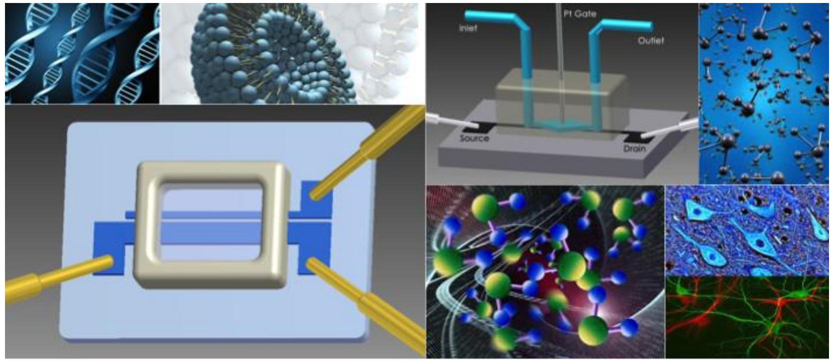
Bioelectronics Based on Organic Electrochemical Sensing and Memristive Devices: a Promising Novel Perspective for Neuromorphic and Biocompatible Systems.



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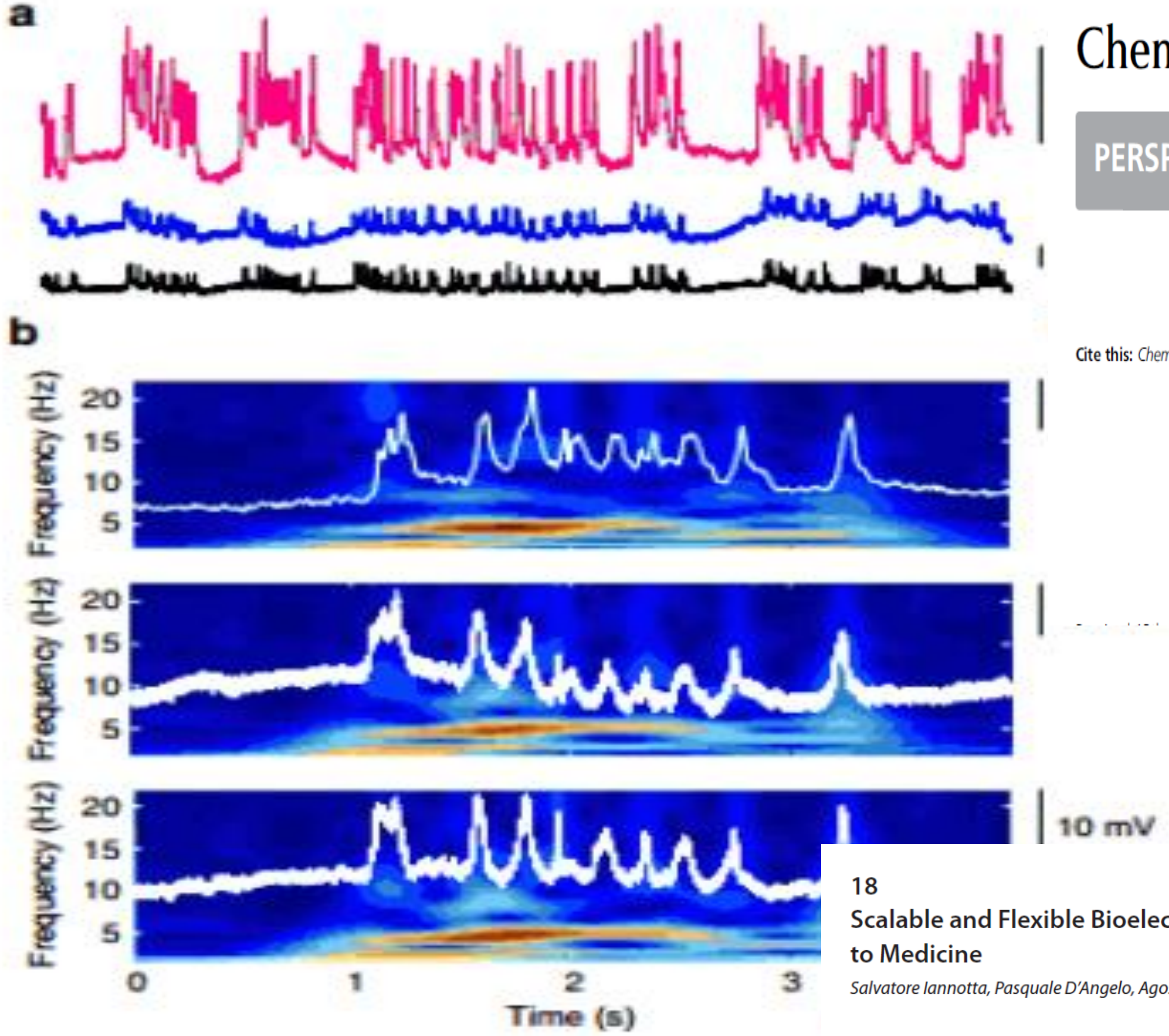
imem



D. Khodagholy et al. ,(2013) Nature Communications 4, 1575
doi:10.1038/ncomms2573

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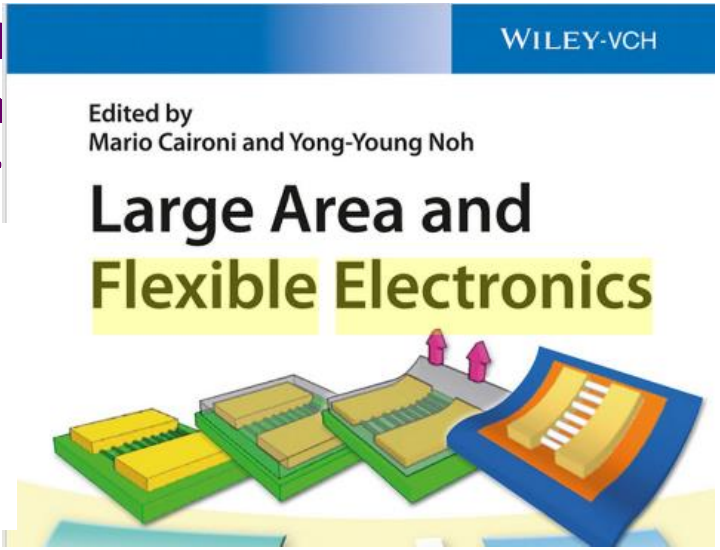
New opportunities for organic electronics and bioelectronics: ions in action

Cite this: *Chem. Sci.*, 2013, **4**, 1395

Giuseppe Tarabella,[a] Farzaneh Mahvash Mohammadi,[b] Nicola Coppedè,[a] Francesco Barbero,[b] Salvatore Iannotta,[a] Clara Santato*[b] and Fabio Cicoira*[c]

This perspective deals with the coupling of ionic and electronic transport in organic electronic devices, focusing on electrolyte-gated transistors. These include electrolyte-gated organic field-effect transistors (EG-OFETs) and organic electrochemical transistors (OECTs). EG-OFETs, based on molecules and polymers, can be operated at low electrical bias (about 1 V or below) and permit unprecedented charge carrier densities within the transistor channel. OECTs can be operated in aqueous environment as

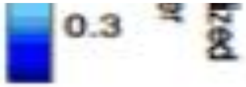
Working in l
Lab-on-a-Ch
Point-of-car



18
Scalable and Flexible Bioelectronics and Its Applications to Medicine

Salvatore Iannotta, Pasquale D'Angelo, Agostino Romeo, and Giuseppe Tarabella

18.1
Biosensing and Bioelectronics: A Fast Growing Field and a Challenging Research Area

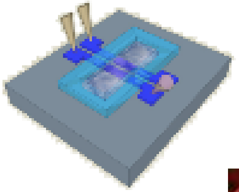


Summary

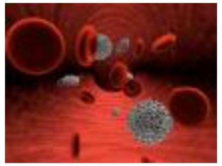
- ✓ Drug Processes Sensing and Bio-medical applications:
  - ➢ *The cotton fibre OECT toward textile integration*
  - ➢ *Micellation: phase transition directly monitored by OECT*
  - ➢ *Liposomes detection (towards monitoring drug release dynamics)*
  - ➢ *Drugs and biomolecules*
- ✓ Cell stress and death monitoring & Bioelectronics
- ✓ Memristors, Memristive devices and Systems (Phychip & MaDEleNA Projects) based on both inorganics and organics
- ✓ An OECT based on a living organism showing memristive properties.
- ✓ The perspective of joining Sensing, Memory and…..

Why OECT?

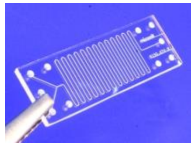
Ion-to-electron *amplified transduction a novel key towards bio-sensing and bio-electronics*



- ✓ ***Operation in aqueous bio-environment***
- ✓ ***Ideal interface between biology and electronics***
- ✓ ***Compatible with photolithographic patterning***



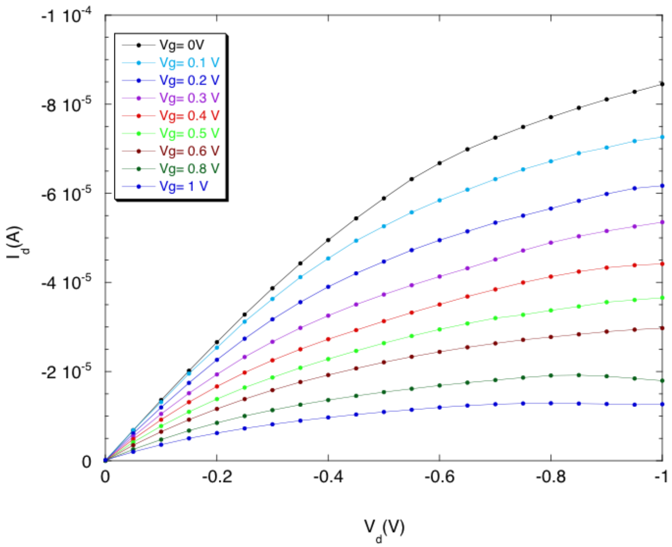
- ✓ ***Low-cost fabrication, plastic substrates***
- ✓ ***Versatile geometry (gate/channel distance and size not an issue)***

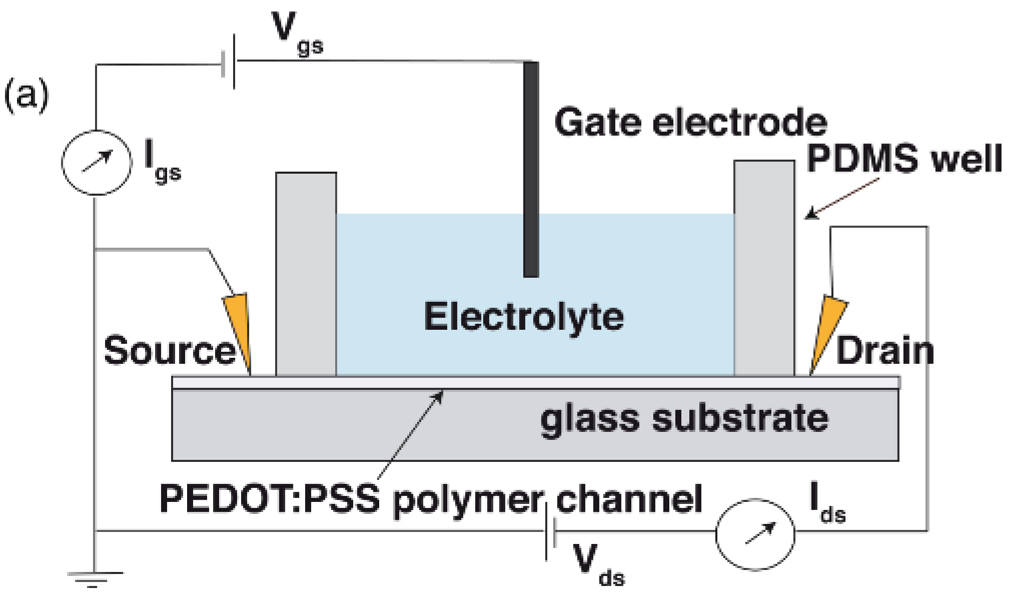


- ✓ ***Integration in circuits (microfluidics, lab on a chip…)***
- ✓ ***Ideal platform to explore device physics, interfaces in liquids, ion intercalation in polymers, double layers, etc.***

(M. Berggren group, Adv. Mater. 2007, 19, 3201; G. Malliaras Group , Chem. Rec. 2008, 8, 13–22 G. Tarabella ….. S. Iannotta .. Chemical Science, Adv. Article 2013)

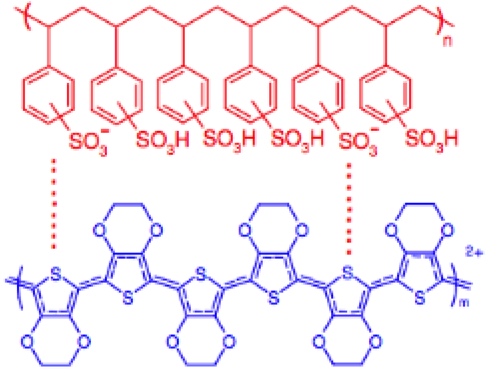
OECT: operating principle





PEDOT:PSS

poly3,4- ethylenedioxy thiophene doped with poly- styrene sulfonate)

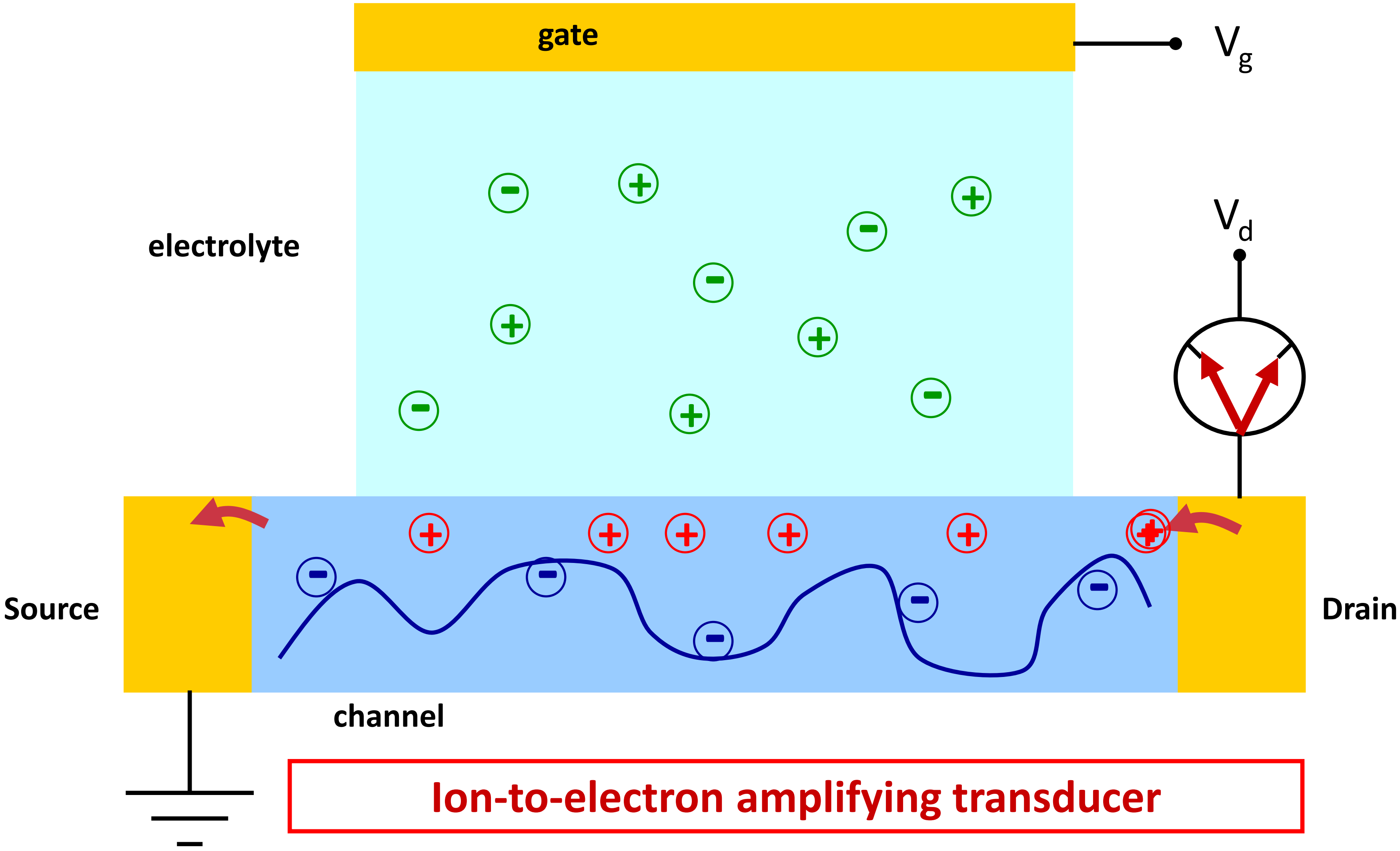


Working principle is based on reversible doping/de-doping of the organic material by electrolyte ions

