Applications of PEDOT in bioelectronic medicine

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The widespread use of conducting polymers, especially poly(3,4-ethylene dioxythiophene) (PEDOT), within the space of bioelectronics has enabled improvements, both in terms of electrochemistry and functional versatility, of conventional metallic electrodes. This short review aims to provide an overview of how PEDOT coatings have contributed to functionalizing existing bioelectronics, the challenges which meet conducting polymer coatings from a regulatory and stability point of view and the possibilities to bring PEDOT-based coatings into large-scale clinical applications. Finally, their potential use for enabling new technologies for the field of bioelectronics as biodegradable, stretchable and slow-stimulation materials will be discussed.

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Why conducting polymers for bioelectronics

Conducting polymers (CPs) have made their mark in the field of bioelectronics in particular as functional additions which can enhance signal transfer properties and act as additions or alternatives to metallic microelectrodes. More recently, the unique qualities polymeric conducting materials have to offer are explored for enabling novel bioelectronic devices beyond what is possible with metals (Figure 1). The predominant polymer used within this space consists of a poly(3,4-ethylene dioxythiophene) (PEDOT) backbone that can be doped with a myriad of synthetic or biological counter-ions, with the most common being polystyrene sulfonate (PSS) [1]. Over the last 20 years, PEDOT-based bioelectronics have proceeded from the very first coated neural probes in 2003 [2] to the first study including PEDOT electrodes on the human brain [3]. Even the substantial challenge of bringing a CP-based material into a US FDA approval process has been successfully tackled for the first time in 2016 as a PEDOT-based coating, 'Amplicoat', was used as part of an invasive CE-marked medical device (Biotectixin in collaboration with Actus Medical).

This attraction toward PEDOT, as a functional coating for bioelectronics, mainly arises from its superior electrochemical properties for recording and stimulation of electrically active cells. When PEDOT is added to a conventional metallic microelectrode it typically lowers electrochemical impedance by several orders of magnitude [2,4–8] and improves charge injection substantially [8–10]. These favorable electrochemical properties arise from the conjugated structure of the polymer chains themselves [11] and are furthermore determined by the intrinsically porous nature of CP coatings. The polymers are, in contrast to metals, permeable to ions in the surrounding electrolyte meaning the entire bulk material becomes accessible for electrochemical interaction. This results in an enlarged electrochemical surface area while maintaining the desired geometric surface area of the microelectrode. In other words, CPs allow individual recording sites to be made a fraction of their size without losing sensitivity or the ability to efficiently inject charge.

Versatility is the second point of attraction for these polymers where a number of different molecules can be electrochemically integrated and/or covalently bound to the CP surface, each providing functionalization for a

Figure 1. Overview illustrating the versatile use of poly(3,4-ethylene dioxythiophene) in bioelectronics, ranging from functional add-on technologies in established applications to novel challenges in new types of devices that rely on the unique properties of this material.
 PEDOT: Poly(3,4-ethylene dioxythiophene).

specific end-purpose. For example, cell surface interactions can be enhanced through blending the electronically conducting matrix of CPs with proteins and pharmaceuticals [12–21]. In addition to chemical functionalization, mechanics of the material can be altered through integration of the CP with other organic or inorganic materials, for example, hydrogels or carbon nanomaterials [22–25]. The importance of these beneficial properties are not limited to microelectrodes but furthermore are of interest for larger electrodes as they can be combined with soft and stretchable substrates. Such softer mechanical qualities are of importance for surface electrodes [26], for example, for electroencephalography, electrocardiography or electromyography, where signal quality critically depends on the ability of the device to conform to the skin [27]. Functionalization of CPs can moreover be employed to realize (bio)sensors, for example, for *in vivo* detection of glucose or dopamine. The CPs can contribute to improved sensors either as an interconnecting conducting mesh, in which functional components can be embedded, or as surface protection system for reducing protein fouling [12,28–30]. From a regulatory point of view, this seemingly endless versatility can be seen as a double-edged sword as each new variation must be analyzed as a novel material with unique properties to be thoroughly validated. Therefore, the strength of having a material that can be endlessly varied makes the process of clinical validation more challenging.

