Biofunctional conducting polymers: synthetic advances, challenges, and perspectives towards their use in implantable bioelectronic devices

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ABSTRACT
Conducting polymers (CPs) are organic semiconductors that have gained popularity in more recent years as components of bioelectronic devices designed to electrically communicate with biological environments. Synergy between the material and biological tissue, both on a structural and functional level, is paramount for the proper performance of an implantable biomedical device. As such, significant progress has been made on understanding the fundamental impact of the molecular and macro structure of CPs on their functional properties such as conductivity and charge mobility. At the same time, the development of a variety of synthetic approaches has yielded a library of CPs with improved mechanical and electronic properties. Specifically, chemical biofunctionalization of CP films has significantly decreased the foreign body response, the main contributor to device failure. Therefore, this review covers the advances and challenges made in the chemical biofunctionalization of CP films for potential implantable devices. This is achieved by covalently attaching the bio-compatible or biofunctional group to the CP backbone via a reactive functional group to create a material with physical and electronic properties that better matches biological tissue. A perspective is presented that this synthetic chemistry approach to biofunctionalization is valuable for the integration of CPs into commercial implantable bioelectronic devices.

ARTICLE HISTORY
Received 21 December 2020
Accepted 3 March 2021

KEYWORDS
Conducting polymers; biofunctionalization; implantable devices; biointerface; bioelectronics

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1 Implantable devices & the potential of CP devices

1.1 Introduction to implantable devices: Properties, challenges & solutions

Electrical signals in the body are crucial for biological function, as they allow the body to communicate through the movement of ions across a cell membrane [1,2]. They play a major role in tissue development and regeneration, and therefore in the maintenance of health and progression of disease [3,4]. Consequently, the control and manipulation of biological electrical signals has provided a platform for medical treatment that has led to the development of a variety of implantable bioelectronic devices. These devices typically use an electrical signal to modulate the body’s internal electrical system. One of the first and most well-known example is the cardiac pacemaker that has been designed and fabricated to treat irregular heartbeat [5,6]. Other examples include neural implants to record or treat brain activity and cochlear implants to treat hearing loss [7,8].

Current devices available commercially are largely based on metal electrodes, including gold, platinum and platinum-iridium alloy [1,9], and have lifetimes that range from 1 to 5 years, with a maximum of 8 to 9 years reported by manufacturers for pacemakers [10,11]. One of the major contributing factors that limit the device lifetime is the foreign body response (FBR). The FBR involves macrophages that encapsulate the foreign material, triggering an immune response, which is characterized by the formation of scar tissue to create a barrier between the electrode and the biological tissue and, thereby, decreasing electrode function and leading eventually to device failure [12]. This then requires expensive surgical procedures to extract the inoperative device from the body and replace it with a new one. Therefore, the improvement of device biocompatibility remains a significant ongoing challenge [13].

An implantable material that will not be susceptible to the FBR should support cell-adhesion, which facilitates intimate contact between the device
Table 1.1 Examples of biological conductivity and Young’s modulus across different biological environments with a range of device applications.

| Biology         | Conductivity (S m⁻¹) | Young’s modulus (kPa) | Device                                           | Ref.   |
|-----------------|----------------------|-----------------------|-------------------------------------------------|--------|
| Brain tissue    | 0.17–0.26            | 0.1–16                | Deep brain stimulation probes                   | [21–24]|
| Spinal cord     | 0.02–1.8             | ~5 for spinal cord neurons, 2600 for spinal cord pia mater | Pain management devices Spinal cord stimulator Implanted bladder stimulators | [25–27]|
| Heart           | 0.05–0.4             | 10–100                | Pacemaker                                       | [28–30]|
| Bone            | 0.006                | 1x10⁶                 | Cochlear implants                               | [28,31–33]|
| Blood & fluid   | 0.7                  | -                     | Blood sugar sensor implant                      | [28,34,35]|

and the cellular environment [14,15]. It requires a mechanical strength that matches the targeted biological tissue, along with other properties including a degree of hydrophilicity, biocompatibility and biofunctionality [16,17]. In addition, if the implantable material is to interface with an electronic device, it must be conductive under biological conditions.

The most common descriptor of mechanical strength is Young’s modulus, a measure of stiffness that describes how elastic a specific material is; the lower the Young’s modulus, the more stretchable the material [18]. As depicted in Table 1.1, biological tissues have a wide range of Young’s moduli, from soft and highly elastic brain tissue through to hard and stiff bone. Table 1.1 also shows how the conductivity associated with various biological tissues and environments varies by four orders of magnitude, from 0.01 to 2 S m⁻¹. The nervous system, including the brain and spinal cord, exhibits conductivities on the higher end of this range due to the large flow of ionic current during an action potential [7,19]. However, in the majority of implantable devices already in use (Table 1.1), the mechanical and electrical properties of their interface materials do not typically match these values [1]. Conductive, low modulus materials that better interface with cellular materials would not only improve implantable device performance and lifetime but also provide new materials for the development of the burgeoning field of bioelectronic medicine or electroceuticals [4,20].

Of the materials available for the electrical interfacing of such implantable devices, conducting polymers (CPs), also known as conjugated polymers, have shown immense potential owing to their inherent nature and characteristics more closely resembling biological tissue compared to the interface materials used in conventional metallic-based implants [4,36]. Some commonly used and widely available CPs include polyaniline (PANI), polypyrrole (PPy) and polythiophene (PTh) and their derivatives (Figure 1.1a).

