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DOI:

[10.1016/j.actbio.2014.02.015](https://doi.org/10.1016/j.actbio.2014.02.015)

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Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Balint, R, Cassidy, N & Cartmell, SH 2014, 'Conductive polymers: towards a smart biomaterial for tissue engineering', *Acta Biomaterialia*, vol. 10, no. 6, pp. 2341-2353. <https://doi.org/10.1016/j.actbio.2014.02.015>

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Checked for eligibility: 10/01/2018

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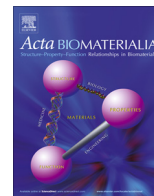
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Review

Conductive polymers: Towards a smart biomaterial for tissue engineering



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ARTICLE INFO

Article history:

Received 21 October 2013

Received in revised form 7 February 2014

Accepted 10 February 2014

Available online 18 February 2014

Keywords:

Conductive polymer

Drug release

Biocompatibility

Polypyrrole

Polyaniline

ABSTRACT

Developing stimulus-responsive biomaterials with easy-to-tailor properties is a highly desired goal of the tissue engineering community. A novel type of electroactive biomaterial, the conductive polymer, promises to become one such material. Conductive polymers are already used in fuel cells, computer displays and microsurgical tools, and are now finding applications in the field of biomaterials. These versatile polymers can be synthesised alone, as hydrogels, combined into composites or electrospun into microfibrils. They can be created to be biocompatible and biodegradable. Their physical properties can easily be optimized for a specific application through binding biologically important molecules into the polymer using one of the many available methods for their functionalization. Their conductive nature allows cells or tissue cultured upon them to be stimulated, the polymers' own physical properties to be influenced post-synthesis and the drugs bound in them released, through the application of an electrical signal. It is thus little wonder that these polymers are becoming very important materials for biosensors, neural implants, drug delivery devices and tissue engineering scaffolds. Focusing mainly on polypyrrole, polyaniline and poly(3,4-ethylenedioxythiophene), we review conductive polymers from the perspective of tissue engineering. The basic properties of conductive polymers, their chemical and electrochemical synthesis, the phenomena underlying their conductivity and the ways to tailor their properties (functionalization, composites, etc.) are discussed.

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1. Introduction

Electroactive biomaterials are a part of a new generation of “smart” biomaterials that allow the direct delivery of electrical, electrochemical and electromechanical stimulation to cells [1–4]. The family of electroactive biomaterials includes conductive polymers, electrets, piezoelectric and photovoltaic materials [4]. Electrets and piezoelectric materials allow the delivery of an electrical stimulus without the need for an external power source, but the control over the stimulus is limited [4,5]. Conductive polymers, on the other hand, allow excellent control of the electrical stimulus, possess very good electrical and optical properties, have a high conductivity/weight ratio and can be made biocompatible, biodegradable and porous [1,5–7]. Furthermore, a great advantage of conductive polymers is that their chemical, electrical and physical properties can be tailored to the specific needs of their application by incorporating antibodies, enzymes and other biological moieties [1,4,7,8]. Additionally, these properties can be altered and

controlled through stimulation (e.g. electricity, light, pH) even after synthesis [3,9–11].

Considering the vast amount of new possibilities conductive polymers offer, we believe they will revolutionize the world of tissue engineering. Thus, we chose to gather together in this review all of the available information on the most commonly used conductive polymers, their biocompatibility, conductivity, synthesis, biomolecule doping and drug release applications.

1.1. The history of conductive polymers

First produced several decades ago [12], today there are over 25 conductive polymer systems [13]. (For a list of conductive polymers see Table 1.) They merge the positive properties of metals and conventional polymers – the ability to conduct charge, great electrical and optical properties – with flexibility in processing and ease of synthesis [13]. The early work on conductive polymers was triggered by the observation that the conductivity of polyacetylene, a polymer that is normally only semiconducting at best, increases by 10 million-fold when polyacetylene is oxidized using iodine vapour [12,14]. The underlying phenomenon was named

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Table 1

A list of conductive polymers and their abbreviations [172–175].

- Polypyrrole (PPy)
- Polyaniline (PANI)
- Poly(3,4-ethylenedioxythiophene) (PEDT, PEDOT)
- Polythiophene (PTh)
- Polythiophene-vinylene (PTh-V)
- Poly(2,5-thienylenevinylene) (PTV)
- Poly(3-alkylthiophene) (PAT)
- Poly(p-phenylene) (PPP)
- Poly-p-phenylene-sulphide (PPS)
- Poly(p-phenylenevinylene) (PPV)
- Poly(p-phenylene-terephthalamide) (PPTA)
- Polyacetylene (PAC)
- Poly(isothianaphthene) (PITN)
- Poly(α -naphthylamine) (PNA)
- Polyazulene (PAZ)
- Polyfuran (PFu)
- Polyisoprene (PIP)
- Polybutadiene (PBD)
- Poly(3-octylthiophene-3-methylthiophene) (POTMT)
- Poly(p-phenylene-terephthalamide) (PPTA)

“doping” and is essential for the conductivity of polymers, as only through this process do they gain their high conductivity (discussed in more detail in Section 4) [13]. As polyacetylene was difficult to synthesize and is unstable in air, the search for a better conductive polymer began [14]. Polyheterocycles since then have emerged as a family of conductive polymers with both good stability and high conductance [15]. This family contains all the currently generally researched conductive polymers: polypyrrole, polyaniline, and polythiophenes [2,4,6,14,16–20].

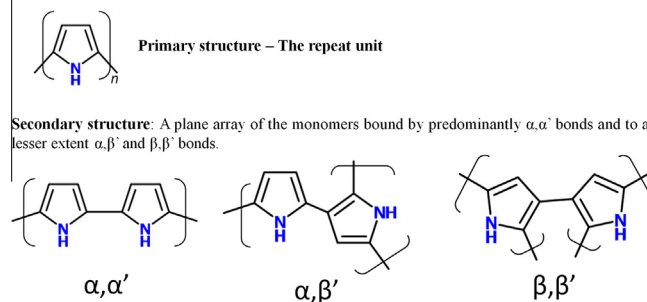
1.2. Polypyrrole

Arguably the most studied conductive polymer, reflected by the amount of publication surrounding its properties and applications, is the conjugated polymer polypyrrole (PPy; Fig. 1) [9,21–26]. PPy possesses many excellent qualities and stimulus-responsive properties, which make it a very promising “smart” biomaterial [9,21]. Most importantly, it has good in vitro and in vivo biocompatibility [8,26–28], good chemical stability in, for example, air and water [25,29], and reasonably high conductivity under physiological conditions [8,26,30–32]. PPy can be easily and flexibly synthesized in large quantities at room temperature in a wide range of solvents, including water [8,22,26,33,34]. It can be fabricated with a large surface area, with different porosities, and can easily be modified to make it more suitable for biomedical applications through the incorporation of bioactive molecules [8,22,26,30,35,36]. PPy is also stimulus responsive, allowing the dynamic control of its properties by the application of an electrical potential [21,31]. Unfortunately, PPy is very difficult to further process once synthesized [2,25,34,37], as its molecular structure makes it non-thermoplastic [25,28], mechanically rigid, brittle [2,28,38] and insoluble after synthesis [39]. Today, PPy is used in numerous applications, including fuel cells [33,39], corrosion protection [40], computer displays [39], microsurgical tools [39], biosensors [2,10] and drug delivery systems [2,31], and as a biomaterial in neural tissue engineering [41], neural probes [42], nerve guidance channels [42,43] and blood conduits [44].

1.3. Polyaniline

The second most investigated conductive polymer after PPy is polyaniline (PANI), also known as aniline black [2,14,45]. It exists in various forms based on its oxidation level: the fully oxidized pernigraniline base, half-oxidized emeraldine base and fully reduced leucoemeraldine base [2,14](Fig. 2). Of these, PANI

Polypyrrole - PPy



Tertiary structure: Mostly amorphous with randomly distributed crystalline areas. In these crystalline regions the polymer chains with the pyrrole rings orient themselves co-planar to the surface.

Fig. 1. The structure of polypyrrole [172,173,176]. Little information is known about the structures of most conductive polymers. This is a result of the difficulty in finding a solvent that produces single crystals of the polymer and the degradation of the polymer in X-ray diffraction studies [172,173,176,177,182].

emeraldine, is the most stable and conductive [2,14]. PANI has many advantages, such as ease of synthesis, low cost, good environmental stability, and the ability to be electrically switched between its conductive and resistive states [46–50]. Unfortunately, its use in biological applications is limited by its low processibility, lack of flexibility and non-biodegradability, and has been noted to cause chronic inflammation once implanted [3,47,51]. PANI has been investigated for biosensors, neural probes, controlled drug delivery and tissue engineering applications [20,52].

1.4. Polythiophene derivatives

A third very interesting conjugated polymer is poly(3,4-ethylenedioxythiophene) (PEDOT), a polythiophene (PTh) derivative [2,53] (Fig. 3). PEDOT is formed by the polymerization of the bicyclic monomer 3,4-ethylenedioxythiophene [14]. Compared to PTh, PEDOT has a dioxyalkylene bridging group across the 3- and 4-positions of its heterocyclic ring (Fig. 4), greatly improving its properties by lowering its band gap, reduction and oxidation potential [14,54]. This is also what grants PEDOT its good electrical, chemical and environmental stability [53], and better conductivity and thermal stability than PPy [14,53].

Today, PEDOT is used in biosensing and bioengineering applications [2], e.g. in neural electrodes [14,53,55], nerve grafts and heart muscle patches [53]. In one interesting example, a neural electrode was interfaced with the surrounding brain tissue through the in situ polymerization of PEDOT [56]. This formed PEDOT filaments extending far enough away from the electrode to breach the glial scar around it and forming sensitive contacts with the plasma membrane of the neurons [56]. PEDOT has also been polymerized within acellular muscle tissue, where it formed a network of elongated tubular structures throughout the tissue [53], in essence converting it into an extensive conductive three-dimensional substrate.

Another PTh derivative of interest is poly(3-hexylthiophene) (PHT) [57]. PHT possesses good solubility in organic solvents, excellent environmental stability and electrical conductivity [57], and has also been successfully electrospun with poly(lactide-co-glycolide) (PLGA) into nanofibres [57].

2. The source of their conductivity

Simply put, conductive polymers can conduct charge thanks to the ease with which electrons jump within and between the chains

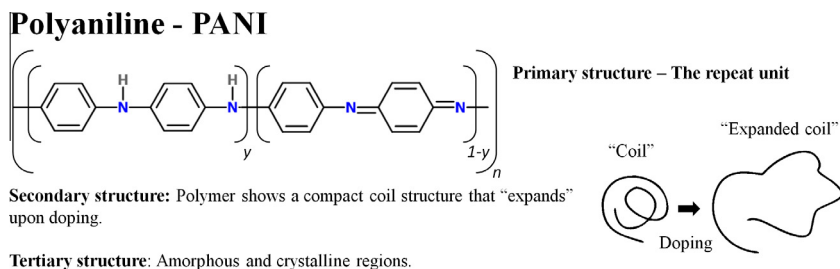


Fig. 2. The structure of polyaniline [174,178–181].

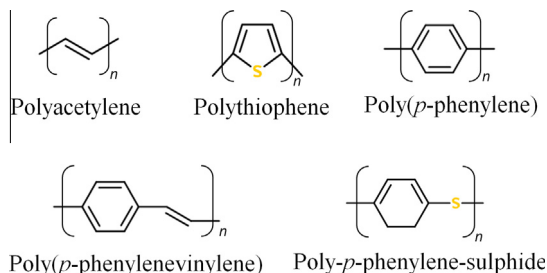


Fig. 3. The repeat units of polythiophene and some further conductive polymers [63,172–174,182].

