Organic electronics for neuroprosthetics

M. J. I. Airaghi Leccardi and D. Ghezzi

Medtronic Chair in Neuroengineering, Center for Neuroprosthetics and Institute of Bioengineering, School of Engineering, École polytechnique fédérale de Lausanne, 1202 Geneva, Switzerland.
E-mail: diego.ghezzi@epfl.ch

Neuroprosthetics aims at restoring impaired or lost neurological and mental functions by exploiting technological advances in implantable and wearable devices. The performance of implantable devices, such as neural interfaces, relies upon the synergy between biology and machines. Should this synergy lack, numerous undesirable consequences might occur, such as rejection, infection, or malfunctioning. Several materials properties like softness, electrochemical behaviour, biocompatibility and biodegradability are among the features affecting the reliability of neural interfaces. In this review, we describe modern polymeric substrates and organic-based electrodes, offering the best combination of such characteristics. Their versatility in merging different properties derives from the accessible control over their molecular structure and blending. Compared to inorganic materials, organic materials have superior mechanical compliance with the soft tissue, and conjugated polymers also have an advantageous electrochemical transport mechanism at the interface with electrolytic solutions, involving both ionic and electronic conductivities. Hence, all-polymer neural interfaces would be convenient for a multitude of benefits, including low-cost manufacturing, increased biocompatibility, lightweight, transparency, and affinity with green electronics. This review also highlights materials strategies supporting the development of safe electronic interfaces based on organic materials and beneficial for various applications neuroprosthetics.

1. Introduction. Hundreds of million people worldwide suffer from neurological and mental disorders [1]. Neurotechnology might offer treatment approaches based on implantable neuroprostheses which allow both the stimulation and recording of the neuronal activity by establishing bidirectional communication between electronic devices and neurons [2]–[4]. Neuromodulation, for instance, allows influencing the activity of neurons via their excitation or inhibition [5]. Consequently, the modulation of the central and peripheral nervous system enables to restore sensory perception (e.g., blindness [6], deafness [7], and amputation [8]), mitigate movement disorders (e.g., Parkinson's disease [9] and spinal cord injury [10]), improve memory deficits (e.g., Alzheimer's disease [11]), alleviate behavioural disorders (e.g. obsessive-compulsive disorder [12] and addiction [13]), and reduce pain (e.g., phantom limb pain [14]).

Clinically adopted implantable neural interface are conventionally manufactured using a limited set of materials, such as platinum (or platinum-iridium alloys) electrodes embedded in thick and robust silicone (or polyurethane) matrix. Platinum-based electrodes emerged because of their high mechanical and chemical stability within the body. Also, such a set of materials meets regulatory compliance and industry standards in the whole production chain, including materials production, medical-grade certification, and manufacturing processes.

However, an efficient interface between the implant and the neural tissue requires a synergy not provided by traditional materials like metals [15]. For instance, mechanically compliant soft neural interfaces were introduced to reduce the mechanical mismatch with the neural tissue [3], [16]. Once an interface is implanted, the high mechanical mismatch and the tissue micro-motions can cause damage to the surrounding tissue and create a chronic glial scar, which reduces the device's performance [17], [18]. Minimizing this mechanical mismatch is pivotal to reduce the chronic scar and improve the lifetime of the implanted device. Polymers, elastomers, and other organic materials are widely used in research-grade neural interfaces for their lightweight, flexibility, softness, and elasticity compared to silicon, metals and metal-oxide materials [19].

Nevertheless, biology is not just about mechanics. A delicate balance between molecular interactions and ion movements governs the signalling within the nervous system [20], [21]. Polymers do not only offer better mechanical match with the tissue; some undergo controlled biodegradation or tailored softening, and others actuate, conduct electricity, have photovoltaic effects, or emit light upon charging [22]. For instance, conductive polymers (CPs) bridge the communication between the stiff, static, inorganic, and dry electronics with the soft, dynamic, organic, and wet environment of the neural tissue (Fig. 1). Some organic materials, *i.e.* π-conjugated polymers blended with polyelectrolytes or polymer electrolytes, are emerging materials for neural interfaces because of their ability to transport charges by mixed ionic–electronic conduction [23]. Ions in the proximity of the polymer can move and jump from chain to chain (ionic transport - 1), and create a large volumetric capacitance for bulk conductivity [24]. Ions can also interact with positive or negative charges on the conjugated backbone (ionic-electronic coupling - 2), which can themselves travel by electronic transport within and between chains (3) and communicate with electronic hardware and *vice versa*.

