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BIOEL 2017

PROGRAM

March 12th, 2017, Sunday

Session I

Chair: Nick Melosh

10:00 – 10:30 Coffee break

Session II

Chair: Şahika İnal

Session III

Chair: Eric Głowacki

March 13th, 2017, Monday

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Chair: Eva-Kathrin Sinner

Session III

Chair: Daniel Palanker

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10:00 – 10:30 Coffee break

Session II

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Session III

Chair: Janos Vörös

March 17th, 2017, Friday

Session I

Chair: Aleksandr Noy

10:00 – 10:30 Coffee break

Session II

Chair: Andreas Offenhäusser

Oral Presentations

Sunday, March 12th – Friday, March 17th

Photovoltaic Restoration of Sight with High Visual Acuity

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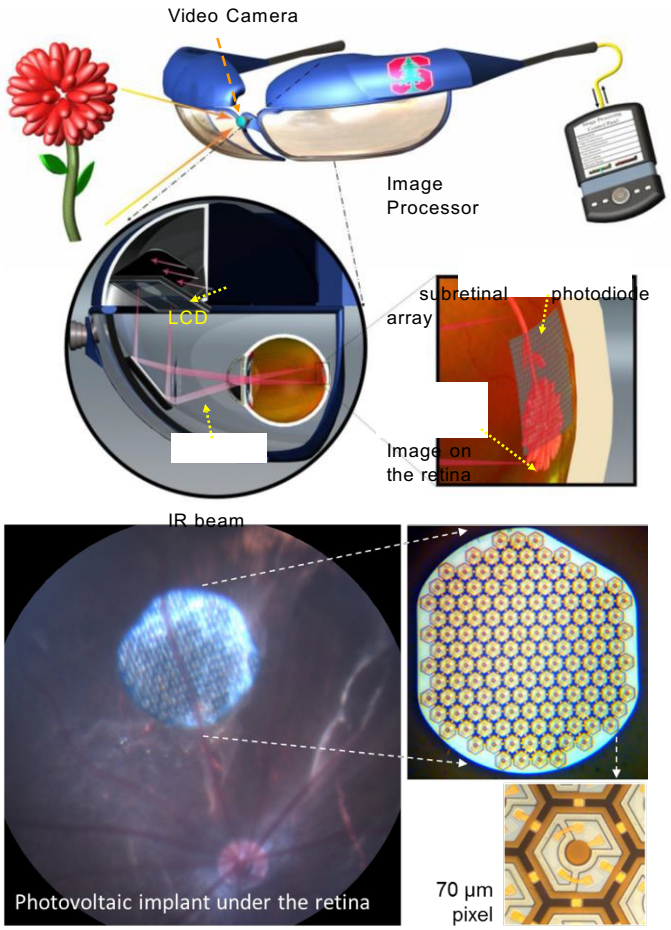
Retinal degenerative diseases lead to blindness due to loss of the "image capturing" photoreceptors, while neurons in the "image-processing" inner retinal layers are relatively well preserved. Information can be reintroduced into the visual system using electrical stimulation of the surviving inner retinal neurons. Some electronic retinal prosthetic systems have been already approved for clinical use, but they provide low resolution and involve very difficult implantation procedures.

We developed a photovoltaic subretinal prosthesis which converts light into pulsed electric current, stimulating the nearby inner retinal neurons.

Visual information is projected onto the retina by video goggles using pulsed near-infrared (~880nm) light. This design avoids the use of bulky electronics and wiring, thereby greatly reducing the surgical complexity. Optical activation of the photovoltaic pixels allows scaling the implants to thousands of electrodes, and multiple modules can be tiled under the retina to expand the visual field.

We found that similarly to normal vision, retinal response to prosthetic stimulation exhibits flicker fusion at high frequencies (>20 Hz), adaptation to static images, antagonistic center-surround organization and non-linear summation of subunits in the receptive fields, providing high spatial resolution. Photovoltaic arrays with 70μm pixels restored visual acuity up to a single pixel width, which is only two times lower than natural acuity in rats. If these results translate to human retina, such implants could restore visual acuity up to 20/250. Higher resolution arrays (55 and 40μm pixels) are currently being made. Ease of implantation and tiling of these wireless modules to cover a large visual field, combined with high resolution opens the door to highly functional restoration of sight.



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Soft "*e-dura*" microtechnology for neural interface applications

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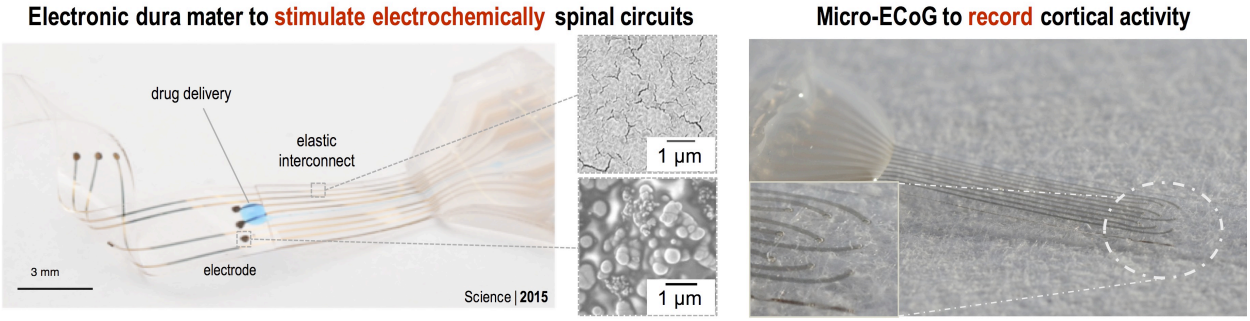
Microtechnology is enjoying ever-increasing popularity amongst researchers and practitioners in the medical field, as many examples of micro-fabricated devices are found today at the interface between body and machine.[1,2] Microtechnology now enables "smart" medical tools that provide enhanced functionality, i.e. long-lasting, communication interfaces between machines and biology. From a physical-mechanical perspective, this means replacing the hard materials used to produce conventional electronics with alternatives that can effectively coexist and integrate with the soft and dynamic physiological environments of the body.[3] To this end, researchers are drawing inspiration from nature and the living world to create systems that behave similarly to their surrounding environment when deployed in-vivo, with characteristics such as softness, stretchability, and biocompatibility.

Our group has developed the so-called "*e-dura*" soft neurotechnology, a technological toolkit enabling the manufacturing of mechanically compliant electronic implants that can be surgically placed in close contact with the neural tissue of the brain and spinal cord.[4] The *e-dura* process borrows fabrication techniques from the field of microtechnology, and therefore inherits the benefits of rapid prototyping and design flexibility. Drawing from examples of soft implants from the lab, the talk will highlight the importance of minimising the physical and mechanical mismatch at the implant-tissue interface, propose a manufacturing route for neurointegrated implants, and outline their therapeutic potential.



Examples of application of the "e-dura" technology to fabricate microelectrode arrays used for the electrical stimulation of the spinal cord (left)[4] and the recording of the cortical activity (right) in rats.

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Single molecular force spectroscopy and recognition imaging: applications in biology and medicine

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In molecular recognition force microscopy (MRFM), ligands are covalently attached to atomic force microscopy tips for the molecular recognition of their cognitive receptors on probe surfaces[1]. Interaction forces between single receptor-ligand pairs are measured in force-distance cycles. The dynamics of the experiment is varied[2], which gives insight into the molecular dynamics of the receptor-ligand recognition process and yields information about the binding pocket, binding energy barriers, and kinetic reaction rates[3]. Combination of high-resolution atomic force microscope topography imaging with single molecule force spectroscopy provides a unique possibility for the localization of specific molecular recognition events[4]. The identification and visualization of receptor binding sites on complex heterogeneous bio-surfaces such as cells and membranes are of particular interest in this context[4]. Antibodies are key molecules for the immune system of vertebrates. The Y-shaped IgGs exhibit C2-symmetry; their Fc stem is connected to two identical Fab arms binding antigens. Antibodies can be considered molecular calipers; bivalent binding of the two Fab arms to adjacent antigens can only occur within a distance of roughly 6 to 12 nm. AFM cantilevers adorned with an antibody can measure the distances between 5-methylcytidine bases in individual DNA strands with a resolution of 4Å, thereby revealing the DNA methylation pattern[6], which has an important role in the epigenetic control of gene expression. Moreover, due to their nano-mechanical properties antibodies exhibit "bipedal" walking on antigenic surfaces[7]. The walking speed depends on the lateral spacing and symmetry of the antigens. Importantly, the collision between randomly walking antibodies was seen to reduce their motional freedom. It leads to formation of transient antibody clusters even at low antibody density. Interestingly, such assemblies are known nucleation sites for docking of the complement system and/or phagocytes as an important initial step in the immune cascade.

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Correlating metabolic levels to epileptiform activity with implantable OECT based in vivo sensors

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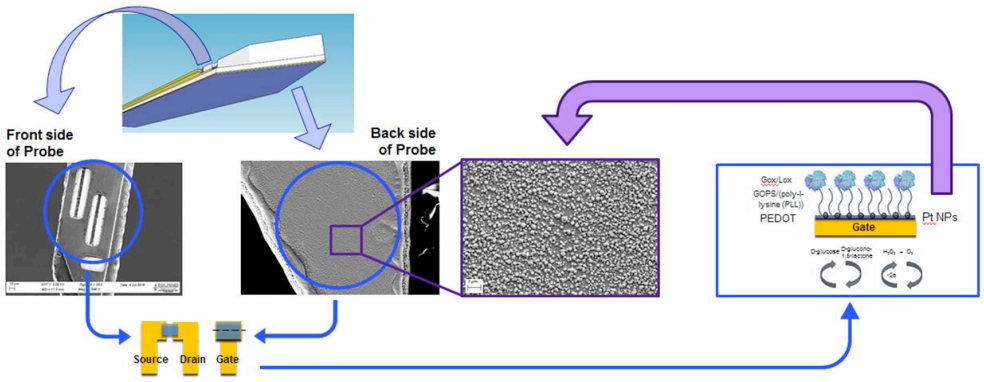
The transition of the brain to epileptic seizure is not well understood. The fluctuation in levels of various biomarkers may provide important information for our understanding of seizure onset.[1] Metabolic sensing, specifically glucose and lactate, is demonstrated here to be capable of detecting the onset of a seizure before pathological electrophysiological activity begins. Enzymatic sensor fabrication is carried out utilizing processing techniques compatible with flexible, non-invasive neural probes. Using the conducting polymer (CP) PEDOT:PSS {poly(3,4-ethylenedioxythiophene) doped with poly(styrenesulfonate)}, we functionalize the gate of the OECT through a stable covalent enzyme immobilization process. In this way the use of flexible scaffolds used for depth implant in vivo may be employed, providing a signal which is sensitive and selective to specific analytes due to incorporation of the bio-recognition element functionalized on the OECT. The amplification properties of the OECT may be exploited in order to clearly monitor glucose and lactate levels with the implantable neural probes as a result of the large currents in comparison to standard electrodes. This allows us to correlate the consumption of glucose and the production and/or uptake of lactate during pre-epileptiform activity to the pathological electrophysiological activity. Distinct rapid local variations in glucose/lactate levels may be detected and correlated to the time frame in which an increase of activity or interictal spiking occurs. This identification of seizure onset prior to the occurrence of spike-wave discharges or bursts of rhythmic spiking may provide significant possibilities for therapeutic local drug delivery to prevent epileptic seizure. The reduction of cross talk between neighboring sensors due to the production and diffusion of hydrogen peroxide has been realized through the use of a second enzyme to create an ‘enzyme stacking’ technique.



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Sub-300-nm thin-film sensors for EMG and ECG monitoring

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Simple, low-cost, and bio-compatible electrodes are necessary for disposable medical electronics, especially for the acceptance of physiological measurements and stimulations. The materials and fabrication of those electrodes should also be compatible with the fabrication of the rest of the electronic circuitry for monolithic ultra-flexible devices. Film, including sensors, thicker than few microns requires additional adhesive material for stable contact, such as conductive gels. This creates a concern as long-term placement of such materials often leads to skin irritation. Furthermore, their poor spatial resolution places a limit on possible applications.

We have fabricated simple, bio-compatible, and highly sensitive dry bio-electrodes. At ~300 nm thin, they are self-adhesive to the skin without any additional adhesive gel or tape, resulting in high fidelity of the measurement. Such an imperceptibly thin film produces no observable skin irritations, reducing the discomfort to the patient typically observed with long-term use of wet (gel) electrodes and possibly reducing motion artifacts (more investigations in-progress). Consisting of a thin layer of gold sandwiched between two layers of parylene (Fig1a), this simple design allows for easy fabrication and integration with previously demonstrated 300 nm thin electronics for future signal processing, such as amplification and filtering.[1] Likely due to the conformal nature of the film, and a subsequent reduction of impedance of this dry electrode as compared to the wet electrode, the ECG signal recorded using these electrodes is nearly identical (Fig1b) to the signal recorded using standard gel electrodes (the size of both electrodes being 1.5 mm x 4.5 mm), while the EMG measurement produced a noticeably stronger recording (Fig1c). This paves the way for skin-laminated, self-contained bio-electronic systems.

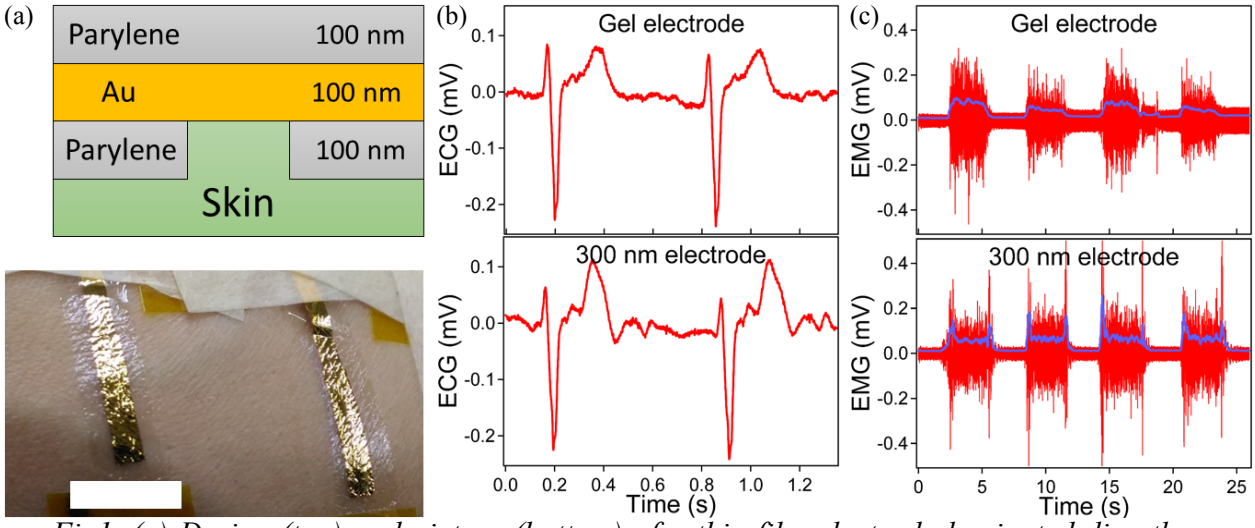

Fig1. (a) Design (top) and picture (bottom) of a thin-film electrode laminated directly on a skin of a patient (scale bar is 1 cm). (b) ECG and (c) EMG obtained with gel (top) and thin-film (bottom) electrodes.

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Brain-Injectable & Bio-Inspired Electronics

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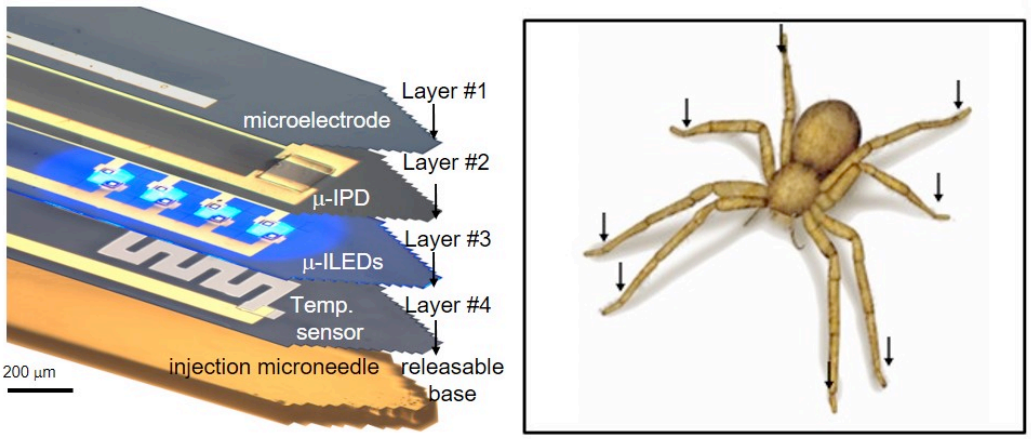
We demonstrate two kinds of unconventional electronics, implantable/bio-inpsired electronics with flexible substrate. The implantable device shows transferrable, bright, and thin micro GaN LEDs and their arrays on flexible substrate utilized in optogenetics[1] and bio-inspired devices show one example for an ultramecha-sensitive nanoscale crack sensors[2]. In the usual optogenetic technique, the enabled modes of use are impossible to realize using standard approaches that rely on rigid, long, glass fiber optics coupled to external, bulky light sources. Our systems exploit ultrathin, flexible substrates populated with microscale inorganic light emitting diodes (LEDs) together with electrophysiological and temperature sensors, all mounted on removable plastic needles that facilitate insertion into the tissue. Detailed experimental and theoretical studies of the operation, ranging from heat flow aspects to inflammation assessments and comparison to conventional devices, illustrate the unique features of this technology. Also we exploit wearable ultrasensitive mechanosensor based on nanoscale cracks inspired by spider slit organ. The sensors are sensitive to strain (with a gauge factor of over 2,000 in the 0–2 per cent strain range) and vibration (with the ability to detect amplitudes of approximately 10 nanometers).[3] The device is reversible, reproducible, durable and mechanically flexible, and can thus be easily mounted on human skin as an electronic multipixel array for detecting human physiology, voice pattern recognition. We believe that these unconventional devices could be useful in diverse applications requiring ultrahigh displacement sensitivity in other areas of implantable diagnostics and therapeutics.