As shown in Figure 1.1a, CPs generally have lower Young’s moduli and electrical conductivities than metals. While their conductivities are more than sufficient for biological processes, their mechanical properties are still not a good match for biological tissue (Table 1.1) [37,38]. Nonetheless, they can be modified through synthetic or material chemistry to exhibit better mechanical properties that promote cell/biomolecule interactions.
Numerous review articles have been published within the last 5 years on CPs in bioelectronics. Of these articles, the majority are focused on the development of CPs for a variety of biological applications \([4,13,39–46]\), while few are focused on the synthesis of CPs to better interface with biosystems. More specifically, synthesis reviews have addressed biodegradable CPs \([47,48]\), specific classes of CPs such as PEDOT \([49–51]\) and poly(aniline) (PANI) \([52]\), co- and graft CPs \([47,53]\), and innovative CP syntheses \([54,55]\). None of these review articles have addressed the synthetic challenges of covalent, functional CP chemistry specifically for implantable devices in the body.

This review highlights the advances and limitations of CP functionalization to enhance the biointerface. This is done by discussing the role of reactive functional groups (RFGs) in bimolecular interactions and how covalently attaching biofunctionality to the polymer or dopant can achieve a sustainable implantable device. While there are many studies concerning the development of CP biomaterials by mixing the polymer with another biomaterial or using various biomaterial dopants, we have chosen not to include these non-covalent approaches.

It should be noted that the majority of studies on the suitability of functionalized CPs as biointerface materials rely on \textit{in vitro} test results. The few \textit{in vivo} studies reported to date are largely limited to non-functionalized CPs \([56–60]\). Acute \textit{in vivo} models have been used to demonstrate the role of CPs as active material in bioelectronics interfaced with tissues \([19,61–64]\). There remains a gap in the literature for comprehensive \textit{in vivo} studies to investigate the long-term functional performance of these materials. The perspective of this review is that the gap between electronics and biology can be bridged by chemical modifications of CPs, enabling improved integration with the tissue and their incorporation into implantable bioelectronic devices.

### 1.2 Introduction to conducting polymers

CPs are soft, organic materials consisting of a \(\pi\)-conjugated backbone that can be oxidized (\(p\)-doped) or reduced (\(n\)-doped) to introduce positive or negative charge carriers, respectively (\textbf{Figure 1.1b}) \([72,73]\). In order to stabilize the net charge of the backbone, an anionic or cationic dopant (\(A^-\) or \(C^+\), respectively) must be incorporated into the polymer matrix. These charge carriers allow for the movement of electrons along the polymer backbone, resulting in conductivity. Moreover, the dopant also facilitates ionic transport through the CP \([74]\). Ionic transport in CPs is another property that makes them potential candidates for use in implantable devices as it better aligns with the body’s electrical system \([40]\).

The potential transport of the dopant in and out of the CP during oxidation and reduction raises the question of the biocompatibility of the dopant. Dopants can be small counterions, larger charged molecules or even polymers. Polymer dopants are advantageous in biological systems since they are unlikely to diffuse out or separate from the CP, providing stability to the oxidized polymer in the
a) Mechanical properties and conductivity of CPs compared to metals

| Name / Abbreviation | Metals incl. Au, Cu, Al etc | Young's modulus | Conductivity |
|---------------------|-----------------------------|-----------------|--------------|
| poly(aniline) PANI  | 1–2 x 10^9 kPa              | 0.9–1.3 x 10^6 kPa | 4 x 10^3 S/m |
| poly(thiophene) PTh | 3.3 x 10^6 kPa              | Up to 3 x 10^3 S/m |              |
| poly(pyrrole) PPy   | 9–10^5 kPa                  | 9.2 x 10^2 S/m   |              |

b) Doping mechanism: p- and n- doping

i. oxidation

ii. oxidation

iii. oxidation

n-doping

p-doping

c) Examples of p-doped polymers

PEDOT:PSS

PEDOT-S

Figure 1.1. (a) Young’s modulus and conductivity of common CPs, including freestanding polyaniline [65,66], polythiophenes based on poly(3-hexylthiophene) free standing films [67,68] and poly(pyrrole) films with polypropylene nanocomposite [69] compared to conventional metals such as gold, copper and aluminium [65, 66, 70]. (b) Formation of p- and n-doped CPs from a neutral CP (ii) by oxidation to introduce a positive electron carrier with an anionic dopant as the counter ion (A^-) (iii) or reduction to introduce a negative electron carrier with a cationic dopant (C^+) (i). (c) Structure of PEDOT:PSS 1, a well-known p-doped CP and PEDOT-S 2, a self-doped CP [71].
aqueous-based biological medium. For example, poly(styrenesulfonate) (PSS) is commonly used as a dopant to stabilize the positive charge on oxidized poly(3,4-ethylenedioxythiophene) (PEDOT) (1, Figure 1.1c). As a result of its stability in aqueous media, PEDOT:PSS is one of the most extensively used p-doped CPs in biological applications [75,76].

While doped CPs are most stable in their oxidized state (Figure 1.1b, iii), reduced or n-doped CPs (Figure 1.1b, i) are typically much less stable in water and air. This instability arises due to the formation of anions upon reduction, which are very reactive in water or air [77,78]. Considering that water and oxygen both have relatively low oxidation/reduction potentials, it is challenging to design n-doped polymers such that their reduction and oxidation occur at lower overpotentials than water or oxygen [79]. Therefore, n-doping for most CPs requires an inert atmosphere to obtain electrical activity. While there are some reports of increased stability of n-doped CPs in water, there are no studies of such materials in vitro or in vivo [80–82]. Thus, they are not yet available for use in implantable devices.

