Conducting polymer-based nanostructured materials for brain-machine interfaces

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**Authors:**

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| **Yasamin Ziai**<br><br>Department of Biosystems and Soft Matter, Institute of Fundamental Technological<br><br>Research, Polish Academy of Sciences, Warsaw 02-106, Poland<br><br>ORCID ID: 0000-0002-0648-761X |
| **Seyed Shahrooz Zargarian**<br><br>Department of Biosystems and Soft Matter, Institute of Fundamental Technological<br><br>Research, Polish Academy of Sciences, Warsaw 02-106, Poland |
| **Chiara Rinoldi**<br><br>Department of Biosystems and Soft Matter, Institute of Fundamental Technological<br><br>Research, Polish Academy of Sciences, Warsaw 02-106, Poland |
| **Paweł Nakielski**<br><br>Department of Biosystems and Soft Matter, Institute of Fundamental Technological<br><br>Research, Polish Academy of Sciences, Warsaw 02-106, Poland |
| **Antonella Sola**<br><br>Department of Engineering "Enzo Ferrari" (DIEF), University of Modena and Reggio<br><br>Emilia, Modena, Italy |

**Massimiliano Lanzi**

Department of Industrial Chemistry "Toso Montanari", University of Bologna, Viale Risorgimento 4, 40136 Bologna, Italy.

**Yen Bach Truong**

Commonwealth Scientific and Industrial Research Organisation (CSIRO), Clayton, VIC 3168, Australia

**Filippo Pierini** *

Department of Biosystems and Soft Matter, Institute of Fundamental Technological Research, Polish Academy of Sciences, Warsaw 02-106, Poland

### Abstract

As scientists discovered that raw neurological signals could translate into bioelectric information, Brain-machine interfaces (BMI) for experimental and clinical studies have experienced massive growth. Fabrication of bioelectronic devices, which can be used for real-time recording and data digitalizing, has three important necessitates which should be covered. Electrical conductivity, biocompatibility, and having mechanical properties similar to soft brain tissue to decrease mechanical mismatch should be adopted for all materials. Inorganic nanoparticles and intrinsically conducting polymers are discussed to offer electrical conductivity to the systems, where soft materials such as hydrogels can offer reliable mechanical properties and a biocompatible substrate. Novel fabrication methods, like electrospinning and 3D printing, allow scientists to customize designs for each application and reach the maximum potential for the system.

## 1. INTRODUCTION

Bioelectronic signals are among the principal activities of our body's routine function, including electrophysiological and biochemical stimulation (Yao et al., 2020). In particular, electronic signals within the nervous system regulate several biological activities, from simple skeletal muscle movements to complex brain functions such as thinking and remembering (Miller, Hermes, & Focus, 2020). Regular brain activities provide the coordinated transmission, oscillation, and synchronization of neural signals, involving a considerable part of the nervous tissue. However, in the case of neurological injuries, disorders, and degenerative processes, the neural population shows an insufficient capacity for self-repairing and regeneration, leading to permanent brain dysfunctions (Rinoldi, Zargarian, et al., 2021). Neurological trauma caused by accidents can provoke injuries in the brain tissue, nerves, or spine and subsequently affect several body functions, including vital organs, blood vessels, and musculoskeletal activities. Car, bike, and sports accidents, as well as accidental falls, are the most common situations which lead to neurological damage (Pichiorri & Mattia, 2020). On the other hand, neurological illness may occur in any person worldwide, regardless of gender, age, education, or wealth, and it has been estimated as 1 billion cases yearly (World Health Organization, WHO)("Neurological disorders affect millions globally: WHO report," n.d.). The high incidence results in several billions of Euros spent annually to sustain the costs related to neurological disease treatments(Y Liu, Feig, Materials, & 2021, 2021). For this reason, the effective detection of neural signals is crucial for obtaining bioelectronic information about cognitive processes and pathways as well as diagnosing and treating related diseases (*e.g.,* schizophrenia, autism, epilepsy, Parkinson and Alzheimer's)(Oldroyd & Malliaras, 2022)(Mcglynn et al., 2021). Therefore, several electrically conductive devices have been lately researched and developed for the fabrication of bioelectronic devices, including brain-machine interfaces (BMIs)(S. M. Won et al., 2018b)(Zhao, Spyropoulos, Cea, Gelinas, & Khodagholy, 2022). These systems are designed to serve as implantable interface electrodes to record and digitize the brain signals in real-time by directly transferring them to a computer for final visualization and analysis(Song, Li, Won, Bai, & Rogers, 2020). Approaches for brain signal recording can be divided into three main categories: i) recording on the top of the scalp (*i.e.,* electroencephalography, EEG); ii) recording under the skull, on the brain cortex surface (*i.e.,* electrocorticography, ECoG); iii) intracortical recording into the brain tissue (*i.e.,* local field potential, LFP) (Figure 1a)(Alahi et al., 2021). According to the position of the related electrodes, EEG, ECoG, and LFP differentiate for two main factors: the invasiveness and the amplitude of acquired potentials(Sung et al., 2020)(M. Lee, Shim, Choi, & Kim,

2019). EEG is a non-invasive strategy and has – consequently - the lowest acquired potentials (~ 1 μV) and spatial resolution. On the other hand, among the invasive approaches, ECoG shows a high signal-to-noise ratio and good spatial resolution. Additionally, it is less invasive than LFP, but it registers signal at lower amplitudes (~ 100 μV for ECoG *vs.* ~ 1 mV for LFP) (Figure 1b)(M. Zhang, Tang, Liu, & Van der Spiegel, 2020).

In this frame, recent advances are aimed at improving the efficiency and functionalities of BMIs in terms of recording, monitoring, and stimulation of bioelectronic signals (Polikov, Tresco, & Reichert, 2005)(N Wu et al., 2021). When designing an ideal electronic device, one should consider inducing minimal traumas during implantation, along with avoiding micromotions by guaranteeing the possibility of deformation according to the native tissue movements (Choi, Kim, Ryu, Kim, & Sohn, 2018a). However, nowadays, many of these proposed devices (*e.g.,* metal- and silicon-based) have the limitation of mismatching the mechanical properties with the brain tissue, which is particularly crucial for successful device implantation (Sunwoo et al., 2020)(Yuk, Lu, & Zhao, 2019a). Indeed, the intrinsic difference between soft, high water-containing brain tissues (1-100 kPa) and stiff, brittle and dry synthetic devices (with mechanical characteristics in the order of GPa) can result in injuries and poor coupling and integration at the implantation site (Shur et al., 2020a)(Llerena Zambrano et al., 2021). This may introduce chronic inflammation reactions and interfacing issues, resulting in an increase in impedance - due to the formation of astrocytic scars and microglia populations - and a decrease in detection and stimulation efficiency - because of delamination phenomena (Figure 1c)(X. Wu & Peng, 2019)(Dhawan & Cui, 2022). The ideal material for BMI applications should observe three main requirements: i) it should be compatible at physical and chemical levels in order not to induce any damage or injury to the brain tissue; ii) it should have high electric conductive characteristics for improving the acquisition of signals; iii) it should be highly biocompatible to minimize the immunological and inflammatory response (Khan, Wilts, Vlaisavljevich, Long, & Verbridge, 2021)(Shur et al., 2020a).
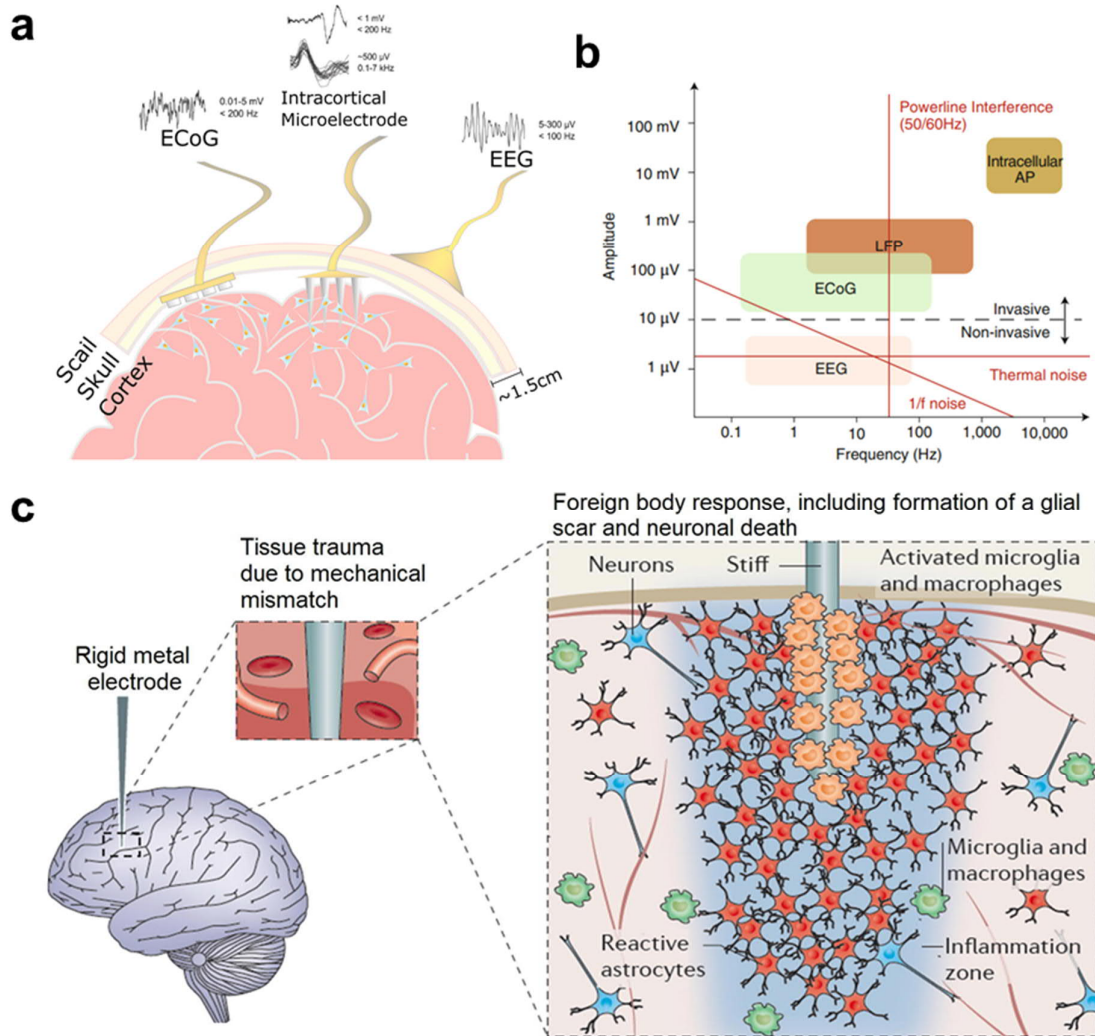
**Figure 1.** Characteristics and features of brain-machine interface. (a) Schematic representation of different brain signal recording approaches, including ECoG, EEG, and LFP (intracortical microelectrode). Reprinted with permission from Alahi et al. (2021)(Alahi et al., 2021). (b) Differences in acquired signal amplitude in the case of different recording strategies. Reprinted with permission from Zhang et al. (2020)(M. Zhang et al., 2020). (c) Schematic illustration of neuroinflammation occurring during the implantation of rigid metal electrodes. Reprinted with permission from Wu et al. (2019)(X. Wu & Peng, 2019).

For this reason, researchers are dedicating considerable efforts to design a new generation of soft and compatible devices at chemical, physical and biological levels, investigating conducting polymer-based nanostructured systems (Yuk et al., 2019a)(Y. Wu, Zhang, Wang, & Wang, 2020a)(Dalrymple et al., 2020)(Cuttaz, Chapman, Syed, Goding, & Green, 2021). Biocompatible conducting polymers are considered great candidates for electronic devices such as BMIs, because of their suitable biological

response as well as tunable electrical, optical and mechanical properties (S. Lee, Ozlu, Eom, Martin, & Shim, 2020)(Yuk et al., 2020a)(Y. Park, Chung, Lee, & Rogers, 2022a)(Goding, Vallejo-Giraldo, Syed, & Green, 2019). Indeed, compared to metal and silicon-based devices, conducting polymers offer a large room for improvements in terms of modification and optimization of the final system. For instance, they have the great ability to modulate their stiffness by applying hierarchical nano-structuration and providing the use of soft hydrogel networks. Thus, conducting polymers can potentially reassemble the brain tissue characteristics, avoiding mechanical mismatching while guaranteeing excellent electrical conductivity for efficient transduction of brain signals (M. Wang et al., 2017)(Goding et al., 2019)(Rylie Green, 2019). The biocompatibility and adhesiveness of those systems can lead to a minimum gap between biological tissues and electrodes, thus minimizing their relative movements and guaranteeing an intimate electrode-tissue contact (Nan Wu et al., 2021). Additionally, they have the great advantage of reducing the interfacial impedance, which is crucial in biomedical applications since biological signals are alternating currents transmitted (Parashar, Prajapati, McIntyre, & Kandasubramanian, 2020).

