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Progress in conducting polymers for biointerfacing and biorecognition applications



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ABSTRACT

Conducting polymers are an exciting class of organic electronic materials, which have attracted an increasing interest in the fields of bioelectronics and their biomedical applications. Their unique features such as mixed ionic-electronic conductivity, good biocompatibility, as well as mechanical softness make them favored candidates for an effective conduit between the worlds of electronics and biology. In addition, the facile synthesis, simple functionalization, and ability to electronically control a range of physical and chemical properties of these materials has enabled considerable development for biorecognition and biosensors devices. In this review, we have turned our attention to recent progress in the tailoring of the conducting polymers functionalities, focusing especially on neural interfaces, molecularly imprinted conducting polymers for biorecognition and bioactive scaffolds for mechanotransduction in living cells.

1. Introduction

Research in electrically organic materials has gained significant attention for developing next-generation soft interfaces for bioelectronics and biomedical devices. Among these, conductive polymers (CPs) have been popular choices that allow direct delivery of electrical, electrochemical and electromechanical signals at the interface between living soft systems with abiotic electronic devices [1–3]. CPs materials can have electrical properties similar to semiconductors and metals while their mechanical properties are relatively similar to conventional polymers [4]. Besides, their response to electrochemical oxidation or reduction can produce a reversible change in conductivity [5], color [6], wettability [7], and volume [8]. Such unique hybrid electronic-ionic conductivity, mechanical softness and biocompatibility make them favored candidates for a wide range of applications including neural interfaces, medical implants, biosensors, drug delivery systems and bioactive tissue engineering scaffolds [1,2,9–11].

Over the past decade, CPs have been integrated in many neuroprosthetic devices to both stimulate nerve tissue and record neuronal activity [12]. CPs coating such as poly(3,4-ethylenedioxythiophene) (PEDOT) and poly(pyrrole) (PPy) showed to provide a more adaptable interface to neural tissue, showing smaller hardness mismatch, offering seamless neural interfaces that cause minimal glial reaction and desirable characteristics including low electrical impedance without substantially increasing site geometric surface area [2,13–15]. It has therefore

attracted much attention as new nanostructured coating materials for developing next-generation neural interfaces with application not only in stimulating and recording devices [16], but also as scaffolds for the regeneration of nerves tissues [17,18] or as modulated drug delivery systems [19–21].

CPs are also one of the promising candidates for constructing biosensing systems due to their outstanding properties in terms of good electrocatalytic activity and strong adsorptive ability when compared to conventional metallic electrodes [22,23]. Several reports showed that electrode with CPs e.g. PEDOT modification enhances the substantial reactivity and detection sensitivity towards neurotransmitters e.g. dopamine, ascorbic acid, serotonin [24–27]. These improvements come from both bulk and surface properties of CPs materials, including large surface-to-volume ratio and specific surface area, good electrocatalytic activity and fast electron transfer kinetics. Besides, the ability to tailor the structure, functionalization and hence the properties of conjugated polymers offers excellent prospects for designing novel systems and enhancing the overall performances of bioanalytical devices, in particular in the fields of biosensing/biorecognition [28].

The step for creating recognition layer during biosensor design is one of the challenging issues when developing any biosensors types. In this context, molecularly imprinted polymer (MIP) technology serves a useful and unique approach for overcoming the challenges in terms of selectivity, specificity, cost-friendly, label-free, storage/chemical and physical stabilities, shelf-life, and reproducibility as well as their

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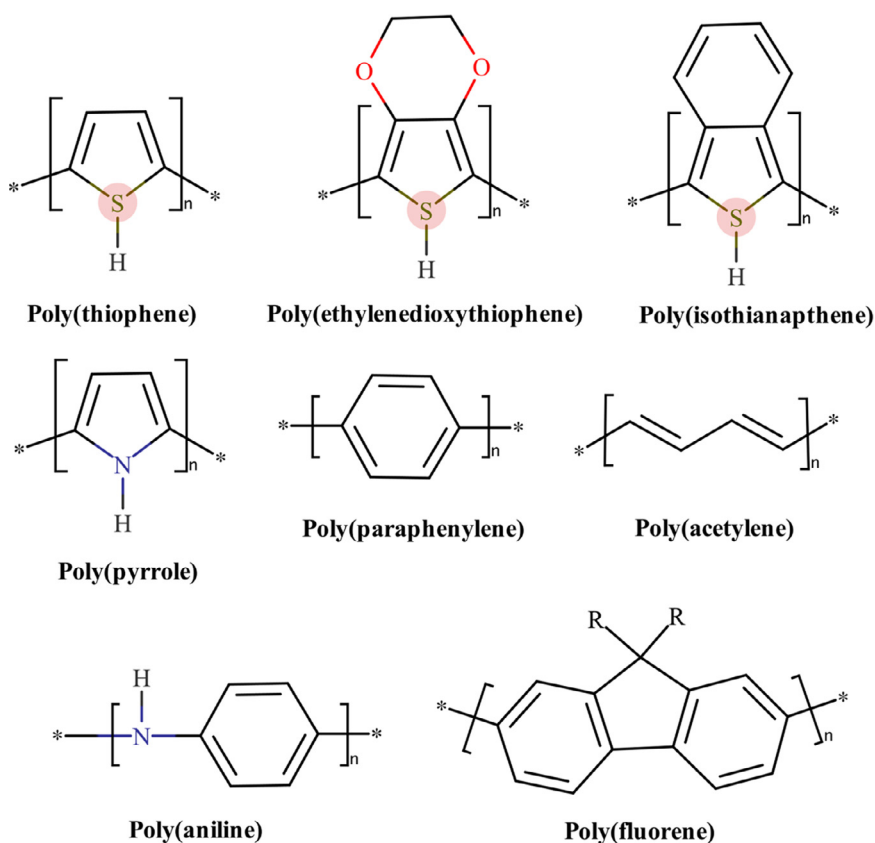


Fig. 1. Chemical structures of commonly used π -conjugated polymers.

biorecognition abilities competing with biological equivalents [29]. The history of MIP application of CPs is not too old and the field is still maiden for new studies because of variety of the conductive polymer and sensor designs. Ramanaviciene et al, the one of the early examples, reported caffeine imprinted PPy electrodes in 2006 [30]. Moreover, the intersection of CPs with MIPs is a growing field due to easy preparation of molecularly imprinted conductive polymers (MI-CPs) via electrochemical polymerization which allows to control film thickness on the electrode surface. Film thickness directly effects the kinetics, selectivity, and specificity of biorecognition process as well as determining the complexity / efficacy and drawbacks of template removal step [31]. Furthermore, the MI-CPs studies have been reported by using different monomers including pyrrole [32,33], phenyldiamine [34], aniline [35], aminothiophenol [36,37], aminophenyl boronic acid [38], aminophenol [39], and thiophene [40] and their copolymers and composites [41,42]. The sensor performances in terms of detection limit were very satisfying in the range of femto/micro-molar levels. Therefore, the researchers' interest in designing new CP-NIP based biosensors has gradually increased and some of these articles are discussed in this review.

Another prime application example of CPs is soft mechanical actuators for biomedical and applications. When immersed in an ionic solution, CPs can undergo dimensional changes in response to an electric charge, and consequently they are capable of transducing the electrochemical energy directly into mechanical work [6]. The latter can be converted into a variety of forms i.e. bending, linear or out of plane deformation according to the different device architectures [43–45]. Considering that they are lightweight, flexible, noiseless, low voltage driven and can present large deformations, they are very promising candidates in numerous actuators applications, including micromanipulation of living cells [46–48] and electromechanically responsive scaffolds for mechanotransduction [49].

In this review, we have highlighted in some various examples of promising research advances in the tailoring of the CPs functionalities and their application in three research fields: neural interfaces,

molecularly imprinted conducting polymers for biorecognition and bio-active scaffolds for mechanotransduction in living cells.

2. Electrically conducting polymers

A defining feature of conducting polymers is their conjugated backbone, consisting of alternating single (σ) and double (π) bonds (Fig. 1). This π -conjugated structure enables some degree of electron delocalization across molecular units and hence electronic conduction [50–54]. Generally, the electrical transport characteristics in conjugated polymers are obtained through the ease of electronic jumps between molecular chains. These electronic jumps occur thanks to the presence of dopant agents, which modify the electrons amount in the band gap. The doping process in analogous to conventional inorganic semiconductors, such as silicon, where large increases in electrical conductivity are observed when the material takes up very small quantities of certain chemical species. Doping conjugated polymers is completely different from doping classical semiconductor. The doping refers to the partial oxidation or reduction of the polymer, where a counter-ion is provided to maintain the electrical neutrality [55]. This may be accomplished chemically or electrochemically by the incorporation of cations or anions to balance the conjugated polymer charge through oxidation (p-doped) or reduction (n-doped). Doping levels in conducting polymers are much higher than classical semiconductors, where a significant fraction of the monomer units (in the range of 1/3–2/3) are often doped, corresponding to a doping concentration in the range of 10^{19} – 10^{21} cm^{-3} . Through the doping process, the charge added to the polymer (or removed) generates charged carriers that are mobile and can move along the conjugated polymeric chain by the rearrangement of the double and single bonds in the conjugated system. The movement of these charge carriers is the main mechanism for the conduction of electricity by the doped conjugated polymer.