CPs can be readily synthesized via chemical or electrochemical oxidation of the conjugated monomer, dimer or oligomer [46]. The former involves polymerizing in the presence of a chemical oxidant, such as persulfate [83], while the latter polymerizes in the presence of an oxidation potential onto a conductive substrate [84,85]. Additionally, metal-catalyzed polymerizations, including Grignard metathesis (GRIM), have been applied to CP synthesis. GRIM polymerization is a form of living radical polymerization that usually uses Ni(II) complexes to catalyze polymerization of Grignard monomers [86]. While GRIM is typically more difficult than oxidative polymerizations, it is advantageous as some monomers do not polymerize via oxidative methods. It also provides control to the polymerization, by a ‘living’ end group, to allow the synthesis of block copolymers [87].

For all methods of CP polymerization, challenges associated with processability arise since the CP typically needs to be integrated into the implantable device. Electrochemically produced films can be used directly after being grown on an electrode but usually for an implantable device, they would need to be removed and applied to another surface, requiring a mechanically stable film. In comparison, the chemically produced CP needs to be sufficiently soluble to either create films or coat on substrates. Soluble CPs can be created using appropriate functionalization, however, oxidative polymerization of functionalized monomers typically results in regioirregular CPs (Figure 1.2b) whose mechanical and electronic properties will differ substantially from their regioregular analogs (Figure 1.2a) [88]. Regioregular polymers can be synthesized via GRIM polymerization due to the controlled nature of the method. While regioregular polymers are generally more crystalline, rigid, and more conductive, they are more challenging to make compared to their regioirregular analogues and therefore most functionalized CPs used for bioelectronics are regioirregular (Figure 1.2b).
Given the challenges in creating processable CPs that are sufficiently conductive and oxidatively stable in aqueous media, it is not surprising that PEDOT:PSS is the most popular and studied CP owing to its enhanced stability, conductivity and biocompatibility compared to other CPs [89,90]. The fusion of the dioxane ring to thiophene results in a reduction in the oxidation potential of thiophene from 1.8 V to 1.1 V (vs Ag/AgCl) for EDOT due to the electron donating oxygens, making polymerization easier, improving the stability of the oxidized polymer and influencing the physical properties of the resulting CP [84,91]. When PEDOT itself is oxidized, it becomes insoluble and difficult to process, however, by doping PEDOT with acidic PSS, water dispersibility is achieved making it processable for the development of implantable devices [92–94].

PEDOT:PSS has revolutionized the field of CPs, yet devices using this polymer composite material are still limited. It tends to aggregate after long periods of time and generally requires extensive post-treatment or additives to provide high conductivity [71,95,96]. PEDOT:PSS also contains large portions of insulating PSS, which may cause toxicity upon dissociation into biological fluid [97]. The acidic PSS chains may also lead to device degradation over time [93]. Additionally, PEDOT:PSS has poor mechanical properties, for example, it is quite brittle, and exhibits hardness, with a Young’s modulus of $2–3 \times 10^6$ kPa, which may not be suitable for a biological environment [90,98–100].

1.3 Improving conducting polymer biocompatibility and biostability

It is well known that incorporating biomolecules into a CP matrix increases the biocompatibility of the CP composite and the viability of cells grown on
it, resulting in a diminished FBR [101,102]. Cui et al. electrochemically polymerized PEDOT:PSS onto neural probes in the presence of a synthetic peptide and observed enhanced cell growth in vitro[103]. The same authors electrochemically polymerized PPy onto a neural probe in the presence of a cell-adhesive peptide. The stability and function of the device was enhanced as the neural tissue attached to the probe, but after 2 weeks, a FBR (gliosis) was observed [56]. More recently, Inal et al. modified PEDOT:PSS for soft tissue applications by mixing it with (3-glycidyloxypropyl)trimethoxysilane and collagen to produce a three-dimensional (3D) scaffold that had enhanced mechanical properties (Young’s modulus of 6 kPa) compared to pure PEDOT:PSS. The scaffold was shown to be suitable for cell-culture in vitro [104].

While biocompatibility is enhanced when biomolecules are mixed with CPs, over time under biological conditions, the structure of the composite materials are expected to change, which impacts the morphology of the CP film [56]. Such changes in morphology of a CP film will influence cell-adhesion [105,106], directly impacting on device performance. Therefore, chemical biofunctionalization of CPs may lead to enhanced structural stability and biocompatibility of CP films in biological environments to improve the biointerface in implantable devices.

CP functionalization is achieved by chemically modifying the conjugated monomer, polymer or dopant with a reactive functional group (RFG). The RFGs can promote interactions with biomolecules in aqueous media or be further functionalized by covalently coupling with biomolecules. This can be achieved pre- or post-polymerization to yield a biocompatible material that can increase cellular and biomolecular interactions, improving the biointerface of implantable devices [101,102]. Thus, the following discussion will address advances and challenges regarding functionalization of CPs and how CP function can be improved for potential use in implantable devices.

2 CP functionalization to improve the biomaterial interface

2.1 Introduction

To introduce biofunctionality into CPs, two approaches can be taken: monomer and polymer functionalization or dopant functionalization (Figure 2.1). The first approach involves functionalizing the monomer by installing RFGs (Figure 2.1a). RFGs are groups such as amines, carboxylic acids and hydroxyl groups that provide a site of reactivity to interact with biomolecules or be covalently bound to them. The biofunctionalized RFGs as well as the RFGs themselves have been explored in the development of CPs as groups that can potentially improve the biointerface since they provide a platform for natural tissue and cells to communicate and interact.
within synthetic materials, potentially preventing a FBR. The second approach uses similar chemistry to introduce biofunctionality via RFGs onto the dopant, most often a polymer (Figure 2.1b).