In this review, we present and critically discuss the most recent scientific literature on conducting polymer-based nanostructured materials for brain machine interfaces. Our focus includes systems based on inorganic nanomaterials and composites - as carbon nanotubes, graphene, graphene oxide, and reduced graphene oxide -, intrinsically conducting polymers and blends - like polyaniline, polypyrrole, and polythiophene -, and conductive interpenetrating polymer hydrogel networks - such as semi-IPNs and IPNs. The advantages and limitations of the reported devices have been highlighted, along with the challenges of fabrication and nanostructuration methods (including electrospinning and 3D printing). Finally, new trends and future perspectives of the BMI field have been discussed.

## **2.** INORGANIC NANOMATERIALS AND THEIR COMPOSITES

The most common devices implanted in the brain are electrodes (Jia & Rolandi, 2020). Several inorganic materials have been considered and studied as electrodes for brain tissue–machine interfaces (N Wu et al., 2021)(Yang et al., 2010)(Scaini & Ballerini, 2018). Among them, noble metal particles have been explored extensively due to their excellent electrical conductivity, chemical stability and good biocompatibility (S. M. Won et al., 2018a). For instance, gold nanoparticles (Au NPs) have gained tremendous popularity because of their capability to be easily bio-conjugated with various biomolecules and create biomimetic architectures (Wellman et al., 2018). To mimic the topographical

cues of the brain, electrode fabrication from metallic materials with nanoscale geometries has been practiced (Aurand et al., 2017). Soon, carbon nanotubes (CNTs) and graphene were introduced into this arena, where their stability and longevity were improved as new microfabrication technologies emerged (John et al., 2015).

Aside from having good mechanical and electrical properties for BMI, an implantable electrode should demonstrate excellent biocompatibility (N Wu et al., 2021). By reviewing the experimental endeavours, it can be deduced that the reduction in the probe functionality over time and the appearance of glial scarring in the implanted tissue are the most cited problems (Spencer et al., 2017)(Dong et al., 2021)(Zou et al., 2021). In another word, an inflammatory response coupled with the degradation in the probe properties happens during the extended utilization of the rigid probes comprised of inorganic nanomaterials (Pavone et al., 2020). This observation magnifies the importance of electrode biocompatibility for BMI. Fulfilling this criterion would prompt the large-scale utilization of these nanomaterials in such applications.

Notwithstanding the high electrical conductivity and ease of surface modification of CNTs and graphene, using these nanomaterials in direct contact with human tissue has faced many challenges (Saleemi et al., 2021)(Z. Wang, Zhang, Vijver, & Peijnenburg, 2021). The gap in the literature between 2012 and 2017 vividly shows the period of rethinking and redesigning the strategies for implementing CNTs in biological applications (*Web of Science*, n.d.). The same goes for pristine graphene (PG), graphene oxide (GO), and reduced graphene oxide (rGO) (Wen et al., 2015).

An evolving promising solution is to restrain the inorganic materials inside a polymeric substrate (Kozai et al., 2012)(Woods, Rommelfanger, & Hong, 2020). The polymeric composites fabricated from different nanostructures of metals or carbon allotropes bring about the functional properties of both components and overcome the performance limits by increasing the longevity and stability of the neural interface. Furthermore, the presence of a polymeric material in a neural probe's substrate adds to the structure's flexibility and compliance with the surrounding bio environment (Kozai et al., 2012). The match between the mechanical properties of the brain tissue and the coating of a neural probe is considered the second prompt of the vast utilization of inorganic nanomaterials in BMI application. In turn, the compatibility between the inorganic materials and polymeric matrix plays a vital role in the coating's final mechanical, thermal, and electrical properties (Smith, LaChance, Zeng, Liu, & Sun, 2019)(Pumera, 2013).

Studies on the disruption of brain tissue during the chronic implantation of inorganic nanomaterials-bearing BMI devices are still at an early stage. Nevertheless, the excellent properties of these nanomaterials are shown to provide a way out of current uncertainties, powering deeper and more dedicated investigation, fuelled by projects such as the Graphene Flagship.

## 2.1 Carbon nanotubes (CNTs)

CNTs excellent physical properties and profound implication in potentiating signaling favour the foundation of proper electrical settings (Pavone et al., 2020)(Feng, Chen, Sun, & Peng, 2021). Combined with their unique structural properties, CNTs became promising in many scientific fields, including energy storage, wearable electrodes, and neuroscience (Y. Wu, Zhang, Wang, & Wang, 2020b)(Q. Zhang, Huang, Qian, Zhang, & Wei, 2013). The single-walled (SW) and multiwalled (MW) forms of CNTs have different thermal properties, conductivity, and electrical percolation thresholds (Moisala, Li, Kinloch, & Windle, 2006)(Sandler, Kirk, Kinloch, Shaffer, & Windle, 2003). These hollow cylinders of carbon layers were introduced to the traditional transition metals utilized in fabricating microelectrode arrays to lower their impedance and unfavourable electrochemical reactions. For instance, the advantages of SWCNTs over platinum for prolonged chronic use of electrocorticographic electrodes were evaluated in an study (Pavone et al., 2020). With some reservation, it can be stated that the biostability of platinum is low as delamination occurs on the explanted arrays (Vomero et al., 2017)(Grabiec, Domanski, Szmigiel, & Hodgins, 2013). On the contrary, it can be deduced that the biocompatibility and biostability of SWCNTs are higher than platinum since limited delamination and degeneration of neurons were observed for the arrays coated with these nanotubes.

The proper distribution and restraining of CNTs inside a polymeric substrate have the potential to diminish their coincidental accumulation inside living tissue. In this context, incorporating CNTs into a polymeric substrate may support the formation of neurons' functional networks and guides axonal growth. It was shown that the presence of MWCNTs in a polydimethylsiloxane (PDMS) elastomeric construct reconnects the segregated explants and guides the regeneration of axons (Aurand et al., 2017). Tissue integration of the interface was another highlight of this study. The pure polymeric substrates had limited interaction with the surrounding brain tissue, and as a result, the integration of these substrates failed. This was in contrast to the implantation results of PDMS/MWCNTs brain interface where neurons infiltrated into the probe construct. In a work of Chen et al., CNTs in combination with poly(3,4-ethylene dioxythiophene) (PEDOT) were electrodeposited on sacrificial

polymeric nanofibers (N. Chen et al., 2020). The achieved structure was in the form of nanotunnels (Fig.2a, 2b) and used as an electrode coating for neural recordings. The authors reported improved adhesion of the coating after the incorporation of CNTs into the structure. Moreover, the topology of the CNTs-PEDOT composite played a significant role in decreasing the impedance of the electrode (Fig.2c) and increasing its electrical fidelity. As CNTs were well anchored in the PEDOT substrate, the diffusion of CNTs into the tissue was reported to be negligible in this study, and with that, the risk of detrimental side effects of CNTs was minimized (Fig.2d). The mentioned advantages of these nanotubes persuaded Ding et al. to develop a biocompatible hydrogel comprising functionalized CNTs as a neural electrode (Ding et al., 2022). In their work, CNTs were used to compensate for the polymeric hydrogels' low conductivity and high impedance. Furthermore, to enhance the dispersion and the affinity of CNTs toward the hyaluronic acid and silk fibroin hydrogel, tyramine monomers were chemically grafted onto the surface of CNTs. This modification allowed the formation of a percolation network with high conductivity and low impedance.

It is difficult to reach a solid conclusion on the safety of CNTs. There is inconsistency in the practiced methods and evaluated biological systems. Their toxicity is an open-ended subject, the mechanism behind it is still being debated, and the suppression methodologies are still being investigated (Saleemi et al., 2021)(Mohanta, Patnaik, Sood, & Das, 2019). However, considering the low impedance, high conductivity, flexibility, and surface compliance of CNTs, the arrays comprised of these nanotubes can still pass the basic requirements for BMI chronic implantation when mixed into a polymeric substrate.

## 2.2 Graphene, graphene oxide, and reduced graphene oxide

The unique arrangement of carbon atoms in a two-dimensional honeycomb structure of graphene turns it into one of the most exciting allotropes of carbon (Jie Li, Zeng, Zeng, Zeng, & Xie, 2021)(Smith et al., 2019). This nanomaterial exhibits excellent thermal conductivity, possesses great electron transport capability, and has a high surface area. These 2D carbon sheets have excellent flexibility and can be used in polymeric conformal coatings (Yiyuan Zhang, Zhang, Huang, & Yang, 2022).

The undisruptive functionalization of PG has been recently explored to break this trade-off. Such functionalization includes microfabrication (Jie Li et al., 2021), complexation with biomolecules (Maughan, Gouveia, Gonzalez, & Leahy, 2022), and structural repatterning (Xiao et al., 2020). PG shielding using a polymeric layer can potentially decrease the adverse effect related to tissue

compatibility. For instance, a microelectrode array bearing a PG fiber core was constructed to serve as a recording device (K. Wang et al., 2019). The surface of these fibers was coated with a layer of platinum, and the whole construct was protected further with a sheet of Parylene-C (Fig.X e). The latter was proven to have good biocompatibility and electrical properties. Although the polymeric sheet prohibited direct contact between the brain tissue and PG, the chronic studies showed the delamination of Parylene-C, exposure of the core material to the implanted region, and, ultimately, the device failure. Recently, a nanostructure biocomposie was fabricated from collagen and PG.(33) Type-I collagen used in this study prevented direct cellular contact with PG and enhanced the biocompatibility of the construct. The electrical conductivity of PG severely diminished but stayed at physiologically required electrical properties. A microneedle array was fabricated to establish the processability of the mentioned nanostructured material in electrocorticography (Fig.X f). Moreover, a circuit was printed using the PG-chitosan, demonstrating the ability of the nanomaterial to be used as a printable bioink (Fig.X g). The first report of a conductive bioink comprised of graphene was also achieved through complexation with a hyperbranched polymer (Cheng et al., 2018). This bioink showed excellent electrical properties and was suspendable and processable in an aqueous solution. In another study, Xiao et al. developed a free-standing ordered graphene network (Xiao et al., 2020). It was shown that the nanopatterned surface of graphene could encode geometrical cues for the neuronal ordered growth and alignment. The wrinkles and ripples in this 3D structure favoured astrocytes, bipolar neurons, and neuronal network activity. Another approach was also practiced to benefit from the patterned graphene. A single-layer PG (SLPG) was deposited on a copper foil via the CVD process and was further moved on a glass cover using a two-step growth procedure (Zummo et al., 2021). Although this single layer was previously shown to support neural activity (Pampaloni et al., 2018), it was further revealed that the synapses on SLPG can maintain their structural functionality while boosting the neuronal activity of the tissue residing in proximity. Interestingly, the author showed that upon the functionalization of SLPG with phenylacetic acid, the cell stiffness and focal adhesion severely changed, and the electrical activity decreased. Their findings show the extent of unknowns for a chemically functionalized PG utilized for BMI.

Benefiting from their abundant functional groups, GO and rGO can maintain or improve the mechanical property of a polymeric composite (Phiri, Johansson, Gane, & Maloney, 2018). However, the structural distortion of the PG after the modification process and the formation of surface oxides severely hampers the conductivity of GO and, to a lesser extent, rGO, making them unattractive for BMI. The PG's high

electrical and thermal properties on the one hand, and the excellent mechanical properties and biocompatibility of its modified forms, on the other, complicated the selection procedure for the BMI applications.
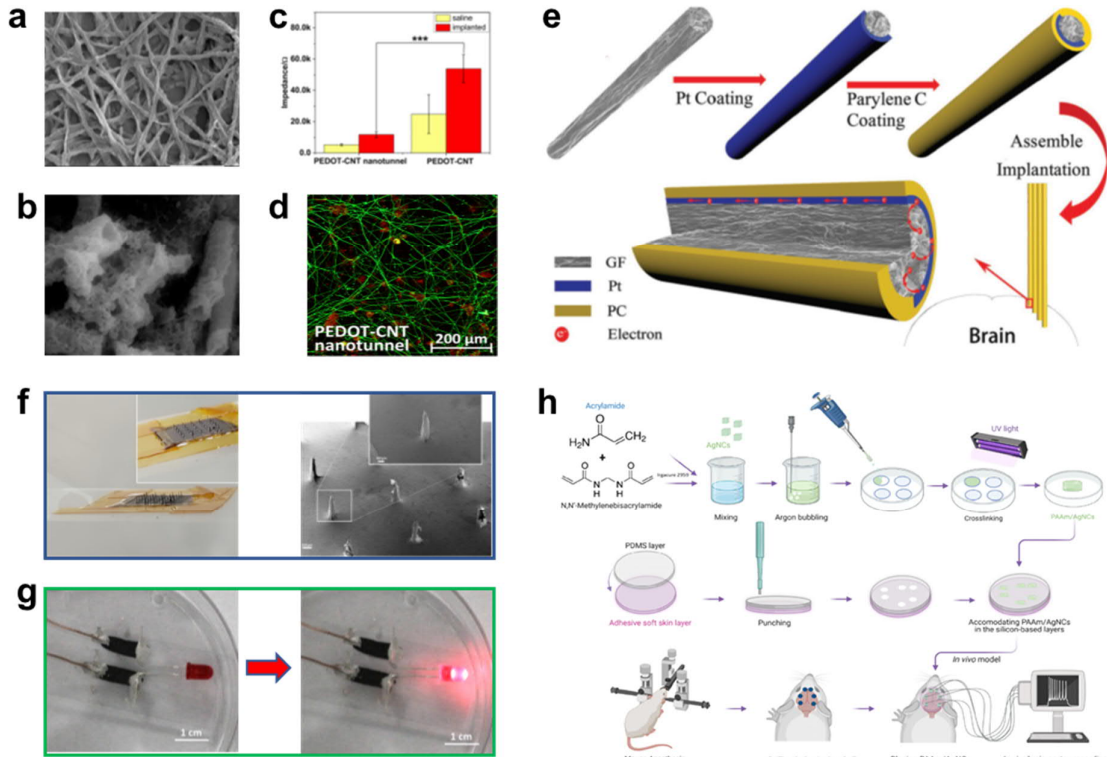