In addition to electrical conductivity, organic conjugated polymers offer an inherent flexibility, since the bonding between adjacent atoms

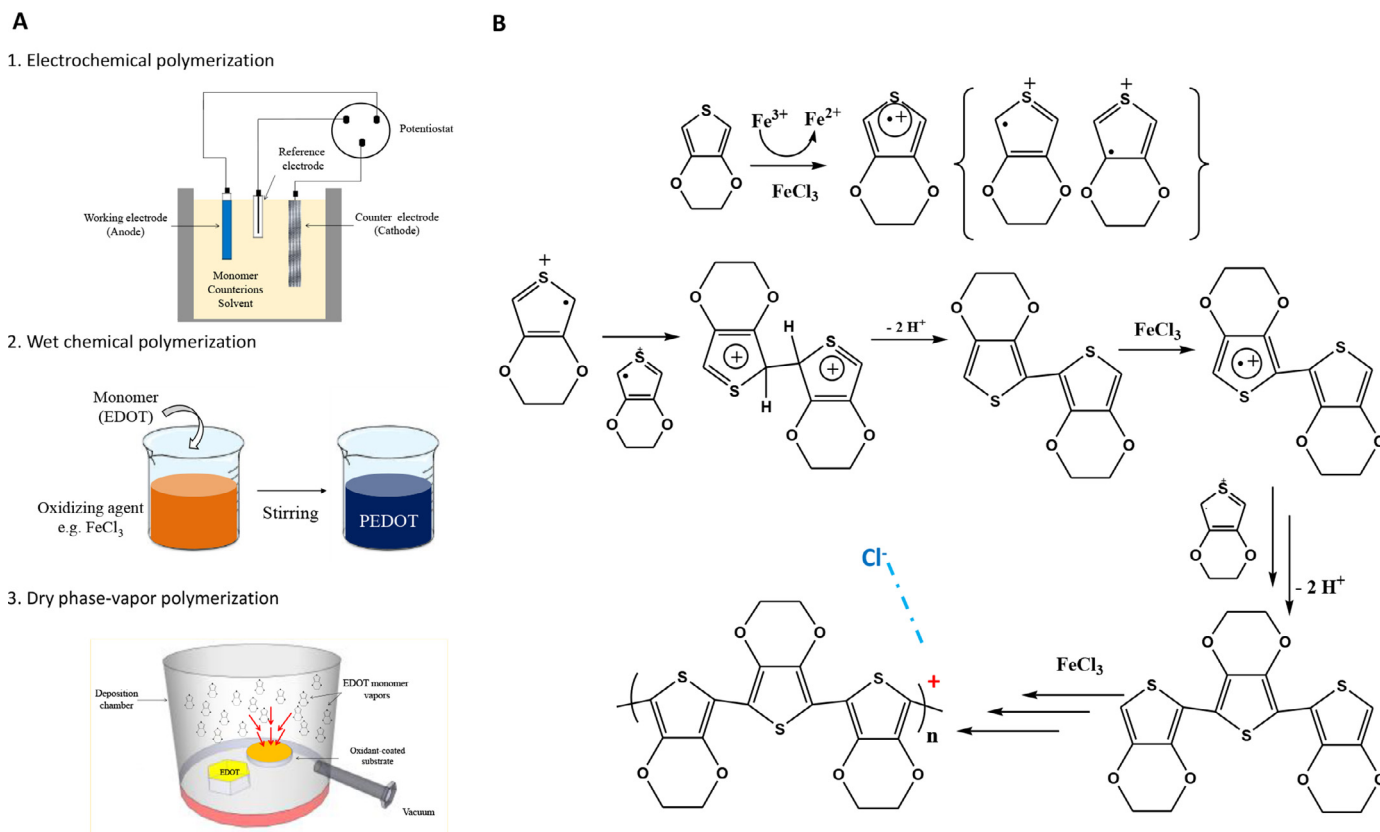


Fig. 2. Synthesis of conjugated polymers. (A) Various polymerization routes of CPs: (1) A three-electrode electrochemical polymerization cell, the solution typically consists of water, the monomer and the dopant, (2) Wet chemical oxidative polymerization and (3) Dry vapor phase polymerization. (B) The chemical oxidative reaction using the oxidative reagent FeCl_3 , resulting in PEDOT polymer where the dopant Cl^- is electrostatically bound to the polymer backbone.

is mostly governed by soft van-der Waals forces and aromatic π stacking interactions. In term of mechanical properties, this renders them similar to soft materials, when compared for example to traditional hard silicon material. The properties of CPs are strongly dependent on their synthesis conditions. To achieve a good charge transport, it is required that the conjugated nature of the monomer is conserved in the repeating unit during the polymerization process, which strongly limits both the choice of monomer and the choice of the deposition pathway. The polymerization of designated CP monomers can be carried out in many ways. However, the most widely used technique is the oxidative coupling involving the oxidation of monomers via chemical or electrochemical routes [56–59]. The various oxidative polymerization routes are presented below.

2.1. Electrochemical route

The simplicity, high selectivity and reproducibility have made electrochemical synthesis the preferred method to synthesize CPs (Fig. 2A) [60]. It has the advantage of producing the material on an electrode facilitating further analysis, and hence eliminating processability problems. Moreover, the electrochemical route has the advantage to allow a good control of the polymer thickness, morphology and degree of the polymer doping by mastering the synthesis parameters such as the quantity of charge injected during the deposition process [60]. The electropolymerization is usually achieved using a two- or three-electrode configuration through the electro-oxidation of a given monomer e.g. pyrrole or 3,4-ethylenedioxythiophene in a solution containing a supporting electrolyte (Fig. 2A). This may be an aqueous electrolyte, typically sodium polystyrene sulfonate (NaPSS) [61], an inert organic solvent, such as propylene carbonate with e.g. bis(trifluoromethane) sulfonimide lithium [60] or an ionic liquid e.g. 1-ethyl-3-methylimidazolium bis(trifluoromethanesulfonyl) amide (EMITFSI) [62]. CPs are

electrochemically synthesized on conducting substrates, such as gold, stainless steel, platinum, indium-tin oxide (ITO)-coated glass or more recently CP-coated textiles [11,63–65]. Applying a current (or a potential) over the working electrode leads to electro-oxidation of monomers and growth of a CP film on the surface of the electrode.

2.2. Chemical route

In some other applications, it is either impractical or undesirable to synthesize the polymer on a conducting surface. In these cases, CPs can often be synthesized using a chemical oxidative polymerization. In typical chemical synthesis, an oxidizing reagent such as iron(III) chloride is used in aqueous or non-aqueous solvents [66,67] to produce a polymer in the conducting form. The polymerization mechanism follows the reaction scheme shown in Fig. 2B. Distinct advantages of the chemical route over electrochemical synthesis are that there is no need for electrochemical instruments such as a potentiostat and that also non-conductive surfaces can be coated. Moreover, chemical polymerization is known to be a simple and fast method, recommended if large amounts of CPs are needed. However, it is difficult to get a direct control over the polymer deposition that results in a lack of accuracy and reproducibility.

An alternative chemical synthesis method is the so-called Vapor Phase Polymerization (VPP) technique. There is much interest in this method because it provides high control over CP film thickness, uniformity and density. Typically, the formation of CPs is carried out directly on the surface of the substrate in a two-step process. First, the oxidant such as iron tosylate is applied on the substrate using solvent coating processes and then the coated surface is exposed to a reactive CP monomer vapor (Fig. 2A). PEDOT films have been reported to have conductivities as high as approximately 3400 S/cm for a thickness of 60 nm, which is equivalent to commercially available indium tin oxide (ITO) [68]. The ability to fabricate CP thin films directly onto substrates

opened the opportunity to integrate them into practical bioelectronics devices [64,69,70].

2.3. Deposition route

CPs processing using commonly employed deposition methods such as spin-coating, solvent-casting or ink-jet printing is virtually impossible since these CPs are relatively insoluble in most solvents. Alternative synthetic routes have been proposed which involve the attachment of soluble functional groups to the polymer or doping with stabilizing polyelectrolytes [71–74]. An aqueous dispersion of PEDOT:PSS is commercially available under the brand names Baytron P or Clevios P [75]. In the aqueous colloidal dispersion solution, PEDOT:PSS tends to form micellar microstructures that consist of hydrophobic PEDOT-rich core and hydrophilic PSS-rich shell. The aqueous mixture of PEDOT:PSS has the advantage of easy processing through simple methods such as spin-coating, drop-casting or inkjet-printing [76,77].

3. Conducting polymers in recent bioelectronics applications

3.1. Neural recording and stimulation

Bioelectrodes are critical elements in numerous medical devices and are typically used for biopotential recording and electrical stimulation in the brain. The major requirement for chronic neural interfaces is the material and electrical stability of the electrode recording performance. While conventional noble metals such as Gold (Au) [78], Platinum (Pt) [79] or Iridium (Ir) [80] have a high conductivity and are corrosion resistant, they are today not suitable for small area electrodes due to their limitation regarding the mechanical, electrical and biological mismatches with the surrounding tissue [81–83].

For neural recording, the microelectrode should have a low impedance across frequencies of interest for electrophysiological recordings (10 Hz–10 kHz), while keeping a spatial footprint as small as possible to record the activity of small neuron population, down to individual neurons (action potentials). This is beneficial to increasing the signal-to-noise ratio (SNR) leading to an improved signal quality. The SNR is often far from ideal because of relatively noise levels, that arise from both multitude of background action potentials (neural noise) and the thermal noise (directly related to the microelectrode impedance values).

The impedance does contribute to the noise, and lower impedance electrodes are expected to have a high SNR during neural recordings.

For stimulation electrodes, charge-balanced current pulses are used for stimulation to avoid damage to electrodes and surrounding tissue. An ideal extracellular microelectrode should display a high storage capability to safely inject millisecond current pulse with current range in the μA thus decreasing both electrode polarization and heat generation during neural stimulation [84]. However, a decrease of electrode area results in low capacitance of the electrode/tissue interface. This inevitably leads to a low charge injection limit.

Electrodes coated with soft CPs provide an excellent foundation for developing next-generation neural recording and stimulating devices focused on improving charge storage capacity and reduction of electrode size [16,85,86]. CPs exhibits several distinctive characteristics including low impedance, high charge capacity, excellent plasticity and good biocompatibility [87–89]. Additionally, it can be facilyly micro and nano patterned into multiple shapes [90], modified by different doping agents [91–95] and regulated to inject both electronic and ionic charge [79] to both stimulate nerve tissue and record neuronal activity [12]. Through electrochemical deposition, CPs can be precisely localized on neural electrode sites with coating thicknesses down to the nanoscale (Fig. 3A) [96]. As compared to purely metallic electrodes, CP-coated electrodes provide a more adaptable interface to neural tissue, showing smaller hardness mismatch. CPs can also significantly decrease the impedance of microelectrodes (by about two orders of magnitude at 1 kHz) and increase the charge transfer capacity of microelectrodes by three orders of magnitude in comparison to bare metallic electrodes (Fig. 3B) [97, 98]. Cui et al reported the surface modification of micromachined neural electrodes by electrodeposition of PPy [99] and PEDOT [100]. Polystyrene sulfonate (PSS) was chosen here as the dopant material because of its stability and reported biocompatibility [101]. The impedances of the microelectrodes at 1 kHz were used for comparison purposes as neural action potentials have a characteristic frequency band centered at that frequency. The magnitude of the impedance of the PPy/PEDOT (PSS) coated electrode decreased with increasing thickness as the film roughens. This decrease in impedance was correlated to the increase in effective surface area. High quality neural signals were recorded acutely from cerebellum of guinea pig through the CP-modified electrodes [102]. Similarly Ludwig and his coworkers demonstrated a surfactant-templated PEDOT coating on the recording sites of standard Michigan probes and evaluated their *in vivo* efficiencies over a six-week period