This short review aims to provide an overview of how PEDOT coatings have contributed to functionalizing existing bioelectronics, the challenges which meet CP coatings from a regulatory and stability point of view and the possibilities to bring PEDOT-based coatings into large-scale clinical applications. Finally, novel possibilities and challenges associated with the use of PEDOT within new types of bioelectronics, such as biodegradable and stretchable devices, and for delivery of slow stimulation signals, will be discussed.

PEDOT - as functional add-on in established applications

PEDOT can be printed, casted or synthesized *in situ* both by chemical and electrochemical routes. The relative ease with which PEDOT can be added to already existing devices, in particular by electrodeposition, is one reason it

Figure 2. Electrodeposition of poly(3,4-ethylene dioxythiophene)/polystyrene sulfonate on the working electrode in a three electrode configuration, the other two electrodes being the reference electrode and the counter electrode. The electrolyte typically consists of water, the monomer (here 3,4-ethylenedioxythiophene) and the dopant (here PSS). Driving a current (or applying a potential) over the electrode leads to oxidation of monomers and selective growth of a polymer film on the surface of the working electrode. The polymerization follows the reaction scheme shown in (I)–(III) resulting in a PEDOT film where the dopant is electrostatically bound to the polymer backbone as shown in (III).

PEDOT: Poly(3,4-ethylene dioxythiophene); PSS: Polystyrene sulfonate.

has come into such widespread use within the bioelectronics community. Electrodeposition of PEDOT is typically performed from an aqueous solution of the monomer 3,4-ethylenedioxythiophene (EDOT), and a supporting electrolyte, resulting in PEDOT growing selectively on the electrode sites as current is driven over the interface [31]. Ions from the electrolyte are built in as dopants in the film meaning PEDOT and dopant contribute roughly equal parts to the resulting material (Figure 2). By functionalizing the monomer, varying the electrolyte or adding further templates or scaffolds, a broad variety of electroactive PEDOT-based coatings can be synthesized as add-on coatings in a mask-less process. Although additional work remains until such functionalization can be fully adopted for clinical application, the electrodeposition route to electrochemically and biochemically tailored microelectrodes is broadly employed scientifically as outlined in the following sections.

Surface functionalized PEDOT & biocomposites

The ability to functionalize CPs with an array of biological molecules to form biocomposites has been reported on by many and holds promise for improving the long-term performance and integration of electrodes at the soft tissue interface required for bioelectronics. The predominant pathway for functionalization is through incorporation of the target molecule into the CP structure through electrochemical doping as described above. In addition, molecules can be physically adsorbed or be covalently bound to the CP surface by including functional anchors in the polymer. Early reports of electrochemical incorporation of neurotrophic factors and peptides such as

Figure 3. A selection of functionalization possibilities for poly(3,4-ethylene dioxythiophene)-based materials. **(A)** PEDOT:PSS surface modification with self-assembled monolayers enables the formation of cell-attracting (APTES) and cell-repelling (FDTS) areas. **(B)** Schematic of a biofunctionalized conductive hydrogel composite which comprises a biological dopant (in red), additional covalently bound proteins (in yellow) and mobile diffusible growth factors (in green). **(C)** Schematic representation of controlled drug release from conducting polymer films showing the reorganization of dopants inside the polymer bulk during different release phases. PEDOT: Poly(3,4-ethylene dioxythiophene); PSS: Polystyrene sulfonate. Reproduced with permission from [36], © WILEY-VCH Verlag GmbH & Co. KGaA (2017). Reproduced with permission from [38], © Elsevier (2014). Reproduced with permission from [39], © Elsevier (2019).