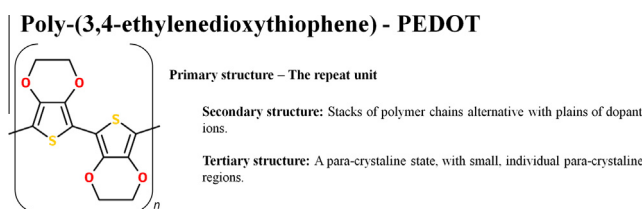


Fig. 4. The structure of PEDOT [183].

of the polymer [2]. The conductivity in reality arises from a combination of a number of factors. The polymers possess a conjugated backbone (Fig. 5), meaning that it is formed by a series of alternating single and double bonds [2,12]. Single and double bonds both contain a chemically strong, localized σ -bond, while double bonds also contain a less strongly localized π -bond [58]. The *p*-orbitals in the series of π -bonds overlap each other, allowing the electrons to be more easily delocalized (i.e. they do not belong to a single atom, but to a group of atoms) and move freely between the atoms [2,8,12,59]. The final key to the conductivity of these polymers is the dopant [2,20,58]. The polymer is synthesized in its oxidized, conducting form, and only in the presence of the dopant molecule (a negative charge/anion in most cases) is the backbone stabilized and the charge neutralized [60]. Parallel to this, the dopant

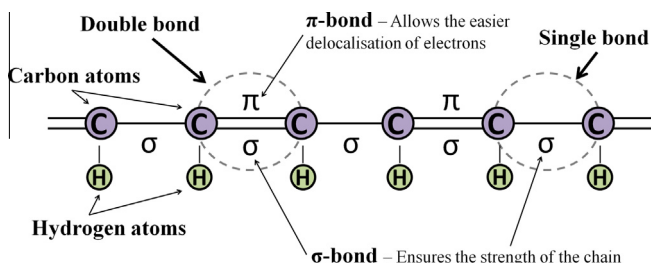


Fig. 5. A simplified schematic of a conjugated backbone: a chain containing alternating single and double bonds.

introduces a charge carrier into this system by removing or adding electrons from/to the polymer chain and relocalizing them as polarons or bipolarons (a loosely held, but localized, electron surrounded by a crystal lattice distortion; Fig. 6) [2,20,58,61]. As an electrical potential is applied, the dopants start to move in or out of the polymer (depending on the polarity), disrupting the stable backbone and allowing charge to be passed through a polymer in the form of the above-mentioned polarons and bipolarons [2,20,58]. For an elegant explanation of the phenomena behind the conductivity of these polymers, see the paper by Bredas and Streer [61].

Conductivity in PPy specifically is due to *p*-type (bipolaron) conduction, the inter-chain hopping of electrons and the motion of anions or cations within the material [13,39,62]. PPy can possess a conductivity of up to $7.5 \times 10^3 \text{ S cm}^{-1}$ (Table 2) [63]. The exact value depends on the charge transfer to adjacent molecules, the polaron, the chain and the conjugation length, and can be controlled by using different types and quantities of dopants [39,64]. The primary factor that limits the conductivity of PPy is the “disorder” (i.e. the defect sites) in the PPy backbone [54,62]. More of these defects can form as a result of redox switching or exposure to oxygen or water, resulting in the slow deterioration of conductivity [54,65].

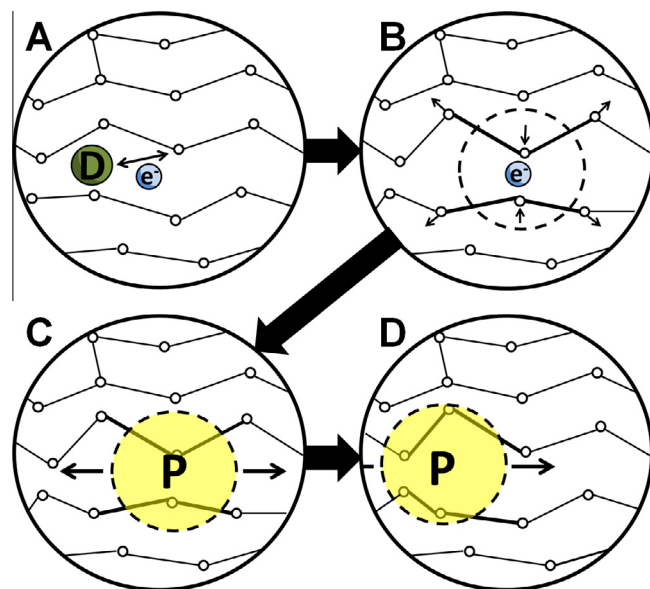


Fig. 6. A simplified explanation of the electrical conductivity of conducting polymers. (A) The dopant removes or adds an electron from/to the polymer chain, creating a delocalized charge. (B) It is energetically favourable to localize this charge and surround it with a local distortion of the crystal lattice. (C) A charge surrounded by a distortion is known as a polaron (a radical ion associated with a lattice distortion [63]). (D) The polaron can travel along the polymer chain, allowing it to conduct electricity.

Table 2
The conductivity values of some conductive polymers (adapted from Ref. [63]).

Polymer	Conductivity (S cm ⁻¹)
Polypyrrole	10 ² –7.5 × 10 ³
Polyaniline	30–200
Polythiophene	10–10 ³
Polyacetylene	10 ³ –1.7 × 10 ⁵
Poly(<i>p</i> -phenylene)	10 ² –10 ³
Poly(<i>p</i> -phenylenevinylene)	3–5 × 10 ³

Emeraldine base PANI has low conductivity in the range of 10⁻¹⁰ S cm⁻¹, while its salt, created by modifying the base's oxidative state, is conductive with 30 S cm⁻¹ [41,45,46,63]. The exact conductivity depends on the method of preparation, and can be controlled by submerging the emeraldine base in aqueous solutions of picric, camphorsulfonic or phosphoric acids [45]. The increase in conductivity between the base and salt forms is explained by the polymer's molecular structure [66]: in its base state the polymer chains are coiled, while in its salt form the additional positive charges in the polymer repel each other extending the chains (Fig. 2) [66]. In its extended coil form electrons are easier to delocalize, thus resulting in an increased conductivity [66]. PANI was reported to maintain its conductivity, albeit reduced by three magnitudes, for 100 h under physiological conditions [67].

3. The key: doping

As mentioned above, it is the doping process that introduces the charge carriers (polarons and bipolarons) into the polymer and renders it conductive [2,15]. Similarly to what happens in semiconductor technology, this can happen two ways: p-doping, where the polymer is oxidized and will have a positive charge, and n-doping, where the polymer is reduced and will possess a negative charge [2,14,58,66].

The doping process occurs during synthesis and can be carried out chemically, electrochemically or via photodoping [15,16,68]. In most cases when the dopant is a biological molecule, as many of them are not capable of the redox chemistry that is necessary for chemical synthesis, the electrochemical method has to be used. In this case, the biological molecule has to be charged and placed with the monomer when the electrochemical synthesis occurs [15,68].

There is a proportional relationship between the amount of dopant used and the conductivity of the doped polymer [64]. The conductivity can be further increased by choosing a different dopant, but this will affect the surface and bulk structural properties (e.g. colour, porosity, volume) of the polymer [2,15,16,59]. The doping is reversible, as an electrical potential applied through the polymer will cause the dopant to leave or re-enter the polymer, switching it between its conductive and insulating redox states [3,16,59].

Dopants can be separated into two categories based on their molecular size: small dopants (e.g. Cl⁻) and large dopants (e.g. sodium polystyrenesulfonate, PSS) will behave and affect the polymer itself differently [2,15,20,65]. Both will affect the conductivity and structural properties of the polymer, but large dopants will affect the material properties more dramatically and can, for example, increase the density. Large dopants are more integrated into the polymer and will not be leached out with time or with the application of an electrical stimulus, granting the polymer greater electrochemical stability [20,60,65]. With the application of a reducing electrical potential, due to their immobility rather than the large dopants expelling, a cation (positive charge) is forced to enter the polymer [20,60]. Small dopants, on the other hand, can leave and re-enter the polymer with electrical stimulation

[15,62], forming the basis of the drug release applications of conductive polymers. This also allows the physical properties of the polymer to be controlled through cycling between doping (oxidation) and dedoping (reduction) [15,62].

Surface roughness, morphology, wettability and stiffness are known to affect the adhesion and proliferation of multiple cell types [69–72]. It is therefore important to note the effect dopants can have on the bulk and surface material properties of conductive polymers [62,73,74]. Indeed, the use of different dopants (and the amount used) has been observed to alter these material properties differently [75–79]: for example, hyaluronic acid (HA) doped PPy is rougher and more brittle than PSS-doped PPy [73]. The roughness of chondroitin sulphate (CS) incorporated PPy increases as a function CS concentration [77]. When the effects of five biologically relevant dopants – dextran sulphate (DS), poly(2-methoxyaniline-5-sulfonic acid) (PMAS), para-toluenesulfonic (pTS) acid, HA and CS – were compared, it was found that the PMAS- and CS-doped films possessed a much lower surface roughness and Young's modulus than the films prepared with the other three dopants [76]. In the same study, it was also noted that the PMAS- and CS-doped films supported the adhesion and differentiation of skeletal myoblasts much better than their counterparts [76]. These observations show the connection between dopant, material property and cellular behaviour, and emphasize the importance of keeping this connection in mind when choosing the doping molecule [76].

Small and polymeric anions, buffer salts and biologically important proteins, enzymes and antibodies have all been used as dopants for PPy [14,37,73,80]. Some dopant molecules, such as poly(glutamic acid) (PGLu), can act as tethers, covalently binding additional molecules into the polymer [36]. This allows the binding of molecules that do not possess charge and thus could not be used as a dopant in a normal case [36]. For example, PGLu was successfully used to bind polylysine and laminin [36].

Similarly to the other conductive polymers, PEDOT needs a balancing counterion as a dopant for its polymerization [14]. One such dopant that is commonly used is PSS [14], but biologically relevant molecules like heparin, nerve growth factor (NGF), HA and fibrinogen [8,55] have also been used, improving the biocompatibility of PEDOT [55].

Doping with a biomolecule can have negative side effects. For example, the use of collagen was shown to result in bad film integrity [24], while HA, when applied to promote angiogenesis, was observed to reduce the electrical conductivity of the polymer [73].

4. Synthesis and processing

There are currently two main methods for synthesizing conductive polymers: chemical and electrochemical [7,14,39,58].

During chemical synthesis the monomer solution is mixed with an oxidizing agent (e.g. ferric chloride, ammonium persulfate) [81,82]. This process creates a powder or a thick film of the polymer, and allows its bulk production, which makes it the method of choice for commercial applications [82,83]. An additional advantage of chemical polymerization is that it can be used to create all types of conductive polymers, including some novel conducting polymers that cannot be synthesized with the electrochemical method [15]. Unfortunately, the conductivity of the polymers when synthesized using the chemical method has always been lower than their electrochemically synthesized counterparts [83]. Additionally, the conductivity of the created polymer is known to be highly sensitive to the choice and purity of the solvent, the oxidant, the relative concentration of the reagents, reaction time, temperature, stirring rate, etc., making reliable and repeatable chemical synthesis a difficult thing to do [83–86].

The polymerization mechanism of the chemical synthesis of PPy was shown in a recent study [81]: as the first step, pyrrole is oxidized to give a radical cation. The radical cation reacts with a neutral monomer, followed by oxidation and deprotonation, giving a dimer (an oligomer of two monomers). The dimer is also oxidized, yielding a dimeric radical cation. This combines with a new neutral monomer, providing a trimer (an oligomer of three monomers). This reaction continues and the chain grows monomer by monomer [81]. The polymerization of PANI and PTh has been suggested to be similar [81].

Electrochemical polymerization (Fig. 7) occurs by applying an electrical current through electrodes placed into a solution containing the monomer of the polymer, the solvent and the doping agent [87–89]. This method allows the deposition of a thin film of the polymer with a well-controlled thickness (down to 20 nm) and morphology [7,15,88]. The electrical current causes the monomer to deposit and oxidize on the positively charged working electrode, forming insoluble polymer chains [15]. The properties of the synthesized film will be specified by the deposition charge and time, the temperature, the solvent, the doping agent and the electrode system [28,68,78,90–93]. Electrochemical polymerization only allows the synthesis of the polymer, if its monomer can undergo oxidation in the presence of an electrical potential [15]. All of the main conductive polymers currently in use (e.g. PPy, PANI, PEDOT) fulfil this criterion [15].

