Organic Electronics in Aqueous Environment for Biological Applications

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Abstract

This review presents a brief overview of the applications of conjugated polymers in the area of bioelectronics. We have highlighted three examples from our laboratory where organic polymers are interfaced with biological media: (i) Soft substrates which are electrically conducting for tissue engineering applications, specific to central nervous system (ii) optoelectronic activity arising from photostimulation of semiconducting polymers in contact with aqueous electrolyte which resemble natural vision system and (iii) the utilization of phospholipid membrane in water-gated organic field effect transistor which can be used for sensor applications. These studies strongly indicate the utility of soft polymeric materials in biomedical applications.

Keywords: organic electronics, conjugated polymers, neurons, transistors, bioelectronics.

1. Introduction

Seamless integration of biological systems from molecular-cellular level to the systems level with soft materials in the external environment having electronic and sensory capabilities opens up interesting possibilities. For instance, the availability of synthetic-soft polymer substrates, which mechanically mimic the in vivo conditions, has helped in rapid advances in the field of tissue engineering. In this review, we highlight the utility of conjugated polymers in biosensing, bio-diagnostics and therapy related problems. Synthetic polymers have been extensively used in many
biomedical applications. The added electronic and optoelectronic properties of these systems enables novel possibilities and unexplored vistas.

Conducting polymers are a special class of π-conjugated materials with both electronic and ionic conductivity. The high conductivity is associated with doped polymers while the semi-conducting form, which exhibits optoelectronic features, is associated with pristine systems. Both these forms of the polymers in certain cases have been shown to be biocompatible. Devices based on such organic materials can be manufactured with features at (µm-nm) length scales using techniques, which are common to plastic processing, such as dip-coating, spin coating, and different forms of printing methods. The added advantage is that these methods can be used for depositing these materials on flexible and conformal substrates.\(^1\)\(^-\)\(^4\)

In biological systems, various molecules and protein complexes play a major role in the binding of the cells with an external surface. The immobilization of such binding sites on the surface of a conjugated polymer can provide a means to anchor specific cells on its surface. Further, the intra- and inter-cellular transport in the system is mediated by specific signalling mechanisms, which are regulated by ions and ion transport; e.g. in the case of neuronal signalling. The possibility of using conjugated polymers in aqueous environments for sensing, probing and controlling ionic transport around the system highlights the utility of these systems for novel bioelectronic hybrid devices.

Electrically active tissues such as brain, heart and skeletal muscles have been coupled to electronic devices to create novel body-machine interfaces as shown in Fig. 1. The interaction between biological systems and electrical circuits, or bioelectronics, has been a growing area of research. The concept of bioelectronics aims at increasing the understanding of various biological phenomena as well as developing potential healthcare devices. The interaction between electronic devices and biological
systems demands biocompatibility and biostability of the electronic circuits under physiological conditions. Further, it is required that the interfacing of the circuit with the living cells should not interfere with the biological function of the cells, and at the same time, the biosignals should be appropriately translated into their electronic equivalences, or vice-versa.

Fig. 1: Schematic showing possible bio-electronic interfaces.

2. Conducting Polymers as Electro-active Substrates for Tissue Engineering and Related Applications

Biocompatible materials with appropriate mechanical and electrical properties can provide ideal platform for anchoring and directing characteristic cells. It is well known that extracellular environment plays major role in determining the shape and function of cells and in turn the tissue systems. The interaction between cells and other biological or artificial surfaces is mediated by protein complexes, such as cell-adhesion molecules (e.g.,
integrins), intermediary filaments (e.g., F-actin bundles), and multi-adhesive matrix proteins (e.g., fibronectin). These signals, combined with intercellular signalling within the organ or tissue, affects the overall structure and morphology of a tissue.

The class of organic polymeric materials satisfy many of the criteria that are required for interfacing and accessing the bioenvironment. These materials mediate the large difference in mechanical modulus between the electrical circuit and the biological system and are also shown to be biocompatible. The key feature of these materials are: (i) Organic materials can be chemically modified with bio-molecular side-groups to promote cell viability. (ii) Conducting polymers are electrochemically active and conduct electrons as well as ions. This property renders these materials to be more selective and sensitive than metal-based or silicon-based materials. (iii) Unlike silicon and metals, these materials are transparent in the thin film form and are hence compatible with microscopy techniques. (iv) Organic conducting materials are soft and can be self-assembled and organized to mimic biological structures. This property has been used to obtain 3-D scaffolds for directed cell growth. (v) Various indicator/enzyme/neurotransmitter molecules can be incorporated on the surface or inside the polymer bulk. (vi) These polymers are stable at physiological temperature and pH.

Conducting polymers such as Poly-(pyrrole), Poly-(aniline) and Poly(3,4-ethylenedioxythiophene) doped with poly(styrene sulfonate) (PEDOT:PSS), have been extensively studied as novel biointerfaces for neural and tissue engineering and are shown to provide a suitable microenvironment for growth and differentiation of cells. The electroactivity PEDOT:PSS, in particular, has been shown to be biocompatible with a wide range of organospecific cell types viz. the epithelial cell lines HeLa and T24, endothelial cell lines, fibroblasts, macrophage-like cells, T cells, as well as primary neuronal cells. PEDOT:PSS has also been used for activation and sensing of neuronal activity in vitro. Apart
from these in-vitro studies, the state of the art PEDOT:PSS microelectrode arrays have been implanted in-vivo as cochlear implants in guinea pigs\(^{15}\) and for electrocorticography (ECoG) in rats\(^{16}\).