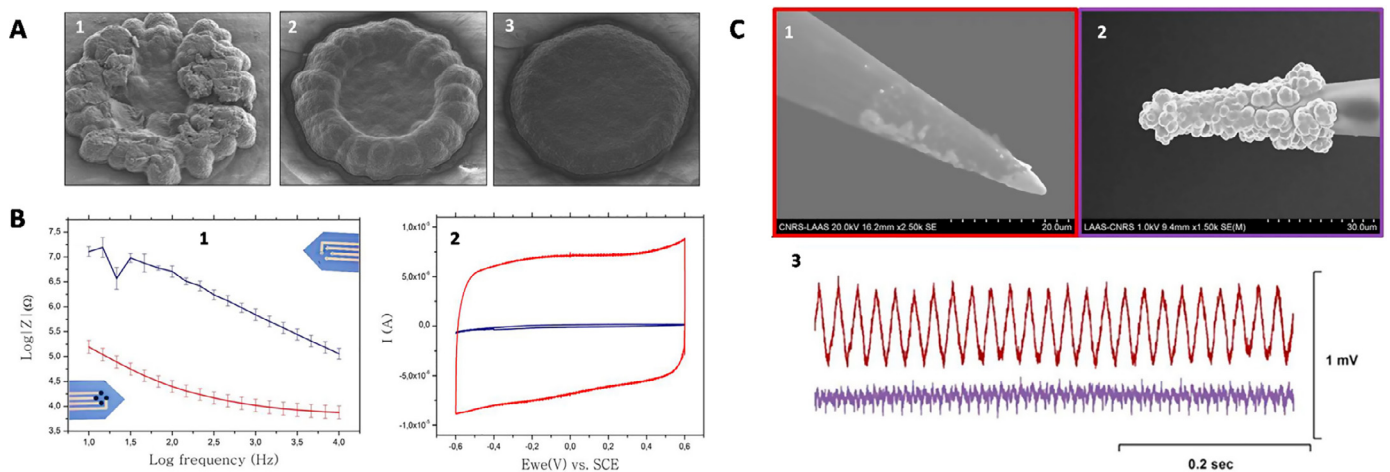


Fig. 3. Conductive polymers for neural interfaces. (A) SEM images of different morphologies of PEDOT:PSS layers related to different electrochemical deposition parameters. For 10 μm -diameter gold electrodes, the use of lower concentrations of monomer, lower upper vertex potentials and lower scan rates leads to a more homogeneous deposition. (B) Electrochemical characterization of parylene-based flexible neural microelectrodes with PEDOT coated surface. (A-1) Electrochemical mean impedance spectroscopy over a range of $10\text{--}10^4$ Hz and related error bar and (A-2) charge storage capacity for the gold electrode (blue) and for the PEDOT-modified electrode (red) for a 10 μm diameter electrode in a NaCl 0.9% solution (Reprinted with a permission from Ref [104]). (C) SEM images of commercially available microelectrodes (alphaOmega, FHC): (B-1) uncoated electrode, (B-2) PEDOT:PSS-coated electrode (B-2). (B-3) Electric hum recorded in a mouse brain slice maintained *in vitro* by using commercial microelectrodes and nano-structured microelectrodes (Reprinted with a permission from Ref [104]).

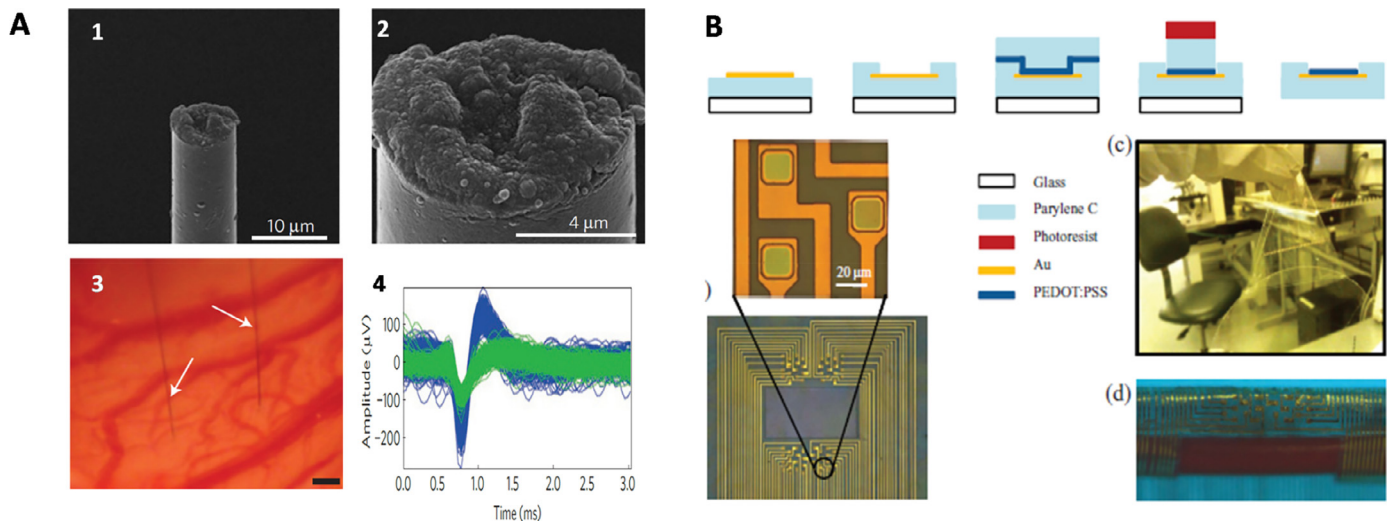


Fig. 4. (A) Ultrascale carbon fiber microthread electrodes. (A-1) and (A-2) SEM images of the ultrascale carbon fiber microelectrode ($\leq 7 \mu\text{m}$ in diameter) coated with PEDOT:PSS. (A-3) The microthread electrodes were implanted 1.6 mm deep into the cortex of adult male Sprague-Dawley rats. (A-4) Piled single-unit neural recordings over 3 min from a carbon fiber-coated PEDOT:PSS device (Reprinted with a permission from Ref [105]). (B) Conformable CP ECoG electrodes. Top: Schematic representation of the fabrication process indicating the cross-section of an electrode (not to scale). Down left: Microscopy images of the array showing the hole through which a silicon probe was inserted and a detailed view of three electrode. Down right: The electrode array is shown to support the weight of a quartz wafer (Reprinted with a permission from Ref [106]).

[103]. PEDOT sites were found to outperform control sites with respect to signal-to-noise ratio and number of viable unit potentials.

Beyond the superior electrochemical performances, the biocompatibility and the long-term reliability of the CP-coated electrodes pose critical challenges that must be improved to make these CP-based technologies viable for widespread use. The long-term stability of coated CPs can be improved by better integration with a substrate electrode. PEDOT:PSS was deposited on ultrascale carbon fiber microelectrodes ($\leq 7 \mu\text{m}$ in diameter) and have led to an improved performance in terms of *in vivo* single-neuron recording (Fig. 4A) [105]. Moreover, the coated fibers were found to elicit much reduced chronic reactive tissue responses in acute and early chronic experiments. More recent reports have shown promise as an alternative to conventional silicon-based devices. Coupling the favorable mechanical softness of biomaterials with a moderate degree of biocompatibility and CP-coating is meant to address both mechanical and electrical needs to ensure greater implant biostability. Khodagholy et al developed a photolithographic process to integrate the commercially available PEDOT:PSS with flexible Parylene C substrate, yielding highly conformable electrode arrays that were $4 \mu\text{m}$ thick (Fig. 4B) [106]. The authors demonstrated their use for *in vivo* electrocorticography (ECoG) in rats, in which sharp-wave events mimicking epileptic spikes were successfully recorded. The authors also reported that the arrays provide high spatial resolution and that PEDOT:PSS electrodes outperform the metallic gold ones of similar geometry. Lecomte et al conceived a Parylene C-based neural probe with PEDOT-nanostructured gold electrodes [104]. The material response to its biological environment was studied through *in vitro* soaking tests and *in vivo* wireless recordings in mice brain, both carried out for up to 6 months [107]. Impedance monitoring and SEM images indicate that over the length of this trial, none of the implants presented with apparent signs of material degradation.

PEDOT coating has proven to be very efficient in enhancing the neural electrode's performance by decreasing the electrical impedance and increasing the charge storage capabilities. However, in some cases, PEDOT-coated electrodes often have issues with delamination and mechanical stability, especially upon prolonged charge injection [108], mechanical deformation [109] or sterilization [92]. PEDOT can crack and delaminate from the substrate, resulting in decreased device performance and lifetime. Different adhesion strategies have been proposed in literature to provide a more reliable and stronger connection between

the metallic electrode and the CP by either modifying the monomer itself [110], using adhesion promoters such as nanostructured Pt or IrOx [111] or by laser roughening the metallic surface prior to CP deposition [92]. Even though the electrodeposited PEDOT films relying on these techniques survived the multiple stressing conditions such as ultrasonication (1 h in [110]), 10 000 cyclic voltammetry scans in [111] or accelerated ageing in 60°C PBS for more than 110 days without delamination [111], these types of stimulation conditions are not ideal to provide realistic stress conditions to the CP since typical neural stimulation is done by millisecond biphasic current pulses.

Charged carbonaceous nanomaterials such as carbon nanotubes CNTs [112], carbon nanofibers (CNFs) [113,114] or reduced graphene oxide [115] (rGO) have been used as well (as dopant) in conjunction with the conductive polymer PEDOT for the purpose of improving the electrochemical stability [116], charge storage delivery [112] and sensitivity of PEDOT electrodes for neural chemical sensing [117]. These improvements come from both bulk and surface properties of these carbonaceous, including large surface-to-volume ratio and specific surface area, better electrocatalytic activity, and fast electron transfer kinetics compared to the bulk polymers. The experimental techniques by which conducting polymers are mixed with other materials are well documented, and the readers can find excellent reviews about hybrid and composite materials based on conducting polymers [118–123].

Considerable effort has been also made to incorporate biologically active molecules into the CPs films in order to improve their long-term performance at the soft tissue interface of devices. For example, PEDOT interfaces doped with laminin peptides, hyaluronic acid, heparin, and fibrinogen were used to support cell attachment and to promote neurite growth [124–126]. A study from Green et al reported the electrochemical co-deposition of PEDOT together with anionically modified laminin [126]. It was found that large peptide dopants produced softer PEDOT films with improved cell adherence bioactivity. However, the incorporation of laminin peptides into PEDOT has reduced the polymer electrochemical stability and lowered adherence of the films. The larger dopant was shown to reduce the efficiency of electropolymerization process and consequently the PEDOT/laminin polymer had lower mechanical adherence. Covalent grafting has provided an alternative route to incorporate biologically active molecules to the CP surface. Bhagwat et al used a laminin-derived peptide to covalently modify the surface of carboxylic-acid-functionalized PEDOT films [125].

The possibility of incorporating bioactive agents in CPs has opened the door to the use of electrostimulation for local drug release with programmed profiles tuned by an appropriate applied current or voltage [127,128]. This approach has been used for the controlled release of various drugs such as anti-inflammatory, anti-cancer, antibiotics, growth factors, etc. [129]. For example, the controlled release of dexamethasone, an anti-inflammatory drug, has been demonstrated from PPy coated electrodes using cyclic voltammetry (CV) [130] and more recently from a conducting polymer hydrogel (PDMAAp/PEDOT) with different trigger signals [131].