laminin [32], NGF [32,33], heparin and hyaluronic acid [34] have highlighted the feasibility of this method and their positive impact on promoting biological integration. It should be noted that reduced mechanical integrity and electrochemical performance could be associated with the relatively large molecular weight (>10 kDa) of biological dopants as well as their poorly conducting nature [35]. Covalent modification of the CP surface, although more synthetically complex, has provided an alternative route to improve biological integration of CP microelectrodes (Figure 3A) [36]. One example involves functionalization of the conventional EDOT monomer to produce EDOT acid, which, upon polymerization exposes a carboxylic acid functional group (COOH) on the polymer surface. This COOH group can then be linked to peptides, such as laminin, through bonding with the N-terminus. Electrochemical and physical stability were demonstrated with this method, as well as improved cellular interactions with the laminin-modified PEDOT surface, when compared with conventional PEDOT/PSS films [37].

Inorganic & synthetic composites (blends)

One additional way to manipulate the properties of the formed materials is to form a composite with a synthetic component. For instance, the hydrogel character of the films can be enhanced by growing PEDOT into a preformed hydrogel network (Figure 3B). This hydrogel can either be a physically cross-linked network of PEDOT:PSS, a

biosynthetic substance, for example, alginate or a chemically engineered scaffold with precisely tailored properties [29,40–46]. Recent work on photocrosslinkable and synthetic hydrogels has facilitated the generation of patterned, surface attached and electrochemically stable hydrogel coatings with electronic conductivity provided by an integrated PEDOT network [24,25,38,47]. The semi-interpenetrating growth of PEDOT is generated by removing all mobile ions from the monomer solution making the charged hydrogel itself the counter ion in the electro-oxidation process. While PEDOT contributes conductivity and electrochemical stability to the hybrid, the hydrogel contributes a softer mechanical character, increased porosity and in addition facilitates further functionalization. As the resulting CP-hydrogel truly merges the qualities of both constituents, the hydrogel itself can be further engineered more or less independently from its PEDOT ‘filling’. CPs can also be blended with nanomaterials such as graphene oxide and carbon nanotubes [12,30,48], either to further stabilize the structure or introduce electrochemically active sites for molecular detection (e.g., neurotransmitters). As the surrounding electrolyte will have access to the particles dispersed, the 3D electronically conducting PEDOT matrix can act both to increase the signal and in addition be tailored to stabilize the sensor by reducing biofouling [12,29,30]. Furthermore, the ability to polymerize CPs around sacrificial templates on the microelectrode surface, adds another dimension of structural control to fine-tune electrochemical properties relevant to bioelectronic recording and stimulation [10,49,50].

Drug release

Polymeric coatings are in general useful as drug carriers and typical mechanisms for controlling the release is either by engineering the porosity of the material or by integrating biodegradable carriers or linkages which gradually free more drugs over time. CPs are no exception but lend themselves to similar concepts. Drug release has been shown, for example, from biodegradable embedded templates, from pores as well as via hydrolyzable linkages in order to maximize the load or match a certain delivery profile [13,17,51]. CPs in addition offer the possibility to combine diffusion with an electrochemically steered component. As electrons move along the conjugated backbone, mobile ions are transported within the material and furthermore exchanged with oppositely charged ions in the surrounding electrolyte. Thereby, an electrically controllable dosage function for ionic drugs can be achieved, either by adding the drugs during synthesis as dopants or by using electrostatics to load them to an already existing film. This electrostatic delivery function, typically acting on the time scale of minutes, is rather unique to CPs and allows on demand release with dynamical control and fairly precise dosage (Figure 3C), for example, to biochemically manipulate a small population of cells right at the interface in a highly localized manner. It should be noted that the underlying mechanism is not driven purely by electrostatics, but acts in combination with diffusion and reorganization within the material, as is described in more detail in a recent paper [39].