**Figure 2.** Brain-machine interfaces based on inorganic nanomaterials and their composites. Tunnel-like electrode coating comprising of CNTs and PEDOT for highly sensitive neural recording: (a, b) SEM images of PEDOT-CNT nanotunnel deposited on the electrode site at different magnifications; scale bar for a) is 10 μm and for b) is 1 μm; (c) impedance of the electrodes coated with PEDOT-CNT nanotunnel and PEDOT-CNT in saline and after implantation during acute signal recording from the rat's peripheral nerve. Data are presented as mean ± s.e.m.(n = 9). Statistical significance is indicated using *** for p < 0.001; (d) image related to the immunostaining of rat's neurons and glial cells cultured on PEDOT-CNT nanotunnel substrate. Cells were isolated for the staining on the fourth day of the in vitro studies. The green color represents the neurons, while the red shows the glial cells. Reproduced with permission.[1] Copyright 2020, American Chemical Society. Durable microelectrodes comprised of graphene fibers coated with platinum and parylene-C: (e) schematic illustration of graphene microelectrode fabrication, and its application as a recording interface during intracortical implantation. Platinum sputter coating on one side of the microfibers was performed to increase the conductivity of the interface reduce the adverse effect of the length on the electric resistance of graphene fibers. The coating of the final polymeric layer served to increase the dielectric property, flexibility and the biocompatibility of the graphene-based electrode. Reproduced with

permission.[2] Copyright 2019, Wiley-VCH. Neural interfacing construct based on pristine graphene and collagen: (f) collagen/pristine graphene (CpG) composite was used to fabricate a 5×5 microneedle array set via dry cast method. The height of the needles was 2.5 mm narrowing at the tip with a diameter of 40–80 μm. The array set under the SEM showed sharp bore and tips for each individual needle. (g) the composite was then modified to serve as a printable bioink. A controllable 3D printing process was optimized capable of creating complex geometries. To demonstrate the composite conductivity, an LED was powered through a printed circuit. Reproduced under the terms of the Creative Commons CC-BY (https://creativecommons.org/licenses/by/4.0/).[3] Copyright 2022, Elsevier. (h) Hyrogel-nanoparticle composite fabrication and application scheme. The hydrogel was formed based on acrylamide using a photoinitiator in deionized water. AgNCs were added to the hydrogel precursor before UV cross-linking. For in vivo study, six hydrogels were placed into dedicated holes punched through layers of soft skin adhesive and PDMS. The final system was placed on the mouse skull with stereotactically drilled holes through which hydrogel could reach the brain cortex and permit a specific ECoG signal acquisition. Reproduced with permission.[4] Copyright 2022, American Chemical Society..

## 2.3 Metal nanoparticles

Several groups developed different methods of obtaining electrodes with gold nanoparticles to study the cellular response to electrical stimuli. To observe nerve cell response *in vitro*, Park et al. used 20 nm Au NPs adsorbed to the positively charged cover glass coated with polyethyleneimine (PEI) (J. S. Park et al., 2009). The PC12 cells extended neurites with a mean length of 98.5 μm on the Au NPs in the presence of electrical stimulation (250 mV for 1 h). In contrast, the neurite outgrowth length without electrical stimulation was approximately 10-20 μm. Studies with libraries of nanoporous gold coatings showed that small (~30 nm) features reduce astrocytic surface coverage by inhibiting focal adhesion formation (Chapman et al., 2017).

More advanced works confirmed that nanoparticles could be applied in neural tissue engineering to develop neural prosthetic devices and bioelectronic interfaces. One of the methods of using nanoparticles is to form a coating layer over the electrode, which can increase the electrochemical surface area (ESA). Nanostructuration of the electrode surface significantly improves the electrochemical properties of the microelectrodes while the geometric surface area (GSA) remains constant. Due to the introduction of nanoscale features, the roughness and porosity of the surface increase charge transfer with a surrounding electrolyte and decreases the impedance.

One of the methods used for nanoporous surface preparation is a selective de-alloying procedure of Ag–Au (Seker et al., 2010)(Y. H. Kim et al., 2015). Such nanoporous porous arrays can tune cell

adhesion and provide a high spatial resolution of electrical recording and stimulation. Besides porous nanosphere-like structures, nanoclusters (Shah, Tolosa, Tooker, Felix, & Pannu, 2013) or nanorods (Jang, Yoon, & Nam, 2022)(Ganji et al., 2018) can further increase the electrode surface area. Zhou et al. show that the AuNR layer (70 nm in diameter and 500 nm in length) on a flexible polyimide has approximately 25 times lower interface impedance than conventional planar electrodes (1.85 kΩ vs 50 kΩ at 1 kHz), which corresponds well with the increase in surface area (Hong-Bo Zhou et al., 2009). Another approach involves the electrochemical or layer-by-layer deposition of Au, Ag or IrOx to create nanoparticles (D. Lee et al., 2018)(Bao et al., 2019)(Chan et al., 2021)(H. Zhang, Shih, Zhu, & Kotov, 2012) or nanograins (R. Kim, Hong, & Nam, 2013) on the electrode surface. Zhang et al. used a layer-by-layer technique to deposit CNTs or Au NPs in poly(diallyl dimethylammonium chloride) (PDDA) on the electrode (H. Zhang et al., 2012). The impedance values were about one order of magnitude lower for the electrodes of pure nanoporous Au. Compared with CNT films, AuNPs films showed increased charge storage capacity (1.32 vs 0.173 mC/cm$^2$), lower impedance (2.68 kΩ vs 9.65 kΩ) and comparable electrochemical stability.

Metallic neural electrodes have certain limitations due to the mismatch between rigid metals and soft neural tissues. The softer electrically conductive electrodes could promote chronic device function. For this purpose, composite materials combining Au NPs and polymers could improve their electrochemical properties for neural stimulation and recording. One of the examples includes the formation of percolating networks in soft polymer matrices. Minev et al. formed polydimethylsiloxane (PDMS) loaded with Pt nanoparticles (0.5–1.2 μm diameter), resulting in low impedances (≈4 kΩ at 1 kHz) (Minev, Wenger, Courtine, & Lacour, 2015). Moreover, the electrochemical and electromechanical responses were robust and stable when subjected to tensile stretching. Krukiewicz et al. compared the electrical percolation threshold for CNT, silver nanowires and poly(hydroxymethyl 3,4-ethylenedioxythiophene) microspheres (MSP) in poly(ε-decalactone) (EDL) matrix (Krukiewicz et al., 2018). These soft and conducting composites exhibited favourable electrochemical characteristics: EDL/CNT—the lowest resistance (1.2±0.3 kΩ) and EDL/AgNW—the highest charge storage capacity (10.7±0.3 mC/cm$^2$). During in vitro study, all the films reduced the presence of reactive astrocytes relative to control electrodes. The electrical properties of such systems can be improved by replacing PDMS or EDL with a conductive polymer such as PEDOT (S. Chen et al., 2013). After electrochemical conditioning, a multilayered PEDOT/Au electrode made by combinational sputter and spin-coating formed fractal-like

assemblies of gold particles. Finally, the electrical impedance exhibited 30 ± 2 Ω at 1 kHz. Electrodes formed by electrodeposition of PEDOT mixed with multiwalled carbon nanotubes resulted in 8 mC/cm$^2$ of charge injection limit and impedance of ~10 kΩ at 1 kHz.

The percolating neural interfaces formed with hydrogels further improve the mechanical matching between the electrode and the brain. Due to their high water content, ionic transfer through hydrogel allows for fast ionic conduction. Rinoldi et al. developed a soft and flexible neural interface from polyacrylamide loaded with silver nanocubes (Fig.X h) (Rinoldi et al., 2022). The mechanical parameters of the hydrogel-nanoparticle composite were chosen to minimise the mismatch between the nerve tissue and the biomaterial (Young's modulus <10 kPa). The electrically conductive hydrogel composite had a low electrical impedance (100 Ω at 1 kHz). Moreover, the soft and flexible electrodes were placed directly on the mouse's cortical surfaces allowing a stable long-term neural recording.

In summary, neural interfaces utilising nanoparticles have been observed to induce advantageous effects on neurons' outgrowth, alignment and orientation *in vitro*. However, consideration of type, size, concentration and capping agents is necessary since released nanoparticles can cause frustrated phagocytosis and apoptosis (Wellman et al., 2018).


## 3. INTRINSICALLY CONDUCTING POLYMERS AND BLENDS

The term "polymers" refers to molecules of high molecular weight (macromolecules), formed by chains of smaller molecules, called monomers, which therefore represent their structural units (Young & Lovell, 2011). When obtained by chemical reaction, usually starting from petrochemical industry products, they are commonly named "plastics". In general, plastics are universally considered electrical insulating materials: in fact, they are commonly used for surrounding metal wires to prevent a direct contact with electricity (Brydson, 1999). However, in the late 70s years, scientists discovered that a synthetic polymer, polyacetylene (PA), when in its trans configuration and doped with bromine or iodine vapors, achieved an electrical conductivity of 3000 S/m, a value slightly lower than that shown by common metals (Heeger, 2001). After the discovery of polyacetylene, an enormous number of scientific papers was published dealing with the new conductive polymers, since this family of macromolecules, which combines the properties of organic polymers (structural versatility, lightness, flexibility and low cost) with the electroconductivity typical of metals, was undoubtedly very intriguing. A new term was even coined to describe these new materials: synthetic metals.

The common feature of these polymers is the presence of unsaturated bonds in the main chain, which gives rise to a delocalization of electrons due to conjugation. Indeed, they are also called indifferently conjugated polymers or conducting polymers (CPs). In particular, the overlapping of $p_z$ orbitals of carbon atoms along the polymeric backbone creates a system of double bonds, which are delocalized over the entire macromolecule. The lateral superposition of adjacent $p_z$ orbitals, each of them containing only one electron, can occur in-phase or out-of-phase, leading to two systems of π-bonds. The set of low energy π-orbitals is called VB (valence band) and that at higher energies, originating from the out-of-phase overlapping of $p_z$ orbitals and corresponding to π*-orbitals, is named CB (conduction band). The VB is filled with electrons, while CB is empty. The energy difference between the highest (in energy) occupied molecular orbital (HOMO) of VB and the lowest unoccupied molecular orbital (LUMO) of CB is called $E_g$, energy gap. $E_g$ is a fundamental parameter for CPs since it directly influences their electrical and electro-optical properties. Indeed, π-electrons are delocalized over the polymeric chains only when promoted to the CB, where they are free to move without energy consumption. Moreover, in the ground state, undoped CPs show an anisotropic one-dimensional electronic structure with limited charge carrier mobility. Electrons can overcome the barrier of energy gap (usually 2-3 eV for conjugated polymers, corresponding to the conventional semiconductor gap size) by heating, use of light radiation or by electrochemical, chemical and photochemical doping. Chemical doping, the most common method to enhance CPs conductivity, is generally obtained by treating the polymer with electron-donor (n-doping) or electron-acceptor (p-doping) species that creates negatively charged (electrons) or positively charged (holes) carriers on the macromolecule that are able to transport electricity over the polymer. Doping usually lowers the energy gap of CPs to 0.5-1 eV (depending on the amount of dopant) by creating energy levels (π non-bonding orbitals) between the energy gap of the polymer, making easier to promote valence electrons to the conduction band. In other words, the reduction of $E_g$ increases the population of the conduction band thus increasing the number of charge carriers. With appropriate doping, the conductivity of CPs can be increased even more than 12 orders of magnitude, making an insulating/semiconductive polymer a conductive material (Bott, 1985).