3.2. Biorecognition / Biosensing based on molecularly imprinted CPs (MI-CPs)

Molecular imprinting is a kind of technology that allows researchers to create synthetic cavities having recognition ability that competes with its biological derivatives. Briefly, the fabrication of MIPs involves: *i*) complementary interactions between functional monomer and template via the non-covalent approach including hydrogen bonding, π - π interactions or weak Van der Waals forces, the covalent approach or the semi-covalent approach based on the covalent bonding of template to the monomer, and the removal of template by hydrolysis, or metal ion coordination approach, *ii*) functional monomer with substituent groups are polymerized with/without crosslinking agents in a porogenic solvent, and *iii*) the removal of template reveals the cavities bearing spatial and chemical recognition memory. These vacant cavities after removal step are responsible for selective and reversible rebinding of template [29] (Fig. 5). In this context, molecularly imprinted polymers (MIPs) are designated as plastic antibodies, plastics enzymes and/or plastic proteins in according to the kind of biomolecules used as template. As mentioned before, it is possible to develop synthetic recognizing elements with proper features such as high affinity, specificity, robustness, mechanical and thermal stability even at extreme pH and temperature, easy preparation, little storage requirements, long shelf life, low production cost and easy combination to various practical applications in biological analyses, food safety evaluation, and environmental monitoring, etc. [132–134]. Hereby, MIPs can be employed for various types of analytes from small molecules such as nucleic acids, drugs, food additives to much larger structures such as proteins, bacteriophages, viruses, and even whole cells [135–139]. The wide spectra of template molecules, the molecules-in-interest, make the MIPs an excellent and intriguing materials in bioanalytical methods as well as in (bio)-sensors, chromatography, solid phase extraction, catalysis, and drug delivery [140–146].

Although MIPs have been produced by many approaches, the most straightforward process includes polymerization *in situ* by photo- or thermally- induced radical polymerization of functional and cross-linking monomers with vinyl or acrylic groups [147]. However, the heterogeneity of binding sites which mainly determine sensing capability, may result in non-specific interactions and unexpected diffusional behavior due to the random nature of polymerization and have led to the use of other controllable polymerization strategies such as reversible addition fragmentation chain transfer (RAFT) [148–150], atom transfer radical polymerization (ATRP) [151,152], initiated chemical vapor deposition (iCVD) [153], and click-chemistry (for grafting) [154–156] to improve MIPs features. Composites bearing multi-organic/inorganic nano/micro-elements, ultrathin films, core shells and soft lithography for patterning have also been performed to improve the response quality and specificity. Also, a variety of MIPs-based sensing systems such as multi-analyte on single substrate arrays, microfluidic biochips, and lab-on-valve system were generated [29].

Molecular imprinting of small compounds (~200–1200 Da) has been pointed to be effective and commercially available. However, imprinting of biological macromolecules, such as proteins, enzymes, polypeptides and/or DNA represents still some challenges due to the inherent restrictions related to poor mass transfer and solubility, permanent entrapment, denaturation and heterogeneity in binding cavities affinity (conformational flexibility). Various 2D and 3D imprinting approaches including metal-coordination polymerization, epitope approach and surface imprinting have been proposed for the imprinting of biomacromolecules. The effective imprinting of biomacromolecules, especially proteins becomes attractive due to the improved stability, price efficiency and versatility, as it enables label free sensing of various biomarkers to be vital in medical diagnosis and bioenvironmental monitoring [157,158].

Molecularly imprinted conducting polymers (MI-CPs) exhibit also further opportunities through integrating the biorecognition properties of MIP with CPs owing to their biocompatibility and their unique optoelectrical properties on to the substrates (electrodes). They can simply be polymerized either chemically or electrochemically by a noble salt or a dopant to enhance conductivity, catalytic activity, and surface area [159–161]. CPs [157,161,162] including polypyrrole, polythiophene, polyaniline, poly-3,4-ethylenedioxythiophene, polyphenol, polyaminophenol, polyphenylenodiamine, poly(aniline boronic acid), polycarbazole and their derivatives due to the easily functionalization ability have been reported to assembly imprinted polymeric matrices of a wide range of low molecular weight substrates including amino acids, vitamins, pesticides, saccharides, hormones, etc. and biomacromolecules such as

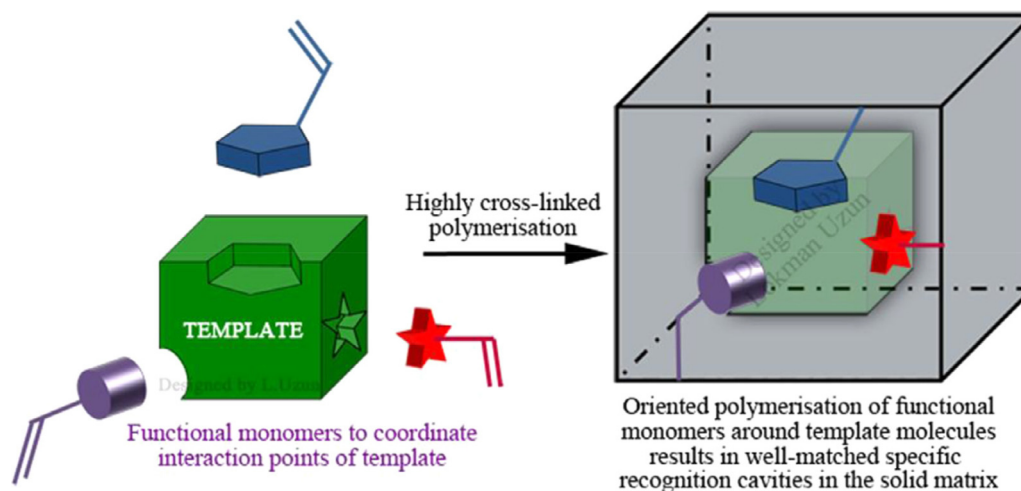
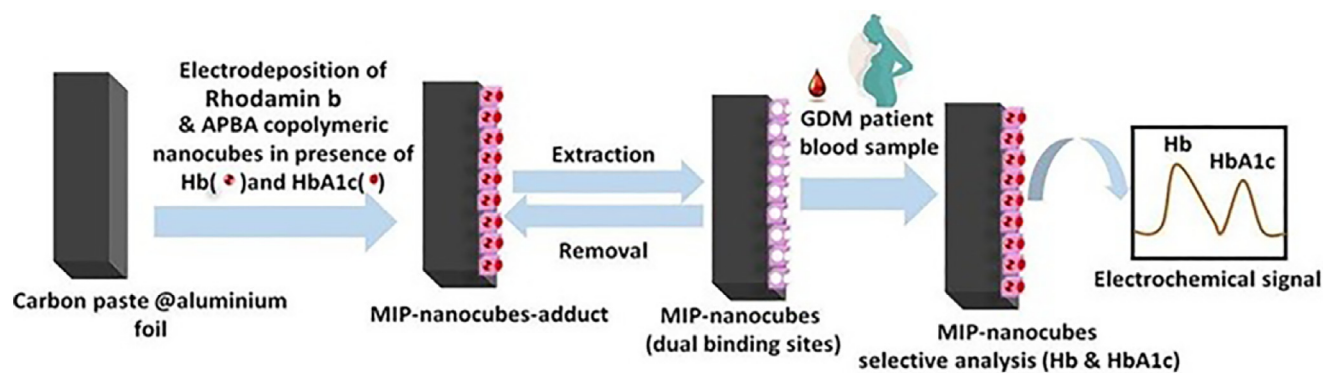


Fig. 5. Schematic illustration of molecular imprinting technique (Reprinted with a permission from Ref [29]).



Tentative imprinting and binding mechanism of Hb and HbA1c in electrosynthesized MIP nanocubes

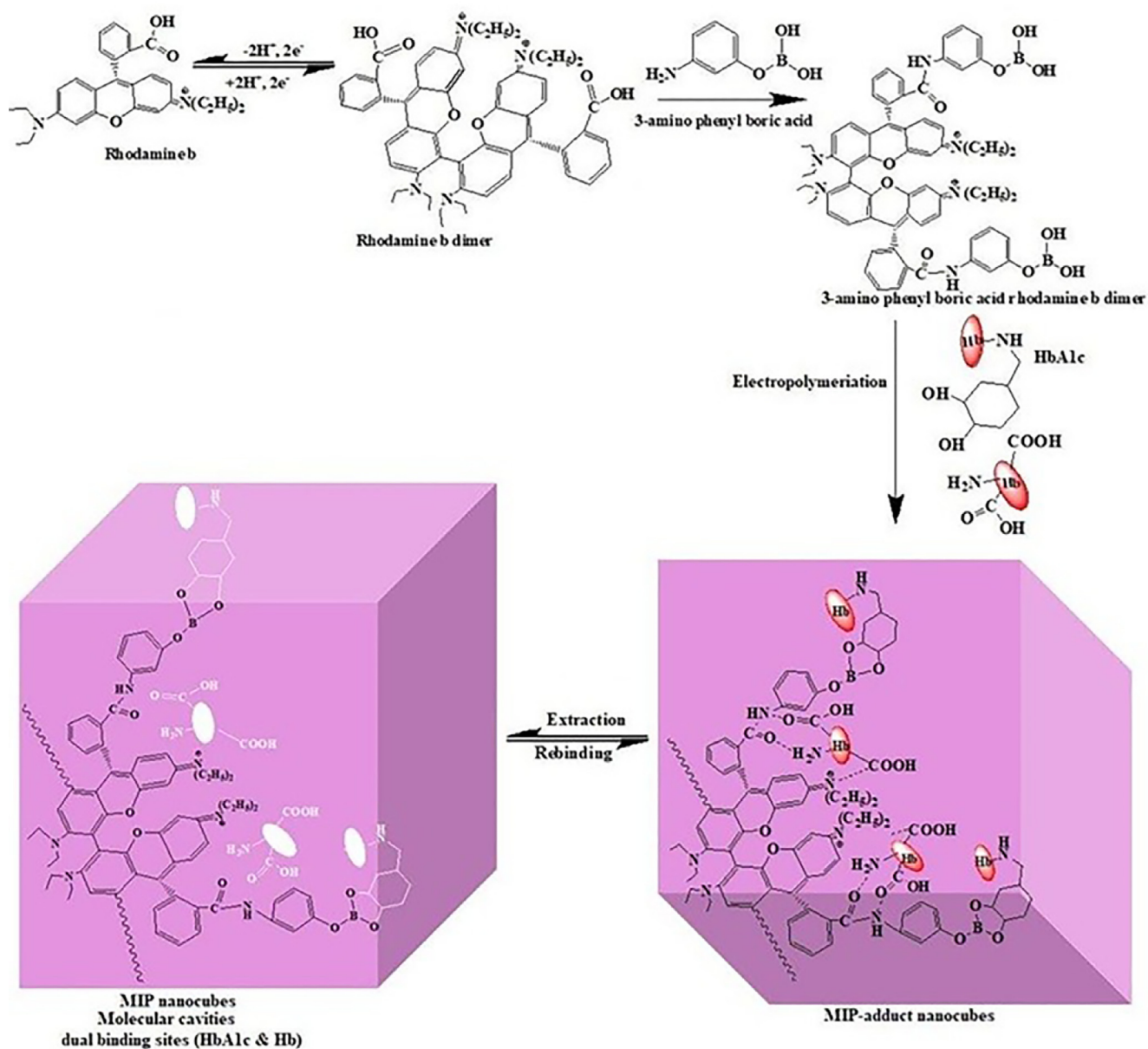


Fig. 6. Schematic synthesis illustration of dual imprinted nanocubes on the surface of carbon paste coated aluminum foil (Reprinted with the permission from Ref [170]).

bovine serum albumin, avidin, bovine hemoglobin, glycoprotein gp51 from bovine leukemia virus, and human cardiac troponin [161]. So, CPs have raised as alternative materials in many biological and biomedical applications, including biosensors and tissue engineering applications [163].

