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Conducting Polymers in Biological Systems

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Abstract

Conducting polymers (CPs) were first fabricated in the 70s of XX century as a novel generation of organic materials that have both electrical and optical properties similar to those of metals and inorganic semiconductors. The fact that several tissues are responsive to electrical fields and stimuli has made CPs attractive for a number of biological and medical applications. This review provides information on desirable CP properties specific to biomedical applications and how CPs have been optimized to generate these properties. The manuscript first introduces different types of CPs, their unique properties and their synthesis. Then specific information is provided on their modification for use in applications such as biosensors, medical engineering, and also neural probes.

Keywords: Organic electronics; Conducting polymers; Biocompatibility; Electrodes; Drug delivery devices

Introduction

Electronics [1,2] based on π-conjugated organic polymers and molecules have been extensively explored during the last years. The significant interest in the development of organic electronics results in part from the fact that this technology offers new or improved electroactive and opto-electronic features as compared to the inorganic counterparts. The organic electronic materials may be flexible [3] and can be also fabricated using printing devices [4,5]. Other characteristics that make organic electronic materials promising as the active material in bioelectronics include:

a) Functionality which can easily be defined at the materials level, giving that chemical biosignals can be translated into electronics signatures or signals within the material itself.

b) In the thin-layer state organic electronic materials are often transparent, which permits optical transmission imaging and use of various microscopy-based techniques when analyzing biological specimens interacting with the tool

c) Organic electronic materials are soft and can be (self-) organized to mimic biological structures

d) Organic conjugated materials conduct electrons as well as ions

e) Organic conjugated materials can be equipped with (bio-) molecular side-groups to promote cell viability [6].

The use of conjugated polymers as interfaces to biological systems dates back to first work on redox enzymes [7,8]. In the 1980's Bull et al. [9] reported that a common catalyst could be incorporated into polypyrrole (PPy) film during electropolymerization.

Next, Umana and Waller [10] suggested that the same procedure could be applied using the enzyme glucose oxidase (GOx). The main idea here was to apply the electronic conductivity and malleability of polymers as a means to wire redox enzymes. GOx was introduced to the system as the counter ion inside PPy, electrochemically created from a solution of glucose oxidase, and electrical connection between the PPy matrix and the enzyme was established, to permit measurements of glucose concentration in a solution. It was induced that there was no adverse effect on the enzyme activity by the process, and that GOx was really entrapped in the formed material. Lifetime of the activity of the obtained system seemed to be directed by gradual leaking of oxidase rather than enzyme denaturation.

Effective introduction of biological molecules was then widely reported, and some matutinal examples are adenosine triphosphate (ATP) [11], human serum albumin (HSA) [12], heparin [13], anti-HAS [14] and urease [15]. The field of biosensors and analytical tools using conjugated polymers has sustained a serious development during recent years [16].

Development of conjugated polymers for the purpose of recording and inducing signals in the neural systems in humans may be utilized to form the interfaces between the two signaling structures of electronics and neural systems. Artificial communication with the nervous system is the goal for a nature of medical tools in the field of neuroprosthetics. Currently artificial hearing tools may be bought off the shelf in the shape of cochlear implants, and research is carried out on brain machine interfaces and artificial vision. Even though this development in the field of neuroprosthetic therapy as well as into more fields of medicine is observed, there are still a number of weaknesses in current neuroprosthetic technology that confuses this evolution. The significant part is the implanted electrode, translating signals between the electronic form in leads and ionic signals in tissue.

This transition engages electrochemical processes which should be controlled not to be detrimental either to the electrode itself or to the tissue. Moreover, in the deficiency of a tough anatomical element where the electrodes can be implanted, soft nervous tissue generally has to be in close contact with the surface of electrode for the signal transition to be feasible.

As an advantage it was demonstrated that the polymer could act as a reservoir of charge allowing more efficient stimulation from miniaturized electrodes [17]. Further investigations of CPs relative to neural interfaces are presented in coming sections.

Conducting Polymers for Improved Neuron Contact

The source of conducting polymers' conductivity

Conductive polymers (CPs) can conduct charge due to the ease with which electrons move between the chains of the polymer [18]. The conductivity in real grows from a combination of a number of

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parameters. The polymers possess a conjugated backbone, that it is formed by a series of alternating single and double bonds [19]. Single and double bonds both contain a chemically strong, localized σ-bond, while double bonds also contain a less strongly localized π-bond [20]. The π-orbitals in the row of π-bonds overlap each other, permitting the electrons to be more delocalized and move loosely between the atoms [18,19]. The final key to the conductivity of these polymers is the dopant [20]. The polymer is synthesized in its oxidized, conducting condition, and only in the presence of the dopant is the backbone stabilized and the charge neutralized [21]. The dopant establishes a charge carrier into the system by removing or adding electrons from/to the polymer chain and relocalizing them as polaronsor/bipolarons [18]. When 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 permitting charge to be passed through a polymer in the form of the above-mentioned polarons and bipolarons [18].

Conductivity in polypyrrole (PPy) specifically is due to p-type (bipolaron) conduction, the inter-chain moving of electrons and the motion of anions or cations within the material [22]. PPy can possess a conductivity of up to 7.5×10^3 S cm^{-1} [19]. The exact value depends on the charge transfer to adjacent molecules, the polaron, the chain and the conjugation length, and may be controlled by using different types and quantities of dopants [23]. The primary factor that limits the conductivity of PPy is the "disorder" (i.e., the defect sites) in the PPy backbone [22]. 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 [24]. Emaraldine base polyaniline (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} [25]. The growth of conductivity between the base and salt forms may be explained by the polymer's molecular structure [26]. In its primary level the polymer chains are coiled, while in its salt form the additional positive charges in the polymer repel each other extending the chains (Figure 1) [26]. In its extended coil form electrons are convenient to delocalize, this resulting in an increasing of conductivity [26].

Biocompatibility aspects on conducting polymers

During fabricating materials that will become integrated with biological systems, it is of great importance to validate the materials' biocompatibility. The suitability of the materials differs vastly, depending on the synthesis route of the bioorganic materials as well as on the overall nature of the conjugated polymers, i.e., its chemical composition, surface charges, or acidity. As a consequence of the chosen material and route of synthesis, the polymer film may contain residuals such as monomers, detergents, solvents, or excessive doping ions. If these components seep out from the film during the course of an experiment, which often takes several days, they can be toxic for cells. Another parameter that affects the interaction between a cell and the surface is the surface topography, which can range from a few nanometers to the micrometer level [27].

The crucial property of polymers is that they can be tailored mechanically, chemically and biochemically to suit a specific application. Biomolecules can be attached to the polymer chains or mixed in during synthesis to form biomolecule/polymer composites. Mechanical parameters may be engineered to anything from stiff and hard films to polymer gels, either biodegradable or aimed to be long term stable. It is feasible to generate polymer electrodes with mechanical properties similar to those of actual cells and it is hypothesized that such soft electrode coatings would behave as mechanical buffering between stiff probes and soft tissue [28]. Moreover, an electrode coating permitting close integration between tissue and implant can lower the strain resulting from micromotion [29]. Additionally, architecture of the polymer surface can be altered. It has also been suggested that similarities between the chemical structure of PPy and naturally occurring hemoproteins and pigments like melanin give promise for future biocompatibility of conjugated polymers.

CPs give the opportunity to create electrode materials mechanically and chemically more similar to neural tissue than metals or silicon, which indicates that they might also stand better chance to stably interface with neurons. Biological tests *in vitro* and *in vivo* are crucial parts of biomaterial development. It has been presented by many that essential cell types can be cultured on top of poly(ethylenedioxythiophene) (PEDOT) and PPy films.