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A scalable approach to neural stimulation & recording

Mina Hanna,[a] Mihaly Kollo,[b] Abdulmalik Obaid,[a] Matt Angle,[c] Andreas Schaefer,[b] Nicholas Melosh [a]

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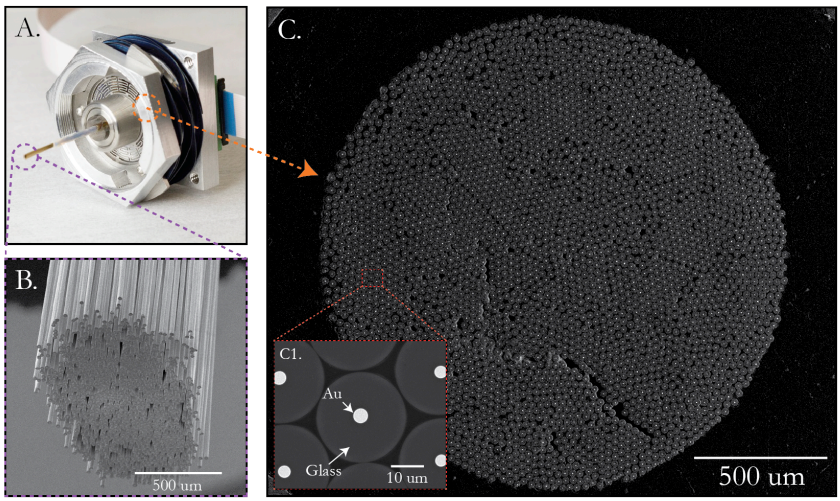
Electrical recording and stimulation with large numbers of electrodes is becoming a critical requirement for next-generation neural interfaces. Electrode to brain interfaces have numerous applications, including neuro-prosthetics, treatment of disorders including epilepsy, depression, Alzheimer's, and restoring function for speech, eyesight, and motion.
One of the most effective electrodes to date has been individual microwires, consisting of a conductive core, and insulating cladding 1-30um in diameter. These wires produce low-immunogenicity and little physiological damage during and after implantation[1,2]. However, scaling from a few wires that are each individually connectorized to more than a thousand wires in parallel has not been possible. Here we describe a new methodology whereby we perform a heterogeneous integration of a bundle of microwires (e.g., a large number of microwires collected together into a cylindrically packed aggregate) to a CMOS microchip. In this scheme the microelectrodes are prepared from a single continuous fiber. We further describe how these microelectrodes can be properly prepared for both heterogeneous connection to the CMOS chip with high yields, as well as preparation for their electrical recording and stimulation function. Moreover, we describe how the spacing of these microwires can be precisely controlled, which is critical for mitigating tissue damage.

(A) Image of passive alignment system for microwire bundle contact to chip. (B) Scanning electron micrograph (SEM, 45°) of polished free microwires to be inserted into brain tissue. (C) Backscatter SEM of polished bundle of ~3.8k microwires. (C1) Individual microwires from (C) highlighting Au core, and glass sheath, illustrating closed-pack conformation.



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Direct electrical activation of a blind retina mediated by optical stimulation of semiconducting organic pigments

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Optical stimulation of neurons using photosensitive materials was demonstrated in recent years.[1–3] These materials are cheap, easy to fabricate, and have unique properties such as flexibility, ability to operate in a wet environment, and biocompatibility. Their realization on soft and transparent thin film carriers can be a promising alternative for contemporary retinal implants, which are based on rigid materials and complex electronics that require dry conditions and external power source. Photo-sensitive devices must achieve direct electrical activation and short neuronal response latency to obtain safe and precise activation respectively. This can be achieved by a sufficient high charge separation to drive the membrane potential to the threshold for action potential, as indicated in numerous prior investigations on retinal stimulation. Such a stimulation also has to be capacitive in nature, avoiding harmful faradaic redox reactions. Currently, the activating mechanisms of these novel materials are not fully elucidated. Specifically, charge density may be too low for electrical activation and the response latency is very long. One plausible mechanism of activation that was recently proposed is a photo-thermal effect that induces changes in the electrical properties of the membrane by heating the close proximity of the cell.[4] Here, we demonstrate for the first time optically induced direct electrical activation of retinal ganglion cells in light-insensitive retinal extracts. Optical stimulation was obtained by high capacitive photoelectric responses of a functional biocompatible semiconductor film made from hydrogen-bonded organic pigments of ubiquitous commercial colorants. In addition, we developed thin, soft transparent film from silk fibroin adhere well to retinal extracts. These films will serve as a substrate for our organic pigments and will be further studied for both in vitro and in vivo retinal stimulation.

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Nanostructured silicon for bioelectric interfaces

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Biological systems are organized hierarchically, with unique characteristics and functionalities spanning multiple length scales; some examples include collagen fibers, metabolic networks, and chromosome organization. Therefore, it is important to select the right organizational length scale for device and biointerface design. In the case of sub-cellular organization, this length scale is on the order of tens to hundreds of nanometers. In this talk, I will present a few chemical strategies for nanostructured silicon-based material synthesis and lithography.[1-3] The materials have been tested with extra- and intracellular components (*i.e.*, phospholipid bilayer, and cytoskeleton) with an initial emphasis on optical control of the bioelectric output and the mechanical biointerface.[1-3] These studies will deepen our understanding of the fundamental limits of physical and biological signal transduction between subcellular components and synthetic systems. At the end of my talk, I will discuss future opportunities in materials science toward seamless bioelectric integration.

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Tailor-made organic semiconductors for bioelectronic applications

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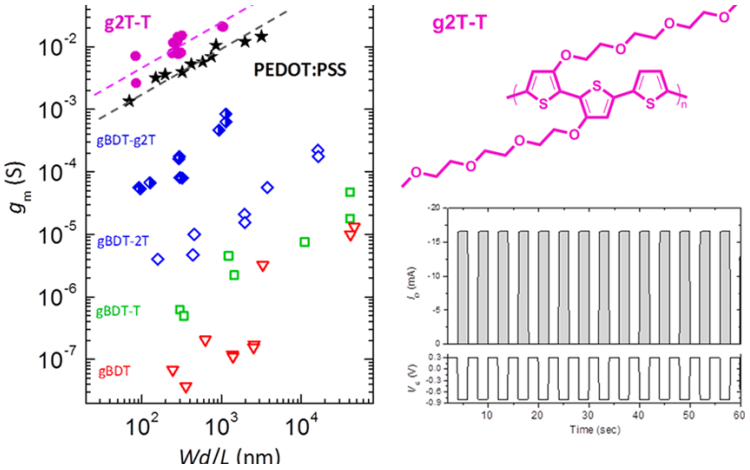
Semiconducting materials have long played a pivotal role in the development and advancement of organic electronic applications such as organic light-emitting diodes, organic field-effect transistors and organic solar cells. More recently, semiconducting polymers have made their entry into the new field of organic bioelectronics, which broadly encompasses any application that couples a relevant function of organic electronic materials with a targeted biological event. In this context, recent endeavours have seen organic electronic materials utilized for example in biologically relevant ion sensing, ion pumps, and as transducers of neural activity.

The organic electrochemical transistor (OECT), capable of transducing small ionic fluxes into electronic signals in an aqueous environment, is an ideal device to utilize in bioelectronic applications. Currently, most OECTs are fabricated with commercially available conducting poly(3,4-ethylenedioxythiophene) (PEDOT)-based suspensions and are therefore operated in depletion mode. Here, we will present a series of semiconducting polymers designed to elucidate important structure-property guidelines required for accumulation mode OECT operation.[1-3] We will discuss key aspects relating to OECT performance such as ion and hole transport, electrochromic properties, operational voltage and stability. The demonstration of our molecular design strategy is the fabrication of accumulation mode OECTs that clearly outperform state-of-the-art PEDOT based devices, and show stability under aqueous operation without the need for formulation additives and cross-linkers.



OECT performance and operational device stability of new bioelectronic semiconductors.

1. A. Giovannitti, D. T. Sbircea, S. Inal, C. B. Nielsen, E. Bandiello, D. A. Hanifi, M. Sessolo, G. G. Malliaras, I. McCulloch and J. Rivnay, *Proc. Natl. Acad. Sci. U.S.A.*, **113**, 12017–12022 (2016).
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3. C. B. Nielsen, A. Giovannitti, D. T. Sbircea, E. Bandiello, M. R. Niazi, D. A. Hanifi, M. Sessolo, A. Amassian, G. G. Malliaras, J. Rivnay and I. McCulloch, *J. Am. Chem. Soc.*, **138**, 10252–10259 (2016).

Numerical modelling of bio sensors based on Organic Electrochemical Transistors

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Conducting polymers have been used in the wide range of electronic devices such as transducers and sensors for chemical detection of different types of analytes. One of the most promising categories of semiconductor-based sensors is organic electrochemical transistor (OECT).
OECTs consist of three electrodes (Source, Drain and Gate) and two active layers: electrolyte and conductive polymer (Figure 1.). In conductive polymer layer the current modulation is generated by a dedoping effect produced by the positive ion penetration from electrolyte, followed by its recombination with negative conductive polymer ion. Since the amount of positive charge carriers in conductive polymer is decreased, current between source and drain electrodes also decreases. This kind of current variations is dependent on electrolyte concentration, gate and drain voltage.

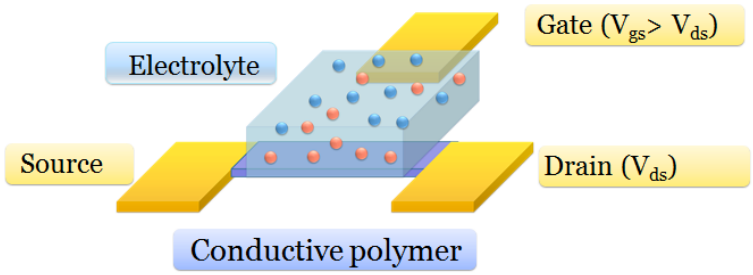

Figure 1.- Organic electrochemical transistor structure

Despite the fact that OECT attracts a lot of attention in the last years[1,2,3], appropriate physical and chemical coupled model to describe precisely the interaction between ionic and electronic charge carriers haven't been yet developed.
For precise understanding of an OECT working mechanism it is very important to model the distribution profile of every charged species including penetrated ions and moving holes. The numerical model (1D or 2D finite elements approach) performed with **COMSOL Multyphysics** software allows to understand an influence of different parameters on the charge carrier distribution and doping-dedoping proses in the polymer layer that leads to building of potential and current distribution profiles.
As a result, with complete numerical model it is possible to optimize an OECT for further building more efficient and sensitive biosensor.

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CMOS-based Monolithic Microelectrode Systems for Subcellular-resolution Electrophysiology

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Microelectrode arrays (MEAs) are devices that can be used in biomedical and basic in-vitro research that provide biochemical and extracellular electrophysiological information about biological systems at high spatial and temporal resolution. Complementary metal-oxide-semiconductor (CMOS)-technology is an enabling technology to batch-produce MEAs with thousands of micro-scale electrodes, placed at high spatial density. The complex microsystems feature - on the very same chip - addressing logic and circuitry units for signal conditioning in order to provide excellent signal-to-noise characteristics.[1,2]

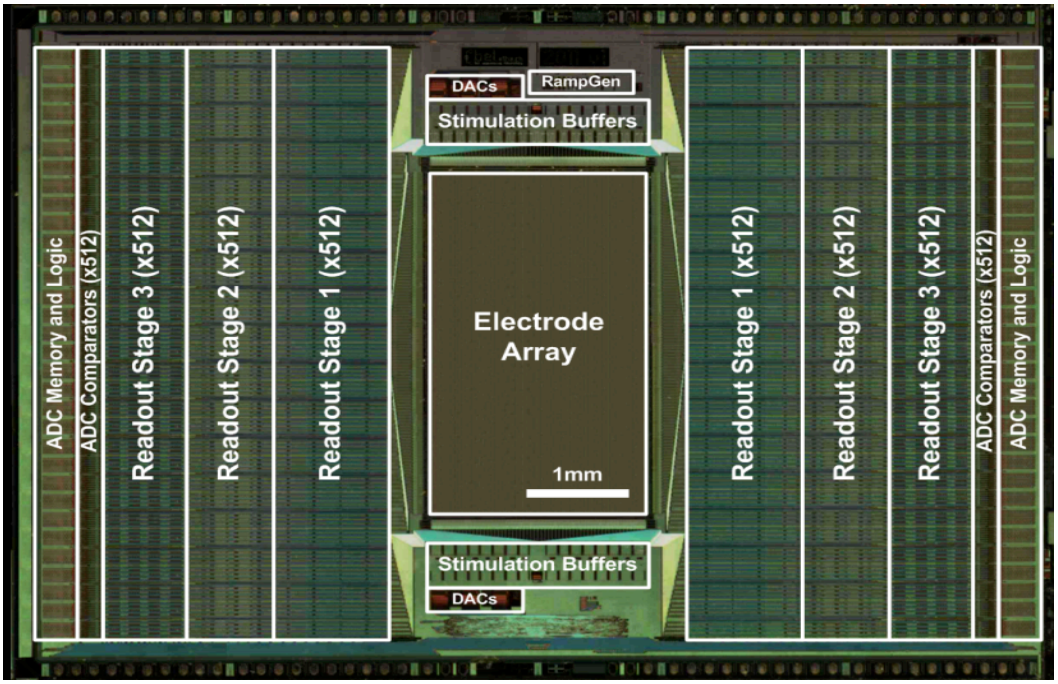

Figure 1: Micrograph of a monolithic microelectrode array system for high-resolution electrophysiology (0.35 µm CMOS technology).[3,4]

High-density MEAs feature a very high spatial density (>3000 electrodes per mm^2) of comparably small electrodes (diameters of 5-7 µm and a center-to-center pitch of <15 µm) and can be used for electrophysiological analysis of complete networks of, e.g., brain cells at cellular or subcellular resolution in dissociated cell cultures, organotypic tissue or slice cultures, and acute tissue slices. All electrodes of those HD-MEAs are bidirectional, i.e., they can be used for signal readout and stimulation, while all needed circuitry and control units are monolithically co-integrated on the same chip (Figure 1).[3,4] Even signals propagating along single axons can be detected and traced across hundreds of electrodes.[5]

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Bioelectronic interfaces by spontaneously organized peptides on 2D atomic single layer materials

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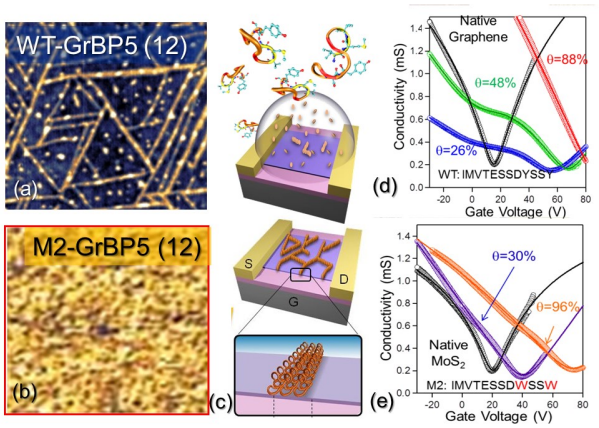
Self-assembly of biological molecules on solid materials is central to the "bottom-up" approach to directly integrate biology with electronics. Inspired by biology, exquisite biomolecular nanoarchitectures have been formed on solid surfaces.

We demonstrate that a combinatorially-selected dodecapeptide and its variants self-assemble into peptide nanowires on two-dimensional nanosheets, single-layer graphene and MoS_2. The abrupt boundaries of nanowires create electronic junctions *via* spatial biomolecular doping of graphene and manifest themselves as a self-assembled electronic network. Furthermore, designed peptides form nanowires on single-layer MoS_2 modifying both its electric conductivity and photoluminescence. The biomolecular doping of nanosheets defined by peptide nanostructures may represent the crucial first step in integrating biology with nano-electronics towards realizing fully self-assembled bionanoelectronic devices.



Peptide nanowires (a) or amorphous monolayer film (b) form on graphene when graphite-binding dodecapeptide assembles in a gFET device (c) exhibiting W-shaped (d) vs V-shaped (e) i-v behavior, respectively.

Research supported by the US-MGI (Materials Genome Initiative) Program through NSF/DMR-DMREF Project and JST, Japan.

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High-throughput integration of well-defined neural networks with microelectrode arrays to probe effects of electrical stimulation

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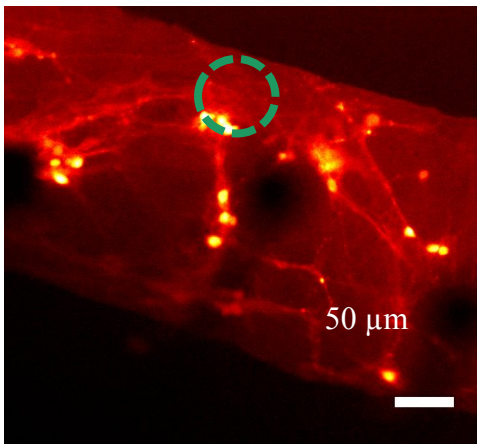
Well-defined activity patterns of neural circuits remain difficult to characterize *in vivo*. It is thus often unclear how localized stimulation of distinctly connected neural circuits influences temporal and spatial dynamics at a network scale. Our objective is to better characterize the effects of specific electrical stimulation protocols and to minimize response variability by creating *in vitro* networks of well-defined architectures on microelectrode arrays (MEAs).[1] To resolve the drawback that neurons need to be cultured long-term, thereby limiting the sample size to the number of available MEAs, which are expensive and have limited reusability, we developed a portable 3D neural substrate that can be transferred to a MEA over multiple time points to probe neural activity and achieve an assay with high sample number. The results aim to complement knowledge of electrical stimulation for therapeutic purposes.

Primary neurons were patterned via a combination of polydimethylsiloxane (PDMS) compartmentalized structures, microcontact printing, and/or laser-cut 3D cellulose scaffolds of different geometries and were then integrated with commercial and custom-made MEAs.[2,3] Custom-made soft electronic MEAs of embedded conductive nanomaterials within PDMS were fabricated via modification of published methods to better match the mechanical properties of the 3D substrate and soft tissues.[4,5] Neurons were additionally transduced with a calcium sensor to simultaneously obtain an optical readout of neural spiking.

By limiting the degrees of freedom of neural outgrowth with optimized and versatile patterning techniques, we could guide the formation of synaptic connections to engineer networks of defined size and topology. The use of soft, stretchable bioelectronics, a technology also being developed for therapeutic implants, greatly improved the neuro-electronic interface and allowed for the manipulation of neural activity over time. Our current focus is to compare network activity dynamics of randomized versus structurally patterned circuits.

Right Image: 3D neural network of laser-cut geometry grown within a portable cellulose-based substrate and integrated with a designed soft electronic MEA. The red gradient scale is the calcium sensor indicative of neural activity, and the green circle highlights one of the MEA electrodes that is brought within µm of the substrate.



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Electronic Plants

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Organic bioelectronics have been mainly oriented towards biomedical applications for controlling physiology, therapy, neural prosthetics and in vitro diagnostics. However the biological world extends beyond the animal kingdom. Plants are an indispensable part of our ecosystem and are essential to our quality of life. They are our primary source of food and oxygen and they play a very important role in the regulation of the climate and water. Recently we have demonstrated the first example of interface between organic bioelectronics and plants with the concept of Electronic Plants.[1] By introducing organic electronic materials into the vascular system and organs of a plant we manufactured analogue and digital circuits, augmenting electronic functionality to plants. The electronic functionality was achieved in localized regions, whereas rational design of materials will allow optimization of the distribution within the plant. Towards this direction we synthesized a new conjugated oligomer that can be distributed and polymerize in vivo from stem to flower without the application of an external stimuli, forming long-range conducting wires. Plant's structure and physiology act as template and catalyst of the polymerization reaction. Using the plant's natural architecture we were able to construct supercapacitors in vivo demonstrating for the first time energy storage in plants. In addition the oligomer can cross cellular barriers in the leaves reaching the apoplast opening pathways for new device concepts. Our results are preludes to autonomous energy systems integrated within plants and distributed interconnected sensor-actuator systems for plant control and optimization.

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Assembly of single-walled carbon nanotube-protein hybrids with single-molecule control

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Bioelectronic devices based on nanomaterials offer the unique advantages of simplicity, portability, low-cost fabrication, and label-free real-time electrical monitoring. Furthermore, as the device approaches the scale of individual biomolecules we can potentially probe single-molecule interactions in real time with high sensitivity and selectivity, allowing for the investigation of electron transport in biological systems and the development of novel biosensors. In this context, integrating functional biomolecules and nanoelectrodes with a high degree of control is a major challenge in assembling bioelectronics interfaces. Here we demonstrate the attachment of individual biomolecules to single-walled carbon nanotubes (SWCNTs) in a 1:1 ratio. The conjugation of single proteins to individual SWCNTs can be confirmed via atomic force microscopy (AFM), as seen in figure 1(a), where both dry and fluid methods have been employed. Additionally, SWCNTs were functionalised with single fluorescent proteins, providing further evidence for coupling by investigation via fluorescence microscopy at the single-molecule level (Figure 1(c)).