Electrochemical synthesis can be carried out using three techniques: the galvanostatic, the potentiostatic and potentiodynamic methods [7,8,14]. In potentiostatic polymerization, the potential of the electrodes is controlled, while the current varies [7]. This protects the integrity of the component to be coated, making this method ideal for the manufacture of biosensors. The electrical current can vary depending on a number of factors (e.g. the electrode material, the plating conditions), thus a coulometer is necessary to control the amount of polymer that is deposited [7,14]. In galvanostatic polymerization, the electrical current is controlled instead of the potential. This means that the rate at which the polymer is deposited is steady and can be controlled accurately [7,14]. During potentiodynamic deposition, the polymerizing potential is swept between a low and high potential limit in cycles [94,95]. This

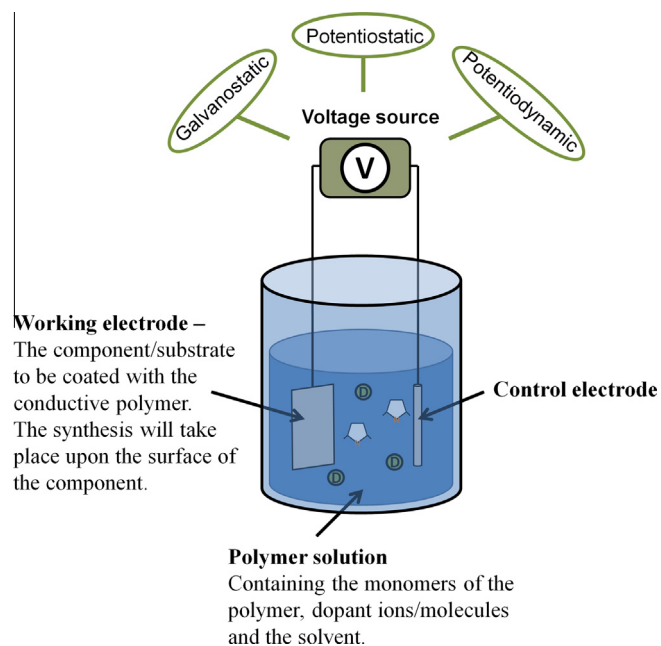


Fig. 7. A schematic of the electrochemical synthesis set-up [7,8,14,15].

causes the polymer to be deposited in layers, with each layer becoming electrically active before the next one is synthesized [96]. Potentiodynamic electrosynthesis has been observed to produce a different surface morphology to the potentiostatic and galvanostatic methods [94]. For example, in a study comparing PEDOT synthesized using the three methods, it was found that the potentiostatic and galvanostatic routes produced a porous, globular surface, while the potentiodynamic method generated a rod-like, fibrous morphology [94].

Electrochemical synthesis enables the rapid deposition of conductive polymers in situ, but the amount of bioactive molecules that can be doped into the polymer this way is limited [28,40]. Additionally, as this method requires an electrode for the polymer to be deposited upon, the range of shapes and quantities that can be synthesized will be restricted by the geometry and surface area of the electrode [65,97]. This requirement for an electrode also makes the creation of composites with this method difficult [65]. In contrast to this, chemical synthesis allows the easy creation of composites and was used to combine PPy with polymers such as poly(D,L-lactide) (PDLLA), poly(methyl methacrylate), polyvinylchloride, polystyrene and polyurethane [28,65].

4.1. Composites

One way to compensate for the shortcomings of a conductive polymer is to use it together with another polymer, combining the positive qualities of both materials [38].

For example, PPy is brittle after synthesis [2,65,98]. To give it flexibility, PPy has been deposited onto polyester [97] and polyethylene terephthalate (PET) fabrics [98]. PPy-coated polyester fabrics were shown to be cytocompatible and support the growth of cells after an initial period of reduced adhesion [97]. Unfortunately, normal deposition will not covalently bind PPy and thus the coating formed will eventually release the surface [99]. In an attempt to overcome this, polyester fabrics were covalently combined with N-modified PPy, which is much less prone to delamination [98,99]. PPy was also combined with PDLLA – either deposited onto its surface as a film or into its matrix as nanoparticles [37,65,100,101] – yielding a flexible, biocompatible and biodegradable composite with improved conductivity compared to the PPy-coated polyester fabrics [35,100,101]. PPy/PDLLA was able to maintain its electroactivity for up to 1000 h, and supported the growth of fibroblasts [65]. In vivo, when implanted in rats, it caused only minor inflammation [101]. Another biodegradable composite was created through the polymerization of PPy in the presence of the natural polymer dextran [102]. The nanocomposite produced was demonstrated to possess good conductivity and an interesting anti-microbial capability [102]. Paper-like nanocellulose-PPy composites have also been created [31]. These have excellent mechanical strength, flexibility and durability, while possessing high conductivity, high capacity and a fast ion exchange speed [31]. When PPy was combined with carbon nanotubes, it produced improved conductivity and gave excellent biocompatibility [62]. In another example, PPy was combined with poly(2-methoxy-5-aniline sulfonic acid) (PMAS), a water-soluble self-doped PANI [20]. PPy-PMAS is a hydrophobic composite with low electrical impedance, and was shown to support the adhesion and proliferation of PC-12 nerve cells [20]. PPy was even combined with animal tissue but, as the monomer was not able to permeate the tissue, it was only deposited on the surface [103,104].

Composites of PANI and polypropylene (PP) were created for neurobiological applications [46]. The PANI-PP fibres produced supported the adhesion of primary dorsal root ganglion neurons well, especially when coated with a ligand [46]. A similar composite was created from PANI and polycaprolactone for cardiac tissue regeneration [47]. PEDOT-based composites were synthesized by

combining the polymer with carbon nanotubes to produce very promising high-performance neural electrodes [105,106].

4.2. Electrospinning

Electrospinning is a versatile process that allows the production of nano- and micrometre-scale fibres from a wide range of polymers [29,33]. During electrospinning, a high-voltage electrostatic field is used to draw a jet from a polymer solution [33]. As this jet travels toward a collector electrode, the solvent evaporates and a polymer fibre is formed [33].

Attempts have been made to process conductive polymers into nano- and microfibres through electrospinning [29,57]. Conductive polymers can be electrospun alone [29,33,107], but this requires organic solvent-soluble PPy [33] or, in the case of PANI, chemical conditions (e.g. doping and dissolution in hot sulphuric acid) that might make the created fibres unsuitable for biological applications [50]. Thus conductive polymers are usually combined with spinnable polymers (e.g. polyethylene oxide, polystyrene) [2,33,57].

One way to do this is to coat electrospun fibres with the conductive polymer [107]. PPy-coated fibroin fibres were demonstrated to support the adherence and proliferation of MSCs and fibroblasts [107]. PPy was also grown on PLGA fibres, and was shown to allow the growth and differentiation of PC-12 cells and hippocampal neurons [6].

Another method is to blend with a carrier material such as poly(ethylene oxide) or poly(vinyl cinnamate) before the electrospinning process [33,50]. Using this method, PANI has been electrospun with polycaprolactone (PCL) to create a substrate for cardiac [47] and skeletal muscle tissue engineering [108]. Nanofibres of PANI-poly(L-lactide-co-ε-caprolactone) (PLCL) have also been electrospun and reported to support the adhesion of human dermal fibroblasts, NIH-3T3 fibroblasts and C2C12 myoblasts [109]. PANI-PCL nanofibres were also successfully used to promote the fusion and maturation of C2C12 myoblasts [110]. Fibres of PANI-gelatine were observed to support the attachment and proliferation of H9c2 rat cardiac myoblasts to an extent similar to tissue culture plastic [19].

The blending affects the material properties of the resultant fibres: electrical conductivity will be compromised [2] and the diameter of the resultant fibres will be decreased [2,57]. Nonetheless, conductive, flexible and biocompatible nanofibrous scaffolds produced through electrospinning are very attractive substrates for neural tissue and other engineering applications [2,33,48].

4.3. Hydrogels

Conductive polymers have also been successfully polymerized inside hydrogel networks [11,55,111]. This allows the creations of electroactive hydrogels, which combine the redox switching capabilities of conductive polymers with the fast ion mobility and biocompatibility of hydrogels [11,112]. These electroactive hydrogels can be produced with a wide range of dimensions, binding bioactive molecules and nanotemplated to mimic the extracellular matrix [111,112]. These properties make them ideal for implantable biosensors, drug release devices and deep-brain stimulators [11,112]. Examples of electroactive hydrogels are the PANI-PVP, PANI-polyacrylamide and PPy/PANI-polyacrylamide hydrogels [11,111].

PPy has also been electrochemically grown within support hydrogels made out of poly(2-hydroxyethyl methacrylate) p(HEMA) [38,112] or made into a hydrogel using a PMAS dopant [68]. The PPy synthesized this way has an extremely large surface area, thus giving the PPy hydrogel an impedance that is much lower than that of a PPy film [17]. A similar hydrogel composite was

created using PPy and complex mucopolysaccharides, and was shown to be able to release the proteins bound in it during synthesis upon the application of an electrical potential [80]. The hydrogel composites were shown to be non-cytotoxic, making them an ideal material for drug release, and neural and muscular tissue engineering [38,112].

5. Biocompatibility

Good cellular response to the biomaterial is essential for many biomedical applications [113,114]. Therefore it is important that many types of conductive polymers (e.g. PPy, PANI, PTH and polyethyleneimine (PEI)) polyethyleneimine) have been shown to support the growth of a large variety of cell types [1,2,67,115]. Additionally, the biocompatibility of conductive polymers, if insufficient, can easily be improved through bonding biocompatible molecules, segments and side chains onto the polymer [116].

Although the biocompatibility of PPy has been questioned in some cases, it was demonstrated to support the *in vitro* adhesion, growth and differentiation of a wide range of cell types [1,2], including bone [1,100], neural [37,43,44,73,100], glial [117], rat pheochromocytoma [8] and endothelial [73,97,100] cells, fibroblasts [24,118], keratinocytes [24] and mesenchymal stem cells [40]. Schwann cells treated with a PPy powder solution showed no signs of acute toxicity, mutagenesis, pyretogen, haemolysis or allergic responses [40]. Composite meshes of PPy-PLGA were shown to be biocompatible with embryonic hippocampal neurons and PC-12 cells [6]. The biocompatibility of polyester fabrics was shown not to be affected by the presence of a PPy coating [98].

PPy's good biocompatibility was also shown in animal models [1,21,39]: results indicate that PPy has no significant long-term effect *in vivo* [97], or induces only a minimal tissue response [114,116]. For example, when PPy films were implanted into the cerebral cortexes of rats, they were tolerated well and allowed the formation of complex neural networks [20]. In a study looking at chemically synthesized PPy, no cytotoxic or allergic response was found in mice [74]. Neither did the spleen, liver and kidney indexes of the mice change as a result of implanting PPy [74]. It was also demonstrated in mice that PPy does not cause haemolysis or changes in blood coagulation [97].

There are also a few reports of reduced biocompatibility. Human mesenchymal stem cells were shown to grow less on silk fibroin mats when those were coated with PPy [107]. Endothelial cells adhered less with increased PPy coating thickness [44]. In a similar investigation, endothelial cells were unable to synthesize DNA on neutral PPy, but no such problems were witnessed if the polymer was in the oxidized redox state [119]. In another study, bovine aortic endothelial cells only poorly adhered to PPy substrates that were not precoated with fibronectin [13]. PPy nanoparticles have also been observed to have an adverse affect on human lung fibroblast and mouse alveolar macrophage viability [120].

This variation in biocompatibility is theorized to be due to the different preparation protocols used in the experiments, as it was shown that rinsing, extraction and ageing all have a significant effect on biocompatibility [31]. If PPy is appropriately prepared with repeated steps of rinsing and extraction, the polymer should be completely cytocompatible [31,118]. These preparatory steps are necessary to remove the impurities, reactants, monomers and shorter oligomers (remnants of the synthesis) that are believed to be the cause of any reduced biocompatibility [13,31]. As mentioned above, the dopants and the synthesis conditions might also have affected the behaviour of cells in a negative way, as these change the surface topography of the polymer, which can result in altered cell behaviour [13].

The reports regarding PANI's biocompatibility are mixed: it was stated to support neural cell growth [2,66], provide acceptable proliferation and adhesion [52], maintain sufficient biocompatibility [2] and not cause significant inflammation [51]. Both the emeraldine base and emeraldine salt forms of PANI were reported to be cytocompatible regarding H9c2 cardiac myoblasts and not to result in inflammation in rodent models [2,48,67]. In a similar investigation, none of the emeraldine, nigraniline and leucoemeraldine forms of PANI were found to invoke an inflammatory response in rats during a 90 day period [121]. It was also stated to be overtly noncytotoxic, but to require surface treatments to enhance its biocompatibility [46]. For example, PC-12 cells were reported to poorly adhere to untreated PANI, but this was greatly improved by coating the polymer with adhesive peptides (e.g. YIGSR) [3,48,67].

Other investigations have reported poor cell adhesion and growth [15], tissue incompatibility [2] and fibrous tissue formation in rats [46]. Considerable cytotoxicity was observed regarding immortalized keratinocyte and hepatocellular carcinoma cell lines [52]. Similarly to PPy, the insufficient biocompatibility is theorized to be the result of small amounts of residual acid dopants and low-molecular-weight by-products still being present and leaking out of the polymer [52,67]. These by-products can be removed by additional curing and purification steps [52,67].