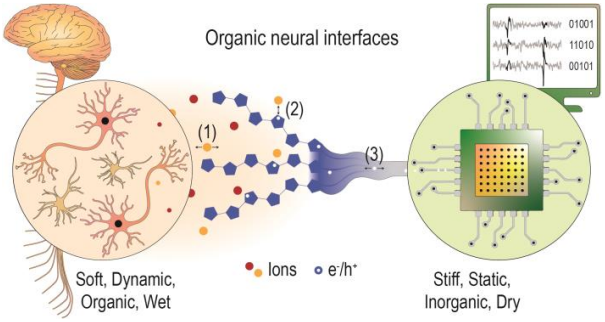

Fig. 1 *Organic materials, such as conjugated polymers, efficiently interface electronics with the nervous tissue thanks to the combination of volumetric ionic transport (1) and ionic-electronic coupling (2) with metallic-like electronic transport of charges (3).*

Organic materials can be synthesized from a large variety of building blocks in a vast amount of combinations, each of which gathering a unique mix of chemical-physical properties and performances. This flexibility and tunability in design, engineering, and manufacturing further motivates the use of polymers as functional materials for neurotechnology and bioelectronic medicine.

This review highlights emerging organic materials used in neural interfaces as substrates, electrodes and transducers. Their properties will be reviewed in light of the current and future needs in neuroprosthetics. Last, we will address some of the hurdles that organic materials should face to be adopted as standard materials for implantable neural interfaces.

2. Polymeric substrates. Polymers are appealing materials for the substrate and encapsulation layers of an implantable neural interface, mostly because they offer a broad range of elastic moduli from kPa to GPa (Fig. 2). Today, several neural prostheses employ (also in clinical research [8], [25]) flexible polymeric substrates with elastic modulus in the range of a few GPa (Fig. 2*G-I*). Polyimide (PI) is an attractive material because it has excellent processability and high compatibility with standard microfabrication processes. Furthermore, it can be used for complex 3-dimensional and multi-layered architectures (Fig. 2*I*) [26]. Parylene-C is another highly stable polymer that can be deposited by chemical vapour deposition for superior coating conformity. Fig. 2*H* shows a retinal prosthesis made of parylene-C and platinum electrodes [27]. These materials are the benchmark for implantable polymeric substrates mainly because of their high-precision manufacturing capability. However, although these flexible materials are two orders of magnitude softer than crystalline silicon (130-169 GPa [28]), their elastic modulus is still six orders of magnitude higher than the brain tissue (0.3-1.9 kPa [18], [29]). To decrease this mismatch and improve the mechanical symbiosis with the tissue, researchers introduced a variety of solutions. For instance, PI is a flexible but stiff polymer that can be micro-structured to reduce its bulk rigidity and acquire conformability [30]. Also, SU-8 can be patterned as a thin mesh to allow injection into the brain and extreme compliance with the nervous tissue (Fig. 2*G)* [31], [32]. The latter is an elegant solution to exploit a rigid substrate as support for metallic connections and electrodes while increasing the overall softness and improving the biocompatibility of the implant. Nevertheless, these flexible mesh electronics may bring additional difficulties in handling and positioning of the device within the implanted region.