SWCNT-protein hybrids have been assembled via two methods: (a) covalent attachment with molecular linkers; (b) supramolecular assembly through DNA hybridisation. Both methods result in end-only functionalisation of SWCNTs. The DNA hybridisation approach introduces other variables, such as length, sequence, and potentially higher order or branched structures. Moreover, the methods discussed can be expanded to the assembly of SWCNTs with other functional molecules or particles. The biohybrid structures presented establish the first step in the fabrication of solution-processable bioelectronic devices with single-molecule control.

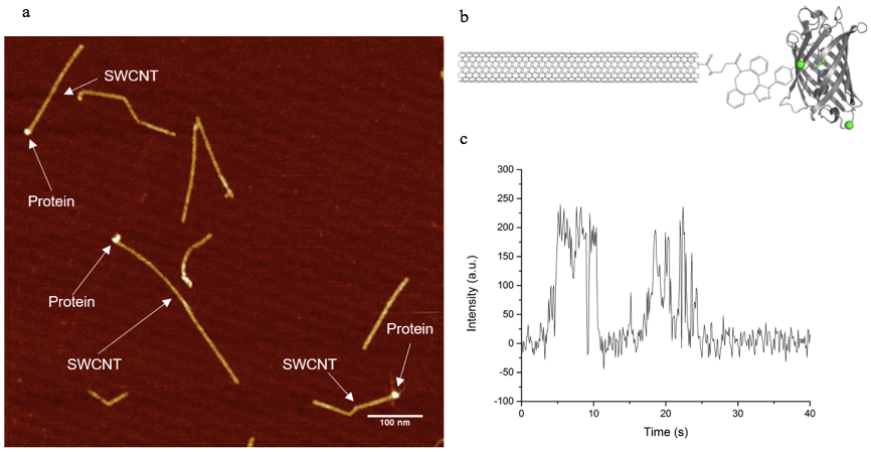

Figure 1. (a) AFM image of SWCNT-protein hybrids with 1:1 ratio of components. (b) Schematic of SWCNT-protein hybrid. (c) Typical fluorescence vs time plot for a single fluorescent protein conjugated to an individual SWCNT obtained through fluorescence microscopy.

Dynamic Materials Inspired by Cephalopods

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Cephalopods, such as the squid shown below, have captivated the imagination of both the general public and scientists for more than a century due to their visually stunning camouflage displays, sophisticated nervous systems, and complex behavioral patterns. Given their unique capabilities and characteristics, it is not surprising that these marine invertebrates have recently emerged as exciting sources of inspiration for the development of unique materials. Within this context, our laboratory has explored the properties of structural proteins known as reflectins, which play crucial roles in the functionality of cephalopod skin. In this talk, I will discuss our work on new types of photonic devices fabricated from reflectin-derived and reflectin-inspired materials. Our findings hold implications for the development of adaptive camouflage systems and renewable energy technologies.

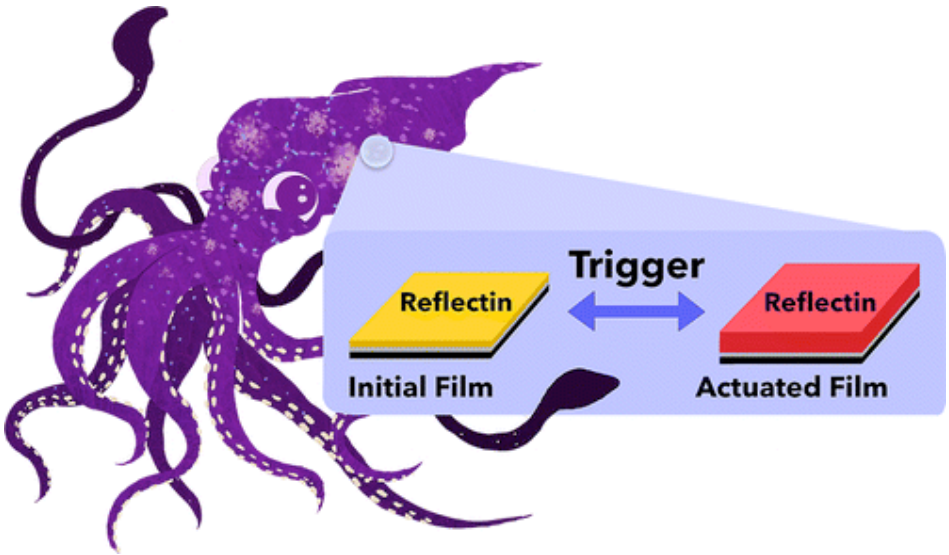

Figure 1: *Illustration of a cephalopod, which provides inspiration for a stimuli-responsive camouflage device. The image is an artistic rendition of an animal found in nature (see https://www.youtube.com/watch?v=lEhYJEQmExE).*

Probing the interface between nanoelectrodes and the cell membrane

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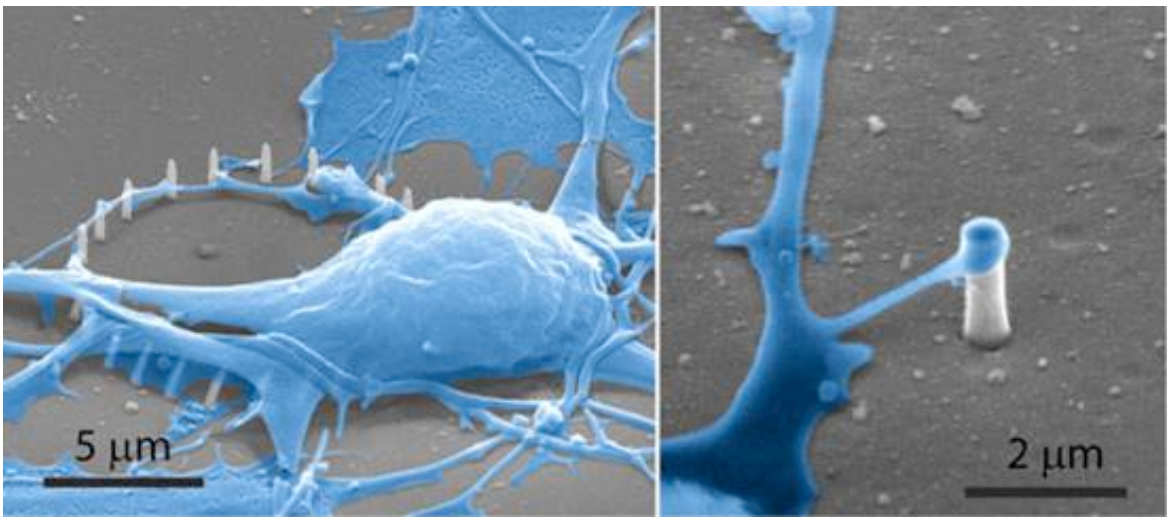
The close distance between the cell membrane and the measuring electrode is crucial for sensitive measurement of cell electric activities. We are interested in exploring nanotechnology and novel materials to improve the membrane-electrode coupling efficiency. Recently, we and other groups show that vertical nanopillars protruding from a flat surface support cell survival and can be used as subcellular sensors to probe biological processes in live cells. The nanopillar electrodes deform plasma membrane inwards and induce membrane curvature when the cell engulfs them, leading to a reduction of the membrane-electrode gap distance and a higher sealing resistance. As an electrode sensor, nanoelectrodes offer several advantages such as high sensitivity, subcellular spatial resolution, and precise control of the sensor geometry. We found that the 3D topology of nanopillars is crucial for its enhanced signal detection. The high membrane curvature induced by vertical nanopillars significantly affects the distribution of curvature-sensitive proteins and stimulates several cellular processes in live cells. Our studies show a strong interplay between biological cells and nano-sized sensors, which is an essential consideration for future development of interfacing devices.



This figure shows hippocampal neurons interacting with vertical nanopillars .

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Engineering Host-Implant Interface to Modulate Cellular Interactions

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Although the use of medical implants became a routine clinical practice, the understanding of the mechanisms at the interface between cells or tissues and the artificial material is still of critical importance. The host response to surface properties of implants mainly determines the performance of implantable devices in various applications including orthopaedics, pacemakers, cardiovascular stents, defibrillators, neural prosthetics or drug delivery systems. Various strategies have been developed to control the cellular response to the substratum by modifying the physical and chemical characteristics of the surface. This work is focused on the fabrication of novel surfaces for hard and soft tissue engineering. The effect of the topography of bone and dental implants on cellular/tissue response have been demonstrated by some case studies[1,2] (e.g. topography driven osteogenic differentiation, reduction of fibrosis encapsulation, reduction of bacteria adhesion and proliferation). Surface modification strategies in cardiac materials is also presented briefly by introducing recent results in the field of thrombosis reduction and restenosis prevention in stents [3,4].

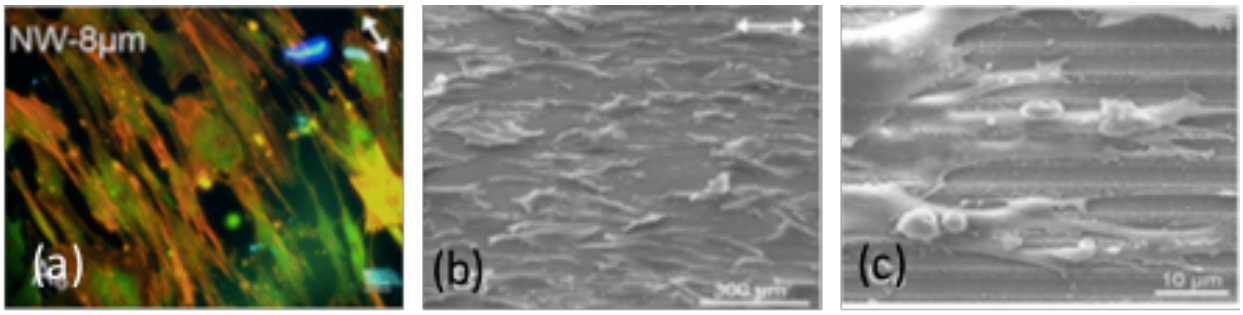

Fig 1: Adhesion and alignment of human cardiomyocytes on patterned $A1_2O_3$ surfaces. Representative (a) fluorescence microscopy and (b), (c)SEM images.

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Is stretchability good for bioelectronics?

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A new class of electronic devices based on stretchable materials can interact with the soft human body in an unprecedented manner. They are highly suitable for epidermal electronics because they can be designed to conform closely to and with the irregular shape of the skin, providing an improved functional interface even during motion, while being imperceptible to the user.[1]
But does the stretchability also provide benefits for in vivo applications? The tutorial part of this lecture will discuss the challenges and possibilities for in vivo stretchable electronics.
The second part will introduce our progress on using metal nanowires embedded in PDMS that can be processed using screen-printing or regular photolithography to create stretchable conductive leads down to 10 micrometer resolution. The process parameters, e.g. type of PDMS, nanowire concentration and arrangement allow for precise tailoring of the electrical and mechanical properties of this composite material. Stretchable and biocompatible microelectrode arrays can thus be realized that enable stimulation of intact spinal cord circuits below an injury to control the movement of the limbs aiding rehabilitation and increasing recovery of spinal-cord injured patients.[2.3]
The technology also allows for creating devices with up to 500% stretchability or with Gauge factors of over 100.[4] A novel fabrication method has been developed to produce various opto-electronic components using wax-pattern assisted filtration. These devices are soft and made of biocompatible materials therefore they are ideal for in vivo applications. For example, LED and electrode arrays can be used to stimulate the brain of optogenetically modified mice or rats, respectively.[5] (See figure below.) In addition, smart and passive RFID tags can be created to measure the filing level of the bladder in handicapped users.[6]

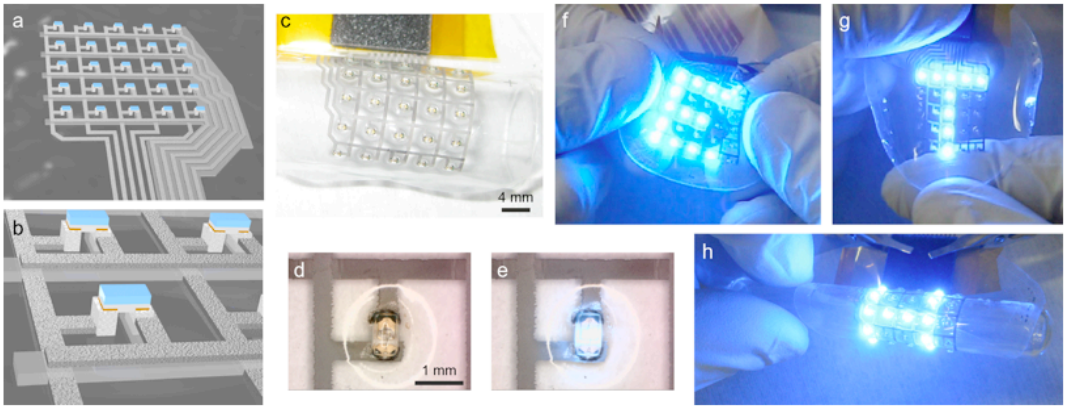

Figure: Stretchable LED diode matrix: a) The LED matrix comprises 5x5 LEDs b) The two addressing planes are isolated from each other by a thin patterned PDMS layer. c) The fabricated LED matrix wrapped around a glass cylinder. d,e) The LED is shown in the off and on state. The circular reflection arises from the PDMS protection layer on top. f-h) The LED matrix can withstand stretching to about 20 % or wrapping around a glass cylinder. The pictures were taken under ambient light conditions, which demonstrate the brightness of the LEDs.

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6. www.urosense.ch

Roll-to-Roll Pilot Line for Large-Scale Manufacturing of Microfluidic Devices

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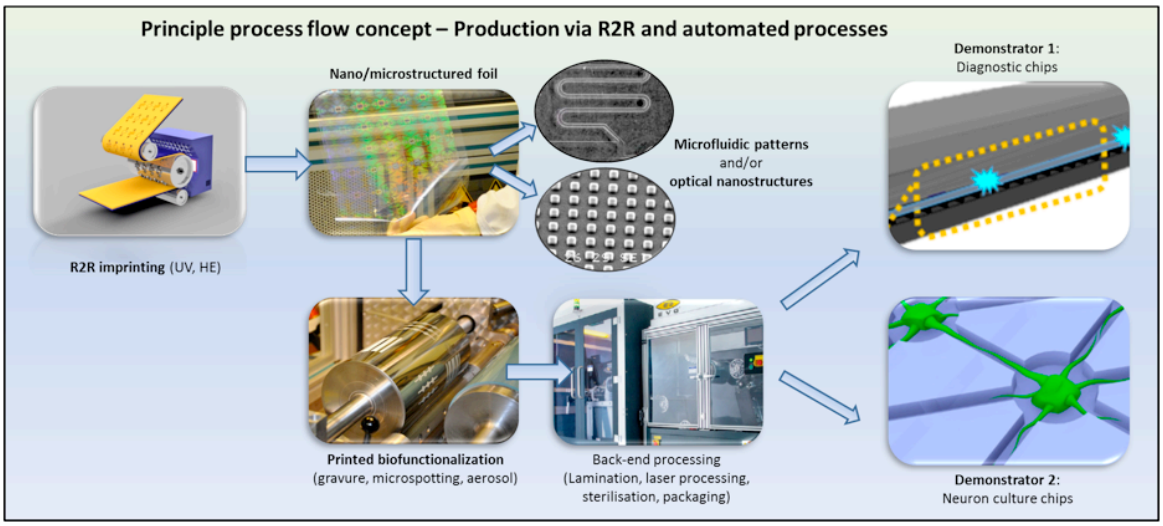
Roll-to-roll (R2R) technologies with roller-based nanoimprinting methods enable manufacturing of highly cost-effective and large-scale sheets of flexible polymer film with precise structures on a micro- and nanoscale.[1] Areas that can benefit strongly from such large scale technologies are microfluidics, biosensors, and lab-on-chip products for point of care diagnostics, drug discovery and food control. Here, R2R fabrication could greatly reduce production costs and increase manufacturing capacity with respect to currently used products.

A pilot line with this technology is investigated in the European Horizon 2020 project R2R Biofluidics and its capabilities are tested on two Demonstrators:

- Demonstrator 1: In-vitro diagnostic chip with imprinted microfluidic channels based on optical chemiluminescence measurement by photodetectors.
- Demonstrator 2: Neuronal cell culture plate with imprinted cavities and channels for controlled culturing and fluorescence imaging of neurons, for high throughput drug screening.

The R2R pilot line will be presented together with results from simulation, mastering, shim fabrication, roll-to-roll imprinting and first fluidic experiments for both demonstrators.



Process concept of the project R2R Biofluidics.

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Environment-dependent conductance of human hemoglobin

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The electrical properties of proteins have been the subject of numerous investigations. In this work we electrically characterize hemoglobin assemblies using platinum nanoelectrodes. Samples with nanoelectrodes were fabricated by conventional electron-beam lithography and chromium/platinum evaporation. An aqueous solution of hemoglobin was prepared by dissolving hemoglobin powder in ultra-pure de-ionized water. It was then drop-casted on top of the nanoelectrodes and dried out, so that a solid-state thin film of proteins is formed. Current-voltage (I-V) measurements were performed on the devices before and after protein deposition at ambient conditions. An increase of the conductance after deposition points at formation of electrical contact between the protein layer and nanoelectrodes. This contact was stable for hours in the presence of a continuously swept bias voltage. No backgate dependence on the conduction at room temperature was detected. Measurements were also conducted at non-ambient conditions. In vacuum, the current dropped to below the noise levels. However, the current values were re-established to its initial state once going back to air (Figure 1). Another example of environmental impact on the conductance was observed in a nitrogen atmosphere. The current was suppressed and displayed only 1/3 of its initial value in air.

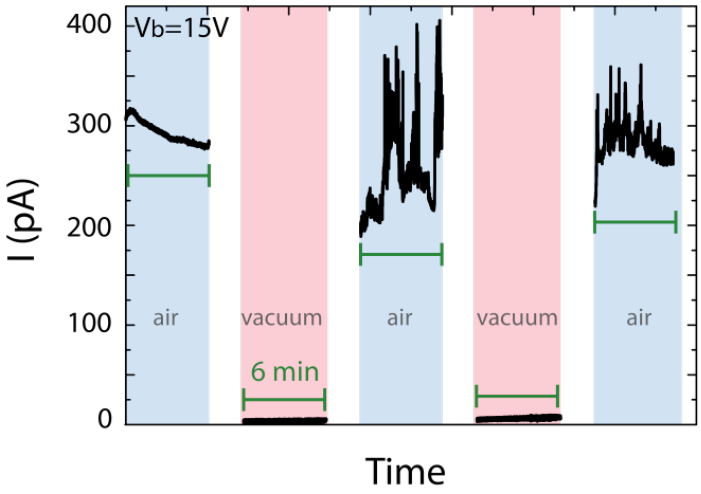

Figure 1 - A change in the current occurs as the hemoglobin network goes from air (blue region) to vacuum (red region). The current drops to zero in vacuum and returns back to its initial value once it's in air again.