Irrespective of the method adopted for their synthesis, the main CPs (polyacetylene, polyaniline, polypyrrole and polythiophene, are not completely soluble in common organic solvents, infusible and generally intractable materials (Quijada, 2020). Substituted analogs have then been polymerized to obtain more processable polymers with side groups linked to the conjugated backbone through flexible

oligomethylenic side chains (Nalwa, 2000). Functionalized CPs have been extensively studied during the last three decades and are always in the limelight owing to their high conductivity, easy synthesis, structural versatility, good mechanical properties (this is particularly true for their composites with inorganic materials) and effortless fabrication of final devices (Namsheer & Rout, 2021). They have also successfully been employed in biomedical applications, including biomaterials and biosensors (Nezakati, Seifalian, Tan, & Seifalian, 2018) and as electrodes between biological tissues and electronic devices, being flexible and capable of both electronic and ionic conductions (Ouyang, 2021).

**3.1 Polyaniline**

Polyaniline (PANI), also known as "aniline black", was known since XIXth century. It was firstly used as a dye for the tissues of priests' cassocks and was prepared with a procedure based on the oxidation of aniline using mineral acids and oxidants like chlorate, dichromate and persulfate (COHEN, 1887). PANI exists in different oxidation states: reduced (leukoemeraldine), partially oxidized (emeraldine) and fully oxidized (pernigraniline). Emeraldine form has an equal ratio of benzoid and quinoid repeating units and, when protonated, become conductive (emeraldine salt) reaching a specific electrical conductivity ($\sigma$) of $10^3$ S/cm (Boeva & Sergeyev, 2014). This kind of "protonic acid doping" is a peculiarity of polyaniline, since no oxidation or reduction have to be made on emeraldine to make it conducting. High quality PANI can be prepared by chemical oxidation of aniline, using an equimolar amount of hydrochloric or sulfuric acid in presence of ammonium peroxydisulfate (N. V. Blinova, J. Stejskal, M. Trchova, J. Prokes, 2007), or by electrochemical oxidation of aniline to emeraldine. Interfacial polymerization is also used to prepare polyaniline: in this method, green nanofibers of PANI were formed at the interface between an aqueous solution of HCl and $NH_4S_2O_8$ and an organic phase composed by a solution of the aniline monomer in $CHCl_3$ (Abdolahi, Hamzah, Ibrahim, & Hashim, 2012). Electrospun hollow-core PANI nanofibers with high conductivity and solubility have recently been prepared with the same reagents used for the interfacial polymerization but avoiding the use of chloroform. After a sulfonation step, nanofibers were employed as a hole transporting layer (HTL) between the active layer and the metallic cathode of bulk heterojunction (BHJ) polymeric solar cells, giving an appreciable value of power conversion efficiency (6.85%) (Haghighat Bayan, Afshar Taromi, Lanzi, & Pierini, 2021). Further examples of PANI applications include selective gas sensors (Z. F. Li, Blum, Bertino, & Kim, 2013), supercapacitors (Z. Li & Gong, 2013), antistatic biodegradable films (Wong, Phang, & Baharum, 2020) and biosensing devices (Kazemi, Naghib, Zare, & Rhee, 2021).

Garrudu et al. have been investigated fabrication of poly (caprolactone) (PCL) electrospun nanofibers with PANi for neural stem cell growth and electrical stimulation. By optimizing the doping mechanism and solvent system, fibers diameter, conductivity and softness of the electrode can be tuned. Cell adhesion is enhanced, and cell differentiation was successful in the tests, where also electrical stimulation using AC current, improved the neural expression (Garrudo et al., 2021). An EEG dry electrode from stainless steel was covered with PANi, which showed significant reduction in impedance compared to metal electrode (Figure 3a). This reduction happened due to the porous structure of the PANi, at the same time intrinsic electrical conductivity allows for efficient charge transfer. Structure of the PANi coating is also showin in Figure 3a, where the porous network structure can be seen vividly (Aghazadeh et al., 2021).

### 3.2 Polypyrrole

Polypyrrole (PPy) is a CP that can be easily synthesized by oxidative polymerization of the corresponding monomer (pyrrole) in organic solvents or aqueous systems (water and mineral acids) in the presence of $FeCl_3$. Even if some other synthesis methods have been recently proposed, such as electropolymerization, ultrasonic irradiation-assisted polymerization, vapor-phase polymerization and photopolymerization, chemical oxidative polymerization is the preferred system for industrial applications owing to its cost-effectiveness and capability to give directly the polymer in its highly conductive (oxidized) form (Pang, Arsad, & Ahmadipour, 2020). During oxidative polymerization, some electrons of the π-conjugated system of the pristine polymer are removed, creating polarons (radical-cations) in the backbone. Two polarons can interact between them leading to stable bipolarons (dications) that are free to move along the polymeric chain acting as charge carriers; basically, PPy is converted into a cationic complex with incorporated counterions (Santos, Brolo, & Girotto, 2007) with a specific electroconductivity up to $10^4$ S/cm. Acting on the preparation method, conducting PPy has been obtained in many different forms: bulk, films, nanoparticles, nanotubes, wires which have been used to prepare LED, supercapacitors, chemical sensors (recently electrochromic pH and $CO_2$ sensors have been prepared using conducting PPy thin films on ITO glass (Ratautaite, Bagdziunas, Ramanavicius, & Ramanaviciene, 2019)), diodes and transistors. PPy, in combination with $Bi_2WO_6$ as a catalyst, has been used for the photocatalytic reduction of $CO_2$ to $CH_3OH$ and $CH_3CH_2OH$ in water while PPy-CdS composites have revealed a great activity in the photocatalytic hydrogen production starting from water solutions of sodium sulfite (Shanmugam et al., 2022). PPy nanocomposites have been successfully

employed for tissue engineering scaffolds, drug delivery systems and photo-thermal therapy (PTT) (EN et al., 2021)(Pierini et al., 2018) thanks to their biological properties, due to the good cell adhesion and growth properties on their surface.
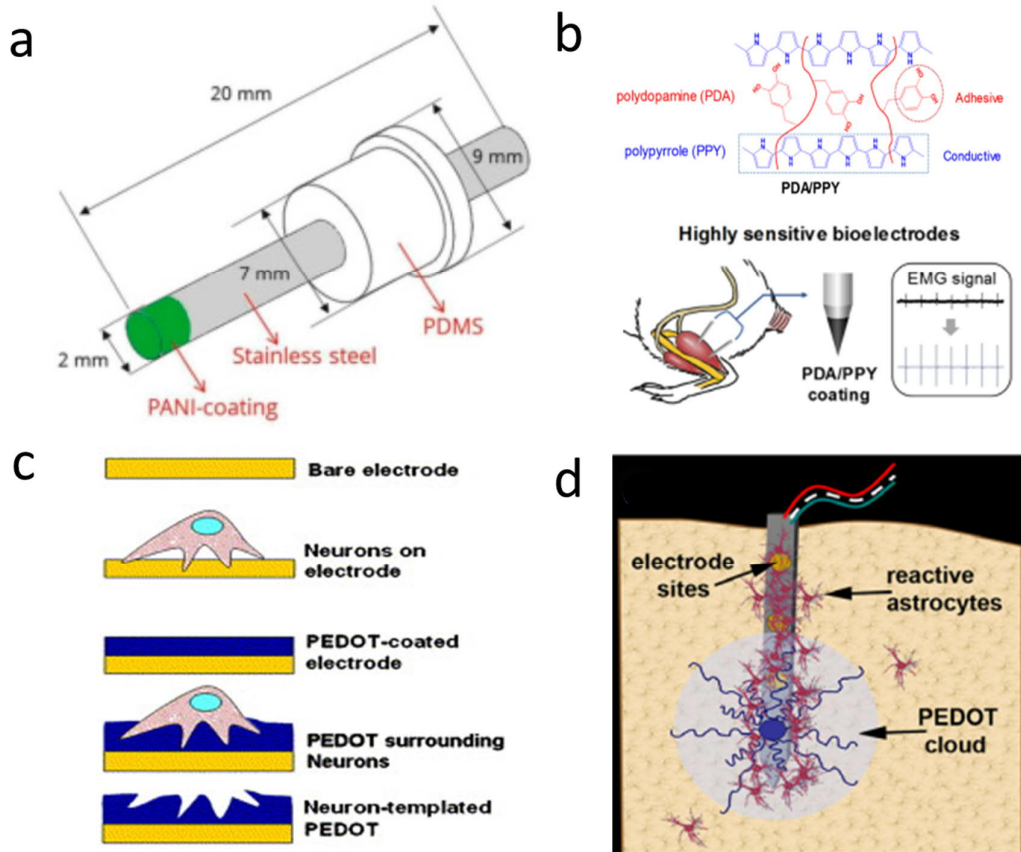


**Figure 3**. Use of intrinsically conducting polymers for BMI application. (a) Digital image of PANI@SS used for brain signal-recording. (b) Schematic of the Electrochemical Copolymerization (PDA/PPY) of Dopamine and Pyrrole and the Use of PDA/ PPY as a High-Performance Biomaterial for Highly Sensitive Bioelectrode (c) bare electrode, neural cells on bare electrode, PEDOT-coated electrode, neural cells embedded in PEDOT matrix, and neural cell-templated PEDOT (d) Diagram representing the process of polymerizing PEDOT directly into brain tissue from a neural electrode device in order to bypass the surrounding glial scar.

### 3.3 Polythiophene

The preparation of conductive polythiophene (PT) started at the beginning of the '80s and since then it has progressively gained a prominent place in the CP field thanks to its structural versatility, high conductivity, thermal and environmental stability. The literature on PT and its derivatives is very extensive with a tremendous increase in the number of articles published in the last years. Poly(3-alkylthiophenes) (P3ATs) are an important class of PT derivatives where the alkylic (or alkyl-

functionalized) side chains allow to obtain soluble and fusible polymers at the price of acceptable losses of conjugation and conductivity. The polymerization of thiophene can be performed using oxidation reactions (usually with $FeCl_3$, $AuCl_3$ or $AlCl_3$), organometallic coupling reactions on 2,5-dihalothiophenes or by electrochemical synthesis. Specific electrical conductivity of PT lies in the 500-1000 S/cm range. Since P3ATs usually absorb in the visible range, they show a very interesting property related to the mean conjugation length of electrons in the main chain and then to electron delocalization. Indeed, they can show a dramatic color shift in response to changes in solvent (solvatochromism), temperature (thermochromism), applied potential (electrochromism), presence of other molecules (affinochromism) or ions (ionochromism), paving the way to the production of very fast and unexpensive chromic sensors (Kaloni, Giesbrecht, Schreckenbach, & Freund, 2017). Moreover, the electronic structure (and then the color) of polythiophene is also influenced by the steric repulsion between substituents or, when directly linked to the thiophenic ring, by their electron-withdrawing or donating effects, making chromism widely tunable. Bulk heterojunction (BHJ) solar cells based on photoactive layers of polythiophene derivatives as electron-donors have reached power conversion efficiencies up to 10% (Guo, Zhou, Lou, & Tice, 2013) and PT-based organic light emitting diodes (OLED) have shown high intensity of emission and tunable colors by simply varying substituents employed on the thiophene unit (Grimsdale, Chan, Martin, Jokisz, & Holmes, 2009). One of the most important PT derivatives is undoubtedly the poly(3,4-ethylenedioxythiophene) (PEDOT) thanks to its high conductivity, thermal stability and easy processability when doped with polystyrenesulfonate (PSS). PEDOT (Figure 1c) has high electroconductivity (around 500 S/cm), sufficient to allow the production of organic LEDs, electrochromic devices and polymeric solar cells and is well soluble in water. It can be easily obtained with spontaneous solid-state polymerization of 5-bromo-2,3-dihydro-thieno[3,4-b][1,4]dioxine by simple heating (Yin, Li, Jin, Tusy, & Xia, 2013). PEDOT is currently studied as neural interface for the communication between neurons and machines, including neuroprosthetic devices, cochlear implants, cardiac pacemakers and vision prostheses (R Green & Abidian, 2015). In the work done by Richardson-Burns, a novel biomaterial based on PEDOT have been designed for cell-templated neural probe coating. This material can also be used as a conducting polymer-live neural cell electrode. PEDOT have been electrochemically deposited around neurons cultured on electrods, where live-cells embedded within polymer matrix remain viable for 120 h after polymerization. (Figure 3c). (Richardson-Burns, Hendricks, Foster, et al.,

2007)Indeed, due to the soft nature of this polymer, a conductive layer of PEDOT on a metallic substrate can lower the mechanical mismatch between the electrode and the tissue, thus reducing the risk of gliosis or inflammation. PEDOT can be also directly polymerized within the brain tissue, leading to a conductive network of polymeric chains as in can be seen in figure 3d (Richardson-Burns, Hendricks, & Martin, 2007).