PEDOT has shown good biocompatibility, amongst others, with epithelial [2], neural [8] and neuroblastoma cells [122], L929 [123] and NIH3T3 fibroblasts [2]. For example, both PSS and tosylate anion-doped PEDOT films were demonstrated to support the adhesion and proliferation of fibroblasts [123]. Similarly, SH-SY5Y neuroblastoma cells adhered well and displayed a healthy morphology on PEDOT-coated PET fibres [122]. There are some reports that PEDOT shows light cytotoxicity, but the inflammatory response towards it *in vivo* is good [2,124]. In an attempt to enhance its compatibility with neural tissue, PEDOT was doped with NGF and indeed supported the growth of PC-12 cells [8]. The doping of PEDOT with multiwall carbon nanotubes yielded an excellent electrode material that, when implanted into rats for 6 weeks, produced a tissue response lower than that of platinum [125]. Similarly, PEDOT nanotube-coated electrodes implanted into the barrel cortex of rats were found to be accompanied by a better tissue response than their uncoated counterparts [126].

6. Functionalization for a specific application

Optimizing the material properties (roughness, porosity, hydrophobicity, conductivity, degradability) of conductive polymers and the binding of biological molecules (that makes conductive polymers so promising for biomedical applications) can be done through four major chemical ways (Fig. 8) [15]:

- (A) Through adsorption. In this method, a solution of the functionalizing agent is placed in contact with the polymer after it has already been synthesized. The biomolecule is physically absorbed due the static interactions between the polymer matrix and the charge of the molecule [127]. Although this method is the simplest to carry out, the outcome is sensitive to pH, and the biomolecule is prone to leaching out and can compromise the conductivity of the polymer [15,127,128].
- (B) By entrapping the molecule inside the polymer [129]. This is achieved by mixing the functionalizing molecule with the monomer of the polymer, the dopant and the solvent prior to synthesis [129]. Upon electrochemical polymerization, the molecules of the functionalizing agent in the proximity of the electrode are incorporated into the growing polymer

[129]. This technique is primarily applied to bind large molecules (e.g. enzymes, DNA), as these will be unable to leave the polymer once entrapped due to their size [130,131].

Both adsorption and entrapping are simple techniques that allow the incorporation of biomolecules without a chemical reaction that could affect their activity – which is something that could happen with, for example, covalent binding [129]. Therefore, these methods lend themselves to biosensor applications. For example, physical absorption has been used to successfully bind calf thymus DNA onto PPy in order to create a biosensor for toxicants [128]. Entrapping has been used to bind enzymes such as glucose oxidase to create glucose sensors [130,132,133], and to bind DNA to detect aromatic amines, cDNA and Hep C virus [131]. Even live bacterial cells have been incorporated in an attempt to create a urea biosensor [134]. Absorption has also been used to improve the biocompatibility of neural electrodes: polylysine absorbed into PEDOT:PSS-coated electrodes was shown to promote the long-term survival of neural cells [135].

- (C) By covalently bonding the molecule to the monomer of the polymer. With this method, the biological molecules will be strongly bound and will not be released, thereby enhancing the long-term stability of the polymer [23,136]. However, the conductivity of the polymer (as with absorption) might be compromised [15]. A good example of the covalent method is the binding of cysteines to the beta-positions on PPy with strong sulfide bonds. These cysteines can then serve as sites to covalently anchor further bioactive molecules [136,137]. Similar binding sites were created through the use of N-hydroxyl succinimidyl ester pyrrole [23,34], an intermediate photocrosslinker consisting of polyallylamine conjugated to an arylazido functional group [35], and poly(ethylene glycol) methacrylate graft copolymerization [26]. These binding sites were successfully used to bind NGF and heparin [23,26]. Such binding sites have been demonstrated to not always be necessary: in a novel study, Bax et al. [138] used plasma immersion ion implantation to modify the surface of PPy allowing the covalent binding of tropoelastin and collagen I without a chemical linking molecule.
- (D) By exploiting the very doping process that renders conductive polymers conductive. This allows the bonding of a wide range of biomolecules as long as they are charged [8,23,139–142]. For example, growth factors, collagen, heparin, chitosan and ATP have already been successfully bound in conductive polymers via doping [2,16,68]. Unfortunately, introducing bioactive molecules through doping allows only a relatively small amount of the molecules to be bound, while also having a greater negative effect on the polymer's conductivity than covalent bonding [2,16,23].

A wide range of biologically important molecules have been used to improve the bioactivity of PPy: for example, dermatan sulphate was used to increase keratinocyte viability [24], heparin was incorporated to promote endothelial cell proliferation [65,143], doping with laminin-derived peptides aided in neuron and astrocyte adhesion [143], NGF and poly-L-glutamic acid enhanced neuronal growth [144], while HA and CS were used for skeletal myoblast growth and differentiation [68]. In one study, PPy was doped using laminin-derived peptides p20 and p31 [144]. Both promoted neuroectoderm formation from human embryonic stem cells, but p20 enhanced neural differentiation more, while p31 better aided adhesion and spreading [144]. In other studies, PPy has been functionalized using HA to enhance vascularization [73,139], NGF to improve compatibility with neural cells [8], and heparin [28] and fibronectin [59] to promote cellular adhesion.

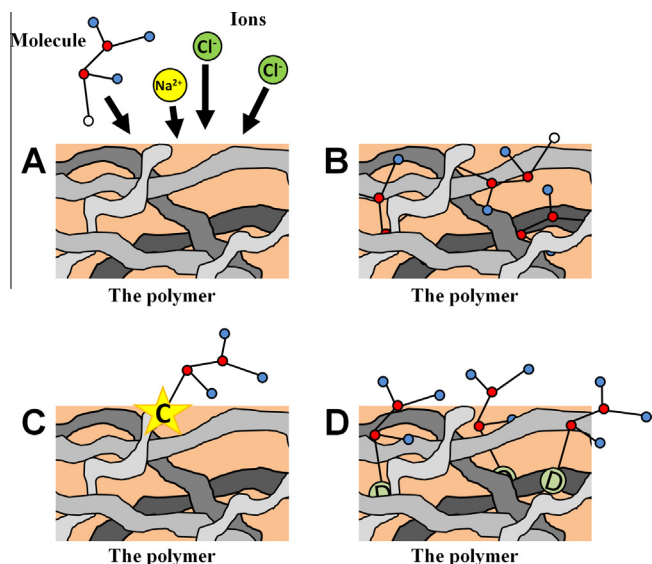


Fig. 8. The four methods of functionalizing conductive polymers: (A) physical absorption, (B) entrapping, (C) covalent bonding and (D) exploiting the doping mechanism.

Covalently binding cell-adhesive agents, such as Arg–Gly–Asp (RGD), fibronectin, heparin and HA, onto the surface of PPy has also been used to enhance the polymer's cytocompatibility [17,25,34,40,137].

Covalent modification has been used to improve the biocompatibility of PANI as well [48]. For example, the adhesive molecule RGD was covalently bound onto the surface of the polymer [48]. A substrate prepared this way was able to support PC-12 cells and induce neuritogenesis in the absence of neurotrophins [48].

Physical guidance cues, such as topographical features, can also be used to make a conductive polymer better suited for a certain application [42] – for example, through increasing the roughness of the surface or micropatterning [2,58]. Microchannel-patterned PPy was shown to increase the speed at which embryonic hippocampal neurons polarize [42].

7. Biodegradability

Although many conductive polymers (e.g. PPy and PTh) are not inherently biodegradable [2,4,41], they can be made to be so [47,58,145]. One of the three main routes is to synthesize the conductive polymer as a composite together with a biodegradable polymer [15,146]. For example, erodible PPy nanoparticle–poly(lactide) (PLA) [18,65] and PPy–PLLA [28,147] composites have been successfully prepared. Although this combines the positive properties of both polymers [101], it does not solve the problem of removing the conductive polymer from the body after the degradable polymer has disappeared [18,146]. An advantage of this method is that the conductivity and rate of degradation can be controlled by choosing the right ratio of the two polymers [15]. The second route is to modify the conductive polymer itself. The addition of ionizable (butyric acid) or hydrolysable (butyric ester) side groups to the backbone of PPy has been reported to render it degradable [1,11,148]. Again, choosing the amount of these groups allows researchers to set the rate of degradation [11]. As a third solution to the problem, small chains of PPy that can undergo gradual erosion and renal clearance simply due to their small size were electrochemically synthesized [148]. (For a more detailed description of the biodegradability of conductive polymers, see the excellent review by Guo et al. [145]).

8. Drug delivery

Many disciplines of science, including the medical, pharmaceutical and agricultural fields, require the controlled delivery of chemical compounds [11]. This has been a great challenge, but now the use of conductive polymers as a substrate material for controllable drug delivery devices promises to overcome this [11,111,141]. Why are conductive polymers so promising? The molecules bound in such polymers through doping can be controllably expelled through the application of a reducing (negative) electrical potential [11,111,141,142]. The fact that they can be made porous and have delocalized charge carriers aids in the diffusion of the bound molecules, adding a further reason why conductive polymers are very suitable for drug release applications [11]. In experiments, many therapeutic drugs, such as 2-ethylhexyl phosphate [149], dopamine [150], naproxen [151], heparin [142], NGF [35] and dexamethasone [141], have already been bound and successfully released from these polymers [141]. Using PPy, neurotrophin-3 [116,140], brain-derived neurotrophic factor (BDNF) [140] and NGF were delivered successfully and initiated neural growth and differentiation [8,21,23]. Heparin was released from a poly(vinyl alcohol) hydrogel formed on a PPy film [142], while in another experiment heparin was not released into the medium, but was exposed on the surface when an electrical potential between -0.4 and -0.7 V was applied for 90 s [9]. The anti-inflammatory drug dexamethasone was successfully released from a 50 nm thin film using cyclic voltammetry [141]. The release was proportional to the number of stimulation cycles [141]. The expulsion of the molecules generally seems to happen quite rapidly, in just a few minutes, which can be considered an advantage or a disadvantage of conductive polymers, depending on the application [27,35,116].

There are, however, a few factors that limit the application of conductive polymers for drug release: for example, the molecules loaded into the polymer tend to leach out through diffusion, to be replaced by other molecules from the polymer's environment [27,35,116]. This passive loss of load is further worsened by the fact that only a relatively small amount of drug can be bound in the polymer in the first place [27,35,116]. Additionally, both charge and molecular weight restrict which molecules can be bound and released [27]. This can be easily overcome through the use of biotin–streptavidin coupling [27]. Biotin acts as the dopant, while the bioactive molecule is covalently bound to the biotin. The molecule is then released with electrical stimulation [27]. A further bonus is that biotin provides more uniform release kinetics [27].

A further hindering problem is the fatigue of conductive polymers with repeated cycles of electrical stimulation [11]: repeated cycles can cause irreversible oxidation in the polymer, which coincides with dedoping and reduced conductivity, which ultimately limits its useful lifetime [11,14]. For example, a PPy/PPS composite was shown to retain only 5% of its original conductivity after the application of 0.4 V for 16 h [14]. Repeated stimulation cycles not only cause functional problems, but also structural ones. The continuous movement of doping agents in and out of the polymer, and the subsequent swelling and deswelling, causes cracks, delamination and the overall degradation of the polymer [14].

9. Electrical stimulation delivered through a conductive scaffold

Electrical stimulation (ES) has many noted beneficial effects, such as enhanced nerve regeneration in vivo [5]. Conductive polymers lend themselves as excellent novel scaffolds for a more efficient delivery of this stimulus type.

The most commonly reported result of ES delivered with this technique is greater neurite outgrowth in nerve cells [20,23,37,116,140,152]. For example, PC-12 cells have been reported to have 50% more neurites on NGF-doped PPy films when ES is applied [35]. Similarly, PC-12 stimulated with 10 mV cm⁻¹ on PPy-PLGA scaffolds formed an increased number of neurites, and the overall length of these neurites was also greater than without stimulation [6]. Very similar results were found on PPy-PDLLA [153] and PLLA-PANI scaffolds [49]. In a recent study by Weng et al. [154], ES was delivered through inkjet-printed collagen-coated PPy tracks to PC-12 cells [154]. The stimulation was shown to increase and direct neurite outgrowth parallel to the PPy tracks [154]. The reason behind this increase in neurite outgrowth has been postulated to be enhanced fibronectin adsorption onto the conductive polymer scaffolds [5], coupled with the effect that the electrical field has on the proteins and ion channels within the cell membrane [154]. ES has been demonstrated to have other desirable effects on nerve cells: 250 Hz biphasic current delivered via PPy/PMAS composite films was observed to increase neural differentiation in the presence of NGF [20]. Similarly, enhanced proliferation and neurite outgrowth was noted when neural cells were stimulated on nanofibrous PANI-PG scaffolds [66]. When ES was delivered through fibrillar collagen-coated PPy scaffolds, rat pheochromocytoma nerve cells displayed signs of increased neural differentiation [152]. Schwann cells cultured on chitosan-PPy composites showed greater viability and increased their NGF and BDNF mRNA expression when a stimulus of 100 mV mm⁻¹ was applied [155].