Organic mixed conductors for bioelectronic applications

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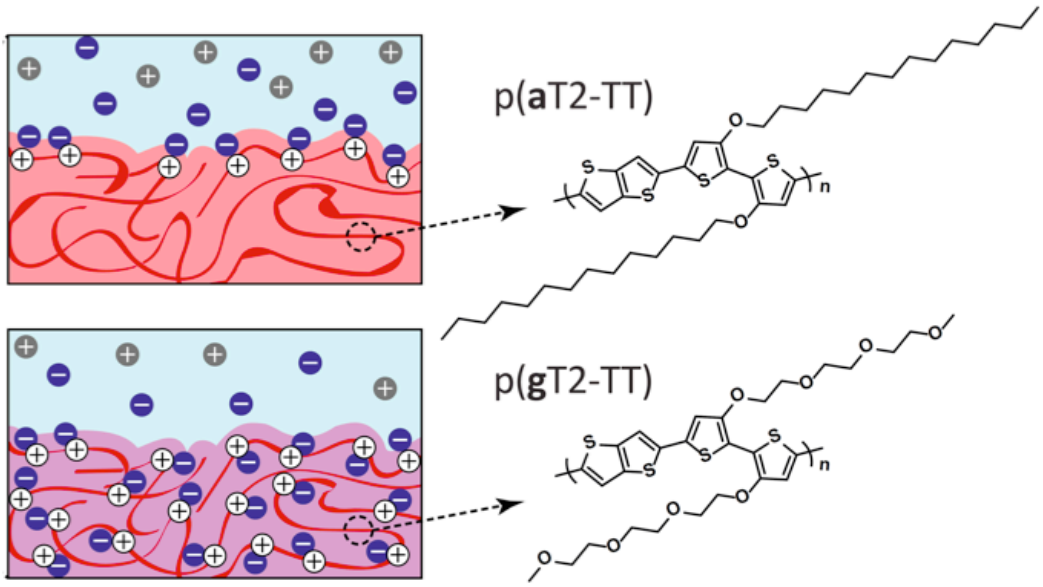
Direct measurement and stimulation of electrophysiological activity is a staple of neural and cardiac health monitoring, diagnosis and/or therapy. Such bi-directional interfacing can be enhanced by the unique properties of organic electronic materials that show mixed conduction (both electronic and ionic transport).[1] One such material, poly(3,4- ethylenedioxythiophene): poly(styrenesulfonate), PEDOT:PSS, has dominated the bioelectronics scene as an active layer for sensing and stimulation devices, actuators and active scaffolds. Little is known, however, about how the molecular design and processing of such materials affect their ionic and electronic transport properties. By investigating microstructure, charge transport and performance of PEDOT-based materials, we are able to tailor devices for specific biological applications and to establish a set of design rules for new formulations/materials. Introducing glycolated side chains to carefully selected semiconducting polymer backbones, for example, has enabled a new class of high performance bioelectronic materials. Glycolated thiophene-based polymers exhibit high volumetric capacitance in aqueous conditions, electrochemical transistor transconductance >10mS (device dimensions ca. 10um), and steep subthreshold switching characteristics.[2] A sub-set of these materials outperform PEDOT:PSS and shows significant promise for biocompatible, low power *in vitro* and *in vivo* biosensing applications. These soft active materials intimately interact with solvated ions, promising to bridge the gap between biology and microelectronics.



Formulation content, processing, and molecular design (shown here), can be used as a means to tune both electronic transport and ionic penetration/transport.

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Liquid metals for stretchable and soft electronics

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This talk will discuss work in our group to use liquid metals as conductors for stretchable, soft, and reconfigurable electronics. We focus on alloys of gallium. These alloys are noted for their low viscosity, low toxicity, and negligible volatility. Despite the large surface tension of the metal, it can be molded into non-spherical 2D and 3D shapes due to the presence of an ultra-thin oxide skin that forms on its surface. The metal can be patterned by injection into microchannels or by direct-write techniques including 3D printing. Because it is a liquid, the metal is extremely soft and flows in response to stress to retain electrical continuity under extreme deformation. The ability of the oxide to reform instantaneously also allows the metal to self-heal in response to damage. In addition, the ability to remove the oxide electrochemically provides a new means to control the shape of the metal for reconfigurable electronics. Finally, we combine the metal with hydrogels to create electrodes, diodes, and memristor memory devices that are composed entirely out of soft, liquid-like materials. These materials create comfortable interfaces with the skin for non-invasive sensing.

Conducting polymers thin films and nanoparticles for optical control of animal behavior

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Use of light for selective and spatio-temporally resolved control of animal specific functions is emerging as a valuable alternative to standard electrical methods, able to overcome many current limitations. Several strategies have been proposed, mainly exploiting photoactive mediators nearby or within the animal tissues: photo-isomerizable or photo-cleavable compounds, infrared neural stimulation, genetic expression of sensitive probes.
Here, we propose the use of organic semiconductors as efficient, versatile and biocompatible optical transducers, suitable for in vitro and in vivo applications. In more detail, we report on poly-hexylthiophene (P3HT)-based materials in form of thin films (a, b) and nanoparticles (c).

(a) We fabricated a fully flexible, organic retinal prosthesis made of conjugated polymers layered onto a silk fibroin substrate. The long-term biocompatibility was extensively assessed by implanting the device in the sub-retinal space of rat animal models. Moreover, electrophysiological and behavioral analyses revealed a significant and persistent recovery of light-sensitivity and visual acuity up to 10 months after surgery.[1]

(b) A similar approach is currently under investigation for the selective and rapid modulation of Transient Receptor Potential (TRP) channels, which are emerging as essential cellular switches that allow animals to respond to the environment. In particular, we demonstrate that illumination of the polymer film leads to reliable, robust and temporally precise control of TRPV1 channels. Interestingly, the activation of the channel is due to the combination of two different, locally confined effects, namely the release of thermal energy from the polymer surface and the acidification of the extracellular environment, both mediated by the polymer photoexcitation in a spatially and temporally precise manner.[2]

(c) We synthesized P3HT nanoparticles, with excellent colloidal stability in aqueous solution and optimal in vitro bio-compatibility. We then explored their use as photo-actuators in animal models of *Hydra Vulgaris*. We show that uptake of organic nanoparticles leads to specific light-activated effects, on both a behavioral and a molecular level. Possible photo-stimulation mechanisms will be critically discussed.[3]

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Characterizing the neuro-electronic interface

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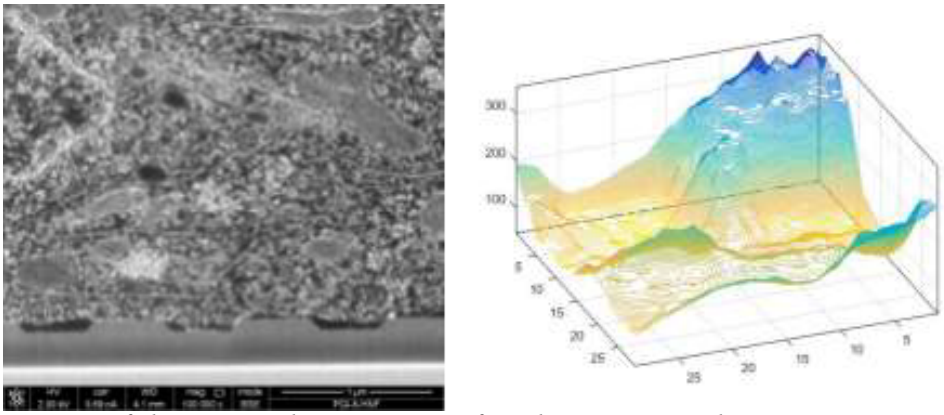
A challenging issue in Neuroscience is tightly monitoring and controlling of the functionality of neural networks. Direct interfacing of devices based on inorganic and organic semiconductor and (non conventional) electrode material with nerve cells and brain tissue open novel perspective for multifunctional electrophysiological tools *in vitro* and *in vivo* with high spatiotemporal resolution and improved sensitivity.

We aim for the fabrication of chip-based sensors that enable an efficient neuro-electronic interface towards precise recording of cellular signals. Within this framework, we have developed a variety of microelectrode array (MEA) designs that enable non-invasive, parallel, multi-site recording of action potentials from primary neurons. We have modified standard planar 64 electrode MEA design with different geometries ranging from nanometer-sized cavities[1] that allow for cellular protrusion into the sensor to mushroom-shaped 3D electrodes[2,3]. Furthermore, we investigate various field-effect transistor (FET) designs ranging from silicon nanowires to graphene[4].

A systematic characterization of cell–electrode interaction and an understanding of the interaction of cells with the electronic sensors is of utmost importance as the recorded signals are generally only in the 100 µV range. To allow a very detailed investigation of the neuro- electronic interface we developed an ultra-thin resin embedding method of individual neurons[5]. In addition we employed surface plasmon microscope (SPM) to monitor in real-time the cell– metal interface and to measure in situ the gap distance of the cleft with the spatial resolution reaching to the optical diffraction limit[6].



Investigation of the neuro-electronic interface by scanning electron microscopy (SEM) (left) and surface plasmon microscope (SPM) (right).

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Specifically designed peptides for bioelectronic applications

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Billion of years of natural evolution has resulted in an enormous amount of proteins that are involved virtually in any biological process. Mimicking the unique features of these effective natural machineries, can be extremely productive for advancing nowadays technologies. Motivated by this approach our group aims at developing bio-inspired materials for electronic and sensing applications. Our approach includes de-novo designs of peptides (short synthetic proteins) that capture desired features of proteins on one hand, and include natural , as well as non-natural, electronic or sensory functional units, on the other hand. This approach will be demonstrated in this talk using three examples applicable for: electron and proton transport,[1,2] small molecules sensing at the single molecule level,[3] and modulating surface electronic properties of inorganic semiconductors.[4] These examples demonstrate that de-novo designed peptides can be powerful building blocks for the preparation of novel, high performance, and biocompatible organic and hybrid bioelectronic materials, fabricated by cost effective and environmentally friendly methods.

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Ion transport and tunable ion selectivity in carbon nanotube porins

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Living systems transmit electronic signals using controlled transport of ions across biological membranes through ion channels that form pores in lipid bilayers. Membrane pores formed by ultra-short carbon nanotubes (CNTs) assembled in the lipid membranes—carbon nanotube porins (CNTPs)—have transport properties that come remarkably close to replicating the transport properties of some of those biological channels. The defining features of these nanostructures are their inner pores that have atomically smooth hydrophobic walls, which can confine water on a molecular level, and, in case of 0.8 nm diameter CNTPs, down to a single-file configuration. We use single nanopore conductance measurements to explore the ion selectivity in these pores and show that it is defined and controlled by the static charges at the nanotube pore entrance. We also show that rational manipulation of these charges allows us to tune this selectivity and even reconfigure the CNTPs into switchable ionic diodes. CNTPs represent a simplified biomimetic system that is ideal for building complex engineered mesoscale structures that could serve as the foundation of next-generation bioelectronic interfaces.

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Instant strong bonding of hydrogels for soft machines and electronics

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Introducing methods for instant strong bonding between hydrogels and antagonistic materials – from soft to hard – allows us to demonstrate elastic, yet tough biomimetic devices and machines with a high level of complexity. Tough hydrogels strongly attach, within seconds, to plastics, elastomers, leather, bone and metals reaching unprecedented interfacial toughness exceeding 2000 J/m^2. Healing of severed ionic hydrogel conductors becomes feasible and restores function instantly. Soft, transparent multi-layered hybrids of elastomers and ionic hydrogels endure biaxial strain with more than 2000 % increase in area, facilitating soft transducers, generators and adaptive lenses. We demonstrate soft electronic devices, from stretchable batteries, self-powered compliant circuits and autonomous electronic skin (Figure 1) for triggered drug delivery. Our approach is applicable in rapid prototyping and in delicate environments inaccessible for extended curing and cross-linking.

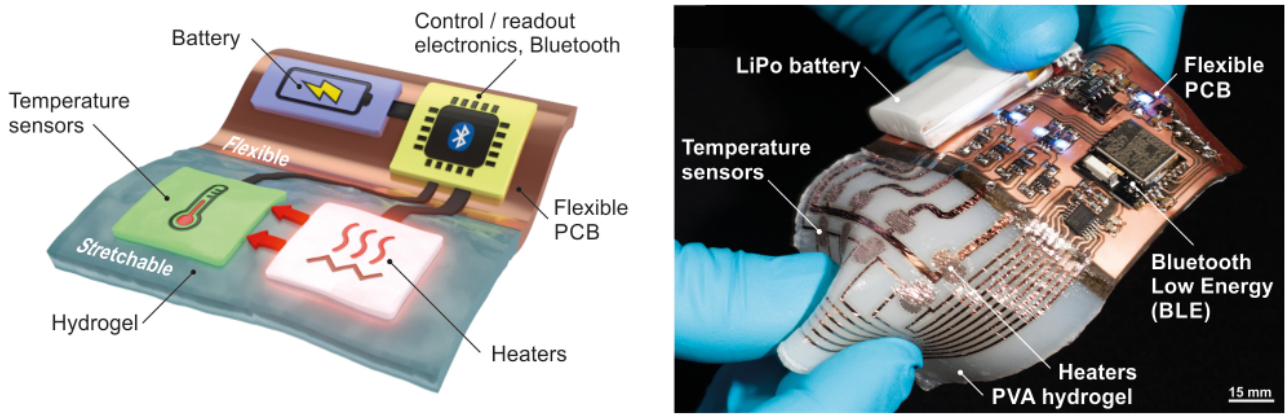

Figure 1: Hydrogel electronic skin. (left) Concept of a hydrogel smart skin, with a flexible unit bearing power supply, control, readout and communication units, and a stretchable transducer batch. (right) Photograph of an untethered electronic hydrogel with four stretchable heating elements and adjoined temperature sensors strongly bonded to a PVA hydrogel. Battery, control, readout and Bluetooth Low Energy communication electronics are hosted on a flexible circuit board.

Biomaterials and Engineering Solutions to Stem Cell Biology

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Regenerative medicine is an emerging interdisciplinary field, which integrates a number of diverse fields including biology, materials and polymer science, physics, engineering, and medicine. In this talk, I will discuss our recent efforts in integrating engineering tools like microfabrication, microfluidics, and mathematical modeling with biomaterials to improve the outcome of stem cell-based therapies and to develop "organs/disease-on-chip" models.

First, I will talk about the design of polymer-based scaffolds as artificial extracellular matrices to regulate various cellular behaviors necessary to promote wound healing, tissue repair, and reinstating the functionality of dysfunctional tissues/organs. In addition to assisting cell and tissue transplantation, such bioengineered scaffolds could be used as devices to activate host endogenous cells to promote tissue repair and as a technological platform to gain new mechanistic insights. I will also discuss how permanently cross-linked hydrogels can be engineered to exhibit self-healing in an aqueous environment, and also discuss possible biomedical applications of such hydrogels.

Next, I will talk about our efforts on understanding the role of physical properties of the matrix in disease progression such as cancer metastasis. Metastatic dissemination of cancer cells is a key contributor to >90% of cancer-related mortality. Though metastasis involves multiple steps, the ability of cancer cells to invade and traverse through dense 3D structures (i.e., extracellular matrix such as collagen network) is a crucial manifestation of cancer malignancy. In order to understand cancer cell invasion and migration, we have developed a single cell resolution quantitative assay to estimate the three-dimensional (3D) traction stresses generated by the cancer cells during their migration. We also examined the effect of material properties on protease independent vs. dependent mode of migration of cancer cells. Such quantitative analysis would lead to identification of new pathways that might be targeted to develop therapies to treat cancer metastasis.

I will end by briefly introducing "organs-on-chip" technological platforms that we are developing to achieve physiologically relevant healthy- and disease- models to study basic concepts and screen drug and small molecules.

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Tailoring Conducting Polymer Scaffolds for Bioelectronics

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Advances in tissue engineering have demonstrated that physical architecture of tissues has a direct influence on correct differentiation and the function of cells *in vitro*. Considering the limited physiological relevance of 2D cell culture experiments, significant effort was devoted to the development of scaffold materials that could support 3D cell cultures *in vitro* and more accurately recreate the *in vivo* cellular microenvironment. A prime example of such a material is conducting polymers (CPs) that are capable of hosting cells in 3D due to their possibility into porous architectures, biocompatibility and compliant mechanical properties. These materials aim to integrate functionality into the 'passive' scaffolds, while addressing the problem of rigidity of 2D metal electrodes. In this talk, I will demonstrate the development of CP scaffolds with a dual purpose – to both *host* and *monitor/ stimulate* cells. The adhesion and pro-angiogenic secretions of mouse fibroblasts cultured within the scaffolds can be controlled by switching the electrochemical state of the polymer prior to cell-seeding. The same device infiltrated by kidney cells, on the other hand, acts as a live-cell monitoring platform that enables electronic sensing of cells. Moreover, the ease of preparation of different compositions of materials allows for the tunability of different properties such as mechanical stiffness and conductivity. I will show how such properties influence the performance of the devices, but also enable tailoring scaffolds for building specific tissue types.

Soft devices: A perspective

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A wide range of materials and material combinations, from hard and brittle to soft and elastic, is now available for the design of soft devices [1]. We combine seemingly antagonistic materials, from liquid metals and gels to elastomers, polymers and small molecules, and from metals to oxides in sophisticated systems. Such future „soft devices“ will form seamless links between living beings and the digital world and become ever more indispensable for improving safety and quality of life, without impairing comfort [2]. The last few years have seen an explosion of soft matter based demonstrators in robotics, electronic skin and energy harvesters. Low-voltage organic flash memories, edible electronics, stretchable batteries, printed ferroelectric active matrix sensors and displays, hydrogen bonded organic semiconductors, imperceptible forms of electronics, large stroke soft actuators and energy converters will be briefly reviewed in this presentation. We are at the brink of a fascinating technological society: Imagine science fiction turning into reality via an evolution of technologies that is blurring the lines between the physical, digital and biological spheres.

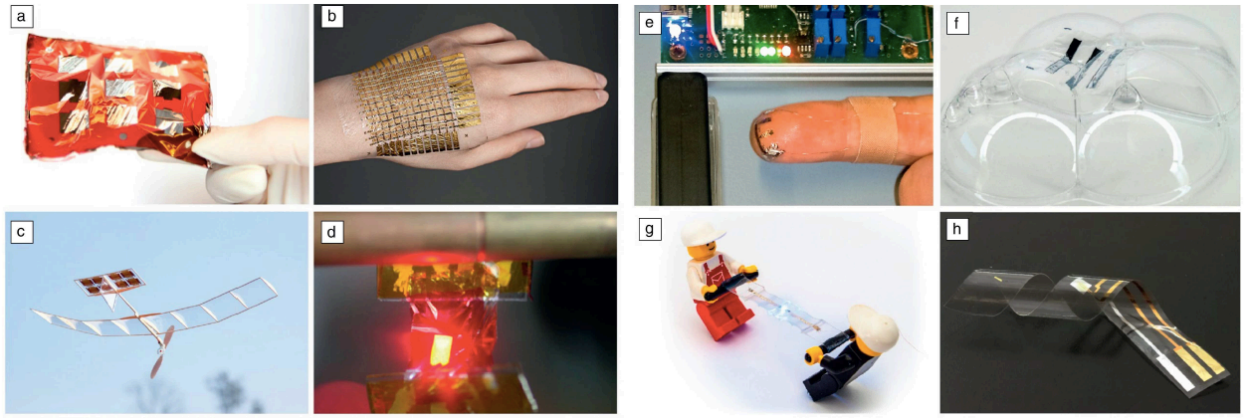

Illustration of the evolution of “imperceptible electronics”, taken from [2]. (a) Ultrathin and light organic solar cells with 10 W/g power per weight. (b) 2 µm thick, 3g/m^2 lightweight active matrix foil sensors conforming to human skin. (c) Air-stable perovskite solar cells with 23 W/g powering an aviation model flying on JKU campus. (d) Light-emitting diodes crumpled like a piece of paper, becoming highly stretchable on elastomer membranes by employing the wrinkling mechanical instability. (e) Sixth-sense magnetoception with giant- magnetoresistance sensor arrays on ultrathin polymer foils. (f) Imperceptible electronic sensor foils foating on soap bubbles. (g) Mechanical characterization of stretchable electronic items with an open-source toy brick tensometer. (h) Shape-memory polymers enabling reconfigurable plastic electronics.