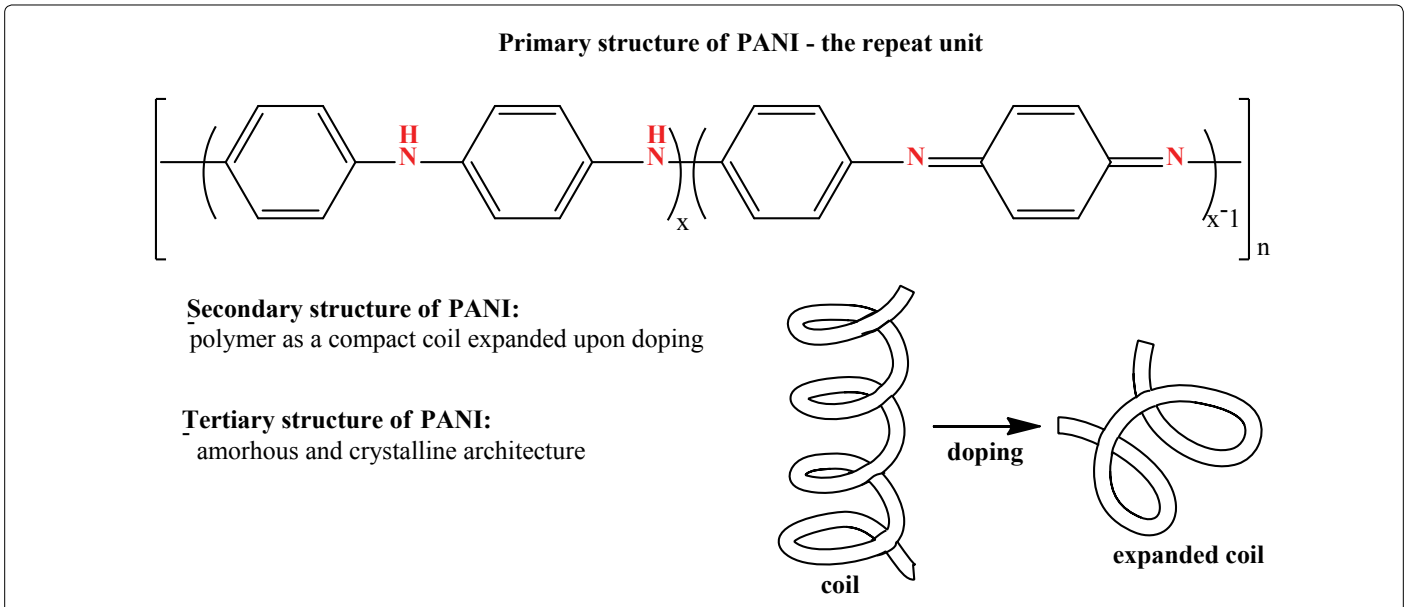

Figure 1: Polyaniline PANI.

Williams et al. [30] found that PPy inflicted minimal tissue response *in situ*. Schmidt et al. [31] investigated inflammatory tissue response to PPy upon intramuscular or subcutaneous implantation and found that inflammation was less severe compared to the response inflicted by poly(*L*-lactic acid). Collier et al. [32] implanted PPy subcutaneously in rats and found no significant long-term inflammation after few weeks. Wang et al. [33] investigated systemic toxicity of PPy through a battery of tests addressing acute and subacute toxicity, cytotoxicity, pyretogenesis, hemolysis, allergic reactions and a mutagenesis test. All according to standard procedures described in ISO 10993 and ASTM F41748-82. All found results pointed out biocompatibility of PPy in all these aspects. The most common cell line model system to evaluate neuron compatibility of these polymers has been the PC12 neuroendocrine tumor cell line, and many publications have confirmed attachment, viability and neurite extension of PC12 cells on different PPy surfaces.

The biological response to PEDOT is rather not as extensively studied as PPy. A couple of studies describe biocompatibility of PEDOT *in vivo*. Luo et al. [34] implanted PEDOT subcutaneously in mice and reported no inflammatory response after 1 week of implantation and only thin layers of tissue capsule after 28 days of implantation. Asplund et al. [35] evaluated tissue reaction to PEDOT coated platinum pieces in rodent cortex. Several studies do, however, report cell cultures on top of various types of PEDOT films i.e., PC12 cells, fibroblasts, endothelial cells, neuroblastoma cells, glial cells and a cortical neuron cell line. Details can be found in Table 1.

No statistically significant differences on cell adhesion and viability were observed when comparing cells cultivated on thin films of PEDOT-PSS versus glass slides. The same results were obtained irrespective of whether cells interacted with the neutral state of PEDOT or the oxidized state, which had been biased by a voltage bias of 1 V versus a second PEDOT-PSS counter-electrode. A panel of cell lines were tested, including the epithelial cell lines HeLa (ATCC CCL-2) and T24 (ATCC CRL-10742), the endothelial cell line BCE-hTERT+, fibroblasts (TGR1), macrophage-like cells THP-1 (ATCC TIB-202), T cells and neuronal cells HCN-2 (ATCC HTB-4) [25]. In addition, primary neuronal cells also grow successfully on PEDOT-PSS. Biocompatibility with such a broad range of organospecific cell types implies that PEDOT-PSS is a prime candidate for manufactured polymer-based bio-electronic devices to be used in medical applications related to, for example, mucosa biology, vascular and angiogenic research and immunology as well as neurobiology.

The structure along a surface as well as inside a scaffold also predicts biocompatibility to a great extent. Historically, the aim when designing structures has been to match that of the final tissue or organ. During the last decades, careful design of nanopatterns has yielded surfaces that define the organization of different biomolecules and that instruct their behavior [9].

Incorporation of biomolecules at electropolymerization

Cellular interaction with the electrode material is of considerable significance for the success of the neural interface. This material preferably should be bioactive and encourage cells to grow close to, or even into the material. The discovery that biological catalysts, incorporated as counterions in PPy, retained their biological activity, opened up for a range of biomedical applications employing this technique to generate biofunctional variants of the conducting species. This procedure has proved its significance for the field of neural interfaces over the last years. There are dual motives why introduction of bioactive element in the electrode material is important for the neural interface. At first, it contains a way to immobilize molecules on the surface of the electrode that may i.e., encourage attachment of neurons and discourage adverse immunological response. Second, the introduced molecule can either passively escape from the material or actively be released by electrochemical activation enabling controlled delivery from the polymer bulk.

Several studies connecting introduction of biomolecules in PPy to provide a biocompatible and biofunctional electrode surface for the cells have followed. Stauffer and Cui [36] reported developments connected with laminin fragments incorporated in PPy. Neuron growth and neurite extension were significantly enhanced for primary cells cultured on the PPy-peptide coatings compared to PPy-PSS coatings. Moreover, there was less astrocytic adhesion on PPy generally, compared to Au surfaces. I was an advantage of the PPy surface. Kim et al. [37] used neural growth factor (NGF) and collagen as a co-dopant in the polymerization of PPy. Films containing NGF induced distinction of PC12 cells in culture pointing on conserved bioactivity of NGF and that incorporated NGF was accessible to cells. Cells adhered rather well to the PEDOT-PBS-collagen films but not to PEDOT-PBS controls. It was clearly taken as a signal of successful collagen introduction. Park et al. [38] deposited PPy with heparin entrapped from aqueous solution containing only pyrrole and heparin salt. The formed material was tested with PC12 cell line. It was found, that stimulation through the PPy-heparin coating encouraged distinction of cells further.

