Implantable modular neuroprostheses to understand and restore neural functions

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Neuroengineering is a novel discipline combining engineering including micro and nanotechnology, electrical and mechanical, and computer science with cellular, molecular, cognitive neuroscience with two main goals: (i) increase our basic knowledge of how the nervous system works; (ii) develop systems able to restore functions in people affected by different types of neural disability. In the past years, several breakthroughs have been reached by neuroengineers in particular on the development of neurotechnologies able to restore sensorimotor functions in disabled people.

In this presentation, I will provide several examples on how implantable interfaces can be used to restore sensory (tactile, position and thermal feedback for hand prostheses, vision), motor (grasping, locomotion), and autonomic functions (for type 2 diabetes and cardiovascular problems) and how they can be used also to understand cognitive functions such as language and decision making.

Printed Electrolyte-Gated Transistors for High-Fidelity Transduction of Intracellular Action Potentials in Cardiomyocytes

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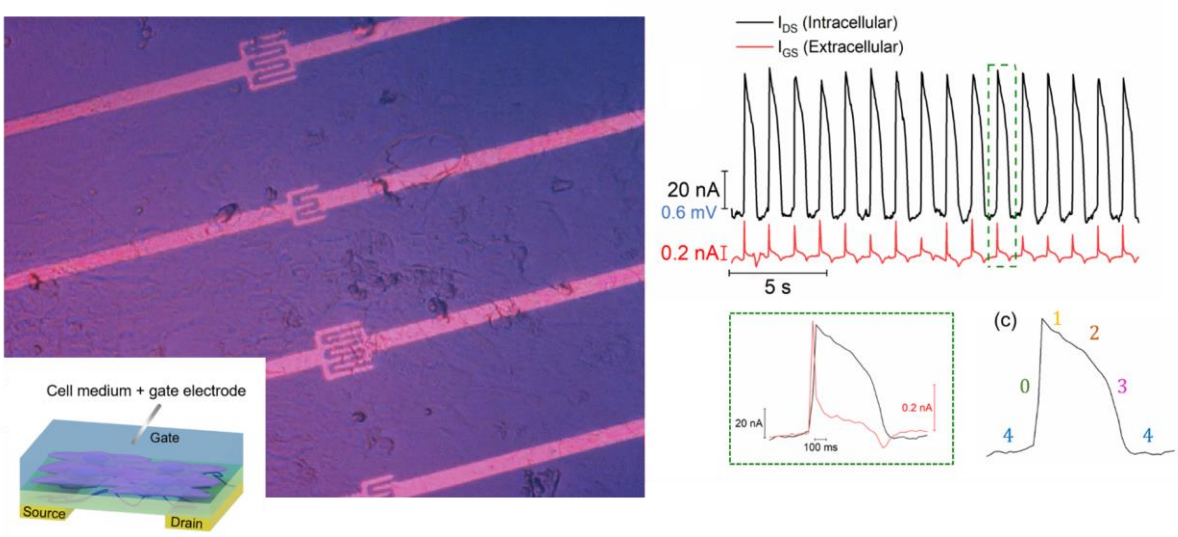
Minimally invasive and high-throughput recording of intracellular action potentials (APs) in electrogenic cells is in high demand. In fact, APs of excitable cells like cardiac cells, skeletal muscle cells and neurons provide crucial information on cells physiology. Most of electrical tools available at present to probe APs are either invasive or require complex manufacturing processes. Achieving a high-fidelity recording with arrays of transducers fabricated with scalable technologies is particular appealing. Here I will first report on the possibility of recording intracellular APs of human induced pluripotent stem cells derived cardiomyocytes with solution processed planar Electrolyte Gated Field-Effect Transistors (EGFETs) based on carbon-nanotubes random networks.[1] Remarkably, despite the planar geometry of the device, we could demonstrate the spontaneous recording of intracellular APs, i.e. without requiring poration procedures. Then, I will report on our more recent findings, where we demonstrate that by replacing the carbon-nanotubes with inkjet printed polymer semiconductors, the transduction can be drastically improved, with recorded signals of patch-clamp like quality, whereas obtained with non-invasive, planar devices. The simplicity of the device combined with the high signal to noise ratio opens up new opportunities for low-cost, reliable, and flexible biosensors and arrays for high quality parallel recording of cellular action potentials.



(Left) Schematic representation of the EGFET transducer and top optical microscopy picture of the EGFETs interfacing human induced pluripotent stem cells derived cardiomyocytes. Adapted from reference 1 (CC-BY 4.0).

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The Faraday Scalpel: precise manipulation of oxygen and reactive oxygen species gradients in biological environment

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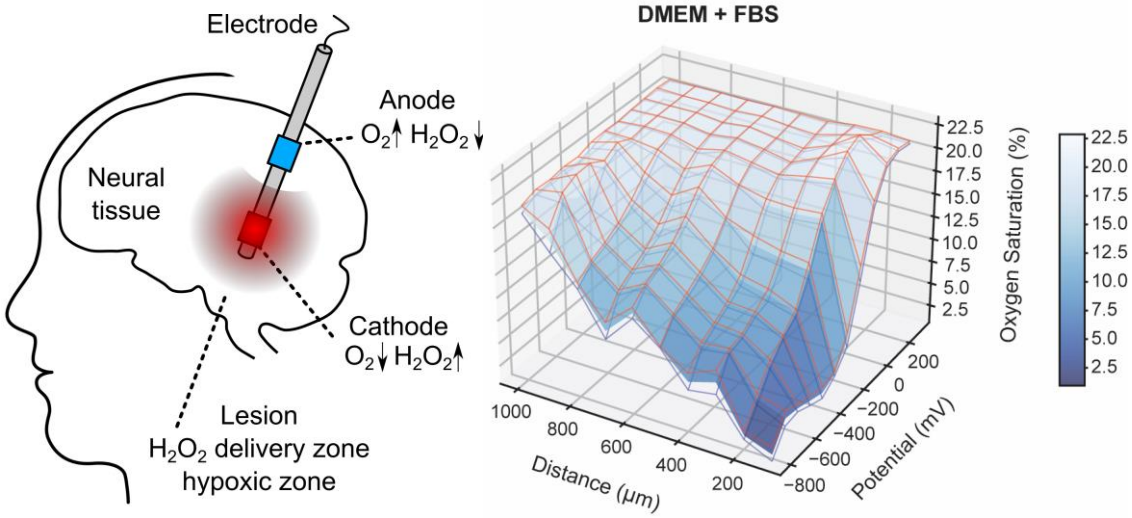
We present the concept of using electrochemical methods to manipulate the levels of oxygen and/or ROS in biological systems. The method relies on the oxygen reduction reaction (ORR). ORR can be tuned to proceed via a 4-electron process, giving hypoxia, or it can be engineered to follow the 2-electron pathway and yield hydrogen peroxide. We show in vitro and in vivo examples of using microelectrode systems to create on-demand hypoxic and/or oxidative stress conditions. Hypoxia can be precisely tuned from normoxic to anoxic levels, depending on electrode geometry and applied electric potential. The two-electron pathway can be turned on by choosing a suitable material. We find that conducting polymers are remarkably good at generating peroxide in biological environments. We demonstrate this method using wired systems, including, as well as wireless variants, allowing precise and remote tuning of hypoxia with micrometric precision. In this presentation, I will showcase the use of Faraday scalpel technology in several use cases: *in vitro* multiwell plate experiments for work with cultured cells, during in vitro electrophysiology experiments, and finally *in vivo* for selective ablation of tissue.



The illustration on the left shows the concept of the Faraday scalpel, whereby electrochemical hypoxia/ROS delivery is used to create lesions in neural tissue. The graph on the right shows how application of constant potential on a clinical PtIr electrode results in a hypoxic zone, which is proportional to distance and to applied voltage. A gradient from full oxygenation (21% tension) to < 2% O_2 is easy to achieve within seconds or minutes.

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Hybrid interfaces between living cells and nanosensors

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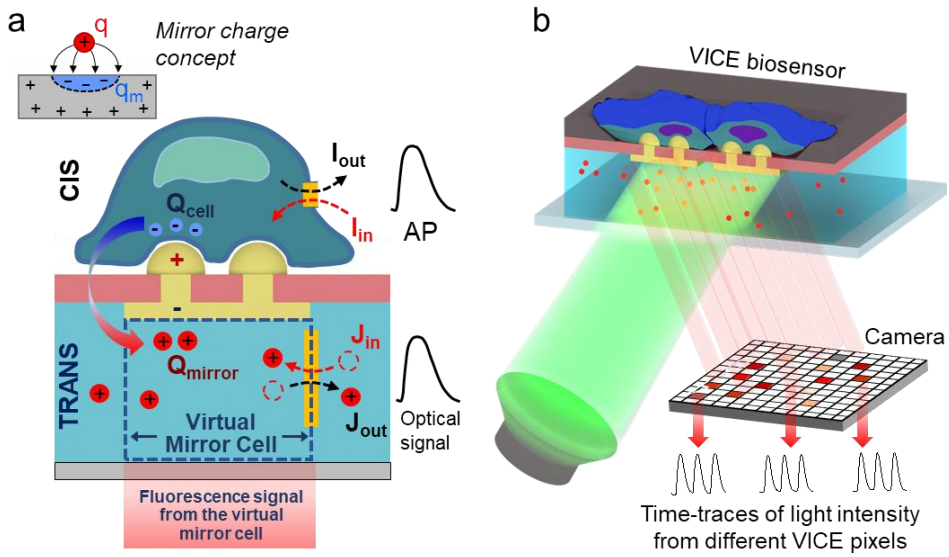
The ability to interact with electrogenic cells and to monitor their status plays a pivotal role in neuroscience, pharmacology and cell biology. We deeply investigated both theoretically and experimentally the interactions of nanostructured surface sensors with living cells such human neurons and cardiomyocytes. The aim is to make an effective interface between the intracellular compartment and different class of nano-sensors including optical sensors for plasmonic enhanced spectroscopies, nanostructured electrodes for electrical measurements and, nano-needles for intracellular delivery or sampling[1-3]. In this regard, we developed a method for opening transient nanopores into the cell membrane with no side effect. After the membrane poration the tip of the sensor is in direct contact with the intracellular compartment thus enabling intracellular investigations which include Raman traces of biomolecules, electrical recording of action potentials of human neurons and cardiomyocites. We demonstrated the possibility of non-invasively testing the effect of relevant drugs on human cells with particular regard of cardio-toxicity that is a fundamental step before the clinical trials. Still in this context, we introduced a radically new concept for monitoring action potentials. It bases on the concept of "mirror charge" in classical electrodynamics (figure 1): electric charges placed in proximity of a conductor affect its spatial charge distribution thus generating mirror charges into the conductor itself. Hence, by monitoring the dynamics of the mirror charges one can monitor the dynamics of the "source charges" and the related electric potential, i.e. the action potential[5,6]. However, being the dyes placed in microfluidic chip, separated from the cell culture, the cells are subjected neither to dye contact, nor to direct light illumination, but are in a perfectly unperturbed physiological state. Remarkably, the optical signal perfectly resembles an action potential even without the need of cell membrane poration as for conventional electrical recording.