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From natural systems to lighting electronics: designing melanin-inspired electroluminescent materials

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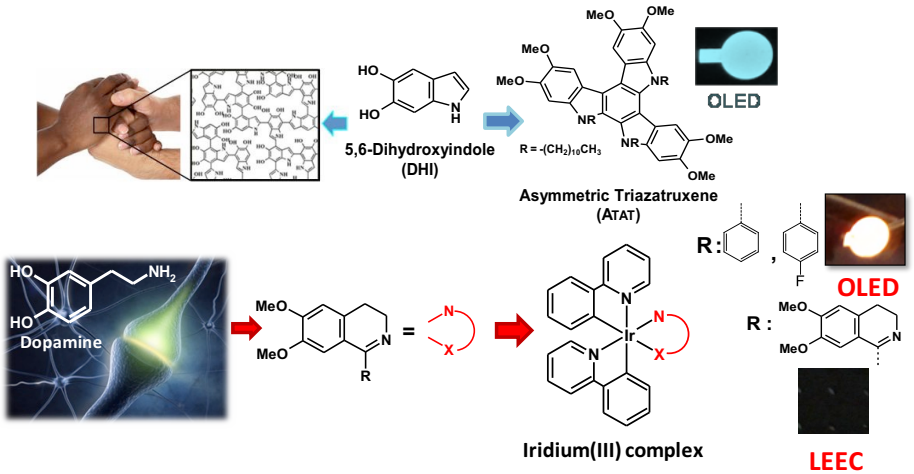
The recent advances in the field of organic light emitting diodes (OLEDs) have been focused mainly on the need to combine the main strengths of this technology, that is the versatility (i.e. wide color tuning, ultrathin, flexible and large area devices) and the eco-compatibility (low-energy consumption), with the efficiency and the lifetime of the devices, with the aim of making OLEDs very appealing and competitive with respect to the inorganic LEDs. In the last few years, another issue has been explored in connection with the growing expansion and impact of the green electronic field, that is the challenge of integrating natural or nature-inspired materials within organic electronic devices, and so in OLEDs.
In the frame of a research plan aimed at studying the role of melanins, the dark pigment found in mammalian skin, hair and eyes, in organic electronics,[1] we have recently explored the potentiality of new heterocyclic platforms designed taking inspiration from the mammalian pigments as eco-compatible electroluminescent materials for OLED applications. Herein we report on the synthesis of two different types of organic emitters, the fluorescent asymmetrical triazatruxene[2] and the phosphorescent iridium(III) complex (Figure 1). The first one has been obtained starting from 5,6-dihydroxyindole, the eumelanin monomer precursor, and the second one has been prepared by using ligands obtained from dopamine, the catecholic neurotransmitter and monomer precursor of the melanic polydopamine pigment. All the compounds obtained have been subjected to structural characterization and investigation of the photo-physical and electronic properties, also with the support of theoretical calculations. Moreover, a comparative study has been carried out to delineate the role of different kind of functional groups on tuning the wavelength of the emitting light. The most promising compounds have been selected for the fabrication of both fluorescent and phosphorescent OLEDs and of the most advanced light emitting electrochemical cell (LEEC) devices. The performances of the devices is also discussed.



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Understanding the capacitance of conducting polymers

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Conducting polymers, in particular PEDOT (poly(3,4-ethylenedioxythiophene)), represent the material of choice for many bioelectronics applications such as electrochemical transistors, sensors, organic electronic ion pumps, electrodes interfacing with neuronal systems and implantable drug delivery devices. In many of the above-mentioned devices the operation principle relies on or is governed by the material capacitive response. In spite of decades of research on conducting polymers, the fundamentals of its bulk capacitance remains poorly understood. Generally, charge storage in supercapacitors is due to formation of electrical double layers or redox reactions, and it is widely accepted that conducting polymers belong to the latter category. Here, we report theoretical modeling that significantly departs from this commonly accepted picture.

We perform *ab initio* density functional theory calculations computing the intrinsic (bulk) capacitance of PEDOT from the first principles. Based on our molecular dynamics calculations we model PEDOT as a π-π stacked crystallite (i.e. an aggregate composed of several polymeric chains) surrounded by molecular counterions, see Figure 1. Sequentially doping the crystallite by positive charges (i.e. adding polarons/bipolarons) we calculate the total capacitance as a function of number of charges N in the crystallite. We find that the capacitance C varies as a function of N because of quantum effects related to the density of states and due to the effect of the electrostatic potential that changes when counterions are added or removed. The average value of the capacitance is $\langle C \rangle \sim 40$ F/cm^3, which is consistent with experimental observations. Our results show that the intrinsic capacitance of PEDOT emerges as a result of charging/discharging of atomistic Stern layers forming on the Ångström scale directly at PEDOT crystallites without invoking an assumption about redox reactions in the system.

Finally, we also discuss the case of PEDOT:PSS, where by applying a 2-phase, 2-dimensional modeling approach based on Nernst-Planck-Poisson equations we demonstrate that the major contribution to the capacitance of the 2-phase PEDOT:PSS originates from electrical double layers formed along the interfaces between nanoscaled PEDOT-rich and PSS-rich interconnected grains that comprises two phases of the bulk of PEDOT:PSS.

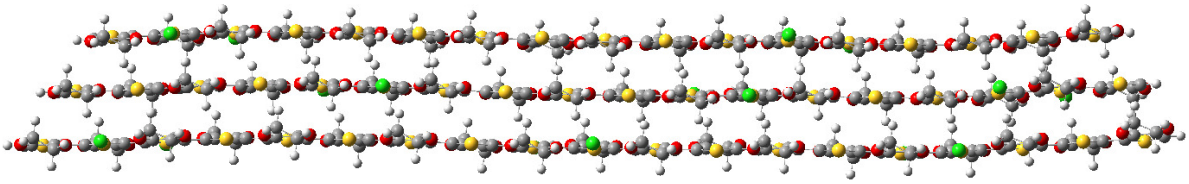

Figure 1: A side view of a crystallite composed of three π-π stacked PEDOT chain used in ab initio capacitance calculations. Different atoms comprising PEDOT are shown in different colours: C atoms (grey), S atoms (yellow), O atoms (red), H atoms (small light gray); negative Cl⁻ counterions are depicted in green.

Chemical and Biochemical Sensor Systems: From Prototype Development to Pilot Manufacturing and Serial Production

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There is a steadily growing demand for miniaturized analytical devices allowing for on-site or point-of-care detection of chemical and biochemical parameters in applications like medical diagnostics, food testing, or environmental monitoring.
Such devices should ideally enable convenient sample-in – result-out type of operation. Therefore, the entire process from sample preparation, reagent incubation, calibration, up to detection should be performed in a single instrument.
Therefore, these are usually integrated systems consisting of benchtop (or handheld) reader-type instruments and some consumable parts. The consumables are in contact with the sample medium and are used for a single or a limited number of measurements. Mostly such consumables themselves are highly functional devices involving e.g. active sensing elements, (micro)fluidics, reagents, electronic circuitry, etc.
To be able to provide such analytical systems, it is necessary to develop advanced strategies for the integration of sensor elements and the implementation of advanced and cost-efficient fabrication technologies.
Today the development focuses mainly on the use of thermoplastic polymer materials as they allow for low-cost high volume fabrication of disposables by techniques such as injection molding. Further progress can be expected from roll-to-roll processing technology for low-cost - large volume micro- and nanofabrication. Technologies such as roll-to-roll nanoimprinting are suitable for the production of complex microfluidic and microoptic structures in flexible polymer films. In combination with printing of functional materials this allows integrating sensor elements into polymer consumables.
This contribution focuses on approaches for electrochemical and optical sensor fabrication by the use of printing processes for the deposition and patterning of functional sensor materials. These are combined with polymer based (micro)fluidic devices. Issues of moving from development of first demonstrators to pilot manufacturing and upscaling for serial production are discussed. In particular, the selection of appropriate materials as well as Design for Manufacturing aspects should be considered quite early in the development phase.

Relationship between bioelectric potentials and physiological activities of plants

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The bioelectric potential of the plant is generated by ions inside the plant cells and the potential response changes corresponding to plant physiological activities. The plant physiological activities are influenced by several environment conditions, especially the light irradiation. We reported that the amplitudes of the potentials vary depending on the photosynthesis activities[1]. In this study, we aim to obtain the relationship between the light irradiation and the plant activity using plant bioelectric potential. The Venus flytrap were used as sample plants. Several papers reported about the action potentials in this plant[2].

The bioelectric potential difference between the two EEG needle type electrodes was measured with a high-input-impedance digital multimeter. In the experiment, the bioelectric potential responses when illumination (Light source: Blue and Red LEDs) was started and stopped every 1 hour were measured and recorded by a computer at a sampling interval of 1 second.

Figure 1 shows the results of the bioelectric potential responses of the Venus flytrap before feeding (Figure 1a) and 11 hours after feeding (Figure 1b) the measured leaf with the boiled white egg. The measured leaf had closed after feeding immediately, and never opened after feeding. The figure indicates that the amplitudes and the peak potential reaching times of bioelectric potential responses relate the digestion process of the Venus flytrap.

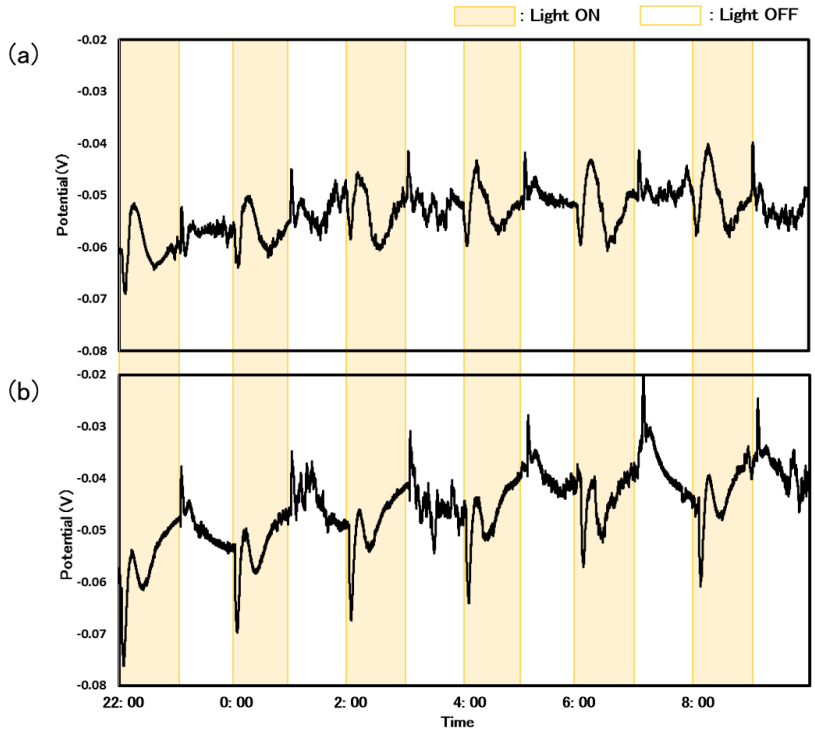

Figure 1. Potential responses of the Venus flytrap (a) before and (b) after feeding.

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Cell-device coupling visualized at the nanoscale

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The interface between biological cells and non-biological materials has profound influences on cellular activities, chronic tissue responses, and ultimately the success of medical implants and bioelectronic devices. Materials in contact with cells can be metals, plastics, silicon, ceramics or other synthetic materials, and their surfaces vary widely in chemical compositions, stiffness and levels of roughness. Moreover, the success of bioelectronic devices for both *in vivo* and *in vitro* applications lies in the effective coupling of cells/tissues with the devices' surfaces. It is known how a large cleft between the cellular membrane and the electrode surface massively affects the quality of the recorded signals or ultimately the stimulation efficiency of a device. However, there remains a critical need to directly examine the aforementioned cleft at the relevant length scale of nanometers. Scanning electron microscopy (SEM) and focused ion beam (FIB) milling are powerful tools in analyzing interfaces for inorganic and organic materials. However, using FIB-SEM for interfaces involving biological specimens has been challenging due to the inherent low contrast of biological samples and the structural artifacts induced by sample drying. Here, we present a new FIB-SEM method that overcomes these limitations to resolve the cleft between cells and devices with 10 nm resolution. Furthermore, we present an overview of this method's application relevant to the bioelectronic field including the investigation of the interface between cells and 3D conductive structures such as nanopillars and PEDOT-based grooves. We will also discuss how 3D structures effectively minimize the cleft, as well as the surprising fact that the material stiffness does not induce local distance changes between cells and nanostructures.

Emulating synapses with an organic device

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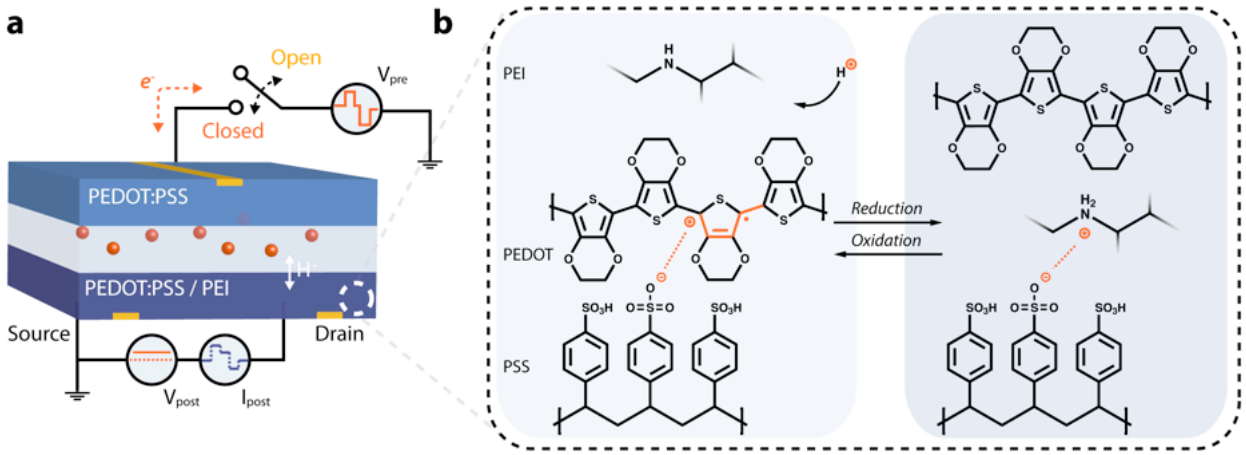
The brain can perform massively parallel information processing while consuming only ~1- 100 fJ per synaptic event. Two-terminal memristors based on filament forming metal oxides (FFMOs) or phase change memory (PCM) materials have recently been demonstrated to function as non-volatile memory that can emulate neuronal and synaptic functions. Despite recent progress in the fabrication of device arrays however, to date no architecture has been shown to operate with the projected energy efficiency while maintaining high accuracy. A major impediment still exists at the device level, specifically, a resistive memory device has not yet been demonstrated with adequate electrical characteristics to fully realize the efficiency and performance gains of a neural architecture. I will describe a novel electrochemical neuromorphic device that switches at record-low energy (<0.1 fJ projected, <10 pJ measured) and voltage (< 1mV, measured), displays >500 distinct, non-volatile conductance states within a ~1 V operating range, and achieves record classification accuracy when implemented in neural network simulations. Our organic neuromorphic device works by combining ionic (protonic) and electronic conduction and is essentially similar to a concentration battery. The main advantage of this device is that the barrier for state retention is decoupled from the barrier for changing states, allowing for the extremely low switching voltages while maintaining non-volatility. I will also demonstrate that plastic ENODEs can be entirely fabricated on flexible substrates unlocking new opportunities for integrating neuromorphic functionality in flexible and stretchable large-area electronic systems, such as "smart skins", that mimic the adaptive properties of biological organs.



Schematic of the organic artificial synapse (a) and chemical reactions describing its working mechanism (b).

Sensing applications of modified all-plastic Organic Electrochemical Transistors

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In recent years, the increasing demand for portable technologies in diagnostics and safety has highlighted the need for versatile, cost-effective platform for sensing. An all-plastic Organic Electrochemical Transistor (OECT), in which both the gate and the channel of the device are entirely made of PEDOT:PSS, meets these requirements. Indeed, this architecture is highly compatible with a wide variety of stretchable substrates and can be easily integrated into flexible circuits and textiles while combining signal amplification, biocompatibility, facile readout electronics and low fabrication costs. A double approach was applied to investigate the potentialities of the all-plastic OECT. First, using a potentiostatic approach we were able to detect redox-active biomolecules of physiological interest, whose electro oxidation at the gate promotes the extraction of carriers in the channel (Fig.1**A**).[1] Then, aiming to address the lack of selectivity, we studied a potentiodynamic approach allowing the variation of both the operating gate voltage and the scan rate. In this case, the transconductance response provided consistent data for calibration plots of each analyte, while effectively separating the redox waves associated to each compound.[2]

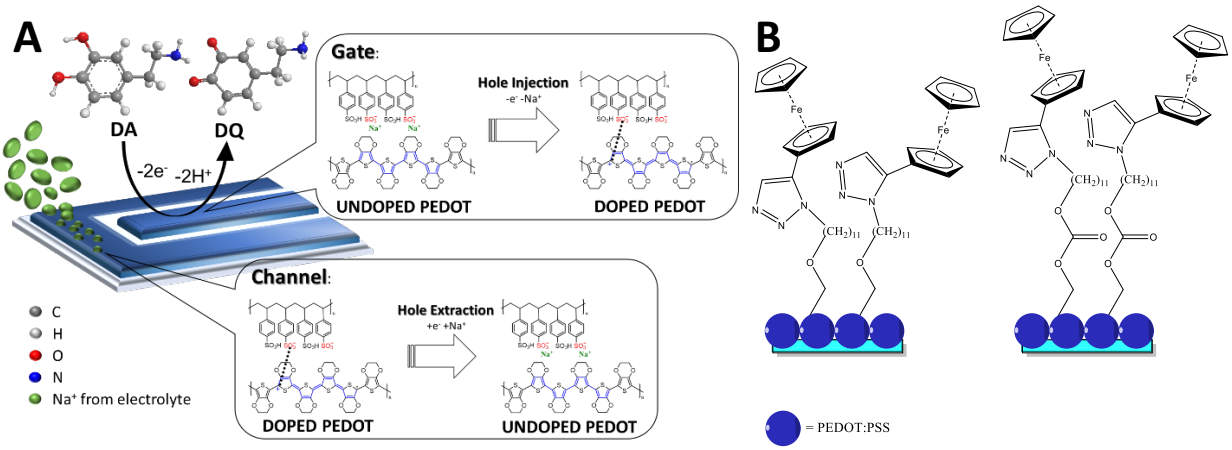

*Fig.1 (**A**) Electrochemical processes occurring at the all-plastic OECT allowing Dopamine (DA) sensing and (**B**) two functionalized sensors obtained by our group.*

Alternatively, the physical and chemical modification of the PEDOT chains in the gate electrode offers great opportunities for the implementation of a selective sensor. Specifically, a pH sensor for biofluids'monitoring has been developed by embedding suitable host molecules in the polymeric film using electropolymerization. Moreover, chemical functionalization of the PEDOT backbone with Ferrocene-based pendants is under study in order to impart specific characteristics to the OECT.[3] Recently, Ferrocene-terminated alkyl chains have been synthesized and anchored in the PEDOT film (Fig.1**B**), via "click chemistry" (i.e. copper-catalyzed azide–alkyne cycloaddition). The resulting modified sensors show electrocatalytic activity towards the target compound, while the steric hindrance of the chain impede bulky interferents to approach the PEDOT sites.

