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Organic Bioelectronics**

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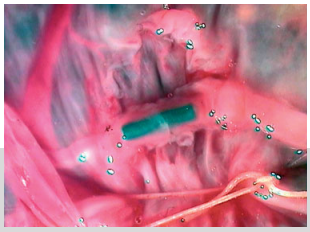

During the last two decades, organic electroactive materials have been explored as the working material in a vast array of electronic devices, promising low-cost, flexible, and easily manufactured systems. The same materials also possess features that make them unique in bioelectronics applications, where electronic signals are translated into biosignals and vice versa. Here we review, in the broadest sense, the field of organic bioelectronics, describing the electronic properties and mechanisms of the organic electronic materials that are utilized in specific biological experiments.

1. Introduction

Using electrical signals to interact with biological systems has helped us to gain insights into different fundamental signaling principles of living organisms. In addition, it has provided us with several important therapy tools. Before the age of enlightenment, nerves were understood as long straws, transporting fluids at a very rapid speed. At the University of Bologna, Luigi Galvani performed a series of experiments in the 1780s that blazed the trail for what today is known as bioelectrogenesis. In one experiment, he applied a brass hook and a steel scalpel to the detached leg muscle of a frog. Galvani found that he could induce muscular activity, which he denoted as "animal electricity". Indeed, Galvani was pioneering the use of bioelectric forces to study tissues of living organisms.

Because of the solid-state-electronics revolution, complex signal-processing circuits are available today that can be used to domesticate electrical signals into desired digital or analogue information at speeds beyond 1 GHz. By combining these solid-state electronic systems with biological specimens, many research groups are currently exploring novel bioelectronic concepts. Naturally, the aim is to gain increased understanding of various biological phenomena as well as to explore the potential use of bioelectronics in health care. One popular theme has been to use transistors, and circuits thereof, to sense and trigger different signaling pathways in live tissues. A silicon-based field-effect transistor has been used to regulate the cation concentration within cells.[1] In addition, neuronal activity can be activated and regulated by triggering signaling at the synapses using large arrays of nanowire-equipped devices.[2]

When studying various aspects of cell biology, the most common approach is to utilize cultivated cells originating from a variety of organs and tissues in selected animals. Such experiments are referred to as in vitro experiments. This is in contrast to in vivo experiments, where experiments are performed within an animal. Plastic, gels, and glass surfaces represent the most commonly used materials for propagation of cells in heated and humidified incubators. Various techniques are used to achieve an optimal cell hosting character among the substrates and scaffolds.[3–5] A few hours after cells are seeded into a sterile culture dish containing a nutrient-rich cell culturing medium they adhere to the surface and start to proliferate. Depending on the cell type cells may differentiate

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into a mature and/or activated form, as exemplified by neurons, see Figure 1. This process may take days to weeks. Other cell types, such as mucosal cells, form large areas of cells firmly attached to each other via specialized protein–protein complexes on each neighboring cell. Other cells, represented by macrophages, grow as independent entities in close proximity to each other. By the use of proper cell hosting scaffolds, cells are allowed to proliferate in three dimensions, which is desirable when the goal is to mimic the architecture of an organ.[6]

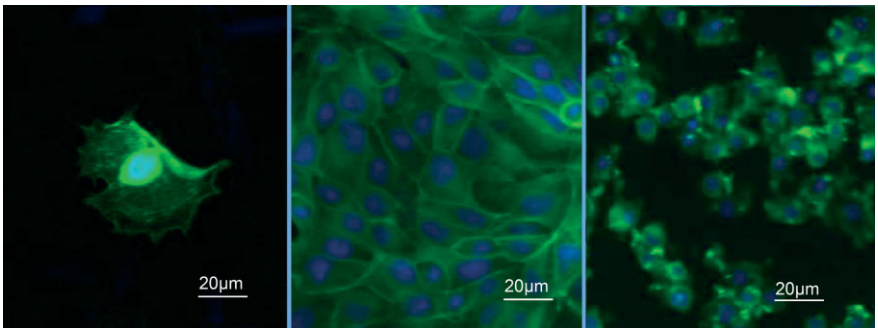

Figure 1. Morphology of various cell types outlined with the actin-binding dye FITC-phalloidin (green). Nuclei are outlined using the Hoechst 33342 dye (blue). left: HCN-2 neuronal cell; middle: MDCK epithelial cells forming a monolayer with intact tight junctions; right: Macrophages growing as single entities.