As aforementioned, MI-CPs can be synthesized by electrochemical polymerization conferring some advantages such as high reproducibility, operation in aqueous solutions, and controlling film thickness and morphology which have a crucial impact upon the sensitivity of MIPs. Besides, π - π interactions between the MI-CPs and templates allow to form more selective imprinted cavities, as π -electrons in the MI-CPs structure assure the stabilization of dispersive interactions between the template and the aromatic ring of the functional monomer [164]. The physicochemical properties of acrylic and vinylic imprinted polymers as recognition units limit also their use as electrochemical sensing systems due to the deficiency of electron conduction [165]. The incomplete template removal from MIPs based on acrylic or vinylic monomers leads to decrease the sensitivity as a result of intensive cross-linking, however, the template can be removed simply by overoxidation, when MI-CPs are utilized [166].

Various approaches have been used to generate thin layer of MI-CPs on electrode surfaces such as (i) electrochemical polymerization of an electroactive functional monomer, (ii) drop casting of prepolymer solution containing CP/CPs, (iii) formation of composite membranes bearing a conducting material (e.g., CNTs, quantum dots, graphene), MIP particles, and a binder (e.g., polyvinyl chloride, polyvinyl alcohol etc.), (iv) chemical copolymerization of a functional monomer and a template [165–168]. MI-CPs have also been fabricated in form of nanowire [169], nanocube [170], nanoparticles [171], and nanonecklaces [172]. Within this context, some of recent studies of MI-CPs employed as sensing elements are described in the following paragraphs.

Proteins are employed as biomarkers for disease status at elevated or depressed levels in serum, saliva or tissue [173]. The ratio of HbA1c in red blood cells is an important clinical biomarker in monitoring long-term glycemic control [174]. Dual templated molecularly imprinted nanocubes on the surface of carbon paste coated aluminum foil were synthesized by electrochemical co-deposition of 3-amino-phenyl boronic acid (APBA) in presence of rhodamine b to determine multiple diabetes biomarkers, glycated hemoglobin (HbA1c) and hemoglobin (Hb) in clinical samples (Fig. 6). The detection limits (LOD) of Hb and HbA1c were calculated as 0.08 and 0.09 ng/mL with a good reusability of 450 times [170]. Human cardiac troponin T (cTnT), a biomarker for diagnostic of

the acute myocardial infarction, imprinted polymeric nanofilm was formed by electropolymerization of pyrrole-3-carboxylic acid (COOH-3-Py) and pyrrole-2-carboxylic acid (COOH-2-Py) on the screen-printed electrode surface functionalized with reduced graphene oxide for analyzing of cTnT in serum samples. It was reported that the use of organic and CP improved the performance of designed sensing system with a low LOD of 0.006 ng/mL [135].

The amount of hormones, chemical messengers through the blood stream have been employed for the diagnosis of various diseases [146]. Progesterone imprinted copolymer using 3,4-ethylenedioxythiophene (EDOT) and hydroxymethyl (3,4-ethylenedioxythiophene) (EDOT-OH) monomer were synthesized to determine progesterone level in urine samples. Urine progesterone may be helpful to monitor corpus luteum function, fertility and endometrial development (Fig. 7). The selectivity was examined by using the competitive structures (the interferences) such as creatinine, testosterone and 17 β -estradiol and urea. LOD of CPs based imprinted sensor was less than 1.0 fg/mL [175]. In another work, several 2D (conductive) structures were used to improve sensing abilities of imprinted sensors. The surface of SPE was coated by the copolymer of aniline and methanolic acid in the presence of target molecule (17- β -estradiol, an estrogen steroid hormone) and tungsten disulfide (WS₂) of 2 μ m. LOD was calculated about 0.06 fg/mL which indicates that CPs can enable higher electrochemical responses than conventional (imprinting) approaches [176].

An ultrathin polymeric film of polyaniline ferrocene sulfonic acid on pencil graphite electrode for chiral detection of L-ascorbic acid in serum was synthesized by an electro-generated molecularly imprinted approach. The enantio-selective imprinted sensor provides the detection of biologically relevant level in micromolar range of ascorbic acid in serum without any possible interferences. The results indicate interferent free detection of L-ascorbic using MI-CPs with a LOD of 1.0 μ M and excellent stability for one week. Moreover, the electropolymerization of MIP film on the surface to the underlying electrode enables to control the film thickness which has a crucial effect on the response sensitivity of MIP [177]. A novel strategy was reported to generate imprinted nanocomposites bearing (PPy) and a new two-dimensional layered black phosphorene quantum dots (BPQDs) electro-deposited on the surface of conducting poly(3,4-ethylenedioxythiophene) nanorods (PEDOT-NRs) to determine vitamin C. BPQDs charged negatively and vitamin C were self-assembled on the surface of the PEDOT-NRs charged positively, then the functional monomer Py was self-assembled in the presence of vitamin C and BPQDs via hydrogen bonding (Fig. 8). The fabricated MI-

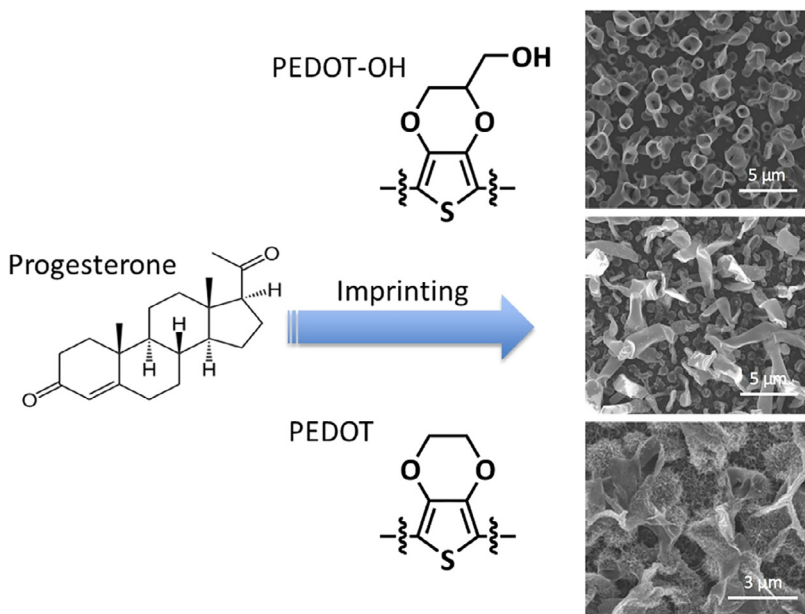


Fig. 7. The fabrication of progesterone-imprinted conductive poly (EDOT-co-EDOT-OH) coated electrodes (Reprinted with the permission from Ref. [174]).

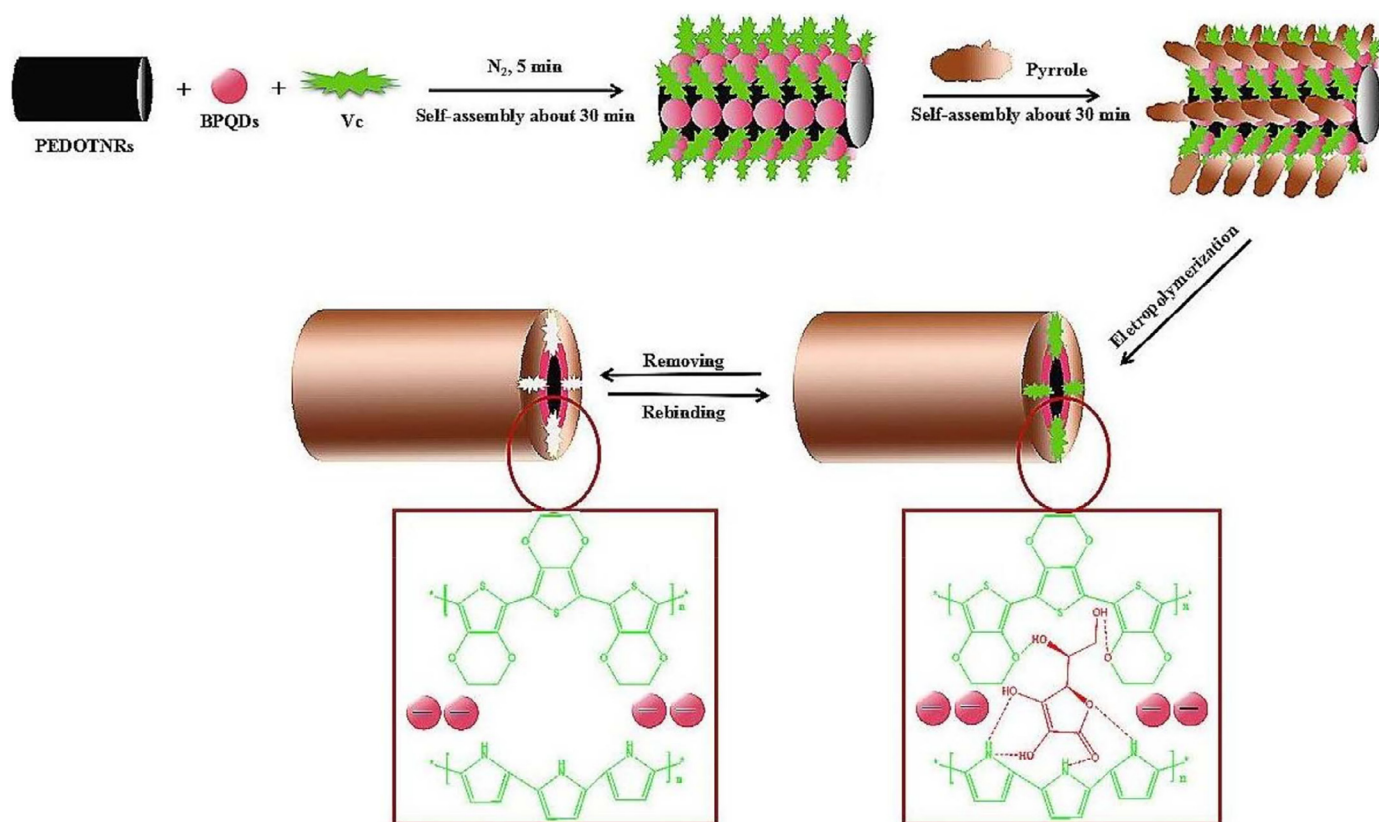


Fig. 8. Schematic illustration of the synthesis of PPy-BPQDs-MIPs/PEDOTNRs imprinted composites (Reprinted with the permission from Ref [167]).