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Organic Semiconductor photomodulation enhances maturation of Pluripotent Stem Cells-derived cardiomyocytes

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Cardiomyocytes differentiated from pluripotent stem cells (PSC-CMs) hold a great potential for the study and the cure of cardiovascular disease; indeed they have been extensively used as platform for disease modeling and drugs testing, and represent a promising source of cells for regenerative therapies. However, the immature phenotype of these cells, which differ from adult cardiomyocytes for molecular, metabolic and morpho-functional properties, is a major hurdle for their full application. Recently, a new technology based on optical excitation of light-sensitive organic semiconductors (OS) has been shown to be able to modulate cell behavior of many cell types by targeting different cellular pathways, as proliferation, angiogenesis, neuronal firing and contractility. Here, we adopted a multidisciplinary approach based on morpho-functional, metabolic and transcriptional analyses to investigate the effect of OS-photoexcitation on PSC-CMs. Analyses were performed on PSC-CMs seeded on either glass (control) or a red-light sensitive OS polymer, namely Poly[2,6-(4,4-bis-(2-ethylhexyl)-4H-cyclopenta [2,1-b;3,4-b′]dithiophene)-alt-4,7(2,1,3-benzothiadiazole)] (PCPDTBT), in form of a thin film. Our results revealed a significant modulation of markers of CM maturation in PSC-CMs exposed to PCPDTBT and photomodulation, showing an increased size, altered membrane capacitance, a shift of their maximal diastolic potential (MDP) toward more negative values, and augmented Ca^{2+} transient amplitude. Moreover, by Scanning Electro-Chemical Microscopy (SECM) we found a decrease in glucose uptake and lactate release upon PCPDTBT light stimulation, potentially indicating a switch toward a more adult-like metabolism in stimulated PSC-CMs. Recently obtained RNA sequencing data are in line with these results, and will provide us with hints on the underlying molecular mechanisms.
In conclusion, our data are in support of a potential effect of polymer-mediated optical photoexcitation in boosting PSC-CMs toward a more mature phenotype. We believe that the proposed approach, with a relevant effect on PSC-CM maturation and functionality, will significantly promote their full applications toward personalized medicine applications.

Thermodynamics and kinetics of biorecognition processes investigated with Electrolyte Gated Organic Transistors

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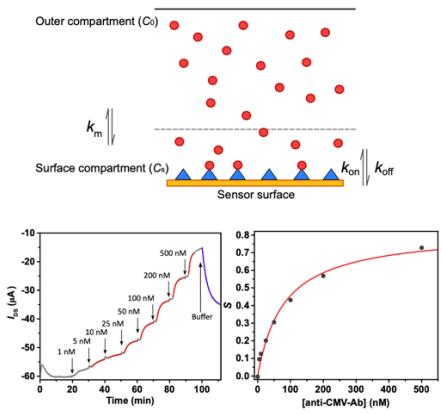
Electrolyte Gated Organic Transistors have proved in the last two decades their potential for bioelectronics-related application, including biosensing. Besides serving as excellent analytical platforms, these devices can also be employed to elucidate fundamental aspects of biorecognition events taking place at one of the relevant device interfaces, typically the one between the gate electrode and the electrolyte solution. As a paradigmatic example, we will report on both steady-state and kinetic measurements of an EGOT sensor operating in a microfluidic flow cell designed to recognize anti-human cytomegalovirus (CMV) antibodies (Abs), featuring a PEDOT:PSS channel and a gate electrode functionalized with the CMV phosphoprotein 65. We not only demonstrate a tool to determine analyte concentration, but, by applying the two-compartment kinetic model analysis, we also investigate both the binding kinetics and thermodynamics of the interaction. We interpret our findings in terms of two co-existing binding site populations, with different affinities toward the target and demonstrate the remarkable sensitivity of the time-dependent experiments carried out with EGOTs to subtleties of the binding kinetics, thus supporting the design of bio(in)organic interfaces for enhancing the sensitivity of biosensing approaches.



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Organic probes all over the electromagnetic spectrum: X-ray contrast agents, photodynamic mediators and optically activated nanoactuators

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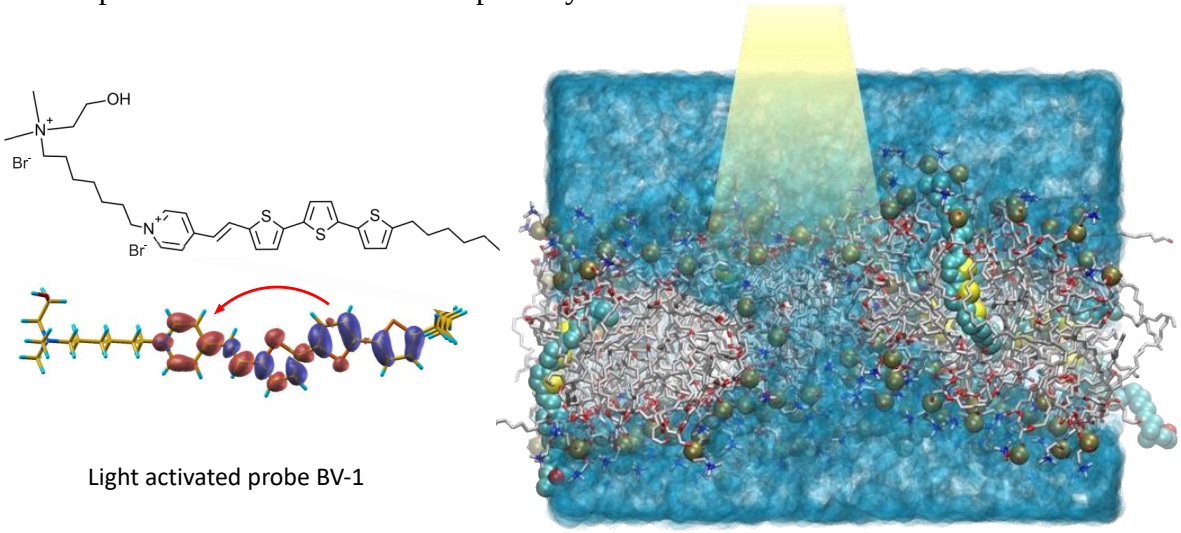
Interaction of electromagnetic radiation with organic molecules gives rise to different phenomena, all of them of interest for imaging and therapy application. Depending on the feature of the organic material and the energy of the impinging radiation organic can behave like contrast agent (X-ray imaging of tissues), fluorescent probes, photosensitizers of reactive oxygen species[1] and – upon photoisomerization and/or redistribution of their electron density – nanoactuators in complex light mediated biological phenomena. Photoinduced modulation of neuronal activity is of particular interest in neuroscience. In addition to the potential represented by optogenetics, research in this field is moving towards the development of nanomachines capable of altering the membrane potential of neuronal cells following light stimulation. The most direct practical application of this type of technology is the development of synthetic retinas capable of restoring photosensitivity to patients suffering from degenerative diseases affecting the photoreceptors present in the eye. I will discuss the design, synthesis and characterization of a family of photosensitive molecules capable of spontaneously localizing into the neuronal membrane. Upon photoexcitation, such derivatives give rise to a complex sequence of phenomena that have two macroscopic consequences on the structure of the neuronal membrane: a membrane depolarization and the formation of pores in the membrane itself.[2] The latter property can be exploited to increase the local permeability of the membrane, providing a much less invasive analogue to the common patch-clamp technique, i.e. the mechanical perforation of the neuronal membrane with special needles. The effects of membrane depolarization and perforation can be discriminated based on the intensity and duration of light stimulation. The same probes can also act as efficient photosensitizers for bacterial photodynamic inactivation.[3]



The figure shows on the left the structure and frontier HOMO orbital of the nanoactuator BV-1 and on the right the simulation of the light induced poration of a lipidic membrane containing BV-1

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Towards real-time dose control during cancer radiation therapies based on full-organic wearable dosimeter