All biological systems are tightly regulated by a multitude of signals. This includes regulation of the life cycle of one individual cell as well as controlling the function of multicellular systems such as tissues and organs. Inside an organism these signals can be transported within the blood stream (the vasculature) and along neurons, where they pass from one neuron to the other via signaling across the synaptic cleft. In addition, signals may be transmitted between large clusters of cells that are tightly linked to each other. In this case, signals are transmitted via protein complexes forming so called gap junctions. The signals are relayed by a vast number of molecules ranging in size and structure from large proteins to single ions. Proteins are common signal substances within the vasculature, where they induce a systemic response. This often involves large populations of different cells throughout the organism, such as the activation of the immune response to various infections. Ions, on the other hand,

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Agneta Richter-Dahlfors received her M.Sc. in Molecular Biology in 1989 at Uppsala University. After giving birth to one child, she completed her Ph.D. 1994 at the Department of Microbiology at the same university. She then joined Biotechnology Laboratories at University of British Columbia, Vancouver, Canada, as a post-doctoral fellow working in the field of bacterial pathogenesis. From 1995–1997, she developed technologies to visualize bacteria-induced tissue rearrangements using small animal infection models. In 1998, she was recruited to the Department of Microbiology, Tumor, and Cell biology at Karolinska Institutet in Stockholm, Sweden, where she established herself in the field of Cellular Microbiology. She is currently a professor in Cellular Biology, heading a research group of 8 people. The major research areas of her group embrace the studies of bacteria-induced alterations of signal transduction pathways in eukaryotic cells with special emphasis on Ca^{2+} signaling, as well as real-time visualization of tissue remodeling that accompanies bacterial infections. Recently, she initiated interdisciplinary research projects aiming to integrate organic electronics technologies in biological applications. Since 2005, she is co-director of the Strategic Research Centre of Organic Bioelectronics.

are common in neuronal signaling, and the strictly regulated perturbation of the ion homeostasis drives the signal along neurons to highly specific targets. Although it is well-documented that oscillations of the intracellular Ca^{2+} concentration regulate processes such as exocytosis, gene transcription, and cell metabolism little is known about these mechanisms at the molecular level.[7,8] Thus, future research will unravel how the chemical characteristics combine with the spatial and temporal nature of a signal to control the physiology of cells and tissues.

Other signals known to affect the shape and function of cells can originate from the extracellular environment.[9] The interactions between cells and biological or artificial surfaces are mediated by endogenous 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).[10] These signals, combined with intercellular signaling within the organ, and signals from other tissues, will affect the overall structure and morphology of a tissue, as the positioning of the cells contains much information about the structure and morphology of the tissue.[11] Collectively, the examples provided here illustrate the complexity of signaling in biological systems, which utilize a variety of different signaling entities that are communicated inside and between cells and organs via a variety of pathways.

Electronic and electrochemical solid state devices base their functionality on i) electronic charge injection, ii) electric field-effects, or iii) electrochemical switching achieved in architectures based on inorganic and/or organic materials. To promote the interaction between such devices and living cells, biocompatibility and biostability of the electronics are of utmost importance. These features include, for example, translation of biosignals into electronic equivalences and translation of electronic signals into biosignals. In addition, the interface between the cell system and the circuit must be designed such that the original biological function of cells is preserved.