Electrochemical incorporation and *in vivo* delivery of the predrug for the anti-inflammatory corticosteroid dexamethasone has for example shown promise in alleviating biotic inflammatory reactions that occur postimplantation [15,18]. Similar systems have been suggested for other anti-inflammatory drugs, for example, tauroursodeoxycholic acid and prednisolone, for pharmaceutical use within cancer treatment as well as fluorescent molecules to mark positions of electrodes within tissue [16,52,53]. The ion conducting capabilities of PEDOT can furthermore be extended to allow transport of small charged drugs in channels integrated within the device itself [54,55]. This way, supply is not limited to the volume of a film, but electrophoretic transport can be used to feed the outlet from an external reservoir. Such a solution would allow for long-term sustainable delivery and could be an interesting option for future microscale pumps.

Challenges for clinical application of PEDOT

Legal aspects: FDA approval & CE marking

Although the biocompatibility of PEDOT is well documented in the literature, and neuroprosthetic applications could clearly benefit from the electrochemical properties of such coatings, the transition of PEDOT into clinical applications remains a challenge. Only with an FDA approval (US market) or a CE mark (European economic area), verifying that a specific medical product meets high safety, health and environmental protection requirements, it is possible to commercially distribute a medical device. Any alterations to such an approved device which might influence the properties of the final product, demand a re-evaluation of the entire device. Keeping in mind that PEDOT rather comprises a material class, providing individual properties depending, for example, on the fabrication technique, the dopant or the functionalization of the polymer, it follows that PEDOT as such cannot be approved for clinical use. Instead, each individual coating would demand an own approval process, granting permission only to the specific application under evaluation. Owing to the large range of PEDOT variations, and

in view of the costly and timely process of validating a medical device, this process has to date been largely avoided, wherefore PEDOT cannot be found in widespread clinical use so far. In view of the steadily growing documentation of the beneficial properties of PEDOT coatings in the literature, it can however be expected that it is only a matter of time before PEDOT will proceed to further clinical applications.

Material aspects: reproducibility & stability

A key requirement for regulatory approval is that the material can be manufactured in a reproducible manner. For PEDOT to be successful in bioelectronic applications it is furthermore important to ensure that it can always be fabricated with identical properties, for example, if multiple electrode sites on a single array are to be modified, but also for wafer-level or batch fabrication. Although multiple process parameters have to be thoroughly controlled, this is possible for PEDOT coatings just as it is for the deposition of metals, or other process steps during the fabrication of bioelectronic devices. In a recent study addressing the translation of PEDOT into clinical use, Ganji *et al.* reported on a fabrication yield of more than 96% for the coating of electrode arrays carrying 56 individual micro contacts [56]. The high reproducibility of the coating process was illustrated by the low distribution of impedance values ($12.63 \text{ k}\Omega \pm 450 \text{ }\Omega$) for three separately coated arrays, in comparison to the uncoated state ($314.79 \pm 37.02 \text{ k}\Omega$). Ganji *et al.* furthermore demonstrated that PEDOT retained its integrity after sterilization in an autoclave (121°C , 20 min), a key requirement for the use of PEDOT in the clinical environment.

Besides sterilizability, the chemical and mechanical stability of CPs presents another challenge which needs to be considered for the use of CPs in bioelectronic applications. Among the large variety of CP versions, PEDOT here presents one of the most stable CPs in relation to its chemical structure, providing overall high thermal, chemical and electrochemical stability [35,57,58]. PEDOT has moreover been reported to be stable toward overoxidation for applied potentials of up to 1.5 V versus Ag/AgCl in aqueous media before losing its conductivity [59]. PEDOT hence provides a large electrochemical window for stable use in bioelectronics, illustrating its potential not only for recording but also for stimulation applications.