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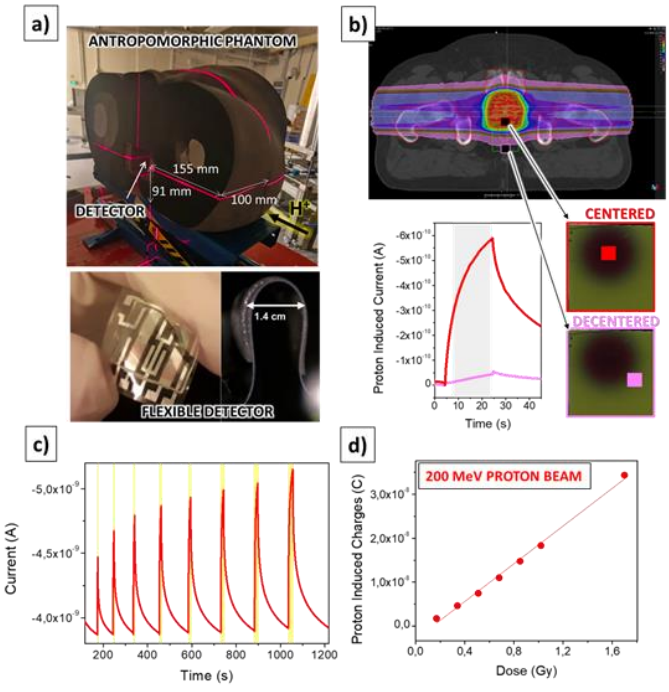
Mechanical flexibility, portability, low cost of fabrication, scalability onto large areas and human tissue equivalence are crucial properties which make organic and hybrid semiconductors excellent candidates for the development of wearable proton dosimeters. Among others, their employment in the medical field (i.e. during proton therapy treatments) to monitor in real-time and in-situ the dose delivered to the patients is extremely interesting. In the last years the scientific community has put big efforts to look for alternative technologies, with the aim to overcome the main limitations presented by conventional materials for dosimetry and to achieve novel functionalitiess requested by cutting-edge applications. We recently reported the results achieved with an innovative fully-organic indirect detector, where a flexible phototransistor (OPT) based on dinaphtho[2,3-b:2′,3′-f]thieno[3,2-b]thiophene (DNTT) is coupled with a plastic scintillator based on polysiloxane (i.e. homopolymer polymethylphenylsiloxane and polyvinylphenyl-co-phenylmethyl). Preliminary tests have been performed at LABEC Ion Beam Center (INFN-Firenze, Italy) under 5 MeV proton beam to mimic the end-of-range conditions typically present at the border of the target during the prostate cancer treatment. To describe the detecting signal, we developed a kinetic model able to precisely reproduce the dynamic response of the device under irradiation and to provide further insight into the physical processes controlling it. To assess this technology as flexible personal dosimeter, the detector has been tested in actual clinical conditions employing an anthropomorphic phantom mimicking the human pelvis, and a therapeutic proton beam provided by the TIFPA proton therapy center (Trento Institute for Fundamental Physics and Applications, TN, Italy) typically employed for prostate cancer treatment (energy in the range [70-200] MeV) (**Fig.a**). The detector has been placed in two different positions in accordance with the Monte Carlo simulation shown in **Fig.b**: (i) centered on the target of the beam (i.e. in the prostate position) and decentered from it, in the region surrounding the tumor (i.e. the rectum which is one of the organs at risk that would benefit from a real-time monitoring of the impinging radiation). The gafchromics reported in **Fig.b** showed the positions of the detector during the tests. The dynamic curve shows that this device is able to monitor in-situ and in real-time the presence/absence of radiation for the accurate recording and mapping of the dose delivered during a treatment plan. Finally, the detector has been characterized as dosimeter when placed centered in the target position under 200 MeV proton beams and, as reported in **Fig.c,d**, it presents dose linearity and provides a stable response even after hard and long-lasting proton irradiation (up to $2 \cdot 10^{10}$ protons, 30 min of operation).



Models of Charge Transport in Polymeric Mixed Ionic and Electronic Conductors

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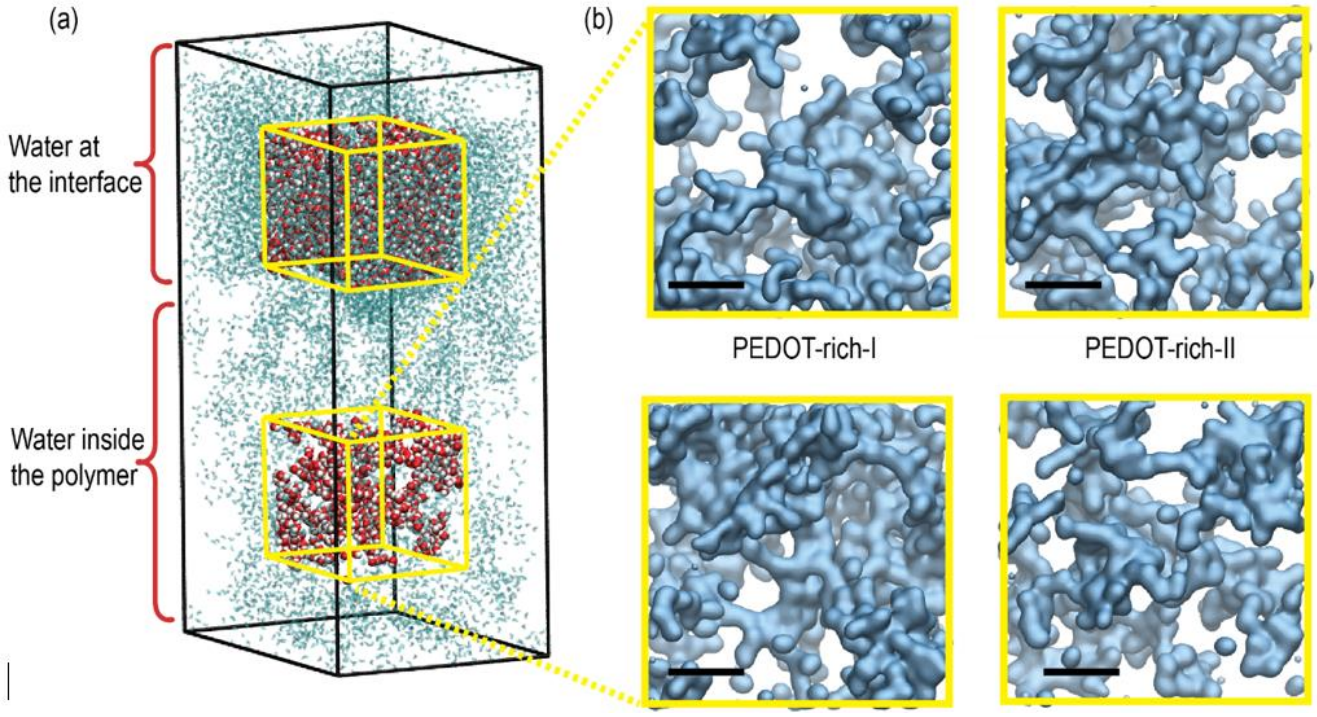
A new model of charge transport in organic polymeric materials with mixed ionic and electronic conduction (OMIEC) is proposed. The excess charge in doped polymers is very mobile and the dynamics of the polymer chain cannot be accurately described with a model including only fixed point charges. Ions and polymer are comparatively slower and a methodology to capture the correlated motions of excess charge and ions is currently unavailable. Considering a prototypical interface encountered in this type of materials, we constructed a scheme based on the combination of MD and QM/MM to evaluate the classical dynamics of polymer, water and ions, while allowing the excess charge of the polymer chains to rearrange following the external electrostatic potential. The study of this model points to a rather new mechanism of charge transport where the electrostatic disorder evolves in time so rapidly that also deep traps are short-lived explaining the concurrent observation of high mobility and large electrostatic disorder.



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New materials and processes for electrochemical transistor design

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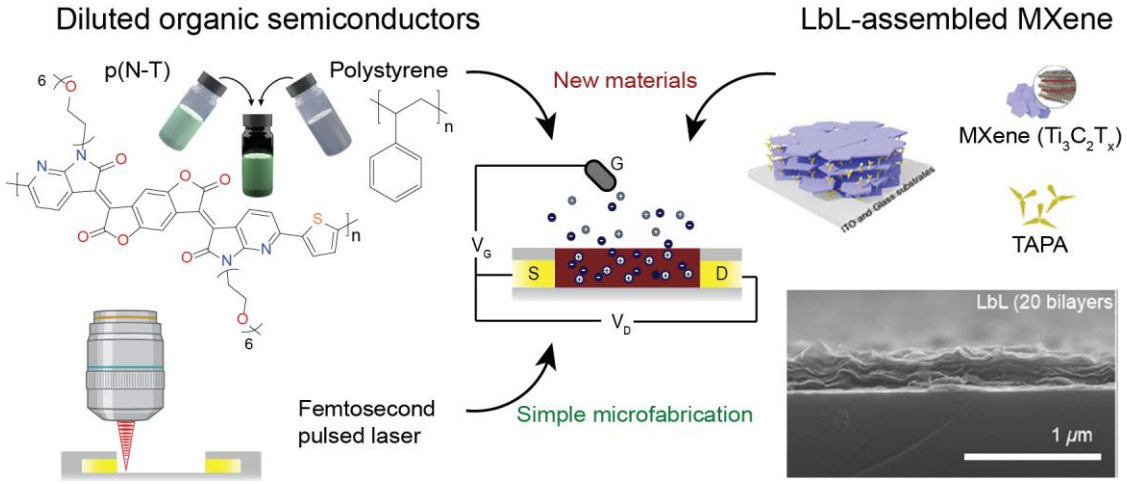
The electrochemical transistor (ECT) offers unique properties in bioelectronic applications ranging from biosensors and monitoring of cellular signaling to biohybrid systems.
ECT operation rely on its core active material – a mixed ionic/electronic conductor in contact with an electrolyte – and the form factor defined by device fabrication. Today, there is rich literature that shows how novel organic semiconductors and high-resolution photolithography can push device performance. However, strategies that combine the performance needed for applications with sustainable material synthesis and patterning are still lacking. To enable the transition from the laboratory to usable products, materials need to be cheap, scalable, and free from toxic precursors. Fabrication methods should enable high resolution while being affordable and allow rapid prototyping. Here, our recent works are aimed at addressing these challenges.
From the materials perspective, we have shown that blending a n-type conjugated polymer p(N-T) with large amounts of insulating commodity polymers (six times more) can improve ECT performance while drastically decreasing the amount of conjugated polymer used in the blend.[1] We found that the improvement in µC* is due to a dramatic increase in electronic mobility by two orders of magnitude, from 0.059 to 1.3 $cm^2\ V^{-1}\ s^{-1}$ for p(N-T):Polystyrene 10KDa 1:6.
To enable rapid device prototyping, we further developed a scalable method based on cleanroom-free polymer patterning using ultrafast focused laser exposure.[2] This approach enabled micrometer resolution while cutting down on the steps needed with conventional manufacturing using photolithography. The utility of this ECT manufacturing approach was demonstrated by fabricating complementary logic (inverters) and biosensors, thereby showing its potential to accelerate ECT research.
Beyond organic semiconductors, we also introduced for the first time 2D materials, such as layer-by-layer assembled MXene, as core components for ECTs.[3] We found that, by controlling the thin film formation of these materials, we can enable percolation of electrolyte ions into the bulk of the film, leading to thickness-dependent capacitance and transconductance similar to what observed for organic semiconductors. This work opens for a new class of inorganic ECTs.



