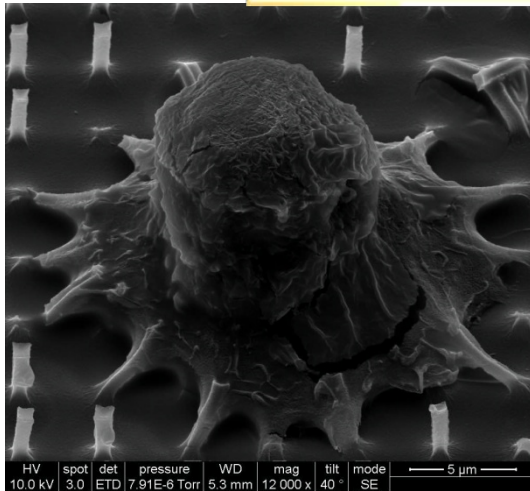
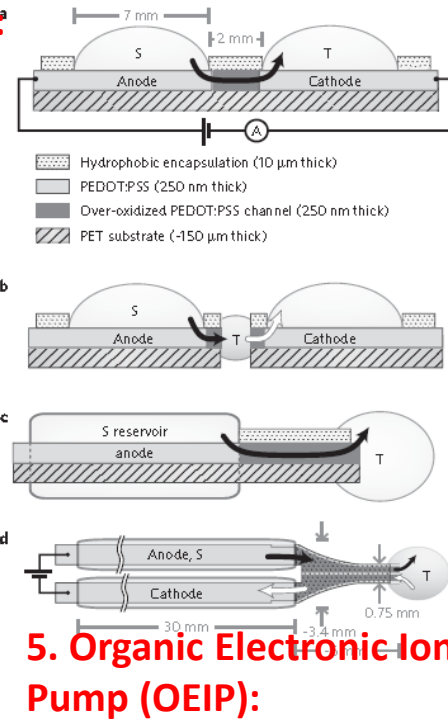
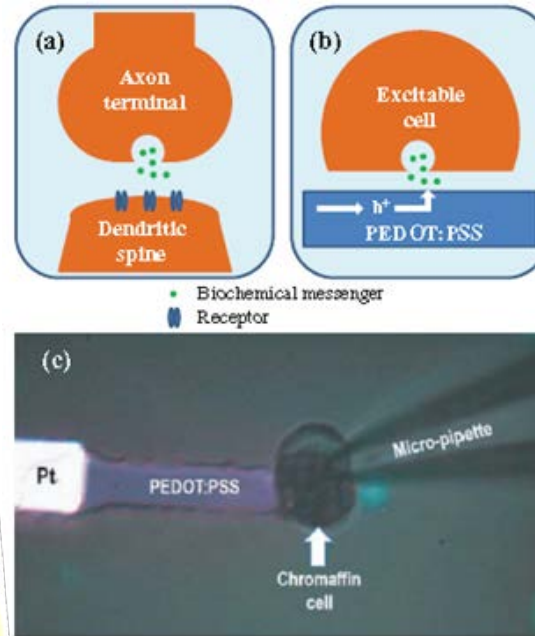


# BI coated MEA-system for in vitro and in vivo

PC12 Cells/ PEDOT pillars:



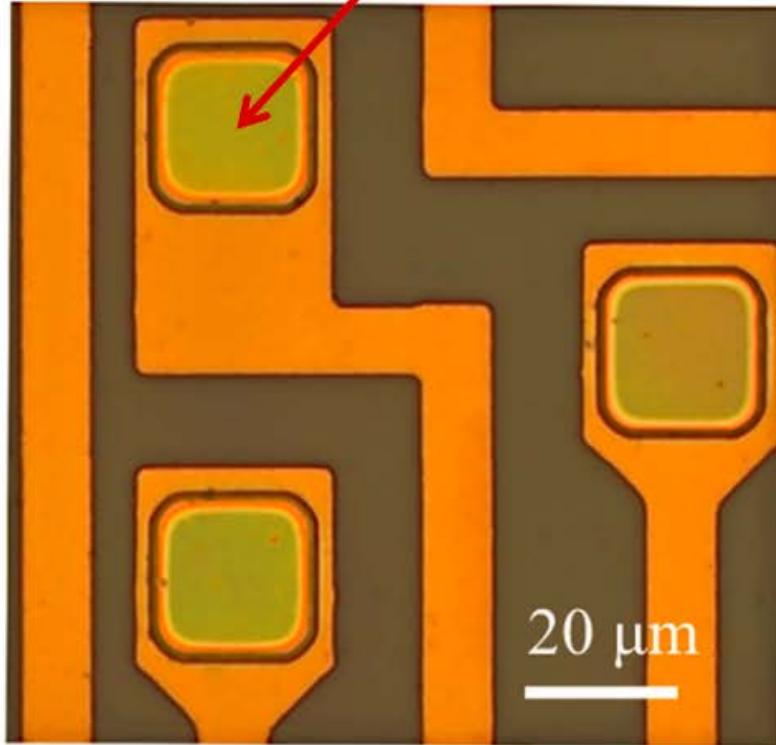
## 4. Probe Mechanotransduction-FET :



MCF7 cells/ PEDOT Nanorod Arrays

# Ultra-conformable PEDOT:PSS microelectrodes

PEDOT:PSS

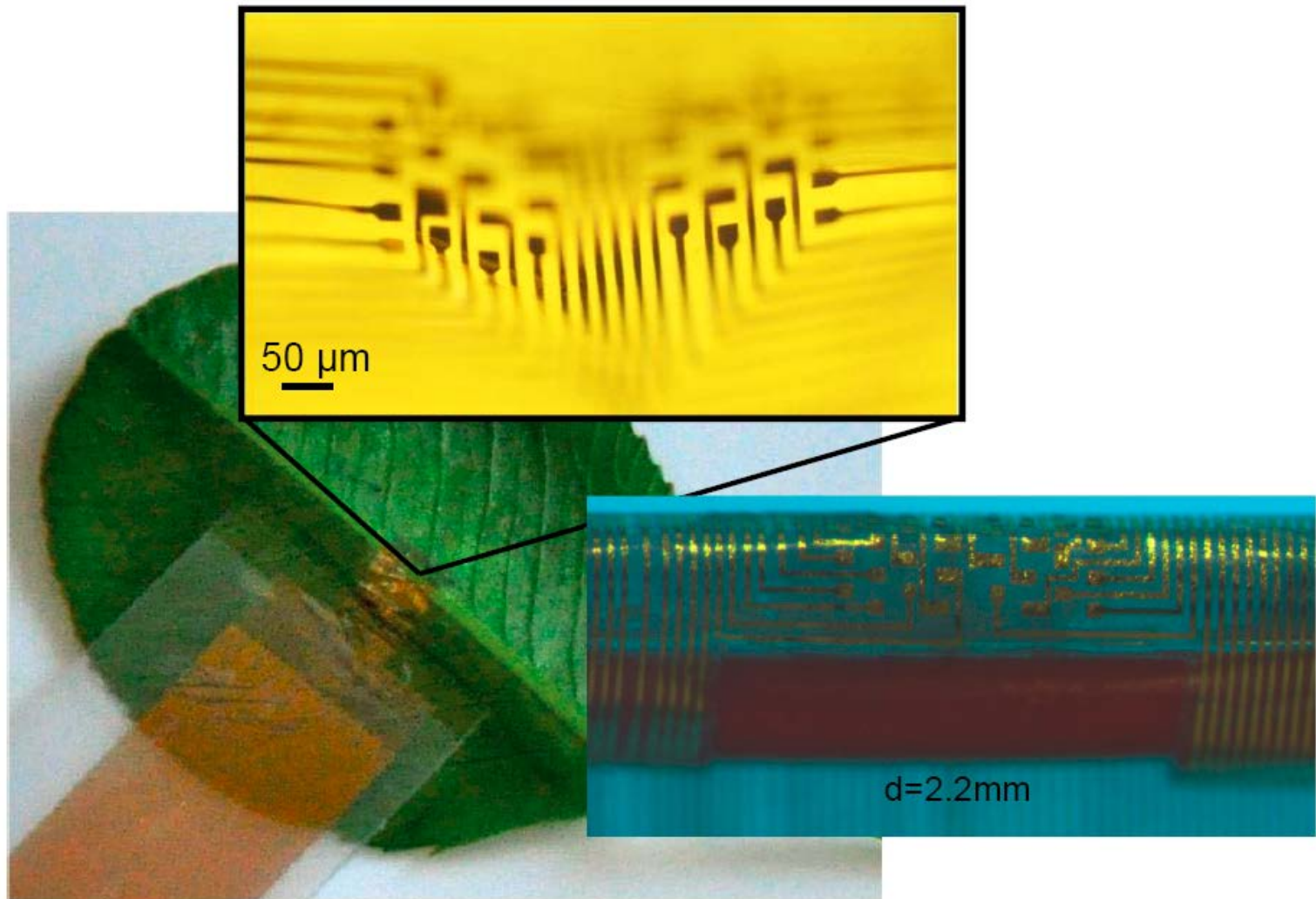


Parylene C – 4  $\mu\text{m}$  thick



D. Khodagholy, T. Doublet, M. Gurfinkel, P. Quilichini, E. Ismailova, P. Leleux, T. Herve, S. Sanaur, C. Bernard, and G.G. Malliaras, *Adv. Mater.* 36, H268 (2011).

# Ultra-conformable ECoG arrays

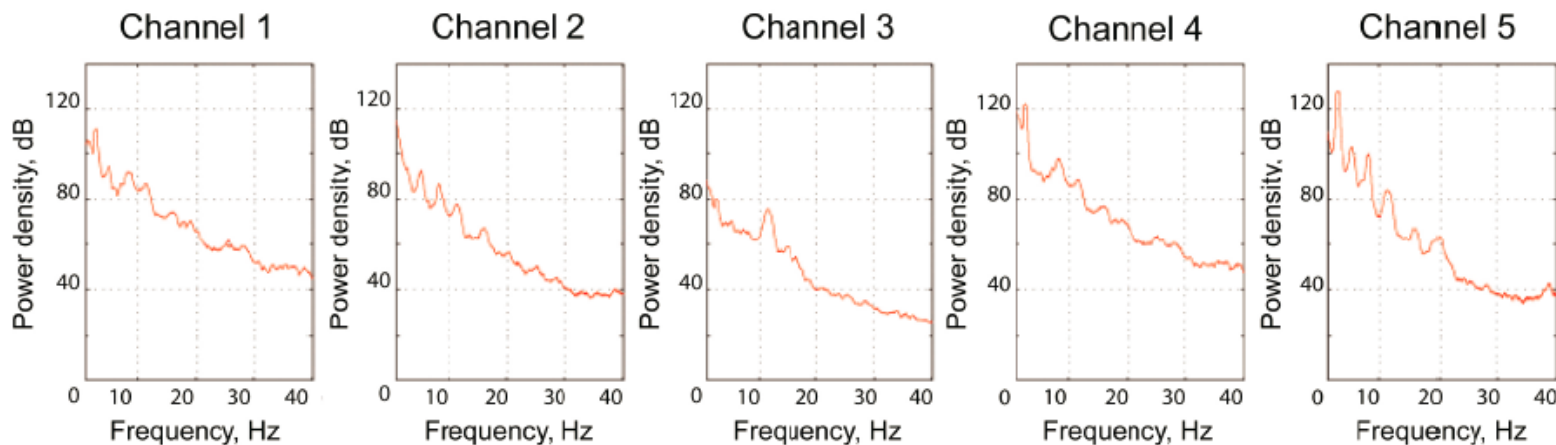


D. Khodagholy, T. Doublet, M. Gurfinkel, P. Quilichini, E. Ismailova, P. Leleux, T. Herve, S. Sanaur, C. Bernard, and G.G. Malliaras, *Adv. Mater.* 36, H268 (2011).