Besides micro-structuring, changing the polymer type would also improve softness. For instance, liquid crystal polymers (LCPs) are inert polymers composed by rigid aromatic segments connected by flexible linkers, resulting in tunable mechanical properties spanning from tens of GPa to tens of MPa [33], [34]. A LCP-based neural implant is shown in Fig. 2*D* [35]. However, to further reduce the stiffness, one can consider elastomers, which are soft and stretchable materials (MPa range, with high elastic elongations [36], [37]). Silicones, such as poly(dimethylsiloxane) (PDMS), are the most common elastomers used for wearable and implantable neural interfaces. The extensive elastic elongation is extremely useful to match moving and deforming regions of the body (like the skin), as well as convoluted surfaces (like the brain) and non-zero Gaussian curvatures (like the eye). However, with stretchable substrates comes the need for matching stretchable electronics, which is not a property of conventional metals. Even if wavy, micro-cracked, or serpentine-like structures could provide a certain degree of elasticity [38]–[40], challenges such as delamination, high-stress corner points, and electrodes cracking will always limit the device's performance. Another approach for the integration of stiff thin-film electrodes into a stretchable matrix consists of engineering the elastic substrate with additional rigid platforms for mechanical protection. This was exploited, for instance, in a PDMS-based spherical, foldable, and photovoltaic retinal prosthesis (Fig. 2*B*), developed to match the retinal surface and to stimulate the retina wirelessly [41].

Hydrogels are the only class of materials with an elastic modulus (0.1-100 kPa) matching the brain softness [42]. Unfortunately, they are far from being processable with conventional microfabrication techniques and compatible with standard electronic components, and they are too soft to stand alone and penetrate the neural tissue. Therefore, hydrogel coatings are, so far, an up-and-coming solution to reduce implantation impact, inflammation reaction, and interfacial stiffness of otherwise rigid substrates (Fig. 2*A*) [43], [44].

In some applications, however, a permanent implant is not always necessary; in such case, the device should be removed. For example, this might be the case for temporary devices monitoring patients' conditions after trauma or surgeries [45], [46] or electrical stimulators for nerve guidance and regeneration [47], [48]. Consequently, transient organic materials and electronics able to spontaneously disappear into the body are an appealing and safer option because they do not need a second surgery for the removal. Among transient materials, silk fibroin is used in numerous applications (tissue engineering, wound dressing, electronic devices) and under various forms (films, sponges, fibres, hydrogels) [49], [50]. The degradation rate and the mechanical properties depend on the silk morphology and degree of crystallinity [49]. Fig. 2*E* shows an example of a degradable silk substrate for transient electronics [51], while other implantable systems can benefit of the peculiar properties of silk in a non-degradable form [52]. Alternatively, biodegradable materials such as polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), and cellulose can also be used as substrates for transient biomedical devices [53]–[55]. Similarly to silk, the degradation rate and the mechanical properties can be tuned by modifying the morphology, using additives, making copolymers and blends, or changing the prevalence [56], [57]. An example of PLGA-based implants is shown in Fig. 2*F*, where 128 metal-oxide-semiconductor field-effect transistors were patterned for high-resolution electrocorticography [58].

Shape-memory polymers (SMPs) are a promising class of organic materials for soft neural interfaces because of their ability to soften and actuate once implanted [59]. Substrates based on soft materials are often too fragile to penetrate most of the biological sheaths (e.g. the dura mater). To overcome this limitation, the glass transition temperature of SMPs, such as thiol-ene/acrylates, can be engineered to maintain the elastic modulus around the GPa range at room temperature to facilitate the insertion, and soften to tens of MPa or less once inside the brain to reduce the mechanical mismatch [60]–[62]. SMPs not only undergo a stiffness transition, but they can also mechanically actuate and change shape thanks to the tailored softening. Fig. 2*C* shows an implantable organic transistor that can self-roll around a warm cylinder (representing a large nerve) for a highly adaptive interface [63]. The full potential of SMPs is envisioned for those applications limited by complex accesses or insertion procedures. For example, a self-steering cochlear implant could be manufactured with SMPs to follow the spiral duct gently and minimize the insertion trauma [64]. Although SMPs offer a smart way to deal with important needs in implantable devices, a glass transition temperature allowing softening at body temperature (30 – 40 °C) falls in the range of temperatures easily reached during most of the microfabrication processes. To overcome this limitation, other room-temperature fabrication methods can be used (such as printing technologies) or a different triggering stimulus can be exploited for the mechanical transition to happen (such as light, ultrasound, magnetic field, or presence of water) [65], [66].