Table 1
MIP based sensor using conducting polymers.

Template	Conducting Polymer	Analytical Technique	LOD	Ref.
Caffeine	Poly(3-thiophene acetic acid-co-3,4-ethylenedioxythiophene)	Colloidal mask-assisted electrochemical polymerization (Cyclic voltammetry (CV))	65.2, 31.6, and 53.8 ng/mL	[179]
Glucose	Poly(aniline)	Chemical oxidative polymerization	1.0048 mmol/L	[180]
Histamine	Poly(pyrrole)	Chemical polymerization	-	[181]
Taurine	Poly(3-thiophene acetic acid-co-3,4-ethylenedioxythiophene)	Electrochemical polymerization (CV)	10^{-2} mol/L	[182]
Melamine	Polyaniline/Polyacrylic acid	Electrochemical polymerization (CV)	0.0172 nmol/L	[159]
Bacteria	Polypyrrole	Electrochemical polymerization	-	[183]
Atrazine	Poly(3,4-ethylenedioxythiophene-co-thiophene-acetic acid)	Electrochemical polymerization (CV)	10^{-7} mol/L	[184]
Nitroaromatics	Poly(thiophene)	Electrochemical polymerization (CV)	10-100 mmol/L	[185]

CPs based sensor exhibited good reproducibility, long-term stability, and LOD of 3.3 μM for the detection of vitamin C in commercial drink soft samples [167].

New thiophene-carbazole derived functional and cross-linking monomers were used to determine the electroactive aripiprazole antipsychotic drug based on molecular imprinting approach. The conformational and chemical complementary between aripiprazole pre-polymerization complex with functional monomers were assessed theoretical calculations namely density functional theory (DFT), molecular mechanics (MM), and molecular dynamics (MD). The LOD was reported as 22 fM with an apparent imprinting factor around 4.95-folds. Moreover, the imprinting effect of the MI-CPs based sensor was examined by using glucose, urea, and creatinine as interferences. Furthermore, the results obtained with the extended-gate field-effect transistor (EG-FET) chemosensor were cross-validated with HPLC-MS. The proposed MI-CPs based sensor was highly selective to glucose, urea, and creatinine [178]. Other MI-CPs used as sensing elements were also reported to determine the amino acids, pesticides, saccharides, explosives, neurotransmitters, food additives, bacteria, etc. Some of these MI-CPs based sensing systems are summarized in Table 1.

3.3. Bioresponsive surfaces and tissue engineering scaffolds using conducting polymers

3.3.1. Mechanotransduction in living cells

Another prime application of conducting polymers is soft mechanical actuators. When immersed in an electrolytic solution, these materials can convert low voltage stimulations into volume or shape changes through reversible redox reactions [8,45]. The actuating principle of CPs such as PPy or PEDOT resembles that of natural muscles, being electrically controlled, wet, and soft. CPs undergo a volume change upon electrochemical oxidation or reduction by applying a low potential of ≤ 1 V. The volume change is predominantly caused by the insertion or ejection of ions and solvent into the polymer matrix. For PPy doped with large, immobile anions (A^-) in contact with an electrolyte containing both mobile cations X^+ and anions, the reaction is shown in Fig. 9. That is, cations X^+ are inserted when PPy is reduced and expelled when the polymer is oxidized in order to compensate for the charge imbalance. More simply the volume of the polymer expands in the reduced state, i.e. when a negative potential is applied and contracts in the oxidized state, i.e. when a positive potential is applied. Since the volume change is

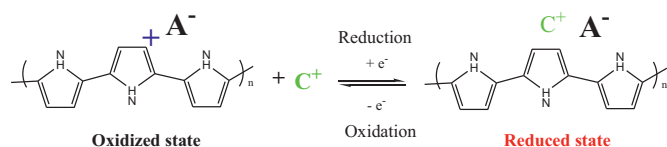


Fig. 9. Molecular mechanisms of volume variation in conducting polymers.

based on ion and solvent motion, the actuators need a (liquid) electrolyte in order to operate. This may be a salt solution, cell culture medium, or blood.

The bulk volume changes in CPs can be converted into a variety of forms and configurations: CPs actuators that use the bulk volume change, bending bilayer or trilayer architectures, where one side of which is made of CP while the other side is made of metal or plastic which has volume expanding variations (bilayer). In the bulk and bilayer actuators, typically an external electrolyte is used as the ion source. However, this restricts the actuators from operating in air. Therefore, trilayer actuators have been developed, where an electrolyte containing layer is sandwiched between two CP actuating layers, either as a three-layered actuator [186] or as an interpenetrating polymer actuator [66,187].

The large deformation and good biocompatibility of CPs makes them interesting in order to fabricate mechanical biomedical devices and their mechanical properties interesting to build electromechanically active tools that may interact safely with living systems. Recently, Svennersten et al produced PPy microactuators chips for the mechanical stimulation of single renal epithelial cells [46,188]. The chips were manufactured on silicon wafers using traditional microfabrication and photolithography techniques (Fig. 10A). The active unit of the chip consists of the conducting polymer PPy that expands upon the application of a low potential (1 V). The cells exhibited good adhesion and spread along the surface of the chip. The microactuators stretched the individual cells and the cellular responses were recorded using live fluorescent imaging as an increase in intracellular Ca^{2+} . This Ca^{2+} response here is caused by an autocrine ATP signaling pathway associated with mechanical stimulation of the cells (Fig. 10B) [47,48].

CPs actuators can be also used as an electromechanically scaffold materials for cardiac regeneration to provide both tight integrations and effective signal transductions with a tissue. For instance, a poly(lactic-

coglycolic acid) (PLGA) fibrous scaffold coated with PPy delivered electrical as well as mechanical stimulation to hiPSC derived CMs (Fig. 11A) [49]. This electroactive scaffold demonstrated an increased expression of cardiac markers for stimulated compared to unstimulated protocols. Similarly, E. Kerr-Phillips et al developed an electroactive elastomeric microfiber mats that show controllable pore size variation upon electrochemical oxidation and reduction processes in phosphate buffered saline solution (Fig. 11B) [189]. The material is comprised of a cross-linked nitrile butadiene rubber and the electrically conducting polymer PEDOT. Although experiments on living cells were not demonstrated, these mats are promising candidates for the development of electroactive 3D- scaffolds for mechanical-transduction studies of cells.

3.3.2. CPs in tissue engineering

Tissue engineering is one of the recent and promising research topics in biomedical application. In general, proper biomaterials, called as scaffold are employed to culture the cell in presence of biologically active components, i.e. growth factor, stock nutrient solutions etc. During differentiation and proliferation of cells on the scaffold, cell-lines/aggregates grow to form an immature tissue, basically. However, overgrowth of the cells results in the unwished cell-death inside of the aggregates due to limitation of the nutrients access into the cell clusters and onto the scaffold. Researchers suggest the use of external stimulants in order to overcome these problems; therefore, several stimuli-responsive materials including thermal-, electrical-, magnetical-, and pH-sensitive polymers have been developed in various configurations [127,190–195]. Indeed, the presence and absence of the stimuli controls / modulates the interaction between cell and scaffold surface. Thanks to electron conjugation and delocalization in the structure of CPs, they are the best fitted biomaterials in accordance to their mechano-transduction and actuation behaviors. In this context, CPs could be used as a scaffold material due to that tissue engineering requires smart and functional 3D-structures. CPs have generally low cytotoxicity, enables neuronal growth and tissue repair, provide localized electrical stimulus, electrical detection of live nerve cells as well as having ability for stimuli-responsive in situ/on site drug delivery properties [196].

Although PPy may exhibit poor mechanical properties because of its brittle backbone, different approaches reported to synthesize its composites to overcome this limitation. It is reported that the composite of PPy and PEDOT has proper biocompatibility and conductivity features in

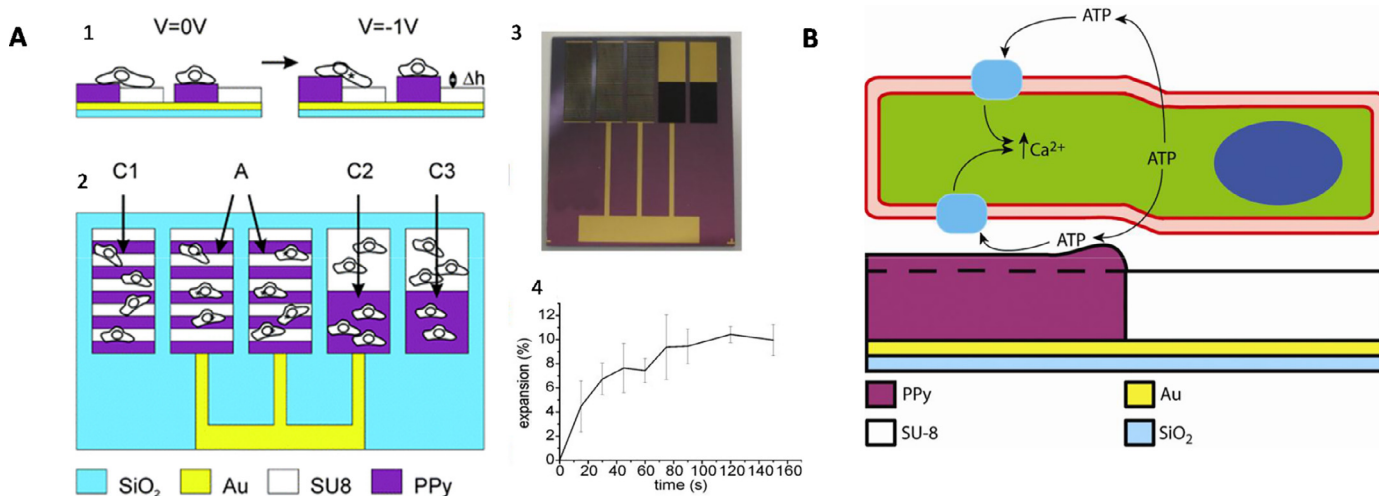


Fig. 10. (A) Mechanical stimulation of epithelial cells using PPy microactuators. (A-1) Schematic illustration of the principle of in vitro mechanical stimulation using PPy microactuators and (A-2) illustration of the chip layout used to build the mechanical stimulation chip. (A-3) photograph of the mechanostimulation chip, 20 mm by 25 mm in size and (A-4) Ex situ measurement of the expansion (%) of PPy microactuators in 0.1 M NaDBS, at $V = -1.0$ V vs Ag/AgCl and activated for 15s for each measurement point (Reprinted with a permission from Ref [46]). (B) Schematic illustration of the PPy expansion and resulting cellular Ca^{2+} response induced by autocrine ATP signaling (Reprinted with a permission from Ref [46]).