A number of publications reported introduction of biological molecules in PEDOT for neuroprosthetic use. However, many also present the need for concomitant dopants or solvents to be introduced for EDOT polymerization to be favorable. A similar study to the work presented by Cui et al. [39] utilizing the peptide sequence (DCDPGYIGSR) paired with PEDOT. They compared physical and biological features of the polymer-peptide with bare platinum and conventional PEDOT-*p*-toluene sulfonate (PEDOT-*p*TS). Although cell attachment (PC12) was improved by all the polymer coatings, an unexpected finding was that cell attachment on PEDOT-*p*TS was superior to the polymer-peptide coatings. Compared to this, neurite extension was enhanced by the polymer-peptides. Also Xiao et al. [40] reported incorporation of adenosine 50-triphosphate (ATP) into PEDOT from aqueous solution. ATP release from the layer to solution was confirmed for the first two days where after it reduced.

Functionalization for a specific application

Optimizing the material features (roughness, porosity, hydrophobicity, conductivity, degradibility) of conductive polymers and the binding of biological molecules (that makes conductive

Study	Type of the cell	References
Pheochromocytoma cells	PC12	[7]
Fibroblasts	NIH3T3	[34]
Cortical neuron cell line	HNC2	[7]
Neuroblastoma cells	SH-SY5Y	[35]
Hepatocarcinoma cells	HepG2	[34]

Table 1: Cell cultures on PEDOT surfaces.

polymers advantageous for medical applications) may be done by four major chemical ways (Figure 2) [41]:

Adsorption: Due to this technique, a solution of the functionalizing agent is placed in contact with the polymer after it has already been synthesized. The biomolecule is y absorbed according the static interactions between the polymer and the charge of the molecule [42].

Entrapping the molecule into the polymer: The procedure of this is due to mixing the functionalizing molecule with the monomer of the polymer, the dopant and the solvent prior to synthesis [16]. By electrochemical polymerization, the molecules of the functionalizing element in the environs of the electrode are introduced into the growing polymer [16]. This procedure is mainly applied to bind big molecules (i.e., enzymes, DNA). Both adsorption and entrapping are simple methods that permit the introduction of biological molecules without a chemical bonding that could affect their [16]. Therefore, the techniques are used often to biosensor applications, i.e., absorption has been utilized to bind calf thymus DNA onto PPy in order to generate a biosensor for toxicants [43]. Entrapping has been used to bind glucose oxidase to fabricate glucose sensors [44,45], as well as to bind DNA to detect aromatic amines, cDNA and Hep C virus [46]. Absorption has also been utilized to enhance the biocompatibility of neural electrodes: polylysine absorbed into PEDOT-PSS-coated electrodes [47].

Covalent bonding: By this procedure, the biomolecules are strongly bound and are not released, thereby enhancing the long-term stability of the polymer [48]. A suitable example of the covalent procedure is the binding of cysteines to the β-positions on PPy with sulfide bonds. These cysteines may then operate as places to covalently bind next bio molecules [49]. Congruous binding places were generated through the use of N-hydroxyl succinimidyl ester pyrrole [50], an intermediate photocrosslinker consisting of polyallylamine conjugated to an arylazido functional group [51], and poly(ethylene glycol) methacrylate graft copolymerization [18]. These procedures were used to bind NGF and heparin [52].

Exploiting: This permits the binding of a wide group of biological molecules as long as they are charged [50]. i.e., growth factors, collagen, heparin, chitosan and ATP have already been bound in conductive polymers *via* doping [53]. Sadly, incorporation of biomolecules by doping permits only a relatively small amount of the molecules to be bound, while also having a negative effect on the polymer's conductivity [50].

The next generation of conductive polymers

There is a great interest to develop a more biocompatible and inherently biodegradable CPs [53]. Conductive quaterthiophene and biodegradable ester have been used to create QAPE, a novel polymer that was shown to support Schwann cells [54]. Another new conductive polymer, ATQD, was synthesized from the emeraldine form of amino-capped aniline trimers [20]. When combined with RGD, ATQD was observed to support PC-12 adhesion and proliferation, and to induce spontaneous neuritogenesis even in the absence of neurotrophic growth factors [20]. Polypyrrole-thiophene (PPy–PTh) oligomers were

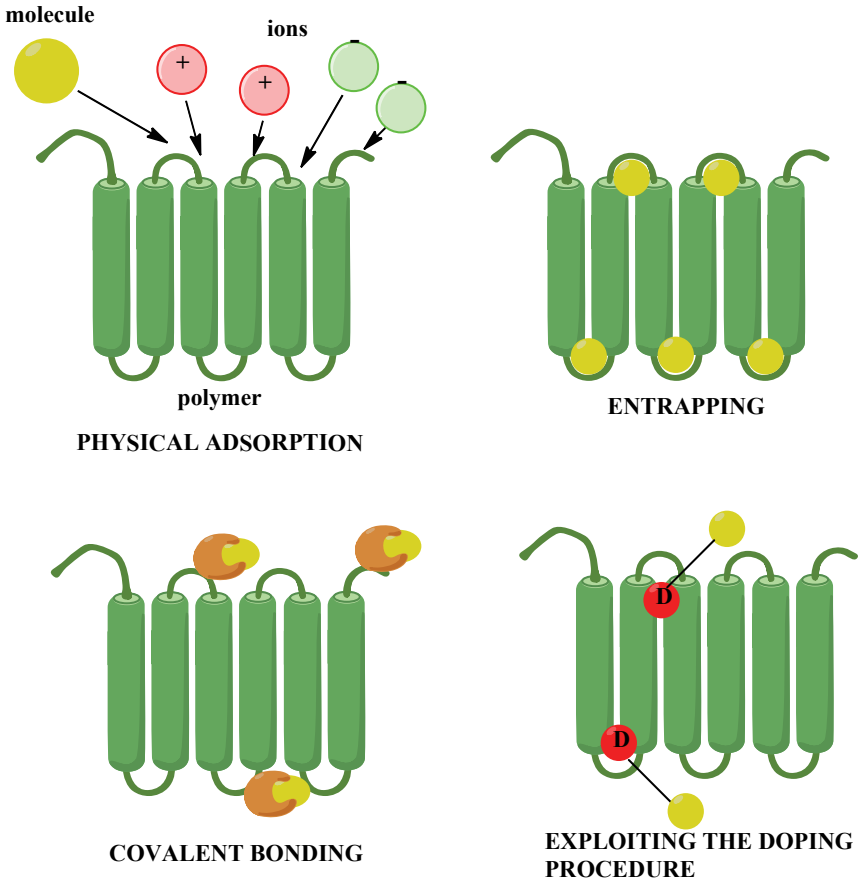

Figure 2: Functionalization of conductive polymers [41].

also combined with ester linkages to generate biodegradable CP [54]. The degradation of PPy–PTh oligomers that could be consumed by macrophages, lowering the chance of any long-term adverse effect *in vivo* [54]. PPy was modified to create poly(3,4-alkylenedioxypyrrole) (PXDOP) [55]. 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 [55].

Polylactide (PLA) and aniline pentamer (AP) were combined to create PLA-b-AP-b-PLA (PAP) [30]. PAP was found to be biodegradable and biocompatible, to have excellent processibility and to possess a conductivity similar to PANI's [30]. AP has also been synthesized with chitosan, and its presence it the composite was shown to be essential for inducing PC-12 differentiation and neurite formation [56]. Many promising composite, modified and co-polymer forms of PPy, PANI and PEDOT exist, but the synthesis of these is not always straightforward.