## 4. CONDUCTIVE INTERPENETRATING POLYMER HYDROGEL

Development of materials which can cover the three required criteria for the BMI application, has been the purpose of the research for many scientists in this field. Developing a material which has mechanical properties similar to soft tissues, as well as conductivity, has been very challenging. The majority of conventional electrode materials (*e.g.*, silicon, gold, platinum, titanium nitride, iridium, tungsten, and tin) exhibit very high Young's moduli over 1 GPa, which are several orders of magnitude higher than that of neural tissues. In the last decade, a number of novel materials and laboratory-level devices have been developed to minimize the biomechanical dissimilarities between electronics and biology. For example, polymeric materials such as plastics (*e.g.*, polycarbonate, polyimide, and parylene C) and elastomers (*e.g.*, epoxy, PDMS, and polyurethane) have been adopted to reduce the modulus gap. However, their Young's moduli (typically 1 MPa to 1 GPa) are still much higher than those of neural tissues ($E \sim 10$ kPa) and not sufficient to provide truly mechanically matching interfaces. While numerous materials as mentioned in previous sections has been studied for BMI technology in the past, innovative nanomaterials with low modulus and low electrical impedance are developed vastly. Hydrogels as three-dimensional polymeric networks can meet the requirements of this area and have been widely used in recent years due to their highly tailorable structures. Their characteristics make them perfect candidates to be used in biomedical applications such as biosensing (Ziai et al., 2022), drug delivery (Nakielski et al., 2020), tissue engineering (Atoufi et al., 2019), and BMI(X. Wang et al., 2022).

These hydrophilic networks with extremely high water intake, have perfect resemblance to mechanical properties of extracellular matrix (ECM)(Hoffman, 2001). As a result, they endow a promising route to ameliorate biomechanical mismatch at tissue–electrode interfaces. Unlike other dry electrode materials, the water- and ion-rich hydrogels have the potential to offer unconventional but improved stimulation/recording performance *via* integrative use of both electronic and ionic activities. (Yuk, Lu, & Zhao, 2019b) Hydrogels have lattice-like intra-structure, with interconnected pores, which not only can retain high water content, but also, other materials can be incorporated in their structure.  As a result,

they can be used also for other purposes in neural bioelectronics like drug delivery and active electrode coatings. As mentioned before, one of the necessitates of the materials for BMI application is electrical conductivity. Using conducting polymers to form hydrogels as well as incorporation of conducting molecules, polymeric chains and nanomaterials inside the hydrogel matrix are popular approaches towards this aim. At the meantime, pure hydrogels as single network materials with weak mechanical properties, are very hard to handle as the sole material to be used solemnly for the final application. In order to enhance the mechanical properties, stability, and other aspects of the hydrogel networks, blended structures were introduced.

Polymers can be blended in systems using mechanical blends and graft copolymers. In mechanical blends, as it is shown by the name, there is no chemical bonding between the components, while primary bonds can be seen between the components in graft copolymers (Zoratto & Matricardi, 2018). Interpenetrating polymer networks, known as IPNs, are networks consisting of two polymers polymerized in the presence of each other, while there are no chemical bonds between different components. According to the presence and type of crosslinking of the polymeric chains, they are classified into subclasses such as block copolymers, Semi interpenetrating polymer networks (semi-IPN), and fully interpenetrating polymer networks (IPN)(Zoratto, Gels, & 2018). BMI technology can benefit from IPNs in several ways. By having an interpenetrated network of more than one polymer, ehnahnced mechanical stability can be developed and no phase separation will happen under any tension and sheer stress.Moreover, Using combinations of natural and synthetic polymers in one system, offers tailorable chemical properties to the system, where synergetic properties of both polymers can be acquired. This property is of key importance in BMI application, where a conducting polymer can be introduced into the system, and the conductivity will be preserved whilst properties of a hydrogel structure is gained in the system.

**4.1 Semi-IPNs**

Semi-IPNs are defined as systems where there is one fully crosslinked network along with a one or more linear or branched other polymeric macromolecules interpenetrated inside the first network. In simple words, semi-IPNs can be defined as one or more linear or branched macromolecule, interapped within the network of another polymer. It is very important to note the fact that there is no bonds between the different components of the system. Figure 1a shows the two main crosslinking pathways of semi-IPN networks, in situ and sequential.

In the in situ approach, all of the reagents needed to polymerize the first polymer will be added at the same time with the already polymerized chains if the other components. Crosslinking of the first polymer will take place in the presence of other polymers, while in the sequential method, first polymer will be polymerized and then will be impregnated with the chains of the other ones (Chikh, Delhorbe, & Fichet, 2011). Using intrinsically conducting polymers as an additive in the network of the hydrogels is one of the main approaches for gaining electrical conductivity for BMI platforms, as discussed in the previous section.

In the work of Golafshan et al. a semi-IPN hydrogel based on alginate and poly(vinyl alcohol) (PVA) was investigated to be used for neural applications. The hydrogel network was incorporated with graphene to develop electrical conductivity, then designed to be fibrous scaffolds using electrospinning technique (Figure 4a). As a result of this fabrication design, considerable improvement in electrical and mechanical properties of the system was detected. Adding Gr nanosheets not only introduce conductivity to the system, but also enhaced the strength and toughness of the system (Figure 4b).

Siddhanta et al. have introduced linear polyaniline into the nanostructured gel network of poly (2-acrylamido-2-methyl propane sulphonic acid) (PAMPS). While the in situ polymerization of the chains of the polyanilinie takes place, a semi-IPN hydrogel with high electrical properties was achieved (Siddhanta & Gangopadhyay, 2005). Chitosan as a biocompatible polysaccharide was also used alongside with conductive polyaniline to form a semi-IPN hydrogel to form a conductive material for neural applications. The electrical conductivity of the samples where checked to be $\sim 10^{-4}$ S/cm, which lies in the range suitable for the biological range needed to mimic neural cells (Bagheri, Babak, et al. 2019)

Another system of a semi-IPN hydrogel was designed by Rinoldi et. al. were they used poly(*N*-isopropylacrylamide-*co*-*N*-isopropylmethacrylamide) (P(NIPAm-*co*-NIPMAm)) as the hydrogel part and sodium poly[6-(3-thienyl) hexanesulfonate] (P3HT6S) was added as an conductive polymer to provide the system with good electrical properties. Electrical tests were performed on the system, demonstrating the notable decrease in the impedence of the platform compared to the pure hydrogel, so neural progenitor cells (NPCs) were cultured on the hydrogel. Results shows the ability of the platform to support the survival of central nervous system cell line, while possible promotion of the neural differentiation of the cells (Rinoldi, Lanzi, et al., 2021a).

Hydrophobic poly (3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) form a semi-IPN with hydrophilic poly (vinyl alcohol) (PVA), where polypyrrole (PPy) was used as a conductive nanoparticle incorporated inside. Preparing the network with a ratio of 70/30, will provide structural reinforcement alongside with hydrogel properties, so that the system can be easily introduced and function in aqueous environments. Electrical properties induced in the system as a result of embedding PPy nanoparticles, gives the system potential to be used for BMI application (Aparicio-Collado, José Luis, et al. 2020).

**4.2 IPNs**

A simple definition of the IPNs is a polymer network consisting of two or more systems interlaced with no covalent bonds. There is no possibility of separating them unless breaking the chemical bonds of each system. In other words, IPNs are basically a combination of at least two polymer networks, each in the lattice form, where each lattice is crosslinked in the immediate presence of the other, while there are no covalent bonds between them (Soman, Mathew, Chacko, Alias, & Vionda, 2015). They can also be described as alloys of crosslinked polymers (Dragan, 2014). A simple scheme of the structure of such networks can be seen in Figure 1a. Like the semi-IPNs, IPNs can be synthesized through two main pathways. In the in-situ pathway, all the reactants of all polymers are mixed together before any crosslinking, although they may or may not start simultaneously. Sequential synthesis, also known as impregnation synthesis, on the other hand, is a process where the first polymeric network will be synthesized, and then all the reagents needed for the polymerization of the second network will be added to the system. Morphological properties of the first system are controlled by both polymers at the same time and can be manipulated by altering the proportions, the order, and the rate of polymerization, whereas in the latter way, morphology is mostly determined by the properties of the first network (Chikh et al., 2011). the presence of hydrogels at tissue–electrode interfaces can potentially compromise electrical performance in spite of enhanced biomechanical interactions. Introducing enhanced electrical property (*e.g.*, lower interfacial impedance and higher charge injection capacity) without compromising their desirable biomechanical features (*e.g.*, low mechanical modulus and biocompatibility) can provide opportunities to further improve tissue–electrode interfaces. One of the most common roots of to modify the properties is to use CPs such as PEDOT and PPy. using these materials not only improves the electrical conductivity of the material, but also, can further facilitate the tissue integration by immobilization of biomolecules. Use of the CPs can be directly or by growing them in the network of the hydrogel. As a result of its soft mechanical properties, it was proposed that the hydrogel can reduce the

mechanical mismatch between the tissue and the electrode material and can act to stabilize the otherwise brittle CP. The hydrogel itself can furthermore serve as an anti-biofouling surface preventing unwanted adhesion of proteins or inflammatory cells.

There are significant enhancements in the use of IPNs for different applications. Physical phase separation cannot occur between the components due to the infinite zero-viscosity of the gel, resulting in a considerable increase in the stability of the system. Also due to the fact that at least there are two crosslinked networks are entangled in the system, mechanical properties of the final network enhanced remarkably (Soman et al., 2015).

There are three main approaches to fabricate conductive hydrogel networks, where the most common one is to deposit the conducting polymer electrochemically within a hydrogel network(B. C. Kim, Spinks, Wallace, & John, 2000) (Lira & Córdoba De Torresi, 2005). The other approaches are chemical crosslinking of the CP in already polymerized hydrogel network or polymerization of all the components together (Dai et al., 2010)(Dai, Qing, Lu, & Xia, 2009).

Kleber et al. have synthesized an IPN system of P(DMAA-co-5%MABP-co-2,5%SSNa) (PDMAAp) hydrogel, with the PEDOT conductive chains growing inside the hydrogel network, making a full IPN as a matrix. PEDOT was successfully integrated into the already patterned hydrogel matrix through a combination of electropolymerization and establishment of ionic interactions between the negative charges of the sulfonate in the hydrogel and the positive charges on the PEDOT. This kind of stable design covers the requirement of the system for homogeneous coating to be attached to the substrate electrode. Significant increase in the SCS as well as reduction in impedance confirmed the effect of PEDOT in hydrogel matrix (Kleber, Bruns, Lienkamp, Rühe, & Asplund, 2017). Abidian et. al have designed a hybrid interface for neural electrodes, with capability of controlled drug release. The construct is consisted of nanofibers for controlling the drug release and a platform for conducting polymer nanotubes and hydrogel layers which acts as an mechanical buffer in the interface of probe and tissue. PEDOT was polymerized on the electrode sites and inside the hydrogel, making an IPN. Electrodes shown in Figure 4c, proved to improved the electrical conductivity of the metal electrode (Abidian & Martin, 2009).

Poly(vinyl alcohol)/poly(acrylic acid) IPNs were prepared by lu et al., where the ionic conductivity maintained for electrode-neural interfaces. A very good stability was observed after six weeks of implantation, as well as homogenous coating (Lu et al., 2009). The same system was also used to

improve the interface and stability after chronic implantation, as shown in figure 4d. PEDOT/PSS was electrochemically deposited into the network, as the conductive component. The higher capacitance and lower impedance due to the conductive material were observed where higher mechanical properties due to IPN network compared to the polymer films was maintained. Chronically optogenetic modulation and electrophysiology recordings took place, both showing stable and improved outcomes, where make the system very good candidate for BMI applications (Lu et al., 2012).
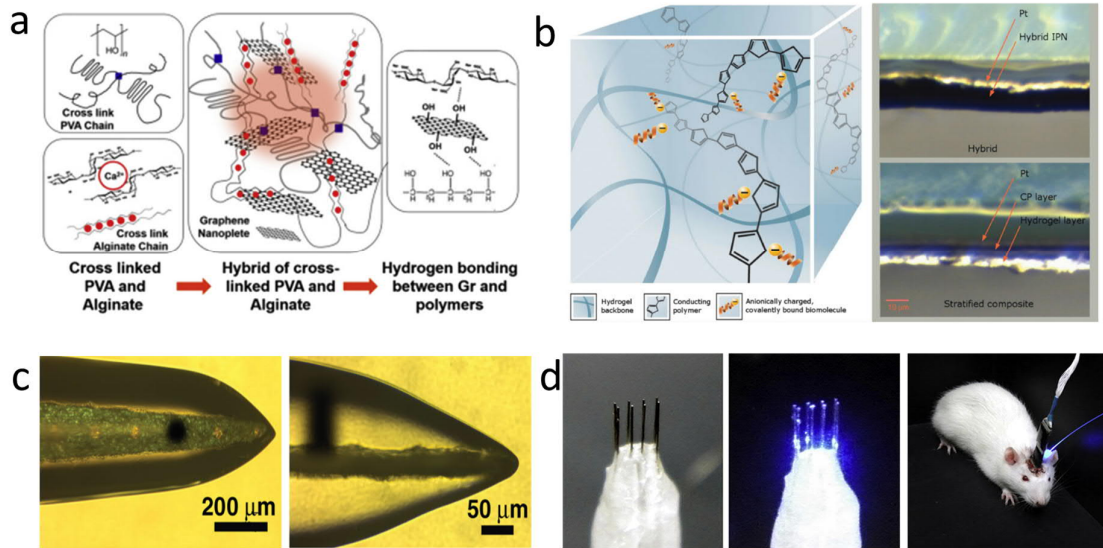


**Figure 4**. hydrogels as soft materials for BMI applications. (a) Schematic illustrating the formation of the interpenetrating network of PVA:SA, via physical crosslinking of PVA by heat treatment and chemical crosslinking of Alginate by CaCl2 solution, as well as the hydrogen bonding between Gr nanosheets and polymer matrix leading to significantly promoted mechanical properties (b) Schematic of ideal hybrid configuration (left) and photo comparison of hybrid material created from using a bound dopant, compared to stratified composite produced from using a free dopant (right). Both material samples are hydrated (c) top view of neural electrode after coating with DEX-loaded electrospun nanofibers and alginate hydrogel in hydrated and dehydrated state c) C-IPN can be micropatterned into pyramidal structures with features as small as 10 μm by casting into silicon molds. Scale bar is 200 μm, Cross-sectional SEM image of freeze-dried C-IPN showing that the final gel is homogeneous and porous. Scale bar is 100 μm C. (d) Tip of optrode array: light off, and light on. Optical stimulation and electrical recording using optrode array implanted in freely moving animal.