Ions enter into the organic material: volume response

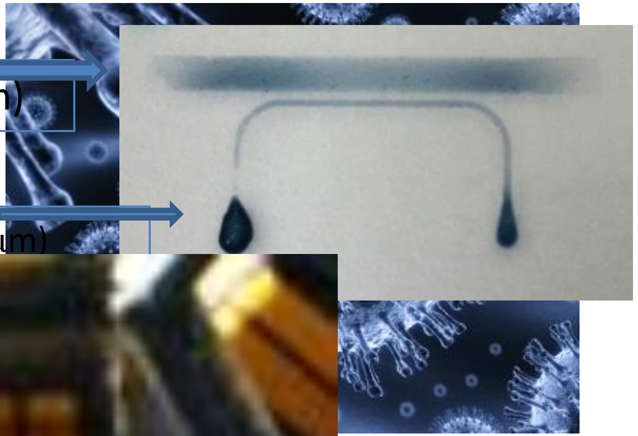
PEDOT:PSS electrochemical transistor - OECT

$PEDOT^+:PSS^- + M^+ + e^- \rightleftarrows PEDOT^0 + M^+:PSS^-$



Ion-to-electron amplifying transducer

OECT and Biosensing Application



Gate (0.8-1 mm)

Drain Source (150-200 μm)

"ink-
dimen
and 15

G and D-S 100 μm

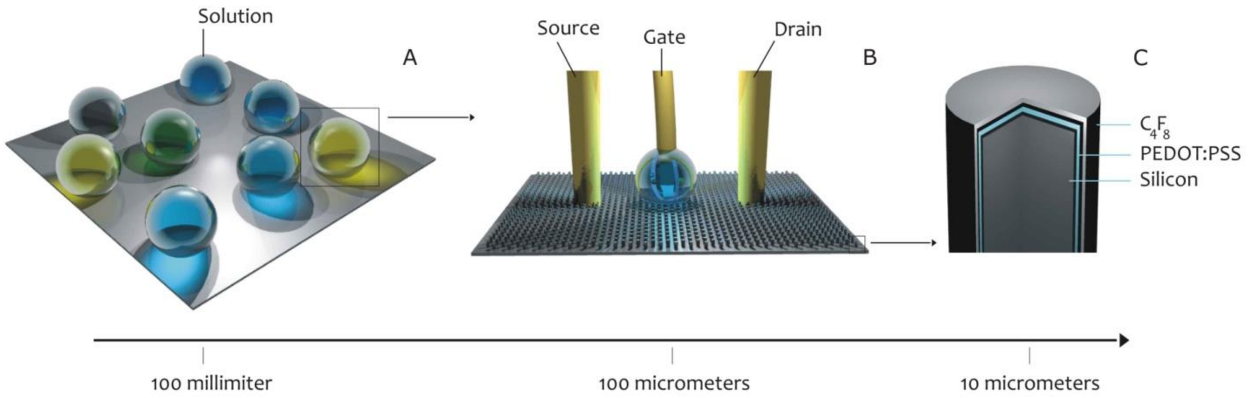
wing the desired
omatic syringe and

ed by a
ringe providing

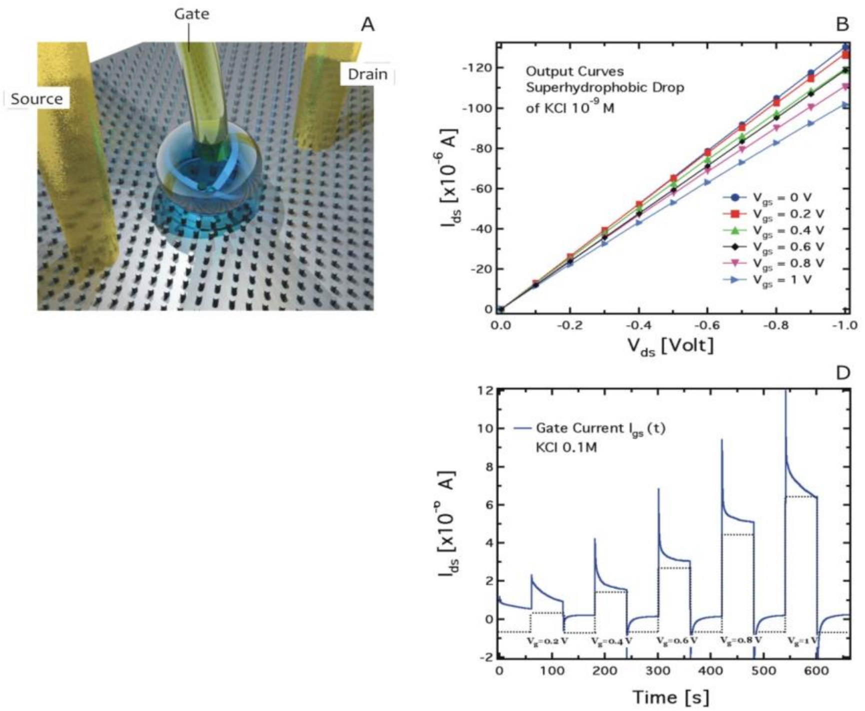
by controlling
oughness) ,
solution

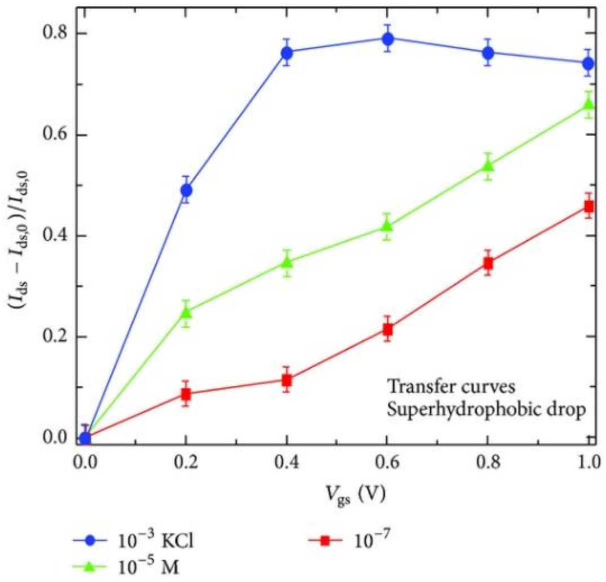
curing treatment at 150°C in oven for 2 hours

OECT Operating on Micro- or Nano-drops



N. Coppedè …S. Iannotta
BioMed Research International 2014 (2014), Article ID 302694

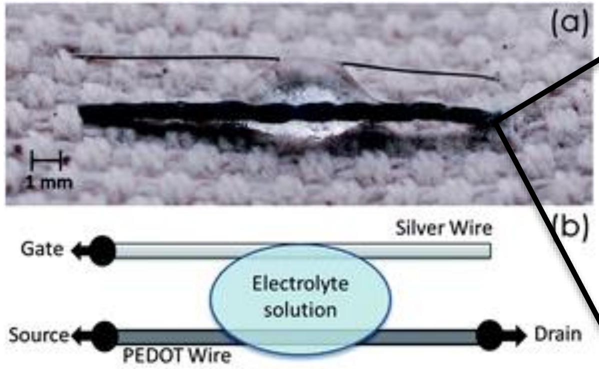


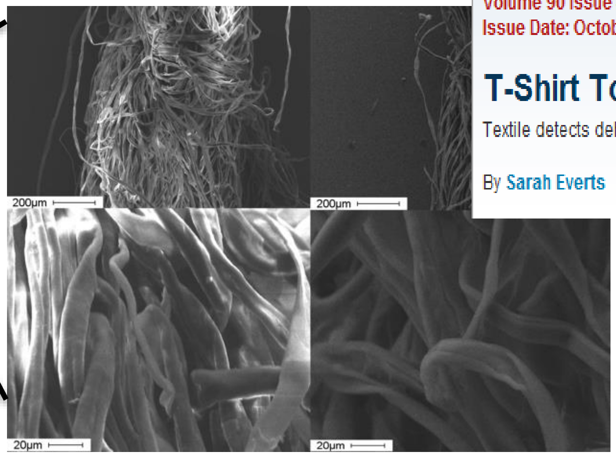


E-Textile: OECT Integrated in Single Cotton Fiber

Towards bio-medical monitorring

Working directly with liquid electrolyte






C&EN
CHEMICAL & ENGINEERING NEWS
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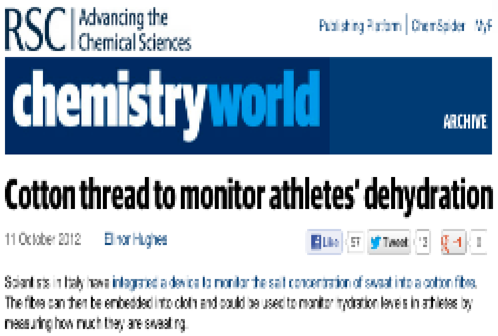
Volume 90 Issue 42 | p. 32 | Concentrates
Issue Date: October 15, 2012
T-Shirt To Athlete: You're Dehydrated
Textile detects dehydration in athletes via redox reactions with salty sweat
By Sarah Everts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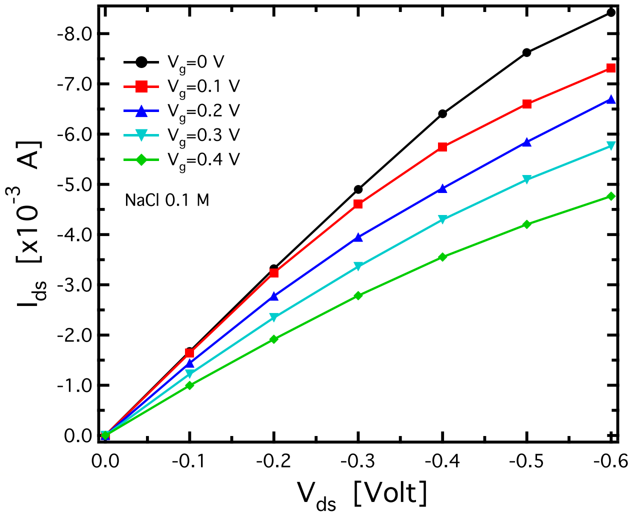
ARCHIVE
Cotton thread to monitor athletes' dehydration
11 October 2012 Elinor Hughes
Scientists in Italy have integrated a device to monitor the salt concentration of sweat into a cotton fibre. The fibre can then be embedded into cloth and could be used to monitor hydration levels in athletes by measuring how much they are sweating.

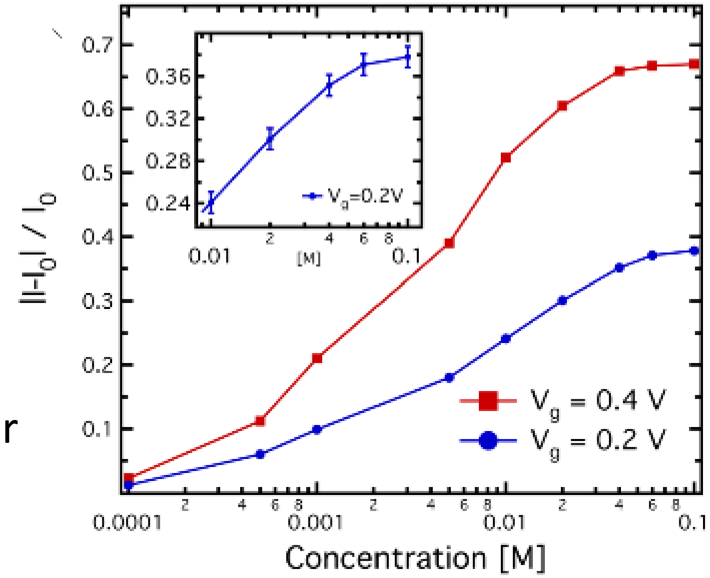


Detection of salt concentrations in sweat:

i.e. athelts stress

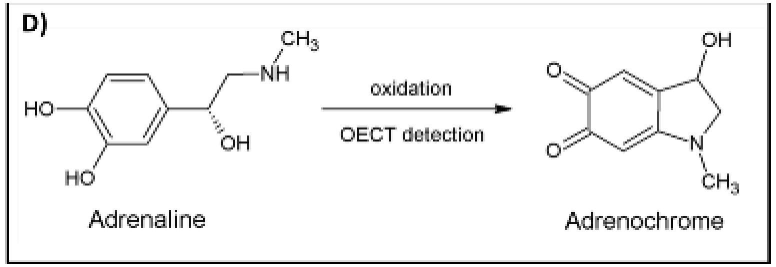
Cystic fibrosis

etc.



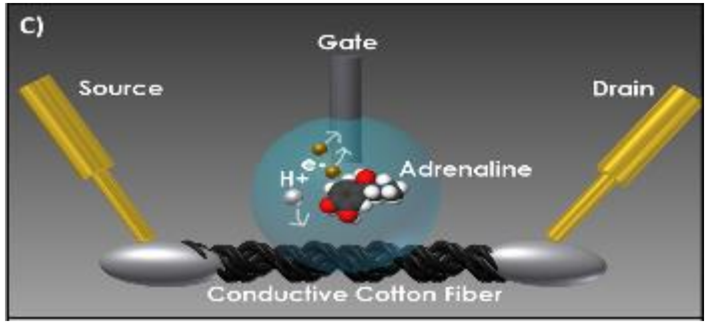
G. Tarabella et al. "A single cotton fiber organic electrochemical transistor for liquid electrolyte saline sensing." ***J. Mater. Chem. 22, 23830-23834 (2012).***

Adrenaline Monitoring in Sweat

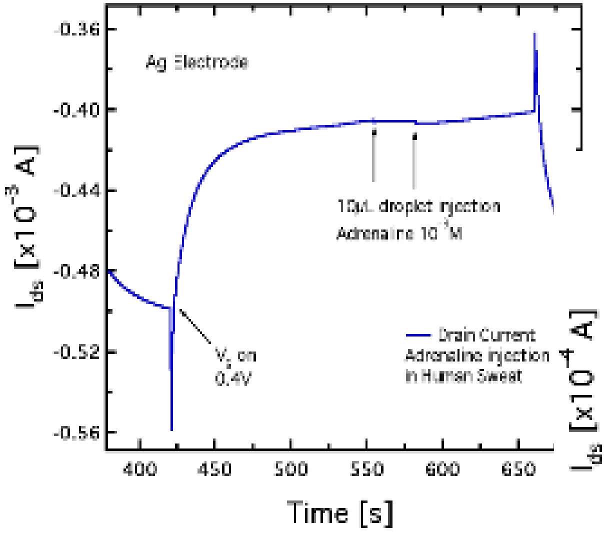


Adrenaline oxidation Process

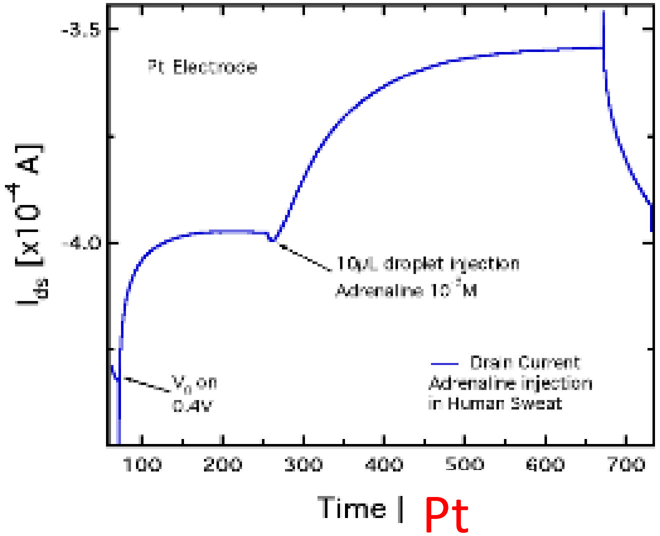
Monitor Panic or Heart Attack



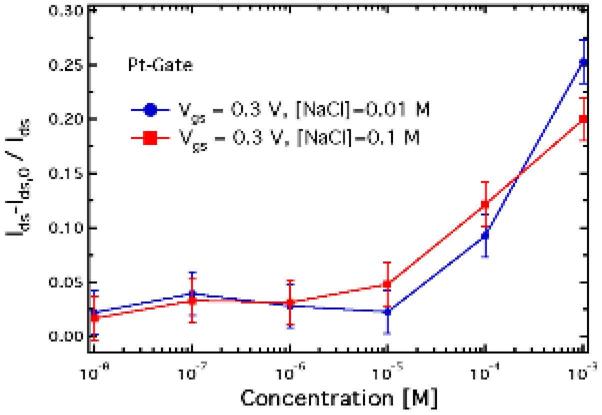
N. Coppedè,..,S Innotta.. J. Mater. Chem. B, (2014) 2, 5620