Organic Bioelectronics

Organic bioelectronics in microfluidics

Organic electronic devices perform well on a wide range of carrying substrates, they are also expected to become easily integrated into muicrofluidics. Commonly, laser diodes and other solid-state light sources are utilized to probe biomolecules inside microfluidics. Nevertheless, lasers are particularly non-compatible with microfluidics, which prevents easy integration of the two methods. Shin et al. developed an organic light emitting device fully integrated with a glass microfluidic system (Figure 3) [57]. To generate a complete fluorescence detecting system, a silicon-based photodetector was introduced into this microfluidic arrangement. The OLED-microfluidic layout was used as the excitation source to a competitive evaluation which contained TMR-biocytin, streptavidin, and D-biotin.

An all-organic polymer-based fluorescence-detection microfluidic arrangement was investigated by the group led by Bradley. Here, an all-polymer layout was obtained that was convenient for single-use bioluminescence applications [58]. Organic electronics can be used also to control the flow of the analyte itself inside the channel, providing the analytes to intermix with reagents in a craved sequence. As the electrochemical state of a CP is switched, its chemical character inside the bulk as well as at the outermost surface is verified. This fact may affect the surface tension, which can be utilized to monitor the movement and flow of liquids [59].

Electrodes

Electrodes for stimulation

The simplest electronic device is an electrode in immediate physical contact with, or in vicinity to, the medium that is evaluated or stimulated. At this place, CPs suggest several benefits over metal electrodes regarding, i.e., selectivity and sensitivity. Generally, conjugated polymer-based electrodes ensure the possibility of immobilizing a wide area of indicating molecules along the surface or inside the polymer bulk [60].

Already in 1986, PPy was estimated as the outer electrode material for neural prosthetic applications [60]. It was proved that PPy grown on the cross sections of platinum wires embedded in glass improved the charge-pulsing capacity compared to bare platinum wires. To stimulate or record neuronal impulses, the impedance characteristics have to be designed to enable signal translation between the electrode and the neuron, which usually occur at the biologically suitable frequency of ca. 1 kHz. The main challenge has been to develop an electrode with the highest possible capacitance for a given electrode area. At optimal polymerization conditions, the effective area of the PPy films was approximately one order of magnitude greater compared to the smooth electrode surface. Furthermore, PPy is electrochemically active, which prefers the charging capacity of the electrode, leading to reduction of the cut-off frequency.

In 2004, Reynolds et al. manufactured neural electrodes coated with a PEDOT derivative. This work presented that hydroxymethylated EDOT monomers could be electrodeposited on gold pads to create highly textured PEDOT-MeOH - PSS coatings [61]. The neuronal tissue frequently reacts to an implanted electrode, i.e., by induction of a district inflammatory response, enhanced expression of intermediate filament proteins and general thickening of the neighboring tissue. Finally, such consequences will exclude the electrode from the neuronal tissue, resulting with suppression of the transferred signal range.

Surface modification methods, such as addition of earmarked biological molecules known to improve electrode adhesion to specific tissues, have been utilized to further enhance the biocompatibility of polymer materials. Recently, Martin et al. reported that nona-peptides (CDPGYIGSR) co-deposited together with PPy onto gold electrodes,

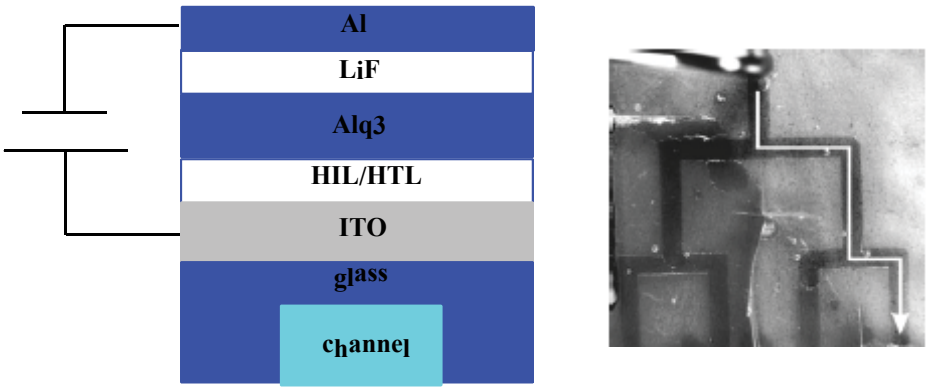

Figure 3: Left: A microfluidic system including an organic light emitting diode serving as the excitation source for fluorescent materials; Right: A microfluidic system, including preceding *y*-intersections. Electrochemical surface tension switches, manufactured along the floor of the channel system, guides the aqueous solution Adapted from [27].

suppress undesired tissue–electrode reactions [62]. This was observed during analysis of the brain tissue of a guinea pig with electrodes implanted for a number of weeks. Asberg and Inganas fabricated PEDOT-PSS hydrogel electrodes mixed with poly(4-vinylpyridine) crosslinked and coordinated by osmium. Their aim was to develop electrodes for cellular interfaces in general and for neurons in particular [63].

Electrodes for sensing

Electrodes can gain and translate signals emitted by cells as a consequence of a particular physiological state. Polymer sensor electrodes, operating in the amperometric [64-66] as well as in the potentiometric [67] mode, have been developed to sense a wide range of biological analytes. Immunosensors have received significant attention for decades, as they can be utilized to control quick, sensitive, and selective immunological signals. These arrangements use the high affinity of antibodies reacting with their correlating antigens.

Recently, the enzyme-linked immunosorbent assays (ELISA) procedure has been combined with amperometric electrodes, generating a sensor where the enzyme is utilized to amplify the primary sensor signal. The electrochemically active elements that are formed or consumed in the enzymatic reaction can be detected at the electrode. The enzyme conjugate is immobilized inside the polymer bulk or at the surface. Commonly, horseradish peroxidase (HRP), glucose oxidase (GOx), [68] and catalase have been utilized as the enzyme conjugate [69].

Using protein conjugates, the activity of an electrochemical species defines the amperometric sensing base. In electrochemical cells, not only the activity of electrodes and species included in the sensor cell anticipates the signal. The impedance characteristics of the electrolyte bulk or over the double layer at the electrode/electrolyte interface also predict the current level that passes through the sensor cell. Piro and Pham investigated a bifunctional amperometric sensor [70] polymer consisting of a quinine-containing monomer (JUG), serving as the ion-to-electron transducer, as well as a carboxylic site (JUGA) for immobilization of oligonucleotides. In this arrangement of JUG *versus* JUGA mers, the oligonucleotide coils form a rather dense layer placed between the electrochemically active (JUG) part of the polymer and the solution. It was observed that a peculiar amperometric signal could be recorded when non-complementary oligonucleotides were introduced to the solution. Moreover, addition of the complementary direct sequence (genome sequences from HIV) induced a significantly higher amperometric index. This was explained by the fact that the complementary target hybridizes with the grafted probe to create double helix structures, which are less flexible than single-stranded, nonhybridized probes. The charge capacity of the hybridized electrode layer grew almost three-fold in comparison to a non-hybridized layer [70].