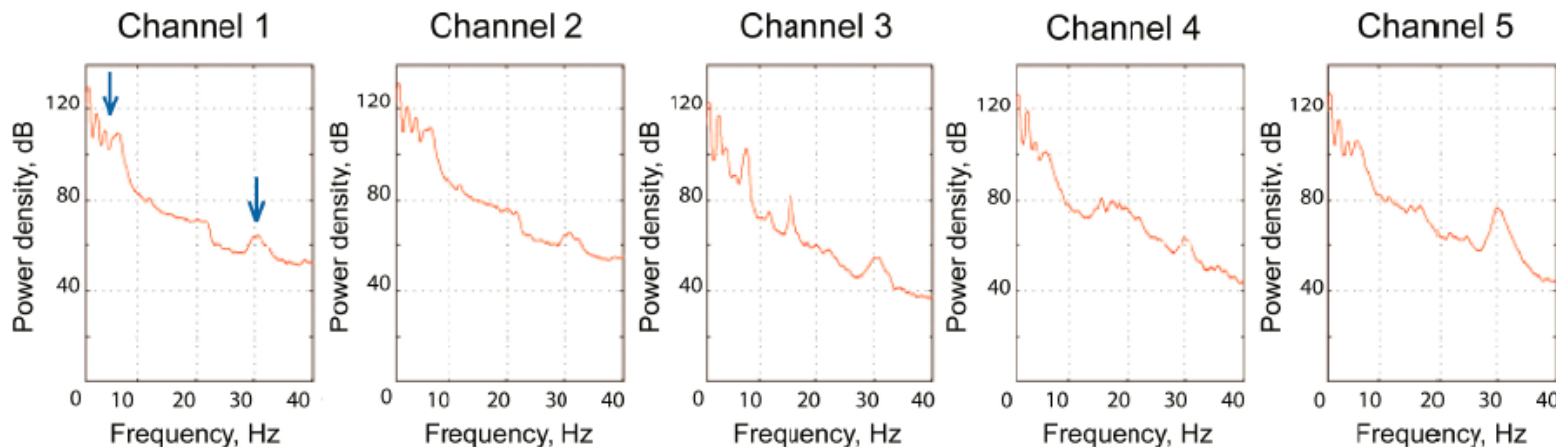


# PEDOT:PSS electrodes outperform Au electrodes

Au  
electrodes



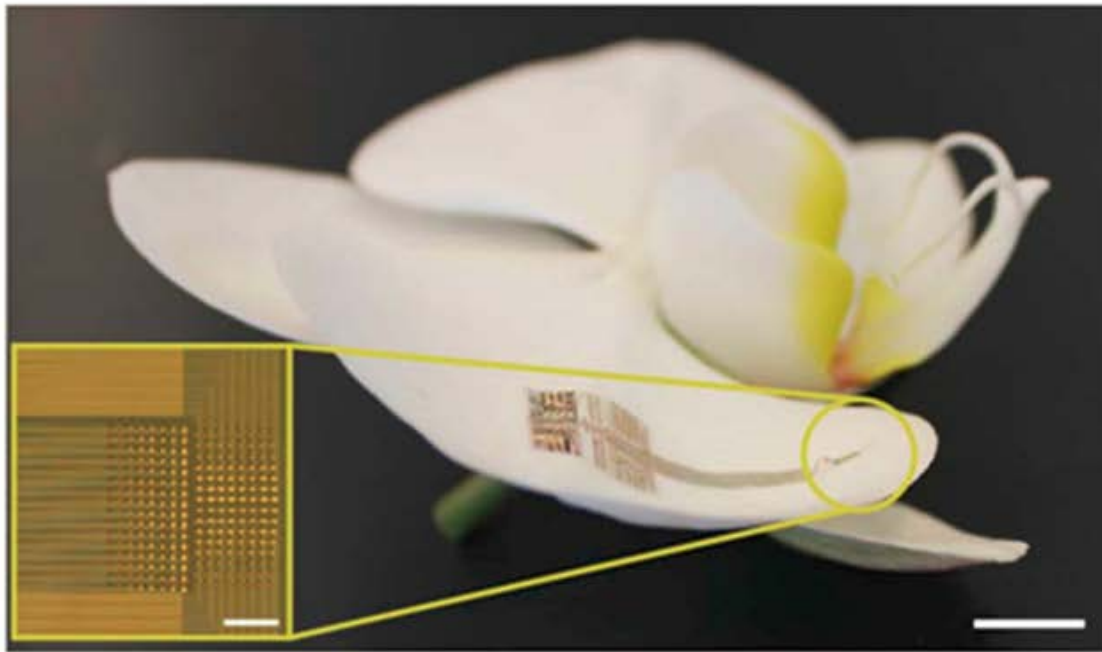
PEDOT:PSS  
electrodes



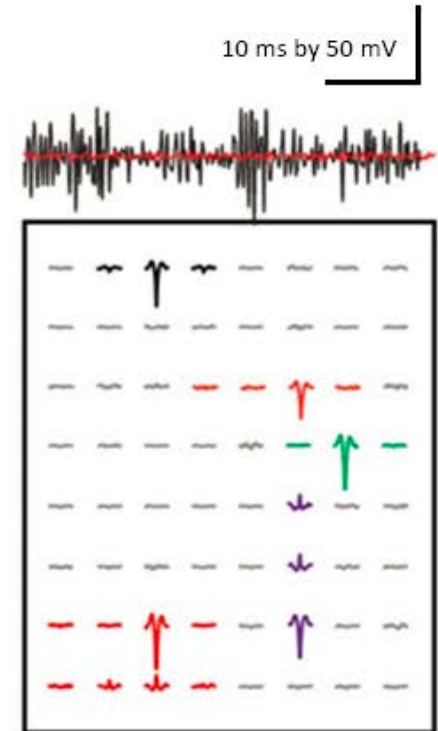
D. Khodagholy, T. Doublet, M. Gurfinkel, P. Quilichini, E. Ismailova, P. Leleux, T. Herve, S. Sanaur, C. Bernard, and G.G. Malliaras, Adv. Mater. 36, H268 (2011).



# Detection of single neurons from brain surface



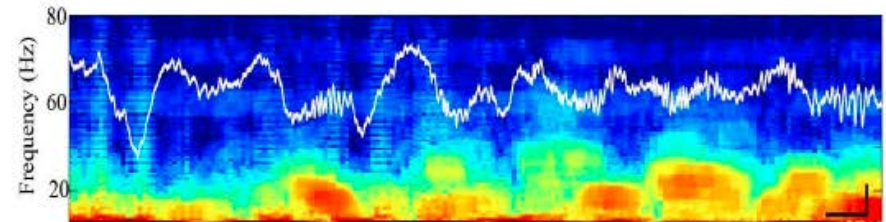
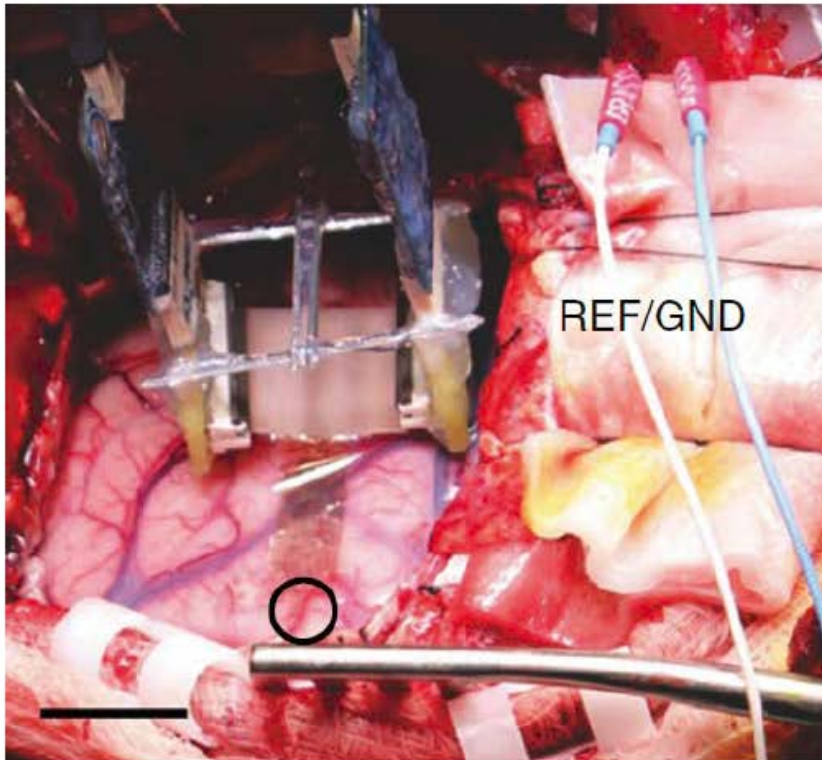
256 electrodes,  $10 \times 10 \mu\text{m}^2$  with  $30 \mu\text{m}$  inter-electrode spacing



## Electrocorticography in rats

D. Khodagholy, J.N. Gelinas, T. Thesen, W. Doyle, O. Devinsky, G.G. Malliaras and G. Buzsáki, *Nature Neurosci.* 18, 310 (2015)

# Translation to the clinic



500 ms by 500 mV



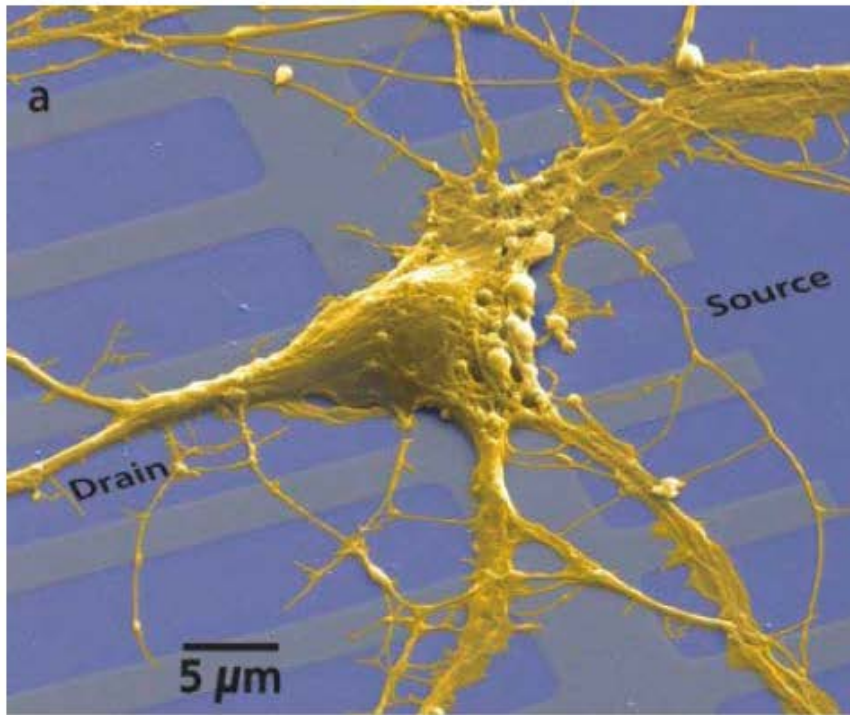
20 ms by 40 mV

## Acute recordings in human patients

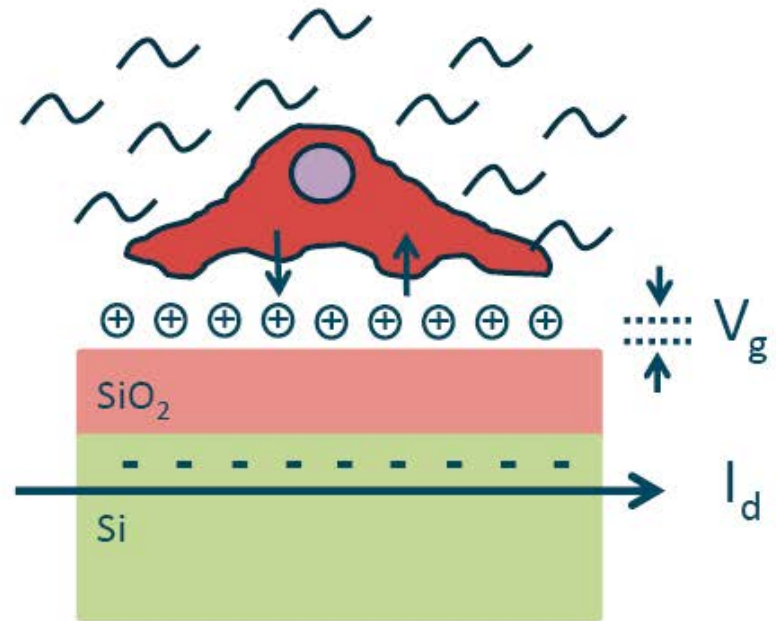
D. Khodagholy, J.N. Gelinas, T. Thesen, W. Doyle, O. Devinsky,  
G.G. Malliaras and G. Buzsáki, *Nature Neurosci.* 18, 310 (2015)

# Organic electrochemical transistors (OECTs) record brain activity with record-high SNR

## Field-effect transistors for neural recordings



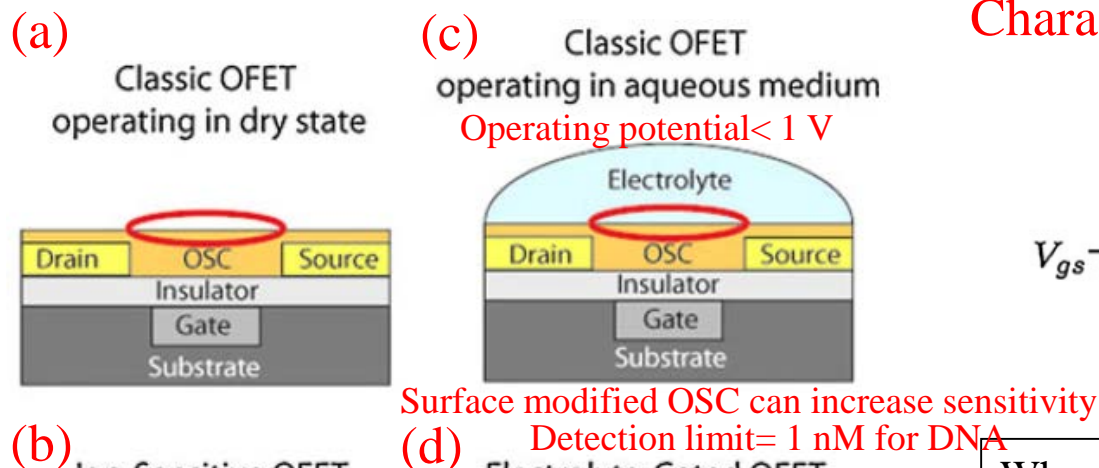
Fromherz group, MPI



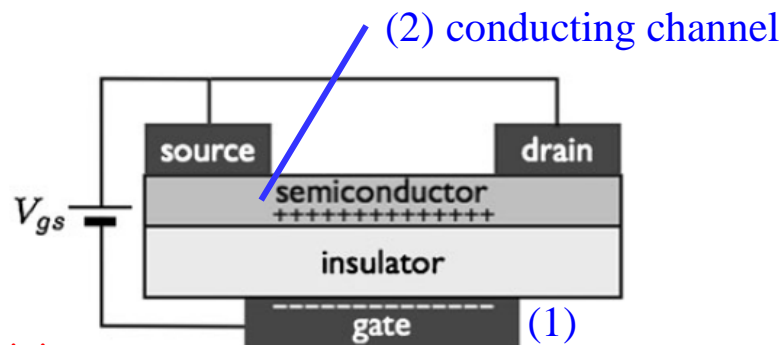
Field-effect transistor (FET)

$$C'_{\max} = 5 \mu\text{F}/\text{cm}^2$$

# Organic Field-effect Transistors (OFET)



## Characterization:



When the gate is negatively (positively) polarized in a p-channel (n-channel) device, free holes (electrons) in the semiconductor are drawn toward the semiconductor-insulator interface to compensate an equivalent negative (positive) charge at the gate-insulator interface.

The gate voltage required to switch the transistor from its “off” to its “on” state, i.e. to establish a conducting transistor channel, is called the threshold voltage.

Operating potential > 10 V

Detection limit = 0.01-25 mM

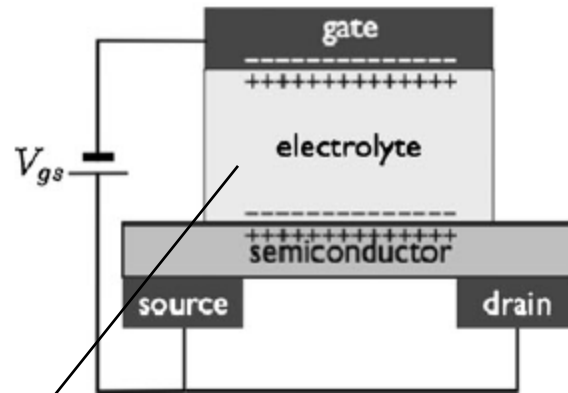
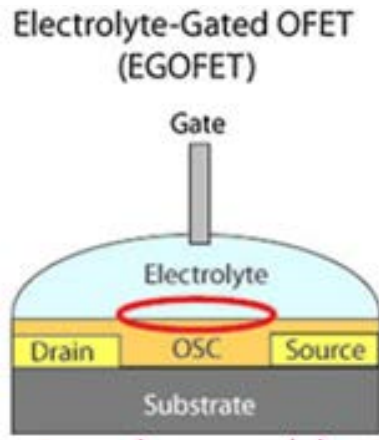
In OFET, the gate is separated from the semiconductor by an insulator. Different dielectrics can be used, e.g. vacuum, oxides, polymers, self-assembled monolayers.