### 2.2 Monomer functionalization

#### 2.2.1 Introducing RFGs

The ability of polymers with various RFGs as side chain terminal groups to enhance the biointerface has been well demonstrated. In an early study,
polymers with amine functionality better supported cell adhesion compared to carboxylic or alkylhydroxy derivatives [107]. This was thought to be due to the basicity of the amine functionality, bearing a positive charge in physiological conditions [107]. However, more recently, Hasan et al. showed that a hybrid functionalized surface consisting of both hydrophilic amines and hydrophobic alkyl chains could significantly increase cell adhesion compared to the amine functionality alone [108]. Consequently, polymers bearing side chain terminal amines have been designed using functionalized monomers in an attempt to improve the biointerface.

Lee et al. synthesized 1-aminopropylpyrrole (3, APy), which was electrochemically copolymerized with varied concentrations of pyrrole onto gold-coated glass slides with PSS as dopant (Figure 2.2a). The resulting copolymers 4 were shown to exhibit a positive charge at pH 7.4. Fibroblasts and Schwann cells adhered well to the polymers containing APy (Figure 2.2b), with significantly more cells adhering to the pure APy polymer (APPy-A100) compared to the PPy (APPy-A0) or copolymer (APPy-A50). This was attributed to electrostatic attraction between the cell adhesive proteins in the serum-containing medium and the amine groups tethered on the polymer. The conductivity of the copolymers decreased with increasing APPy (Figure 2.2c), although it remained similar in magnitude to the typical values found in biological systems as listed in Table 1.1 [109].

![Figure 2.2.](image)

**Figure 2.2.** The effect of amine functionality on cell adhesion and conductivity: (a) Synthesis of monomer APy 3 and electrochemical polymerization of pyrrole and/or APy with NaPSS, (b) in vitro measurements of cell adhesion for the three different polymer types (# indicates significance p > 0.05) and (c) the relative conductivities of each polymer. APPy-A0 is the homopolymer of PPy; APPy-A50 is the copolymer consisting of 1:1 PPy:APPy; APPy-A100 is the homopolymer of APPy. Reproduced with permission from Lee and Schmidt [109].
As amines are very stable as quaternary salts, they are also useful for synthesizing zwitterionic functionality that have both positive and negative charge [110]. Zwitterions are beneficial chemical moieties in CPs as they provide water solubility as well as controllable antibacterial properties. Zwitterionic CPs have been synthesized previously by attaching common zwitterionic groups such as phosphoryl choline that has a side chain terminal quaternary amine [111], or by reacting tertiary amines with sultone groups to yield a sulphobetaine group (Figure 2.3a) [112,113].

The PEDOT sulphobetaine 6 in Figure 2.3a was synthesized via electrochemical oxidation from the zwitterionic monomer 5. The resulting CP film was shown to kill up to 89% of attached bacterial cells when a potential of 0.6 V (vs. Hg/HgCl₂) was applied to the film demonstrating its antifouling potential [112]. Furthermore, cell-adhesion was switchable depending on the oxidation state of the film, as the oxidized film led to electrostatic attraction between the cells and the film, while the neutral polymer absorbed a layer of water due to its zwitterionic character, preventing cell attachment (Figure 2.3b) [114].

**Figure 2.3.** Synthesis and application of zwitterionic CPs: (a) Total synthesis of PEDOT sulphobetaine from a tertiary amine group [112] and (b) the antifouling behavior of these zwitterion polymers through the formation of a hydration layer on the polymer [114]. The structure in (b) was adapted with permission from Singha et al. [114].
Similar synthetic chemistry has been used to introduce net negative functional groups into CPs. While negative functionality has shown to be less effective for stimulating cell growth, they can provide a self-doping mechanism where the counterions (or dopants) are covalently bound to the CP backbone, stabilizing the oxidized CP and eliminating the need for an additional dopant ion [115,116]. For example, Yano et al. functionalized EDOT with an alkylsulfonate side chain to yield a water soluble monomer that was chemically polymerized in an aqueous sulfuric acid solution with FeSO₄ as catalyst and ammonium persulfate as oxidant. The resulting CP (PEDOT-S₂, Figure 1.1c) was water soluble and had a conductivity of up to $1.1 \times 10^5 \text{ S m}^{-1}$ [71]. This self-doping provides a way to keep a film intact without the potential leaching of dopant into biological fluid or addition of insulating doping material that can reduce the conductivity of the CP backbone.

Likewise, boronic acids are interesting RFGs since they can not only readily interact with biomolecules but can also exhibit self-doping behavior. For example, fluorinated boronic acids have been reported to self-dope PANI derivatives in neutral and mild alkaline conditions [117,118]. Boronic acid groups have been attached to conjugated monomers such as aniline and EDOT via side chain terminal amine groups (7, Figure 2.4a). The resulting

![Chemical structures and diagrams](image)

**Figure 2.4.** Boronic acid functionality as RFGs: (a) An example of the synthesis of a PEDOT-boronic acid CP and (b) the process of cell adhesion for boronic acid RFGs by biofunctionalization of the boronic acid CP in vitro followed by cell adhesion.
boronic acid functionalized EDOT 8 was electrochemically polymerized to yield a boronic acid CP 9 that could form reversible complexes with biomolecules, such as sialyllactose, in vitro [119–121]. It has also been shown in other polymeric materials that boronic acids promote cell adhesion in vitro by forming boronate esters with cell adhesive proteins to potentially enhance the biointerface (Figure 2.4b) by promoting cell adhesion [122,123]. Most studies using boronic acid functionalized CPs have been applied to biosensing applications [121,124,125]. However, this chemistry has unexplored potential for implantable devices as it may promote cell adhesion as well as provide sensing and drug release in a device that has been implanted for long-term use.