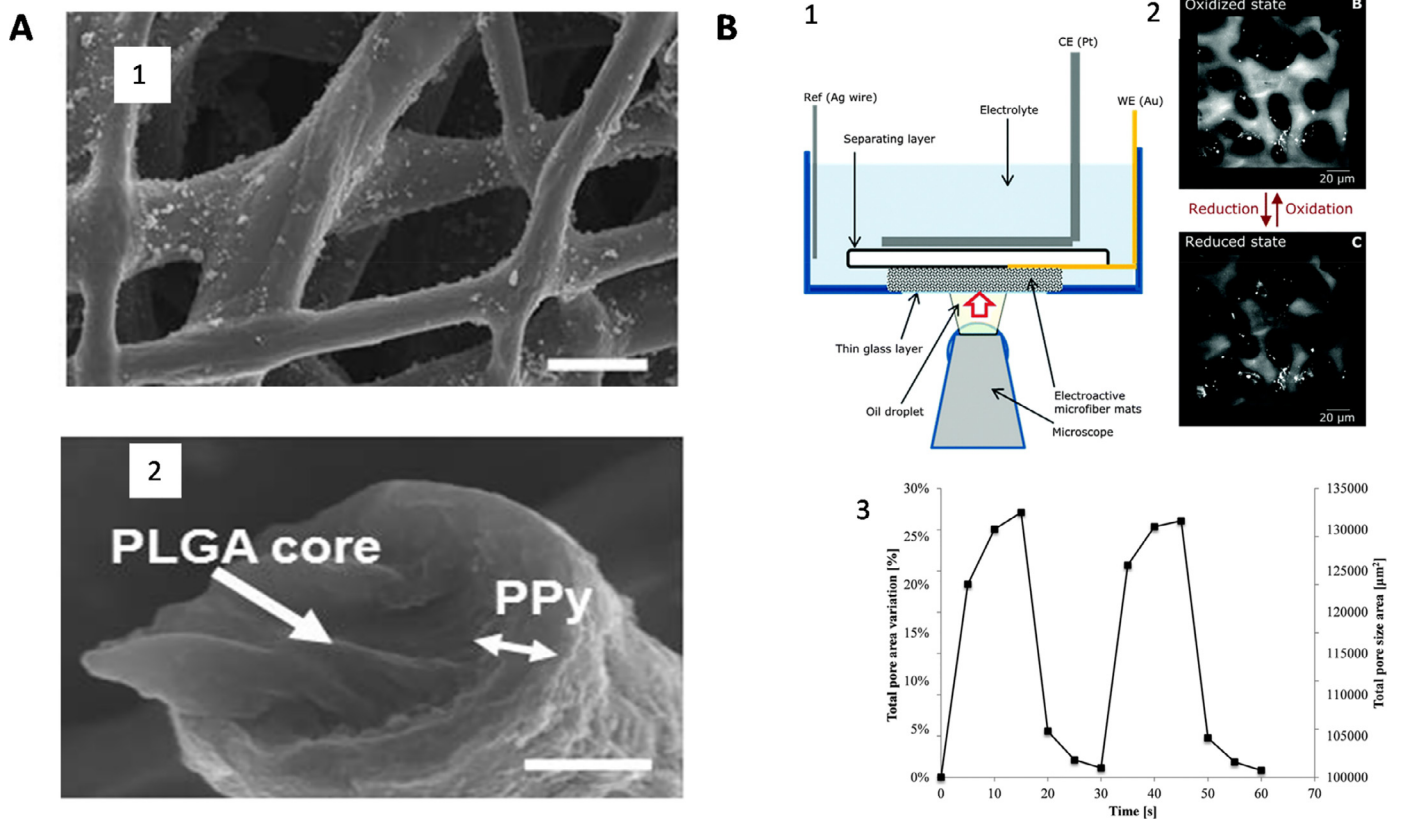


Fig. 11. (A) Electromechanically active scaffold for mechanical stimulation of stem cells. (A-1) The poly(lactic-co-glycolic acid) (PLGA) fiber scaffold coated with conductive polymer PPy (DBS) and (A-2) Cross-sectional view of PPy(DBS) fibre with PLGA core and PPy coating marked with arrows (Reprinted with a permission from Ref [49]). (B) Electrospun rubber fiber mats with electrochemically controllable pore sizes. (B-1) The actuation is characterized using confocal microscope setup with (B-2) the reflectance mode confocal microscopy images of the fibrous mats, for the oxidized and the reduced fiber mat. (B-3) Variation of the pore size changes (left axes) and total pore size area (right axes) over time upon 2 oxidation–reduction cycles (Reprinted with a permission from Ref [189]).

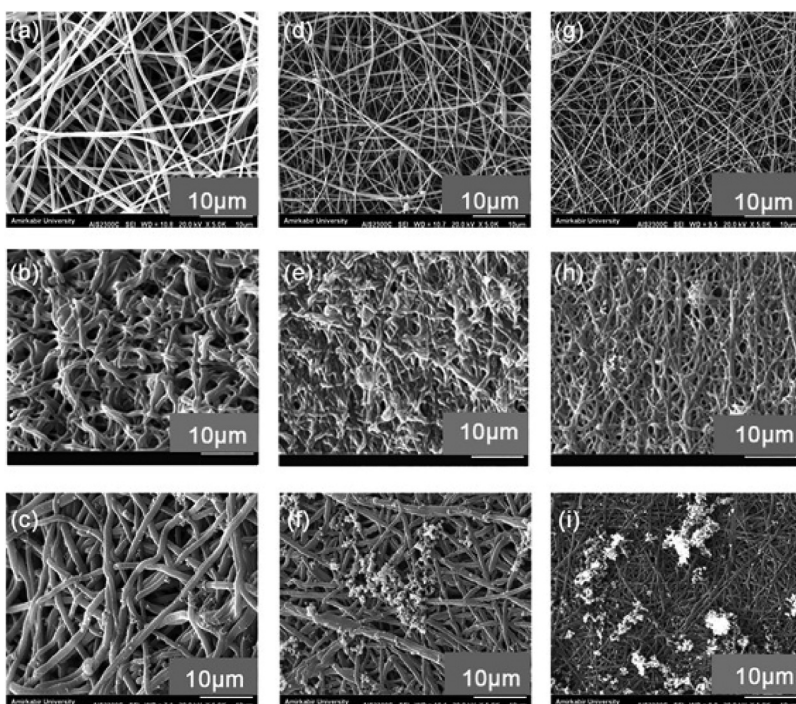


Fig. 12. Scanning electron micrographs ($\times 5,000$) of (a) PVA fibers, (d) 80% PVA–20% chitosan fibers, (g) 60% PVA–40% chitosan fibers. (b), (e), and (h) Micrographs of crosslinked fibers, and (c), (f), and (i) micrographs of polypyrrole-coated PVA, 80% PVA–20% chitosan, and 60% PVA–40% chitosan fibers. The presence of electroactive agent resulted in a larger fibers and created a new surface structure (Reprinted with a permission from Ref [191]).

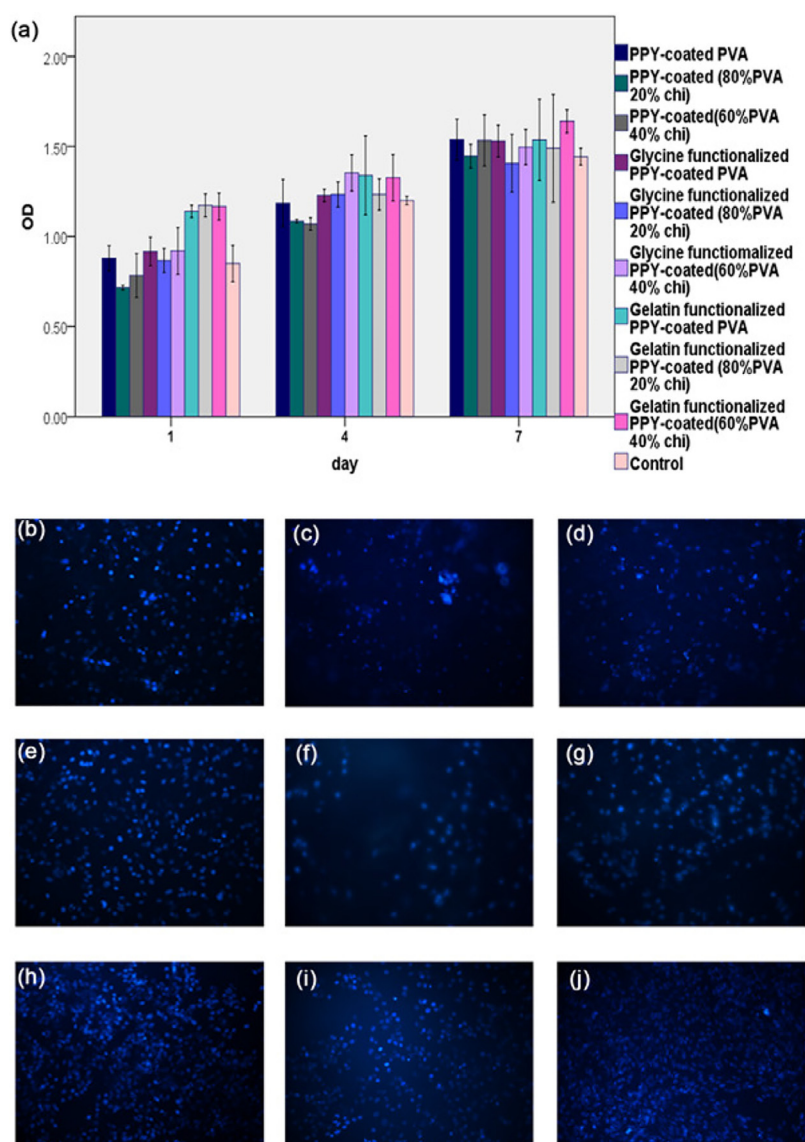


Fig. 13. (a) MTT results confirmed biocompatibility of polypyrrole-coated PVA, 80% PVA-20% chitosan, and 60% PVA-40% chitosan samples and gelatin and glycine-functionalized polypyrrole-coated PVA, 80% PVA-20% chitosan, and 60% PVA-40% chitosan scaffolds. DAPI PC12 nucleus staining images ($\times 10$). (b) Polypyrrole-coated PVA, (c) 80% PVA-20% chitosan, and (d) 60% PVA-40% chitosan. (e) Promoted PC12 attached cells on glycine-functionalized polypyrrole-coated PVA, (f) 80% PVA-20% chitosan, and (g) 60% PVA-40% chitosan scaffolds. (h) Accelerated PC12 cell adhesion on gelatin-functionalized polypyrrole-coated PVA, (i) 80% PVA-20% chitosan, and (j) 60% PVA-40% chitosan scaffolds. DAPI: 4',6-diamidino-2-phenylindole dihydrochloride; MTT: 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl tetrazolium bromide (Reprinted with a permission from Ref [191]).