Operating potential < 1V

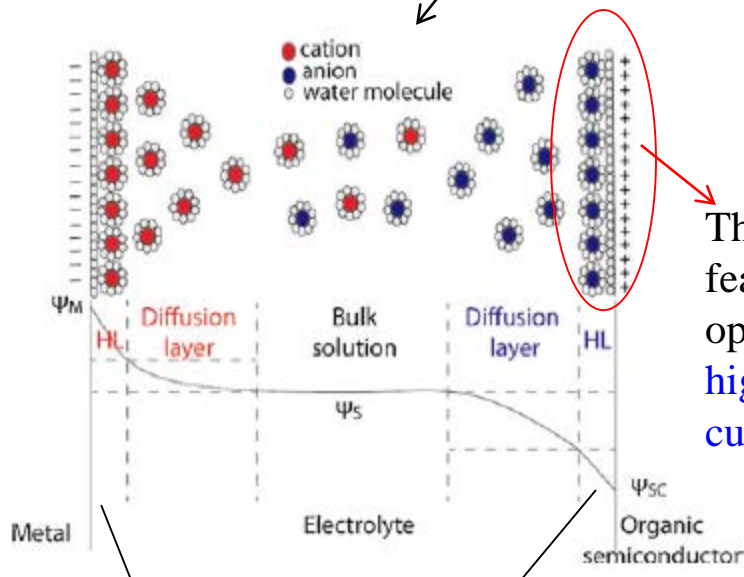
Faster response than OECT



# Electrolyte-gated Organic Field-effect Transistors (EGOFETs)



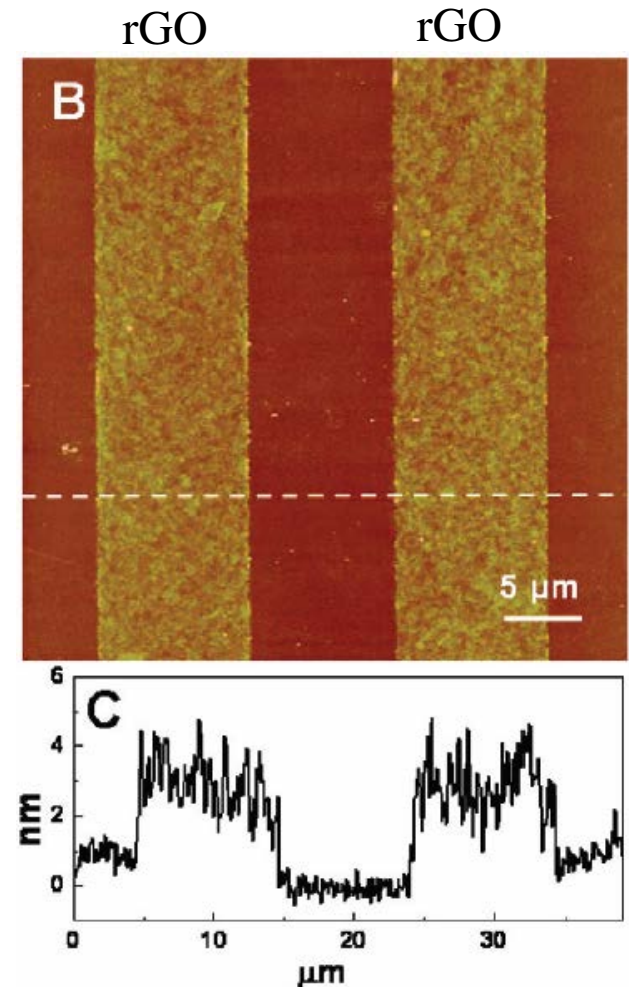
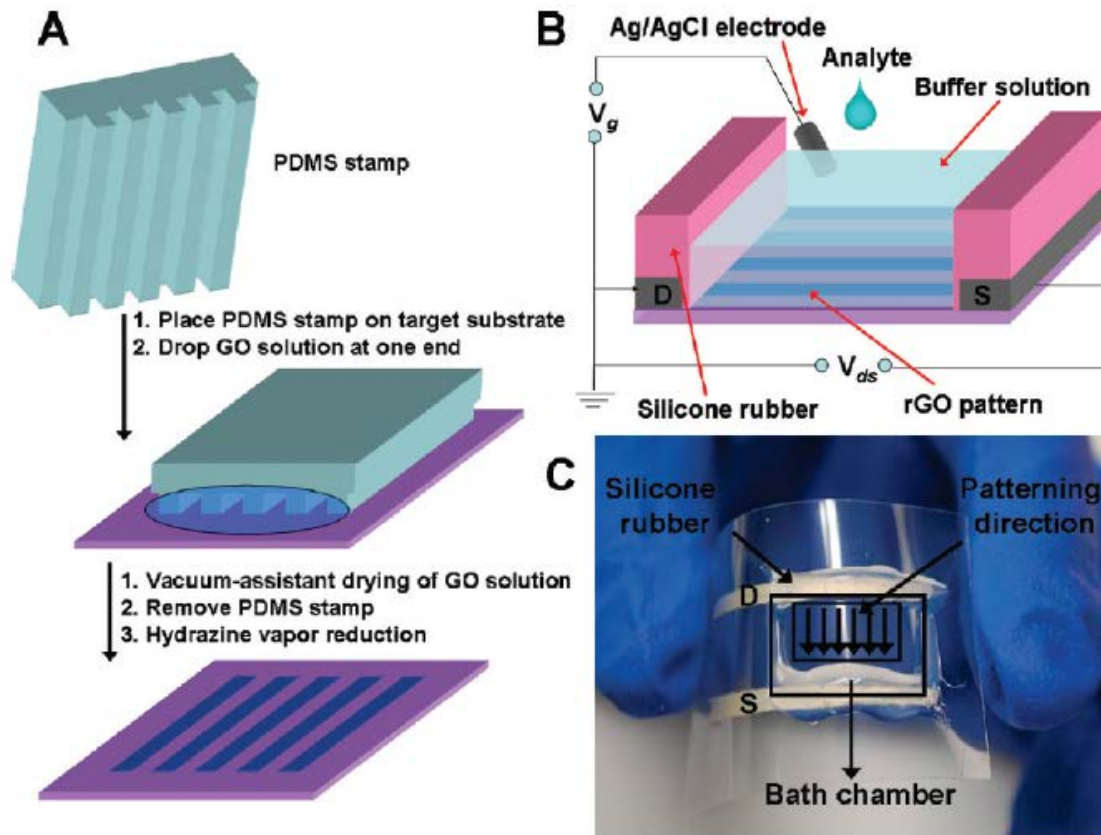
In a p-channel EGOFET device, upon positive polarization of the gate, the anions of the electrolyte migrate away from the electrolyte–semiconductor interface, while cations are attracted toward the electrolyte–gate interface, resulting in the formation of an **electrical double layer (EDL)** at both interfaces.



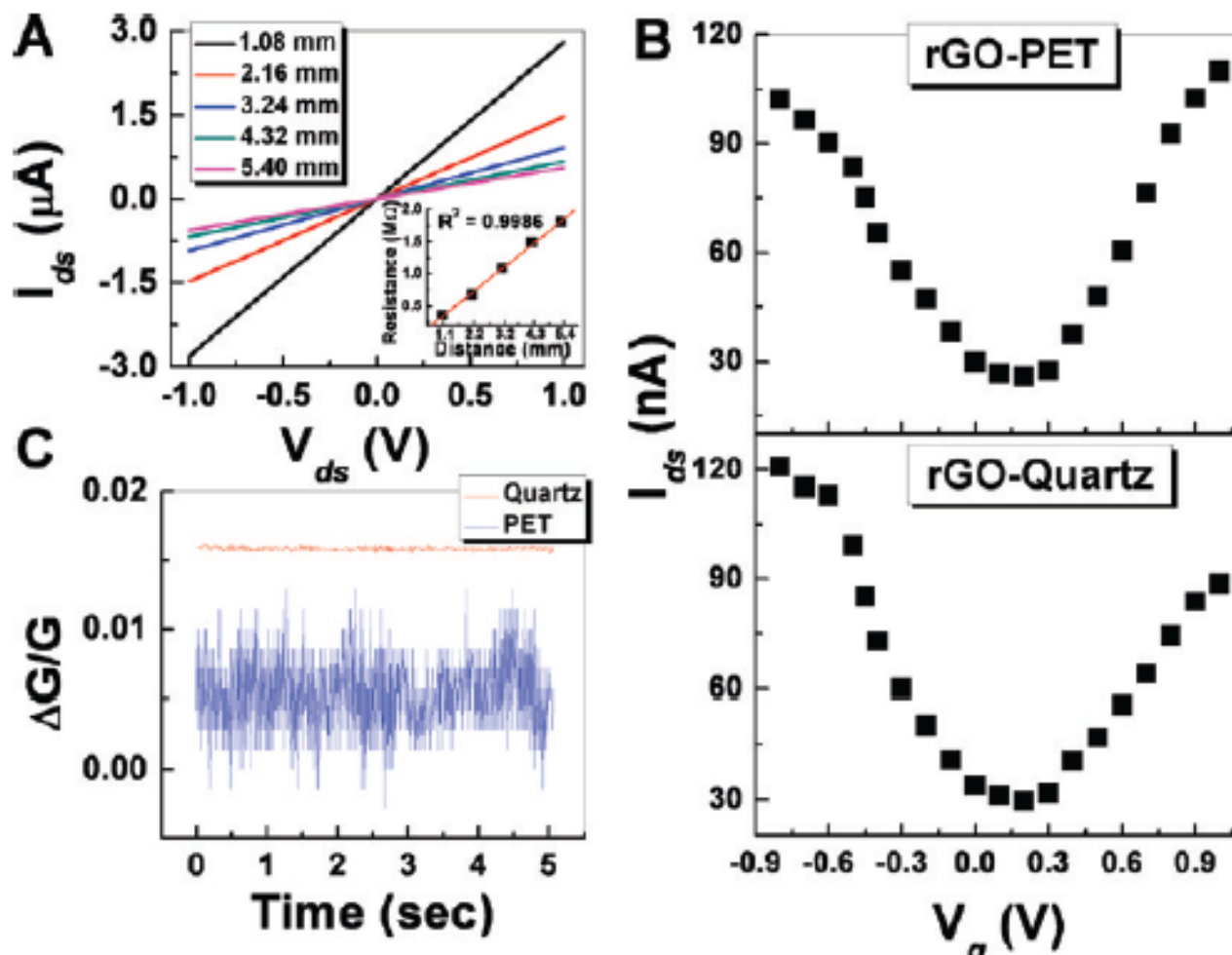
The **thin EDL (0.01 nm)** can be compared to a **capacitor** featuring high capacitance, which enables the transistor to be operated at very **low potentials**. Furthermore, it generates a **higher charge density**, thus **higher mobility** and **output currents**.

**Helmholtz layer (HL)**

# Centimeter-Long and Large-Scale Micropatterns of Reduced Graphene Oxide Films: Fabrication and Sensing Applications



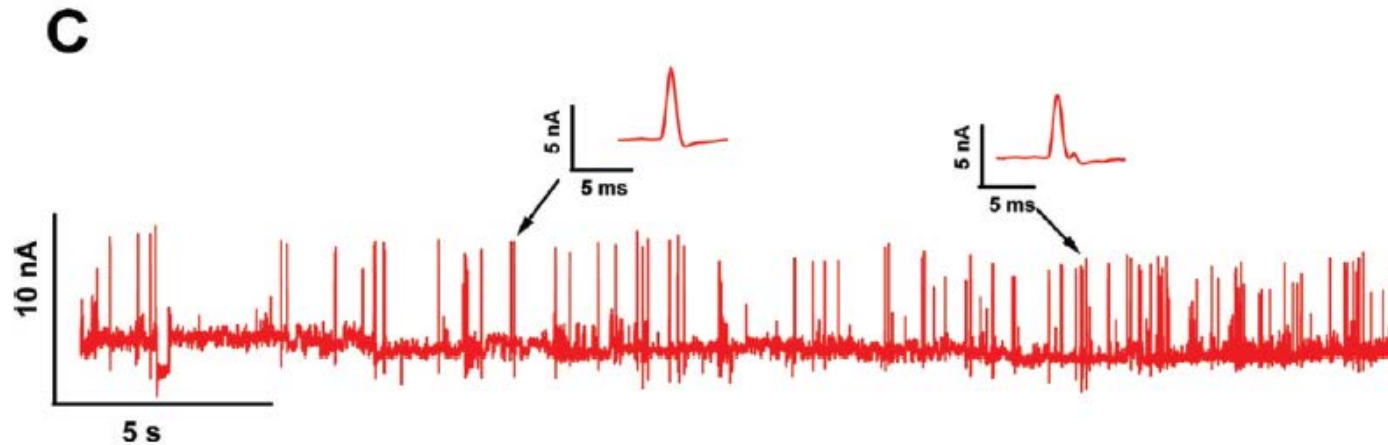
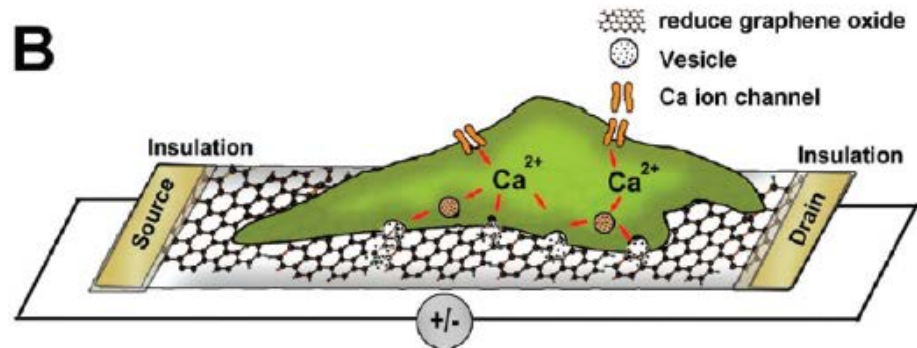
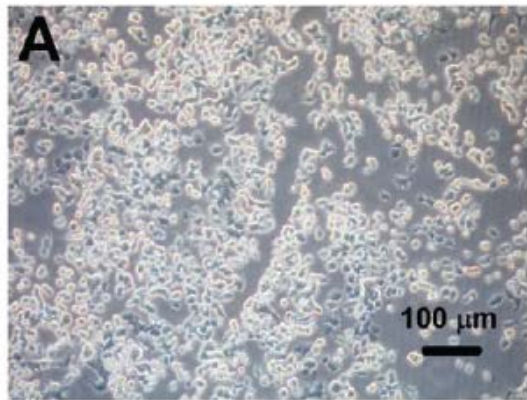
Schematic illustration of the experimental setup of front-gate FET for sensing application.