Other cell and tissue types could also benefit from ES delivered through a conductive scaffold. The growth of NIH-3T3 fibroblasts was increased by ES delivered through a PANI-based electrospun scaffold [109]. This effect on fibroblast proliferation was also observed with DC current stimulation delivered through PPy-PDLLA scaffolds [65]. In another study, human cutaneous fibroblasts stimulated on PPy-PLLA films showed greatly increased viability, mitochondrial activity, and IL-6 and IL-8 secretion [146,147]. Aortic endothelial cells cultured on fibronectin-coated PPy spread out when an oxidizing potential was applied, but were rounded and synthesized DNA to a lesser extent when the polymer was reduced to its neutral state [59]. Cardiomyocytes cultured on PANI-PLGA composite nanofibres have been shown to synchronize their beating as a result of ES [156].

These beneficial effects have been theorized to be the result of negative ion release from and positive ion (e.g. Na⁺) uptake by the polymer [5,15], electrophoretic redistribution of cell surface receptors [5] and the increased adsorption of ECM molecules like fibronectin onto the polymer [26,142]. It is also worth noting that applying an electrical current through the conductive polymer will gradually increase its resistivity, thereby limiting its useful life time [37], and that long-term exposure of cells to high electrical currents (in the range of 1 mA and above) can have a cytotoxic effect [118].

10. The electromechanical effect

PPy, PANI and PEDOT can undergo considerable volume change when being switched between redox states, suggesting another two potential applications [157–160]: to serve as bioactuators and artificial muscles [14,16,161]. Similarly to natural muscle, these polymers are capable of exerting a controlled mechanical force based on an electrochemical reaction and can work in physiological fluids [16]. Conductive polymers are already used in, for example, blood vessel sealers and microgrippers [16]. Conductive polymer-based actuators require only a small amount of electrical potential (in the range of 1 V) to function, can exert quite strong

mechanical forces (1 MPa) with volume changes of up to 35% [162], are lightweight and can function at physiological temperatures [15,16]. Their greatest limitation is their slow reaction speed, thus methods to increase the ion mobility in such polymers (i.e. allowing faster doping/dedoping) are currently being sought [15,16]. There are two phenomena behind the electrically induced volume change: (i) changes in the structure of the polymer backbone; and (ii) the osmotic movement of solvents in and out of the polymer [161]. The osmotic movement is caused by the change in ionic content in the polymer upon doping/dedoping during the redox switch [161]. The extent of the volume change and whether the polymer expands or contracts during reduction or oxidation depends on the choice of dopant [76,157]. For example, it has been noted that CS-, DS-, HA- and PMAS-doped PPy films expand, while PPy-pTS films contract during reduction [76]. This is because there are two different ways in which the polymer can maintain its charge balance when an electrical potential is applied: it can happen by either expelling the dopant or, if the dopant is not mobile, by incorporating cations/anions from the electrolyte surrounding the polymer [157,163]. Expulsion leads to contraction, while incorporation results in expansion [157]. Therefore the mobility of the dopant defines whether the polymer will undergo contraction or expansion when reduced/oxidized [157,163].

Mechanical stimulation has well-known benefits for tissue engineering and is widely used to influence the behaviour of cells [164,165]. With this in mind, Svennersten et al. [166] developed a PPy-based microactuator system on a chip. This system was successfully used to deliver mechanical stimulation to individual renal epithelial cells. The stimulation resulted in increased internal calcium levels, a known cellular response to mechanical stimulation [166–168].

To the best of the authors' knowledge, no study, other than the one conducted by Svennersten et al. [166], has been performed exploiting the electromechanical capability of PPy, PANI and PEDOT for tissue engineering purposes. This is very surprising, considering that the properties of these polymers (e.g. the ability to function in physiological fluids [16] or at a low working voltage [162]) lend themselves to such an application.

11. The next generation of conductive polymers

There is an ongoing effort to develop a more biocompatible and inherently biodegradable conductive polymer [18]. Conductive quaterthiophene and biodegradable ester have been combined to create QAPE, a novel polymer that was shown to support Schwann cells [18]. Another novel conductive polymer, ATQD, was synthesized from the emeraldine form of amino-capped aniline trimers [48]. When combined with RGD, ATQD was observed to support PC-12 adhesion and proliferation, and to induce spontaneous neurogenesis even in the absence of neurotrophic growth factors [48]. Polypyrrole-thiophene (PPy-PTh) oligomers were successfully combined with ester linkages to create another biodegradable conductive polymer [4]. The degradation of PPy-PTh produced oligomers that could be consumed by macrophages, lowering the chance of any long-term adverse effect in vivo [4]. PPy was modified to create poly(3,4-alkylenedioxyppyrrrole) (PXDOP) [54]. PXDOP possesses increased electrochemical stability, retaining a greater proportion of its conductivity even after 3000 reduction-oxidation cycles, increasing the useful lifetime of the polymer [54].

Poly(lactide) (PLA) and aniline pentamer (AP) were combined to create PLA-b-AP-b-PLA (PAP) [116]. PAP was found to be biodegradable and biocompatible, to have excellent processibility and to possess a conductivity similar to PANI's [116]. However, the mechanical properties of PAP are not good enough for practical application; hence the polymer was modified to give an alternative

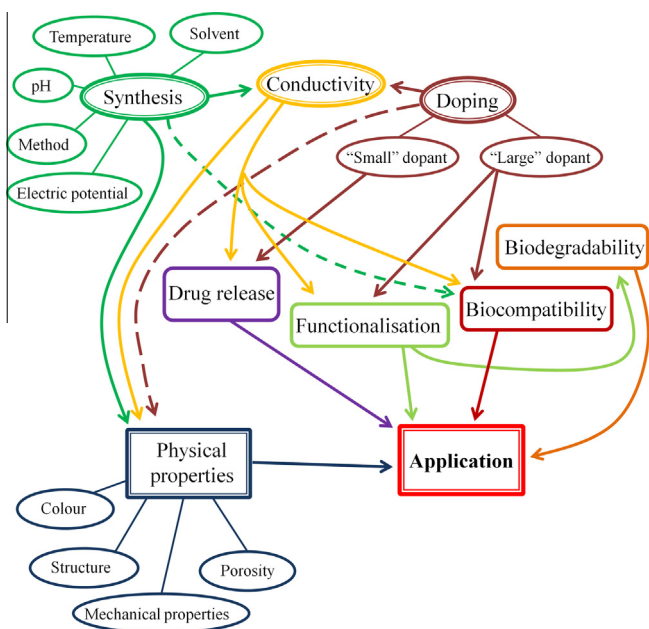


Fig. 9. Everything is connected in the world of conductive polymers.

combination of PLA and AP: PLAAP [3]. PLAAP has all the advantages of PAP but possesses improved mechanical properties [3].

AP has also been synthesized with chitosan, and its presence in the composite was shown to be essential for inducing PC-12 differentiation and neurite formation [169].

PAP was combined with glycine ethyl ester to increase cell attachment, producing polyphosphazene [51]. Polyphosphazene is conductive, soluble in common organic solvents, degrades in water into harmless products, and was shown to support RSC96 Schwann cell adhesion and proliferations in vitro [51,115]. A great advantage of polyphosphazene is that it can be made with side groups of amino acid ester, imidazole, alcohol and polyether, making grafting of further biomolecules a relatively simple task [51,115]. PANI has been modified to produce poly(aniline-co-ethyl 3-aminobenzoate) [170] and poly(aniline-co-3-aminobenzoic acid) [171]. These copolymers, when electrospun together with PLA, have been noted not only to support the proliferation of COS-1 fibroblasts, but also to possess a very high antibacterial activity, making them excellent materials for skin tissue engineering and wound dressing substrates [170,171].

Conductive polymers can now be synthesized in many versatile ways. Their biocompatibility has been well characterized. Many methods are available for rendering them biodegradable. What can still be improved?

The biocompatibility of these polymers has mostly been tested with cancer-derived cell lines. These cell lines are very resilient; therefore, in the authors' opinion, it would be desirable to more extensively test conductive polymers using primary and stem cells. These cells are much more sensitive to the culture conditions and are the ones that will be used in a clinical setting. Many promising composite, modified and co-polymer forms of PPy, PANI and PEDOT exist, but the synthesis of these is not always straightforward. An inexpensive, off-the-shelf, easy-to-use version of them is desirable – one that does not require cytotoxic or hazardous reagents for synthesis. The fatigue of conductive polymers with repeated ES [11] is a serious hindrance. Novel polymers, like PXDOP [54], show great promise, but more work is still necessary in this regard. Reliable electrical performance, together with the ability to bind large quantities of molecules over the long term and release them in a well controllable manner, would be very beneficial for drug release applications and tissue engineering.

12. Conclusion

The greatest advantage of conductive polymers is their vast versatility (Fig. 9). The key to this is the dopant. The choice of dopant defines the properties of the polymer and allows its functionalization for a specific application [8,15]. Using ES, the dopant can be expelled and incorporated again into the polymer, allowing the control of these preset physical properties [3,16]. If the chosen biomolecule cannot be used as the dopant, it can still be incorporated using an intermediating doping molecule [36]. If doping is not the right way to make the conductive polymer better suited for an application, physical adsorption, entrapment and covalent bonding offer alternative routes [15]. Synthesizing chemically or electrochemically, perhaps as composites, electrospun fibres or hydrogels, can also be used to improve the usefulness of the end product [39,55,57]. The conductive polymer substrate will be biocompatible [1,67], and can be made biodegradable through various methods [47,58]. Applying an electrical signal through a conductive polymer substrate allows the behaviour of the cells or tissue cultured upon it to be influenced [20,23,109] using an electrical or electromechanical stimulus [157]. These multiple levels, where conductive polymers can be easily modified, grant a degree of control over the properties of the material, before and after synthesis, that no other material can provide. This is why we believe that we will soon be seeing a lot more examples of the application of this smart material in tissue engineering, and we hope that we were able to convince the reader of the same.

Acknowledgements

The authors thank Orthopaedic Research UK and the EPSRC DTA award for funding this work. We also thank Dr. Jimbo Dugan and Judit Balintne Farkas for their help in preparing the manuscript.

Appendix A. Figures with essential colour discrimination

Certain figures in this article, particularly Figs. 1–9, are difficult to interpret in black and white. The full colour images can be found in the on-line version, at <http://dx.doi.org/10.1016/j.actbio.2014.02.015>.

References

- [1] Lakard B, Ploux L, Anselme K, Lallemand F, Lakard S, Nardin M, et al. Effect of ultrasounds on the electrochemical synthesis of polypyrrole, application to the adhesion and growth of biological cells. *Bioelectrochemistry* 2009;75:148–57.
- [2] Ghasemi-Mobarakeh L et al. Application of conductive polymers, scaffolds and electrical stimulation for nerve tissue engineering. *J Tissue Eng Regen Med* 2011;5:e17–35.
- [3] Huang L et al. Synthesis of biodegradable and electroactive multiblock polylactide and aniline pentamer copolymer for tissue engineering applications. *Biomacromolecules* 2008;9:850–8.
- [4] Rivers TJ, Hudson TW, Schmidt CE. Synthesis of a novel, biodegradable electrically conducting polymer for biomedical applications. *Adv Funct Mater* 2002;12:33–7.
- [5] Kotwal A, Schmidt CE. Electrical stimulation alters protein adsorption and nerve cell interactions with electrically conducting biomaterials. *Biomaterials* 2001;22:1055–64.
- [6] Lee JY, Bashur CA, Goldstein AS, Schmidt CE. Polypyrrole-coated electrospun PLGA nanofibers for neural tissue applications. *Biomaterials* 2009;30:4325–35.
- [7] Wallace GG, Smyth M, Zhao H. Conducting electroactive polymer-based biosensors. *Trends Anal Chem* 1999;18:245–51.
- [8] Kim DH, Richardson-Burns SM, Hendricks JL, Sequera C, Martin DC. Effect of immobilized nerve growth factor on conductive polymers: electrical properties and cellular response. *Adv Funct Mater* 2007;17:79–86.
- [9] Garner B, Georgevich A, Hodgson AJ, Liu L, Wallace GG. Polypyrrole-heparin composites as stimulus-responsive substrates for endothelial cell growth. *Inc. J Biomed Mater Res* 1999;44:121–9.
- [10] Aoki T, Tanino M, Sanui K, Ogata N, Kumakura K. Secretory function of adrenal chromaffin cells cultured on polypyrrole films. *Biomaterials* 1996;17:1971–4.