Fabrication of polymer electrode coatings

The general method for applying CP coatings is electropolymerization. It is direct and simple to build adherent conducting polymer layers on conducting substrates and the obtained material is insoluble in water. Shortly, current is directed through an electrode immersed in a solution containing the monomer and one or a number of different counterions. Consequently, monomers build up polymer chains at the working electrode incorporating the counterion (CI) in the process (Figure 4). Despite the fact, there are several other approaches besides electrochemical polymerization, this procedure has prevailed the field of neural interfaces. In comparison to chemical polymerization this method has the benefit of limitation the coating to the underlying electrode, connecting the manufacturing and geometrical patterning step into one [71]. The created polymer is

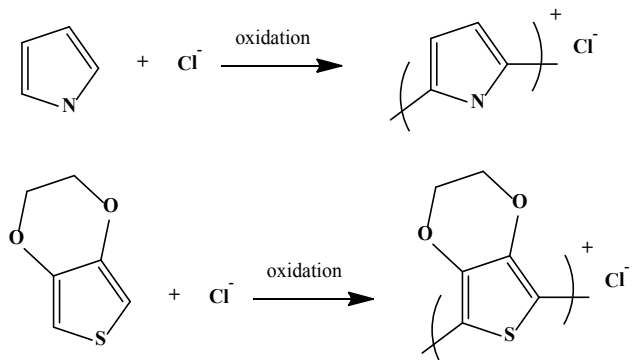

Figure 4: Polymerization procedures of a/polypyrrole as well as b/ PEDOT. The Cl^- is incorporated into the polymer as counterion.

tightly bound to the conducting surface. Moreover, it supplies suitable monitoring of film architecture and thickness by several technique parameters. The used deposition charge, counterion concentration, solvent influence and electrodeposition procedure, galvanostatic or potentiostatic, influence physical parameters of the formed film [71].

It has been demonstrated that for extended deposition times the topography of the film transforms from nodules to clusters [71] resulting in an increase of impedance at continued deposition. These transition levels have also correlated well with mechanical features of the polymer [72]. A major coating process used is that of pyrrole electropolymerization even though a shift to the use of ethylenedioxythiophene (EDOT), due to its superior stability, can be noticed [73]. Other materials used include EDOT derivatives [74] and polyaniline [25].

The character of the counterion affects on physical features of the generated material i.e., softness, stability, surface structure, permeability and wettability [75]. When the obtained material is destined for biomedical applications, often, the most common solvent is water. If the solubility of the monomer in water is poor, as is the case with EDOT, surfactants are proposed as counterions. Widespread surfactants are polystyrene sulfonate (PSS) and dodecylbenzenesulfonate (DBS) [75].

Drug Delivery Devices

Pharmaceutical species range from small ions to large and complex proteins and molecules. To obtain a suitable response to the treatment, the pharmaceuticals have to be delivered inside the body at an optimum rate, and in some cases, at a well-defined place. Drug delivery devices and materials [76] have recently and are extensively used in different kinds of treatments. Due to the fact, an investigation into CP-based devices has been carried out extensively to find how they can behave as electrically monitored drug delivery systems inside the body. The main challenge is to investigate a CP drug delivery system that permits direct and strict control of the ON/OFF level. Moreover, such a device have to be able to deliver the drug at doses that are required to observe the treatment effect. Miller et al. investigated a range of different electrochemically driven drug delivery devices. At first, films of cobalt(III) complexes were loaded with neurotransmitters [77]. By reducing this electrode, the neurotransmitters were efficiently released into the solution. In 1986, the Miller group reported [78] the use of polythiophenes (PT) and PPy in electrochemically gated drug delivery films. By coupling anions, i.e., acetylsalicylate, or cations, i.e., dopamine, to the conducting polymer matrix, it was observed that the reduction and oxidation fronts propagated at a much faster rate in the conducting polymers, in comparison to the situation when polystyrene

was used as the electrode coating material. In addition, the associated drug delivery rate was found to grow significantly.

During the late 1990s Sundholm and co-workers optimized the electropolymerization route for PPy-based drug delivery films [79] for a range of different anionic drug molecules that exhibit specific treatment activity, i.e., salicylate, naproxen, and nicoside. The membranes were produced of electropolymerizing films of PPy-sodium tosylate. To evaluate the electrochemically triggered drug delivery characteristics, the drug loaded PPy films were exposed to increasingly negative voltages. There was found wide variations in the triggered release of the drug molecules tested, probably as a result of their great differences in electroactivity [80].

Recently, Langer et al. reported a drug release system based on surface switching effects in PPy doped with biotin [81]. A monolayer of streptavidin was immobilized at the biotin places along the PPy surface. Finally, biotinylated neural growth factors were permitted to adhere along the PPy surface.

Lastly, Martin reported also a drug releasing system based on PEDOT-coated fibers. Using this approach, poly(lactide-*co*-glycolide)-dexamethasone fibers were created and grown using electrospinning onto a supporting electrode [82], and PEDOT was thereafter electrochemically grown along the surface of the fibers. The cumulative mass release of dexamethasone was found to grow dramatically as short voltage pulses were addressed to the electrode hosting the PEDOT/poly(lactide-*co*-glycolide)-dexamethasone fibers (Figure 5).

Scheme of controlled release of dexamethasone; on the left - PEDOT tube in neutral electrical condition; right – external electrical stimulation control the delivery (releasing) of dexamethasone from the PEDOT tube due to contraction or expansion of the PEDOT. By applying a positive voltage, electrons are injected into the chains and positive charges in the polymer chains are compensated. To maintain overall charge neutrality, counterions are expelled towards the solution and the tubes contract. This shrinkage causes the drug molecules to come out the ends of tubes according to Ref. [82].

Recent progress in RNA biology has broadened the scope of therapeutic targets of RNA drugs for cancer therapy (Figure 6). However, RNA dugs are rapidly degraded, thereby required delivery tool for efficient transport to the target cells. To present, several delivery formulations have been investigated from cationic lipids, inorganic nanoparticles as well as polymers for systematic delivery of siRNA [83].

Conjugated polymers such as polythiophenes [84] and poly(*p*-phenylene ethynylene) [85] and their nanoparticles have emerged as novel gene delivery vectors, due to their potential cell-penetrating ability owing to their rigid chains, and such polymers are easy to use as efficient delivery tools [86]. For example, monodispersed polyfluorene nanoparticles showed outstanding RNA-binding capacity and induced a knockdown efficiency of 23.9% with no significant cytotoxicity [87].

Discussion and Future Focus

Today, organic bioelectronics represents a group of prominent devices, ready to attend research related to biology and medicine. The outlook for these technologies are advantageous. To this moment, organic electronics have primarily been explored as recording and regulating tools that interface biological systems in the form of planar surfaces. Nevertheless, the morphology of cells/tissues is neither planar nor static. By contrast, tissues are soft, flexible, and consist different degrees of natural movement as part of the physiological activities. Then, the softness and flexibility of organic electronics have to be enhanced to grow its biocompatibility and biostability. Moreover, the modern technology have to a greater extent mimic the overall structure in different biological individuals. Perhaps this is suitable to obtain by utilizing the biological system as template for generating tools.

On the other hand, besides molecules and charge polarization, influence biological signaling approaches. This is exemplified by the nature of a surface, or scaffold, which cells adhere to. It is well-known that proteins such as integrin, used by cells to operate with a surface, may infer signaling approaches resulting in cell death in case the surface is not suitable. Therefore, many reports present that cell adhesion and proliferation can be monitored by defined nanopatterns of a surface. This raises the possibility that organic electronics can be used to realize texture switches to control the life cycle of cell systems.