CPs are typically used in the form of thin coatings, making stable adhesion to the underlying substrate a key requirement for their success, especially in long-term applications. In consequence to the polymeric nature, PEDOT however does not readily provide long-term stable bonding mechanisms to typical metallic surfaces used in bioelectronics, such as platinum or gold. Delamination of CP coatings has therefore often been a concern with the use of such materials [60,61]. With the introduction of techniques to roughen the substrate material [62], by modifying the monomer itself [63], or by using adhesion promoters like IrOx [64], multiple solutions have been presented in the literature to address this challenge. PEDOT coatings relying on these techniques, and fabricated by well-controlled electrochemical polymerization, have in fact been shown to provide stable performance as electrode material over several months both *in vitro* [65] and *in vivo* [15]. This verifies that the stability issues have been successfully addressed for these materials, clearing the way for further use of PEDOT in future biomedical applications. A large variety of PEDOT derivatives has moreover been synthesized during recent years, which enables application specific adaption of material properties in order to address further material-related concerns [66].

PEDOT: in novel challenging applications

In the first section we outlined the various opportunities where PEDOT can be used to enhance the properties of a metallic substrate. Looking into the future we expect that full advantage of these polymer-based conducting materials will be drawn toward the new generations of stretchable and biodegradable bioelectronics. New mechanics and signaling dynamics will be possible when metals are no longer the main construction material of these interfaces.

Slow stimulation

Two growing application fields that could particularly benefit from the use of CPs are low frequency alternating current stimulation or direct current (DC) stimulation [67,68]. These stimulation types do not only allow the modulation of brain states, for example, for cognitive enhancement or the treatment of neurological disorders, but also provide a means to actively inhibit neural conduction which is not readily possible at fast biphasic current stimulation. Since conventional metal electrodes however cannot provide low frequency stimulation without undergoing corrosion and thus violating safe charge injection, new electrode materials are required to support the growing interest in slow stimulation signals. CPs here present themselves as ideal material thanks to their low impedance and the ability to support even DC charge transfer over extended periods without suffering from degradation or corrosion [69,70]. This is made possible by their combined electronic and ionic conductivity in

relation to the conjugated backbone and the electrostatic incorporation/release of ionic dopant molecules. PEDOT hence offers a unique possibility for safe neural stimulation at low frequencies and thereby opens the way for numerous new applications that previously were not possible due to the lack of suitable electrode materials.

Biodegradability

CPs, such as polypyrrole (PPy), polyaniline (PANI) and PEDOT, are not themselves inherently biodegradable, however, resorbable versions of CPs would truly be an asset to the bioelectronics community. Certain invasive applications are needed over transient time frames only, and biodegradable bioelectronics would exclude the need for surgical explantation. In general, two pathways could be followed to accomplish biodegradability: either by composites with biodegradable scaffolds or by adapting the CP backbone itself. For the latter, typically enzymatically cleavable or hydrolyzable linkages are added as connections between smaller segments with electronic conductivity. Both principles rely on that a small proportion of nondegradable fragments could be tolerated, and that such fragments could still be cleared or phagocytized without irritating surrounding tissue.

A substantial challenge for biodegradable CPs is that a relatively high proportion of electronically conducting subunits is necessary for reasonable conductivity to be achieved. A trade-off must be sought between degradability on the one hand and electronic function on the other. While some applications use larger conducting patches, many rely on micro-sized features and signals in the range of μV , implying conductivity is critical. It should here be noted that conductivity refers to the 'sheet conductivity' of the material, which is different from the commonly evaluated electrochemical impedance of a coated electrode.

It is beyond the scope of this text to present an exhaustive review of biodegradable CP materials but some general design concepts can be outlined taking polyaniline, in particular aniline pentamer (AP), as example. Much work has been invested into biodegradable conducting materials based on APs connected by hydrolyzable or enzymatically cleavable segments, for instance with polylactic acid or poly(glycine ethyl ester) phosphazene [71,72]. In particular, it has been shown that with improved control of the macromolecular architecture of the material, the conductivity can be increased reaching the range of 10^{-5} S/cm, for the same overall proportion of AP [73]. This highlights a key point for further progress: by better controlling the 3D arrangement the contribution of the conducting subunits to overall conductivity can be made more efficient, so that the amount of nondegradable material included can be minimized. This concept hopefully can be transferred also to oligothiophenes enabling a variety of improved biodegradable CPs in the future [74].