# 5. FABRICATION AND NANOSTRUCTION

Choosing the materials needed for specific application follows with the next step to single out the best fabrication method, which can provide all the aspects of the final material. Ideal BMI devices should be able to reach out to neurons and successfully sense and transmit the signals throughout the system. Depends on the application, the feature size, shape and dimension of the devices can vary. For instance, deep brain stimulation electrodes have a size of 4-8 millimeters, where in case of neural recording the size can reduces to 10-100 microns. In some cases, multi-electrode arrays are more desired, which specific shape and design needs to be implemented. (10,11)

Electrospinning and 3D printing are considered two major fabrication methods to obtain final favored nanostructures. Electrospinning known as a technique which can provide materials in the form of nanofibers, with tunable properties, and can be used encountering variety of polymers. One of the most important features of this technique for biomedical applications, specially BMI, is that fibers produced using this technique, have high surface-to-volume ratio. This property make them perfect candidates for any neural interface by enhancing the neural signaling and cell integration. It has been shown by many studies that using nanofibers, can induce cell growth and proliferation in desired way. Low price and easy processing are the other aspects of this technique which make it more prominent by time.

3D printing has been adopted for many application since invention, as it gives the possibility to create complex geometries, which were not possible through conventional fabrication techniques. The use of 3D printing methods for biomedical applications lies within the fact that it is possible to develop biomimetic tissue constructs, soft robots and customized drug delivery systems with extremely high precision.

### 5.1 Electrospinning

In the past couple of decades electrospinning (Nayak, Padhye, Kyratzis, Truong, & Arnold, 2012) has become a popular technique for fabrication materials and biomaterials for a range of applications. The electrospinning technique is used to fabricate continuous nanoscale fibers with diameters in the sub-micrometer to nanometer range using a high-voltage power supply. This leads to materials with high surface area and potential for alignment, giving rise to a range of applications such as filtration and thermal insulation, and in the manufacture of protective clothing, sensors, conducting devices and a range of biomedical applications.

A review published 15 years ago focusing on the electrospinning technique to fabricate materials for biomedical applications from a range of non-conducting natural and synthetic polymers showed a few types of fiber morphologies (Agarwal, Wendorff, & Greiner, 2008). Nowadays, the electrospinning technique can produce nanofibers with a range of different morphologies and microstructures (X. X. Wang et al., 2021) from conducting and non-conducting polymers.

Conducting polymer-based nanostructured materials can be fabricated using different variants of the electrospinning techniques. Conductive polymers (CPs) are promising organic semiconductors for many essential applications because of their tunable physical/chemical properties, mechanical flexibility, low weight, reversible doping, good biocompatibility, and scalable production.

However, some of their undesirable physical characteristics such as insolubility, infusibility, brittleness, and dimensional stability are the drawbacks of CPs. These limitations are the main reasons why CPs have not achieved their expected application potential in conventional processing forms. Due to the drawbacks of CPs, novel strategies are necessary to fabricate nanostructured materials. Different electrospinning approaches, including direct or neat electrospinning of CPs into fibers, co-electrospinning with a carrier polymer to give blended fibers, co-axial electrospinning and coating of electrospun fiber have been developed.

Direct or neat electrospinning of CPs is difficult to achieved as they tend to have rigid backbones, low molecular weights, and low degrees of chain entanglement, which make them unsuitable for electrospinning purposes. There have been limited reports of successful electrospinning and nanofiber formation from pure CP solutions.

One of the earliest direct electrospinning of a CP was published in 2006 using poly-pyrrole (Chronakis, Grapenson, & Jakob, 2006) as the CP to produced pure poly-pyrrole conductive nanofibers by electrospinning organic solvent soluble poly-pyrrole using the functional doping agent di(2-ethylhexyl) sulfosuccinate sodium salt. They measured the electrical conductivity of the nanofiber web was about $2.7 \times 10^{-2}$ S/cm but did not demonstrate an application.

A more recent paper on direct electrospinning of polyaniline has been demonstrated via doped polyaniline solutions in common organic solvents were processed into nanofibers using a convenient single-nozzle electrospinning technique (Spiers et al., 2021) with nanofibrous membranes generated substrates subsequently employed in colorimetric gas sensing for ammonia. These substrates

demonstrated linearity of response upon exposure to 50−5500 ppm ammonia at ambient (50 ± 10% RH) and high (80% RH) humidity.

Co-electrospinning with a carrier polymer has been a common approach to overcome the spinnability of CPs. There are numerous publications using this approach to produce a blended electrospun fibrous materials. The research group of Nobel Prize winner Alan MacDiarmid conducted some of the early investigations into electrospun CPs utilizing carrier polymers. They electrospun blends of doped PANI with PEO (Norris, Shaker, Ko, & MacDiarmid, 2000) and found that fiber diameter varied with the concentration and nature of the carrier polymer. In a separate paper by the same group, PS was used as a carrier polymer (MacDiarmid et al., 2001). However, a clear disadvantage of employing co-electrospinning approach is that it caused significant reductions of electrical conductivity of the final materials

Coaxial electrospinning (Yoon, Yang, Lee, & Yu, 2018) or electrospinning with a two-capillary spinneret (Yu, Fridrikh, & Rutledge, 2004) is another approach that can be used to fabricate continuous core–shell CP composite fibers and pure CP nanotubes. To overcome problems associated with electrospinning PANI (Yuxi Zhang & Rutledge, 2012) utilized coaxial electrospinning to generate PANI/PMMA nanofibers, using emeraldine base PANI dissolved in chloroform for the inner core and poly (methyl methacrylate) dissolved in N,N-dimethylformamide as the outer shell. Smooth and continuous PANI/PMMA nanofibers were obtained with diameters ca. 1440 nm. The PMMA outer shell could be removed via immersion in an isopropanol solution for 1 h to yield neat PANI nanofibers with decreased diameters of ca. 620 nm and conductivities of 50 S/cm$^{-1}$.

Another approach to produced conducting polymer-based nanostructured materials is coating of the CP onto a substrate. Electrospun nanofibers can be used as a template substrate for fabricate coaxial CP fibres. Both organic or inorganic electrospun fibres can provide a robust and stable template during the growth of 1D nanostructures of various CPs. Particularly, the nanofiber template can be removed during or after the polymerization process of CPs. Presently, two methods are used to grow CPs on electrospun fiber templates: solution deposition polymerization and vapor deposition polymerization.

Dip coating have been demonstrated to produce conductive polymeric materials by Ding et al for a textile application. They coated electrospun polyurethane with PEDOT:PSS. conductivity of the e-PU

nonwovens increased relative to the number of dip coatings applied, sample that were dip coated three times yielded a conductivity of 2 S/cm.

Another interesting example that uses the coating approach where they were able to produce electrically conductive biomaterial in 2 stages (J. Y. Lee, Bashur, Goldstein, & Schmidt, 2009). They electrospin PLGA first and then coated the coated the PLGA meshes with poly-pyrrole. They found that electrical stimulation of PC12 cells on these conductive fibres improved neurite outgrowth compared to non-stimulated cells.

It is possible to produce conducting polymer-based nanostructured materials by overcoming the barriers of CP electrospinning by using different approaches. These CP electrospun materials find applications in many different areas, including the biomedical field, where the high surface areas of electrospun nanofibers often prove advantageous. Two of the approaches, co-axial electrospinning and coating post-electrospinning) described may prove to be challenging when large volumes of materials are needed for the applications such as filtration media or textile. The volume required for biomedical purposes are much smaller compared to other industrial applications and current electrospinning approaches should provide sufficient materials. In another study done by Kim et. al. a highly aligned electrospun material was designed with to coat a nerve conduit. As shown in Figure 5a, external and internal layers of random-aligned fibers are rolled to form the coating. The reason behind is that the internal part with growth factor embedded aligned fibers, will improve the nerve regeneration, at the same time, the external layer of random fibers increase the mechanical strength (J. I. Kim, Hwang, Aguilar, Park, & Kim, 2016). PCL was combined also with conductive copolymer PAT which is a mixture of aniline tetramer (AT), dopamine (DOPA) and polyethylene glycol (PEG), used for electrospinning and shown in figure 5d. The effects of nanofiber structure on the proliferation and differentiation of neuro stem cells was studied by Yan et. al. (Yan et al., 2020).
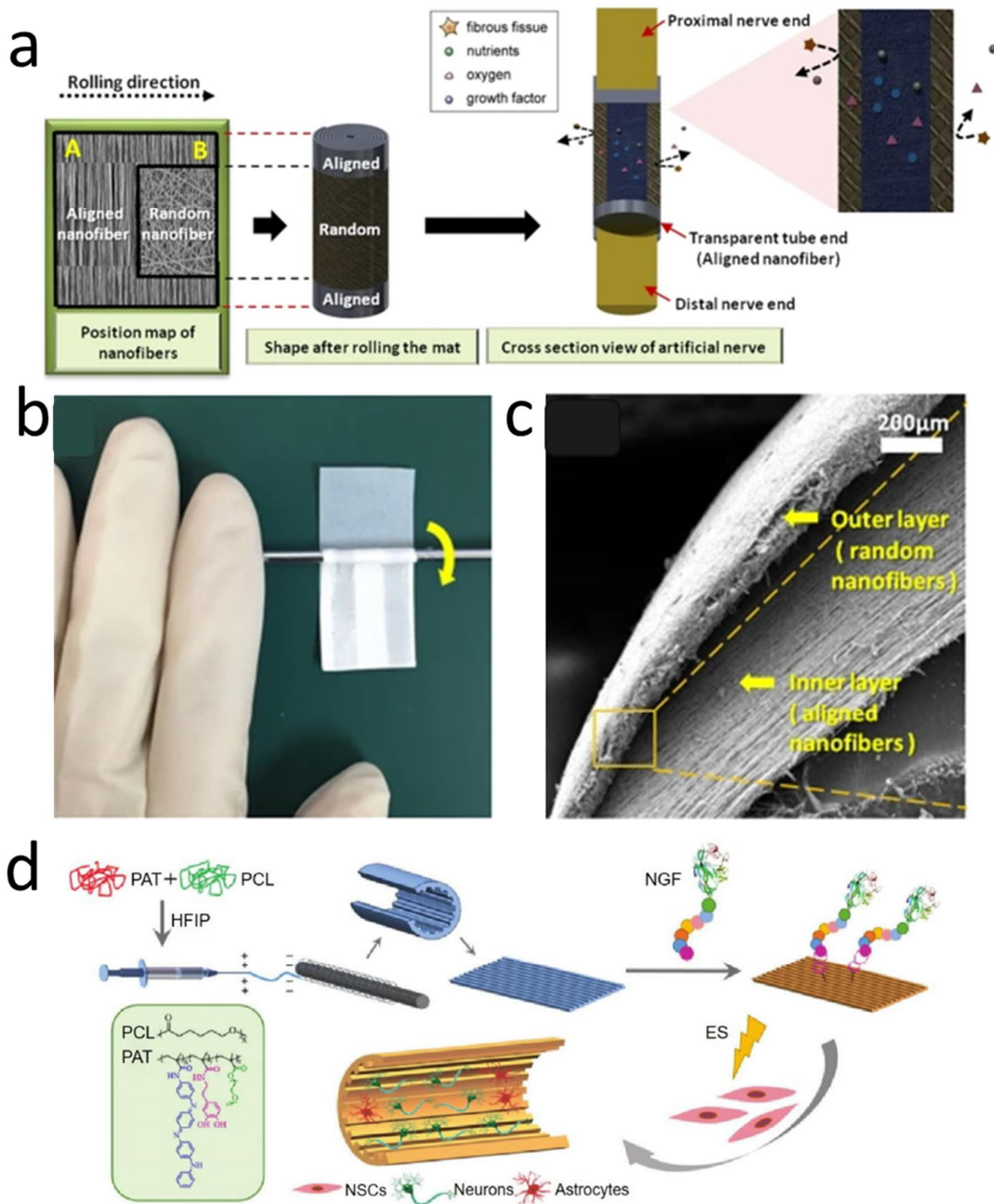
**Figure 5**. Electrospinning a technique for fabricating BMI. (a) Schematic 3D illustration of the nerve guide conduit (the position map of nanofiber, shape after rolling the mat and cross section view of the conduit is shown in this figure) (b) A digital photo of rolling the angled U shape mat on a rod (c) SEM images of the cross section view of the nerve tube. (d) Schematic diagram of the combination of nerve growth factor with an electrically conductive PAT/PCL micropatterned nanofiber mesh, and combined with electrical stimulation to effectively promote the differentiation of neural stem cells into neurons and inhibit astrocyte formation.