Ag
gate



Pt
gate

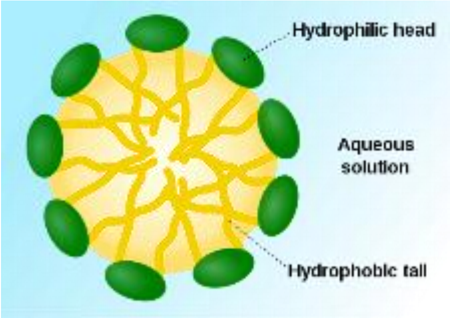


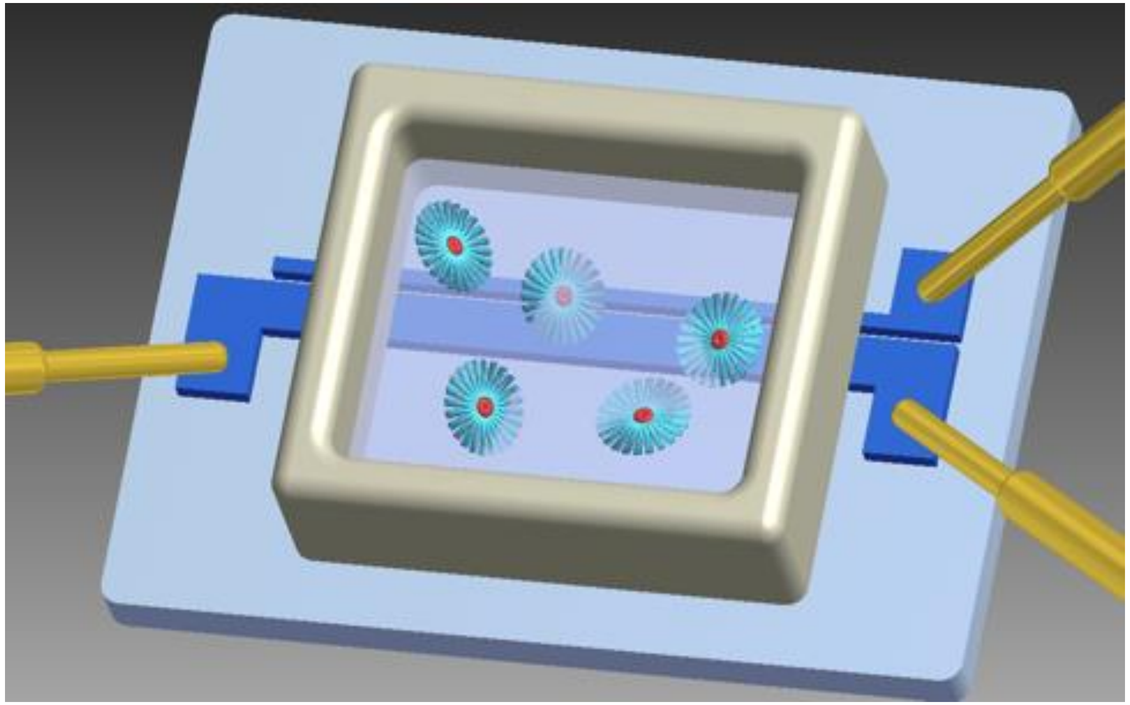
Cotton OECT detect Selectively
Adrenaline
vs
saline concentration

OECT and biosensing application

Monitoring of

Micelle formation

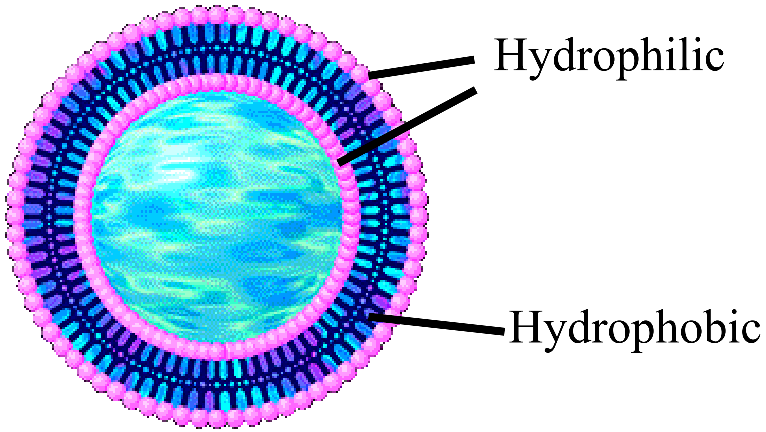


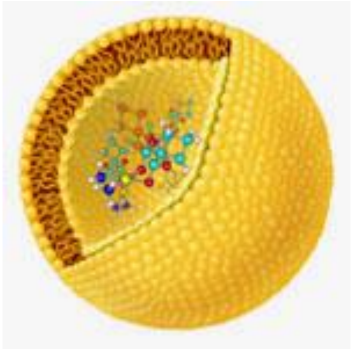


- personal care products,
- Cosmetics
- pharmaceuticals

Lecithin Liposomes Sensing and Monitoring

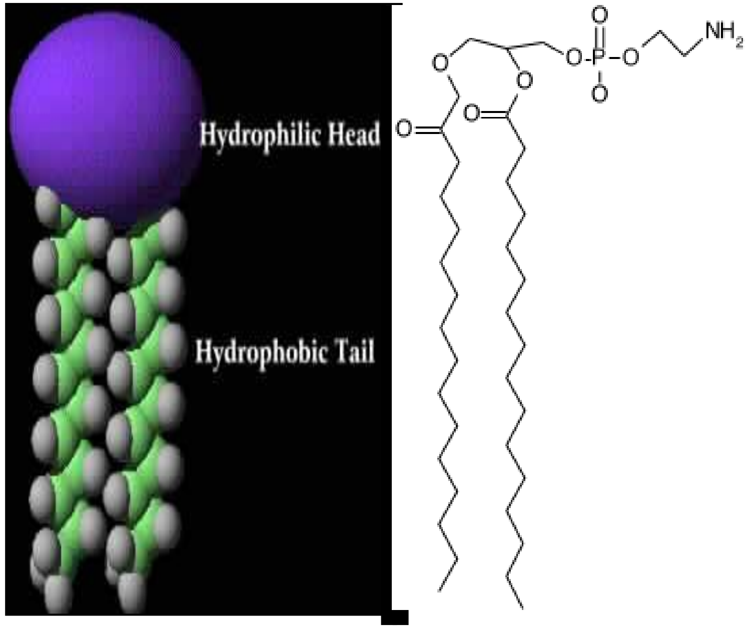
Spherical vesicles with a phospholipid bilayer





Surface often functionalised to increase liposome stability

Henriksen, 1994



Diagnostic imaging of tumors

Cosmetics

Study of membranes

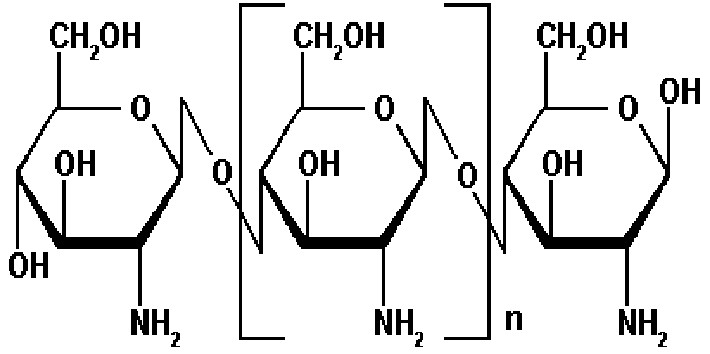
Drug Delivery:
liposomes as drug carriers

Lecithin: Chitosan Nanoparticles (Liposomes-based Nanoparticles NLC)

Sonvico et al. Int. J. Pharm., 324 (2006) 67-73 .

- nanoparticulate system constituted of lecithin vesicles stabilized with chitosan (20:1).
- The presence of chitosan determines the formation of a stable structure due to the interaction of negative lipid material with the positively charged polysaccharide.
- the chitosan mucoadhesion properties and its action as a penetration enhancer give rise to enhanced encapsulated drug bioavailability for poorly water-soluble drugs.

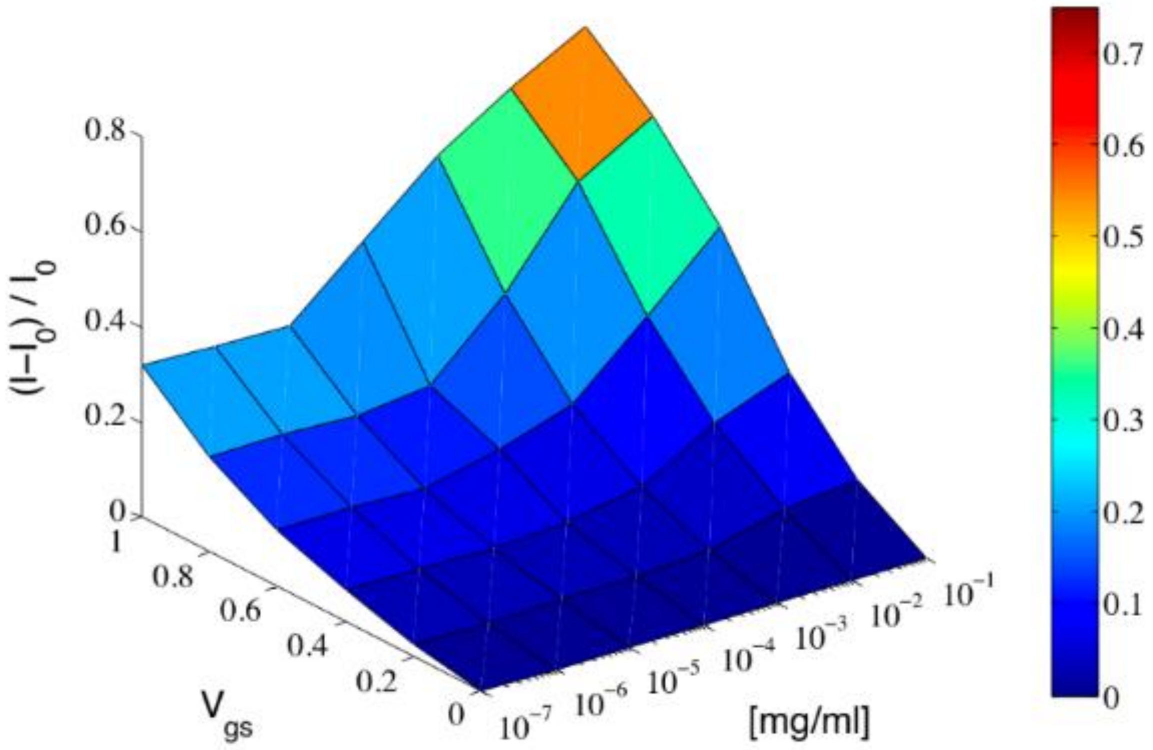
Size = 245 nm
Zeta Potential = + 45mV



Chitosan

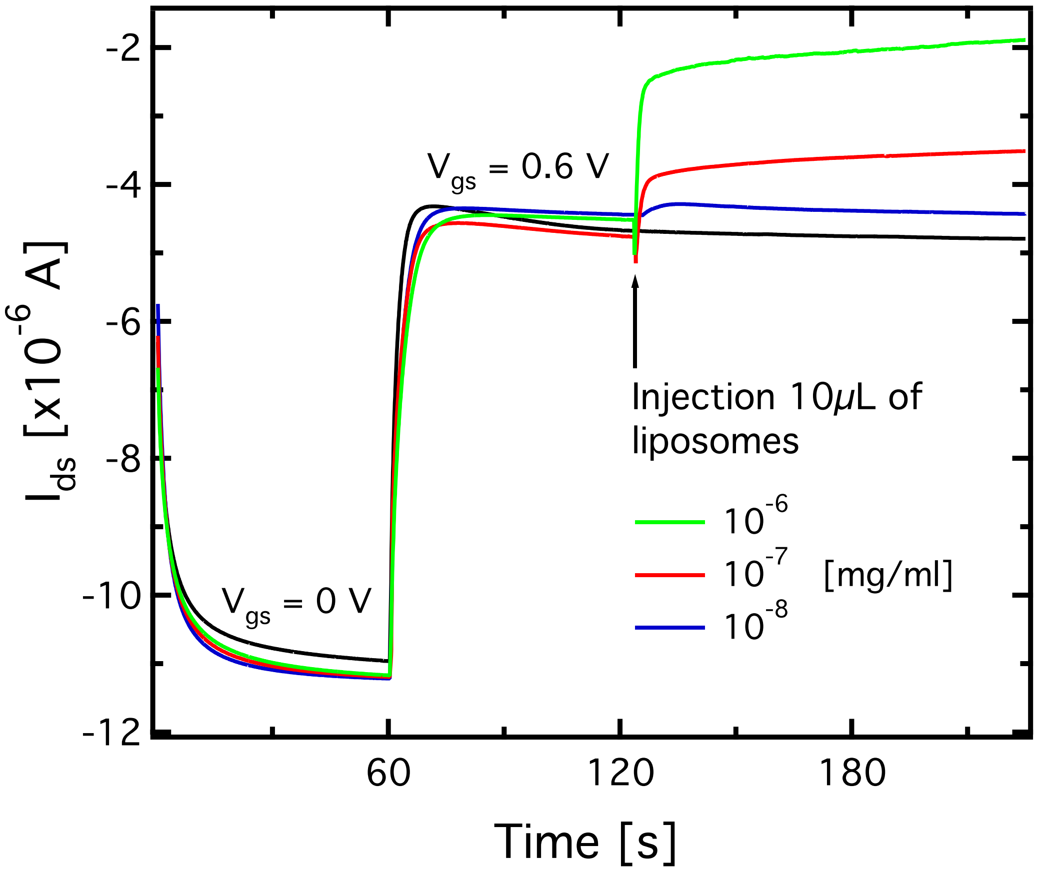
3-Dim Sensing

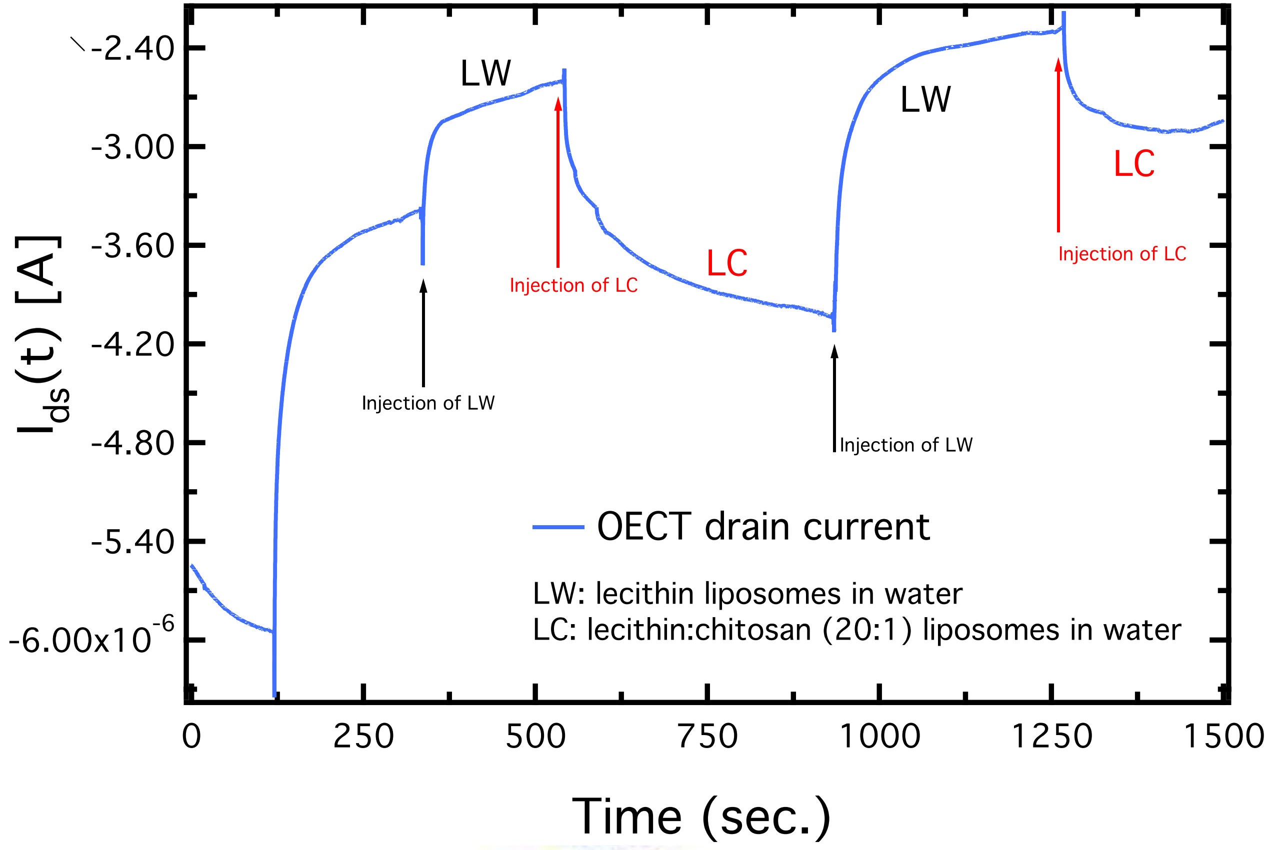
NLC, 3D-plot



G. Tarabella, A. G. Balducci, N. Coppedè, S. Marasso, P. D'Angelo, S. Barbieri, M. Cocuzza, P. Colombo, F. Sonvico, R. Mosca, and S. Iannotta.
Sensing and Monitoring of Liposomes by Organic Electrochemical Transistors Integrated in Microfluidics
Biochimica Biophysica Acta 1830, 9, 4374-4380 (2013)

Liposomes sensing in Microfluidics





G. Tarabella ..S. Iannotta., Sensing and Monitoring of Liposomes by Organic Electrochemical Transistors Integrated in Microfluidics. *Biochimica Biophysica Acta, 1830, 9, 4374-4380 (2013)*

Monitoring drug-induced cell stress and death

- Optimization of drug treatments

- Cell death: Apoptosis / Necrosis — Evidence of cell death (apoptosis and/or necrosis)

- Classical methods for cell-death detection:
  - agarose gel electrophoresis
  - caspase-3 quantification
  - Tunel assay
  - morphological charac. on stained or unstained cells
  - ...