Current noise on rGO-quartz and rGO-PET devices. The distance between the drain and source electrodes in the devices in panels B and C is fixed at 1 cm.

$$V_{ds} = 400 \text{ mV}$$

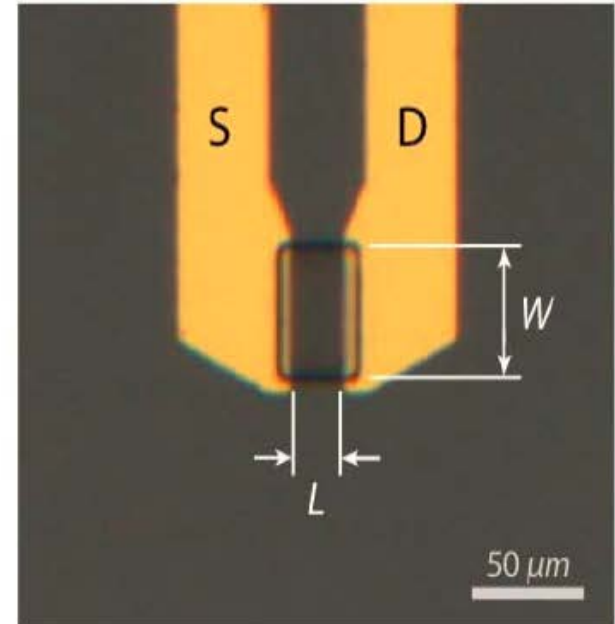
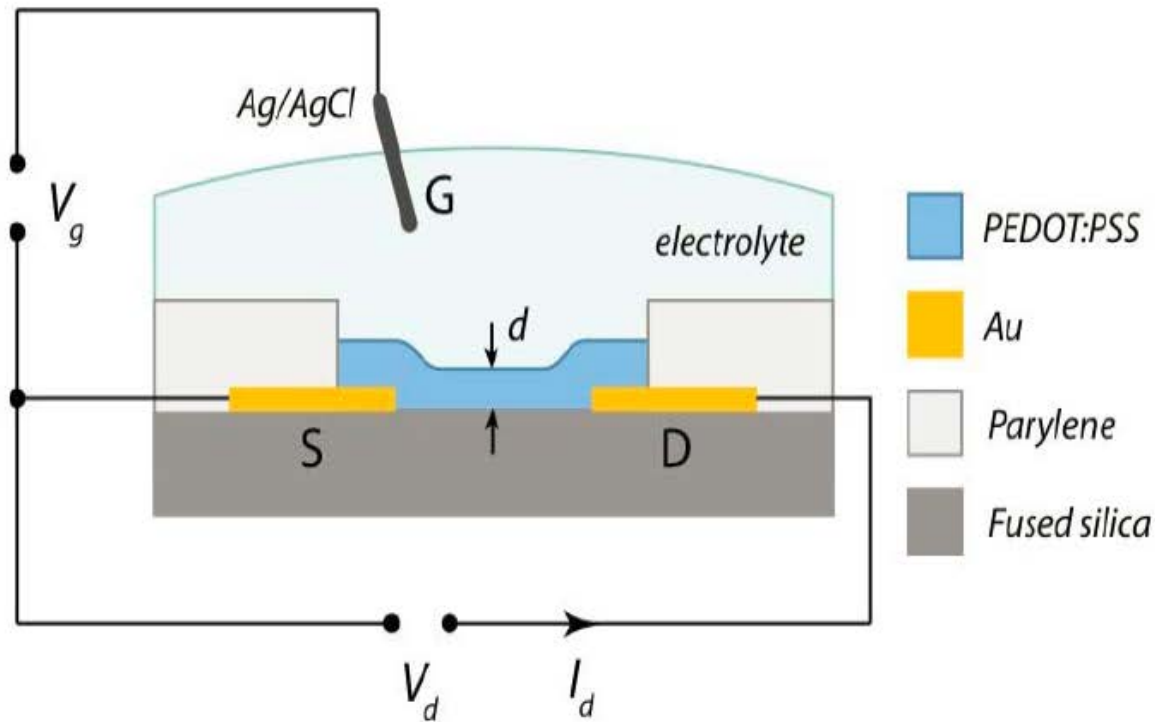




Real-time response of rGO-PET FET to the vesicular secretion of catecholamines from PC12 cells stimulated by high  $\text{K}^+$  solution.  $V_{\text{ds}} = 100 \text{ mV}$ ,  $V_{\text{g}} = 0 \text{ V}$ . The distance between the drain and source electrodes in the device is fixed at 1 cm.

ACS Nano 2010, 4, 3201.

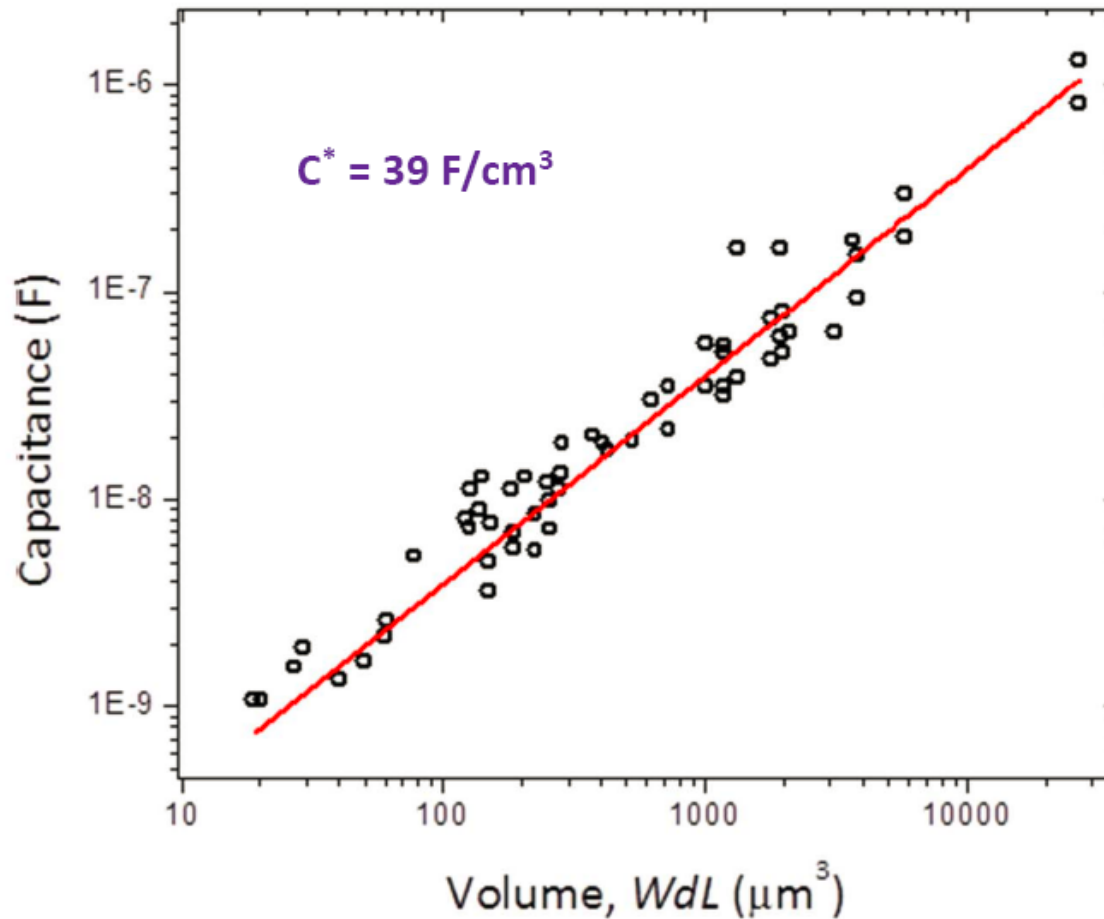
# The organic electrochemical transistor (OECT)



No insulator between channel and electrolyte

First OECT: H.S. White, G.P. Kittlesen, and M.S. Wrighton, *J. Am. Chem. Soc.* 106, 5375 (1984).

# Volumetric response of capacitance in PEDOT:PSS



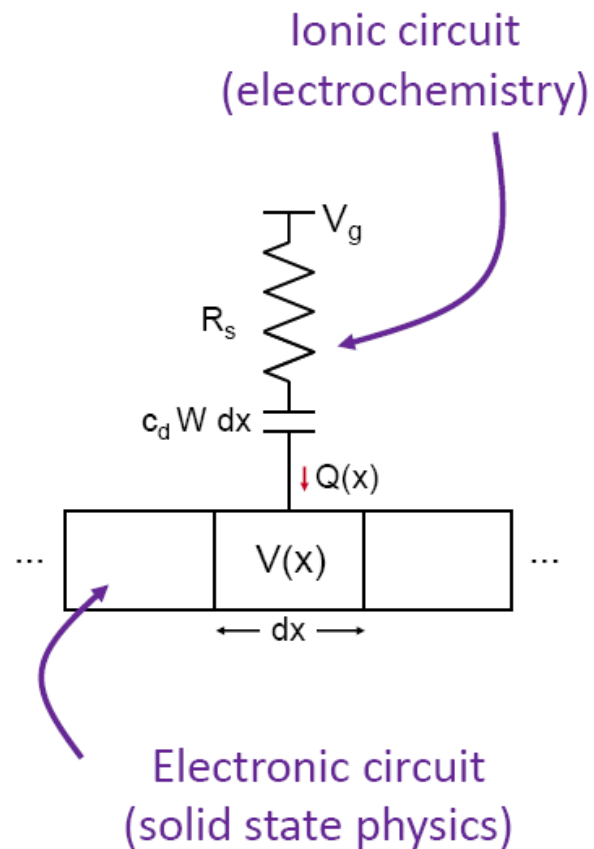
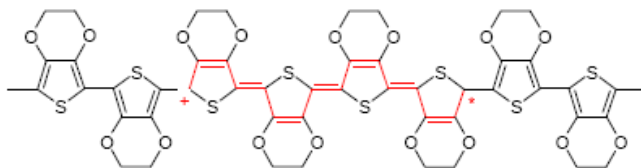
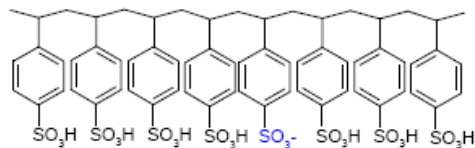
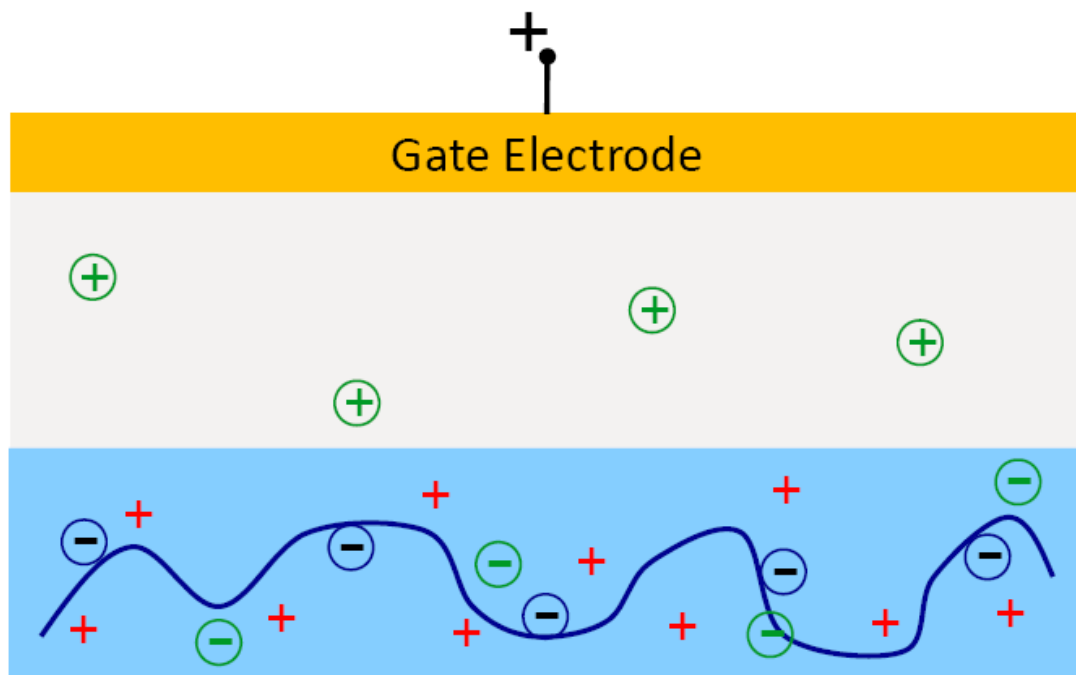
For  $d=130 \text{ nm}$ :  
 $C' = 500 \mu\text{F/cm}^2$

100× larger than  
double layer capacitance

J. Rivnay, P. Leleux, M. Ferro, M. Sessolo, A. Williamson, D.A. Koutsouras, D. Khodagholy, M. Ramuz, X. Strakosas, R.M. Owens, C. Benar, J.-M. Badier, C. Bernard, and G.G. Malliaras, *SCIENCE Advances* 1, e1400251 (2015).