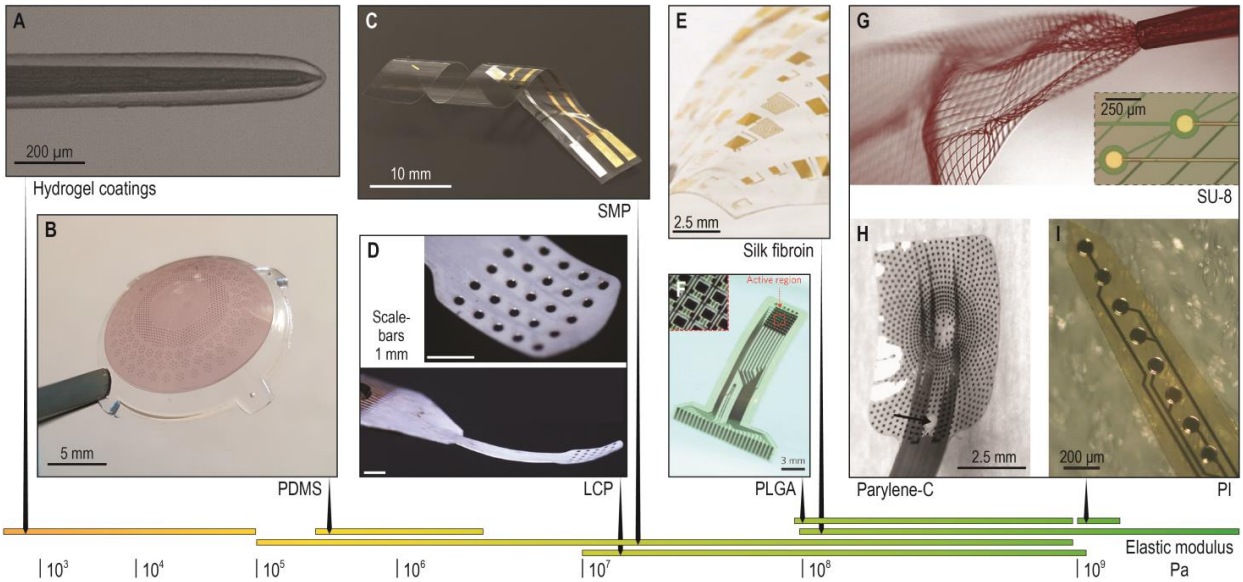

Fig. 2 *Overview of common implantable substrate materials and their ranges of elastic modulus, from hydrogel coatings (A), to PDMS (B), SMP (C), LCP (D), Silk fibroin (E), PLGA (F), SU-8 (G), parylene-C (H), and PI (I). Reproduced with permissions: A © Wiley 2004* [43], *B © Springer Nature 2018* [41], *C © Wiley 2014* [63], *D © Elsevier 2019* [35], *E © ACS 2019* [51], *F © Springer Nature 2016* [58], *G © Springer Nature 2015* [32], *H © Elsevier 2008* [27], *I © IOP 2019* [26].

With SMPs, but also with stretchable or degradable substrates, the major challenge lays in matching their mechanical properties with the material used for electrodes and other active parts (such as metal). The mismatch between the two sets of materials can nullify the benefits provided polymeric substrates. It is therefore interesting to look at organic materials also for electrodes and transducers.