Electronics and opto-electronics[12–16] based on π-conjugated organic polymers and molecules have been extensively explored during the last 20 years, and are currently entering the market. The tremendous 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 systems can be flexible[17] and can be manufactured using printing tools.[18–23] Other special characteristics that make organic electronic materials truly unique and promising as the active material in bioelectronics include: i) functionality can easily be defined at the materials level, giving that chemical biosignals can be translated into electronics signatures or signals within the material itself; ii) in the thin-film state organic electronic materials are often transparent, which allows optical transmission imaging and use of various microscopy-based techniques when analyzing biological specimens interacting with the device; iii) organic electronic materials are soft and can be (self-)assembled and (self-)organized to mimic biological structures; iv) organic electronic materials conduct electrons as well as ions; and v) organic electronic materials can be decorated with (bio-)molecular side-groups to promote cell viability.[24]

Here, we review the current state of the field of organic bioelectronics, aiming to describe the devices that have been used to address long-standing questions in biology.

2. Organic Bioelectronic Devices

2.1. Organic Bioelectronic Materials Must Be Biocompatible

When producing materials that will become integrated with biological systems, it is of the utmost importance to validate the materials' biocompatible features. 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-polymer system, for example, 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 dope-ions. If these components seep out from the film during the course of an experiment, which often spans several days, they can be highly 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.[25] Finally, the absorption and organization of proteins on the surface is also important, as this defines to a great extent cell adhesion and other interfacing properties.

Various kinds of standard cell viability tests exist and have been explored to evaluate the biocompatibility of electroactive polymers for applications in biology. These include simple staining procedures, where the viability of a cell is defined as the capacity of a cell to exclude the dye Trypan Blue. Lack of this barrier function, as in dead cells, allows the dye to enter the cell, which can be observed as blue when analyzed under the microscope. More sophisticated test exists, using immunohistochemical staining with various antibodies, as well as testing whether cells attached to the electroactive polymer are able to proliferate when transferred to a glass surface.

Our laboratories have investigated the biocompatibility of several different pristinely doped as well as undoped conjugated polymers. While dodecabensosulfonate-dopded (DBSA) polyaniline (PANI) was found to be highly toxic to cells, other materials, such as thin films of poly(dioxyethylenethiophene) (PEDOT) doped with poly(styrenesulfonate) (PSS), were found to perform very well as a cell-culturing material. 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+,[26] fibroblasts (TGR1), macrophage-like cells THP-1 (ATCC TIB-202), T cells and neuronal cells HCN-2 (ATCC HTB-4). 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.

Coating the surface with matrix proteins can dramatically alter the biocompatibility of a material. One major source of such proteins is the serum, which is usually added to the cell-culturing medium. When Wong, Langer and Ingber in 1994[27] tried to cultivate endothelial cells on polypyrrole (PPy) thin films electrochemically polymerized onto indium-tin-oxide electrodes, they observed poor attachment of cells when the experiment was performed under serum-free conditions. However, coating the PPy surface with the extracellular matrix protein fibronectin before addition of cells dramatically improved the biocompatibility of the material. As the coated PPy thin films were switched between the neutral and oxidized states, it was also found that the cell hosting characteristics were controlled by the voltage bias. In the pristine, fully oxidized state of PPy, good cell adhesion followed by excellent cell growth and development of cell extensions were observed. In contrast, when cells were seeded onto surfaces switched to a partly neutral state (@–0.25 V) very few cells attached to the surface. Although the molecular mechanism behind these observations is unknown, it was suggested that different electrochemical states of the PPy film alter the protein synthesis in cells. Alternatively, the different electrochemical states of the PPy film were suggested to affect the cation concentration at the cell/surface interface. PPy has been used extensively in bioelectronic devices and its biocompatibility has been studied by several groups.[28]

One major advantage of organic materials is that they can easily be distributed on unorthodox substrates, with the aim of mimicking the structure and elasticity of biological systems. Various approaches have been explored, as exemplified by conducting polymer/hydrogel 3D electrodes.[29] Zhang and coworkers investigated the possibility of using PPy-coated polyester fibers, and fabrics of this material as candidate for vascular (electroactive) prostheses.[30] The PPy-polyester fabrics were sterilized with ethylene oxide. In the vasculature, biocompatibility translates into specific parameters. Measuring the amount of released hemoglobin by using a hemolysis assay shows whether or not the material has any detrimental effects on the red blood cells (hemolysis denotes the release of hemoglobin from red blood cells). Other biocompatibility tests included in vitro analysis of the blood coagulation time, as well as cell adhesion and cell proliferation. Finally, the effect of PPy-coated polyester fibers was analyzed in vivo by investigating the acute systemic toxicity of the material in a mouse model. It was concluded that PPy exhibits very promising characteristics suitable for electroactive vascular prostheses applications.