Other RFGs that are commonly used in CPs include hydroxy and carboxylic acids. In both cases, interchain hydrogen bonding is possible in organic solvents, resulting in a larger Young’s modulus and thus a stiffer and potentially less biocompatible material [126]. However, this is not expected to be a problem in biological media since water and proteins can hydrogen bond to the CP disrupting polymer interchain hydrogen bonding. Nevertheless, a loss in hydrogen bonding does not preclude an increase in mechanical strength as it was shown by Shinde et al. that by employing ionic groups, such as ammonium salts, in a CP network, there was a decrease in interchain hydrogen bonding but a concomitant enhancement in mechanical properties due to the ionic groups acting as crosslinkers [127].

Covalently cross-linking carboxylic acid RFGs has also been used to control mechanical biocompatibility. This results in the synthesis of CP hydrogels, a network of cross-linked hydrophilic polymers that can absorb up to 99% water by weight [128]. For example, Mawad et al. chemically polymerized a thiophene-3-acetic acid monomer to yield carboxylic acid functionalized polythiophene, whose terminal carboxylic groups were cross-linked using carbonyldiimidazole (CDI) to yield a conducting hydrogel, with mechanical strengths matching that of muscle tissue and a conductivity of 0.1 S m⁻¹ [129].

The same group synthesized a PEDOT-based hydrogel using a carboxylic acid functionalized EDOT 11 (Figure 2.5a). An ester EDOT 10 was initially polymerized to prevent the free carboxyl groups interfering with FeCl₃ oxidation. As shown in Figure 2.5a, the carboxyl groups of 11 were reacted with N-(3-aminopropyl)methacrylamide hydrochloride via EDC coupling to yield a polymer 12 with terminal double bonds. Copolymerization with vinyl monomers (acrylic acid (AA) and/or 2-hydroxymethylmethacrylate (HEMA)), via controlled radical polymerization using 2,2′-azobis(2-methylpropionitrile) (AIBN) initiator and poly(ethylene glycol) dimethacrylate as a crosslinker, yielded conductive hydrogels with tailored mechanical properties; Young’s modulus varied from 70 to 182 kPa depending on the ratio of the vinyl monomers used [130,131]. The variation in the mechanical properties of the scaffold significantly influenced the behavior of cardiac cells.
seeded on the surface of the hydrogels with variations in cellular morphology (Figure 2.5b, i–iii) and ratio of cell growth depending on cell type (Figure 2.5b, iv–vi). Thus, conducting hydrogels have been developed to better integrate with the softness and elasticity of natural tissue while also providing a high water content that is desirable in biological material and perhaps implantable devices [132,133].
2.2.2 Monomer biofunctionalization

Biomolecules or biocompatible molecules can be attached to the CP via the monomer RFGs prior to polymerization [134]. For example, dopamine has been commonly used in this regard owing to its amine and phenolic groups that provide sites for biological interactions and cross-linking. Using this approach, Liang et al. developed conductive hydrogel implantable patches for treatment of myocardial infarction (MI) [134,135]. The conductive hydrogel was synthesized from a hyperbranched poly(dopamine-co-acrylate) copolymer containing vinyl groups that were further reacted with pyrrole through Michael addition (Figure 2.6) [135]. Polymerization of the terminal pyrrole groups was initiated by FeCl₃ where Fe³⁺ served dual

![Figure 2.6](image.png)

**Figure 2.6.** Synthetic route to a hyperbranched PPy to produce a conductive, biocompatible hydrogel cardiac patch. Reproduced with permission from Liang et al. [135].
functionalities. It initiated the polymerization of pyrrole to produce PPy nanoparticles, introducing conductivity (up to 0.065 $\text{S m}^{-1}$) in the network, and it complexed with the dopamine groups resulting in a hydrogel network with improved adhesion properties in the wet state. Gelatin was also added to the hydrogel to enhance its biocompatibility. The system exhibited biologically relevant mechanical strength, with a storage modulus of 35 kPa, along with significant tissue adhesion attributed to the dopamine catechols binding to amine and sulfhydryl groups in the tissue. The conductive hydrogel patch also enhanced the transmission of electrophysiological signals. In addition, although neutrophils were generated during an initial FBR in vivo, they disappeared after 28 days, overall demonstrating the potential of CPs with suitable conductivity, mechanical properties, and biocompatibility for implantable devices.

However, monomer biofunctionalization using larger biomolecules or biocompatible molecules is limited as they contribute to steric strain on the backbone. Nonetheless, this issue has been addressed through copolymerization of the bulky biofunctionalized monomer with an unmodified monomer. For example, Molina et al. were unsuccessful when they electrochemically polymerized EDOT functionalized with a bulky polycaprolactone (PCL) due to steric hindrances [136]. Therefore, the group solved this problem by copolymerizing EDOT-PCL with EDOT under the same conditions. The unmodified EDOT provided spacing between the bulky PCL groups enabling the polymerization to successfully proceed. They reported a decrease in cytotoxicity and increased biocompatibility of the polymer by supporting cell adhesion compared to PEDOT alone.