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Graphene acetic acid: synthesis, characterization and implementation into electronic devices towards biosensing applications

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Among graphene-related materials (GRMs), only graphene oxide (GO) and its reduced form (rGO) satisfies the stringent requirements to be successfully implemented in supercapacitors and liquid-gated transistors (LGTs). Here, we present a green and robust protocol for processing a novel derivative of graphene, namely graphene acetic acid (GAA), whose backbone differs from graphene acid (GA)[1] by the presence of a methylene unit between the C sp2 basal plane and the carboxylic groups (-COOH), as shown in the figure. Its satisfactory water dispersibility together with a conductivity similar to the rGO[2] allows one to implement GAA into supercapacitors and LGTs with a straightforward and robust protocol. In particular, a Zn hybrid supercapacitor shows a state-of-the-art capacitance equal to 400 F/g at a current density of 0.05 A/g. Furthermore, the successful fabrication of a liquid-gated transistor (LGT) relies on the deposition of two different GAA layers, namely one placed onto the gate terminal and another one placed onto the interdigitated electrodes (see figure). This type of transistor shows similar performances compared to the rGO-based one,[3] namely V_{DIRAC} > 100 mV (i.e. p-doping), field-effect mobility equal to 10^{-1} $cm^2V^{-1}s^{-1}$ and a potentiometric sensitivity down to 3 mV. Moreover, it boasts a more straightforward fabrication and sound robustness for prolonged measurements (i.e. > 1 h) in an aqueous solution driven by paper fluidics. Sustainability and device throughput are the strongest advantages of exploiting GAA, thereby opening promising opportunities towards biosensors.

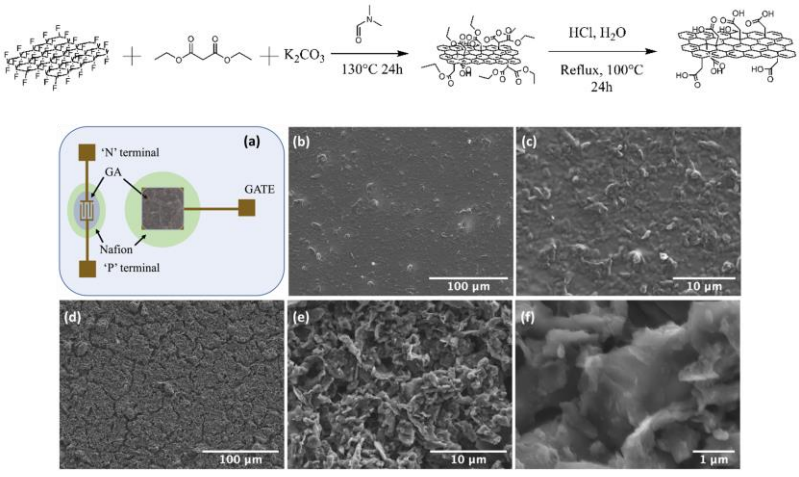

Figure 1 Upper panel shows the synthetic scheme for GAA. **a)** Top view of the GAA-based LGT. **b),c)** show the GAA layer onto the interdigitated electrodes. **d),e),f)** show the GAA coating onto the gate electrode.

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Organic and natural materials for bioelectronics

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Organic electronics offer materials and devices that can be suitable applied in healthcare, biochemical sensing, wearable electronics and drug delivery.
This presentation will showcase various applications developed by our research group in these areas.
Our approach begins with the fundamentals properties of natural materials, applying them on the skin for drug delivery systems, in-vivo wound through animal models, real-time bio-potential monitoring, or biochemical sensing.
I will present prototype devices including a skin-patch made from the silk-extracted cocoons Fibroin/Sericin applied on skin as a patch,[1] for ECG monitoring,[2] a voltage-controllable implantable drug delivery strip, and a calibrated graphene biochemical swab for IL-6 detection in real saliva samples.[3]
Our method focuses challenge of continuous, unobtrusive monitoring of biochemical human parameters. I will show the in-progress work of in-vein / in-vessel prototypal devices within the framework of the EU-funded project IV-LAB.[4]
Finally, I will introduce a new fundamental research direction involving the use of unconventional materials for biosensing and computing applications. Examples will include the use of minimal peptides (proteinoids)[5] and bacterial cellulose,[6] illustrating the different approach behind our research.

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In-situ and *operando* studies of organic mixed conductors: do charges and electrolyte alter the polymer microstructure?

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Polymeric mixed conductors have elicited much interest lately for their ability to translate ionic fluxes into electronic currents. These materials are being considered in a wide swath of applications ranging from bioelectronics to brain-like computing and electrocatalysis. From the fundamental point of view, it is important to consider how these soft semiconductors interact with the electrolyte (the vehicle of ionic fluxes) and how these interactions alter the materials' structure due to swelling. Furthermore, volumetric charging with ions allows the materials to reach high charge densities ($>10^{21}$ cm^{-3}) where charge-induced structural distortions may be pervasive and alter the microstructure. In this talk I will show how using a multi-modal approach that combines optical spectroscopy, x-ray diffraction and TEM, we can unravel these interactions and determine how charge density and electrolyte swelling affect the microstructure and thereby the electronic properties of these materials.

Multiparametric nanocharacterization of electrolyte gated organic transistors in operando

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Electrolyte-Gated Transistors (EGTs) have emerged as an integral part of numerous applications in biosensing and bioelectronics, owing to their remarkable ability to efficiently transduce biological events into amplified electronic signals while stably operating in aqueous electrolytes. Understanding these devices at the nanoscale is paramount to leverage their respective, or combined, functionality for various applications. However, probing the nanoscale properties under operating conditions has been challenging due to the complications arising from the electrolyte environment. In this communication, we will present the progress made towards developing an advanced scanning probe microscopy technique able to probe different functional properties of the semiconductor materials (morphology, electrical, mechanical) at the nanoscale in operating electrolyte-gated transistors (EGTs). The technique is based on in-Liquid Scanning Dielectric Microscopy (in-Liquid SDM)[1] to which we added automated functionalities[2] and multiparametric characterization capabilities for comprehensive and simultaneous probing of the nanoscale electrical, mechanical and morphological properties in operating EGTs. Examples of applications to Electrolyte Gated Organic Field Effect Transistors (EGOFETs)[1-3] and Organic Electrochemical Transistors (OECTs) will be presented.[4]

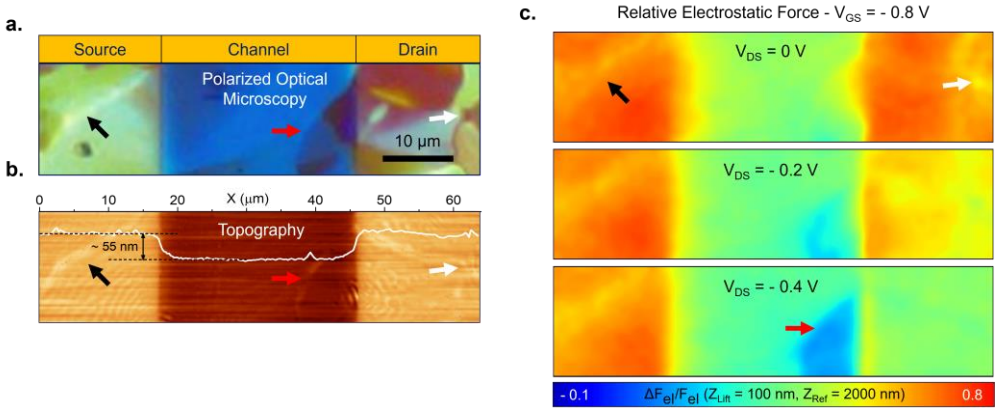

Figure. (a) Polarization light micrograph of an area of an EGOFET transistor. **(b)** AFM topography of the same area with the topographic profile superimposed. **(c)** Relative electrostatic force lift-mode images for V_{GS}=–0.8 V and V_{DS}=0 V, –0.2 V and –0.4 V showing the effect of a grain boundary on the conductivity distribution.

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Transforming antigenic portable technologies into highly dependable screening devices

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The emerging field of ionic and electronic devices for biosensing applications, holds promise for advancing the development of innovative diagnostic technologies. The endeavor to screen asymptomatic organisms, encompassing humans, animals, and plants, through the utilization of point-of-care-testing (POCT) technologies boasting high diagnostic accuracy is both visionary and promising. Efficient surveillance necessitates the development of user-friendly, cost-effective, and highly reliable in-vitro diagnostic devices that are ultra-portable and readily deployable as needed. While such devices are not yet commercially available, there are encouraging advancements at readiness-level 5, notably the Clustered-Regularly-Interspaced-Short-Palindromic-Repeats (CRISPR) lateral-flow-strip tests and the Single-Molecule-with-a-large-Transistor (SiMoT) bioelectronic palmar devices.

These technologies embody essential features as stipulated by the World Health Organization for POCT systems, exhibiting a minimal occurrence of false-positive and false-negative errors (<1-5%) and ensuring diagnostic selectivity and sensitivity (> 95 – 99 %). Furthermore, they offer a low limit of detection for various markers. The CRISPR-strip functions as a molecular assay, capable of detecting even a few copies of DNA/RNA markers in blood, while the SiMoT test can identify single oligonucleotides, protein markers, or pathogens in a minute sample of blood, saliva, or olive sap.