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.[3] Various approaches exist along this line, for example, using lithography techniques as well as different self organization approaches at the 2D and 3D level.

2.2. Electrodes

2.2.1. Electrodes for Stimulation

The perhaps simplest electronic device is an electrode in direct physical contact with, or in close proximity to, the medium that is measured or stimulated. Here, conjugated polymers offer several advantages over metal electrodes regarding, for example, selectivity and sensitivity. Moreover, a conjugated-polymer electrode can suppress various parasitic interface reactions. Finally, conjugated-polymer electrodes provide the possibility of immobilizing a vast array of indicator molecules along the surface or inside the polymer bulk.[31]

As early as 1986, PPy was evaluated as the outer electrode material for neural prosthetic applications.[31] It was shown that PPy grown on the cross sections of Pt wires embedded in glass improved the charge-pulsing capacity compared to bare Pt wires, see Figure 2a. To stimulate or record neuronal impulses, the impedance characteristics must be designed to enable signal translation between the electrode and the neuron, which usually occur at the biologically relevant frequency of ca. 1 kHz. The signals are transmitted over the electric double layers connected in series with a spreading resistance existing

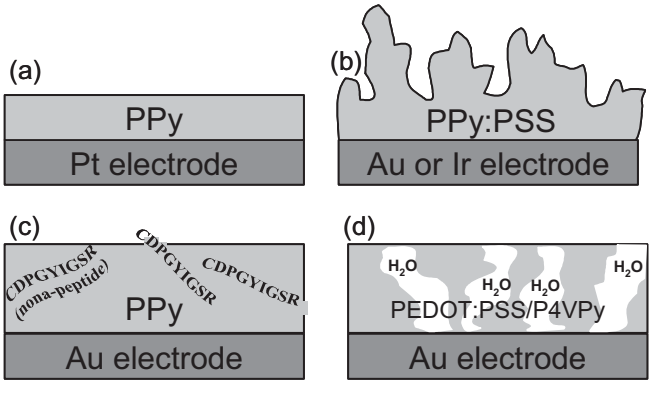

Figure 2. Electrode concepts for stimulating tissues and other cell systems; a) PPy-coated Pt-wire [32], b) textured PPy:PSS coatings formed on metal electrodes via electropolymerization, c) improved biocompatibility by including the nona-peptide molecule CDPGYIGSR in the PPy matrix [33], d) PEDOT:PSS hydrogel electrodes mixed with poly(4-vinylpyridine) [29].

along the tissue. One major challenge has been to develop an electrode with the highest possible capacitance for a given electrode area. David C. Martin and colleagues at the University of Michigan approached this by electropolymerizing thick PPy-coatings on Au and Ir electrodes.[34] At optimal polymerization conditions, the effective area of the PPy films was approximately one order of magnitude greater compared to the smooth electrode surface (Fig. 2b). Moreover, PPy is electrochemically active, which favors the charging capacity of the electrode, resulting in reduction of the cut-off frequency. The optimal thickness of the PPy film was found to be 13 μm, which corresponds to a peaking root mean square value of the nodular PPy surface roughness. In Martin's study, the impedance at 1 kHz was reduced by a factor of 26. Coating metal electrodes with a conjugated polymer to increase the effective surface area is not restricted to PPy. In 2004, the group of John Reynolds at the University of Florida teamed up with the Martin group to manufacture neural electrodes coated with a PEDOT derivative. This work demonstrated that hydroxymethylated EDOT monomers could be electrodeposited on gold pads to form highly textured PEDOT-MeOH:PSS coatings, see Figure 3.[35]