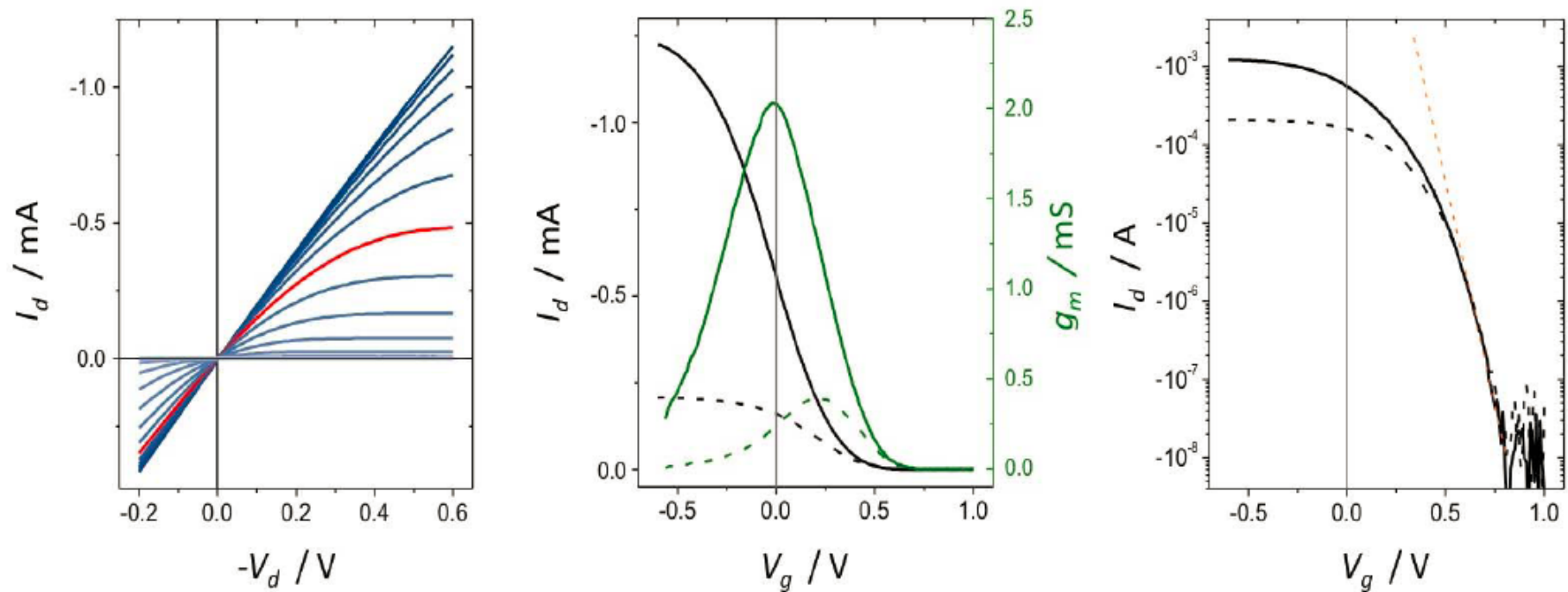


# Device model



D.A. Bernards and G.G. Malliaras,  
*Adv. Funct. Mater.* 17, 3538 (2008)

# Characteristics of OECTs



J. Rivnay, P. Leleux, M. Sessolo, D. Khodagholy, T. Hervé, M. Fiocchi, G. G. Malliaras, Adv. Mater. 25, 7010 (2013).

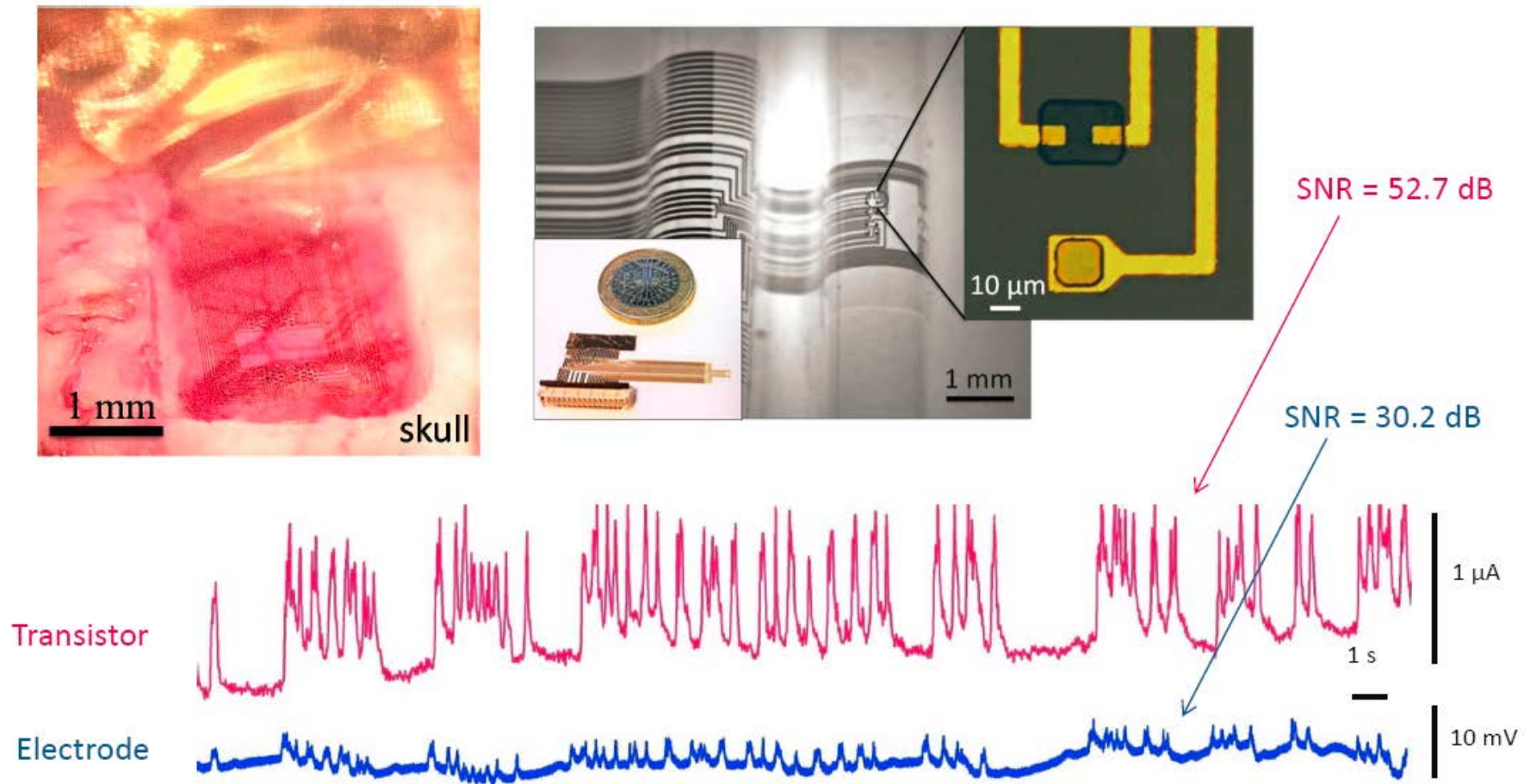
# High transconductance OECTs

Active material	Dielectric material	W ( $\mu\text{m}$ )	L ( $\mu\text{m}$ )	V <sub>G</sub>   (V)	V <sub>D</sub>   (V)	<i>g<sub>m</sub></i> ( $\mu\text{S}$ )	<i>g<sub>m</sub>/W</i> ( $\text{S m}^{-1}$ )	<i>g<sub>m</sub>/ V<sub>D</sub> </i> ( $\mu\text{S V}^{-1}$ )
<i>Aqueous electrolyte</i>								
PEDOT:PSS (best)	NaCl	10	10	0.2	0.6	4,020	402	6,700
PEDOT:PSS (typical)	NaCl	10	5	0.275	0.6	2,700	270	4,500
Graphene <sup>17, (18)</sup>	PBS + NaCl	40	20	0.25	0.1	420	11	4,200
Diamond <sup>19</sup>	PBS + KCl ( <i>in vitro</i> )	~20	~5–20	0.22	0.2	18	0.9	90
Silicon <sup>20</sup>	SiO <sub>2</sub> /TiO <sub>2</sub> ( <i>in toto</i> )	20	20	0.25	0.25	15	0.75	60
Silicon NW <sup>21</sup>	SiO <sub>2</sub> , PBS	20	2	~0.4	0.03	5	0.25	167
<i>Ionic liquid/gel, solid electrolyte</i>								
ZnO <sup>22</sup>	IL (DEME/TFSI)	200	500	1.2	0.1	160	0.8	1,600
ZnO NW <sup>23</sup>	Solid electrolyte (PVA/LiClO <sub>4</sub> )	0.018	0.94	~1.5	0.5	2.79	155	5.58
Organic semiconductor: P3HT <sup>24, (15)</sup>	IL (EMIM/TFSI) gel (PS-PEO-PS)	100	20	~4	1	50	0.5	50
<i>Solid-state</i>								
ZnO <sup>25, (26)</sup>	Al <sub>2</sub> O <sub>3</sub>	50	1	5.1	4	1,400	28	350
Graphene <sup>27, (28,29)</sup>	SiO <sub>2</sub> (BG); Y <sub>2</sub> O <sub>3</sub> (TG)	2.7	0.31	~1.2	2	1,863	690	932
III-V NW: n-InAs NW <sup>30, (31)</sup>	SiN <sub>x</sub>	0.05	2	0.56	1	97.5	1,950	98
III-V Bulk: GaN/InAlN <sup>32, (33,34)</sup>	SiN <sub>x</sub>	NR	0.06	1.75	2	NR*	1,105	NR
Carbon nanotube (mat) <sup>35, (36)</sup>	HfO <sub>2</sub>	10	1.5	~1	0.5	50	5	100
Organic semiconductor: DNTT <sup>37, (38,39)</sup>	AlO <sub>x</sub> /SAM	10	1	~2	2	12	1.2	95
Silicon NW <sup>40</sup>	SiO <sub>2</sub>	0.01	0.8–2	~2–4	NR	2	200	NR

D. Khodagholy, J. Rivnay, M. Sessolo, M. Gurfinkel, P. Leleux, L.H. Jimison, E. Stavrinidou, T. Herve, S. Sanaur, R.M. Owens, and G.G. Malliaras, Nature Comm. 4, 2133 (2013).



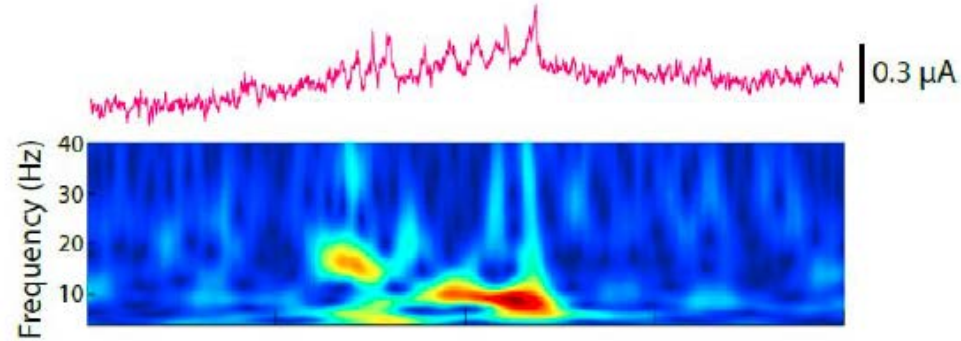
# In vivo recordings using transistors



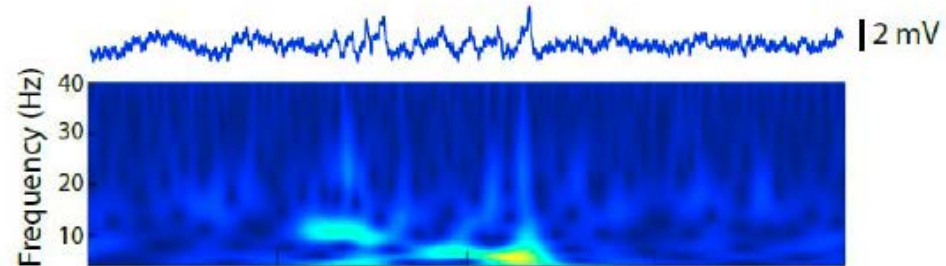
D. Khodagholy, T. Doublet, P. Quilichini, M. Gurfinkel, P. Leleux, A. Ghestem, E. Ismailova, T. Herve, S. Sanaur, C. Bernard, and G.G. Malliaras, *Nature Comm.* 4, 1575 (2013).

# Transistors enable less invasive recordings

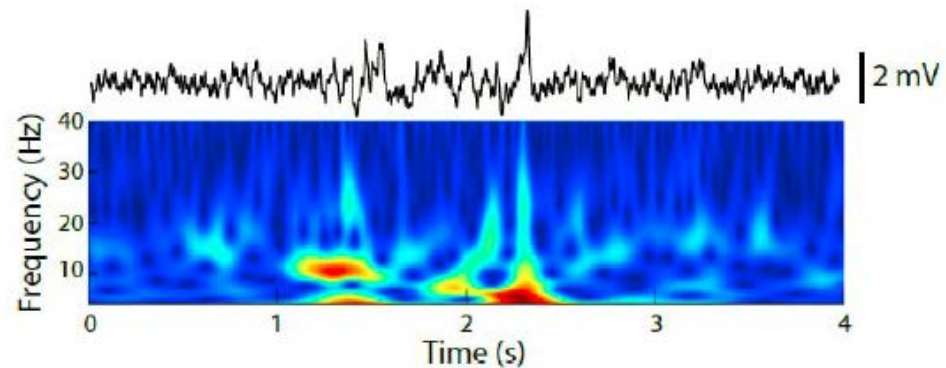
Transistor



Surface  
electrode

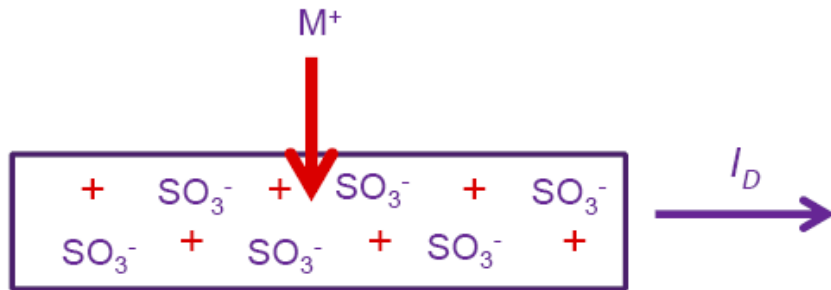


Depth  
electrode



D. Khodagholy, T. Doublet, P. Quilichini, M. Gurfinkel, P. Leleux, A. Ghestem, E. Ismailova, T. Herve, S. Sanaur, C. Bernard, and G.G. Malliaras, *Nature Comm.* 4, 1575 (2013).