The major problem with current drug release (electrochemically active) polymer electrodes is the difficulty of obtaining a high enough concentration of the released species. Efforts have to be directed towards developing a truly electronic (not a mechanical) release

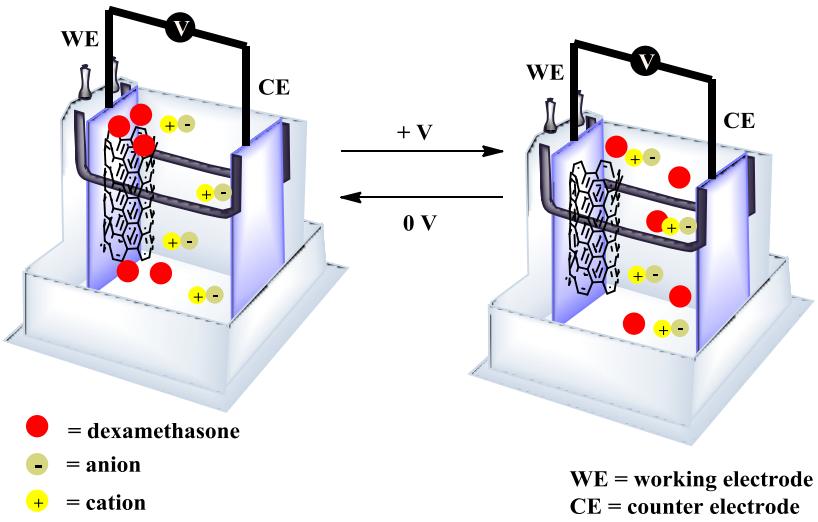

Figure 5: Scheme of controlled release of dexamethasone.

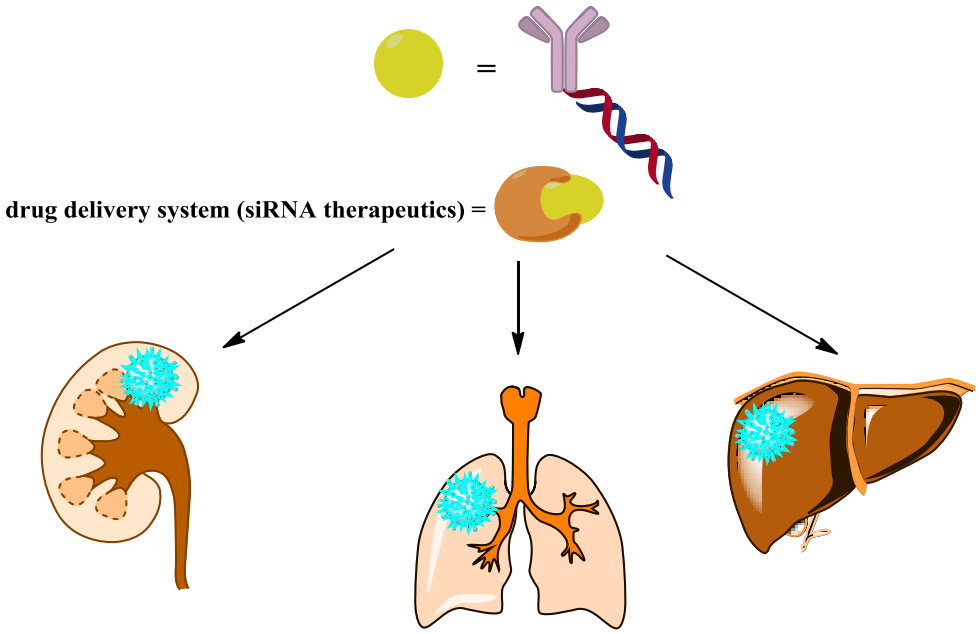

Figure 6: siRNA therapeutics for cancer treatment [83].

tool with a potential to launch significantly higher numbers of drug molecules per area.

Many preliminary researches have presented advantageous results on the potential of both PPy and PEDOT to considerably enhance both recording and stimulation properties of the neural interface. These benefits are very clear in terms of the reduced impedance, the enhanced charge capacity and the time response. Some of these advantages can persist also when more knowledge has been get on the long term features of materials and devices in contact with real biological systems. The cost for these improvements is less experience of long term performance of these materials *in vivo* in comparison to already established biological materials. The prospect of releasing entrapped biomolecules and drugs to mitigate the immune response and attract neurons to the interface presents a potential tool for realizing stable interfaces.

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References

1. Pei Q, Zuccarello G, Ahlskog M, Inganas O (1994) Electrochromic and highly stable poly(3,4-ethylenedioxythiophene) switches between opaque blue-black and transparent sky blue. Polymer 35: 1347-1352.
2. Burroughes JH, Bradley DDC, Brown AR, Marks RN, Mackay K, et al. (1990) Light-emitting diodes based on conjugated polymers. Nature 347: 539-541.
3. Gustafsson G, Cao Y, Treacy GM, Klavetter F, Colaneri N, et al. (1992) Flexible light-emitting diodes made from soluble conducting polymers. Nature 357: 477-479.
4. Yoshioka Y, Jabbour GE (2006) Injekt printing of oxidants for patterning of nanometer-thick conducting polymer. Adv Mater 18: 1307-1312.
5. Sirringhaus H, Kawase T, Friend RH, Shimoda T, Inbasekaran M, et al. (2000) High-resolution inkjet printing of all-polymer transistor circuits. Science 290: 2123-2126.
6. Tengvall P, Lundström I, Liedberg B (1998) Protein adsorption studies on model organic surfaces: an ellipsometric and infrared spectroscopic approach. Biomaterials 19: 407-422.
7. Asplund M, Nyberg T, Inganas O (2010) Electroactive polymers for neural interfaces. Polym Chem 1: 1374-1391.
8. Foulds NC, Lowe CR (1986) Enzyme entrapment in electrically conducting polymers. J Chem Soc Faraday Trans 1 82: 1259-1264.
9. Bull RA, Fan FR, Bard AJ (1983) Polymer films on electrodes. J Electrochem Soc 130: 1636-1638.
10. Umana M, Waller J (1986) Protein-modified electrodes. The glucose oxidase/polypyrrole system. Anal Chem 58: 2979-2983.
11. Boyle A, Genies E, Fouletier M (1990) Electrochemical-Behavior of Polypyrrole Films Doped with Atp Anions. J Electroanal Chem 279: 179-186.
12. John R, Spencer M, Wallace GG, Smyth MR (1991) Development of a polypyrrole-based human serum albumin sensor. Anal Chim Acta 249: 381-385.
13. Naarmann H (1988) Electrochemical polymerization. Angew Makromol Chem 162: 1-17.
14. Hodgson AJ, Spencer MJ, Wallace GG (1992) Incorporation of proteins into conducting electroactive polymers. Reactive polymers. React Polym. 18: 77-85.
15. Adeloju SB, Shaw SJ, Wallace GG (1993) Polypyrrole-based potentiometric biosensor for urea part 1. Incorporation of urease. Anal Chim Acta 281: 611-620.
16. Cosnier S (1999) Biomolecule immobilization on electrode surfaces by entrapment or attachment to electrochemically polymerized films. A review. Biosens Bioelectron 14: 443-456.
17. Nyberg T, Inganas O, Jerregard H (2002) Polymer Hydrogel Microelectrodes for Neural Communication. Biomed Microdevices 4: 43-52.
18. Ghasemi-Mobarakeh L, Prabhakaran MP, Morshed M, Nasr-Esfahani MH, Baharvand H, et al. (2011) Application of conductive polymers, scaffolds and electrical stimulation for nerve tissue engineering. J Tissue Eng Regen Med 5: e17-35.
19. Balint R, Cassidy NJ, Cartmell SH (2014) Conductive polymers: towards a smart biomaterial for tissue engineering. Acta Biomater 10: 2341-2353.
20. Ravichandran R, Sundarrajan S, Venugopal JR, Mukherjee S, Ramakrishna S (2010) Applications of conducting polymers and their issues in biomedical engineering. J R Soc Interface 7 Suppl 5: S559-579.