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Organic Electrochemical Transistors based on PEDOT:PSS

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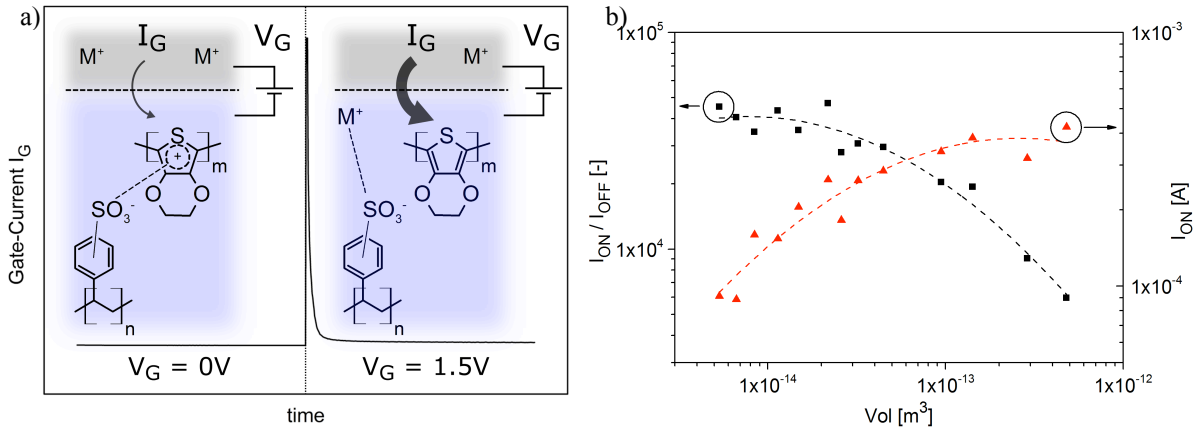
Organic electrochemical transistors (OECTs) based on PEDOT:PSS as organic semiconductor are used for more than a decade now.[1] It is this materials versatility, concerning processing methods and combinability with other materials, that is substantially contributing to the large field of possible applications of those OECTs. Applications range from biosensing on a point-of-care testing chip to circuitry for disposable electronics.[2,3]
We investigated the correlation between the volume of PEDOT:PSS in the transistor channel and the electrical charge consumed during switching.[4] In the course of these investigations intrinsic parameters of the used PEDOT:PSS are determined and their influence on the electrical behavior is discussed. Not only is an understanding of the relation between charge consumption and the volume of PEDOT:PSS essential for designing high performing transistors, these measurements can also be used to determine the amount of electrochemically active PEDOT:PSS. With this knowledge the efficiency of the switching process can be evaluated. The entirely screen-printed lateral OECTs used for those investigations were also used for fabricating logic circuits.[5] Highly reproducible output signals of those circuits, consisting of up to 36 printed transistors and 60 printed resistors, demonstrate the high uniformity and reproducibility of the screen printed components.



a) Graphical representation of the switching process at the electrode/electrolyte interface, depicting the flowing gate current. b) Dependence of the on/off-current ratio and the off-current on the volume of PEDOT:PSS in the transistor channel.

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Melanins: the new challenge of bioelectronics for an old preserved pigment

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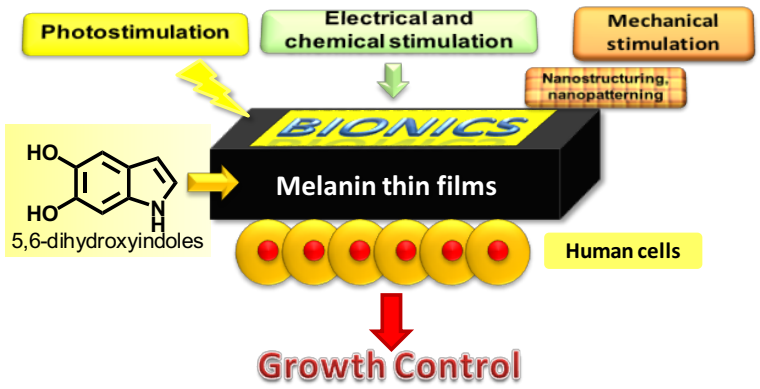
Melanins are a class of natural pigments appeared in living organism since the early stages of the evolution and today are a wide spread pigment diffused from bacteria to mammals and man. These pigments feature a peculiar set of physical-chemical properties, i.e. broadband absorption in the UV-visible range, intrinsic free radical character, water-dependent hybrid ionic–electronic conductor behavior,[1] which are at the root of the notable interest towards their exploitation in bioelectronics (Figure1).

To date, a number of conceptual and technological gaps still hinder rapid progress of melanin-based organic electronics and bioelectronics, including in particular the limited contribution of electronic conductivity and current decay with time under biasing.

Herein, we provide a concise overview of the structural and optoelectronic properties of melanins with a view to the most recent applications from OPV to OECT devices, up to the design and investigation of melanin-based bio-interfaces for stem cells adhesion, proliferation and differentiation.[2] Basic structure-property function relationships, fundamental tailoring strategies, processing and the balance of ionic-electronic processes underling the design of melanin-inspired functional materials will also be addressed, with particular attention to the synthesis of new heterocyclic platforms and with representative examples of eumelanin-based hybrids to orient ongoing efforts toward efficient and competitive eumelanin-based technology.[3]



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Conductance imaging of electronic materials and redox proteins in aqueous solution at the nanoscale

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Electron Transfer (ET) plays essential roles in crucial biological processes such as cell respiration and photosynthesis. It takes place between redox proteins and in protein complexes that display an outstanding efficiency and environmental adaptability. Although the fundamental aspects of ET processes are well understood, more experimental methods are needed to determine electronic pathways in these redox protein structures. Understanding how ET works is important not only for fundamental reasons, but also for the potential technological applications of these redox-active nanoscale systems.

Electrochemical Scanning Tunneling Microscopy (ECSTM) is an excellent tool to study electronic materials and redox molecules including proteins[1]. It offers atomic or single molecule resolution and allows working in aqueous solution, in nearly physiological conditions in the case of proteins, and under full electrochemical control. Beyond imaging, ECSTM allows performing current-voltage and current-distance tunneling spectroscopy. We adapted the current-voltage spectroscopy mode of ECSTM to include a sinusoidal voltage modulation to the STM tip and current measurement by means of a lock-in amplifier, which renders a signal that is proportional to the differential conductance dI/dV of the studied surface[2]. With this setup we recorded for the first time spatially resolved, differential conductance images under potentiostatic control (differential electrochemical conductance (DECC) imaging). We validated and optimized the technique using an iron electrode, whose reversible oxidation in borate buffer is well characterized[3].

We applied DECC imaging to gold Au <111> surfaces coated with P. Aeruginosa Azurin. Azurin is a redox metalloprotein with a copper center that can be immobilized on single crystal Au <111> surfaces via a dithiol covalent bond, representing a model system to study biological ET processes[4]. DECC imaging provides simultaneously the surface topography and local conductance with a resolution of a few nanometers, and reveals regions with different conductance within the protein. The characterization of conduction pathways in redox proteins at the nanoscale would enable important advances in biochemistry and would cause a high impact in the field of nanotechnology[5].

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Getting to the Point: Current Progress in Nanoneedles and Nanopillars

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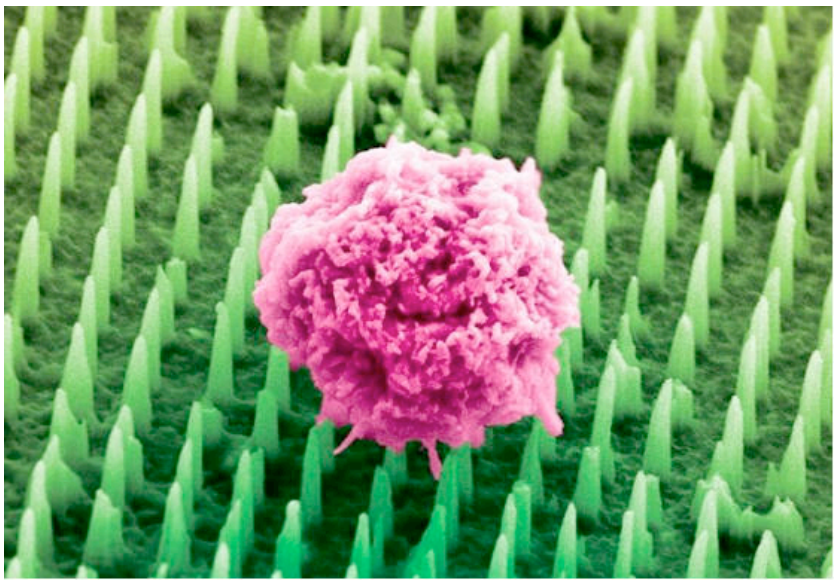
Nanoneedles and nanopillars offer an exciting new platform for studying mechanotransduction in living cells,[1] transfection of nucleic acids,[2] as a tool for intracellular electrical recording,[3,4] and can be combined with techniques such as scanning ion conductance microscopy.[5] The fabrication of these structures takes techniques from the traditional silicon microfabrication and engineering environments and apply them to solve biologically relevant problems.[6,7]

Here we will give an overview of the state-of-the-art research using nanoneedles and nanopillars, and review the different fabrication approaches that make them possible. We will identify new areas and challenges for the use of these nanostructures.



False-colour SEM micrograph showing a cell interfacing a porous silicon nanoneedle array.[2]

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Poster Presentations

Poster Session: Wednesday, March 15th, 19:00

(organized alphabetically by last name of presenting author)

Elastic microelectrodes for bioelectronic recording from peripheral nerves

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Monitoring of bioelectric signals in peripheral nerves is crucial to gain understanding of how the autonomic nervous system controls specific body functions related to disease states such as inflammatory response.[1,2] In order to achieve long-term, chronic recordings, that do not interfere with nerve function or animal behaviour, a low-invasive wireless electrode technology has to be developed.

In this work, we present our efforts to achieve a wireless peripheral nerve interphase based on stretchable electrodes to record from the splanchnic nerve in rats. Polydimethylsiloxane (PDMS) is used as elastic substrate and encapsulation material for electrodes and interconnects made of thermally evaporated Ti/Au. A kinked electrode shape has been introduced to facilitate the surgical procedure to position and fix the electrodes at the nerve. An electropolymerized layer of the doped organic semiconductor Pedot:Pss is deposited on the electrodes to reduce impedance and improve signal quality. Bioelectronic signals are then amplified and digitized by a subdermal battery operated transmitter. We show that our electrode is able to record neural activity of the splanchnic nerve during chronic experiments in free moving animals.

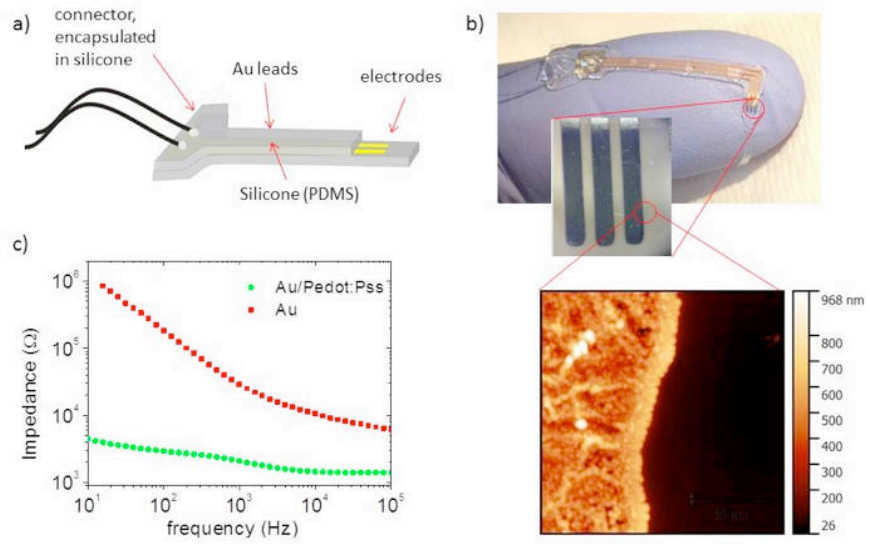

Figure: a) Scheme of electrode structure, b) Optical images and AFM topography image of stretchable electrode, c) Reduction of electrochemical impedance by electropolymerized PEDOT:PSS on the electrodes.

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Organic Electrochemical Transistors (OECTs) for low-cost and non-invasive monitoring of cell tissue

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The standard method to investigate cell stress response induced by drug treatment is based on the evaluation of in vitro cell colture conditions (adhesion and growth) by optical monitoring. Although optical techniques have high reliability and sensitivity, they require complex instrumentation and laboratory protocols. This has generated an increasing demand for easier, faster and portable tools for cell viability screening. A viable alternative is electrical monitoring using Organic Electrochemical Transistors (OECTs). In OECTs, the electronic current flowing in the conducting polymer channel is modulated by the ionic current crossing the interface with an electrolyte solution. The presence of cell monolayer at this interface limits the number of ions interacting with the conducting polymer, thus providing an electronic readout of the layer integrity. Moreover, the transistor configuration enhances the sensitivity due to amplification of the ionic current.

In our work, we realize, by low-cost fabrication techniques, OECTs based on poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) as conducting channel, for its biocompatibility as cell-culturing material,[1] its high conductivity and its transparency, that allows optical microscopy to validate electrical measurements (Fig.). Electrical monitoring is based on two parameters: the current modulation and the response time of the OECT to a potential step applied to the gate. We find that these parameters are quantitatively realted to cell layer integrity and confluence. Our devices provide a simple, label-free, non-invasive, and dynamic method to monitor cellular adhesion, proliferation and reaction to toxic agents, with the potential for high throughput and low-cost screening of drug discovery or toxicology.

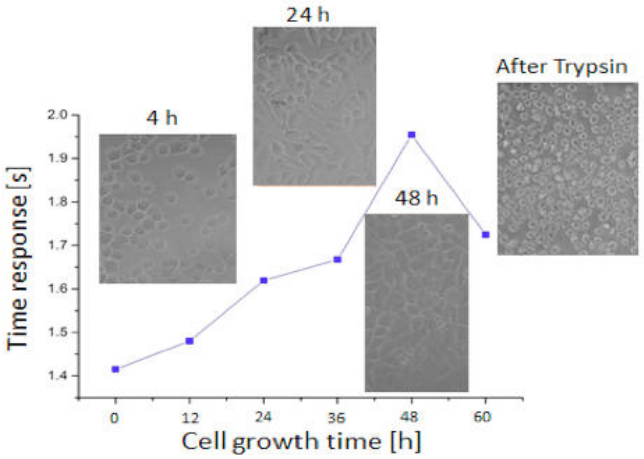

Figure: Response time of organic electrochemical transistor at different cell coverages (HeLA) and after the use of Trypsin-EDTA (an enzyme that detaches cells from the substrate).

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Lysinated-DPP semiconductor polymer for biological applications

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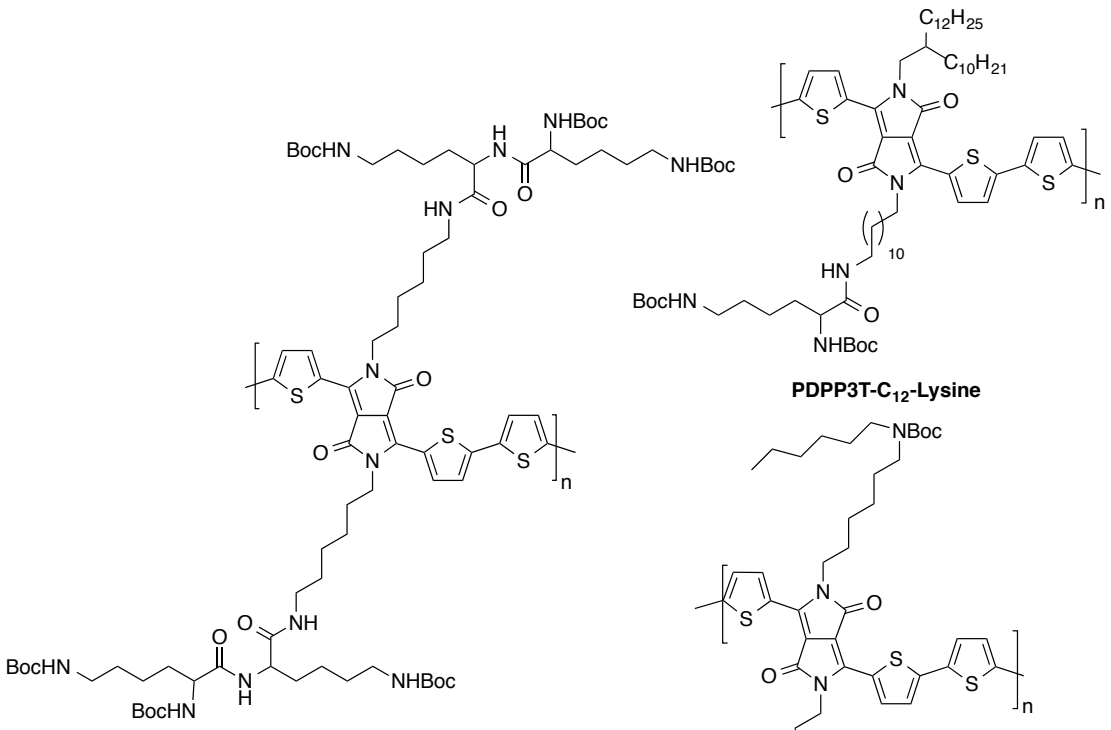
Organic semiconductors are being increasingly used for a variety of biological applications.[1] However, the poor adhesion of biological materials to such hydrophobic materials often results in their poor device performance. In this work we have developed a semiconducting polymer, based on diketopyrrolopyrrole (DPP),[2] with lysine side chains incorporated to increase adhesion, particularly for neural cells.[3] The synthesis and properties of this promising candidate for bioelectronics will be discussed.