# Model for OECT operation



$$I_D = W \cdot d \cdot e \cdot \mu \cdot p(x) \cdot [dV(x)/dx]$$

$$p(x) = SO_3^- - M^+(x)$$

$$M^+(x) = (C^*/e) \cdot [V_G - V(x)]$$

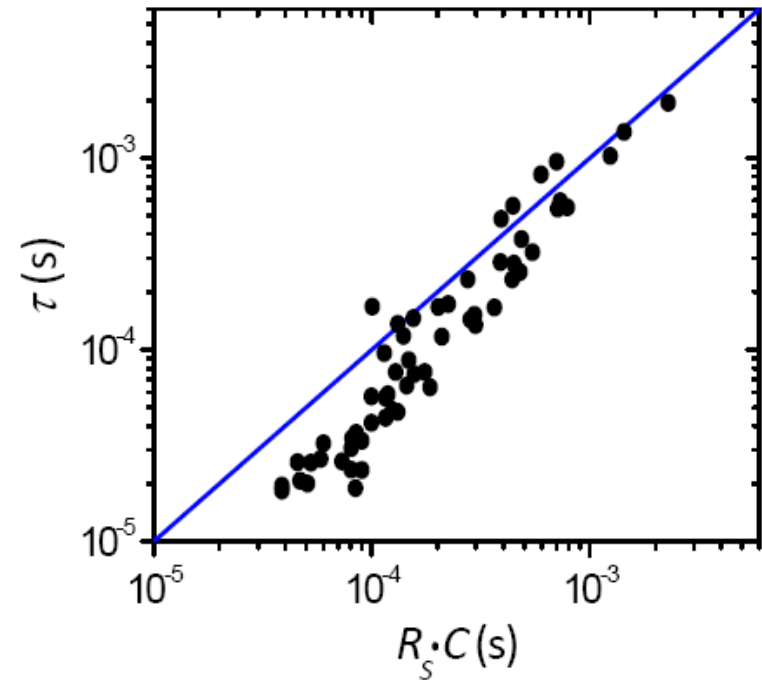
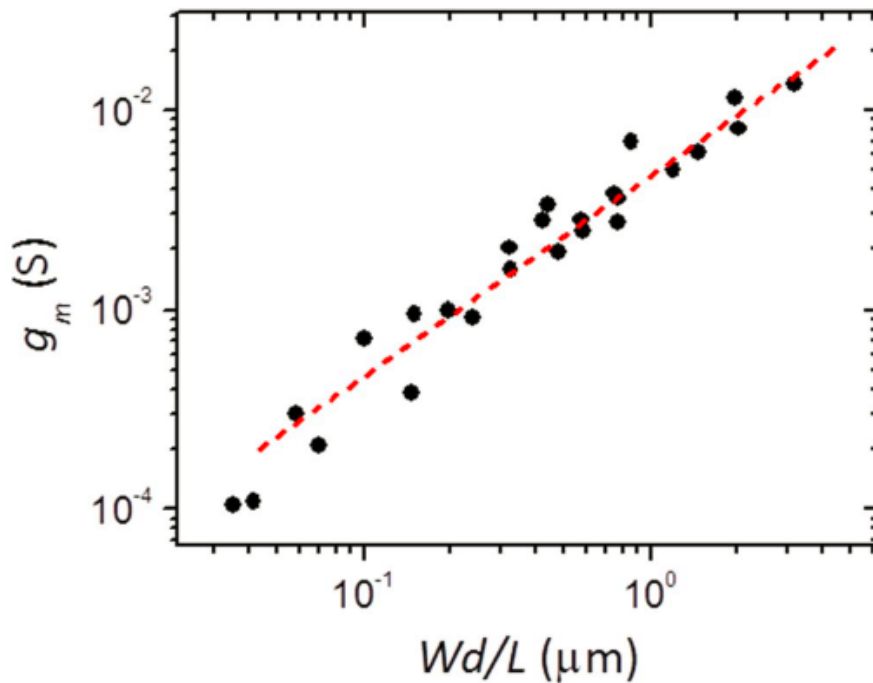
Integrating  $I_d$  over the length of the channel:

$$I_D = (W \cdot d / L) \cdot \mu \cdot C^* \cdot [V_T - V_G + V_D / 2] \cdot V_D$$

$$V_T = e \cdot SO_3^- / C^*$$

$$I_D^{SAT} = [W / (2 \cdot L)] \cdot d \cdot \mu \cdot C^* \cdot [V_T - V_G]^2$$

# Scaling with geometry



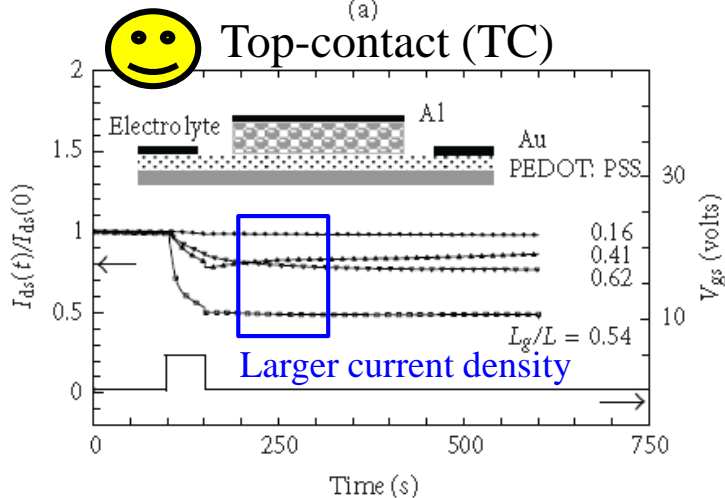
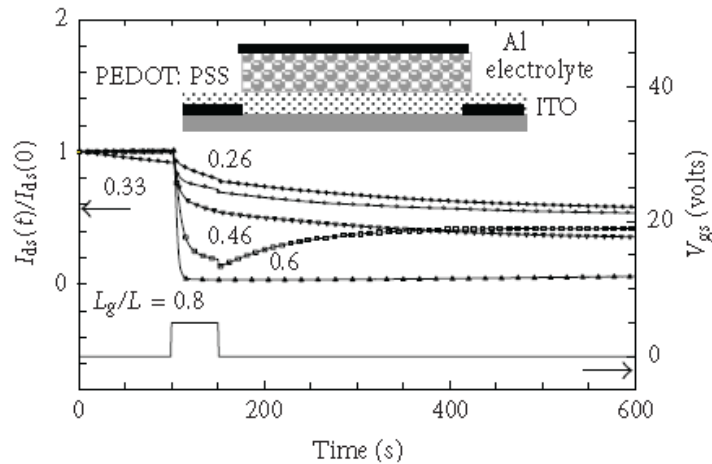
$$g_m = (W \cdot d / L) \cdot \mu \cdot C^* \cdot (V_T - V_G)$$

J. Rivnay, P. Leleux, M. Ferro, M. Sessolo, A. Williamson, D.A. Koutsouras, D. Khodagholy, M. Ramuz, X. Strakosas, R.M. Owens, C. Benar, J.-M. Badier, C. Bernard, and G.G. Malliaras, *SCIENCE Advances* 1, e1400251 (2015).



# Geometry Design of OECTs for improving device sensitivity

## Bottom-contact (BC)



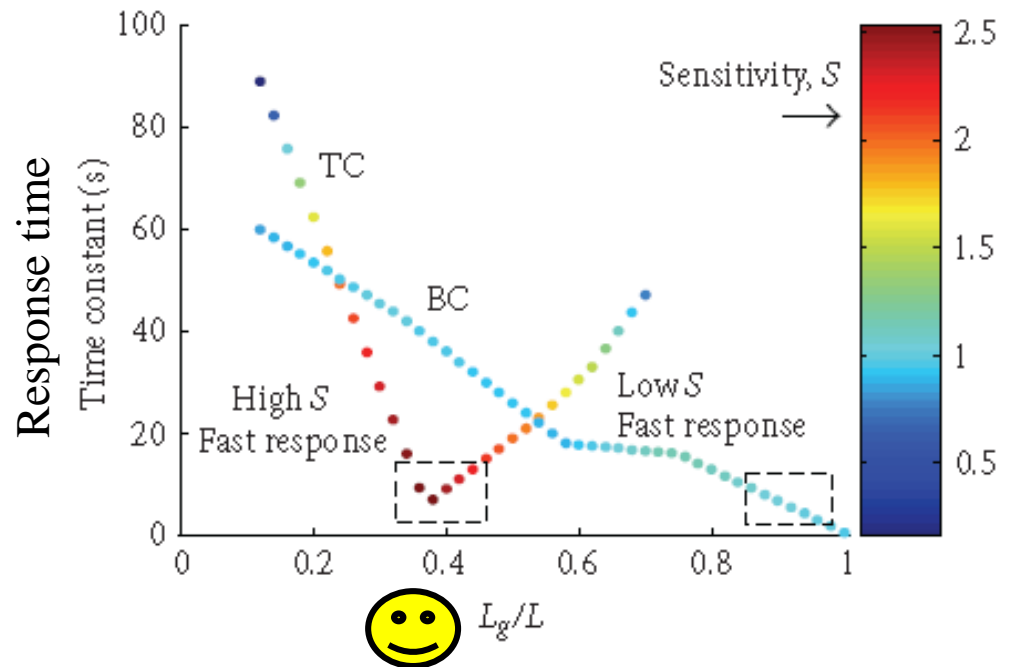
(b)  
Solid-electrolyte: PVA

$$S \text{ (sensitivity)} = \beta / (L_g/L)$$

$$\beta = \Delta I_{ds} / I_{ds}$$

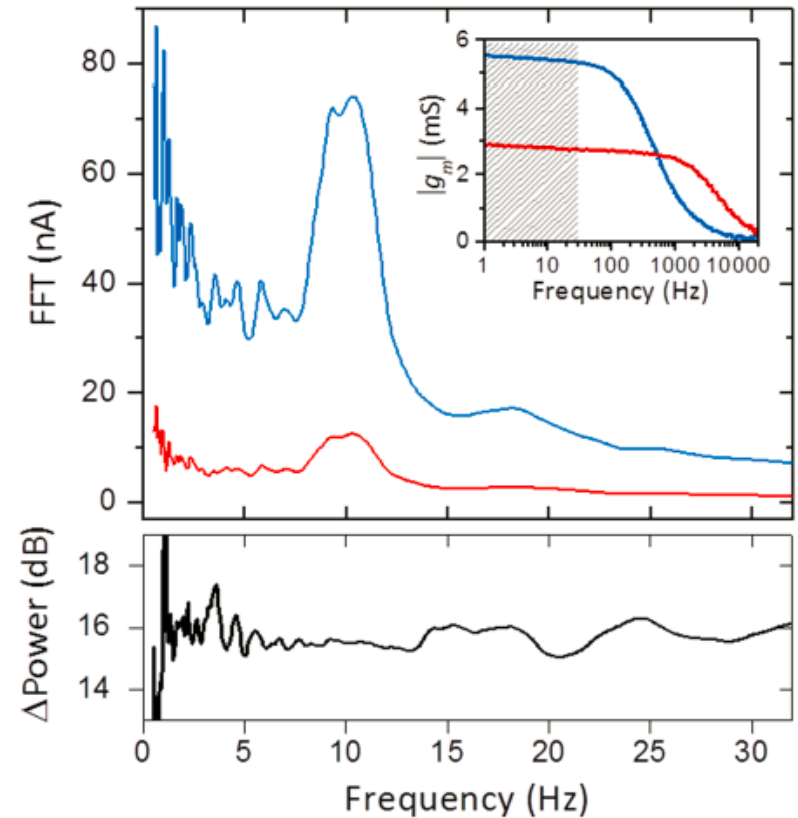
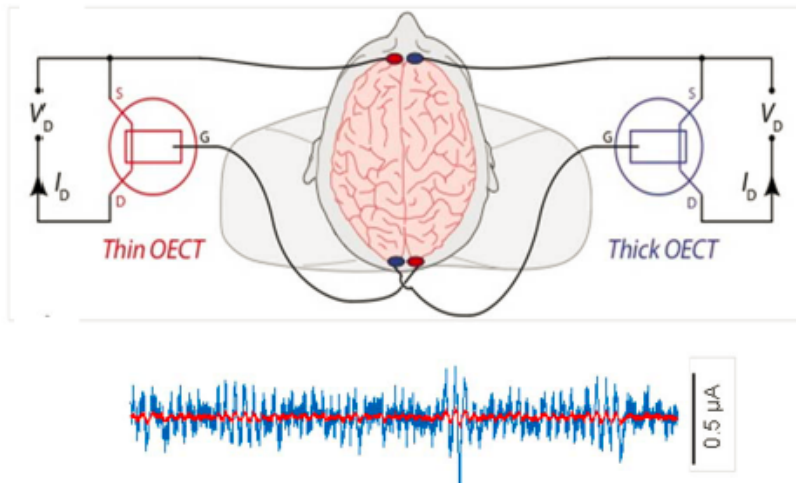
Channel length ( $L$ ) = 12 mm; Width ( $W$ ) = 3 mm

Gate length ( $L_g$ )



Journal of Sensors, Volume 2008, Article ID 702161.

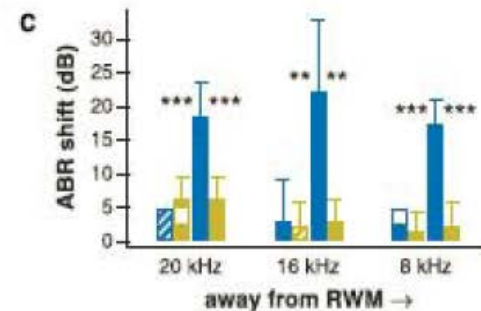
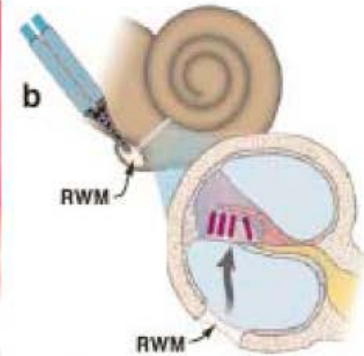
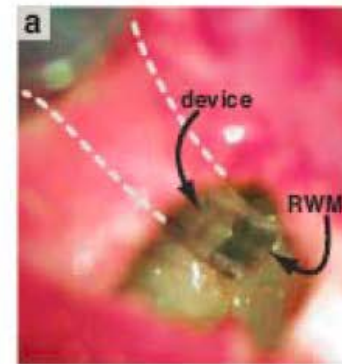
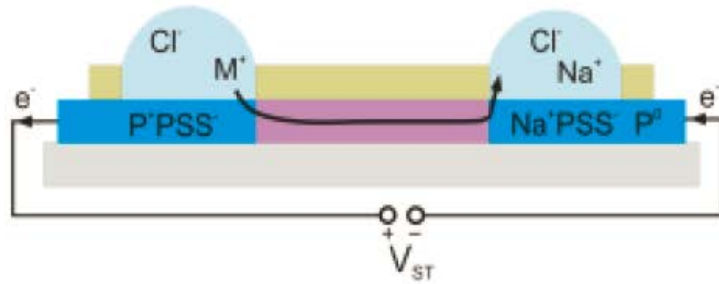
# High transconductance means high SNR