3. Polymeric electrodes and transducers. Organic materials can play an important role also in functional elements of neural prostheses, such as electrodes. Electrical conductivity in organic materials is, for most cases, the result of electrons delocalization in multiple π-conjugated bonds and intermolecular interactions of such molecules. The corresponding molecular energy levels increase and shift the longer the chain of the oligomer until reaching a continuous valence and conduction band for the conjugated polymer with *n* monomers. Still, at this stage, the polymer is semiconducting, and doping is necessary to increase further the electrical conductivity (Fig. 3*A*). After doping, additional available energy states are formed within the bandgap and are stabilized by the formation of complexes due to the Coulomb attraction. The more heavily doped is the polymer, the larger is the additional band, which is eventually used for charge transport. Perfect polymer crystals achieve band conductivity due to the absence of defects or trapped states, whereas real systems have a certain degree of disorder and amorphism. This disorder induces fringing of the energy bands, thus favouring incoherent electronic transport (a mixture of band-like conductivity with charges hopping and tunnelling within and between molecules) and reduced charge mobility compared to crystals [67]–[69]. The sketch of the chemical structure of the π-conjugated polymer poly(3,4-ethylenedioxythiophene) (PEDOT), doped by the polyelectrolyte poly(styrenesulfonate) (PSS), reveals how the stabilized positive bipolaron can create a more effective electron delocalization along the backbone of PEDOT, increasing its electrical conductivity and allowing for water solubility (Fig. 3*B*). Different conjugated polymers have different intrinsic and doped conductivities (Fig. 3*C*) [70].

CPs, such as PEDOT:PSS, are used in a variety of biomedical applications like regenerative medicine, tissue engineering, biosensors, and neuroprosthetics [70]–[72]. They can be manufactured by spin-coating, printing, drop-casting, or electrodeposition. Usually, CPs are used as organic coatings directly onto metal electrodes (Fig. 3*D*, left) [73], mainly because of the manufacturing ease and the combined hybrid performances with thin-film, metallic conductors. These organic coatings not only improve the electrode-tissue interface by exploiting the mixed ionic-electronic conductivity, but also the biocompatibility and the mechanical interaction with the soft neural tissue. To further decrease the mechanical mismatch between electrodes and tissue (and achieve the kPa softness), conductive hydrogels (CHs) can be deposited onto or grow from the metal surface or the CP-based coating (Fig. 3*D*, middle) [73], [74]. CHs are an emerging class of biomaterials composed by either a gelled CP or by an insulating polymer hydrogel loaded with a conductive component, such as an interpenetrated network of CPs [74]–[76]. It was shown that the electrochemical impedance at the CH-electrode and the electrolyte interface is decreased (the cut-off frequency of the capacitive rise is shifted towards lower values) and the charge storage capacity increased, even compared to electrodes coated with CPs only [43], [77]. Since the structure of CHs is swelled in aqueous solution, the charge transfer mechanism and efficiency from CPs is likely extended to a larger volume. Moreover, ions in solution can travel between chains more easily in CHs than in CPs, thus increasing further the volumetric capacitance of the coating.

With the many advantageous characteristics and the vast choice of organic materials, one could develop an all-polymer neural prosthesis with organic substrates, organic conducting feedlines, and CH coatings (Fig. 3*D*, right). Polymer science has opened the possibility to obtain soft, stretchable, thin, and bioresorbable interfaces for fully organic, highly reliable neuronal recordings and stimulation capabilities [53], [78]. Recently, a few works have shown the potential of all-polymer probes for bio-electronic interfaces [79]–[81], and surely this tendency will continue for future developments.