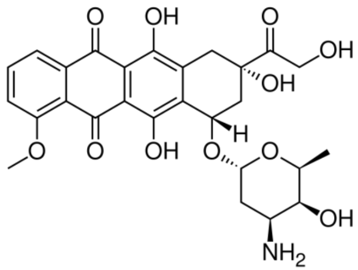
} Require expensive biological kits, lab equipments, scientific expertise. Results are not immediate

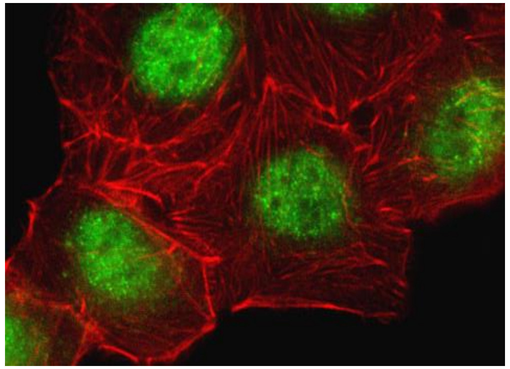
OECT
as fast, easy, portable and low cost diagnostic tool for monitoring cell stress and death

imem

Experimental setup: biological conditions

- Cell line: A549 (human lung adenocarcinoma) and Human non-small-cell lung carcinoma (NSCLC) HCC cell line
- Drug: Doxorubicin (anti-cancer DNA-damaging)
- Drug concentration range: 0.01 – 10 µM
- Cultivation in µ-porous Transwell inserts (10^5 cells/insert)
- growth for 48 hours prior to any electrical measurement



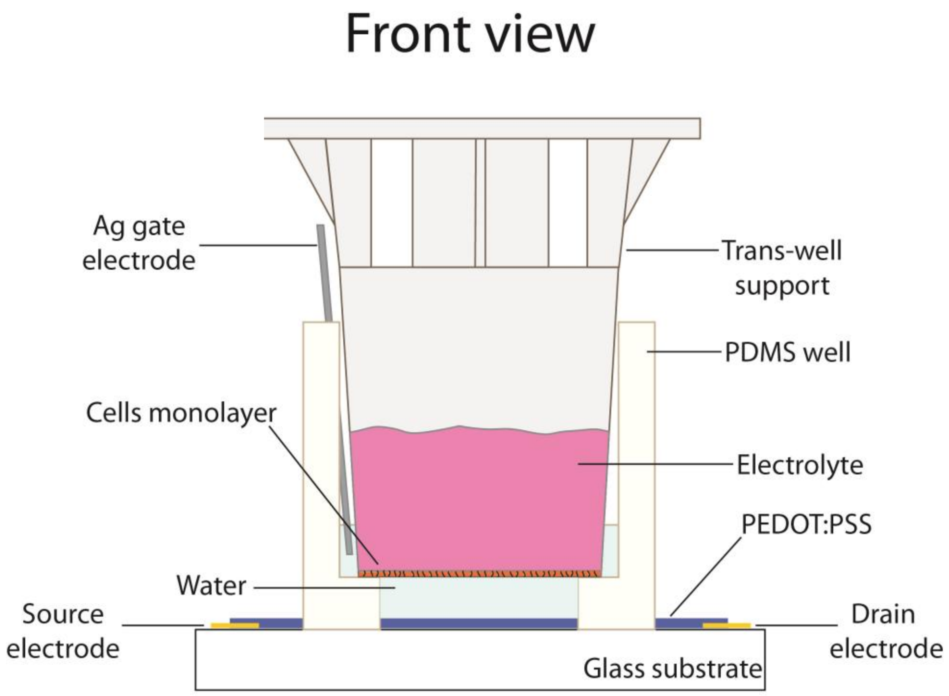


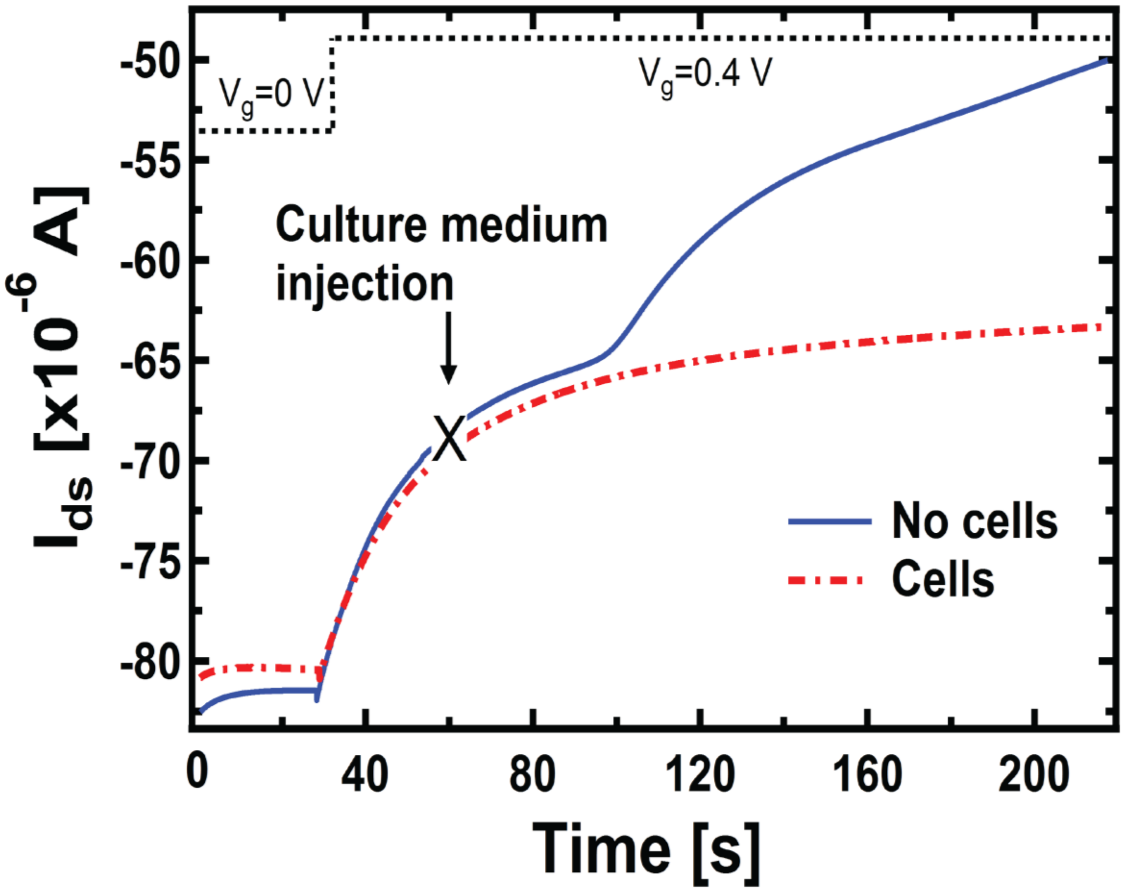
0.4-µm pore size and membrane area of 0.33 cm^2

Transwell inserts

Ø= 6.5 mm

Experimental setup: tl





$$I_{ds} \sim \gamma \cdot t$$

$$\gamma = \beta \frac{Nr^4}{r_0^4} K_d \frac{N_\theta}{n} C_1 = dI_{ds}/dt$$

on

- OECT measurement

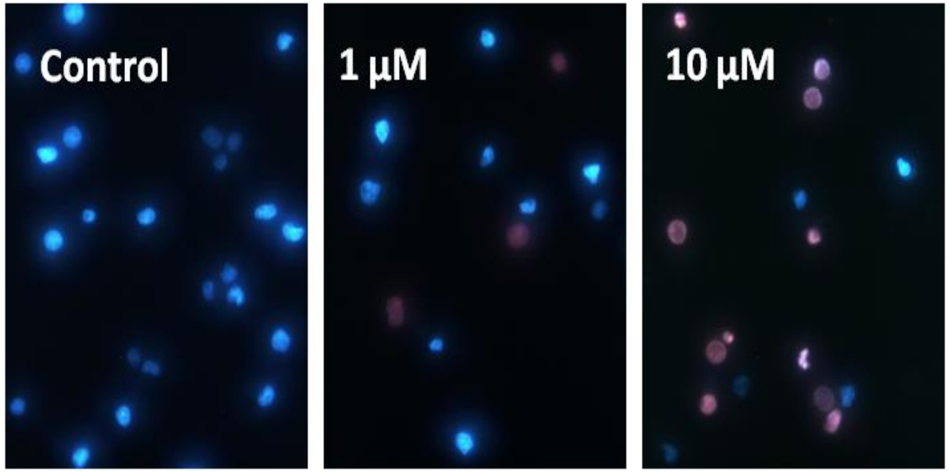
Fick's law for a concentration gradient applied it to our specific case in the form:

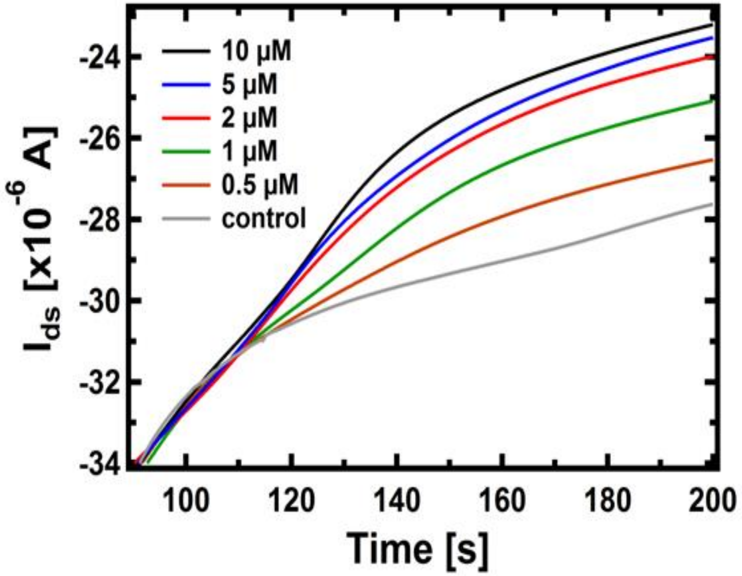
$$J = \frac{1}{G_0} G \cdot K_d \Delta C$$

A. Romeo, …. and S.Iannotta

Biosensors and Bioelectronics 68, 791 (2015)

Doxorubicin Dose-dependence effects
after 72 hours exposure





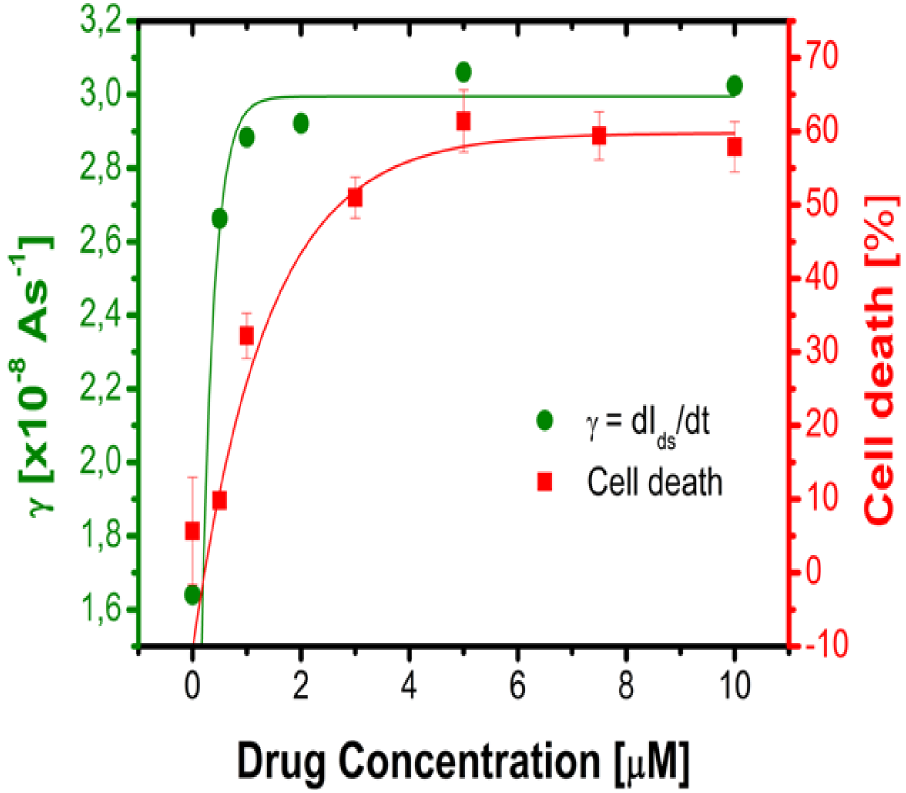
Live/dead fluorescence assay upon 72h exposure to increasing doses of doxorubicin.
An increasing number of red cells (PI-positive) is observed as drug concentration increases.

Device dynamic response (I_{ds} *vs.* time): The number of ions crossing the micro-porous membrane is strongly increasing as the pores are cleared by the cells that die.