Activation and sensing of neuronal activity has mostly been performed in vitro. This is also true for most biocompatibility tests performed on organic bioelectronic materials. The neuronal tissue often reacts to an implanted electrode, as exemplified by induction of a local inflammatory response, elevated expression of intermediate filament proteins and general thickening of the surrounding tissue. Eventually, such effects will isolate the electrode from the targeted neuronal tissue, leading to suppression of the transferred signal level. Surface modification techniques, such as addition of targeted biomolecules known to enhance electrode adhesion to specific tissues, have successfully been used to further improve the biocompatibility of polymer materials. In a recent study, Martin reported that nona-peptides (CDPGYIGSR) co-deposited together with PPy onto Au electrodes, suppress undesired tissue–electrode reactions (Fig. 2c).[32] This was found when analyzing the brain tissue of a guinea pig with electrodes implanted for several weeks. Based on soaking experiments in vitro, it was shown that the nona-peptide was trapped inside the PPy-bulk. The nona-peptide/PPy coating promoted the overall neuronal attachment but could not entirely suppress undesired tissue–electrode reactions, such as gliosis.

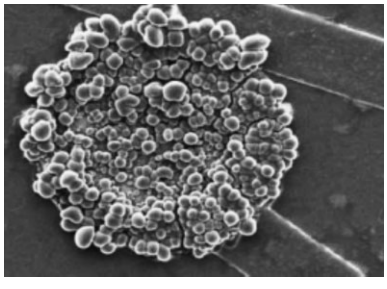

Figure 3. A scanning electron microscopy image of a PEDOT-MeOH:PSS coated electrode. Reproduce with permission from [35]. Copyright 2004 Elsevier Ltd.

Tissues within an organism are rarely structured along planar interfaces, nor are the associated signals. It may therefore be desirable to develop 3D soft scaffold electrodes that offer a porous structure. This has the advantage that cells can grow into the scaffold, which in addition enables fast diffusion of analyte molecules and signal substances. Following this strategy, P. Åsberg and O. Inganäs at Linkoping University, Sweden, manufactured PEDOT:PSS hydrogel electrodes mixed with poly(4-vinylpyridine) crosslinked and coordinated by osmium (Fig. 2d). Their aim was to develop electrodes for cellular interfaces in general and for neurons in particular.[29]

2.2.2. Electrodes for Sensing

So far, we have discussed the use of polymer (coated) electrodes to convert an electric addressing signal into the proper stimulation of a cell system. Conversely, electrodes can capture and translate signals emitted by cells as a result of a specific physiological situation. Polymer sensor electrodes, acting in the amperometric[36–38] as well as in the potentiometric[39] mode, have been developed to sense a vast array of biologically relevant analytes and a subset of examples are reviewed below.

Immunosensors have gained great attention for decades, as they can be used to monitor quick, sensitive, and selective immunological responses. These systems utilize the high affinity of antibodies interacting with their corresponding antigens. The approach has been to realize so-called enzyme-linked immunosorbent assays (ELISAs). The ELISA sensor system is then combined with different photometric and chromatographic techniques to couple the analyte sensing part to proper signal recording. Recently, the ELISA approach has been combined with amperometric electrodes, producing a sensor system where the enzyme is used to amplify the primary sensor signal. The electrochemically active species that are formed or consumed in the enzymatic reaction can then 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),[40] and catalase have been utilized as the enzyme conjugate.[41] The coupling of the target in the analyte and the corresponding antibody defines the primary signal.

One problem in using mediators, enzymes, and antibodies, is that they may leak into the analyte solution. Farzana Darain and co-workers, at Pusan National University in Korea, addressed this problem by polymerizing carboxyl terthiophene monomer (TCAP) onto screen-printed carbon electrodes.[41] The carboxyl groups represent immobilizing sites for HRP via amide bonds (Fig. 4a). The electrode was subsequently exposed to streptavidin (which binds covalently to TCAP), biotin, and the specific antibody anti-rabbit IgG (RIgG). The analyte then contains a known concentration of RIgG-GOx, glucose, and also the target, the RIgG molecule. RIgG and