## 5.2. Additive manufacturing

According to the standard ("ISO - ISO/ASTM 52900," n.d.), additive manufacturing (AM), commonly known as 3D printing is the "process of joining materials to make parts from 3D model data, usually layer upon layer". This synthetic definition conveys the fundamental idea that starting from a digital model, which can be a computer-aided design (CAD) file or a 3D scan of a physical sample, AM builds up the targeted object by means of the progressive addition of material. This is in stark contrast to conventional fabrication methods, which either change the shape of the bulk of material through melting and casting or through solid-state plastic deformation (formative methods), or rely on the progressive removal of material where it is not needed (subtractive methods) (Onuh & Yusuf, 1999).

AM is gradually progressing from being a rapid prototyping tool to playing a fundamental role in the Industry 4.0 revolution. The adoption of AM offers key advantages, especially in the biomedical field. If body scans are fed in as the digital model, implants can be fabricated to exactly reproduce the anatomy of the patient. Moreover, since AM is a mouldless technology, the printed geometry can be easily changed job-by-job without incurring additional costs. This ultimately enables the timely and cost-effective obtainment of biomedical devices that conform to the patient's physical structure and physiology (Shidid, Leary, Choong, & Brandt, 2016). Faithful reproductions of organs and anatomical details can also be helpful in pre-surgical planning and training (Bibb, Eggbeer, Evans, Bocca, & Sugar, 2009). The selective deposition of material where it is needed according to a computer-controlled toolpath opens the way for fabricating extremely complicated architectures, including lattices and topologically optimized structures. 3D models that reproduce the intricacy of natural constructs are crucial in tissue engineering. They create a biomimetic environment for cell growth and tissue regeneration *in vitro* and *in vivo* (Chandrasekaran et al., 2017). AM is also poised to be a game-changer in the production of implantable sensors, including optogenetic probes, as 3D printing does not necessarily require expensive materials, long processing times, and special cleanroom machines as often seen with conventional microfabrication procedures (Parker et al., 2022).

Historically, research in AM has been focused on structural materials, with the final target being the optimization (i.e., the maximization) of the mechanical stiffness and strength of the printed object. Driven by the increasing need for appropriate interfaces with neural tissue, it has only been very recently that attention has also been paid to extra-soft and compliant printable materials (Shur et al., 2020b). However, some AM technologies are intrinsically unsuitable for processing extra-soft and compliant

materials because of their very functioning mechanism. In fused filament fabrication (FFF), for example, the feedstock, which is typically a thermoplastic material, cannot be printed if the ratio between (compressive) modulus and molten viscosity is lower than a critical value in the range of $3 \times 10^5$ to $5 \times 10^5$ s$^{-1}$ (considering a print nozzle of 508 μm) (Venkataraman et al., 2000) and this explains why thermoplastic elastomers having a stiffness in the order of several MPa ($10^6$–$10^9$ Pa) are currently the "softest" materials printable by FFF (Awasthi & Banerjee, 2021). Even provided that extra-soft and compliant materials can be printed, they are likely to collapse. For this reason, extra-soft and compliant materials are often 3D printed with the structural support of a stiffer material to avoid sagging (Pati et al., 2014) or processed in a hydrogel- or granular gel-based bath that counteracts the force of gravity ("embedded printing") (Kajtez et al., 2022). Bi-dimensional electrode coatings can be directly screen-printed on stretchable substrates such as polydimethylsiloxane (PDMS) (Shur et al., 2020b).

Another obstacle is represented by the printing temperature. Many AM methods require heating the feedstock material to induce inter-layer bonding, which is a precondition for fabricating a solid object (Sola, 2022). The input of thermal energy, either through direct heating or through the interaction with a high-power laser or electron beam, is incompatible with cell-laden bioprinting. As a consequence, cells must be seeded on the part's surface after printing, as opposed to being co-printed and thus spatially distributed within the scaffold's architecture, as would be the case with living tissues (Jipeng Li, Chen, Fan, & Zhou, 2016). Whilst relatively uninfluential when printing neural probes, the ability to co-print living cells becomes very important for neural tissue engineering. Moreover, the melt-to-solid transition is typically accompanied by a substantial increase in stiffness, which may undermine the mechanical compatibility with neural tissue.

Presently, few AM techniques exist that are able to cope with these obstacles. 3D printing of soft materials compatible with neural tissue has been mainly accomplished either via vat photopolymerization (VPP: light-based approach) or via material extrusion (MEX: ink-based approach) (Y. Park, Chung, Lee, & Rogers, 2022b). For example, as for VPP methods, Rinoldi et al. combined a soft and biocompatible hydrogel based on poly(N-isopropylacrylamide-co-N-isopropylmethacrylamide) with polythiophene, an intrinsically conductive polymer (ICP), to obtain a printable semi-interpenetrating polymer network (semi-IPN) with good electrical properties. *In vitro* tests proved that the new hybrid hydrogel was highly compatible with neurons and astrocytes and could even promote the differentiation of neural cells. **Figure 6**a, illustrates the printing workflow, where scaffolds could be successfully built

up with feature sizes as small as 3 μm via UV light-based stereolithography (SLA) (Rinoldi, Lanzi, et al., 2021b).
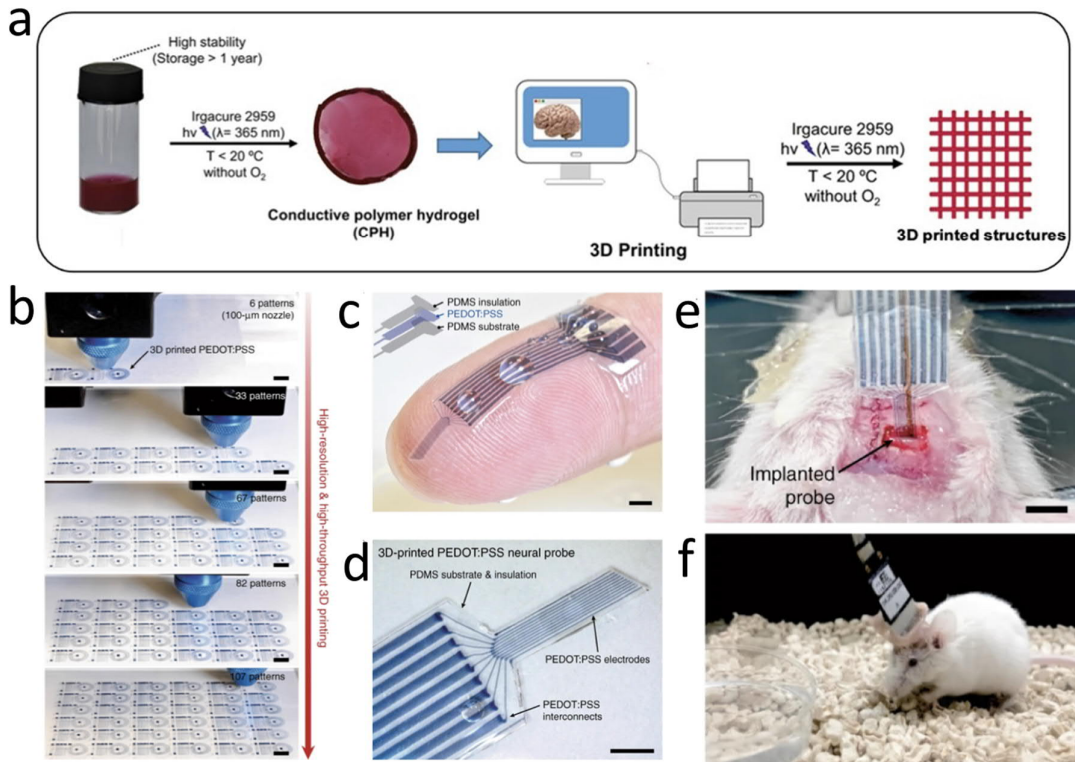


**Figure 6.** Additive manufacturing of flexible structures by vat photopolymerization (VPP) of extra-soft and conductive hydrogels: a) Schematic representation of the manufacturing workflow. *Reused under the CC BY-NC-ND 4.0 license from Rinoldi et al. [2021], Figure 7*. (b-f) Additive manufacturing of conducting polymer devices by material extrusion (MEX) of PEDOT:PSS-based inks: (b) high throughput fabrication of high-density flexible electronic circuit patterns (scale bar: 5 mm); (c-d) 3D-printed soft neural probe with 9-channels as seen at (c) low magnification and (d) high magnification (scale bars: 1 mm); (e-f) *in vivo* testing of the probe in a mouse model, showing (e) the craniotomy site (scale bar: 2 mm) and (f) a freely moving mouse with the implanted probe. *Adapted under a Creative Commons Attribution 4.0 International License from Yuk et al. [2020], Figure 4*.

Since AM affords on-the-fly design customization, Lee et al. developed scalable optogenetic probes based on SLA substrates whose size and layout could be easily adapted to mammalian brain models with different sizes (J. Lee et al., 2020). After printing, the substrates, whose surface was micro-grooved, received a silver paste coating to render the electrode pattern and a microscale inorganic light-emitting diode. Finally, the shanks were coated with a PDMS/parylene C bilayer to impart

biocompatibility, chemical inertness, and waterproofing. Owing to the high print accuracy enabled by SLA, the substrates were just 60 μm thick, which is comparable to the thickness of a human hair. This enhanced the flexibility of the probes for biomechanical compatibility with soft brain tissue. Meanwhile, the probes were stiff enough to penetrate phantom brain tissue without bending. In a mice model, the bare probes without parylene coating produced significantly larger lesions than conventional probes. However, parylene coating reduced the inflammatory response to levels comparable to fibre implants. Moreover, the new probes are suitable for the implementation of wireless functionality, which allows neural activity to be monitored in freely behaving animals (Parker et al., 2022).

Even if the spatial resolution is lower with respect to VPP, MEX-based AM is a viable option for printing probes and electrodes for neural interfaces owing to its compatibility with a wide range of materials, high throughput (example in Figure 6b), and multi-material printing capability (Y. Park et al., 2022b). For example, Yuk et al. formulated a conductive polymer ink based on poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS). In order to achieve appropriate rheological properties for 3D printing, an aqueous solution of PEDOT:PSS was freeze-dried in a cryogenic condition and then redispersed in water and dimethyl sulfoxide (DMSO) mixture (Yuk et al., 2020b). After printing, the free-standing PEDOT:PSS structures needed drying and annealing to remove the solvents and facilitate the establishment of a conductive percolation pathway. The resultant dry parts could be easily converted into a pure PEDOT:PSS hydrogel (equilibrium water content ~ 87%; Young's modulus below 1.1 MPa) by swelling in a wet environment, as shown in Figure 6c-d. PEDOT:PSS hydrogel electronic circuits were co-printed with PDMS ink for insulating encapsulation. In this way, a flexible neural probe could be readily fabricated in less than 20 minutes in a single-step process. As illustrated in Figure 6e-f, in *vivo* tests demonstrated the capability of the probe to record continuous neural activity in a freely moving mouse.

## 6. NEW TRENDS

Nowadays, novel strategies and approaches for designing more efficient, reliable, and functional BMIs have been explored. In order to guarantee stable contact and long-term communication with the neural tissue, the improvement of biocompatibility, the enhancement of electrical properties, and the decrease of mechanical characteristics are considered the most crucial aspects in the new generation of neural

interfaces (Choi, Kim, Ryu, Kim, & Sohn, 2018b). Indeed, properly tuning each of these key properties might result in higher fidelity and quality of signal transmission between the brain and machines.