- [11] Guiseppi-Elie A. Electroconductive hydrogels: synthesis, characterization and biomedical applications. *Biomaterials* 2010;31:2701–16.
- [12] Shirakawa H, Louis EJ, MacDiarmid AG, Chiang CK, Heeger AJ. Synthesis of electrically conducting organic polymers: halogen derivatives of polyacetylene, (CH)_x. *J Chem Soc Chem Commun* 1977:578–80.
- [13] Ateh DD, Navsaria HA, Vadgama P. Polypyrrole-based conducting polymers and interactions with biological tissues. *J R Soc Interface* 2006;3:741–52.
- [14] Zhou DD, Cui XT, Hines A, Greenberg RJ. Conducting polymers in neural stimulation applications. In: Zhou DD, Greenbaum E, editors. *Implantable neural prostheses*, vol. 2. Berlin: Springer; 2010. p. 217–52.
- [15] Guimard NK, Gomez N, Schmidt CE. Conducting polymers in biomedical engineering. *Prog Polym Sci* 2007;32:876–921.
- [16] Cortés MT, Moreno JC. Artificial muscles based on conducting polymers. *e-Polymers* 2003;4:1–42.
- [17] Kim DH, Abidian M, Martin DC. Conducting polymers grown in hydrogel scaffolds coated on neural prosthetic devices. *J Biomed Mater Res* 2004;71A:577–85.
- [18] Guimard NKE, Sessler JL, Schmidt CE. Toward a biocompatible and biodegradable copolymer incorporating electroactive oligothiophene units. *Macromolecules* 2009;42:502–11.
- [19] Li M, Guo Y, Wei Y, MacDiarmid AG, Lelkes PI. Electrospinning polyaniline-contained gelatin nanofibers for tissue engineering applications. *Biomaterials* 2006;27:2705–15.
- [20] Liu X, Gilmore KJ, Moulton SE, Wallace GG. Electrical stimulation promotes nerve cell differentiation on polypyrrole/poly(2-methoxy-5 aniline sulfonic acid) composites. *J Neural Eng* 2009;6:1–10.
- [21] Garner B, Hodgson AJ, Wallace GG, Underwood PA. Human endothelial cell attachment to and growth on polypyrrole–heparin is fibronectin dependent. *J Mater Sci Mater Med* 1999;10:19–27.
- [22] Cui X, Hetke JE, Wiler JA, Anderson DJ, Martin DC. Electrochemical deposition and characterization of conducting polymer polypyrrole/PSS on multichannel neural probes. *Sens Actuators A-Phys* 2001;93:8–18.
- [23] Lee JY, Lee JW, Schmidt CE. Neuroactive conducting scaffolds: nerve growth factor conjugation on active ester-functionalized polypyrrole. *J R Soc Interface* 2009;6:801–10.
- [24] Ateh DD, Vadgama P, Navsaria HA. Culture of human keratinocytes on polypyrrole-based conducting polymers. *Tissue Eng* 2006;12:645–55.
- [25] Bousalem S, Mangeney C, Chehimi MM, Basinska T, Miksa B, Slomkowski S. Synthesis, characterization and potential biomedical applications of N-succinimidyl ester functionalized, polypyrrole-coated polystyrene latex particles. *Colloid Polym Sci* 2004;282:1301–7.
- [26] Li Y, Neoh KG, Kang ET. Plasma protein adsorption and thrombus formation on surface functionalized polypyrrole with and without electrical stimulation. *J Colloid Interf Sci* 2004;275:488–95.
- [27] George PM, LaVan DA, Burdick JA, Chen CY, Liang E, Langer R. Electrically controlled drug delivery from biotin-doped conductive polypyrrole. *Adv Mater* 2006;18:577–81.
- [28] Meng S, Rouabhia M, Shi G, Zhang Z. Heparin dopant increases the electrical stability, cell adhesion, and growth of conducting polypyrrole/poly(L-L-lactide) composites. *J Biomed Mater Res* 2008;87A:332–44.
- [29] Cetiner S, Kalaoglu F, Karakas H, Sarac AS. Electrospun nanofibers of polypyrrole–poly(acrylonitrile-co-vinyl acetate). *Text Res J* 2010;80:1784–92.
- [30] Akkouch A, Shi G, Zhang Z, Rouabhia M. Bioactivating electrically conducting polypyrrole with fibronectin and bovine serum albumin. *J Biomed Mater Res* 2010;92A:221–31.
- [31] Ferraz N, Strømme M, Fellstrom B, Pradhan S, Nyholm L, Mühranyan A. In vitro and in vivo toxicity of rinsed and aged nanocellulose–polypyrrole composites. *J Biomed Mater Res A* 2012;100a:2128–38.
- [32] Zhang X, Manohar SK. Bulk synthesis of polypyrrole nanofibers by a seeding approach. *J Am Chem Soc* 2004;126:12714–5.
- [33] Chronakis IS, Grapenson S, Jakob A. Conductive polypyrrole nanofibers via electrospinning: electrical and morphological properties. *Polymer* 2006;47:1597–603.
- [34] Bousalem S, Yassar A, Basinska T, Miksa B, Slomkowski S, Azioune A, et al. Synthesis, characterization and biomedical applications of functionalized polypyrrole-coated polystyrene latex particles. *Polym Adv Technol* 2003;14:820–5.
- [35] Gomez N, Schmidt CE. Nerve growth factor-immobilized polypyrrole: bioactive electrically conducting polymer for enhanced neurite extension. *J Biomed Mater Res A* 2007;81(1):135–49.
- [36] Song HK, Toste B, Ahmann K, Hoffman-Kim D, Palmore GTR. Micropatterns of positive guidance cues anchored to polypyrrole doped with polyglutamic acid: a new platform for characterize neurite extension in complex environments. *Biomaterials* 2006;27:473–84.
- [37] Zhang Z et al. Electrically conductive biodegradable polymer composite for nerve regeneration: electricity-stimulated neurite outgrowth and axon regeneration. *Artif Organs* 2007;31(1):13–22.
- [38] Brahim S, Guiseppi-Elie A. Electroconductive hydrogels: electrical and electrochemical properties of polypyrrole–poly(HEMA) composites. *Electroanalysis* 2005;17:556–70.
- [39] Lee JW, Serna F, Nickels J, Schmidt CE. Carboxylic acid-functionalized conductive polypyrrole as a bioactive platform for cell adhesion. *Biomacromolecules* 2006;7:1692–5.
- [40] Castano H, O'Rear EA, McFetridge PS, Sikavitsas VI. Polypyrrole thin films formed by admicellar polymerization support the osteogenic differentiation of mesenchymal stem cells. *Macromol Biosci* 2004;4:785–94.
- [41] Bettinger CJ, Bruggeman JP, Misra A, Borenstein JT, Langer R. Biocompatibility of biodegradable semiconducting melanin films for nerve tissue engineering. *Biomaterials* 2009;30:3050–7.
- [42] Gomez N, Lee JY, Nickels JD, Schmidt CE. Micropatterned polypyrrole: a combination of electrical and topographical characteristics for the dtimulation of cells. *Adv Funct Mater* 2007;17:1645–53.
- [43] George PM et al. Fabrication and biocompatibility of polypyrrole implants suitable for neural prosthetics. *Biomaterials* 2005;26:3511–9.
- [44] Alikacem N, Marois Y, Zhang Z, Jakubiec B, Roy R, King MW, et al. Tissue reactions to polypyrrole-coated polyesters: a magnetic resonance relaxometry study. *Artif Organs* 1999;23(10):910–9.
- [45] Blinova NV, Stejskal J, Trchova M, Prokes J. Control of polyaniline conductivity and contact angles by partial protonation. *Polym Int* 2008;57:66–9.
- [46] Cullen DK, Patel AR, Doorish JF, Smith DH, Pfister BJ. Developing a tissue-engineered neural–electrical relay using encapsulated neuronal constructs on conducting polymer fibers. *J Neural Eng* 2008;5:374–84.
- [47] Borriello A, Guarino V, Schiavo L, Alvarez-Perez MA, Ambrosio L. Optimizing PANi doped electroactive substrates as patches for the regeneration of cardiac muscle. *J Mater Sci: Mater Med* 2011;22:1053–62.
- [48] Guo Y et al. Electroactive oligoaniline-containing self-assembled monolayers for tissue engineering applications. *Biomacromolecules* 2007;8:3025–34.
- [49] Prabhakaran MP, Ghasemi-Mobarakeh L, Jin G, Ramakrishna S. Electrospun conducting polymer nanofibers and electrical stimulation of nerve stem cells. *J Biosci Bioeng* 2011;112:501–7.
- [50] Yu QZ, Shi MM, Deng M, Wang M, Chen HZ. Morphology and conductivity of polyaniline sub-micron fibers prepared by electrospinning. *Mater Sci Eng B-Solid* 2008;150:70–6.
- [51] Zhang QS, Yan YH, Li SP, Feng T. Synthesis of a novel biodegradable and electroactive polyphosphazene for biomedical application. *Biomed Mater* 2009;4:1–9.
- [52] Humpolicek P, Kasparkova V, Saha P, Stejskal J. Biocompatibility of polyaniline. *Synth Met* 2012;162:722–7.
- [53] Peramo A, Urbanchek MG, Spanning SA, Povlich LK, Cederna P, Martin DC. In situ polymerization of a conductive polymer in acellular muscle tissue constructs. *Tissue Eng Part A* 2008;14:423–32.
- [54] Thomas CA, Zong K, Schottland P, Reynolds JR. Poly(3,4-alkylenedioxyppyrrrole)s as highly stable aqueous-compatible conducting polymers with biomedical implications. *Adv Mater* 2000;12:222–5.
- [55] Asplund M, Thanning E, Lundberg J, Sandberg-Nordqvist AC, Kostyszyn B, Inganäs O, et al. Toxicity evaluation of PEDOT/biomolecular composites intended for neural communication electrodes. *Biomed Mater* 2009;4:1–12.
- [56] Richardson-Burns SM, Hendricks JL, Martin DC. Electrochemical polymerization of conducting polymers in living neural tissue. *J Neural Eng* 2007;4:L6–L13.
- [57] Subramanian A, Krishnan UM, Sethuraman S. Axially aligned electrically conducting biodegradable nanofibers for neural regeneration. *J Mater Sci: Mater Med* 2012;23:1797–809.
- [58] Ravichandran R, Sundarajan S, Venugopal JR, Mukherjee S, Ramakrishna S. Applications of conducting polymers and their issues in biomedical engineering. *J R Soc Interface* 2010;7:5559–79.
- [59] Wong JY, Langer R, Ingber DE. Electrically conducting polymers can noninvasively control the shape and growth of mammalian cells. *Proc Natl Acad Sci USA* 1994;91:3201–4.
- [60] Wallace G, Spinks G. Conducting polymers – bridging the bionic interface. *Soft Matter* 2007;3:665–71.
- [61] Bredas JL, Streer GB. Polarons, bipolarons and solitons in conductive polymers. *Acc Chem Res* 1985;18:309–15.
- [62] Peltó J et al. Electroactivity and biocompatibility of polypyrrolehyaluronic acid multi-walled carbon nanotube composite. *J Biomed Mater Res* 2010;93A:1056–67.
- [63] Dai L. Conducting polymers. In: Dai L, editor. *Intelligent macromolecules for smart devices: from materials synthesis to device applications*. London: Springer; 2004. p. 41–80.
- [64] Kaynak A, Rintoul L, George GA. Change of mechanical and electrical properties of polypyrrole films with dopant concentration and oxidative aging. *Mater Res Bull* 2000;35:813–24.
- [65] Shi G, Rouabhia M, Wang Z, Dao LH, Zhang Z. A novel electrically conductive and biodegradable composite made of polypyrrole nanoparticles and poly lactide. *Biomaterials* 2004;25:2477–88.
- [66] Ghasemi-Mobarakeh L, Prabhakaran MP, Morshed M, Nasr-Esfahani MH, Ramakrishna S. Electrical stimulation of nerve cells using conductive nanofibrous scaffolds for nerve tissue engineering. *Tissue Eng Part A* 2009;15:3605–19.
- [67] Bidez III PR, Li S, Macdiarmid AG, Venancio EC, Wei Y, Lelkes PI. Polyaniline, an electroactive polymer, supports adhesion and proliferation of cardiac myoblasts. *J Biomater Sci Polym Ed* 2006;17:199–212.
- [68] Gilmore KJ et al. Skeletal muscle cell proliferation and differentiation on polypyrrole substrates doped with extracellular matrix component. *Biomaterials* 2009;30:5292–304.