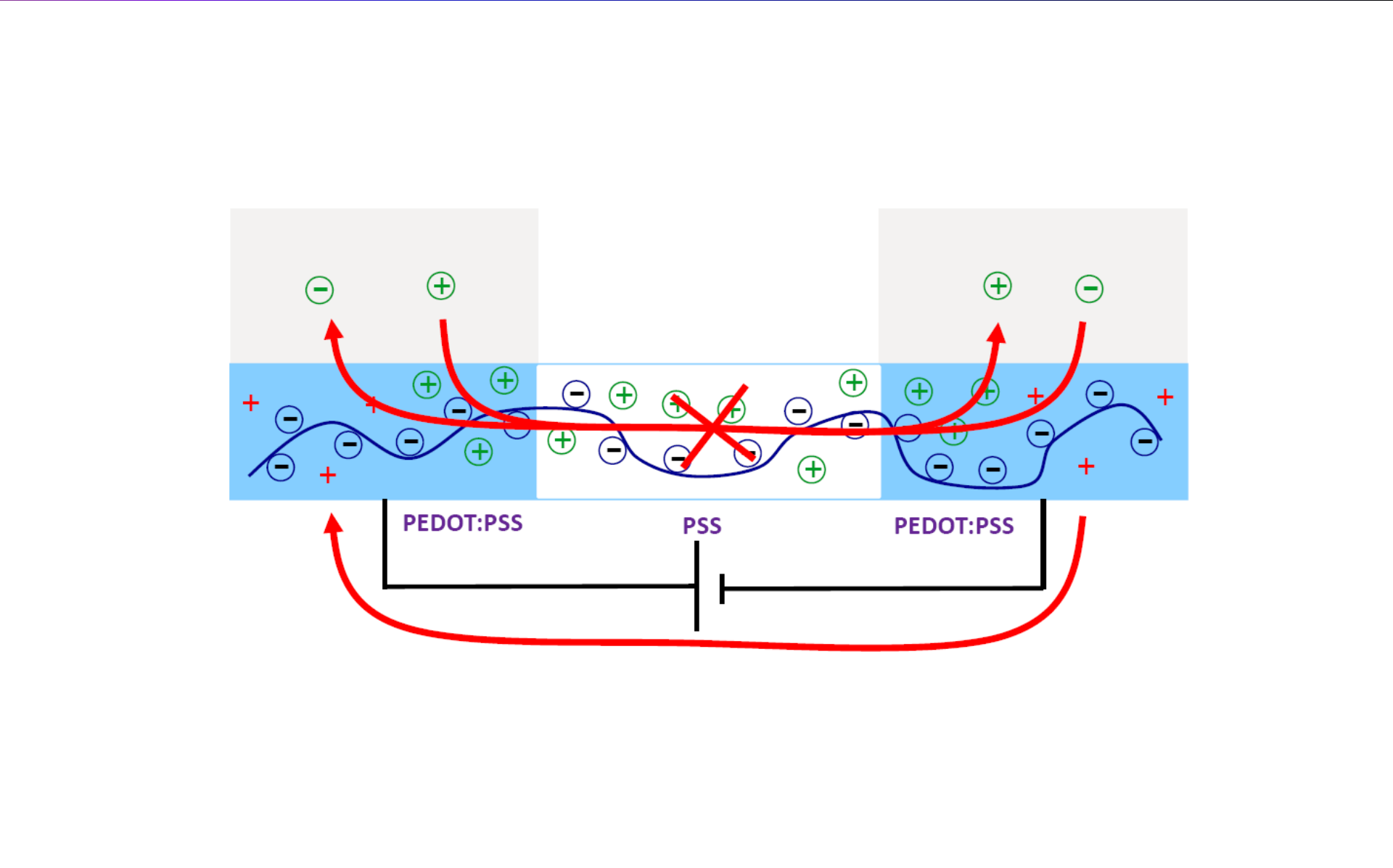
J. Rivnay, P. Leleux, M. Ferro, M. Sessolo, A. Williamson, D.A. Koutsouras, D. Khodagholy, M. Ramuz, X. Strakosas, R.M. Owens, C. Benar, J.-M. Badier, C. Bernard, and G.G. Malliaras, *SCIENCE Advances* 1, e1400251 (2015).

# Organic electronic ion pumps control epileptiform activity

## The organic electronic ion pump

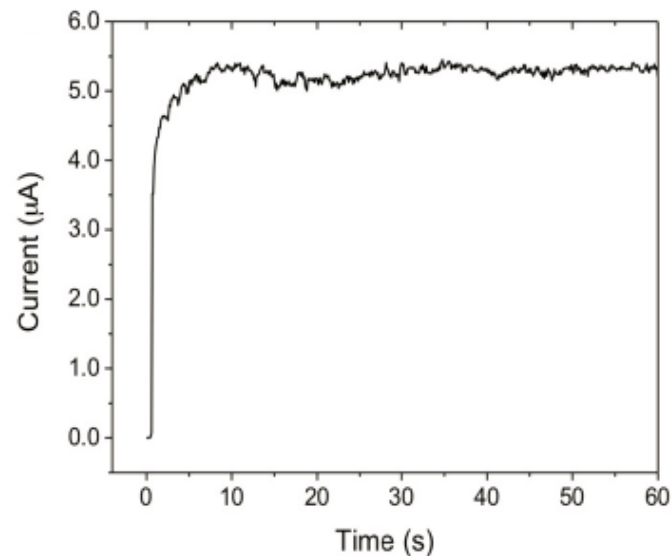
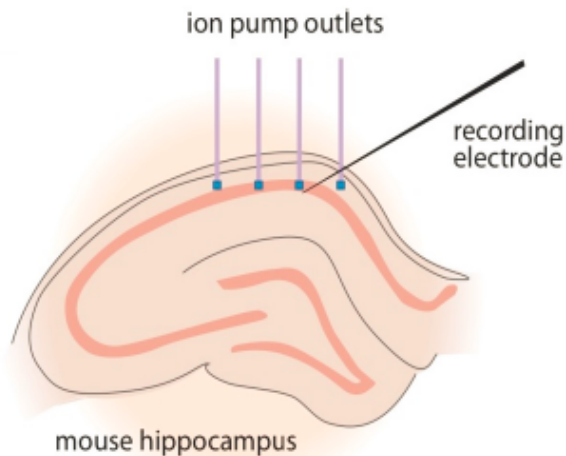
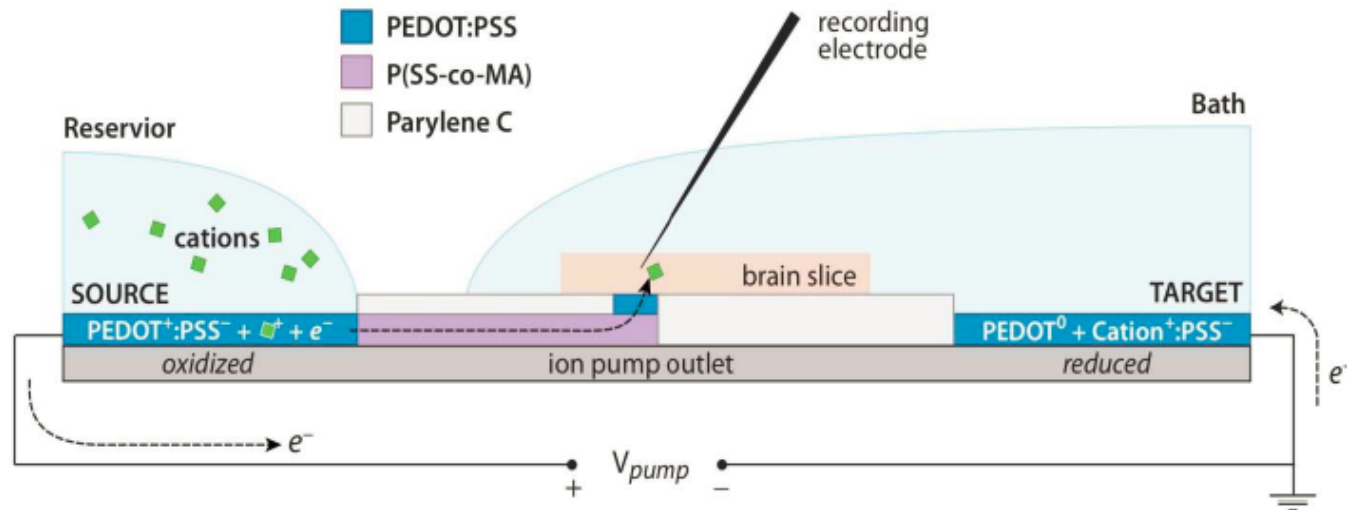


D. T. Simon, S. Kurup, K. C. Larsson, R. Hori, K. Tybrandt, M. Goiny, E. H. Jager, M. Berggren, B. Canlon, and A. Richter-Dahlfors, *Nature Materials* 8, 742 (2009).

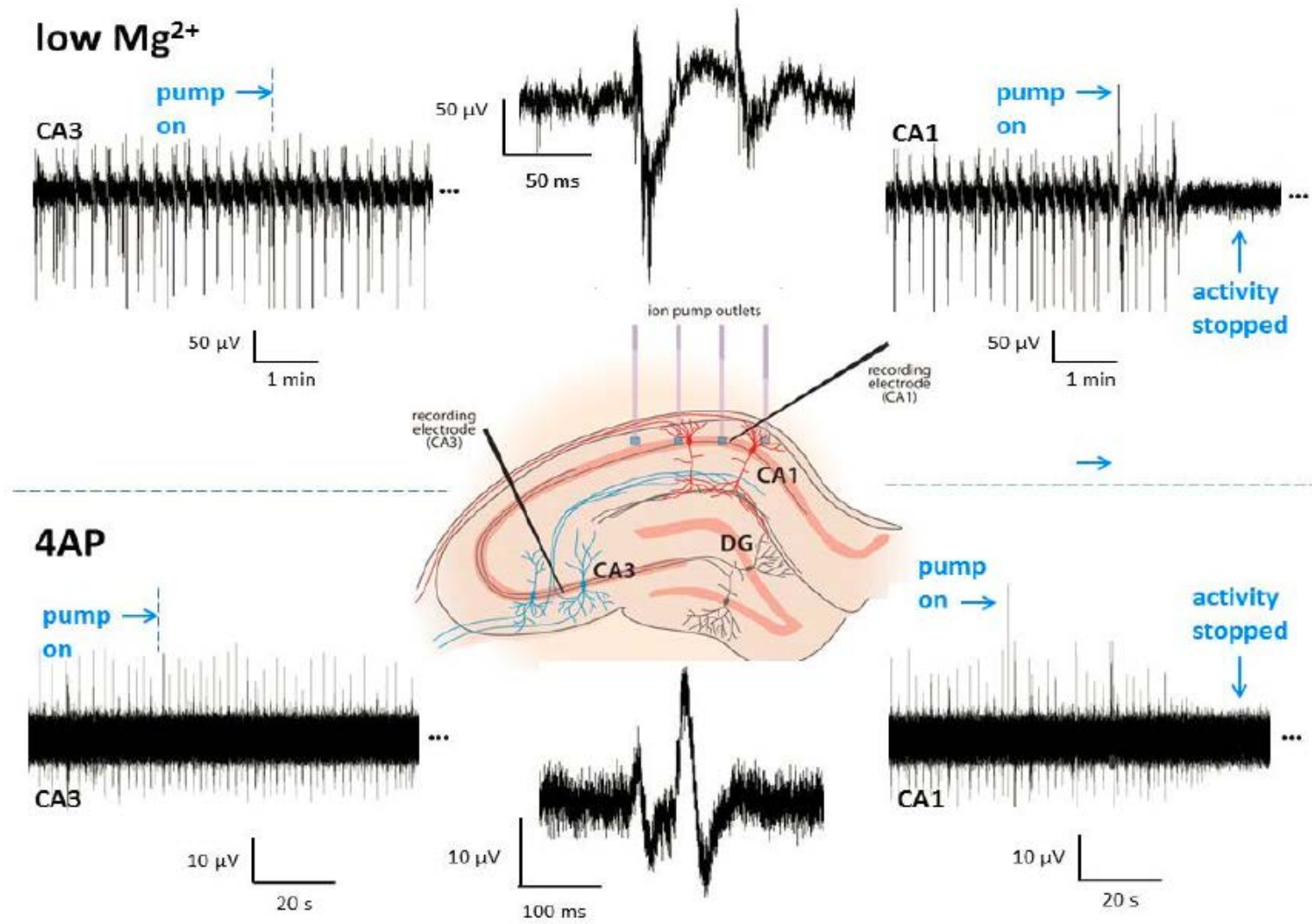




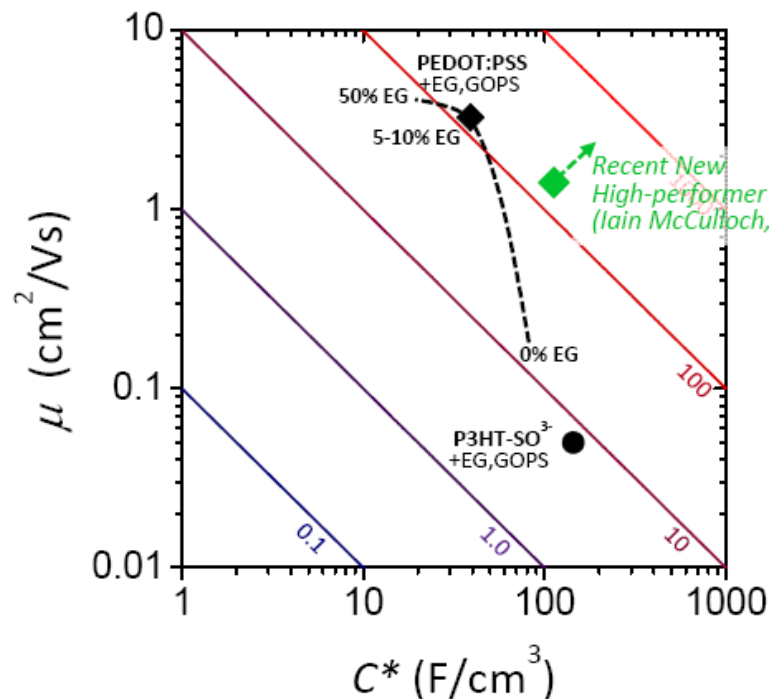
# Ion pump for local delivery in neural networks



# Local delivery of GABA suppress seizure activity



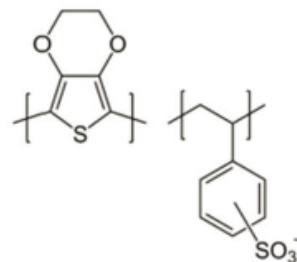
# $\mu C^*$ as the materials figure of merit



Such maps provide a way to compare materials as potential candidates in OECTs

## PEDOT:PSS

(+EG, +GOPS)