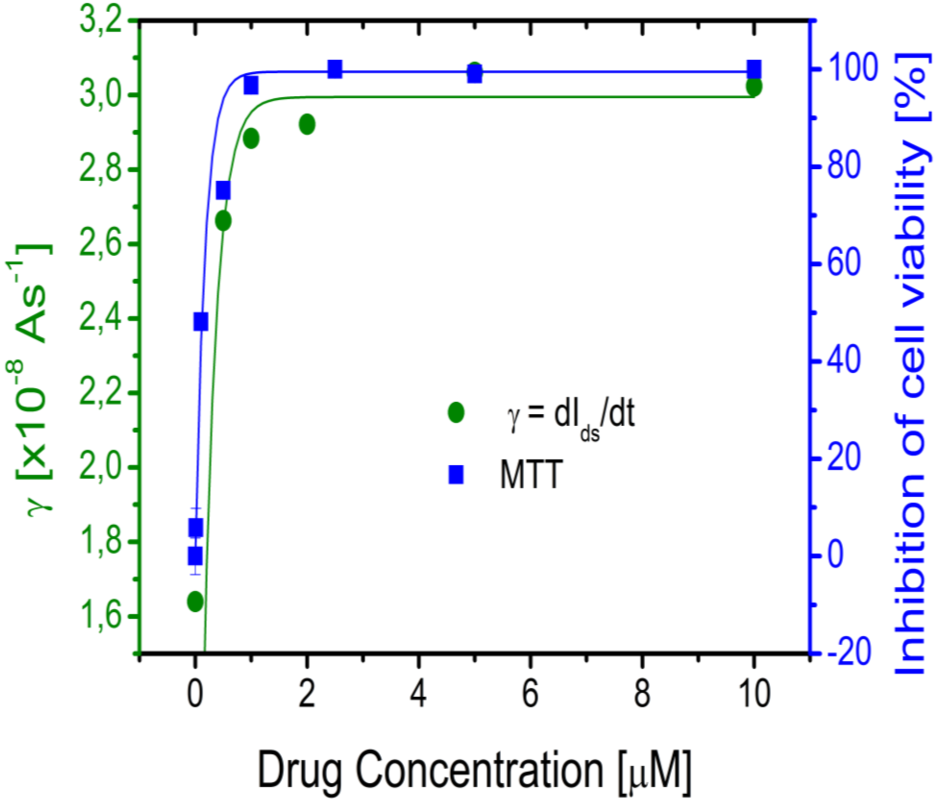
A. Romeo, …. and S.Iannotta, Biosensors & Bioelectronics 68, 791 (2015)

Doxorubicin **Dose-dependence: OECT Sensing**

versus Fluorescence assay



versus MTT viability assay



$$I_{ds} \sim \gamma \cdot t$$

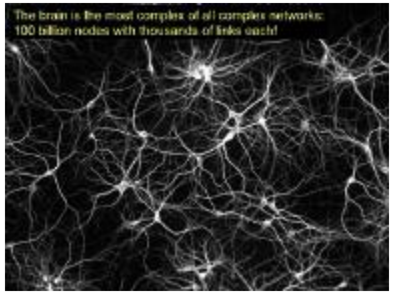
$$\gamma = \beta \frac{N r^4}{r_0^4} K_d \frac{N_\theta}{n} C_1 = dI_{ds}/dt$$

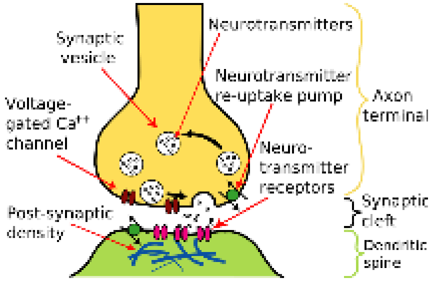
A. Romeo, …. and S.Iannotta
Biosensors & Bioelectronics 68, 791 (2015)

Organic Memristive Devices

COMPUTER

BRAIN



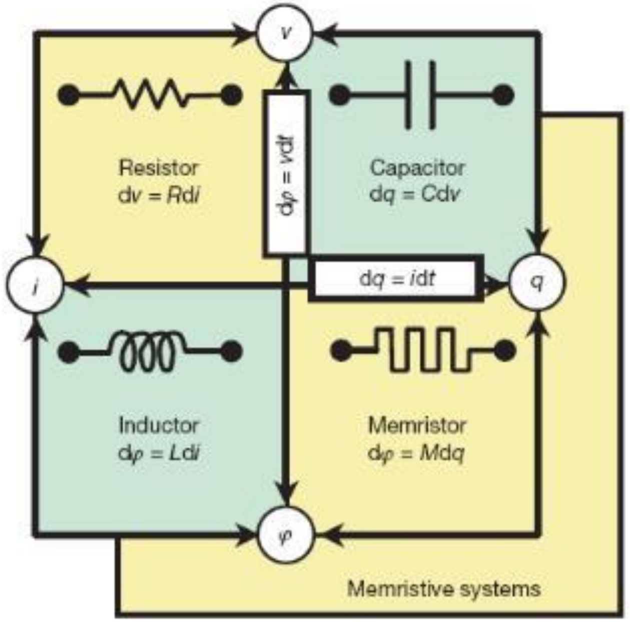


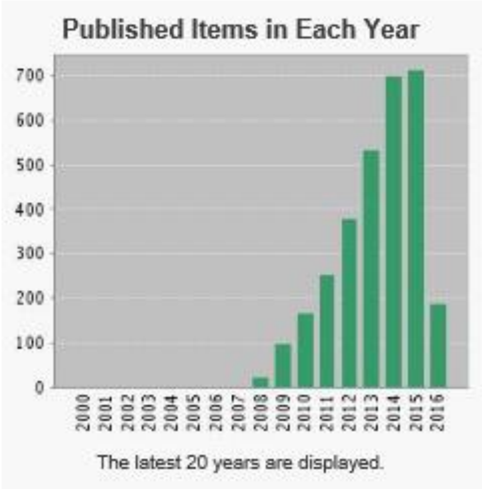
PROCESSOR MEMORY

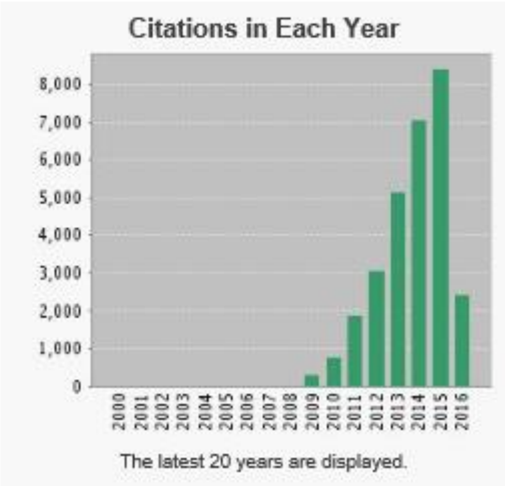
PROCESSOR AND MEMORY

NEW ADAPTIVE SYSTEMS WITH LEARNING AND
DECISION MAKING ABILITIES REQUIRE NEW ELEMENTS

The memristor



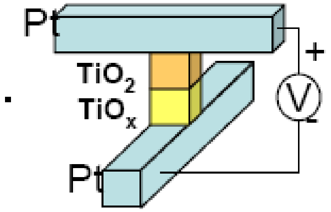




- **Any element with resistance dependent on current history can be called a 'memristor'**
- **Predicted by Chua in 1971 , claimed for the first time in 2008 at HP labs**

PANI/PEO based devices V. Erokhin, et al. *J. Appl. Phys.*, 97, 064501 (2005)

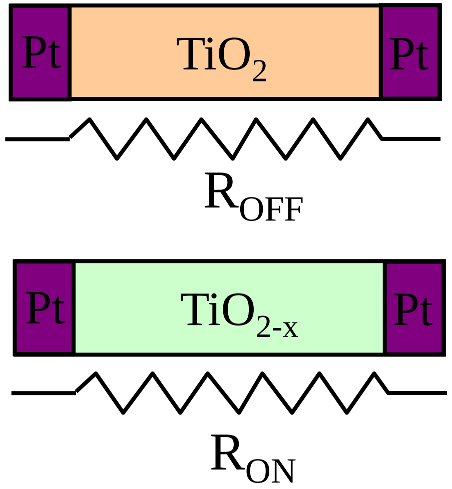
Hewlett-Packard Memristor

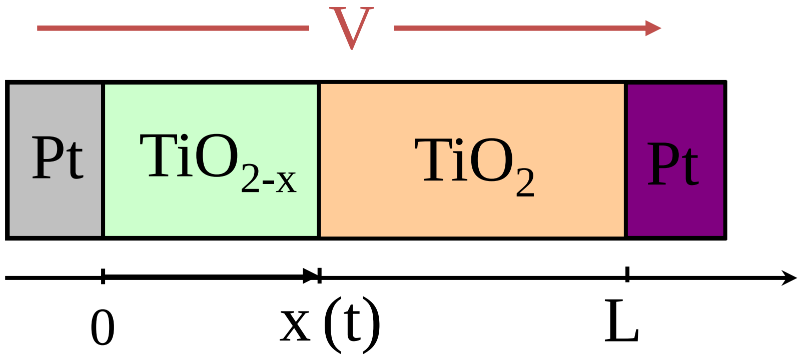


< 30x30 nm^2

migration of oxygen vacancies

$$\frac{R_{OFF}}{R_{ON}} > 1000$$





$$R = R_{ON}\frac{x}{L} + R_{OFF}\left(1 - \frac{x}{L}\right)$$

displacement proportional to the charge

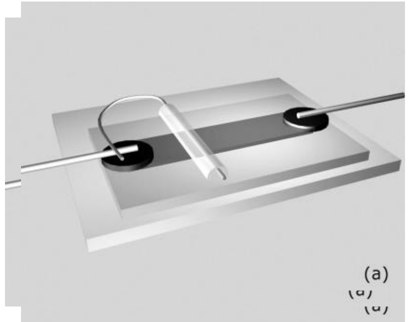
$$x \propto q$$

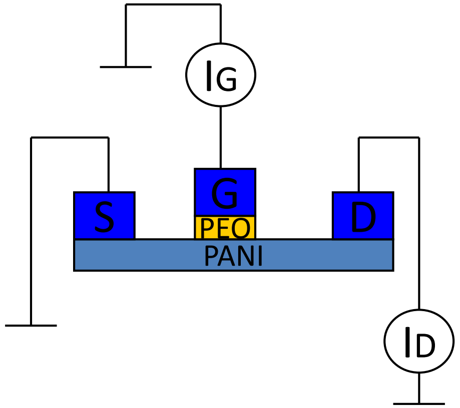
$$\Rightarrow$$

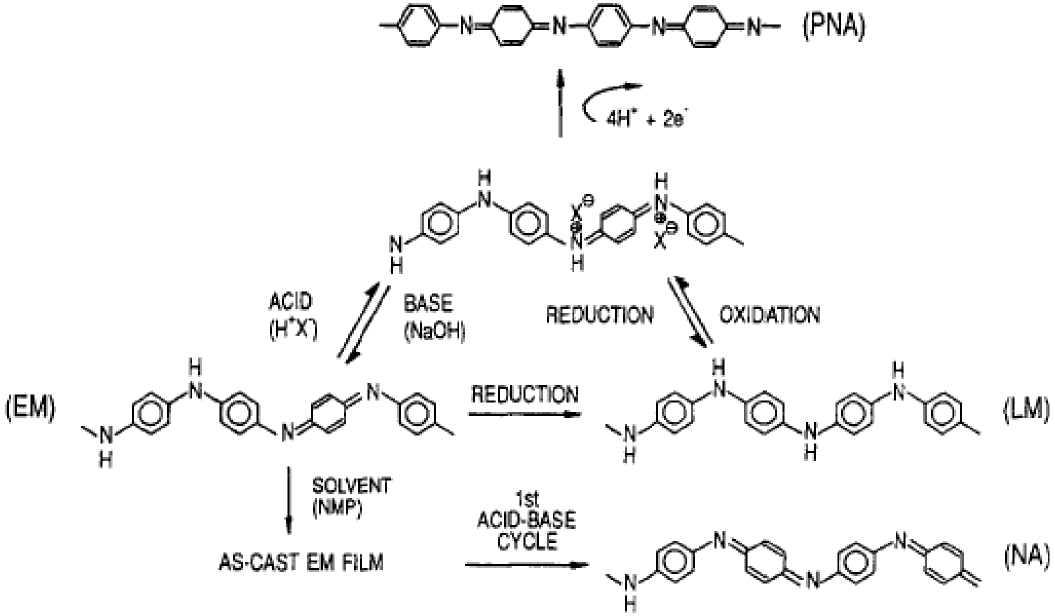
$$M(q) \cong R_{OFF}\left[1 - \mu\frac{R_{ON}}{L^2}q\right]$$

Strukov, Snider, Stewart & Williams, Nature 453 (2008)

ORGANIC MEMRISTOR - SYNAPSES ANALOG @ IMEM - CNR







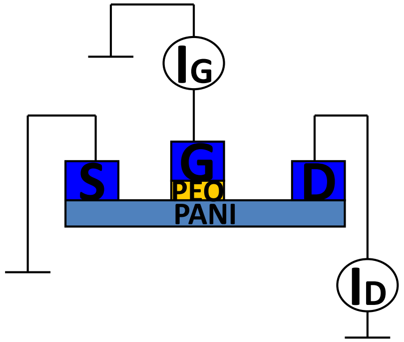
E.T. Kang, K.G. Neoh, and K.L. Tan, *Progr. Polymer Sci.*, **23**, 277-324 (1998)

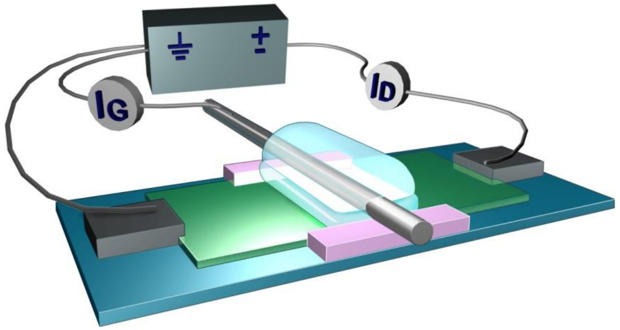
Oxidized polyaniline – conducting

Reduced polyaniline - insulating

V. Erokhin, et al. *J. Appl. Phys.*, 97, 064501 (2005)

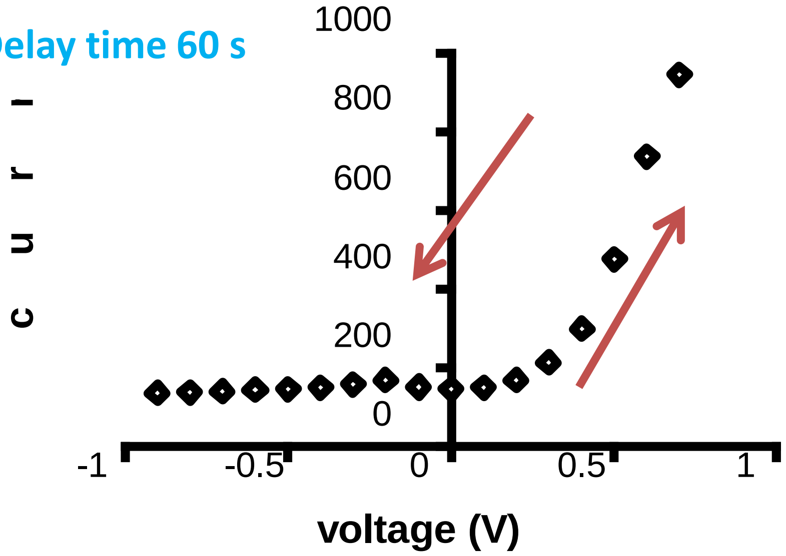
ORGANIC MEMRISTOR:





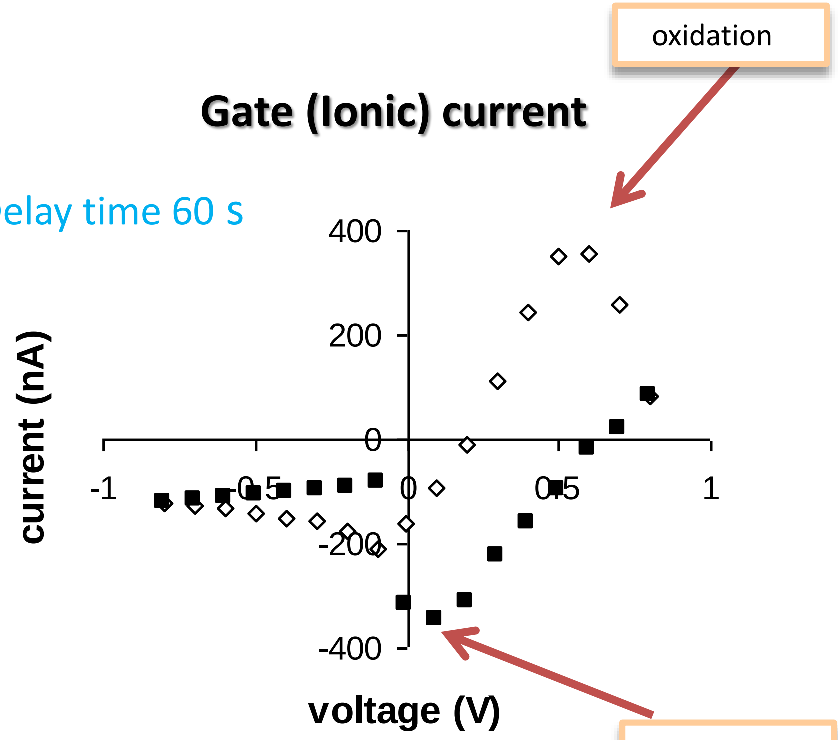
Differential (electronic) current

Delay time 60 s



Gate (Ionic) current

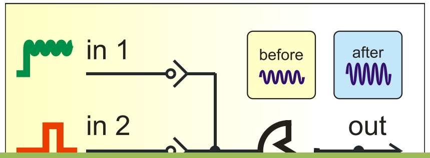
Delay time 60 s

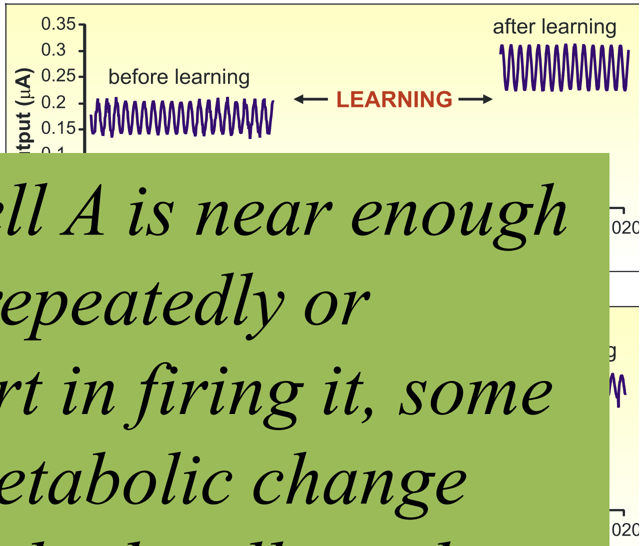


Empty squares – increasing V

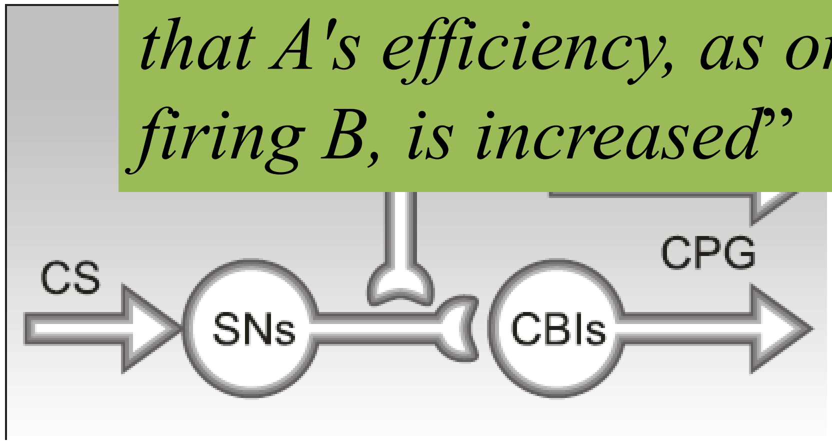
Filled squares – decreasing V

The synapse analog





"When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased"