21. Wallace G, Spinks G (2007) Conducting polymers – bridging the bionic interface. Soft Matter 3: 665-671.

22. Pelto J, Haimi S, Puukilainen E, Whitten PG, Spinks GM, et al. (2010) Electroactivity and biocompatibility of polypyrrole-hyaluronic acid multi-walled carbon nanotube composite. J Biomed Mater Res A 93: 1056-1067.

23. Kaynak A, Rintoul L, George GA (2000) Change of mechanical and electrical properties of polypyrrole films with dopant concentration and oxidative aging. Mater Res Bull 35: 813-824.

24. Shi G, Rouabhia M, Wang Z, Dao LH, Zhang Z (2004) A novel electrically conductive and biodegradable composite made of polypyrrole nanoparticles and polylactide. Biomaterials 25: 2477-2488.

25. Cullen DK, Patel AR, Doorish JF, Smith DH, Pfister BJ (2008) Developing a tissue engineered neural-electrical relay using encapsulated neuronal constructs on conducting polymer fibers. J Neural Eng 5: 374-384.

26. Ghasemi-Mobarakeh L, Prabhakaran MP, Morshed M, Nasr-Esfahani MH, Ramakrishna S (2009) Electrical stimulation of nerve cells using conductive nanofibrous scaffolds for nerve tissue engineering. Tissue Eng Part A 15: 3605-3619.

27. Berggren M, Richter-Dahlfors A (2007) Organic Bioelectronics. Adv Mater 19: 3201-3213.

28. Kim DH, Abidian M, Martin DC (2004) Conducting polymers grown in hydrogel scaffolds coated on neural prosthetic devices. J Biomed Mater Res A 71: 577-585.

29. Lee H, Bellamkonda RV, Sun W, Levenston ME (2005) Biomechanical analysis of silicon microelectrode-induced strain in the brain. J Neural Eng 2: 81-89.

30. Williams RL, Doherty PJ (1994) A Preliminary Assessment of Poly(Pyrrole) in Nerve Guide Studies. J Mater Sci: Mater Med 5: 429-433.

31. Schmidt CE, Shastri VR, Vacanti JP, Langer R (1997) Stimulation of neurite outgrowth using an electrically conducting polymer. Proc Natl Acad Sci USA 94: 8948-8953.

32. Collier JH, Camp JP, Hudson TW, Schmidt CE (2000) Synthesis and characterization of polypyrrole-hyaluronic acid composite biomaterials for tissue engineering applications. J Biomed Mater Res 50: 574-584.

33. Wang X, Gu X, Yuan C, Chen S, Zhang P, et al. (2004) Evaluation of biocompatibility of polypyrrole in vitro and in vivo. J Biomed Mater Res A 68: 411-422.

34. Luo SC, Mohamed Ali E, Tansil NC, Yu HH, Gao S, et al. (2008) Poly(3,4-ethylenedioxythiophene) (PEDOT) nanobiointerfaces: thin, ultrasmooth, and functionalized PEDOT films with in vitro and in vivo biocompatibility. Langmuir 24: 8071-8077.

35. Asplund M, Thaning E, Lundberg J, Sandberg-Nordqvist AC, Kostyszyn B et al. (2009) Toxicity Evaluation of PEDOT/Biomolecular Composites Intended for Neural Communication Electrodes. Biomed Mater (Bristol, UK) 4: 045009.

36. Stauffer WR, Cui XT (2006) Polypyrrole doped with 2 peptide sequences from laminin. Biomaterials 27: 2405-2413.

37. Kim DH, Richardson-Burns SM, Hendricks JL, Sequiera C, Martin DC (2007) Effect of immobilized nerve growth factor on conductive polymers: electrical properties and cellular response. Adv Funct Mater 17: 79-86.

38. Park KH, Jo EA, Na K (2007) Heparin/Polypyrrole (PPy) Composite on Gold-Coated Matrix for the Neurite Outgrowth of PC12 Cells by Electrical Stimulation. Biotechnol. Bioprocess Eng 12: 463-469.

39. Cui X, Wiler J, Dzaman M, Altschuler RA, Martin DC (2003) In vivo studies of polypyrrole/peptide coated neural probes. Biomaterials 24: 777-787.

40. Xiao YH, Li CM, Toh ML, Xue R (2008) Adenosine 50-triphosphate incorporated poly(3,4-ethylenedioxythiophene) modified electrode: a bioactive platform with electroactivity, stability and biocompatibility. J Appl Electrochem 38: 1735-1741.

41. Guimard NK, Gomez N, Schmidt CE (2007) Conducting polymers in biomedical engineering. Prog Polym Sci 32: 876-921.

42. Ahuja T, Mir IA, Kumar D, Rajesh (2007) Biomolecular immobilization on conducting polymers for biosensing applications. Biomaterials 28: 791-805.

43. Arora K, Chaubey A, Singhal S, Sigh RP, Samanta RB et al. (2006) Application of electrochemically prepared polypyrrole–polyvinyl sulphonate films to DNA biosensor. Biosens Bioelectron 21: 1777-1783.

44. Nien PC, Tung TS, Hoa KC (2006) Amperometric glucose biosensor based on entrapment of glucose oxidase in a poly(3,4-ethylenedioxythiophene) film. Electroanalysis 18: 1408-1415.

45. Wang J, Myung NV, Yun M, Monbouquette HG (2005) Glucose oxidase entrapped in polypyrrole on high-surface-area Pt electrodes: a model platform for sensitive electroenzymatic biosensors. J Electroanal Chem 575: 139-146.

46. Prabhakar N, Arora K, Singh SP, Singh H, Malhotra BD (2007) DNA entrapped polypyrrole-polyvinyl sulfonate film for application to electrochemical biosensor. Anal Biochem 366: 71-79.

47. Collazos-Castro JE, Polo JL, Hernández-Labrado GR, Padial-Cañete V, García-Rama C (2010) Bioelectrochemical control of neural cell development on conducting polymers. Biomaterials 31: 9244-9255.

48. De Giglio E, Sabbatini L, Zambonin PG (1999) Development and analytical characterization of cysteine-grafted polypyrrole films electrosynthesized on Pt- and Ti-substrates as precursors of bioactive interfaces. J Biomater Sci Polym Ed 10: 845-858.

49. De Giglio E, Sabbatini L, Colucci S, Zambonin G (2000) Synthesis, analytical characterization, and osteoblast adhesion properties on RGD-grafted polypyrrole coatings on titanium substrates. J Biomater Sci Polym Ed 11: 1073-1083.

50. Lee JY, Lee JW, Schmidt CE (2009) Neuroactive conducting scaffolds: nerve growth factor conjugation on active ester-functionalized polypyrrole. J R Soc Interface 6: 801-810.

51. Gomez N, Schmidt CE (2007) Nerve growth factor-immobilized polypyrrole: bioactive electrically conducting polymer for enhanced neurite extension. J Biomed Mater Res A 81: 135-149.

52. Li Y, Neoh KG, Kang ET (2004) Plasma protein adsorption and thrombus formation on surface functionalized polypyrrole with and without electrical stimulation. J Colloid Interf Sci 275: 488-495.