Stretchability

As the bioelectronics community moves away from rigid to more stretchable and conformable implantable devices to improve integration in dynamically moving biological systems, a need for stretchable electronic tracts arises. The challenge for stretchable devices is in the fabrication of conductive tracts which can handle the strain requirements of their respective application. Pristine CP films synthesized from commercial sources, with the main example being PEDOT:PSS, are not considered stretchable due to their low yield strain capacity (<6%) [75], however, enhancement of this property can be achieved through additives which weaken ionic interactions between PEDOT and PSS chains, increasing the free volume within the polymer and subsequently enhancing stretchability. Plasticizers achieve this effect and are capable of rendering PEDOT:PSS to withstand strains of up to 50%, with the most common plasticizers being xylitol [76], glycerol [77] and ionic liquids [78,79]. The incorporation of water-soluble polymeric blends, such as poly(ethylene glycol) (PEG) [80] and poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly(ethylene glycol) triblock copolymer [81] to PEDOT:PSS has also been shown to result in stretchability of up to 100%, however a drawback of this method is the decrease in conductivity as the concentration of non-CP (e.g., PEG) increases. Physical approaches to improve stretchability can be utilized through deposition of PEDOT:PSS on elastomeric substrates such as poly(dimethyl siloxane) and polyurethane [22], with the aid of surfactants to improve adhesion, wettability and to an extent, conductivity through actions as a secondary dopant. These avenues for improving stretchability of conductive PEDOT layers hold promise for the fabrication of robust stretchable electronics in the future and the reader is further guided to a comprehensive review by Kayser *et al.* [78] for more information on this topic.

Conclusion & future perspective

CPs, specifically PEDOT, have displayed their applicability as functional additions to existing bioelectronics in the form of electrode coatings. Favorable electrochemical parameters, ease of fabrication and versatility are factors

behind its widespread use within the field of neural bioelectronics. Furthermore, as PEDOT materials now can fulfill biostability, scalability and reproducibility criteria, we expect that future use will expand to bioelectronics beyond the scope of neural interfaces. In addition, the unique properties of PEDOT materials have enabled the fabrication of new bioelectronic devices and concepts which traditional metals cannot accommodate. Concepts which require materials that are capable of slow electronic stimulation, biodegradability and flexibility can all be made possible with the use of PEDOT in its conventional or slightly modified state. We expect that future devices (where PEDOT is a main construction material, used not only as a coating) will draw even more advantage of these qualities which metals cannot rival.

Executive summary

Poly(3,4-ethylene dioxythiophene) in established applications

- Superior electrochemical properties for recording and stimulation of electrically active cells.
- High versatility in fabrication, dopant selection and subsequent modification possibilities enable functionalization for a specific end purpose.
- Surface functionalization improves the long-term performance and integration of electrodes at the soft tissue interface.
- Interpenetrating networks of conducting polymers (CPs) in hydrogels form synthetic composites that combine the advantageous properties of both materials.
- Ion conducting properties enable controlled drug release from CP films.

Poly(3,4-ethylene dioxythiophene) in novel challenging applications

- CPs enable low-frequency and direct current stimulation where metals fail.
- Chemical engineering of the polymer structure provides a promising strategy for the realization of biodegradable bioelectronics.
- Fully polymeric electronics can be achieved which allow stretchability beyond 100%.

Challenges for the transition into clinical applications

- High versatility presents a challenge with respect to regulatory approval (the US FDA and CE-marking).
- Reproducibility and stability define key requirements for regulatory approval and future clinical use.

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