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Total-Internal-Reflection Fluorescent Microscopy for Measuring Dopant Concentrations in Organic Electrochemical Transistors

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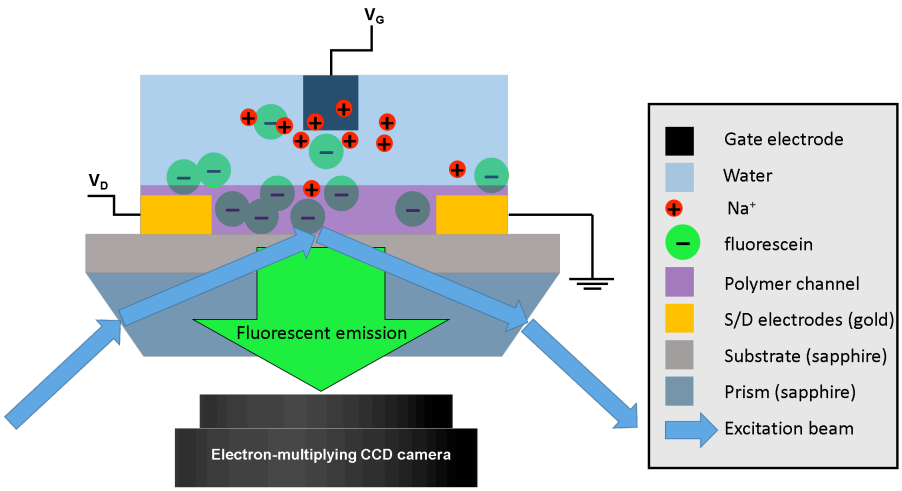
Organic electrochemical transistors (OECTs) are hybrid ionic/electronic biosensors, which have shown high signal-to-noise electrocorticography[1] and electrocardiography recordings,[2] metabolite[3] and DNA sensing,[4] and detection of single-cell cardiac action potentials.[5] OECTs operate in aqueous electrolyte environments, and are composed of source, drain, and gate electrodes with an organic semiconductor channel. Although the general ion-to-electron transduction in OECTs is well-described in the literature,[6] many details are still lacking. In this work, we show that total-internal-reflection fluorescent (TIRF) microscopy can provide a better understanding of ion-hole interactions in OECT channels. In particular, we provide quantitative measurements of ion concentration profiles in the OECT channel. These measurements yield fundamental understanding of OECTs that can be generalized to other hybrid ionic/electronic biosensors. They will not only allow more accurate interpretation of measurement signals, but they also will inform the design of biosensors with higher sensitivity and lower power consumption.



Experimental setup of TIRF microscopy for OECTs. The excitation beam is coupled into the substrate with a right-angle prism, and undergoes total internal reflection at the substrate-semiconductor interface. This allows for detection of fluorescent dopants in the OECT channel without interference from the dopants in the electrolyte.

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Synthesis of indigo nanocrystals with transient stability *in vivo* for application in photothermal therapy

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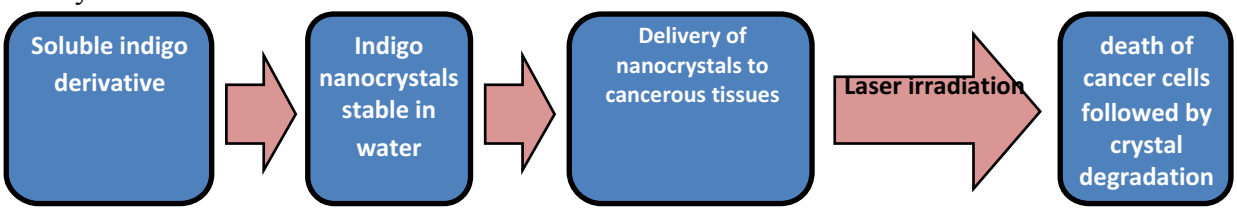
Semiconductor nanocrystals are modern materials with unique electronic and optical properties, widely investigated since 1982. From that time many methods of synthesis of well-designed inorganic nanocrystals were developed. That allows to have a good control over shape, size, physical and colloidal properties. Despite the enormous progress in chemistry of inorganic nanocrystals, organic semiconductor nanocrystals have been seldom investigated so far. Amongst organic conductors which can be synthesized in the form of nanocrystals, hydrogen-bonded organic pigments, like indigo, quinacridone and indanthrene seem to be promising[1], as they are biocompatible, have well-defined crystal structure, photocatalytic properties[2] and excellent photostability. Although they are widely applied as a pigments in fabric, paints, and inkjet toners, their semiconductive properties have not been widely investigated. Despite their low molecular weight and lack of conjugated π-bond system, transfer of charge carriers in these materials can be very efficient, due to strong $\pi - \pi$ stacking and creation of intermolecular hydrogen bonds. For example, efficient and air stable field-effect transistors have been obtained for indigo[3] and quinacridone[4]. An interesting feature of indigo is efficient photoinduced proton transfer, which leads to increase of temperature of light irradiated indigo solutions or solid crystals. What is more, absorption spectrum of indigo matches near-infrared window in biological tissue[3].

In this report we show our first results of synthesis of indigo nanocrystals for the targeted application in photothermal cancer treatment. The aim of this work is to synthesize indigo nanocrystals which can be injected to tumor tissue, irradiated with near infrared light, and then safely degrade and bioresorb. This approach has been widely investigated for gold nanoparticles[5] however their bioserobability remains a problem. In the synthesis of indigo nanocrystals, we used soluble indigo derivative, protected with *tert*-butoxycarbonyl group. In presence of secondary amines, the compound undergoes the deprotection reaction, with the formation of indigo nanocrystals. Their colloidal stability is provided with amine ligands, coordinated to the nanocrystals surface.



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External Quantum Efficiency measurements on an organic semiconductor – electrolyte interface

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There is yet a cure to be found for inherited retinal dystrophies, such as Retinitis Pigmentosa. As an alternative, artificial photoreceptors can serve as retinal implants for vision restoration in blinded patients. As a result, silicon based optoelectronics for retinal prosthesis has advanced to the level of clinical trials on patients.[1] However, silicon-based devices suffer from poor biological affinity, biocompatibility and mechanical flexibility. These difficulties can be reduced by the utilization of organic conjugated polymers and small molecules. The conjugated polymer, poly(3-hexylthiophene) (P3HT), has been successfully employed in restoring light sensitivity in explanted retinas[2] and even after implantation in the subretinal space of blinded rats.[3]

Our work focuses on the fundamental understanding of the enabling attributes that enhances the neuro-electrical coupling between an organic semiconductor-based photoreceptor and neuronal model cells.[4] Our studies are performed on the organic blend of a squaraine dye (SQIB) and PCBM in a bulk heterojunction structure. This blend, acting as the active layer, is deposited by spincoating on ITO-coated glass and is subsequently annealed. Optional, a dielectric coating is vapor-deposited on top. The work presented here is focused on EQE measurements. These measurements are applied to the artificial photoreceptor in contact with physiological Ringer's solution as shown in Fig.1. Since EQE is measured with chopped light illumination, the observed photocurrent contains contributions from conduction and displacement currents. We investigate the influence of chopping frequency, white light and voltage bias on the measured photocurrent.

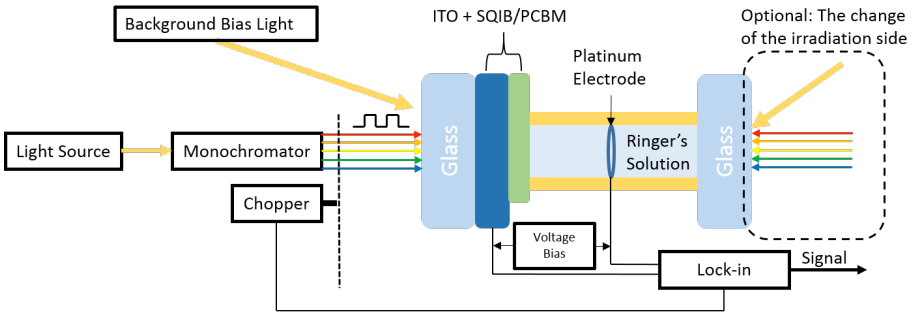

Figure 1: *The EQE setup to study the organic semiconductor/liquid interface.*

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Sub-Micron Lithographic Patterning of Sensitive Materials

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Conventional photolithography involves organic solvents that are incompatible with sensitive organic materials such as biological molecules and conductive polymers. Likewise, fabrication release layers generally require harsh organic solvents, acids, bases, or oxidizers for removal. Here we describe the use of germanium, a low temperature deposition semiconductor, as a barrier/liftoff layer for submicron patterning of sensitive biological molecules and conductive polymers that are sensitive to the aforementioned, but not to water. Specifically, we demonstrate, to our knowledge, the fastest PEDOT:PSS based OECT ever reported, showing an ON/OFF speed of 48.54 kHz with a 60 nm gate (Fig 1 A-B). Additionally, we demonstrate patterning of supported lipid bilayers, showing removal of the Ge layer leaves behind no residue (confirmed via XPS), and is a 'green' process, as it only involves water (Fig 1 C-D). Whereas "specialized" photoresists for patterning conductive polymers exist, they can have detrimental effects compared to water (only solvent seen by the final device). Additionally, this process allows use of standard photoresists, which continue to benefit from decades of person-years of optimization from industry, guaranteeing resolution and reproducibility.

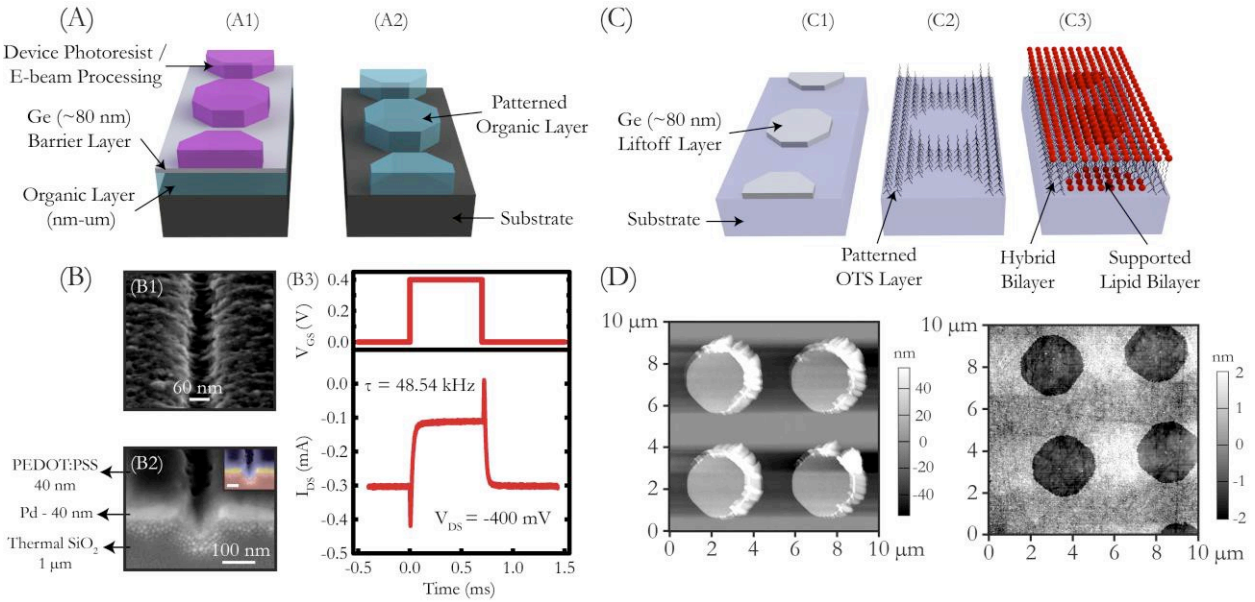

Figure 1. (A) Schematic of fabrication summary, highlighting (A1) standard photoresist use, Ge barrier & organic layer. (A2) Patterned organic layer. (B1) Scanning Electron Microscopy (SEM) images of 60 nm channel length, and (B2) corresponding cross-sectional SEM. Top right false colored to highlight layers labeled. Scale is 100 nanometers. (B3) Drain-Transient curve, showing ON/OFF speed of 48.54 kHz; to our knowledge, the fastest PEDOT:PSS based OECT ever reported. (C1-3) Schematic of fabrication summary, highlighting patterning of sensitive biological molecules. (D) Corresponding Atomic Force Microscopy (AFM) images for (C1), left, and (C2), right, respectively.

Bioinspired Soft Machines

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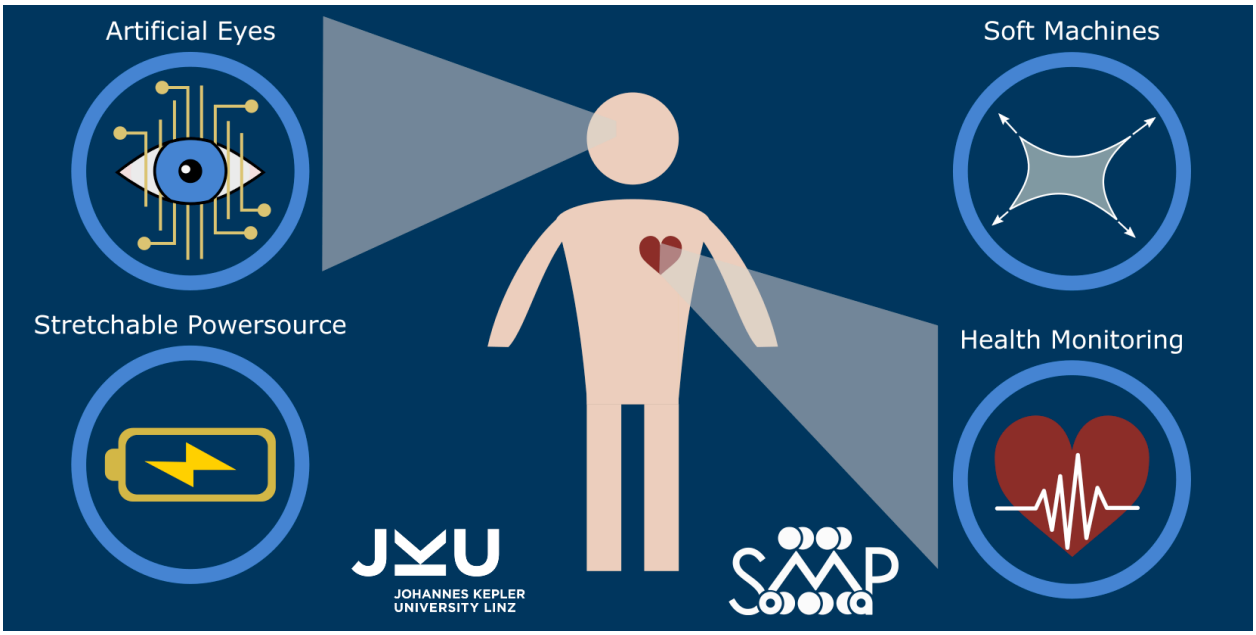
The architecture of living beings – from marine creatures to mammals – assembles modules of hydrogels to create machines of high complexity. The interaction of tissue, muscles and tendons enable us to see, move and communicate. These natural hydrogels range from extremely soft to tough gels, which are even conductive, transparent, or light sensitive. Engineered hydrogels for soft robots and bioelectronics can mimic these properties, leading to novel machines, sensors, and interfaces for machine-human communication. Here we present approaches to engineer smart hydrogel materials with different mechanical and optical properties. In combination with strong bonding methods, the hydrogels attach to a wide range of materials and enable the demonstration of an electrically driven, variable focus lens, stretchable batteries and stretchable optical waveguides.[1] Besides the progress of stand-alone robots, the advances in the synthesis of hydrogels renders the implementation of soft machines inside the human body possible – either as monitoring systems or functional, biocompatible prostheses.



Applications of soft machines for health monitoring and battery powered prostheses.

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Organic hydrogen-bonded semiconductors in aqueous environments – from bioelectronics to catalysis

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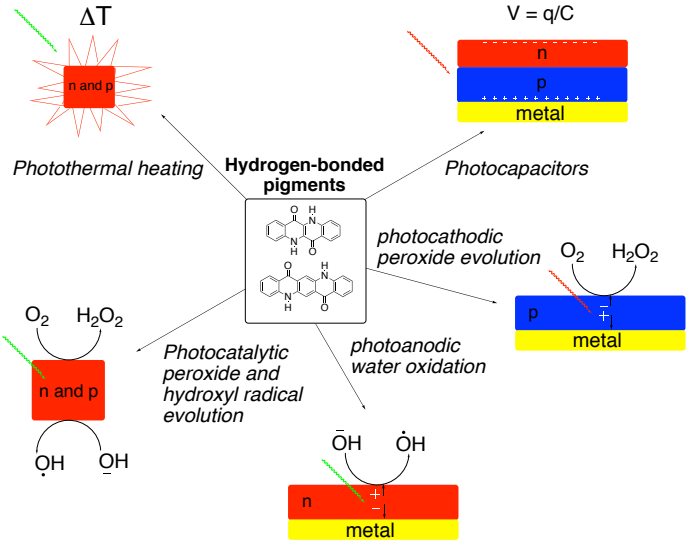
Organic conducting polymers such as PEDOT are routinely successfully deployed in bioelectronics devices. Organic semiconductors, especially organic small molecules, usually have problems with operational stability and degradation reactions in aqueous environments which greatly limits their utility in such devices. Recently, we have explored organic hydrogen-bonded semiconductors as materials which combine desirable (opto)electronic properties with outstanding stability in a wide range of aqueous conditions. We have elaborated different nanocrystalline structure of the hydrogen-bonded semiconductors which can form close interfaces with cultured cells without observable cytotoxicity. Developing cell/semiconductor interfaces with minimal clefts is of major interest to form effective optoelectronic connections with cells. We discuss results of photostimulation on the single-cell level, as well as on an electrogenic tissue – a blind embryonic chicken retina. During the course of ongoing work on photostimulation of cells, we have discovered that certain hydrogen-bonded materials also are photo- and photoelectrocatalysts, operating with remarkable efficiency and stability and therefore introducing new types of functionality. Overall a rich optoelectronic behavior of these materials in a wide range of aqueous environments opens up many avenues in both bioelectronics and photocatalytic energy devices.



Indigoidine – Biosynthetized Organic Semicunductor

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Semiconducting organic materials have attracted a particular interest over past decades due to their flexibility, easy processing, potential low fabrication cost, and large area fabrication. Even though in comparison with conventional inorganic semiconductors organic ones can be considered as more "environmentally responsible" due to low processing temperatures, ease of utilization (by incineration) and relative non-toxicity, most of the techniques of synthesis, purification and deposition require using toxic halogenated solvents. On the other hand, compared with conventional chemical synthesis, biosynthetic approaches offer particular advantages; enzymes, used in biosynthesis, generally operate in "biologically friendly" environment, mostly in aqueous media, neutral pH at ambient temperatures and atmospheric pressure. Generally biosynthetic approach enables to obtain complex molecule from cheap and abundant materials.
Recently, an efficient way of producing indigoidine dye by mimicking the organism's biosynthetic machinery inside a heterologous host cell was found [1]. Indigoidine is a deep blue dye, originally considered as a promising alternative to the synthetic dyes used to color jeans, leather, food and paper. However, indigoidine is a semiconductor with a band gap of ~1.77 eV with high extinction coefficient, perfectly planar structure allowing intra- and intermolecular hydrogen bonding and well-adjusted energy levels. These properties of the molecular structure can be a sign of high charge carrier mobilities, which allows proposing using indigoidine in OFET devices or solar cells. Moreover, the molecule has such functional groups as carboxyl and amine open a path for the application of indigoidine in supercapacitors and batteries (carbonyl, carboxy, or quinone-based compounds have been demonstrated to be biomimetic energy storage electrode materials) or carbon dioxide capture by amine groups.