Current progress includes developing biomimetic interfaces which can enhance cell adhesion and induce specific cell spreading. In this frame, efforts in designing conducting polymer materials that can be loaded with cells are crucial to increase the biocompatibility of the proposed devices. The housing cultured cells have the function of promoting the integration of the implant in the host tissue, thus improving the quality, fidelity, and long-term stability of the brain tissue-electrode interface (Rochford et al., 2020). Wu *et al.* produced a biomimetic extracellular matrix for neurogenesis composed of electroconductive polypyrrole (PPy) nanoparticles embedded in collagen hydrogel microfibers loaded with PC12 cells (Figure 7a) (C. Wu et al., 2019). The particles were modified to obtain higher hydrophilicity, thus achieving a uniform dispersion into the hydrogel network. The final system was created by using microfluidic technology, resulting in a conductive, biocompatible, and highly-oriented 3D structure that can mimic the neural microenvironment and transfer electrical signals. In another work, a tissue-inspired conducting polymer multinetwork hydrogel was developed to reproduce the native extracellular matrix properties. Intrinsically conducting PEDOT was polymerized *in situ* with polyacrylamide hydrogel loaded with nanoclay Laponite (Tondera et al., 2019). The hydrogel was then coated with a layer of adhesive peptide and polysaccharide dextran sulfate to improve the biocompatibility and suitability of the system for human induced pluripotent stem cell attachment and differentiation. Additionally, the resulting neural electrode showed adequate electrical conductivity (*i.e.,* 26 S/m) - thanks to the presence of PEDOT doped with Laponite -, stretchability (*i.e.,* 800%), and elastic modulus comparable with the one of native tissue (*i.e.,* 15 kPa) - imparted by the polyacrylamide hydrogel -, revealing its potential as tissue-mimetic BMI.

Several efforts in reducing the mechanical characteristics of BMIs have been made in order to narrow the mechanical mismatch with the brain tissue and prevent severe neuroinflammatory reactions (Osmani et al., 2020). For this purpose, the choice of using conducting polymer-based nanostructured hydrogels as materials for producing BMIs has become more and more popular in recent years due to their unique softness and flexibility, which can induce minimal stress on the brain tissue and stability of the implants in the long-term (Yuk, Wu, & Zhao, 2022). In this frame, Wang *et al.* have developed a bioadhesive ultrasoft interface composed of dopamine methacrylate-hybridized PEDOT nanoparticles embedded in a hydrogel structure. The system showed comparable modulus with the brain tissue and

negligible host immune response, permitting an efficient and long-term acquisition of biosignals (X. Wang et al., 2022). By targeting the same goal, Liu *et al.* developed a conductive hydrogel-based electrode with high stretchability (20%) and Young's modulus values similar to the native tissue (in the order of kPa). A final thin-film elastronic electrode array was produced using the micropatterning technique by photopatterning a micropatterned electrically conductive PEDOT:PSS hydrogels with two elastomeric external layers of dimethacrylate-functionalized perfluoropolyether, resulting in a promising system for soft tissue-like BMI (Figure 7b) (Yuxin Liu et al., 2019). On the other hand, recent studies have demonstrated that matching the viscoelastic properties might also be beneficial for improving the functionality, long-term stability, and biocompatibility of BMIs. Xiong *et al.* fabricated a conductive multilayered graphene hydrogel membrane, showing the role of viscoelasticity in decreasing nerve compression during implantation while inducing only a mild inflammatory response in the long-term (*i.e.,* eight weeks) (Xiong et al., 2022).

Besides, it is worth underlining how crucial it is to overcome the trade-off between mechanical and electrical characteristics of materials and individuate a proper balance of the mechanoelectrical properties. This is probably the biggest challenge in the field and has recently motivated researchers to explore and propose new solutions (P. Wang et al., 2020). Won *et al.* designed a novel neural probe with a core-shell fiber structure, where the core is made of Au-embedded polyurethane-based filament and a shell of PDMS and PEG polymers (Figure 7c) (C. Won et al., 2022). The resulting fiber showed excellent electrical conductivity of $7.68 \times 10^4$ S/m and impedance of $2.88 \times 103$ $\Omega$ at a physiologically relevant frequency (*i.e.,* 1 Hz), while the mechanical properties were comparable to the brain tissue characteristics (in the order of kPa; *i.e.,* 170 kPa). The system was implanted *in vivo* in a mouse model, reporting stable long-term signal acquisition for up to 4 months (both spontaneous and evoked potentials) with minimal immune response. Similarly, Krukiewicz et *al.* proposed a few BMI core-shell systems composed of soft poly($\varepsilon$-decalactone) filled with conductive particles such as carbon nanotube, Ag nanowires (AgNWs) or microspheres made of poly(hydroxymethyl 3,4-ethylenedioxythiophene, P(EDOT-OH)) (Krukiewicz et al., 2021). Data showed that: i) the addition of carbon nanotubes led to lower resistance (1.2 $\pm$ 0.3 k$\Omega$): ii) the presence of AgNWs resulted in the highest charge storage capacity (10.7 $\pm$ 0.3 mC cm$^{-2}$); iii) the composite with P(EDOT-OH) microspheres possessed the highest interphase capacitance (1478.4 $\pm$ 92.4 $\mu$F cm$^{-2}$). Authors reported *in vitro* data to demonstrate the cytocompatibility of the systems, revealing the potential of the proposed materials as BMIs.

Finally, researchers have recently dedicated increasing efforts to developing advanced conducting polymer-based materials for producing shape memory and stimuli-responsive BMI systems. Indeed, shape memory materials can be tuned to have 2D geometry and stiff characteristics for easier implantation, while recovering in a 3D shape with softer mechanical features after being implanted in the human body at 37°C (Sadeghi, Afshari, Hashemi, Kaplan, & Mozafari, 2023). On the other hand, stimuli-responsive materials possess outstanding characteristics as they can intelligently respond to different stimuli, including electrical, optical, mechanical, ultrasonic, and magnetic stimuli. This trend has the potential to achieve wireless, direct, and reciprocal interactions with the nervous system, avoiding invasive wiring and the implantation of energy sources (Sadeghi et al., 2023).
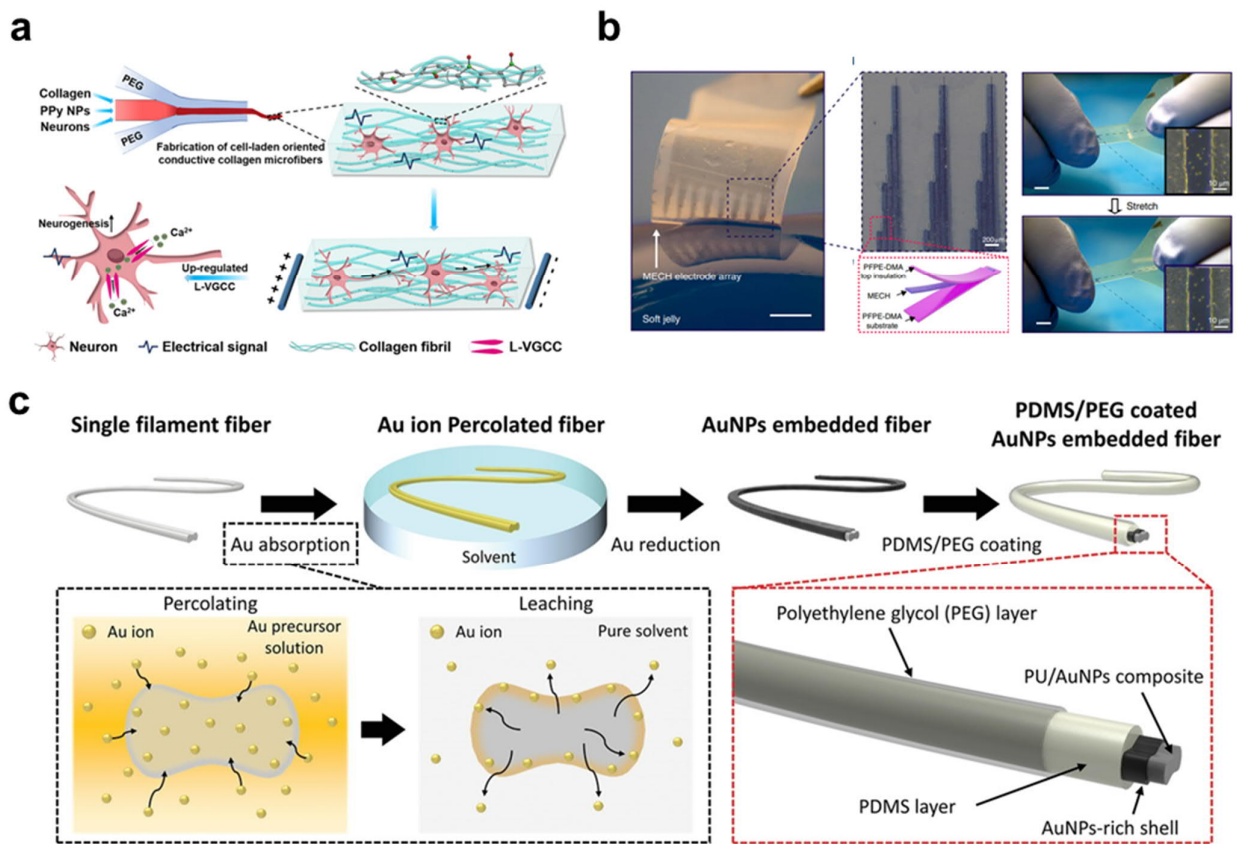


**Figure 7.** New trends in conducting polymer-based systems for brain-machine interfaces. a) Electrical conducting hydrogels consisting of cell-laden collagen-PPy NPs hybrid hydrogels having the shape of a microfiber for promoting cell alignment and electrical conductivity. Reprinted with permission from Wu et al. (2019) (C. Wu et al., 2019). b) Lithographically micropatterned electrically conductive hydrogels with high resistance to mechanical

tensile stretching (up to 20% strain). Reprinted with permission from Liu et al. (2019)(Yuxin Liu et al., 2019). c) Schematic representation of neural probes made of PDMS/PEG-coated AuNPs-embedded fiber. Reprinted with permission from Won et al. (2022) (C. Won et al., 2022).

## Conclusion and Future perspectives

Current progress and advancements in neuroscience and neurotechnology have been strongly related to the growing interest in researching novel and more efficient BMI systems. The promising potential of BMIs has been explored to acquire and study brain signals, stimulate brain tissue, and develop strategies for neurological disease treatments. Up to date, conducting polymers are considered among the best candidates as materials for BMI fabrication since they have the unique advantage of being easily tuned and optimized to obtain desired and convenient characteristics. For this reason, conducting polymers-based BMIs can simultaneously offer sufficient electrical properties, mechanical features similar to native tissue, and excellent biocompatibility, highlighting their extraordinary potential for this application. Thanks to these outstanding features, those systems are able to maintain stable and intimate contact with the electrode-tissue interface and reduce the foreign body response in terms of scarring and neuroinflammation, allowing an efficient recording of high-quality neural signals in the long term. The field has grown enormously in recent years, providing devices with ameliorated electrical and mechanical properties while improving their biocompatibility. Nowadays, several different conducting polymer-based nanostructured systems have been reported in the literature, including BMIs formed from i) inorganic nanomaterials and composites (*e.g.*, carbon nanotubes, graphene, graphene oxide, and reduced graphene oxide); ii) intrinsically conducting polymers (*i.e.,* polyaniline, polypirrole, polythiophene); iii) conductive interpenetrating polymer hydrogels (*i.e.,* semi-IPNs and IPNs). Different production and fabrication methods to obtain BMIs have also been deeply explored (*e.g.,* electrospinning and 3D printing). In this frame, intrinsically conducting polymers evidence higher potential than polymers embedded with conductive nanofillers, showing enhanced electrical and mechanical properties. Designing BMIs with balanced mechano-electrical properties seems to be, nowadays, the direction of this research area; while high-resolution miniaturizing of devices is considered the most probable future perspective for enhancing the special resolution. Besides, the possibility of loading and releasing anti-inflammatory drugs from BMIs in a controlled manner holds a high potential to suppress the foreign body response.

Furthermore, the development of smart conducting polymer-based materials (*e.g.,* thermo-responsive and shape memory materials) looks promising for BMI applications. Shape memory materials will provide easy-to-handle systems during the implantation procedure. Advanced thermo-responsive materials will play as a wireless neural transducer, preventing the use of invasive wires and the implantation of energy sources.

We believe that the future of the field may also include high-resolution integrated technologies and nanotechnologies to develop multi-modal high-performing BMIs with the ability to detect electrical and optical signals simultaneously. Additionally, it is foreseen that artificial intelligence and machine learning will also assist in the modeling and designing of novel advanced materials for BMI fabrication with outstanding properties in the near future (Sadeghi et al., 2023).

Finally, we believe that the next generation of neural interfaces will provide the combination of conducting polymer-based BMI with cell transplantation to restore and repair neurological function in the most effective manner. Indeed, it is well known that both approaches are of crucial importance for successful clinical translational neuromodulation therapies. This might pave the way for novel treatment opportunities by recording/stimulating signals while regenerating the damaged neural tissue. Thus, we expect that the concept of biohybrid conducting polymer-based interfaces will take over the field in close future, offering conductive implantable interfaces loaded with cells that will be integrated into the host tissue. This will result in highly promising systems that would be able to detect or stimulate signals while promoting the regeneration of the tissue, thus controlling and restoring neural functions.

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