SiMoT single-sensor prototype, comprising a palmar electronic-reader and a disposable bioelectronic-cartridge, will reach TRL7 in a couple of years at most through a clinical-trial kicked-off in February 2024 involving 1.500 assays of peripheral-fluids (urine/plasma/serum) from oncological patients. This effort is conducted within the Apulian Regional Innovation-Center for Single-Molecule Digital-Assay (www.singlemolecule.center), chaired by Torsi, at the "Giovanni Paolo II" Scientific Institute for Research, Hospitalization, and Healthcare, the main oncological hospital in Bari.

The SiMoT technological breakthrough hold the potential to enable systematic and dependable surveillance of asymptomatic individuals prior to the aggravation or spread of illnesses, thereby facilitating timely diagnosis and prognosis. This proactive approach could establish a healthcare ecosystem that delivers effective treatments to all living organisms, fostering widespread well-being at manageable costs.

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Cell-Driven Supramolecular Assembly of Organic Nanofibers

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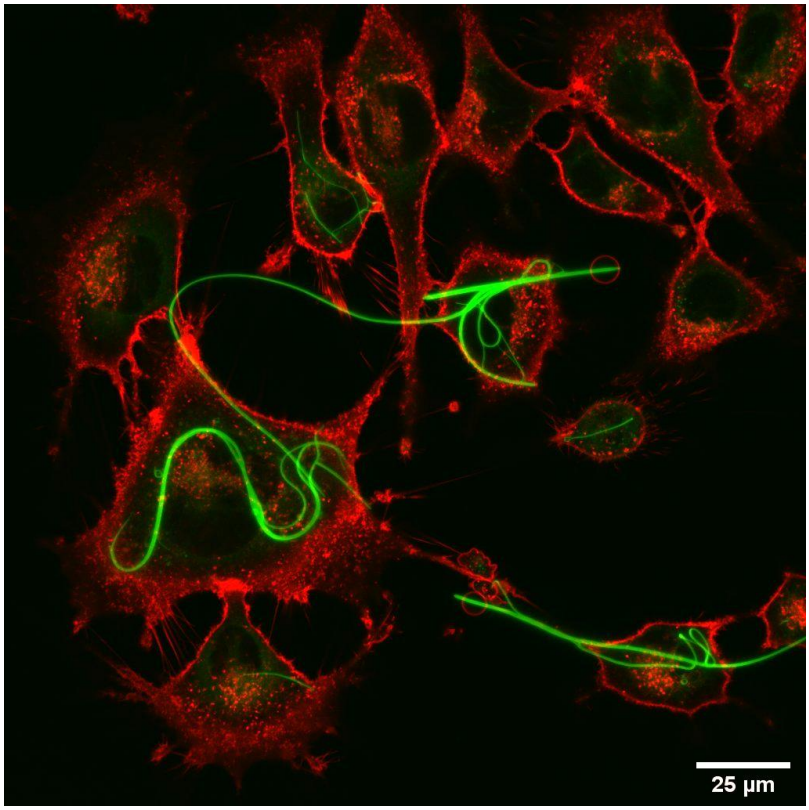
The assembly of supramolecular structures within living systems is an innovative approach for introducing artificial constructs and developing biomaterials capable of influencing and/or regulating the biological responses of living organisms. Here we study the cell-driven assembly of 2,6-diphenyl-3,5-dimethyl-dithieno[3,2-b:2,3-d]thiophene-4,4-dioxide(DTTO) molecules into fibers within living cells[1]. Indeed, X-ray diffraction reveals that cell-grown DTTO fibers present a unique molecular packing leading to specific morphological, optical, and electrical properties. We report mainly on the photophysical characterization of DTTO in fibers[2]. These biomaterials may have disruptive applications in the stimulation and sense of living cells, but more crucially, the study of their genesis and properties broadens the understanding of life beyond the native components of cells.



Confocal microscopy image showing DTTO-fibers grown within C2C12 cells. Sometime the fibers cross the barrier connecting adjacent cells.

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Polyhalogenated Thiele hydrocarbons: a promising tool for NIR-emitting optoelectronic devices

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Efficient electroluminescent devices operating in the first biological transparency window (650-900 nm) are essential for bioimaging and biosensing applications.[1] In this context, inert polyhalogenated triphenylmethyl radicals (PTMs) have emerged as the most promising metal-free materials for organic electroluminescence in the near-infrared (NIR) region.[2] However, free radicals often face issues related to the presence of an unpaired electron.[2] An alternative is singlet diradicaloids (SDs), which are molecular compounds with two unpaired electrons in an open-shell configuration that couple antiferromagnetically, resulting in a singlet spin state. Their significance in organic chemistry stems from their unique electronic configuration, leading to intriguing magnetic, optical, and conductive behaviors. A prominent group of SDs is para-quinodimethanes (pQDMs).

By utilizing polychlorination as a synthetic tool, we successfully stabilized the Thiele hydrocarbon, creating a new species named TTH (Figure 1).[3] TTH exhibited intense photoluminescence, NIR emission, and solvatochromic properties. Using transient spectroscopic techniques and supported by multireference quantum-chemical calculations, we demonstrated that this emission arises from a zwitterionic doubly excited state. For the first time, we tested this derivative as an emitter in an n-type organic light-emitting transistor (OLET) (Figure 1), showcasing the great potential of this class of emitters in organic optoelectronics.

Additionally, we are investigating the structure-property correlations of these molecular materials. While previous studies focused on the influence of para-halogens on the electro-optical properties of Thiele hydrocarbons,[4] our current work explores the effects induced by structural variations. We synthesized new polyhalogenated Thiele hydrocarbons with different halogenation patterns to highlight the relevance of molecular geometry on the photophysical properties of these derivatives, thereby providing fresh insights into the molecular design of SDs.

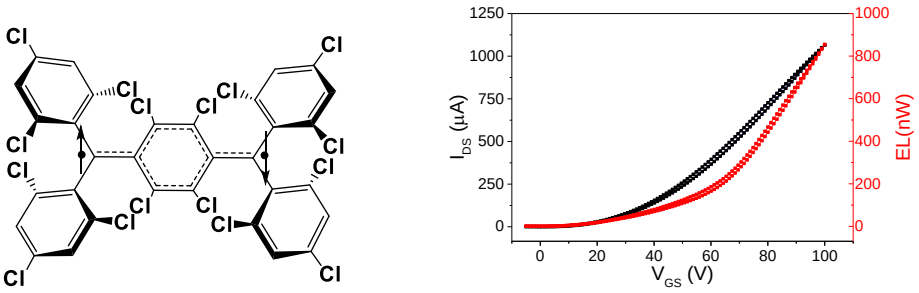

Figure 1:(left)molecular structure of TTH; (right) Saturation transfer n-type curve of TTH-OLET.

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Graphene-organic nanocomposites for electronic applications

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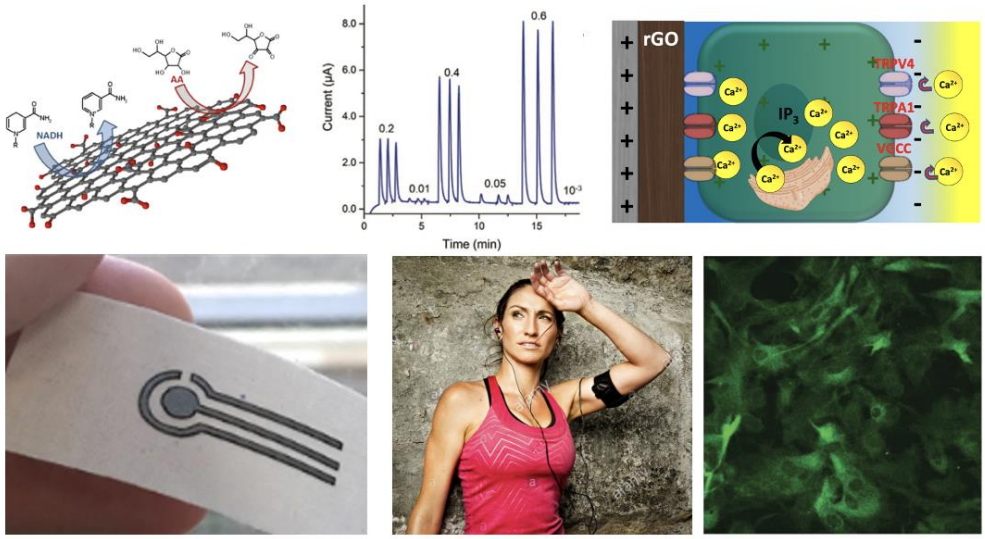
Graphene-based nanosheets are a recent addition to our materials for carbon-based electronics. Produced on the ton scale by exfoliating graphite, they can be chemically modified and processed in solution to yield charge mobility or conductivity on par with, or better than, other organic conductors.
Here, I will present some of the latest results that we obtained using graphene-based materials for various electronic applications:

- 2D-3D nanocomposites for AI-powered chemical sensors. [1–5]
- "Janus" graphene-organic composites for sodium-ion batteries. [6]
- Laser-patterned electric circuits and sensors in graphene-polymer composites for automotive use.[7]
- GO-RGO electrodes for brain cell electrical stimulation. [8]



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Organic optoelectronic smart-integrated and multifunctional devices for optical biosensing and brain-inspired computing