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Bio-inspired riboflavin derivatives for organic electronics and biomimetic energy storage

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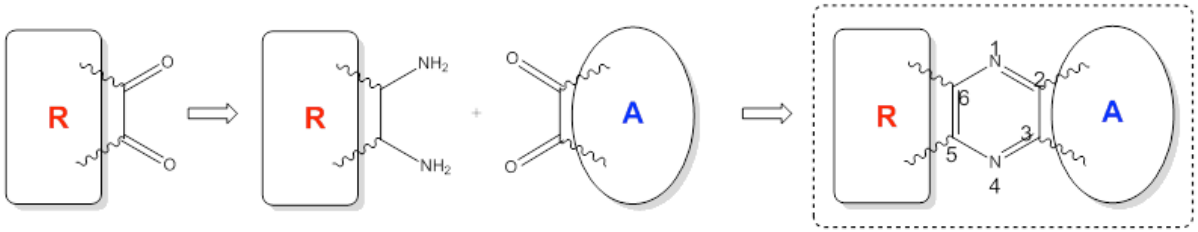
Biologically inspired molecular engineering is a promising way towards environmentally responsible, cheap, non-toxic and efficient materials for organic electronics and energy storage. Additionally, to natural conjugated materials used in organic electronics ability to tune molecular structure allows to improve stability and performance of the original material. As an example, flavines are one of most structurally and functionally versatile redox centers in nature, which act as catalyzers in a wide range of biotransformations and electron-transfer reactions. A strongly electron-withdrawing diimide group on the pyrazine core allows electron transfer through the redox cascades in the biological systems. Dimide highly extended π-conjugated structure produce strong π–π intermolecular interaction and the controllable physicochemical properties by introducing a variety of alkyl chains on the *N*-position in diimide group.[1]



Present work demonstrates the implementation of riboflavin inspired derivatives in organic electronics applications; such as semiconducting materials and bio-inspired redox centers for biomimetic energy storage. Using pyrazine core with diimide groups as a building unit allows intermolecular hydrogen bonding of the compounds, therefore assuming that flavin molecules are planar high overlapping of the molecular orbitals, thus high charge-carrier mobilities can be achieved.
Novel bioinspired-materials topic spreads the wide experience of our multidisciplinary team on the field of preparation and characterization of smart organic systems.[2,3]

Acknowledgement: This work was supported by Czech Science Foundation via project No. 15-05095S, research infrastructures were supported by project *MEYS* No. LO1211.

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A bioinspired approach for tailoring surface electronic properties of ITO

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Controlling energy band alignment at the interfaces of indium tin oxide (ITO), one of the most commonly used electrode in optoelectronic devices, is crucial for improving device performance. Grafting Organic monolayers at the interface has been shown to be an attractive approach to achieve this task. In this work, I will show that bioinspired peptide monolayers are perfectly suited for such applications, due to their versatility and ease of design and preparation.

As a first step to reveal peptide design rules, the effect of peptide side chains on the electronic properties of ITO in the context of monolayers of single amino acids will be presented. Using monolayers of positively and negatively charged, neutral and aromatic amino acids, I will demonstrate a correlation between the molecular dipole and changes in the surface work function of ITO. Monolayers of tyrosine will be shown to strongly passivate the surface. Similar behavior will be presented for a series of unnatural aromatic amino acids, indicating that the aromatic group derives the passivation effect. Amino acid monolayers are shown to enable tuning ITO's work function in the range of 430 meV.

Based on the single amino acid studies, a series of peptides with varying amount of positive charge were designed, aiming at reducing the ITO work function. Indeed, a correlation between the amount of positive charge and the work function will be presented, where the larger the peptide charge is, a smaller work function is measured. These results demonstrate the tunability gained by using amino acids and peptides for tailoring the electronic properties of ITO.

Making Sense of miRNAs: Highly-Sensitive Early Detection of Pancreatic Cancer

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Pancreatic cancer is one of the most lethal cancers in existence; it is the only cancer with 5-year survival rates of less than 10%[1] and is projected to rank second in cancer-related deaths as early as 2020.[2] Early detection remains a current challenge owing to the absence of symptoms that do not manifest until advanced stages – leading to late-stage detection and very poor prognosis. High medical costs reveal the heavy financial burden posed to the health system as well as to the patients by this disease.[3]

To address this long-standing malignancy, we have designed a nanobiosensor for detecting early-stage cancer biomarkers. The device works by sensing miRNAs expressed at various disease stages, which are released into the bloodstream and also excreted in urine and/or saliva. The biosensor exploits the evolving abnormal miRNA expression profile, thereby achieving immediate cancer detection, as well as identification of the type and stage of cancer. By using chimeric heterofunctional constructs involving two different biopolymers, and employing organic and graphene field-effect transistors[4] (OFET/gFET) strategies, these biosensors can achieve high sensitivity and selectivity, specifically detecting circulating miRNAs by enhancing the detector signal upon miRNA biorecognition.

Research supported by Amazon-Catalyst Program via UW-CoMotion and MGI Program through NSF-DMR.

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Development of electron transport semiconducting polymers for bioelectronic applications

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Organic semiconducting materials have rapidly emerged as promising candidates for efficient signal transduction between electron- and ion-mediated systems, offering numerous possibilities for bioelectronic applications.[1] A particular transistor architecture which has attracted a great deal of interest in recent years is the organic electrochemical transistor (OECT). Most high performance OECTs are fabricated using the commercially available polymer blend poly(3,4-ethylenedioxythiophene): poly(styrenesulfonate) (PEDOT:PSS), which offers limited opportunities for chemical modification and optimisation of the transistor parameters. Recent investigations of a series of semiconducting thiophene-based polymers with various degrees of triethylene glycol (TEG) side chain densities and orientation led to several enlightening structure-property relations which can guide the development of novel high-performing OECT materials for hole transport (p-type).[2] However, there is a lack of studies focused on electron transport (n-type) or ambipolar active materials, which limits the development of complementary circuits and sensor technologies.[3] In the search for novel n-type polymers with combined ionic and electronic transport properties, we report the synthesis of a systematic range of naphthalene diimide-based copolymers with polar side chains. The effect of increased glycol chain density on the overall performance of the device was investigated, aiming to identify optimum structural features for both efficient ion transport and high electron mobility. Recent progresses in incorporating a naphtho[2,3-b:6,7b′]dithiophene diimide unit into the backbone of the polymer will also be presented.

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In vivo measurement of electrical signals in live plants using organic electrochemical transistors

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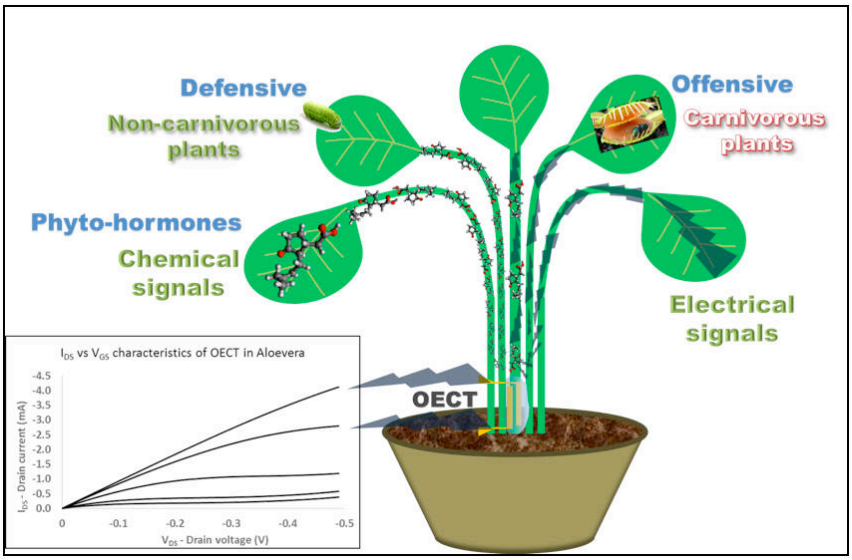
Plants, unlike animals, have been considered to be non-bioelectric until the late 19th century. Investigation of bio-electric signals in plants due to external stimulations can be traced back to Charles Darwin and Burdon Sanderson (1873).[1] It is known that, compared to chemical (hormonal) signals, electric signals in living organisms are vital in fast and long distance communications. Moreover, the effects of variations in external environmental conditions, herbivore attacks, and biotic and abiotic stresses, can trigger intra and inter plant defense mechanisms. However, the physiological significance and link between electric and chemical signals in plants is crucial in understanding communication within and between the plants. Cheap, fast, and electronic measurements of 'phyto' signals is thus a demand from plant physiologists.[2,3]

We present, *in vivo* measurement of electrical signals in Aloe vera using organic electrochemical transistors (OECTs) and surface-mounted electrodes. In addition to low cost, flexibility, and low power operation, OECTs offer the added advantages of localized signal amplification and the capability of detecting ionic species in different media. Changes in electrical signals due to defense hormones and variations in external factors were investigated. Such sensors can provide an important tool in answering a plethora of lingering questions about how plants communicate.



The figure elucidates different communication mechanisms in plants and an organic electrochemical transistor (OECT) incorporated into a plant. Inset shows typical output characteristics of an OECT operating in vivo.

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2. Mousavi et al., Nature, 500, 422-426 (2013).
3. S. Lautner et al., Plant, Cell and Environment 30, 249–257 (2007).

Organic electrochemical transistors for real-time cell culture monitoring

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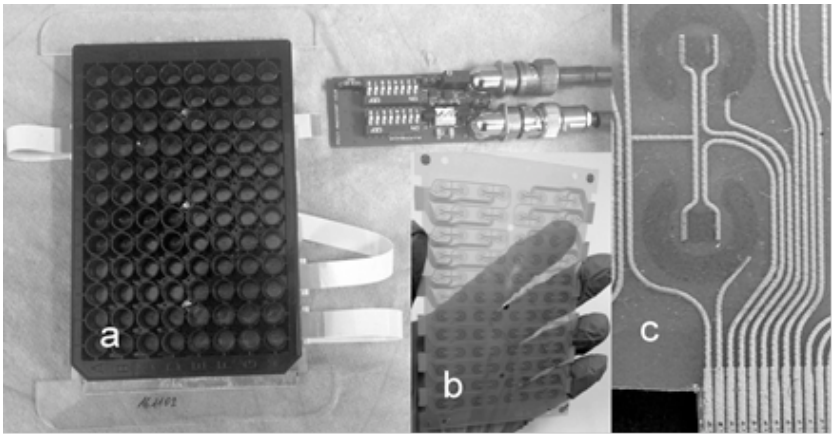
Cardiotoxicity is a serious problem of many already well-established drugs. The most prominent example is the fact that administration of some anticancer drugs may result in therapy-related cardiovascular disease. But especially, the cardiotoxicity complicates the drug development in general. Thus, proper handling of cardiotoxicity assays may speed up drug design greatly, providing patients with safer treatment in more reasonable time.
The cultivation of human cells in vitro is potentially powerful tool for investigation of drug interaction with the organism for treatment and toxicity testing. In our work the microplate with multielectrode array of 96 organic electrochemical transistors (OECTs) based on semiconductive polymer PEDOT:PSS was developed and fabricated by the screen printing method.
The results of simulation regime without biomaterial but with electrolyte bring the setup information of the experimental conditions. The transconductance g = 1.4 mS was achieved in wide range of gate voltage $V_G = \pm 0.4$ V) when the drain potential $V_D = -0.75$ V was set and the long term relaxation was compensated. The device was tested on 3T3 fibroblasts cell culture and the sudden environmental changes were recorded.



a) Encapsulated OECT 96 well microplate for electrogenic cells cultivation and investigation with power source and signal amplifier b) foil with the all screen printed OECT array c) detail of the OECT with PEDOT:PSS printed channel and gate electrode.

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Organic Electronic Ion Pumps Based on Capillary Fibers

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Organic bioelectronics, in form of the organic electronic ion pump (OEIP), have been used to modulate cell and tissue function using flow-free delivery of small biological signaling compounds with high spatiotemporal resolution.[1,2] Methods to fabricate OEIP based devices have traditionally used photolithographic techniques on planar substrates to sequentially pattern active and passive areas.

While such methods offer great flexibility in OEIP design, when it comes to devices for implantation into biological systems, traditional planar designs face significant scale and rigidity issues.[3] Namely, high aspect ratio features and the presence of substrate and encapsulation layers greatly increase overall device size and can place significant restrictions on insertion or implantation capabilities in living tissues.

Here we investigate OEIP devices utilizing a new form factor – glass capillary fibers – that are filled with a polyelectrolyte. Capillary fibers offer several design advantages for use with implantable OEIP devices. Importantly, because the capillary fiber simultaneously serves as both encapsulation and substrate, OEIP devices at the scale of the human hair (50 – 100 μm) are readily achievable.

Such devices can be easily inserted and brought into close proximity to targeted cells and tissues. Here, we demonstrate capillary fiber based OEIPs on living plant tissue. Device performance is characterized for Zn^{2+} ions, and insertion into plant tissue is investigated.

Our results provide a starting point for other fiber based OEIP technologies enabling favorable implantable device geometries.

1. Simon, D. T. *et al.* Organic electronics for precise delivery of neurotransmitters to modulate mammalian sensory function. *Nat. Mater.* 8, 742–746 (2009).
2. Tybrandt, K. *et al.* Translating electronic currents to precise acetylcholine-induced neuronal signaling using an organic electrophoretic delivery device. *Adv. Mater.* 21, 4442–4446 (2009).
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High performance porous platinum electrodes for stretchable microelectrode arrays

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While traditional electronic devices are fabricated as rigid and planar structures, the new generation of biomedical devices needs to be soft, flexible and biocompatible in order to adapt to the curvilinear shapes of the human body. These features are combined in polydimethylsiloxane (PDMS), a stretchable and biocompatible elastomer with a Young's modulus around 1MPa, currently used in soft and stretchable electronics. It already has shown to be a suitable material for several biomedical applications as brain recordings, cardiac recordings and epidermal sensors.[1,2]

We developed a fast fabrication process, which allows us to produce a fully functional structure of up to several dozen electrodes within a day. The filter technique developed by Tybrandt et al. was adapted using a photolithography-patterned membrane, to assure limited material waste.[3]

The produced soft microelectrode array (MEA) consists of biocompatible conductive nanomaterials, which are embedded in PDMS. Its microelectrodes are porous pillars that show a decreased impedance due to the gain in electrode surface and stable stimulation when compared to other stretchable microelectrodes. This is especially important for frequencies below 1 kHz, when measuring on a single cell level. The electrode grid as well as the electrodes themselves can be freely defined with desired shapes and sizes, opening new possibilities in stretchable electronics.

Our fabricated MEAs perfectly adapt to their surroundings, improving the cell-electronic interface of three dimensional cell cultures *in vitro* for stimulation and recording of the electrical excitable cells. Additionally, they are currently tested *in vivo* for long-term measurements, demonstrating the broad field of applications possible with this technique and electrodes.

Acknowledgment:
Thanks to Stephen Wheeler & Martin Lanz for their help in the workshop and cleanroom and to ETH Zurich, Nano-Tera and SNF for funding.

1. Towne, C., Montgomery, K. L., Iyer, S. M., Deisseroth, K. & Delp, S. L. Optogenetic control of targeted peripheral axons in freely moving animals. PLoS One 8, e72691 (2013).
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Capacitative and heat induced modulation of ion-channels by the organic pigment semiconductor quinacridone

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The semiconductor quinacridone was transformed into 3D structures, including shapes of hedgehog-shaped like crystals. These structures were produced in a similar size than single living mammalian cells. The hedgehog-shaped crystals were co-cultured with human and rat cells and yielded specific contact sites, representing ideal interfaces for semiconductor optoelectronic cellular stimulation. The semiconductors are perfectly biocompatible based on cytotoxicity tests and provided a platform to enhance cell growth. Whole-cell patch-clamp technique was used to directly measure how ion-channels are modulated by attached quinacridone semiconductor stimulation. Specifically, endogenous K^+ currents from a rat immune cell line were recorded. Photo-stimulation of quinacridone based 3D structures resulted in capacitative- and heat-induced modulation of the K^+ currents. This work demonstrates that a colorant used for inks and cosmetics can work as functional 3D semiconductor to shape ion-channel signaling in single living cells.

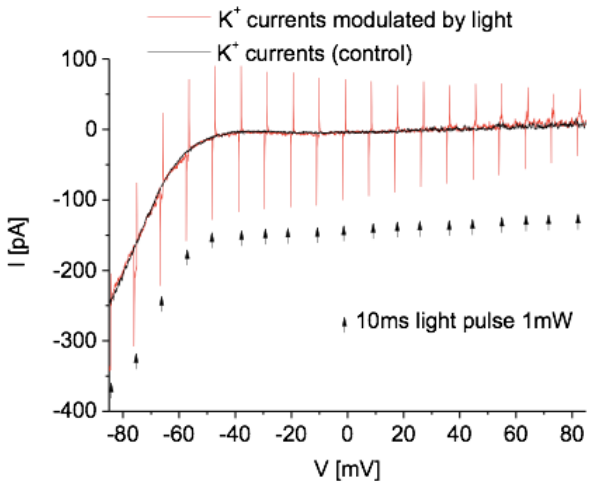

Fig. : Ion channel current modulation by light. Hedgehog shaped quinacridone was stimulated by short laser pulses that were in direct contact with a single rat mast cell. Arrows indicate 10ms pulses of 1mW laser light. Current-voltage relationship is measured by applying repetitive voltage ramps (red trace). Control trace without light stimulation is shown in black.

Notes:

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BioEl 2017

	Saturday March 11th	Sunday March 12th	Monday March 13th	Tuesday March 14th	Wednesday March 15th	Thursday March 16th	Friday March 17th	Saturday March 18th
07:30 – 08:30		Breakfast						
Session I		Chair: Melosh	Chair: Gorodetsky	Chair: Sariciftci	Chair: Rivnay	Chair: Yumusak	Chair: Noy	
08:30 – 09:30	*Arrival Day*	**Palanker** *(tutorial)*	**Tian** *(tutorial)*	**Cui** *(tutorial)*	**Dickey** *(tutorial)*	**Varghese** *(tutorial)*	**Salleo** *(tutorial)*	*Departure Day*
09:30 – 10:00		**Schiavone**	**Nielsen Shirinskaya**	**Aktaş**	**Antognazza Offenhäusser**	**Inal**	**Mariani Hütter**	
10:00 – 10:30		Coffee breaks						
Session II		Chair: Inal	Chair: Sinner	Chair: Hierlemann	Chair: Cui	Chair: Dickey	Chair: Offenhäusser	
10:30 – 11:30		**Hinterdorfer** *(tutorial)*	**Hierlemann** *(tutorial)*	**Vörös** *(tutorial)*	**Ashkenasy** *(tutorial)*	**Bauer** *(tutorial)*	**Pezzella** *(tutorial)*	
11:30 – 12:00		**Donahue Nawrocki**	**Sarikaya Thompson-Steckel**	**Smolka Holovchenko**	**Noy Kaltenbrunner**	**Criscuolo Zozoulenko**	**Lopez-Martinez Higgins**	
12:00 – 17:30		Free form discussions						
17:30 – 19:00		Dinner						
Session III		Chair: Glowacki	Chair: Palanker	Chair: Stavrinidou		Chair: Vörös		APPENDIX
19:00 – 19:30	*REGISTRATION*	**Kim**	**Stavrinidou**	**Rivnay** *(tutorial)*	POSTER SESSION	**Köstler**	**Bauernbuffet** (Festive final dinner in traditional Tyrolean style)	Tutorial and invited talks
19:30 – 20:00		**Hanna Rand**	**Freeley Gorodetsky**			**Hasegawa Santoro**		Contributed talks
20:00 – 20:30						BIOEL International Advisory Board Meeting		Events
20:30 – 21:00	**Welcome Wine**							