Recently, our group has used stretched and electrified PEDOT:PSS coated Styrene Ethylene Butylene Styrene (SEBS) substrates for differentiation of mouse embryonic stem cell derived neural progenitors (ES-NPs) into neurons.\(^{17}\) Narayan and co-workers have introduced SEBS as a novel biocompatible, flexible and stretchable substrate which can be used to tune the electroactivity of PEDOT:PSS upon application of strain.\(^{17}\) It has been shown that the mechanical properties of the stretched-electrified substrate effect both differentiation and distribution of ES-NP cells. These results can have implications in designing flexible implants, scaffolds or sensors for the regeneration of axons in injured tissue areas.\(^{17}\)

### 3. Semiconducting Polymers for Optical Stimulation of Neurons

Organic semiconductor materials are optically active and have been widely adopted in research areas related to organic solar cells, organic light emitting diodes and organic field effect transistors (OFETs). The hybrid interface of organic semiconductors with electrolytes has also attracted much attention in the last few years due to their potential applications in electrochemical and electrolyte-gated field effect transistors, photoelectrochemical cells, and tandem photovoltaic and dye-sensitized solar cells.

Various conjugated polymers and molecules have been demonstrated to work as photosensitive layers in direct contact with aqueous electrolytes.\(^{18-21}\) The materials include regioregular poly(3-hexylthiophene) and poly(3-octylthiophene) (rr-P3HT and P3OT), MEH-PPV, poly[2-methoxy-5-(3′,7′-dimethyloctyloxy)-1,4-phenylene vinylene] (MDMO-PPV), poly [2,6-(4,4-bis-(2-ethylhexyl)-4Hcyclopenta[ 2,1-b;3,4-b′]-dithiophene)- alt-4,7-
(2,1,3-benzothiadiazole)] (PCPDTBT), poly{[N,N0-bis(2 octyldodecyl)naphthalene-1,4,5,8-bis-(dicarboximide)-2,6-diyl]-alt-5,50-(2,20-bithiophene)} (N2200) and PC60BM.

Our group has recently demonstrated the fabrication of a single-layer, multi-color detector based on the organic semiconductor/electrolyte interface. The device structure does not require any color filtering or sub-pixelation and works without external bias. The detection is based on appropriate thickness of the polymer layer in contact with aqueous electrolyte, which results in characteristic polarity and temporal profile of the photocurrent signals in response to various incident colors. The use of water and aqueous electrolytes serves as an effective barrier interface in the device, which modifies the electronic photocurrent to characteristic transient profiles. The device conditions closely resemble the environment offered by physiological buffer-solutions involved in natural vision systems.

We have further shown that the device characteristics (photovoltages, photocurrents and time scales) resemble features observed in certain natural biological systems, such as bacteriorhodopsin, photosynthetic membranes and more importantly, mammalian retinas. These interfaces have a significant potential in the field of neuromorphic engineering for the development of artificial neural systems as well as in bio-inspired light-detection systems like the retina. The device structure offers an alternative to the materials presently utilized in artificial retina solutions.

Similar potentials arising from the conjugated polymer/electrolyte interface have been recently utilized for stimulation of hippocampal neurons cultured onto the polymer surfaces. Further, certain conjugated polymers like P3HT have been extensively studied for their biocompatibility properties. We have also cultured primary retinal-neurons on many of these polymers in our laboratory and demonstrated their non-toxicity towards the cells (Fig. 2). The ongoing efforts of our group are
towards integrating these conjugated polymers with the degenerated retina models, aiming to restore the photosensitivity of the receptors, which have lost their ability to detect light.

![Images](a) (b) (c) (d)

Fig. 2: Primary retinal neurons cultured onto (a) Glass (b) Glass/ITO (c),(d) Glass/ITO/blend films of certain donor:acceptor systems of thiophene and naphthalene based organic semiconductors.

4. **OFET structures for Biosensing**

The use of organic bioelectronic devices where the conducting polymers are in contact with aqueous media, such as field effect electrochemical transistors, drug delivery systems and actuators, has been reviewed elsewhere. 28 OFETs which operate in low voltage, non-electrochemical regime in aqueous media have received considerable attention in past few years due to the wide range of their sensing capabilities. The analytes are typically introduced in the aqueous gate-dielectric media and quantified using the transistor characteristics. Alternatively, the gate electrode can also be sensitized to bind biomolecules, which modifies the threshold voltage characteristic of the OFETs. In these device
structures the active semiconductor layer needs to be protected from the salt solution. Various media like air\textsuperscript{29}, high-permittivity dielectrics,\textsuperscript{30,31} organic mono-layers\textsuperscript{32} and electrolytes\textsuperscript{33-38} have been used as electronic barrier between the gate and the channel. In similar lines, self-assembled monolayers and multilayers of nanometer thickness have been used as thin gate insulators in OFETs to obtain negligible leakage current.\textsuperscript{39} For instance, bilayers of phospholipid (PL) film were used as the dielectric layer in field-effect devices, where vesicles of PL have been spin coated over the organic P3HT semiconducting layer\textsuperscript{40} and SiO\textsubscript{2}\textsuperscript{41} to obtain mobilities of the order of $\sim 10^{-3}$ cm$^2$/Vs. Our group has recently demonstrated a novel facile method to obtain a self-assembled ultrathin dielectric layer of PL on P3HT and obtained a low operating voltage PL-water gated OFET with a mobility value $\mu \approx 10^{-2}$ cm$^2$/Vs.\textsuperscript{42} The introduction of a thin PL layer largely prevents the electrochemical modification of the polymer layer, reduces the leakage current and ensures the transistor operation in field effect mode. Such PL-water gated OFETs can be used for sensor applications in aqueous physiological media.

5. Summary

In summary, we have highlighted a few examples, which demonstrate the utilization of artificial organic-electronic systems in biological environment. This interdisciplinary approach of using engineered soft-substrates to access, examine, probe, and control active-biosystems should be of tremendous importance in advancing biomedical tools in variety of applications.

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