- [69] Ranella A, Barberoglou M, Bakogianni S, Fotakis C, Stratakis E. Tuning cell adhesion by controlling the roughness and wettability of 3D micro/nano silicon structures. *Acta Biomater* 2010;6:2711–20.
- [70] Huang HH, Ho CT, Lee TH, Lee TL, Liao KK, Chen FL. Effect of surface roughness of ground titanium on initial cell adhesion. *Biomol Eng* 2004;21:93–7.
- [71] Deligianni DD, Katsala ND, Koutsoukos PG, Missirlis YF. Effect of surface roughness of hydroxyapatite on human bone marrow cell adhesion, proliferation, differentiation and detachment strength. *Biomaterials* 2001;22:87–96.
- [72] Rosales-Leal JI et al. Effect of roughness, wettability and morphology of engineered titanium surfaces on osteoblast-like cell adhesion. *Colloid Surf A: Physicochem Eng Aspects* 2010;365:222–9.
- [73] Collier JH, Camp JP, Hudson TW, Schmidt CE. Synthesis and characterization of polypyrrole–hyaluronic acid composite biomaterials for tissue engineering applications. *J Biomed Mater Res* 2000;50:574–84.
- [74] Ramanaviciene A, Kausaite A, Tautkus S, Ramanavicius A. Biocompatibility of polypyrrole particles: an in vivo study in mice. *J Pharm Pharmacol* 2007;59:311–5.
- [75] Fonner JM, Schmidt CE, Ren P. A combined molecular dynamics and experimental study of doped polypyrrole. *Polymer* 2010;51:4985–93.
- [76] Gelmi A, Higgins MJ, Wallace GG. Physical surface and electromechanical properties of doped polypyrrole biomaterials. *Biomaterials* 2010;31:1974–83.
- [77] Moreno JS, Panero S, Artico M, Filippini P. Synthesis and characterization of new electroactive polypyrrole–chondroitin sulphate A substrates. *Bioelectrochemistry* 2008;72:3–9.
- [78] Han DH, Lee HJ, Park SM. Electrochemistry of conductive polymers. XXXV. Electrical and morphological characteristics of polypyrrole films prepared in aqueous media studied by current sensing atomic force microscopy. *Electrochim Acta* 2005;50:3085–92.
- [79] Silk T, Hong Q, Tamm J, Compton RG. AFM studies of polypyrrole film surface morphology. I. The influence of film thickness and dopant nature. *Synth Met* 1998;93:59–64.
- [80] Hodgson AJ, Gilmore K, Small C, Wallace GG, Mackenzie IL, Aoki T, et al. Reactive supramolecular assemblies of mucopolysaccharide, polypyrrole and protein as controllable biocomposites for a new generation of “intelligent biomaterials”. *Supramol Sci* 1994;1:77–83.
- [81] Tan Y, Ghandi K. Kinetics and mechanism of pyrrole chemical polymerization. *Synth Met* 2013;175:183–91.
- [82] Armes SP. Optimum reaction conditions for the polymerization of pyrrole by iron (III) chloride in aqueous solution. *Synth Met* 1987;20:365–71.
- [83] Calvo PA, Rodriguez J, Grande H, Mecerreyes D, Pomposo JA. Chemical oxidative polymerization of pyrrole in the presence of m-hydroxybenzoic acid- and m-hydroxycinnamic acid-related compounds. *Synth Met* 2002;126:111–6.
- [84] Cao Y, Andreatta A, Heeger AJ, Smith P. Influence of chemical polymerization conditions on the properties of polyaniline. *Polymer* 1989;30:2305–11.
- [85] Kudoh Y, Akami K, Matsuya Y. Chemical polymerization of 3,4-ethylenedioxythiophene using an aqueous medium containing an anionic surfactant. *Synth Met* 1998;98:65–70.
- [86] Pron A, Genoud F, Menardo C, Nechtschein M. The effect of the oxidation conditions on the chemical polymerization of polyaniline. *Synth Met* 1988;24:193–201.
- [87] Martins NCT, Moura e Silva T, Montemora MF, Fernandes JCS, Ferreira MGS. Electrodeposition and characterization of polypyrrole films on aluminium alloy 6061-T6. *Electrochim Acta* 2008;53:4754–63.
- [88] Herrasti P, Díaz L, Ocón P, Ibáñez A, Fatas E. Electrochemical and mechanical properties of polypyrrole coatings on steel. *Electrochim Acta* 2004;49:3693–9.
- [89] Choi S, Park S. Electrochemistry of conductive polymers. XXVI. Effects of electrolytes and growth methods on polyaniline morphology. *J Electrochem Soc* 2002;149:E26–34.
- [90] Li CM, Sun CQ, Chen W, Pan L. Electrochemical thin film deposition of polypyrrole on different substrates. *Surf Coat Technol* 2005;198:474–7.
- [91] Kaplin DA, Qutubuddin S. Electrochemically synthesized polypyrrole films: effects of polymerization potential and electrolyte type. *Polymer* 1995;36:1275–86.
- [92] Sutton SJ, Vaughan AS. On the morphology and growth of electrochemically polymerized polypyrrole. *Polymer* 1995;36:1849–57.
- [93] Kaynak A. Effect of synthesis parameters on the surface morphology of conducting polypyrrole films. *Mater Res Bull* 1997;32:271–85.
- [94] Patra S, Barai K, Munichandraiah N. Scanning electron microscopy studies of PEDOT prepared by various electrochemical routes. *Synth Met* 2008;158:430–5.
- [95] Mondal SK, Prasad KR, Munichandraiah N. Analysis of electrochemical impedance of polyaniline films prepared by galvanostatic, potentiostatic and potentiodynamic methods. *Synth Met* 2005;148:275–86.
- [96] Girija TC, Sangaranarayanan MV. Investigation of polyaniline-coated stainless steel electrodes for electrochemical supercapacitors. *Synth Met* 2006;156:244–50.
- [97] Zhang Z, Roy R, Dugre FJ, Tessier D, Dao LH. In vitro biocompatibility study of electrically conductive polypyrrole-coated polyester fabrics. *J Biomed Mater Res* 2001;57:63–71.
- [98] Jiang X, Marois Y, Traoré A, Tessier D, Dao LH, Guidoin R, et al. Tissue reaction to polypyrrole-coated polyester fabrics: an in vivo study in rats. *Tissue Eng* 2002;8:635–47.
- [99] Tessier D, Dao LH, Zhang Z, King MW, Guidoin R. Polymerization and surface analysis of electrically-conductive polypyrrole on surface-activated polyester fabrics for biomedical applications. *J Biomater Sci Polym Ed* 2000;11:87–99.
- [100] Wang Z, Roberge C, Wan Y, Dao LH, Guidoin R, Zhang Z. A biodegradable electrical bioconductor made of polypyrrole nanoparticle/poly(D,L-lactide) composite: a preliminary in vitro biostability study. *J Biomed Mater Res* 2003;66A:738–46.
- [101] Wang Z et al. In vivo evaluation of a novel electrically conductive polypyrrole/poly(D,L-lactide) composite and polypyrrole-coated poly(D,L-lactide-co-glycolide) membranes. *Biomed Mater Res* 2004;70A:28–38.
- [102] Zare EN, Lakouraj MM, Mohseni M. Biodegradable polypyrrole/dextrin conductive nanocomposite: synthesis, characterization, antioxidant and antibacterial activity. *Synth Met* 2014;187:9–16.
- [103] Khor E, Li HC, Wee A. In situ polymerization of pyrrole in animal tissue in the formation of hybrid biomaterials. *Biomaterials* 1995;16:657–61.
- [104] Khor E, Li HC, Wee A. Animal tissue–polypyrrole hybrid biomaterials: shrinkage temperature evaluation. *Biomaterials* 1996;17:1877–9.
- [105] Chen S et al. PEDOT/MWCNT composite film coated microelectrode arrays for neural interface improvement. *Sens Actuator A* 2013;193:141–8.
- [106] Luo X, Weaver CL, Zhou DD, Greenberg R, Cui XT. Highly stable carbon nanotube doped poly(3,4-ethylenedioxythiophene) for chronic neural stimulation. *Biomaterials* 2011;32:5551–7.
- [107] Aznar-Cervantes S, Roca MI, Martínez JG, Meseguer-Olmo L, Cenis JL, Moraleda JM, et al. Fabrication of conductive electrospun silk fibroin scaffolds by coating with polypyrrole for biomedical applications. *Bioelectrochemistry* 2012;85:36–43.
- [108] Ku SH, Lee SH, Park CB. Synergic effects of nanofiber alignment and electroactivity on myoblast differentiation. *Biomaterials* 2012;33:6098–104.
- [109] Jeong SI, Jun ID, Choi MJ, Nho YC, Lee YM, Shin H. Development of electroactive and elastic nanofibers that contain polyaniline and poly(L-lactide-co-ε-caprolactone) for the control of cell adhesion. *Macromol Biosci* 2008;8:627–37.
- [110] Chen MC, Sun YC, Chen YH. Electrically conductive nanofibers with highly oriented structures and their potential application in skeletal muscle tissue engineering. *Acta Biomater* 2013;9:5562–72.
- [111] Small CJ, Too CO, Wallace GG. Responsive conducting polymer–hydrogel composites. *Polym Gels Netw* 1997;5:251–65.
- [112] Justin G, Guiseppi-Elie A. Electroconductive blends of poly(HEMA-co-PEGMA-co-HMMA-co-SPMA) and poly(Py-co-PyBA): in vitro biocompatibility. *J Bioact Compat Pol* 2010;25:121–40.
- [113] Zhang Q, Yan Y, Li S, Feng T. The synthesis and characterization of a novel biodegradable and electroactive polyphosphazene for nerve regeneration. *Mater Sci Eng C* 2010;30:160–6.
- [114] Huang L et al. Synthesis and characterization of electroactive and biodegradable ABA block copolymer of polylactide and aniline pentamer. *Biomaterials* 2007;28:1741–51.
- [115] Cui X, Lee VA, Raphael Y, Wiler JA, Hetke JF, Anderson DJ, et al. Surface modification of neural recording electrodes with conducting polymer/biomolecule blends. *Biomed Mater Res* 2001;56:261–72.
- [116] Williams RL, Doherty PJ. A preliminary assessment of poly(pyrrole) in nerve guide studies. *J Mater Sci Mater Med* 1994;5:429–33.
- [117] Wang X et al. Evaluation of biocompatibility of polypyrrole in vitro and in vivo. *J Biomed Mater Res* 2004;68A:411–22.
- [118] Richardson RT et al. The effect of polypyrrole with incorporated neurotrophin-3 on the promotion of neurite outgrowth from auditory neurons. *Biomaterials* 2007;28:513–23.
- [119] Jakubiec B et al. In vitro cellular response to polypyrrole-coated woven polyester fabrics: potential benefits of electrical conductivity. *J Biomed Mater Res* 1998;41:519–26.
- [120] Kim S, Oh WK, Jeong YS, Hong JY, Cho BR, Hahn JS, et al. Cytotoxicity of, and innate immune response to, size-controlled polypyrrole nanoparticles in mammalian cells. *Biomaterials* 2011;32:2342–50.
- [121] Kamalesh S, Tan P, Wang J, Lee T, Kang ET, Wang CH. Biocompatibility of electroactive polymers in tissues. *J Biomed Mater Res* 2000;52:467–78.
- [122] Bolin MH, Svennersten K, Wang X, Chronakis IS, Richter-Dahlfors A, Jager EWH, et al. Nano-fiber scaffold electrodes based on PEDOT for cell stimulation. *Sens Actuator B* 2009;142:451–6.
- [123] Karagkiozaki V, Karagiannidis PG, Gioti M, Kavatzikidou P, Georgiou D, Georgeraki E, et al. Bioelectronics meets nanomedicine for cardiovascular implants: PEDOT-based nanocoatings for tissue regeneration. *Biochim Biophys Acta* 2013;1830:4294–304.
- [124] Luo SC, Ali EM, Tansil NC, Yu HH, Gao S, Kantchev EAB, et al. Poly(3,4-ethylenedioxythiophene) (PEDOT) nanobiointerfaces: thin, ultrasmooth, and functionalized PEDOT films with in vitro and in vivo biocompatibility. *Langmuir* 2008;24:8071–7.
- [125] Zhou H, Cheng X, Rao L, Li T, Duan YY. Poly(3,4-ethylenedioxythiophene)/multiwall carbon nanotube composite coatings for improving the stability of microelectrodes in neural prostheses applications. *Acta Biomater* 2013;9:6439–49.
- [126] Abidian MR, Ludwig KA, Marzullo TC, Martin DC, Kipke DR. Interfacing conducting polymer nanotubes with the central nervous system: chronic neural recording using poly(3,4-ethylenedioxythiophene) nanotubes. *Adv Mater* 2009;21:3764–70.
- [127] Ahuja T, Mir IA, Kumar D, Rajesh. Biomolecular immobilization on conducting polymers for biosensing applications. *Biomaterials* 2007;28:791–805.