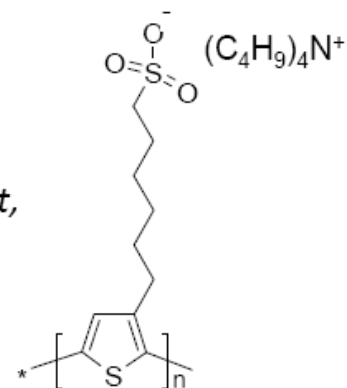
$$\mu C^* = 128 \text{ F/cmVs}$$

$$\mu = 3.3 \text{ cm}^2/\text{Vs}$$

$$C^* = 39 \text{ F/cm}^3$$

## P3HT-SO<sub>3</sub><sup>-</sup>

(+EG +GOPS)



$$\mu C^* = 7.2 \text{ F/cmVs}$$

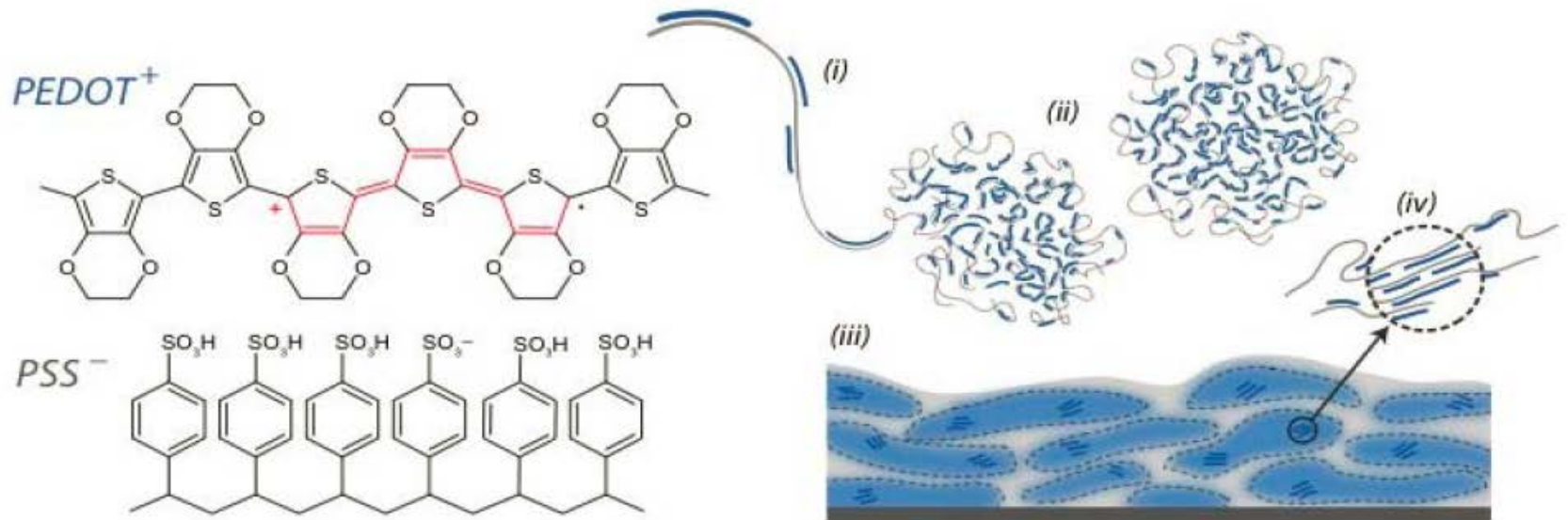
$$\mu = 0.05 \text{ cm}^2/\text{Vs}$$

$$C^* = 144 \text{ F/cm}^3$$

w/ M. Thelakkat,  
U. Bayreuth

S. Inal, J. Rivnay, P. Leleux, M. Ferro, M. Ramuz, J.C. Brendel, M. Schmidt, M. Thelakkat, and G.G. Malliaras, Adv. Mater. 26, 7450 (2014).

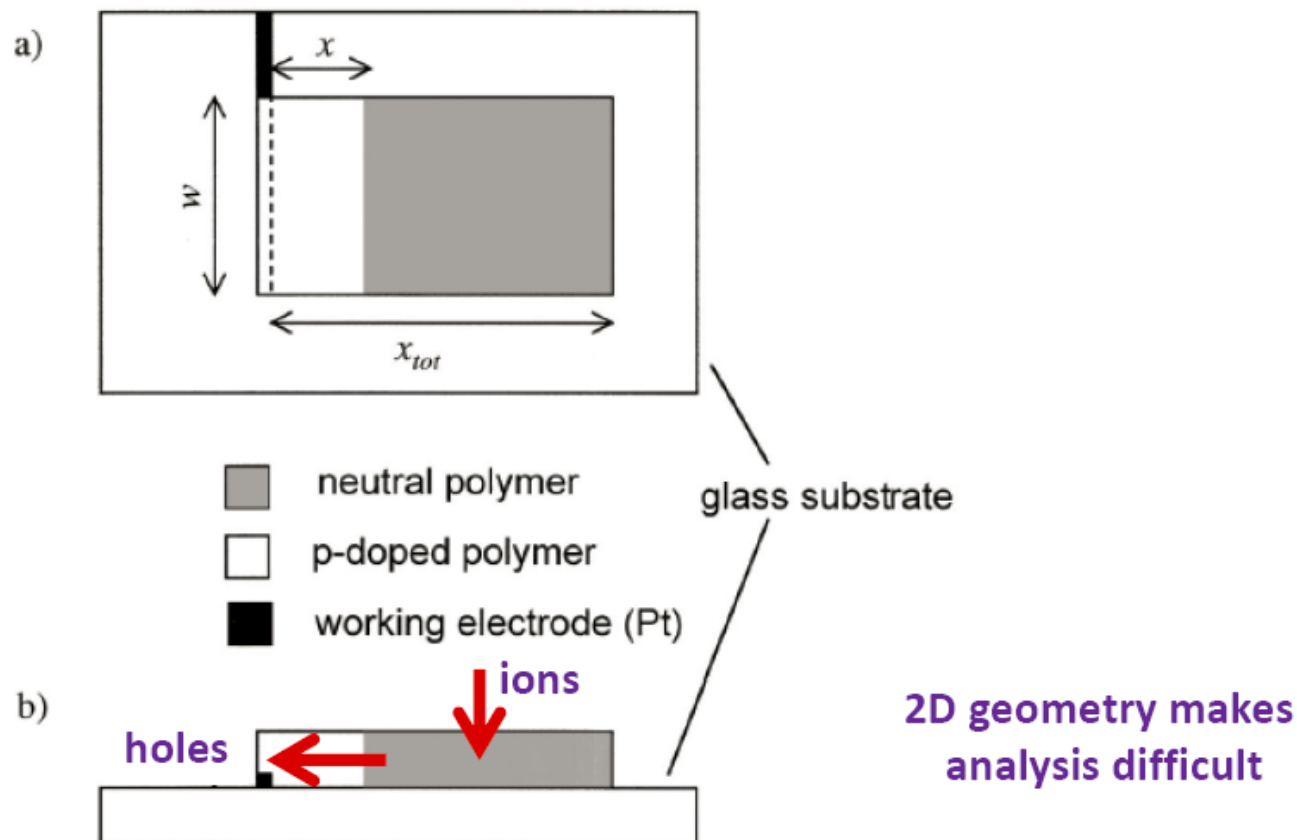
# PEDOT:PSS as a champion material



- Phase separated morphology
- Hole transport in PEDOT-rich domains, ion transport in PSS matrix



# “Moving front” measurements

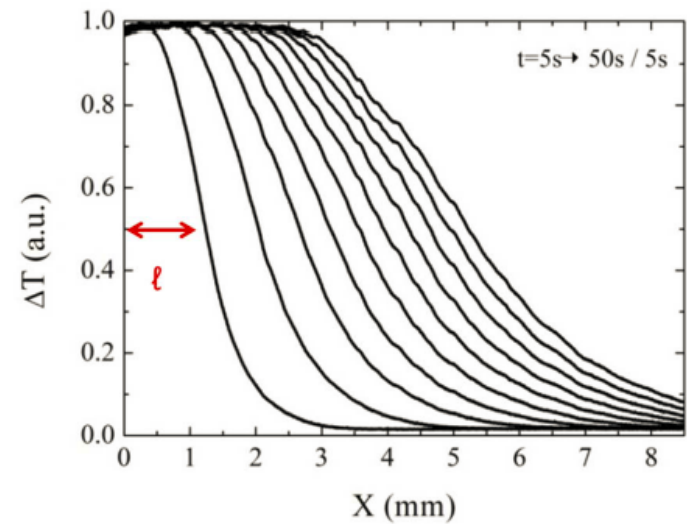
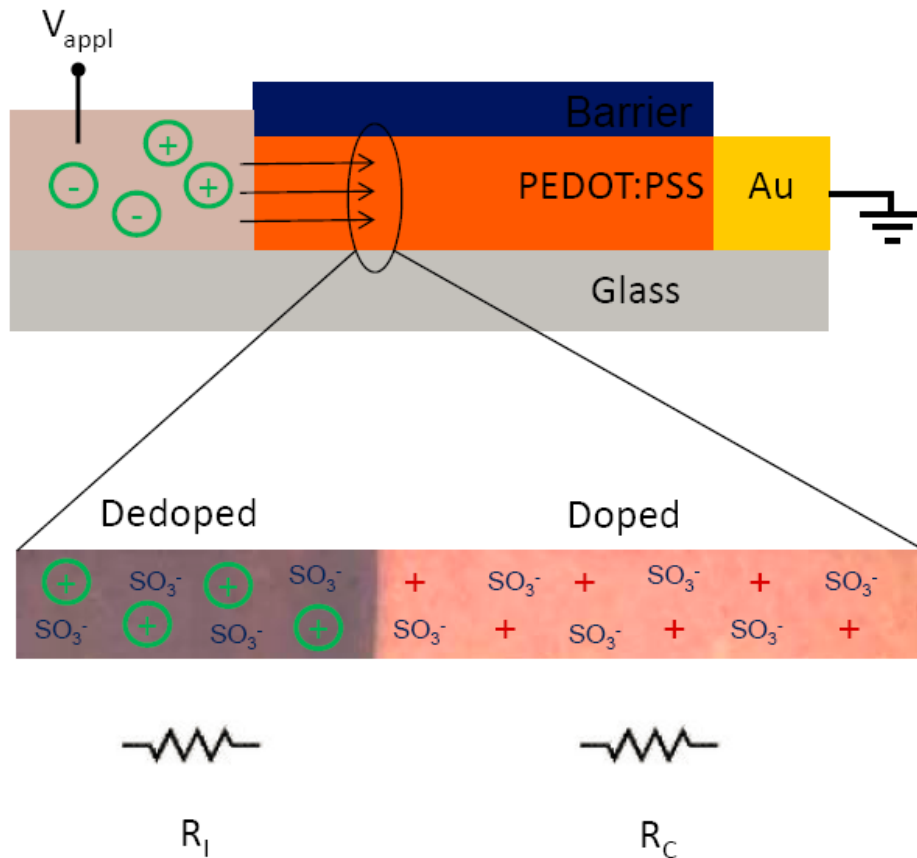


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# A simple way to measure ion transport

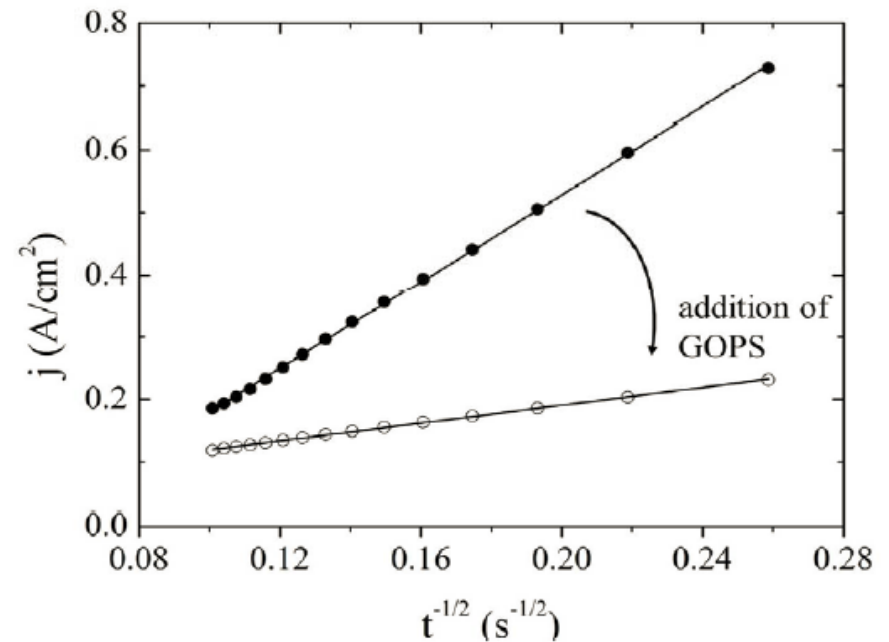
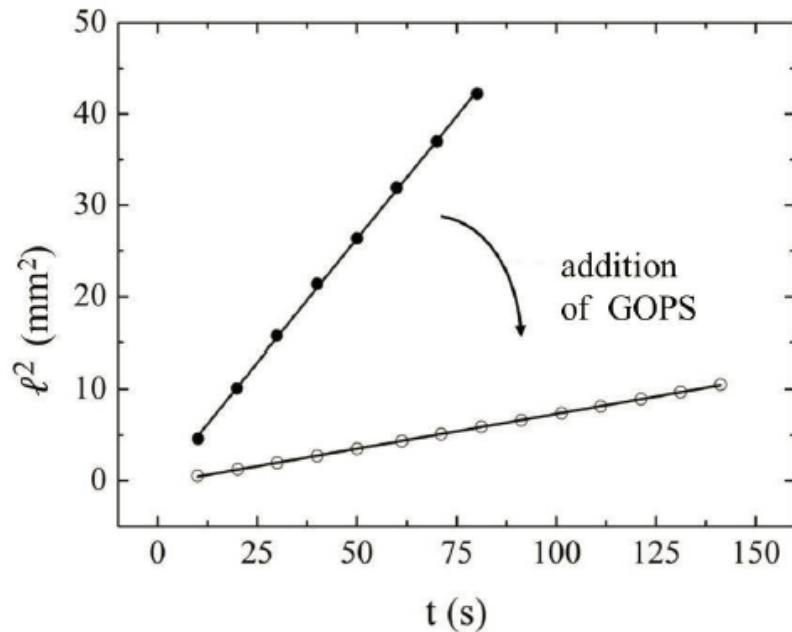


$$\ell^2 = \mu \cdot V_{appl} \cdot t$$

$$j = \frac{e \cdot P \sqrt{2 \cdot \mu \cdot V_{appl}}}{2\sqrt{t}}$$

E. Stavrinidou, P. Leleux, H. Rajaona, D. Khodagholy, J. Rivnay, M. Lindau, S. Sanaur, and G.G. Malliaras, Adv. Mater. 25, 4488 (2013).

# Ions are highly mobile in PEDOT:PSS



	$K^+$ mobility in film ( $\text{cm}^2\text{V}^{-1}\text{s}^{-1}$ )	$K^+$ density in film ( $\text{cm}^{-3}$ )
PEDOT:PSS	$1.4 \cdot 10^{-3}$	$5.9 \cdot 10^{20}$
PEDOT:PSS :GOPS	$1.9 \cdot 10^{-4}$	$3.2 \cdot 10^{20}$

E. Stavrinidou, P. Leleux, H. Rajaona, D. Khodagholy, J. Rivnay, M. Lindau, S. Sanaur, and G.G. Malliaras, Adv. Mater. 25, 4488 (2013).