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Organic electronic and optoelectronic devices might enable the definition of new miniaturized detection schemes to boost the advent of compact sensors for on-site analysis, given their inherent structural versatility and capability of smart monolithic integration in nm-thick multi-stack devices on almost any surface [1]. When combined with neuromorphic computing, organic devices could represent the next generation of bioelectronics. Ranging from point-of-care systems and biosensing to implants and prosthesis, organic devices could be capable of sensing, computing, and regulating in situ in a biologically relevant way.
However, challenges such as monolithic integration, fabrication scaling, and long-term stability must be addressed before the development of these closed-loop and self-adapting systems. Moreover, the physical separation of sensors and processors in conventional architectures leads to an inherent bottleneck when moving data.
In the first part of this talk, we report the integration of organic light-sources and -detectors (such as light-emitting diodes and transistors, and organic photodiodes) into ultra-compact systems for plasmonic- and fluorescence-based detection without the implementation of bulky optical components. Suitable nanostructured bidimensional plasmonic photonic components (such as nanoplasmonic grating and Distributed Bragg Reflector, respectively) are implemented for enabling and improving the sensing capabilities [2]. The components and the layout of integration were suitably designed to make the elements work cooperatively in a reflection-mode configuration. In particular, the organic photodiode was vertically stacked onto the source electrode of an organic light-emitting transistor thus providing electrical switching, light-emission and light-sensing capability in a single organic multilayer architecture [3]. We demonstrated remarkably low sensor size as low (0.1 cm^3) regardless the optical detection modality, while providing (i) a quantitative and linear response that reaches a limit of detection of 10^{-4} refractive index units for surface-plasmon resonance (SPR) [4] and (ii) significant increase of the signal-to-noise ratio allows for halving the detection limit to 9.2 μM for a relevant fluorescent-dye detection [5].
In the second part of the talk, we report the engineering of all solution-processed organic phototransistor capable of providing a dual-mode optoelectronic synapse. The device, comprising the ferroelectric terpolymer as the dielectric layer, and a radical-based bulk heterojunction as photoactive layer, enables modulated neuroplasticity: while only short-term plasticity is mimed with blue light excitation, short-term and long-term plasticity characteristics are recorded under near-infrared light. Moreover, the combination of both the electrical and optical stimuli not only enables long-term plasticity also under blue-light excitation but also can be effectively used to mimic the dendrite-like nonlinear integration of inputs observed in neurons.
Such multifunctional and multi-stimuli organic devices are expected to be unique components for in-memory computation in sensor-rich systems such autonomous vehicles, wearable electronics and miniaturized biodiagnostics.

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Self-Healing, stretchable and recyclable electronics

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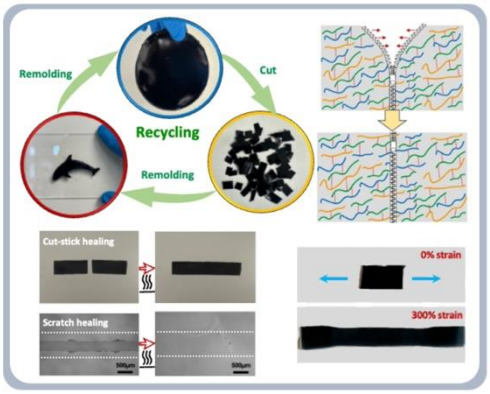
Materials able to regenerate after damage have attracted a great deal of attention since the ancient times. For instance, self-healing concretes, able to resist earthquakes, aging, weather, and seawater are known since the times of ancient Rome and are still the object of research.

While several mechanically healable materials have been reported, self-healing conductors are still relatively rare, and are attracting enormous interest for applications in electronic skin, wearable and stretchable sensors, actuators, transistors, energy harvesting, and storage devices, such as batteries and supercapacitors.[1] Self-healable and recyclable conducting materials have the potential to reduce electronic waste by enabling the repair and reuse of electronic components, which can extend the lifespan of electronic devices. Furthermore, they can be used for wearable electronic and biomedical devices, which are often subject to mechanical stress causing damage to their components.

Conducting polymers exhibit attractive properties that makes them ideal materials for bioelectronics and stretchable electronics, such as mixed ionic-electronic conductivity, leading to low interfacial impedance, tunability by chemical synthesis, ease of process via solution process and printing, and biomechanical compatibility with living tissues. However, they show typically poor mechanical properties and are therefore not suitable as self-healing materials.
In our group, we produced several self-healing and stretchable conductors by mixing aqueous suspensions of the conducting polymer poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) with other materials providing the mechanical characteristics leading to self-healing, like for instance polyvinyl alcohol (PVA), polyethylene glycol, polyurethanes and tannic acid. [2-10] In this talk, various types of self-healing will be presented and correlated with the electrical ad mechanical properties of the materials. The use of the self-healing gels and films as epidermal electrodes and other devices will be also discussed.



Conductive materials obtained from blends of polyurethane-PEDOT:PSS and PEG showcase exceptional stretchability, toughness, and self-healing properties. Moreover, these materials can be recycled several times and maintain their mechanical and electrical properties.

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Neuromorphic Organic Devices for Translational Neurosciences

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Neuromorphic Organic Devices (NODs) operated in the liquid environment are subject to extended investigation as bio-sensors - since their temporal evolution is ultimately dictated by the composition of the operational environment[1] - and as processing units, performing low-power signal pretreatment in real time thanks to their selective response to frequency.[2,3] The synergy between the aforementioned sensitivities, namely to chemo-/bio-signals and to temporal evolution of the electrolyte potential, make NODs the most promising technological candidates to approach the multi-faceted task of achieving bidirectional exchange of information with neural tissue, especially considering the inherent match between the response timescales, the chemical identity of the charge carriers and the notable analogy between the logic paradigms. Despite this, the integration of NODs in neuroelectronic interfaces designed specifically for translation to clinics poses pratical, ethical, regulatory and conceptual hurdles which should be addressed, from both sides of the biotic/abiotic interface. Scope of this talk is to discuss these critical issues and to present some of the possible strategies for overcoming them, hoping to trace a useful vademecum for translational NODs development.

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Double Gated Organic Thin Film Transistor for Tactile Sensing

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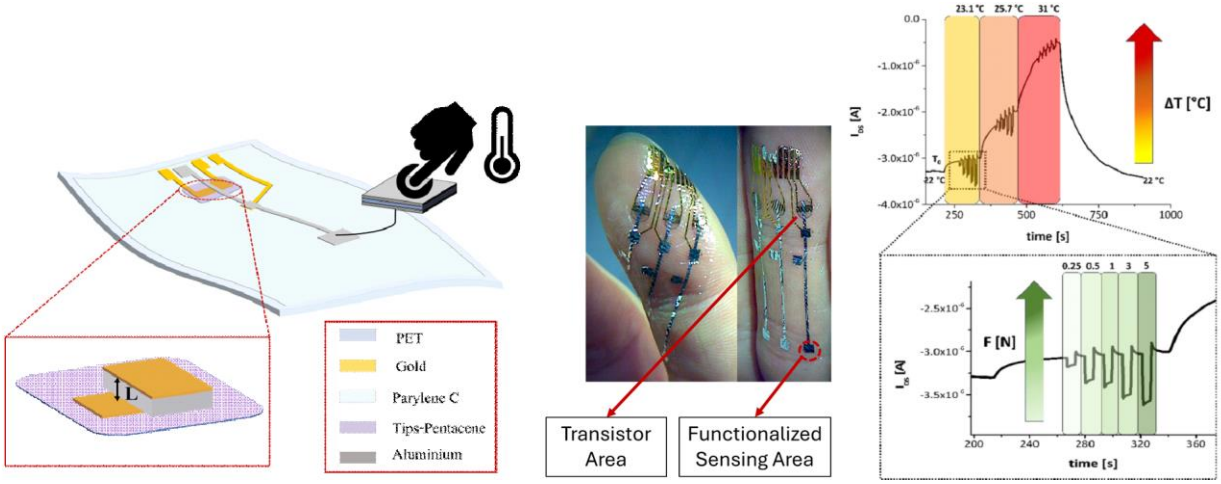
The realization of an artificial tactile sensing system is very challenging as requires the integration of different types of sensors into one system that should cover large and complex areas, while keeping fabrication costs low. In this respect, organic electronics represents a step forward.
In this presentation, after revising some of the approaches reported recently in the literature, I will demonstrate that the employment of double gate organic transistor could be a valuable solution for the fabrication of flexible and highly sensitive multimodal tactile transducers.
In the first example we report the employment of a flexible sub-micrometer channel Organic Charge Modulated Field Effect Transistor (OCMFET) coupled with a pyro/piezoelectric element (i.e. a poly-vinylene difluoride (PVDF) film) for the fabrication of highly sensitive multimodal tactile transducers capable to simultaneous detect temperature and force. The reduction of the channel length, obtained by employing a low-resolution vertical channel architecture, allowed to maximize the ratio between the sensing area and the transistor's channel area, a technological approach that allows to considerably enhance both temperature and force sensitivity, while at the same time minimize the sensor's dimensions.
In a second example I will introduce a stacked double gated transistor structure, that allowed us on one side to dramatically reduce aging effects due to environmental exposure of the active layer and, on the other side to finely tune transistor threshold voltage by playing with the second top gate electrode. This architecture has a great potential in the fabrication of different kinds of sensing systems. I'll demonstrate that by coupling such device with pyro/piezoelectric element, it is possible, also in this case, to obtain highly sensible and stable multimodal tactile sensors.



Schematic representation and picture of a conformable multimodal tactile sensor (left)and its response to temperature and force (right)

Innovative sensing devices for biosensing applications

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In this contribution, I will summarize some ongoing activities in Naples concerning the detection of biomolecules, through the use of organic electrochemical transistors (OECT)[1-3] and screen-printed electrodes (SPE), as well as the development of pressure sensors of interest for biological applications. In particular, the response of Aerosol Jet-printed OECT based on PEDOT:PSS active channels were tested in presence of either reduced (free) and oxidized Homocysteine (Hcy)-based solutions[3] and compared with conventional techniques. In our study, two experimental protocols were followed: the former relying on gold (Au) electrodes' biothiol-induced thiolation, while the latter simply using bare platinum (Pt) electrodes in the presence of albumin-bound Hcy, with this being, physiologically, the most abundant oxidized Hcy-form in circulation. OECT were found to display final limit of detection (LoD) values of 80 nM and 180 nM, respectively, for Au- and Pt-gated devices. Moreover, we demonstrated the possibility to detect Transglutaminase 2 (TG2) down to attomolar concentration by OECT driven by gold electrodes functionalized with anti-TG2 antibodies. We observed a direct correlation between the TG2 concentration and the transistor transconductance values. Overall, our findings highlight the potentialities of this new biosensing approach for the detection of TG2 in the context of pathological diseases, offering a rapid and cost-effective alternative to traditional methods

SPE is a robust technique where electrodes offer advantages in terms of being versatile, economical and easy to use. We have fabricated SPE devices on a flexible PET substrate, equipped with gold working (circular, 4 mm diameter) and counter electrodes and silver electrode references. Two types of devices, made on two different substrates in polyester terephthalate (PET and double-matted PET), were considered. In detail, the two electrode configurations have been characterized by standard electrochemical methods (CV, EIS), showing performances comparable to those of commercial SPEs. Upon completion of this characterization, the SPEs under analysis will be functionalized for the development of a biosensor.