nanotube structure for *in vitro* neural cell cultures [127]. Das and Prusty reported a composite 3D-structure by using blending natural polymers and CPs via electrospinning to form perfect porosity, high surface area, good biocompatibility and biodegradability [190]. Naghavi Alhosseini et al followed multistep polymerization strategy with PPY coated PVA/chitosan nanofibers for neurogeneration by using gelatin and glycine as interfacier to enhance cellular interactions [191]. They reported that electroactive coated layer resulted in nanofibers in a larger diameter meanwhile PPY completely covered the nanofiber surface and created a new morphology (Fig. 12). They used these nanofibers for evaluating accelerated proliferation of the PC12 nerve cells after determining cytotoxicity via MTT analyses (Fig. 13). According to DAPI nucleus staining images of nanofiber scaffolds a higher number of attached PC12 cells was observed on the gelatin-functionalized polypyrrole-coated samples [191]. Song et al reported a three-dimensional composite scaffold by using reduced-graphene oxide/polypyrrole/hydroxyapatite at room temperature for bone tissue engineering [192]. They showed that incorporation of hydroxyapatite into composite structure provides scaffold to enhance proliferation of MC3T3-E1 cells with 6.6 times upregulation at the 4th day with respect to the composite without hydroxyapatite as a control group. Alerget et al reported an attractive review article compiling key features of 3D-conductive scaffolds for biomedical applications

as they offer large surface areas for cell or biomaterial attachment, proliferation, biosensing and drug delivery applications [193].

Yang et al developed an electrically conductive hybrid hydrogels by forming a composite of PPY and alginate and used them for human mesenchymal stem cell (hMSC) culture [194]. They demonstrated that the conductive hybrid hydrogels could be employed as a smart interface to stimulate stem cell via the effects of electrical and mechanical signals and reported a promising scaffold for multifunctional neural tissue engineering (Fig. 14). They reported that the increase in Py and oxidant concentration changed color of hydrogels from brown to black and a clear solution obtained after PPY polymerization. In cell culture studies, the results figured out that conductive hybrid hydrogels well interacted with hMSCs because the hMSCs derived into larger and more elongated shapes when other substrates used. Moreover, Xu et al reported a conductive composite scaffold consisting of carboxymethyl chitosan (CMCS) and PEDOT for neural tissue engineering [195]. Herein, they utilized CMCS as a biodegradable element whereas PEDOT as a conductive polymer layer *in vitro* cell culture (neuron-like rat pheochromocytoma, PC12 cells) studies. Herein, the results revealed that composite hydrogels not only had no cytotoxicity, but also supported cell adhesion, viability and proliferation whereas the incorporation of conductive layers enhanced mechanical strength, conductivity and kept the biocompatibility.

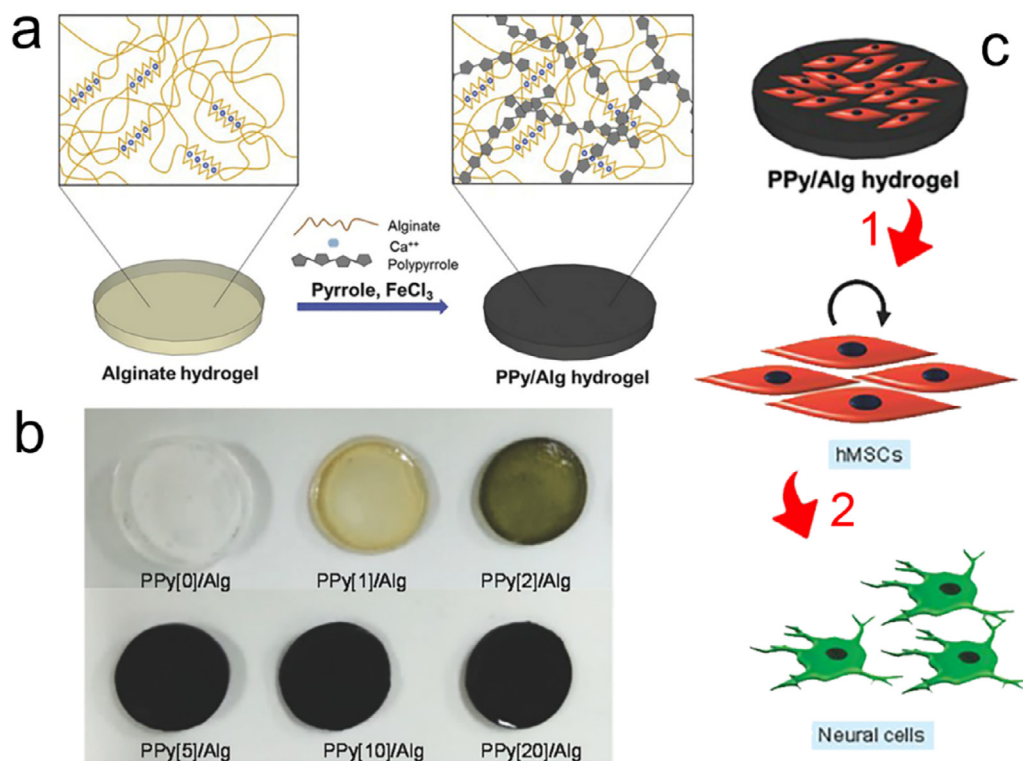


Fig. 14. a) Schematic of PPy/Alg hybrid hydrogels from alginate by chemical polymerization of PPy. b) Photographs of various PPy/Alg hydrogels synthesized with different pyrrole monomer and oxidant concentrations. c) Schematical representation of differentiation of human mesenchymal stem cell into neural cells (Reproduced with a permission from Ref [194]).

4. Conclusions and future aspects

Conducting polymers have attracted wide scientific attention owing to their unusual structure and properties, as well as commercial interest in bioelectronics and their biomedical applications. In this review, we have discussed recent research progress in the use of soft conducting polymers in biointerfacing and biorecognition applications, focusing on three specific research fields: neural interfaces, molecularly imprinted conducting polymers for biorecognition and bioactive scaffolds for mechanotransduction in living cells.

Concerning neural interfaces, coating metal electrodes with PEDOT has proven to be very efficient in enhancing the neural electrode's recording performance by decreasing the electrical impedance and increasing the charge storage capabilities. The recent developments of nanocomposites made of PEDOT with carbon nanomaterials are now enlarging the scope of applications towards the biodetection of neurotransmitters making neural probes multifunctional devices for stimulation, recording and biochemical sensing [113, 122, 197].

However, the long-term reliability and the moderate biocompatibility of conducting polymers still pose critical challenges that must be improved to make these CP-based technologies viable for widespread use for biomedical. The directions, such as functionalization of the conducting polymer itself and the use of biological complexness (for instance peptides), have in fact shown very promising results. This suggests that stability and biocompatibility issues will be successfully addressed for these materials, making this research field more exciting. Another critical issue is the low stretchability of conducting polymers. Their plasticization with common additives such as polyethylene glycol, dimethyl sulfoxide, zonyl, GOPS, etc. can lead to significant improvement of their mechanical properties reducing delamination and making them more suitable for flexible implantable and wearable sensors [198]. Electrical bioadhesive interfaces may also help to address the long-term challenges in the tissue-device integration. For example, the use of thin layer of graphene nanocomposite has recently been reported to improve

the tissue-device interface and increase the performance of bioelectronic devices [199]. The non-biodegradability of CPs is also a major concern for some biomedical applications. Various strategies have been explored to synthesize blends and composites of biodegradable and conducting polymers [200].

We also summarized the recent progress of preparing various molecularly imprinted conducting polymers (MI-CPs). Although common polymerization techniques were widely used for creating synthetic recognizing sites into polymeric network, researchers have been utilized recent popular polymerization techniques such as RAFT, ATRP, iCVD, and click-chemistry [148–156] to control the thickness of polymerization layer on the substrate surface for improving recognition capability and kinetics. Moreover, the utilization of organic/inorganic elements to synthesize composite MIPs is the one of recent approaches to enhance responsive performances of MIPs as well as multi-analyte on single substrate arrays, microfluidic biochips, and lab-on-valve system were attractive recent technologies in terms of MIP applications. The use of conductive monomers allowed to develop MIP-based networks by applying chemical and electrochemical routes as same as conductive polymer synthesis strategies except addition of template removal step via overoxidation. The combination of excellent opto-electronic features of CPs with intriguing selectivity and sensitivity of MIPs resulted in a synergetic feature for MI-CPs. Although there is still exponential increase in the numbers of papers in MIP literature, the numbers of papers including MI-CPs are still limited and be waiting for new researches as a virgin field.

CP-based actuator technology has been tremendous progress from concept to a plethora of devices in the field of electroactive polymers. The large deformation and good biocompatibility of conducting polymers make them interesting to fabricate soft actuating devices and their mechanical properties interesting to build electromechanically active tools that may interact safely with living systems. In particular, CP-based tissue scaffolds with biomimetic electrical, mechanical and topographical properties have been demonstrated, some of which have been

presented here. Without doubt, there is a great potential for the development of more complex CP-based tissue toward clinically relevant systems. We foresee the development of active scaffolds that can be used for growing any *in vitro* tissues that require chemical electrical and/or mechanical stimulation. Additional sensing capabilities such as pH, heat and drug-delivery capabilities may be useful as well to provide a more comprehensive guideline model on the condition of engineered tissues.

Most of the technologies presented in this review rely on wired electrical connections both for power delivery and signal acquisition. Indeed, seamlessly interconnected wireless devices need to be developed to ease their use in daily-life activities especially implantable and wearable devices with battery-free designs [201]. As a conclusion, we tried to demonstrate the recent progress in conducting polymers after introducing fundamentals of CPs and MIPs. Herein, we focused our attention on compiling promising and novel applications of CPs in terms of smart biointerface, artificial biorecognition and tissue engineering. We hope this review would be helpful for researchers who are interesting in conducting polymers and molecular imprinting as well as inspiring them to generate innovative ideas for further studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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