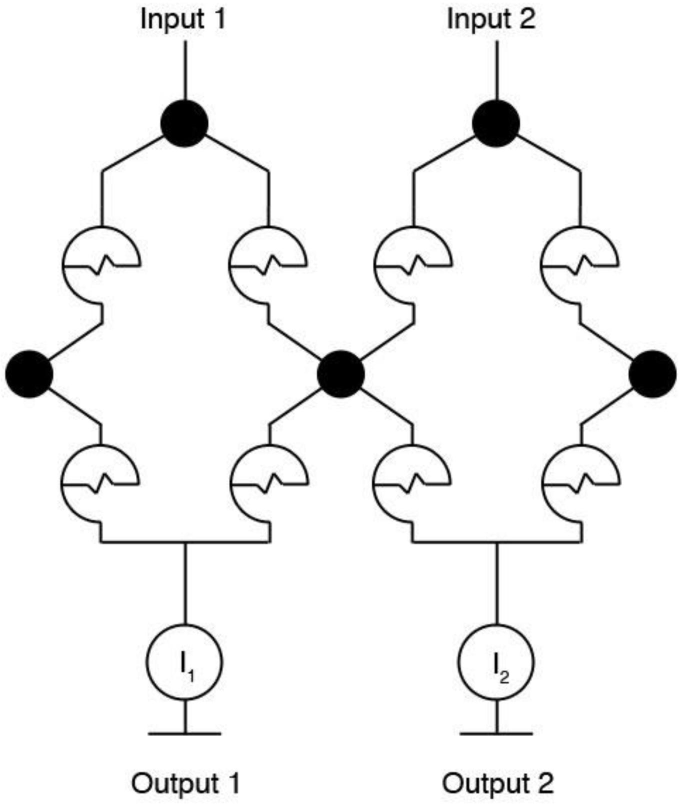
nduced

ation in

Hebbian rule

Erokhin V et al. , BioNanoScience, 1, 24 (2011).

MODEL ADAPTIVE NETWORK

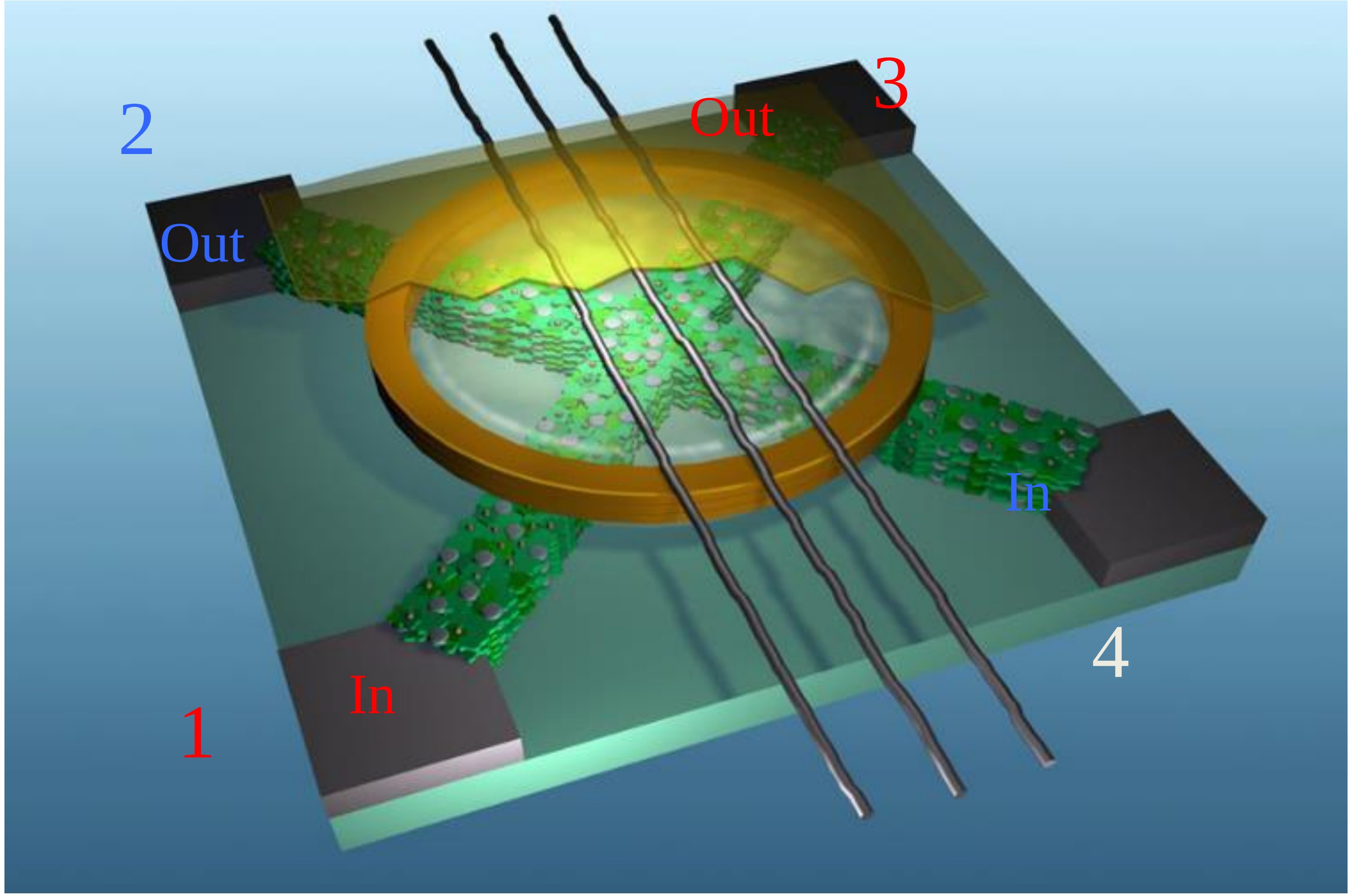


Training by applying –0.5V between 1-st input and 1-st output;
+1.2V between 1-st input and 2-nd output

Task: reinforcement of the In1-Out2 connection and inhibition of the In1-Out1 connection

	Out 1 (nA)	Out 2 (nA)
Before training	120	32
After training	65	124

V. Erokhin, et al., *Cryst. Rep.*, **52**, 159-166 (2007)



Simultaneous and sequential training: voltages of opposite polarity are applied to red and blue pairs

V. Erokhin et al., J. Mater. Chem., 22, 22881 (2012).

SIMULTANEOUS TRAINING

- Conductivity ratio is about 1 order of magnitude
- Possibility of multiple adaptations
- Short-term memory

SEQUENTIAL TRAINING

- Conductivity ratio is more than 2 orders of magnitude
- N0 multiple adaptations
- The system itself tend to return to the state established after the first learning
- Long-term memory

	Volt	electrodes	«1-3"	Volt	electrodes	«2-4"
1 day		0	0,5654 μA		0	0,233500 μA
training 1	+0,8	2 hours	5,1492 μA	-0,2	2 hours	0,011436 μA
		4 hours	7,3604 μA		3 hours	0,009191 μA
control 1	+0,4		0,4120	+0,4		0,008350
			0,2353			0,005650
training 2	-0,2	0	2,4344	+0,8	0	0,619300
		4 hours	1,6990		4 hours	0,163300
2 day	+0,4		2,4250	+0,4		0,147300
control 2						
3 day	+0,4		5,0578	+0,4		0,144200
control 3						

Long-term sequential training results in the formation of stable signal pathways with no possibility of next adaptations (baby learning)

PERCEPTRON

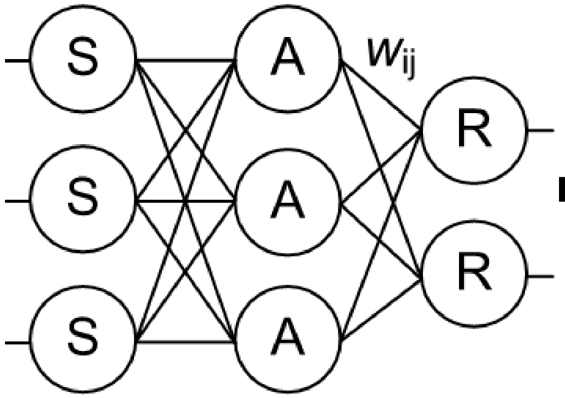
Machine learning

- algorithm for supervised classification of an input into one of several possible non-binary outputs.
- linear classifier, i.e. a classification algorithm that makes its predictions based on a linear predictor function combining a set of weights with the feature vector.
- The algorithm allows for online learning, in that it processes elements in the training set one at a time.
- The perceptron algorithm dates back to the late 1950s; its first implementation, in custom hardware, was one of the first artificial neural networks to be produced.

Perceptron

Memristive Single-layer (without associative hidden layers) perceptron

Input images (patterns) as the encoded combinations of simple signals (features)

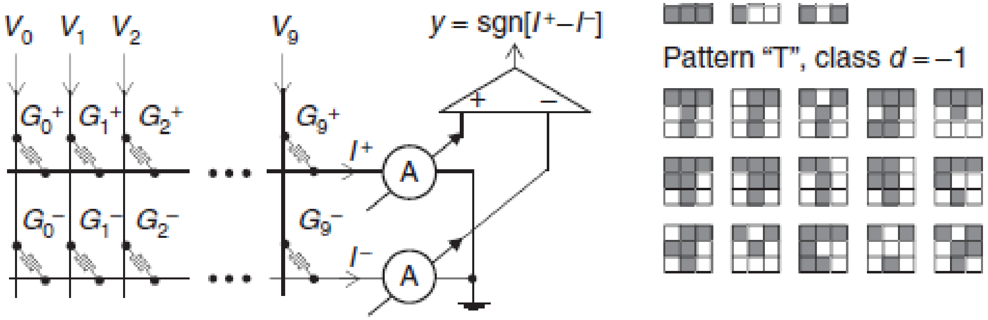


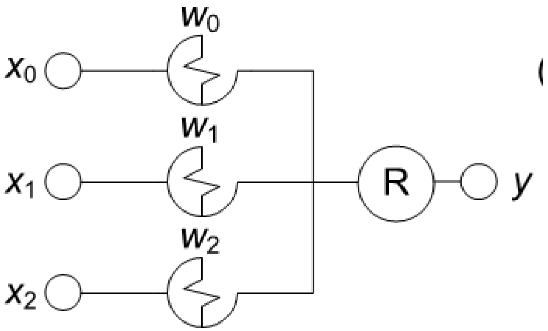
Output category of input image (pattern ecognition)

Rosenblatt perceptron. S stands for the sensor neurons, A – for associative, and R – for responsive neurons. Only the second layer of links w_{ij} is adaptive.

Alibart F. et. al., **Nat. Commun. 4**, 2072 (2013)

Demin V. et. al., **Organic Electronics 25**, 16 (2015)

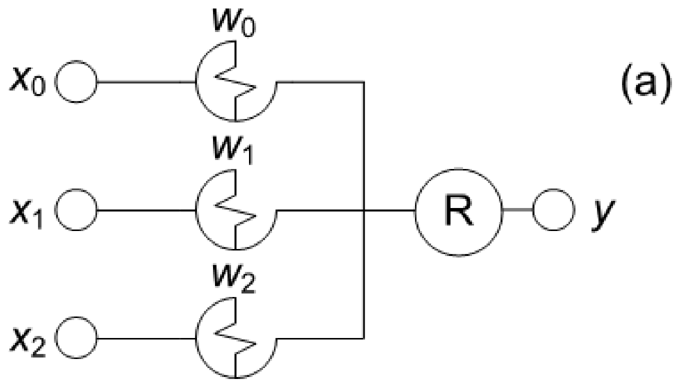


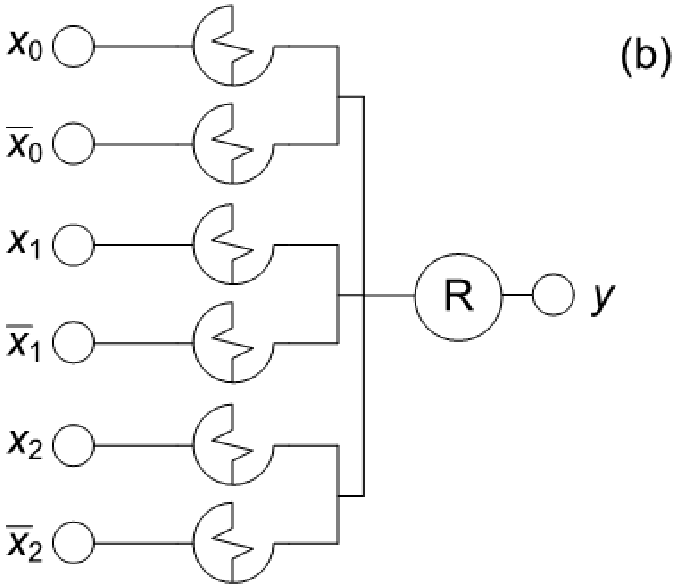


Simple 'letter' pattern recognition

NAND and NOR tasks learning

Linearly separable tasks!





LEARNING:

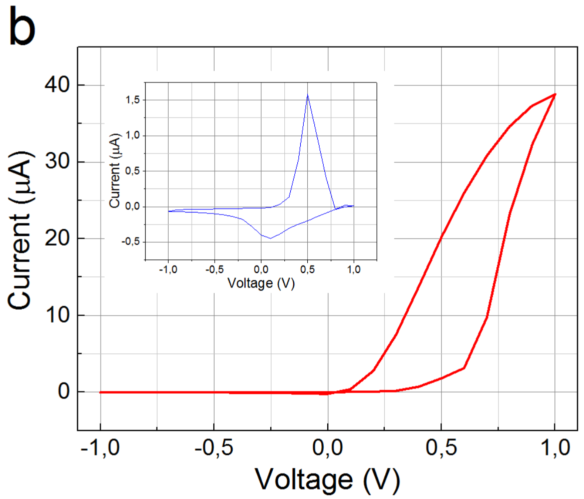
If out(exp)-out(theor) = 0
No training

If out(exp)-out(theor) = -1
Reinforcing

out(exp)-out(theor) = 1
Suppression

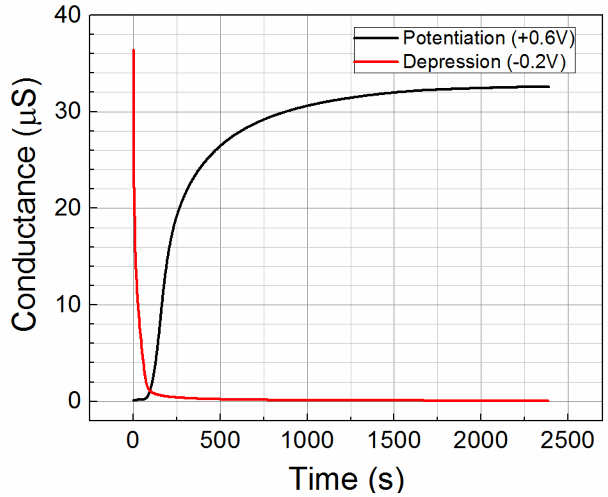
Characteristics of PANI-based Memristive Devices