Despite these successful approaches, there have been few other reports of the functionalization of monomers with biomolecules. Most of the biofunctionalization of CPs in the literature have used polymer functionalization.

### 2.3 Polymer functionalization

The commonly used solution to steric hindrance caused by large biological groups, such as proteins or peptides is through post-functionalization (or polymer functionalization). This is achieved via coupling of the RFGs on the polymer with groups, typically amines, on the biomolecule. For example, as outlined in Figure 2.7a, Aydin et al. prefuctionalized pyrrole with an N-attached alkylcarboxylic acid, protected as the methyl ester for chemical polymerization with FeCl$_3$ [137]. After coating the resulting PPy ester on ITO, the deprotected carboxyl groups were post modified with CC chemokine receptor 4 (CCR4) antibodies via ethyl(dimethylaminopropyl) carbodiimide (EDC)/(N-hydroxysuccinimide (NHS) coupling chemistry to yield a functional film with terminal proteins (Figure 2.7b). This
biofunctionalized CP film was successfully applied as an impedimetric sensor for prostate cancer biomarkers.

Similar chemistry has been performed by other research groups to attach various biomolecules to CPs functionalized with RFGs including siallactose [119], hyaluronic acid [138], urease [139], nerve growth factors [140], lactate dehydrogenase [141] and cell adhesive peptides [142–144]. In one of the latter studies, Lee et al. electrochemically polymerized a perchlorate-doped poly(terthiophenecarboxylic acid) 14 on FTO glass (Figure 2.8). Terthiophenes allow control of the ratio of monomers in the polymer, i.e. no matter how many repeating units there are, the ratio will always be 2 thiophenes to 1 carboxyl functionalized thiophene. This provided adequate spacing for all the carboxylic acid groups to be post-functionalized with large biomolecules, such as fibronectin derived arginylglycylaspartic acid (RGD) peptide. The modified polymer, with a conductivity of 122 S m\(^{-1}\), was shown to enhance cell adhesion and viability for potential bioelectrode applications [142].

Alleviation of steric effects that may significantly enhance the biointerface of CP films can also be achieved by inserting a spacer between the

Figure 2.7. Synthetic route for (a) synthesis of N-functionalized PPy carboxylic acid and (b) post-functionalization of the PPy carboxylic acid with a CCR4 antibody via EDC/NHS coupling on an ITO surface. Reproduced and adapted with permission from Aydin et al. [137].
conjugated monomer and the biofunctional group. Bhagwat et al. produced a copolymer film 17 consisting of EDOT-COOH and EDOT at a ratio of 0.75 and 0.25 via electrochemical polymerization (Figure 2.9a) [143]. The carboxylic acid group of 17 was post modified with YIGSR-based peptides by being either physically absorbed (PA) with (n = 3 or 10) or without (n = 0) attached PEG spacers, 18, or covalently attached (CC) with and without the PEG spacers 19 via hexafluorophosphosphate azabenzotriazole tetramethyl uronium (HATU)/N,N-diisopropylethylamine (DIPEA) coupling chemistry. The conductivity was similar for the peptide functionalized polymers 19 compared to PEDOT-COOH copolymer 17 alone, indicating that the biomolecules had no impact on the electrochemical properties of the PEDOT. However, the CC PEDOT-peptides 19 increased PC12 cell attachment over the PA PEDOT-peptides 18 and 17 (EA75) (Figure 2.9b), with the largest enhancement due to the PEG10 spacer (CC PEG10-YIGSR), highlighting the benefit of separating the functional biomolecule from the conjugated chain.

CPs can also be modified through end-functionalization, which involves reacting the ends of the polymer chain with another functional monomer or polymer to introduce an RFG [145]. Lee et al. electrochemically polymerized pyrrole onto ITO glass and reacted the ends of the polymer chain with a single pyrrole-COOH monomer (Figure 2.10) [146]. The conductivities of the PPy film and the carboxyl end-capped PPyCOOH film 20 were 281 and 278 S m⁻¹, respectively. The end terminal COOH unit was post-modified with a cell adhesive peptide via EDC/NHS coupling. The peptide end-capped PPy film 21 exhibited enhanced cell adhesion and spreading compared to the PPy film alone.

**Figure 2.8.** One pot synthesis of conductive poly(terthiophene) with fibronectin derived peptide RGD (RGD-grafted-PTThCOOH) 16 from 3’-bromo-2,2’,5’,2”-terthiophene 13. The cell adhesive RGD motif was attached to poly(3’-carboxy-2,2’,5’,2”-terthiophene) 14 using EDC/NHS coupling by way of intermediate 15 [142].
An alternative approach to end-functionalization involves the use of block copolymers. A typical example includes ABA triblock CPs that are obtained through GRIM polymerization using a Ni(II) catalyst \cite{47,87,147}. For example, Yu et al. end-functionalized poly(3-hexylthiophene) (P3HT) with allene groups \textbf{22} to yield a coil-rod-coil type morphology that could be tailored for different biological effects \cite{148,149}. As shown in \textbf{Figure 2.11}, an allene moiety that was attached to either a cholesterol, PEG or hexadecyloxy group was polymerized in the presence of a Ni(II) catalyst to give Block A. Following that, P3HT was modified with a Grignard reagent (isopropyl magnesium chloride, $i$-PrMgCl) \cite{149} and polymerized in the presence of