Finally, we will report about a comprehensive system consisting of gloves equipped with 12 tactile sensors strategically positioned for data acquisition, along with a radio frequency module for wireless data transmission that can be of interest for many applications including biomedical ones[4]. The sensors were subjected to a sterilization process being also treated with two different bacteria (B. Subtilis; P. Fluorescens) and subsequently cleaned with a hydrogen peroxide solution. We checked the impact of the sterilization process on the sensors response and, more specifically, we found that the piezoresistive performances were not affected by the treatments.

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Organic neuromorphic biointerfaces

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The replication of neural information processing in electrical devices has been extensively studied over the years. The paradigm of parallel computing, which allows information to be simultaneously detected, processed, and stored, is required for numerous applications in many fields. In the case of brain-computer interfaces, another important requirement is the suitability of the device for communication with cells. Organic electrochemical transistors (OECTs) based on PEDOT:PSS are used for this purpose due to their ionic-to-electronic signal transduction and biocompatibility. Many works have demonstrated the reproduction of neural plasticity mechanisms, such as short-term facilitation and long-term potentiation. In each device, the physical mechanism of transduction may be different, but it is known that the electrolyte plays a key role in the functioning of these devices, as it provides the ions responsible for the chemical transmission of information. Focusing on long-term memory, this can be reproduced in the OECTs with the oxidation of the neurotransmitter, as in the case of the biohybrid synapse. It is crucial to understand the influence of the material chemistry, electrolyte composition and neurotransmitter-mediated memory effect of the device, as long-term modulation is based on a change in the ionic balance between the electrolyte and the organic polymer.

This electrolyte composition (*i.e.,* bioegel) and neurotransmitter-dependency plasticity will be discussed also to consider the use of neuromorphic OECTs to be interfaced with living neurons to establish biohybrid synapses and neuronal networks. In fact, neurohybrid interfaces can be achieved through bidirectional closed loop communication with various neurotransmitters such us dopamine and glutamate.

Furthermore, I will discuss how conjugated polymers can be engineered with azopolymers (opto-sensitive polymers which switch from cis to trans conformation upon certain light exposure) to feature diverse optoelectronic short- and long-term plasticity, enabling the use of creating functional biointerfaces with living neurons. In fact, conductive polymers and light-sensitive surface coating can also enable electromechanical coupling with neuronal cells, enhancing the cell-chip coupling at different scales. These biomimetic materials will enable a new class of bioelectronic device used for neuronal interfaces towards their application in implantable probes.

Graphene-Based Transistors as Biological Sensors to Monitor the Activity of a CRISPR/Cas for the Detection of Nucleic Acids

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RNA detection is a crucial step in the identification of viral or bacterial infections in humans and animals.[1] To date, the Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) remains the gold standard for RNA detection and identification, however this method suffers from a major drawback: the potential reduction of selectivity due to its extreme sensitivity to experimental conditions (temperature, incubation time and ionic strength) which are not always trivial to control; in addition to that, RT-PCR also requires heavy and expensive machines to be performed.[2] Clustered Regularly Interspaced Short Palindromic Repeats associated to Cas endoribonuclease particles (CRISPR/Cas) have recently revolutionised the recognition step of two RNA types i.e., the CRISPR-RNA and the target, because they provide much better selectivity compared to the naked hybridisation on which RT-PCR is based.[3] In this study, we combine the high sensitivity of a CRISPR/Cas system (CRISPR/Cas13a) with the transduction and amplification capabilities of an Electrolyte-Gated Graphene Field-Effect Transistors (EGGFETs) for the detection of specific nucleic acid sequences. In these devices, fabricated on flexible plastic substrates, the transistors' active material (reduced Graphene Oxide – rGO) is deposited by additive printing techniques. The rGO is then functionalised by using Au nanoparticles decorated with polyU RNA strands immobilised by thiol-gold linkage.[4] In this system, the CRISPR/Cas13a complex works as the target analyte: in the presence of a specific RNA sequence, the enzymatic function is activated and the polyU RNA strands are cleaved from the Au nanoparticles, inducing a loss in negative charges to the rGO layer. This phenomenon results in measurable modifications of the transistors' electrical parameters (such as, for instance, the Dirac voltage). The working principle of our devices is schematically depicted in the following Figure 1.

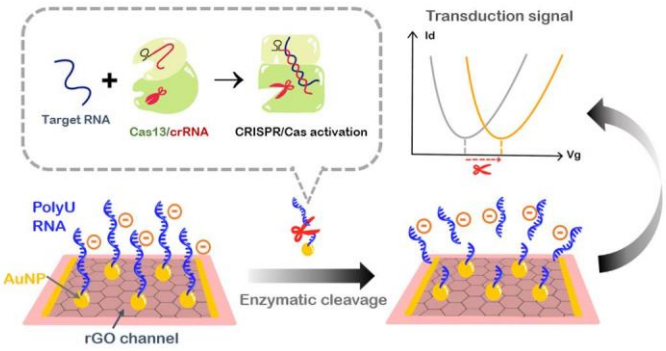

Figure 1. Working principle of our sensors based on EGGFETs exploiting the enzymatic activity of the CRISPR/Cas complex.

Our sensors were tested for the detection of Sars-CoV-2 RNA and exhibited a linear response in the range 10^{-7} – 10^{2} ng.µL^{-1} with a Limit Of Detection (LOD) which can be roughly estimated at 10 fM. This work is an important milestone for the development of the next generation of point-of-care RNA sensors.

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Recent advances in iontronic drug delivery

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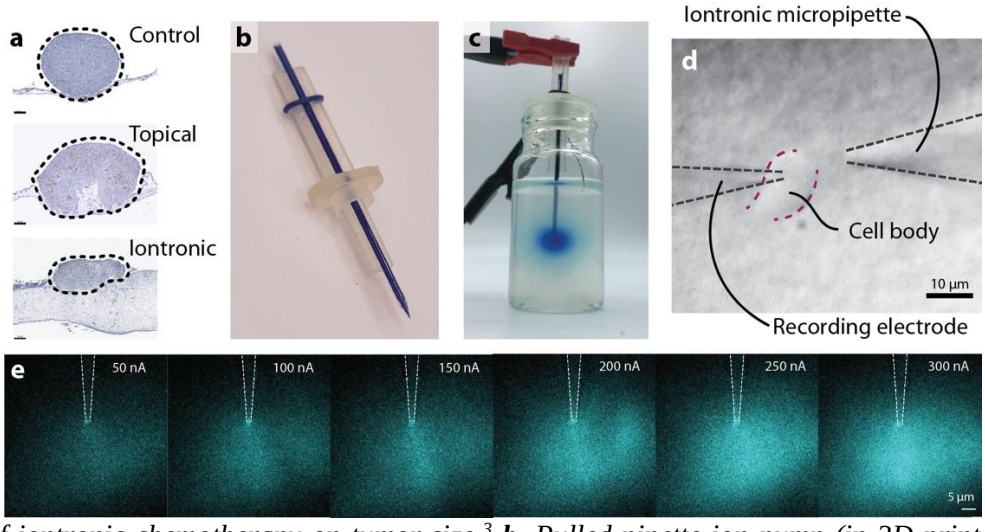
Over the past decades, our group has developed so-called iontronic drug delivery, most notably exemplified by the organic electronic ion pump.[1] Ion pumps, and other such iontronic devices, convert electronic addressing signals into precise electrophoretic transport of charged substances (*e.g.*, signaling ions, drugs, neurotransmitters, plant hormones) from a liquid or gel reservoir through thin organic polymer films out to a target region (*e.g.*, tissue, cells). The result is electronic control of dosage with high spatiotemporal resolution and without requiring liquid flow.

Over the past couple of years, we have been focused on advancing iontronics with new capabilities and application areas. These efforts have been focused along multiple tracks: (*i*) enabling delivery of significantly larger substances, such as pharmaceutical molecules or even proteins, using click-chemistry; (*ii*) boosting performance (*e.g.*, dose precision) through rational design of the core ion-exchange materials; (*iii*) developing single-cell scale delivery/stimulation via a pulled-pipette format;[2] and (*iv*) expanding our focus on cancer therapy.[3]

In this presentation, I will detail our efforts in these directions, the materials and methods that have gotten us to where we are today, and our various application areas *in vitro*, *in vivo*, and even in plantae. I'll conclude with our vision of an "iontronics-enabled" future and our efforts to get there.



***a**, Effect of iontronic chemotherapy on tumor size.[3] **b**, Pulled-pipette ion pump (in 3D-printed holder). **c**, Delivery of methylene blue into tissue-mimic gel. **d**, Single-cell ion pump experiment.[2] **e**, Dye-enabled visualization of K^+ delivery based on varying iontronic currents.[2]*

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Organic electrochemical neurons for closed-loop bioelectronics

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Future brain-computer interfaces will require electronic circuits capable of localized and highly individualized signal processing within living tissues and the nervous system. Traditional silicon-based neuromorphic systems face several challenges in bio-integration due to poor biocompatibility, circuit complexity, and low energy efficiency. Emerging bioelectronic technologies, such as those based on organic electrochemical transistors (OECTs), offer a solution to these limitations. OECTs can strongly couple ions and electrons, enabling efficient signal transduction and making them an ideal platform for interfacing electronics with biological systems. This presentation will explore the use of OECTs to develop organic electrochemical neurons (OECNs) with ion-mediated spiking. These devices, which mimic the dynamics of biological neurons, can efficiently transduce sensory information, proving their potential for high-frequency, low-energy neural interventions. OECNs can achieve firing frequencies up to 500 Hz with energy consumption as low as 120 pJ per action potential, making them comparable to biological neurons. This innovation could lead to next-generation closed-loop implantable devices for neurological disorders, offering enhanced functionality and improved long-term safety.