- [128] Arora K et al. Application of electrochemically prepared polypyrrole–polyvinyl sulphonate films to DNA biosensor. *Biosens Bioelectron* 2006;21:1777–83.
- [129] Cosnier S. Biomolecule immobilization on electrode surfaces by entrapment or attachment to electrochemically polymerized films. A review. *Biosens Bioelectron* 1999;14:443–56.
- [130] Genies EM, Marchesiello M. Conducting polymers for biosensors, application to new glucose sensors GOD entrapped into polypyrrole, GOD adsorbed on poly(3-methylthiophene). *Synth Met* 1993;55–57:3677–82.
- [131] Prabhakar N, Arora K, Singh SP, Singh H, Malhotra BD. DNA entrapped polypyrrole–polyvinyl sulfonate film for application to electrochemical biosensor. *Anal Biochem* 2007;366:71–9.
- [132] Nien PC, Tung TS, Hoa KC. Amperometric glucose biosensor based on entrapment of glucose oxidase in a poly(3,4-ethylenedioxythiophene) film. *Electroanalysis* 2006;18:1408–15.
- [133] Wang J, Myung NV, Yun M, Monbouquette HG. Glucose oxidase entrapped in polypyrrole on high-surface-area Pt electrodes: a model platform for sensitive electroenzymatic biosensors. *J Electroanal Chem* 2005;575:139–46.
- [134] Jha SK, Kanungo M, Nath A, D'Souza SF. Entrapment of live microbial cells in electropolymerized polyaniline and their use as urea biosensor. *Biosens Bioelectron* 2009;24:2637–42.
- [135] Collazos-Castro JE, Polo JL, Hernández-Labrado GR, Padial-Cañete V, García-Rama C. Bioelectrochemical control of neural cell development on conducting polymers. *Biomaterials* 2010;31:9244–55.
- [136] De Giglio E, Sabbatini L, Zamboni PG. Development and analytical characterization of cysteine-grafted polypyrrole films electrosynthesized on Pt and Ti-substrates as precursors of bioactive interfaces. *Biomater Sci Polym Ed* 1999;10:845–58.
- [137] De Giglio E, Sabbatini L, Colucci S, Zamboni G. Synthesis, analytical characterization, and osteoblast adhesion properties on RGD-grafted polypyrrole coatings on titanium substrates. *J Biomater Sci Polym Ed* 2000;11:1073–83.
- [138] Bax DV et al. Cell patterning via linker-free protein functionalization of an organic conducting polymer (polypyrrole) electrode. *Acta Biomater* 2012;8:2538–48.
- [139] Cen L, Neoh KG, Li Y, Kang ET. Assessment of in vitro bioactivity of hyaluronic acid and sulfated hyaluronic acid functionalized electroactive polymer. *Biomacromolecules* 2004;5:2238–46.
- [140] Thompson BC, Richardson RT, Moulton SE, Evans AJ, O'Leary S, Clark GM, et al. Conducting polymers, dual neurotrophins and pulsed electrical stimulation – dramatic effects on neurite outgrowth. *J Control Release* 2010;141:161–7.
- [141] Wadhwa R, Lagenaur CF, Cui XT. Electrochemically controlled release of dexamethasone from conducting polymer polypyrrole coated electrode. *J Control Release* 2006;110:531–41.
- [142] Li Y, Neoh KG, Kang ET. Controlled release of heparin from polypyrrole–poly(vinyl alcohol) assembly by electrical stimulation. *J Biomed Mater Res* 2005;73A:171–81.
- [143] Stauffer WR, Cui XT. Polypyrrole doped with 2 peptide sequences from laminin. *Biomaterials* 2006;27:2405–13.
- [144] Zhang L, Stauffer WR, Jane EP, Sannak PJ, Cui XT. Enhanced differentiation of embryonic and neural stem cells to neuronal fates on laminin peptides doped polypyrrole. *Macromol Biosci* 2010;10:1456–64.
- [145] Guo B, Glavas L, Albertsson AC. Biodegradable and electrically conducting polymers for biomedical applications. *Prog Polym Sci* 2013;38:1263–86.
- [146] Shi G, Rouabhia M, Meng S, Zhang Z. Electrical stimulation enhances viability of human cutaneous fibroblasts on conductive biodegradable substrates. *J Biomed Mater Res* 2008;84A:1026–37.
- [147] Shi G, Zhang Z, Rouabhia M. The regulation of cell functions electrically using biodegradable polypyrrole–polylactide conductors. *Biomaterials* 2008;29:3792–8.
- [148] Zelikin AN, Lynn DM, Farhadi J, Martin I, Shastri V, Langer R. Erodible conducting polymers for potential biomedical applications. *Angew Chem Int Ed* 2002;41:141–4.
- [149] Massoumi B, Entezami AA. Electrochemically stimulated 2-ethylhexyl phosphate (EHP) release through redox switching of conducting polypyrrole film and polypyrrole/poly(N-methylpyrrole) or self-doped polyaniline bilayers. *Polym Int* 2002;51:555–60.
- [150] Miller LL, Zhou XU. Poly(N-methylpyrrolylium) poly(styrenesulfonate). A conductive, electrically switchable cation exchanger that cathodically binds and anodically releases dopamine. *Macromolecules* 1987;20:1594–7.
- [151] Kontturi K, Pentti P, Sundholm G. Polypyrrole as a model membrane for drug delivery. *J Electroanal Chem* 1998;453:231–8.
- [152] Liu X, Yue Z, Higgins MJ, Wallace GG. Conducting polymers with immobilised fibrillar collagen for enhanced neural interfacing. *Biomaterials* 2011;32:7309–17.
- [153] Xu H et al. Conductive PPY/PDLLA conduit for peripheral nerve regeneration. *Biomaterials* 2014;35:225–35.
- [154] Weng B, Liu X, Shepherd R, Wallace GG. Inkjet printed polypyrrole/collagen scaffold: a combination of spatial control and electrical stimulation of PC12 cells. *Synth Met* 2012;162:1375–80.
- [155] Huang J, Hu X, Lu L, Ye Z, Zhang Q, Luo Z. Electrical regulation of Schwann cells using conductive polypyrrole/chitosan polymers. *J Biomed Mater Res* 2010;93A:164–74.
- [156] Hsiao CW et al. Electrical coupling of isolated cardiomyocyte clusters grown on aligned conductive nanofibrous meshes for their synchronized beating. *Biomaterials* 2013;34:1063–72.
- [157] Gandhi MR, Murray P, Spinks GM, Wallace GG. Mechanism of electromechanical actuation in polypyrrole. *Synth Met* 1995;73:247–56.
- [158] Kaneto K, Kaneko M, Min Y, MacDiarmid AG. "Artificial muscle": electromechanical actuators using polyaniline films. *Synth Met* 1995;71:2211–2.
- [159] Madden JD, Cush RA, Kanigan TS, Hunter IW. Fast contracting polypyrrole actuators. *Synth Met* 2000;113:185–92.
- [160] Okuzaki H, Suzuki H, Ito T. Electrically driven PEDOT/PSS actuators. *Synth Met* 2009;159:2233–6.
- [161] Bay L, Jacobsen T, Skaarup S. Mechanism of actuation in conducting polymers: osmotic expansion. *J Phys Chem B* 2001;105:8492–7.
- [162] Smela E, Gadegaard N. Surprising volume change in PPy(DBS): an atomic force microscopy study. *Adv Mater* 1999;11:953–7.
- [163] Jager EWH. Conducting polymer actuators for medical devices and cell mechanotransduction. In: *IEEE/ASME international conference on advanced intelligent, mechatronics*; 2013. p. 1661–6.
- [164] Chiu LLY, Radisic M. Cardiac tissue engineering. *Curr Opin Chem Eng* 2013;2:41–52.
- [165] Subramony SD, Dargis BR, Castillo M, Azeloglu EU, Tracey MS, Su A, et al. The guidance of stem cell differentiation by substrate alignment and mechanical stimulation. *Biomaterials* 2013;34:1942–53.
- [166] Svennersten K, Berggren M, Richter-Dahlfors A, Jager EWH. Mechanical stimulation of epithelial cells using polypyrrole microactuators. *Lab Chip* 2011;11:3287.
- [167] Demer LL, Wortham CM, Dirksen ER, Sanderson MJ. Mechanical stimulation induces intercellular calcium signalling in bovine aortic endothelial cells. *Am J Physiol-Heart C* 1993;264:H2094–102.
- [168] Jager EWH, Bolin MH, Svennersten K, Wang X, Richter-Dahlfors A, Berggren M. Electroactive surfaces based on conducting polymers for controlling cell adhesion, signalling, and proliferation. In: *International solid-state sensors, actuators and microsystems conference*; 2009. p. 1778–81.
- [169] Hu J et al. Electroactive aniline pentamer cross-linking chitosan for stimulation growth of electrically sensitive cells. *Biomacromolecules* 2008;9:2637–44.
- [170] Gizdavic-Nikolaidis M, Ray S, Bennett J, Swift S, Bowmaker G, Easteal A. Electrospun poly(aniline-co-ethyl 3-aminobenzoate)/poly(lactic acid) nanofibers and their potential in biomedical applications. *J Polym Sci Part A: Polym Chem* 2011;49:4902–10.
- [171] Gizdavic-Nikolaidis M, Ray S, Bennett JR, Easteal AJ, Cooney RP. Electrospun functionalized polyaniline copolymer-based nanofibers with potential application in tissue engineering. *Macromol Biosci* 2010;10:1424–31.
- [172] Kumar D, Sharma RC. Advances in conductive polymers. *Eur Polym J* 1998;34:1053–60.
- [173] Wan M. Introduction of conducting polymers. In: Wan M, editor. *Conducting polymers with micro or nanometer structure*. Berlin: Springer; 2008. p. 1–15.
- [174] Epstein AJ. Electrical conductivity in conjugated polymers. In: Rupprecht L, editor. *Conductive polymers and plastics in industrial applications*. Norwich, NY: William Andrew Publishing/Plastics Design Library; 1999. p. 1–9.
- [175] Kirchmeyer S, Reuter K. Scientific importance, properties and growing applications of poly(3,4-ethylenedioxythiophene). *J Mater Chem* 2005;15:2077–88.
- [176] Ribo JM, Acero C, Anglada MC, Dicko A, Tura JM, Ferrer-Anglada N, et al. On the structure and transport properties of polypyrroles. *Butll Soc Cat Cien* 1992;13:335–51.
- [177] Street GB, Lindsey SE, Nazzari AI, Wynne KJ. The structure and mechanical properties of polypyrrole. *Mol Cryst Liq Cryst* 1985;118:137–48.
- [178] MacDiarmid AG, Epstein AJ. Secondary doping in polyaniline. *Synth Met* 1995;69:85–92.
- [179] MacDiarmid AG, Chiang JC, Richter AF. Polyaniline: a new concept in conducting polymers. *Synth Met* 1987;18:285–90.
- [180] Pouget JP, Jdzefowicz ME, Epstein AJ, Tang X, MacDiarmid AG. X-ray structure of polyaniline. *Macromolecules* 1991;24:779–89.
- [181] Tourillon G, Garnier F. Morphology and crystallographic structure of polythiophene and derivatives. *Mol Cryst Liq Cryst* 1985;118:221–6.
- [182] Batz P, Schmeisser D, Gopel W. Electronic structure of polypyrrole films. *Phys Rev B* 1991;43:9178–89.
- [183] Aasmundtveit KE, Samuelsen EJ, Pettersson LAA, Inganäs O, Johansson T, Feidenhans R. Structure of thin films of poly(3,4-ethylenedioxythiophene). *Synth Met* 1999;101:561–4.