\textbf{Figure 2.9.} Enhancing cell adhesion through covalent attachment of peptides with PEG chain spacers: (a) Synthesis of biofunctionalized EDOT copolymer from commercial EDOT and EDOT-COOH with a n=0, 3 or 10 PEG spaced YIGSR-based peptide and (b) plot of the average number of PC12 cells cm$^{-2}$ attached to the surface of the PEDOT-COOH films chemically coupled (CC) with YIGSR based peptides compared to the control (EA75) or physically adsorbed (PA) peptides. Figure (b) reproduced with permission from Bhagwat et al. \cite{143}.
the poly(R-allene) with the Ni(II) terminal group to give the AB polymer. Finally, the same allene moiety was added to the 'pot' resulting in an ABA triblock copolymer 23 with tunable properties. For example, when the R group was PEG, the block copolymer was amphiphilic and water soluble but when the R group was cholesterol, there were regions of biofunctionality. Furthermore, due to the method of polymerization, this polymer exhibited a degree of regioregularity that enhanced polymer chain packing.

Figure 2.10. Synthesis of end-capped PPy with a cell adhesive peptide 21 via EDC/NHS coupling with a terminal carboxylic acid polymer 20 [146].

Figure 2.11. Synthesis of an ABA triblock copolymer CP via Ni(II) catalyzed Grignard metathesis (GRIM) polymerization [148,149].
Previous studies used cholesterol to add chirality to the block copolymer. Other groups have used cholesterol to add liquid crystallinity (a liquid crystalline material is one that is orientated like a solid but flows like a liquid) to the polymer [150–156] and were shown to mimic the physical dynamic properties and functionality of biological membranes [153,157,158]. While there are no reports showing the effect of liquid crystalline materials on cell adhesion, there is potential for this type of polymer in implantable devices, as cholesterol could enhance cell adhesion by intercalating into a cell membrane [159]. Amphiphilic block copolymers may also be useful for implantable devices since they can be dialyzed in water to induce self-assembled micelle structures that could allow electrochemically controlled drug-release for an electroceutical implantable device [160].

Thus, polymer functionalization has proven to be a valuable method to add biofunctionality to the CP since the challenges associated with polymerizing a highly functionalized monomer can be avoided and it can solve the steric hindrance issues associated with bulky biomolecules, although polymer chain disruption can still occur affecting the CP mechanical and electrical properties. One way to avoid this polymer backbone disruption is to functionalize the polymer dopant.

### 2.4 Dopant functionalization

An alternative approach for the biofunctionalization of CPs is through the RFGs present in the dopant (Figure 2.1b). While the dopant is not an intrinsic part of the CP, it usually remains bound within the polymer network and therefore has been used to further attach biomolecules for improving biocompatibility. Many studies have shown that biodopants such as hyaluronic acid significantly improve the biointerface [142,161–165], and generally polymeric dopants have shown to increase stability, electron transfer and overall cellular interactions of CP films [97,166,167]. Building on these findings, research groups have modified pendant carboxylic acids on the dopant with biomolecules to enhance conductivity, biocompatibility and mechanical properties while leaving the pristine CP backbone unmodified. For example, Liu et al. electrochemically deposited pyrrole on gold electrodes with a chondroitin sulfate (CS) dopant. The carboxylate groups of CS were post-modified with collagen via EDC/NHS coupling to produce a CP with a biomimetic three-dimensional (3D) extracellular matrix (ECM) structure. The CP was shown to enhance cell attachment and differentiation, in vitro, for potential implantable bioelectrodes [168].

Similar chemistry has been performed with synthetic polymeric dopants and was shown to enhance the biointerface of CP films in vivo. As shown in
Figure 2.12a, Alves-Sampaio et al. synthesized poly(styrene sulfonate-co-maleic acid) P(SS-co-MA) 24 as the dopant for PEDOT, which was electrochemically deposited on carbon microfibers [169]. To enhance the biointerface, the maleic acid RFG was post-functionalized with polylysine through EDC/NHS coupling [170] to give functionalized PEDOT 25 while the

**Figure 2.12.** Enhancing cell-adhesion through dopant functionalization: (a) Synthesis of PEDOT: P(SS-co-MA) functionalized with polylysine and incubated with cell-adhesive proteins on carbon microfibers (MFs) and (b) plots of the enhancement of the biointerface through cellular interactions based on the presence of various cellular factors (MAP2, NF, GFAP, NG2) 2 months after implantation (i) and the decreased immune response based on the presence of immunoreactive cellular components (PDGFRβ, VIM, COL IV, or ED1) around the MFs (ii) [169,170]. Figure (b) reproduced with permission from Alves-Sampaio et al. [169].
styrene sulfonate provided processibility, stability, and negatively charged groups to neutralize the positive charge on PEDOT. Following biofunctionalization, heparin, human bFGF cells, and fibronectin were self-assembled into the polymer structure. The functionalized polymer showed excellent integration into the neural system compared to the control. It was also demonstrated that the fully biofunctionalized PEDOT:P(SS-co-MA) system could bridge the damaged spinal cord in rats to provide spatial and chemical cues for guiding axonal growth. The cellular responses were quantified to show that the biofunctionalized polymer significantly enhanced the biointerface compared to the polymer alone (Figure 2.12b, i) with a decrease in the generation of immunoreactive cells (Figure 2.12b, ii). Without this biofunctionalization, the polymer triggered some inflammation and neural death after 2 months in vivo.

From these examples, it is evident that dopant functionalization may prevent complex polymer syntheses as the conjugated monomers such as EDOT, pyrrole and aniline do not require any prefunctionalization. This approach also allows the pristine CP backbone to remain intact, retaining many of the inherent polymer properties, while cell-adhesion is favored to enhance the biointerface. However, the question of polymer stability remains and whether the structural integrity of the CP backbone is compromised in biological environments overtime, negatively impacting cell-adhesion.