Plant bioelectronics for decoding and stimulating plant signaling

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The climate change and growing population calls for plants with increased tolerance to stress and plants with higher productivity. In my group we develop bioelectronic tools with the aim to overcome limitations of conventional methods but also to enable new possibilities. Electrical signals are mediators of long-distance signaling and correlate with plant movements and responses to stress. These signals are studied with single electrodes that cannot resolve signal propagation and integration, thus impeding their decoding and link to function. We developed conformable multielectrode arrays based on organic electronics for large-scale and high-resolution plant electrophysiology[1]. As a model system we studied the generation and propagation of the action potential in Venus flytrap, revealing key properties of this signal. With this work we also establish the capacity of organic bioelectronics for resolving electrical signaling in plants contributing to the mechanistic understanding of long-distance responses. Apart from monitoring electrical signals, in another work we developed a bioelectronic platform that stimulates plant growth in hydroponics. We demonstrated that Barley grows well within the bioelectronic platform and when stimulated, the biomass increased by 50%[2]. This work opens the pathway for enhancing plant growth in hydroponics using bioelectronics, that may result in more sustainable food production.

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Organic Artificial Neurons and Bioelectronic Systems for Biointerfacing and Sensing

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Organic bioelectronics enable direct communication and interfacing with ions, biomolecules, soft tissues, cells, and organs within the aqueous biological environment, creating opportunities for both in-vitro and in-vivo applications. This presentation will cover organic electrochemical transistor technologies and device architectures,[1] bioelectronic circuits[2] and point-of-care diagnostic systems[3]. Beginning with the properties of organic transistors operating in a liquid environment, the talk will then explore various applications such as high-sensitivity ion detection and amplification,[4,5] real-time monitoring of cellular barrier functionality,[6] selective multi-bio-marker detection systems capable of single-molecule identification,[7,8] and artificial spiking neurons with electrobiochemical control for in-situ neuromorphic sensing and biointerfacing.[9,10] The presentation will highlight the achievements from my collaborative journey with diverse multidisciplinary and geographically-distributed research groups, showcasing the potential for next-generation intelligent bioelectronics and neuromorphic biointerfacing.

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Smart Bandaid for Real-Time Monitoring of Wound Healing

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The wearable technologies market has seen exponential growth in recent years, and this trend is expected to continue in the coming years. However, in the context of wound monitoring, there is still a lack of quantitative and minimally invasive tools for managing the healing process. Hard-to-heal wounds are often associated with particular pathologies or afflictions such as diabetes, immunodeficiencies, compression traumas in bedridden people, skin grafts, or third-degree burns. The study of the wound healing process is also of great interest for monitoring the health of astronauts, as exposure to microgravity has been shown to alter the wound healing process. In these situations, it is critical to constantly monitor the healing stages and overall wound conditions without removing the bandage and disturbing the wound bed. The approach that we propose is the integration of fully biocompatible textile sensors in the bandage, to directly gain real time information on relevant parameters correlated to the wound status.

In this contribution we describe the realization of three sensors, obtained by screen printing poly(3,4-ethylenedioxythiophene):poly(styrene-sulfonate) (PEDOT:PSS) on a medical gauze, in the desired configuration, to monitor the moisture, the pH and uric acid concentration of wound exudate. Moisture is a relevant parameter since a low amount of exudate can desiccate the wound, while a high level will lead to maceration. pH and uric acid concentration are important biomarkers related to the wound health status, since their value can be correlated with infections or necrotization processes.

The textile sensors are combined with other medical grade dressings with different absorption properties, thus leading to a final smart bandaid ensuring the delivery of a continuous wound exudate flow across the sensor area.

The moisture sensor, that exploits the intrinsic electrochemical properties of PEDOT:PSS, operates in real time by monitoring impedance variations that span over several orders of magnitude between dry and wet states. The sensor is directly integrated with an RFID chip, implementing a real-time wireless monitoring. [1]

The pH two terminal sensor, realized by embedding iridium oxide particles in PEDOT:PSS exhibits a reversible and fast response in the medically relevant pH range for wound monitoring (pH 6-9).[2]

The sensor for UA is based on all PEDOT:PSS OECT and it can reliably and reversibly detect UA concentration in synthetic wound exudate in the biologically relevant range of 220−750 μM.[3]

Thanks to the careful selection of the textile materials and to the compactness of the final assembly, as well as the robustness of the sensing elements and transduction mechanisms, the smart dressings showed excellent resiliency to mechanical deformations and temperature variations.

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Developing a bioelectronic tool for analytical purposes based on organic technology: constraints and opportunities

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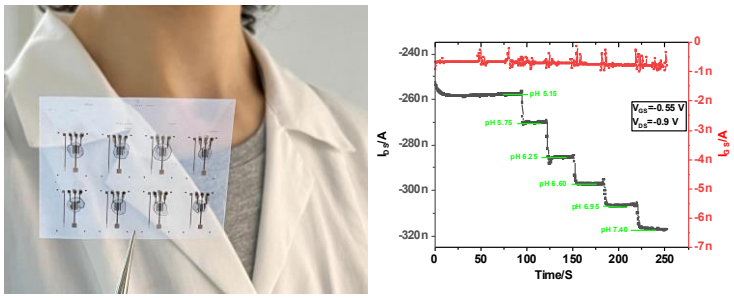
The development of a bioelectronic tool for analytical purposes requires a careful analysis of limits and constraints related to material properties and device mechanisms. In this contribution we will explore several aspects related to the use of organic technology for sensor applications. The proposed sensors are designed to detect and analyze biological signals with high precision, offering a novel approach to monitoring physiological and biochemical processes. We will analyse the use of different organic materials to obtain sensitive, flexible, biocompatible, reproducible devices, with the primary intent of creating tools that can be exploited in realistic real-life scenarios. Our approach demonstrates the potential of organic bioelectronics to enhance analytical capabilities in various biomedical applications, paving the way for innovative diagnostic solutions for modern healthcare, but at the same time, shows what are the limits and the factors that should be taken into consideration when addressing the most important open scientific questions that are still present in this field.



This figure shows something representative about the topic presented. Any scales or legends should be easily readable.

To print or not to print? Two approaches to thin wearable sensors

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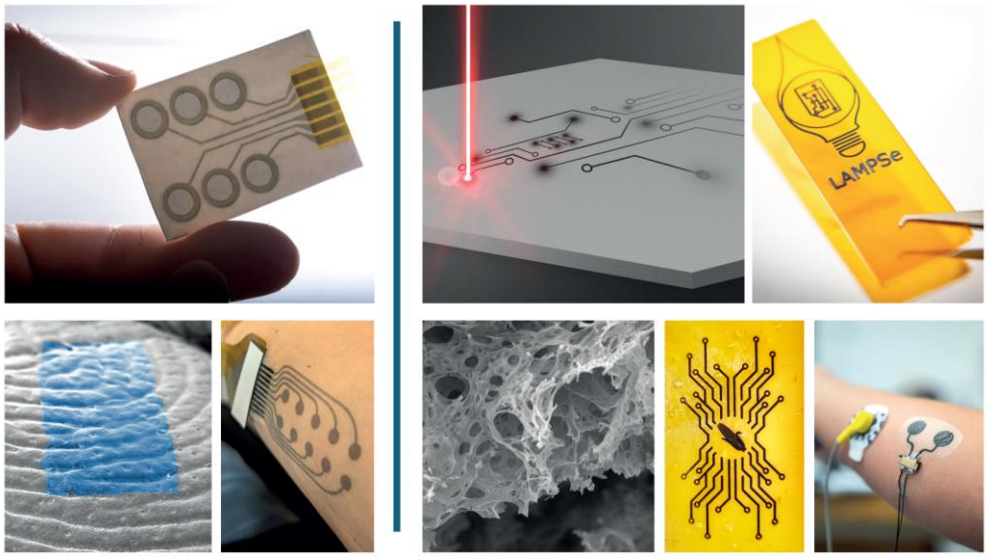
The deposition and patterning of soft conductive materials on thin, flexible, conformable substrates is utilized to create nearly invisible skin-contact sensors for health and personal monitoring purposes. In this talk I will introduce and compare two distinct methods: I) printing of conjugated polymers and II) direct laser writing of conductive carbon.
Temporary tattoo paper offers a straightforward, cost-effective, and versatile platform for "transferable" electronics. In particular, we focused on the production of disposable, ultra-conformable electrodes for skin-contact electrophysiology recordings, such as EMG, ECG, EEG, and EDA. These Temporary Tattoo Electrodes (TTE) are manufactured through ink-jet or screen printing of the conjugated polymer PEDOT:PSS. Various array and interconnector configurations are tailored for specific applications in bioengineering and biorobotics scenarios.[1,2]
Laser-Induced Graphene (LIG) is a porous conductive carbon created via laser-induced pyrolysis of polymer precursors like polyimide. This technique allows for rapid, maskless circuit engraving on insulating precursors, fostering advancements in flexible/stretchable/wearable electronics and soft robotics.[3] By embedding LIG in thin elastomer films (PDMS, medical grade Polyurethane), we developed stretchable connectors, skin-contact electrodes, and soft wearable sensors (physical: temperature, strain/pressure; and electrochemical: analytes in sweat).[4,5] In our group we further investigate natural materials and bioderived polymers (e.g., agricultural and food industry waste, shells) as sustainable substrates/precursors for LIG-based sensors and green electronics.[6]



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