53. Guimard NKE, Sessler JL, Schmidt CE (2009) Toward a biocompatible and biodegradable copolymer incorporating electroactive oligothiophene units. Macromolecules 42: 502-511.

54. Rivers TJ, Hudson TW, Schmidt CE (2002) Synthesis of a novel, biodegradable electrically conducting polymer for biomedical applications. Adv Funct Mater 12: 33-37.

55. Thomas CA, Zong K, Schottland P, Reynolds JR (2000) Poly(3,4-alkylenedioxypyrrole)s as highly stable aqueous-compatible conducting polymers with biomedical implications. Adv Mater 12: 222-225.

56. Hu J, Huang L, Zhuang X, Zhang P, Lang L, et al. (2008) Electroactive aniline pentamer cross-linking chitosan for stimulation growth of electrically sensitive cells. Biomacromolecules 9: 2637-2644.

57. Shin KS, Kim YH, Paek KK, Park JH, Yang EG, et al. (2006) Characterization of an integrated fluorescence-detection hybrid device with photodiode and organic light-emitting diode. IEEE Electron Device Lett 27: 746-748.

58. Wang X, Hofmann O, Huang J, Barrett EM, Das R, et al. (2006) SPIE-BioMEMS and Nanotechnology II. Brisbane, Australia, December.

59. Isaksson J, Tengstedt C, Fahlman M, Robinson N, Berggren M (2004) A solid-state organic electronic wettability switch. Adv Mater 16: 316-320.

60. Cooreman P, Thoelen R, Manca J, vandeVen M, Vermeeren V, et al. (2005) Impedimetric immunosensors based on the conjugated polymer PPV. Biosens Bioelectron 20: 2151-2156.

61. Xiao Y, Cui X, Hancock JM, Bouguettaya M, Reynolds JR, et al. (2004) Electrochemical polymerization of poly(hydroxymethylated-3,4-ethylenedioxythiophene) (pedot-meoh) on multichannel neural probes. Sens Actuators B 99: 437-443.

62. Foos JS, Erker SM (1986) Rate enhancement in modified polypyrrole electrodes. J Electrochem Soc 133: 1983-1984.

63. Asberg P, Inganäs O (2003) Hydrogels of a conducting conjugated polymer as 3-D enzyme electrode. Biosens Bioelectron 19: 199-207.

64. Jedrychowska A, Cabaj J, Swist A, Soloducho J (2014) Electrochemical laccase sensor based on 3-methylthiophene/3-thiopheneacetic acid/bis(3,4-ethylenedioxythiophene)-N-nonylacridone as a new polymer support. J Electroanal Chem 720-721: 64-70.

65. Cabaj J, Chyla A, Jedrychowska A, Olech K, Soloducho J (2012) Detecting platform for phenolic compounds – characteristic of enzymatic electrode. Opt Mat 34: 1677-1681.

66. Jedrychowska A, Malecha K, Cabaj J, Soloducho J (2015) Laccase biosensor based on low temperature co-fired ceramics for the permanent monitoring of water solutions. Electrochim Acta 165: 372-382.

67. Vazquez M, Bobacka J, Luostarinen M, Rissanen K, Lewenstam A, et al. (2005) Potentiometric sensors based on poly(3,4-ethylenedioxythiophene) (PEDOT) doped with sulfonated calix[4]arene and calix[4]resorcarenes. J Solid State Electrochem 9: 312-319.

68. Mell LD, Maloy JT (1976) Amperometric response enhancement of the immobilized glucose oxidase enzyme electrode. Anal Chem 48: 1597-1601.

69. Darain F, Park SU, Shim YB (2003) Disposable amperometric immunosensor system for rabbit IgG using a conducting polymer modified screen-printed electrode. Biosens Bioelectron 18: 773-780.

70. Piro B, Haccoun J, Pham MC, Tran LD, Rubin A, et al. (2005) Study of the DNA hybridization transduction behavior of a quinone-containing electroactive polymer by cyclic voltammetry and electrochemical impedance spectroscopy. J Electroanal Chem 577: 155-165.

71. Cui XY, Hetke JF, Wiler JA, Anderson DJ, Martin DC (2001) Electrochemical deposition and characterization of conducting polymer polypyrrole/PSS on multichannel neural probes. Sens Actuators A 93: 8-18.

72. Yang JY, Martin DC (2006) Microporous conducting polymers on neural. J Mater Res 21: 1124-1132.

73. Ludwig KA, Uram JD, Yang J, Martin DC, Kipke DR (2006) Chronic neural recordings using silicon microelectrode arrays electrochemically deposited with a poly(3,4-ethylenedioxythiophene) (PEDOT) film. J Neural Eng 3: 59-70.

74. Xiao Y, Martin DC, Cui X, Shenai M (2006) Surface modification of neural probes with conducting polymer poly(hydroxymethylated-3,4- ethylenedioxythiophene) and its biocompatibility. Appl Biochem Biotechnol 128: 117-130.

75. Green RA, Lovell NH, Poole-Warren LA (2010) Impact of co-incorporating laminin peptide dopants and neurotrophic growth factors on conducting polymer properties. Acta Biomater 6: 63-71.

76. Barry BW (2001) Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci 14: 101-114.

77. Zinger B, Miller LL (1984) Mediated release of glutamate and GABA by cathodic reduction of cobalt complexes. J Electroanal Chem Interfacial Electrochem 181: 153-172.

78. Miller LL (1987) Electrochemically controlled release of drugs and other chemicals. React Polym Ion Exch Sorbents 6: 341-341.

79. Kontturi K, Murtomaki L, Pentti P, Sundholm G (1998) Preparation and properties of a pyrrole-based ion-gate membrane as studied by the EQCM. Synth Met 92: 179-185.

80. Kontturi AK, Kontturi K, Murtomaki L, Quinn B, Cunnane VJ (1997) Study of ion transfer across phospholipid monolayers adsorbed at micropipette ITIES. J Electroanal Chem 424: 69-74.

81. George PM, Lavan DA, Burdick JA, Chen CY, Liang E, et al. (2006) Electrically controlled drug delivery from biotin-doped conductive polypyrrole. Adv Mater 18: 577-581.

82. Abidian MR, Kim DH, Martin DC (2006) Conducting-Polymer Nanotubes for Controlled Drug Release. Adv Mater 18: 405-409.

83. Lee SJ, Kim MJ, Kwon IC, Roberts TM (2016) Delivery strategies and potential targets for siRNA in major cancer types. Adv Drug Deliv Rev 104: 2-15.

84. Carreon AC, Santos WL, Matson JB, So RC (2014) Cationic polythiophenes as responsive DNA-binding polymers. Polym Chem 5: 314-317.

85. Zhang L, Yin QH, Li JM, Huang HY, Wu Q, et al. (2013) Functionalization of dendritic polyethylene with cationic poly(p-phenylene ethynylene) enables efficient siRNA delivery for gene silencing. J Mater Chem B 1: 2245-2251.

86. Zhang L, Yin Q, Huang H, Wang B (2013) Conjugation of cationic poly(p-phenylene ethynylene) with dendritic polyethylene enables live-cell imaging. J Mater Chem B 1: 756-761.

87. Jiang R, Lu X, Yang M, Deng W, Fan Q, et al. (2013) Monodispersed brush-like conjugated X polyelectrolyte nanoparticles with efficient and visualized SiRNA delivery for gene silencing. Biomacromolecules 14: 3643-3652.