3 From the laboratory to commercial application

The ideal material for a chronic implantable bioelectronic device is a highly stable conductive material that can endure implantation, mechanical strain and attack from endogenous biomolecules [97,103,171]. The device should be able to remain in the biological environment for long periods of time [165], without being rejected by the body nor fouled to decrease performance [5]. However, it must still be able to intimately interact with cells and proteins representing a significant material challenge. The benefits of such a material would therefore warrant the risk and cost of surgery to implant the device [172]. From a commercial perspective, it needs to be cost-effective, relatively easy to synthesize and well-studied in vivo, with approval from regulatory bodies before it can be used in implantable devices [173].

CPs have come a long way since their first use in biological systems over 25 years ago [174,175] and, through synthetic and other approaches, are becoming more stable in biological environments over time. Many different biofunctionalized CPs have been synthesized with potential applications in implantable devices. Similarly, more research groups are investing in the field of CPs with creative ideas to revolutionize the field, yet, to the best of our knowledge, there are no commercially available CP-based devices for
biomedical applications. This arises from the lack of in vivo and human data that is required to make an impact in the real world [176]. Fidanovski and Mawad have discussed the biointerface challenge through analysis of the major in vivo studies available for CPs and concluded that our incomplete understanding of material behavior in vivo is the major hurdle in commercializing CPs [42].

The first and only human study was performed with PEDOT:PSS in 2015. In this study, the authors used the CP on parylene C as an interface material to provide adherence on the brain for recording action potentials during epilepsy surgery. While the material was effective during the short period of surgery, it was also shown that it caused inflammation in rats after 10 days [177]. Despite this study highlighting the need for long term in vivo studies following successful acute outcomes, there remains a limited amount of in vivo data for both short-and long-term material use [42]. Biofunctionalized CPs targeted at implantable devices must be subjected to these type of studies if their full potential is to be realized.

Finally, the field of organic bioelectronics is shifting towards the development of advanced bioelectronic circuitry that can identify, process, and modulate electrophysiological signals. Organic bioelectronic circuits based on the organic electrochemical transistor (OECT) are being developed with promising functionalities at the biointerface [178–182]. The development of n-type conducting polymers, for example, will enable the development of complementary logic circuits with reduced power draw and low operating voltages [180,181]. Integration of these novel conducting polymers into complex circuits will expand their therapeutic potential. Thus, there is an urgent need for new chemistries to design materials with exceptional properties unattainable with currently available conducting polymers.

4 Conclusion

In this review, we have discussed the significant potential of conducting polymers to enhance the biointerface since their electrical and mechanical properties can be matched to the properties of the biological system. While this can be done through both physical and chemical interactions, synthetic biofunctionalization of CPs is a facile way to achieve this. We have shown that there are several successful strategies for installing biofunctionality onto the CP backbone using reactive functional groups (RFGs). These strategies involve covalent attachment of biomolecules to CP monomers followed by polymerization (pre-functionalization chemistry) or onto the polymer itself (post-functionalization chemistry). In addition, biomolecules can be attached to the CP dopant.

Monomer pre-functionalization via RFGs is typically straightforward, allowing easy characterization of the resulting monomer structures prior
to polymerization. However, processing and polymerization of such bulky biofunctionalized monomers can be difficult, leading to sterically disrupted conducting polymers, although this has been overcome using copolymerization of the bulk monomer with an unmodified monomer. CPs prepared by monomer pre-functionalization have shown better compatibility of their electrical and mechanical properties with biological systems compared to the most commonly used CP, unsubstituted PEDOT:PSS, along with improved foreign body response (FBR).

Alternatively, post-functionalization provides a way to install larger biofunctional groups without causing significant steric hindrance of the backbone. This not only provides better control of the properties of the substituted CP but also allows the fabrication of a variety of architectures, such as block co-polymers and hydrogels that may better suit a particular biointerface. Nonetheless, steric effects may still be difficult to overcome and processing of these biofunctionalized polymers can be challenging. Despite this, most CPs prepared from polymer biofunctionalizations have been shown to enhance cell adhesion and viability highlighting their suitability for potential bioelectronic applications.

In contrast, functionalization of the dopant provides a simpler chemistry with less synthetic steps which may answer the ‘ease of synthesis’ requirement for commercialization of CP devices. This has been most effective for polymeric dopants resulting in biofunctionalized CPs that have shown good interactions with biointerfaces both in vitro and in vivo.

While biofunctionalized CPs have yet to find their way into commercially implantable devices, preliminary short-term in vivo studies have demonstrated their potential. Nonetheless, it is clear that long term in vitro and in vivo studies are necessary in order to realize this potential in real-world devices.

Consequently, this review has demonstrated that by harnessing synthetic chemistry for the development of biofunctionalized CPs and through their in vivo testing, we will significantly improve our understanding of how these materials interface with tissue and cells. This will result in enhancing communication and signaling between electronics and biological environments and should lead to the development of next-generation implantable devices for a wide variety of medical applications.

Acknowledgments

The authors gratefully acknowledge a University of Wollongong Australian Government Research Training Program Scholarship for CB, and funding from the Australian Research Council Centre of Excellence Scheme (Project Number CE140100012) and Discovery Project DP190102560.
Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Australian Research Council [DP190102560]; Centre of Excellence for Electromaterials Science, Australian Research Council [CE140100012].

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