Typical IV curves



0.0 V ⇔ logic "0"
0.4 V ⇔ logic "1"

Typical switching kinetics



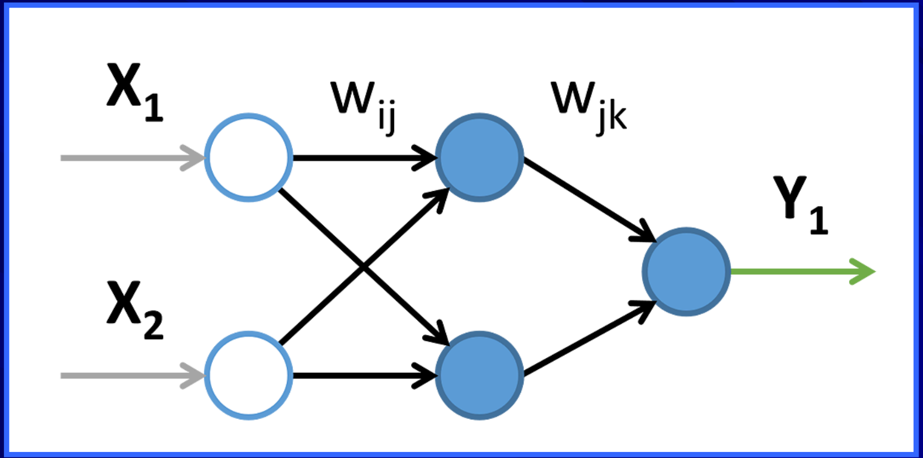
Conduction variation depends on initial conductance and approximately corresponds to exponential character of kinetics

Learning of the perceptron

N	Input			Output, μA	Logic output	Desired output	Error	Correction time[a)], s		
	x_0	x_1	x_2					0	1	2
1	1	0	0	1.8	0	1	-1	p600	-	-
2	1	0	1	-0.3	0	1	-1	p600	-	d30
3	1	1	0	4.8	1	1	0	-	-	-
4	1	1	1	3.5	1	0	1	d30	p600	p600
5	1	0	0	4.5	1	1	0	-	-	-
6	1	0	1	4.1	1	1	0	-	-	-
7	1	1	0	0	0	1	-1	p600	d30	-
8	1	1	1	3.8	1	0	1	d30	p600	p600
9	1	0	0	5.3	1	1	0	-	-	-
10	1	0	1	5.1	1	1	0	-	-	-
11	1	1	0	0	0	1	-1	p600	d30	-
12	**1**	**1**	**1**	**2.5**	**0**	**0**	**0**	**-**	**-**	**-**
13	**1**	**0**	**0**	**4.6**	**1**	**1**	**0**	**-**	**-**	**-**
14	**1**	**0**	**1**	**4.5**	**1**	**1**	**0**	**-**	**-**	**-**
15	**1**	**1**	**0**	**4.0**	**1**	**1**	**0**	**-**	**-**	**-**

Demin et al., Organic Electronics, 25, 16-20 (2015)

Double-layer perceptron

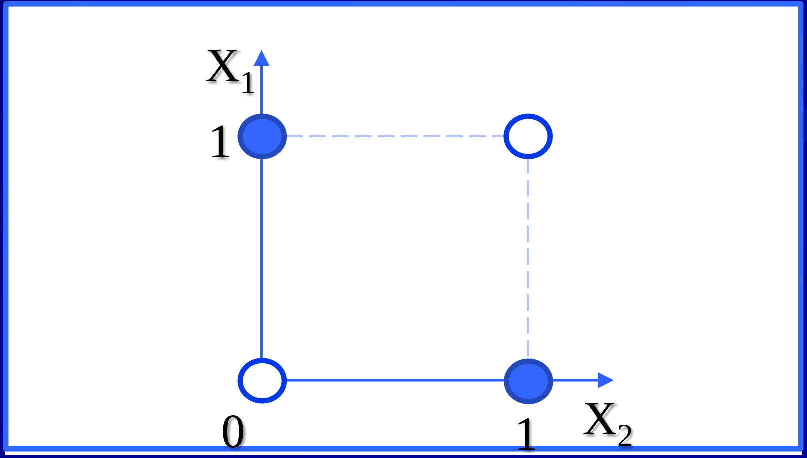


XOR task – historical benchmark of linearly non-separable task

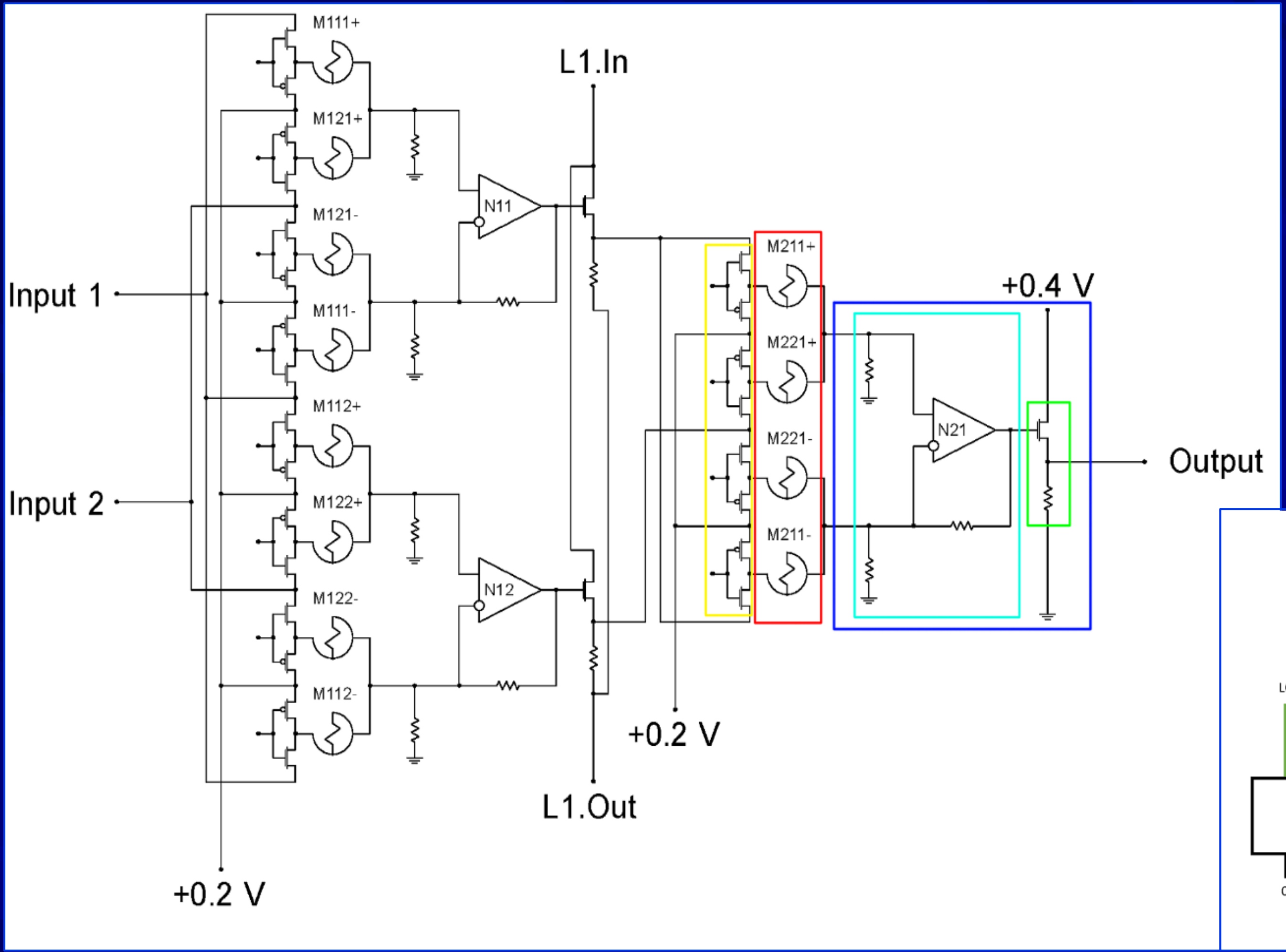
XOR truth table

X_1	X_2	Out
0	0	*0*
0	1	*1*
1	0	*1*
1	1	*0*

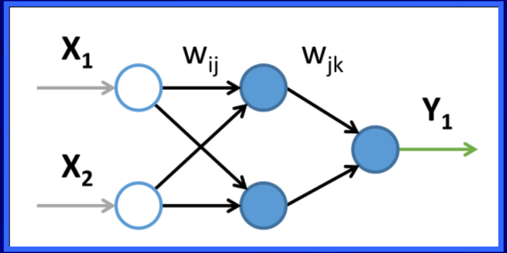
XOR graphical representaion



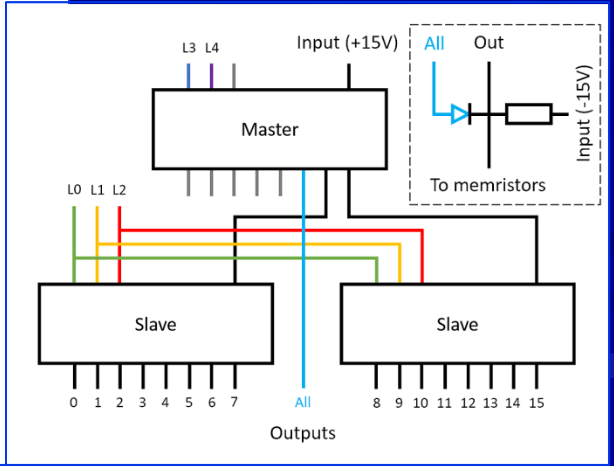
Double-layer perceptron based on PANI memristors



Circuit diagram for a hardware memristor-based double layer perceptron with highlighted logic blocks at the second layer: an access system (yellow), memristors (red), differential summator (cyan), activation function (green) and the whole "neuron body" (blue)

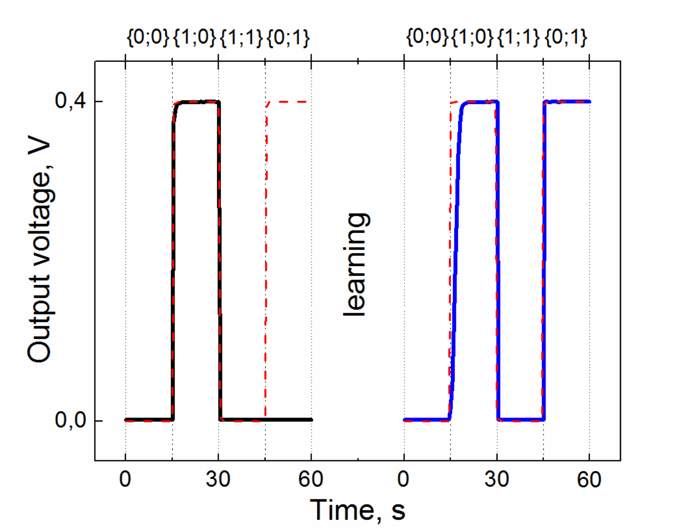


Logic scheme of the implemented neural network



Logic scheme of the commutator used with 5 logic inputs (L0 – L4) and 16 outputs

Learning of double-layer perceptron

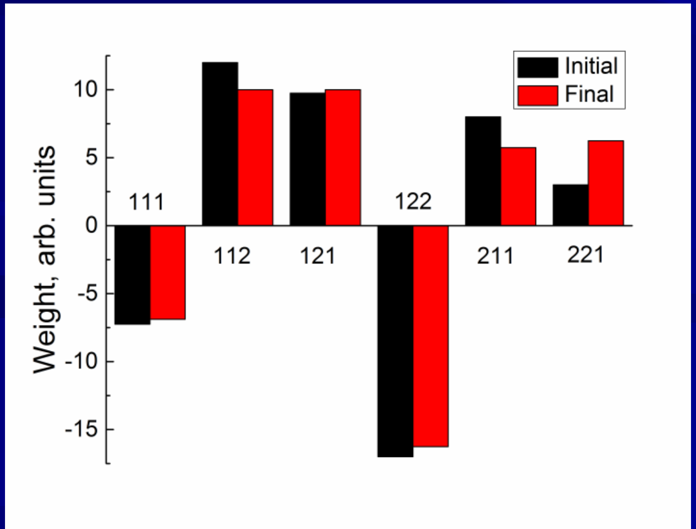


Back-propagation algorithm with batch correction

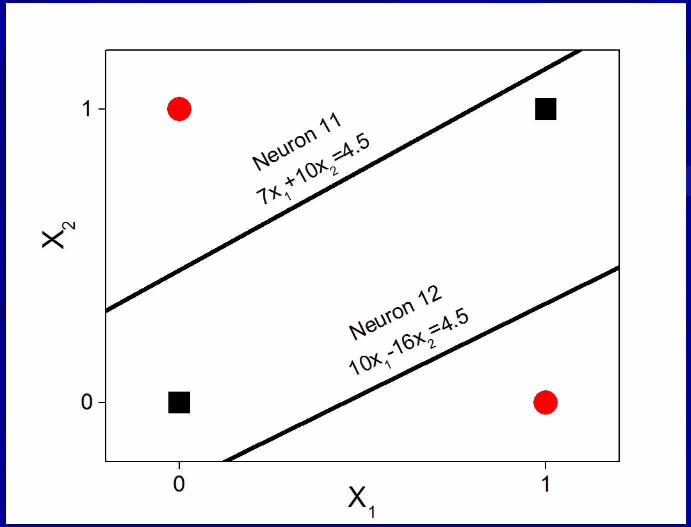
$$\Delta w_{ij} = -\eta \sum_k y_i^{(k)} \delta_j^{(k)},$$

$$\delta_j^{(k)} = \begin{cases} -y_j^{(k)}\left(1-y_j^{(k)}\right)\left(t_j - y_j^{(k)}\right), for\ the\ output\ layer; \\ -y_j^{(k)}\left(1-y_j^{(k)}\right) \sum_{l \in Child(j)} \delta_l^{(k)} w_{jl}, for\ the\ hidden\ layer. \end{cases}$$

Weight corrections were recalculated to the training pulses durations due to exponential approximation of conductivity kinetics

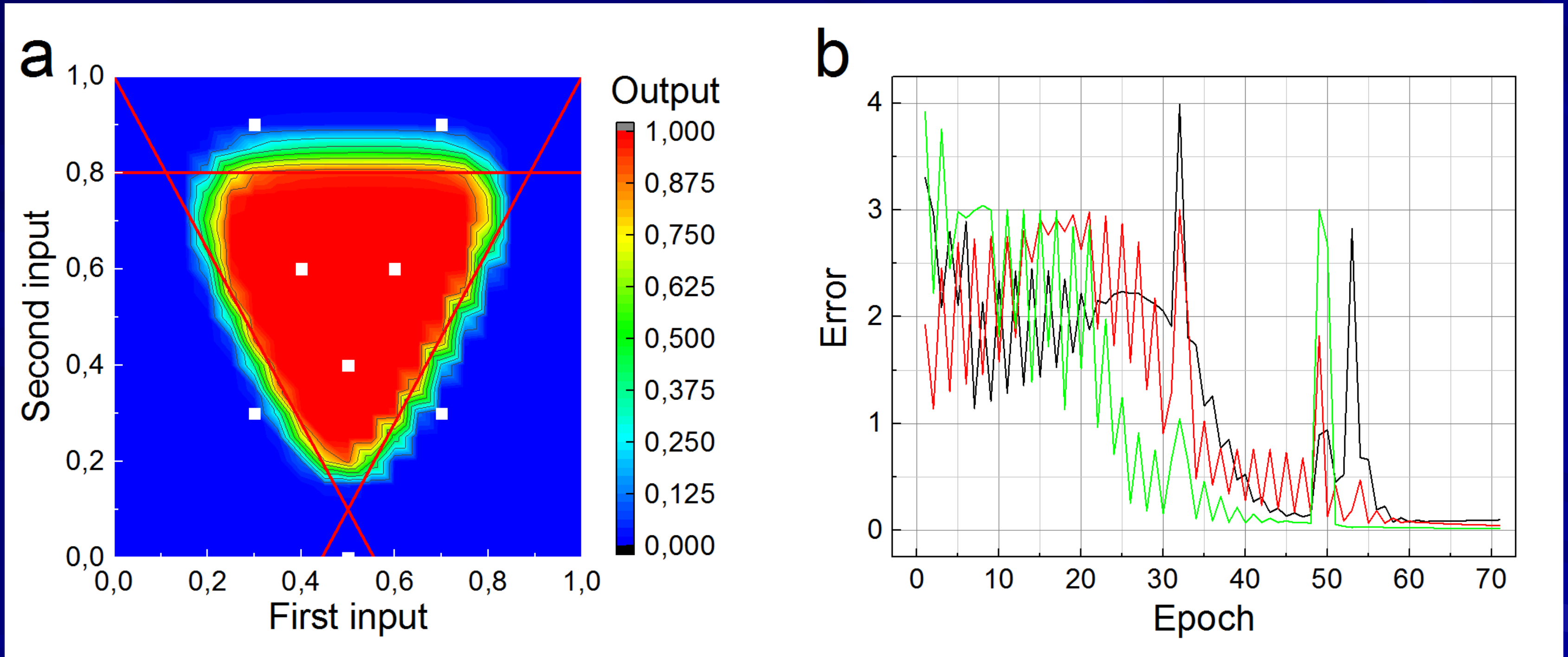


$\Rightarrow$



Analogue task solving by DLP (numerical simulation)

2-3-1 double-layer perceptron based on PANI memristors was simulated.