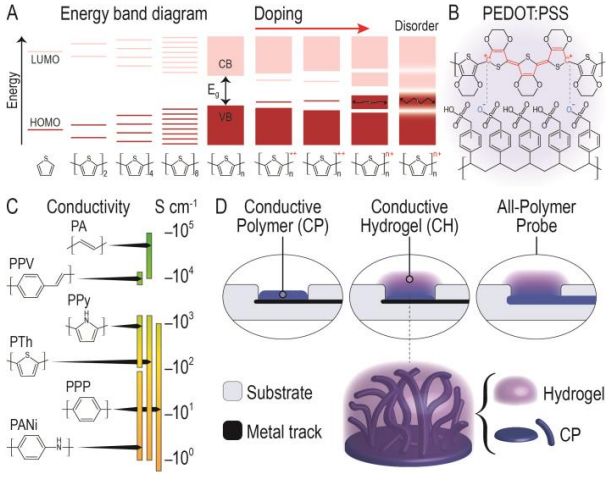

Fig. 3. *A) Simplified energy diagrams of poly(thiophene) monomer, oligomers (n = 2, 4, 8), undoped polymer, different degrees of doped polymers, and a heavily doped polymer affected by disorder. HOMO: highest occupied molecular orbital; LUMO: lowest unoccupied molecular orbital; E_g: bandgap energy; VB: valence band; CB: conduction band. B) Chemical structure of PEDOT:PSS. C) Chemical structure of conjugated (semi)conducting polymers classified based on their range of electrical conductivities, including the ones achievable with doping. PA: poly(acetylene); PPV: poly(phenylene vinylene); PPy: poly(pyrrole); PTh: poly(thiophene); PPP: poly(p-phenylene); PANi: poly(aniline). D) Cross-sections of electrodes with various coatings. CPs and CHs can be deposited onto metallic electrodes to improve the electrochemical properties by mixed ionic-electronic conductivity and reduce the mechanical mismatch with the biological tissue. If CPs are used also for feedlines, an all-polymer probe can be obtained. The schematic structure of a conductive hydrogel is visible at the bottom.*

Ultimately, the best way to minimize invasiveness and maximize biocompatibility is to avoid wires and electrical connections. Organic materials can provide not only electrical conductivity but also other communication modalities and transduction mechanisms such as photothermal stimulation or energy conversion from light, ultrasound, and magnetic field [82]–[89]. For instance, various research groups exploited organic semiconductors for photovoltaic activation of neurons and retinal ganglion cells [52], [90], [91]. Finally, the ideal probe for neuromodulation and recordings would be a soft and non-toxic particle, capable of cell-specific targeting and wireless transduction of signals at a large scale. This particle could be an organic microparticle, nanoparticle, or even a small molecule [86], [92], able to "hide" within the neural tissue for the perfect bio-artificial symbiosis.

At last, within the various benefits offered by organic bioelectronics, one should not neglect that this class of materials belongs to the low-cost and environmentally friendly "green electronics", which can also mitigate the challenge of limited precious metals availability [93], [94]. Furthermore, biodegradable organic electronics avoid the ecological problem of electronic waste and recycling issues.

4. Conclusion. The large pool of molecular design possibilities for organic materials favours the development of all-polymer electronic interfaces with improved biological synergy for biomedical applications, such as neural interfaces. The possibility to obtain ideal geometrical, mechanical, optical, electrical, and electrochemical properties, together with improved biocompatibility, seems increasingly achievable. Organic devices can be engineered to last for years in the body, or be tuned to soften, change shape, or degrade with time and temperature. Moreover, an interest in organic optoelectronic materials (among other modalities) is continuously increasing for the wireless and non-toxic modulation of neurons with light, a tool that has revolutionized the field of neurotechnology.

Yet, a certain degree of scepticism toward the inorganic-organic transition of implantable electronics is understandable. Because of the recent adoption in biomedical research, the variety of potential organic materials and their characteristics might not be entirely acknowledged. Although this assortment represents more a possibility than a limitation, the inquiry and the doubts about their performances, as well as adhesion and long-term stability are inevitable. Also, the traditional inorganic technology developed for microelectronics represents a more comfortable and reliable manufacturing method for implantable neural prostheses nowadays. Last, novel materials with enhanced performance but more restrictive manufacturing methods must be largely adopted by the medical industry in order to become standard materials in this field. This is not an easy step since the industrial acceleration of novel technologies and materials requires a large investment; for such reason, the medical industry might prefer to remain anchored to their established technologies. In order to become attractive for the industry, new materials and devices must meet regulatory and industry standards, and this is still not the case for many organic electronic materials.

Nevertheless, efforts for establishing processes and standards have just started for organic technology. The field could (and should) have a different face in a few years from now, opening numerous opportunities in neuroprosthetics.

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