Simulated output signal and corresponding separating lines.

Error function value within the learning procedure for 3 different sets of initial weights.

- Memristive devices are suitable for multilayer hardware perceptron. For the first time, we built a double-layer perceptron and demonstrated the possibility of its physical learning to perform nonseparable combinatorial logic classification (XOR logic task).

- Perceptron is ideally suitable for solving analogue tasks.

- The physical realization of double layer perceptron demonstrates the ability to form the hardware-based neuromorphic networks with the use of organic memristive devices. This approach could be extended (but not directly) to larger ANNs and other machine learning algorithms for more complex and data-intensive tasks.

BIO-OECT INTEGRATING MEMRISTIVE RESPONCE?

Physarum Polychephalum (Slime Molds)

The Greek name means
πολύς κεφαλή = several heads

Several Nuclei dispersed in the cytoplasm

Amoebozoa, myxomycetes class, in the past referred as fungi, today “slime molds” (slime moulds)

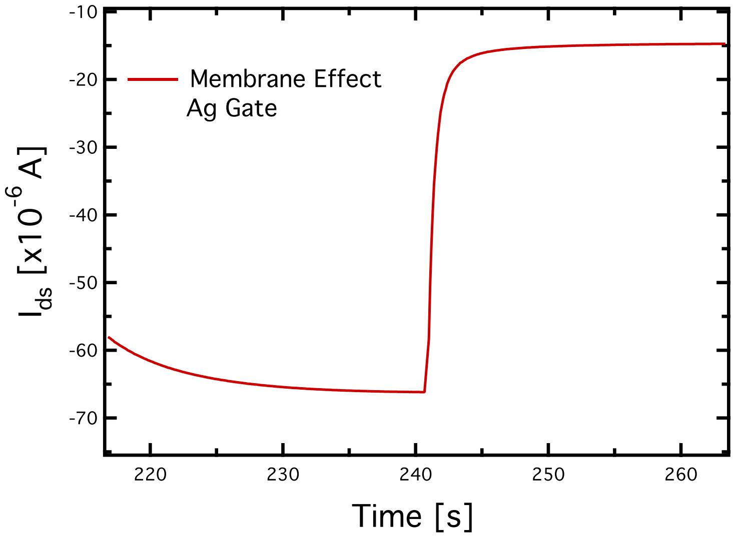
Wet environment, about 23ºC - shaded

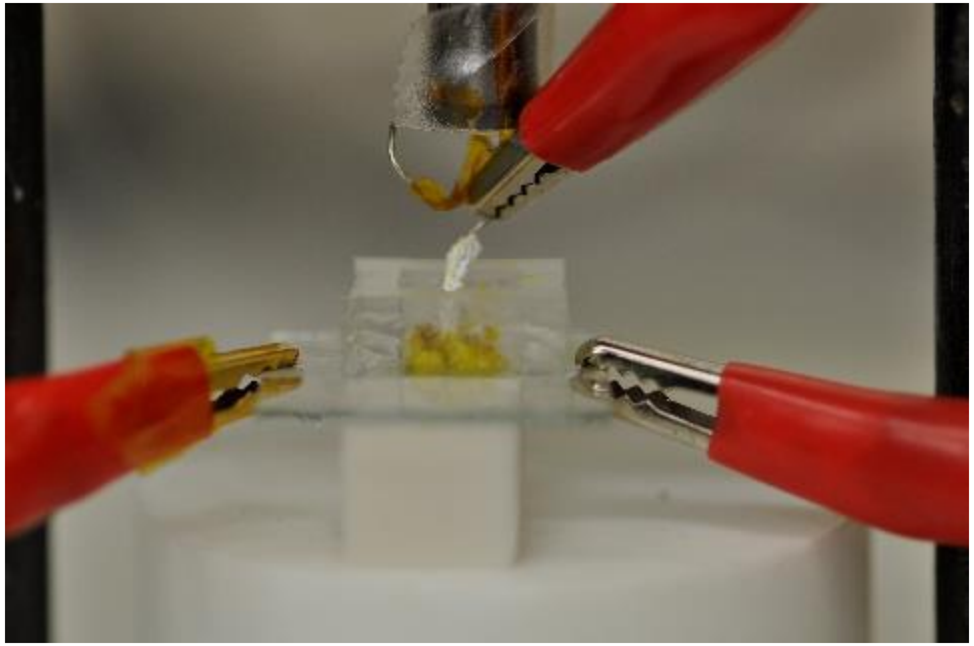
Shorter patway to catch food, greater nutritional with Physarum Polycephalum

That are awesome features for a organism that spends most of its life as a single cell, feeding on bacteria.

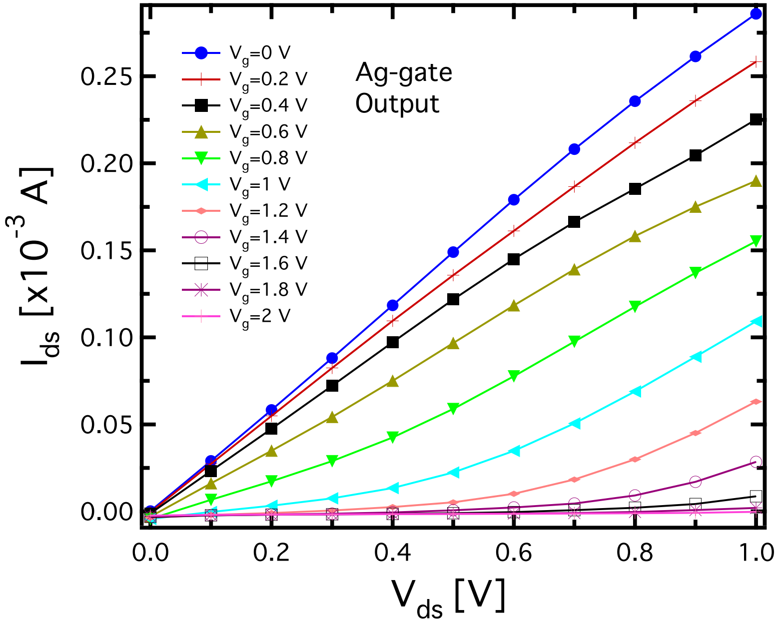
Famine: Amoebe unite to move better
in the richest areas and as they reproduce
creating spores.

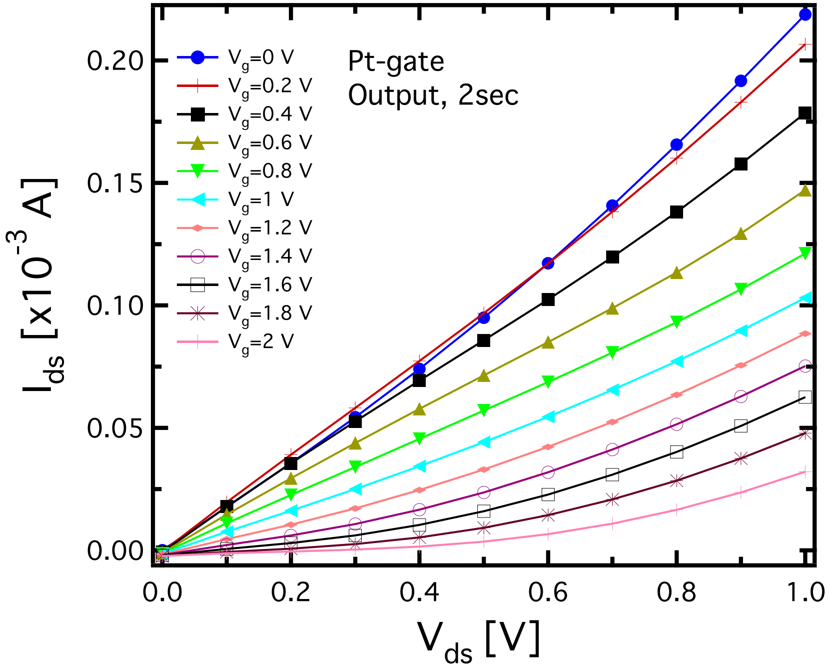
Physarum Polycephalum a Unicellular Organism Operated as an OECT

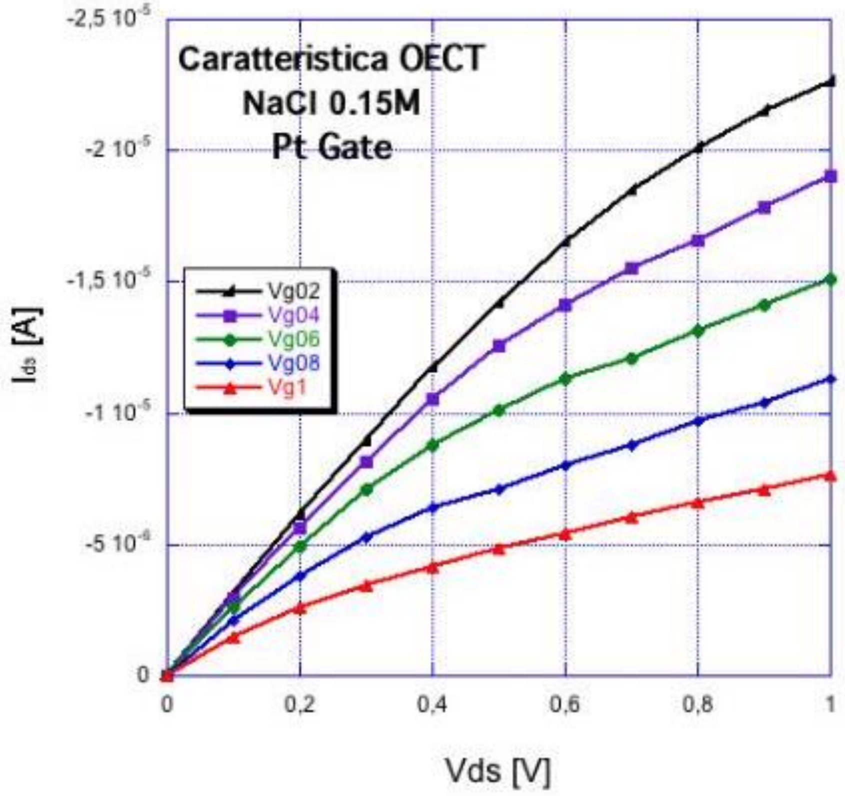




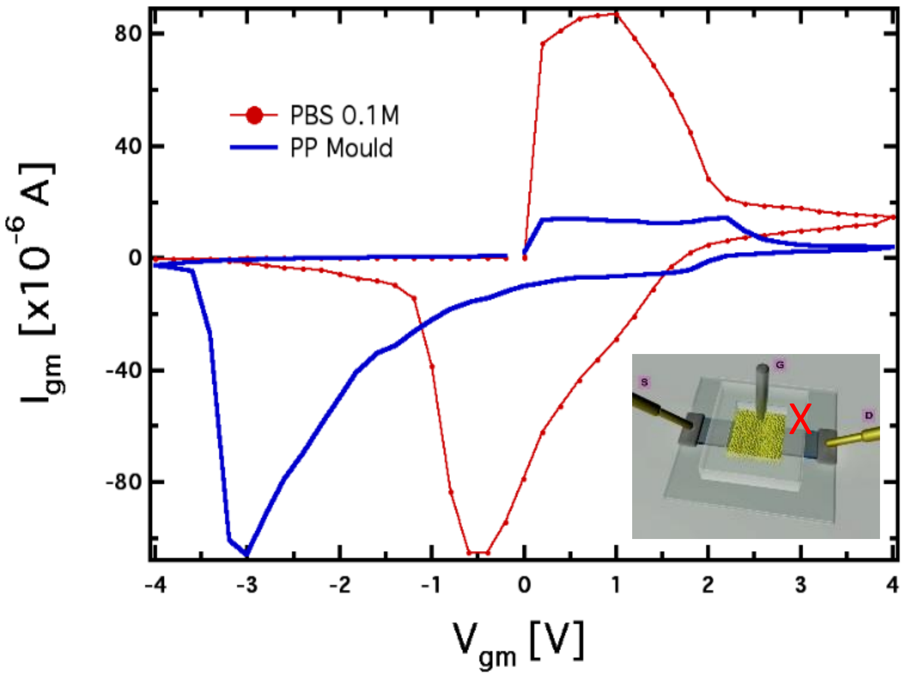
Physarum Polycephalum
a Unicellular Organism Operated as an OECT

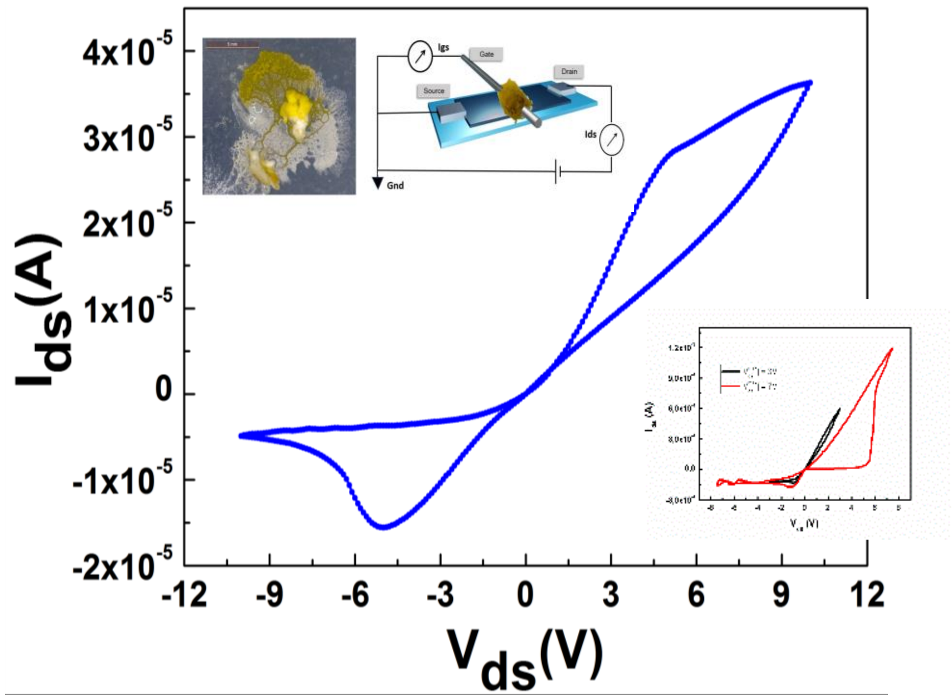






OECT Architecture With or Without PP





G. Tarabella… S. Iannotta,
An Hybrid Biological/Organic Electronic Device Endowed with Sensing and Memristive Properties Based on the Physarum Polycephalum Cell.
Chem. Sci., 2015, 6, 2859.

Electrochemical transistors: take-home messages

✓Organic electrochemical transistors made of PEDOT:PSS are ideally suitable for real time sensing and monitoring a variety of systems of interest for Monitoring Drug Processes: surfactant transition phase, micelles, liposomes or nanoparticles;

✓ Their application in Nanomedicine and Bioelectronics is envisaged as very promising- Being able to monitor in real time cellular stress and death

- ✓ They develop adaptive behavior when interfaced "electrically/ionically" with leaving systems
- ✓ They appear to be ideally suitable to interface natural brains

OUTLOOK – the perspective I am proposing

We are working towards developing a new paradigm towards integrating sensing, memory and logic in a novel approach to hybrid bio-electronics:

Sensing and bioelectronics interfaces given by the OECT approach

Memristive logic where learning is inherent in the materials response (memory and logic in the same device)

↓

Hybrid natural–synthetic bio-hybrid and bio- inspired systems for novel logic, learning and smart prosthetics

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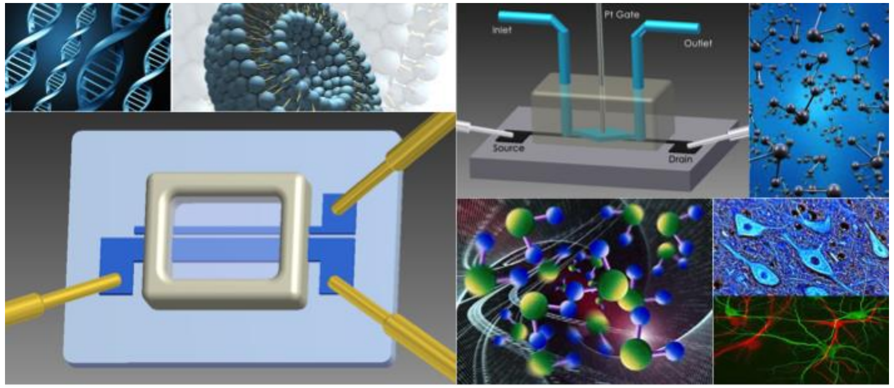
Progetto Therseo RER



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