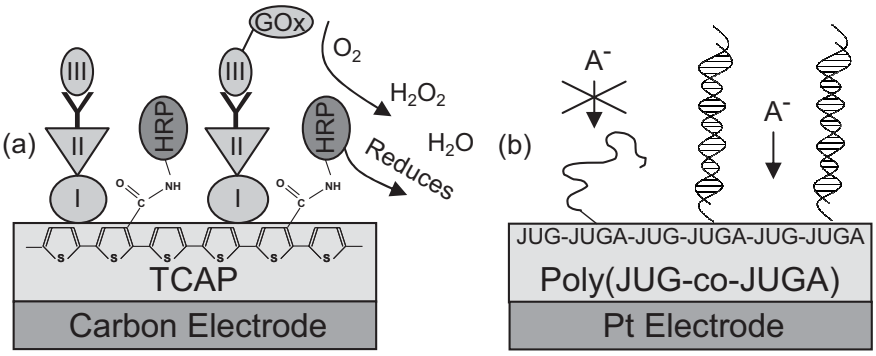

Figure 4. a) The electrode structure used for amperometric sensing of rabbit IgG. b) A different amperometric sensing approach including oligonucleotides stained along the conjugated polymer electrode surface.

RIgG-GOx compete for the anti-RIgG sites. Depending on the concentration of the RIgG target, H_2O_2 (produced by RIgG-GOx) oxidizes HRP to a different extent. The level of oxidation of HRP is recorded at the electrode (reflected in reduction of HRP at cathodic potentials). The catalytic current was monitored amperometrically versus the Ag/AgCl reference electrode and the detection limit was estimated to 0.33 $\mu g\,mL^{-1}$.

Using enzyme conjugates, the activity of an electrochemical species defines the amperometric sensing principle. In electrochemical cells, of course, not only the activity of electrodes and species included in the sensor cell predicts the amperometric 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. Benoit Piro and Minh Chao Pham, at Université Paris 7-Denis Diderot in France, developed a bifunctional amperometric sensor[42] polymer consisting of a quinine-containing monomer (JUG),[43,44] serving as the ion-to-electron transducer, as well as a carboxylic site (JUGA) for immobilization of oligonucleotides (Fig. 4b). At the surface of thin films of this poly(JUG-*co*-JUGA) polymer, the probe oligonucleotides form random coil-like structures. Electrodes of poly(JUG-*co*-JUGA) coated on Pt electrodes were immersed into phosphate-buffered saline (PBS) solutions. In this composition of JUG versus JUGA monomers, the oligonucleotide coils form a fairly compact layer localized between the electrochemically active (JUG) part of the polymer and the solution. The electrodes were included in a cell and characterized using a standard three-electrode setup, and the impedance characteristics of the electrode were investigated using impedance spectroscopy. It was found that a particular amperometric signal could be recorded when non-complementary oligonucleotides were added to the solution. In contrast, addition of the complementary target sequence (genome sequences from HIV were used in this experiment) induced a considerably higher amperometric signal. This was explained by the fact that the complementary target hybridizes with the grafted probe to form double-stranded (double helix) structures, which are much less flexible than single-stranded, non-hybridized probes. As a consequence of hybridization, the capacitive and the resistive properties, at the electrode/solution interface as well as inside the film, were modulated and this defined the sensing principle. The charge capacity of the hybridized electrode film increased almost three-fold compared to a non-hybridized film.

2.3. Transistors

In sensor and cell stimulating electrodes, ionic charges either cross or polarize at the outermost surface of the polymer electrodes. Hence, signals are transferred between the polymer electrode and the analyte or the biological system, via faradaic or galvanic effects, respectively. If this signal polarization or exchange is associated with control of the lateral electronic conduction properties of the polymer film, the sensory signal can be read out as an amplified signal in a transistor. Both organic field-effect (OFET)[45] and electrochemical organic thin-film transistors (EC-OTFT) have been extensively studied for biosensor applications.[46,47]

2.3.1. Field-Effect Sensor Transistors

Bottom-gate OFETs[14,22] are built according to a lateral structure, with the transistor channel facing the ambient.

In 2000, the groups led by Ananth Dodabalapur (at that time at Bell Laboratories, USA) and Luisa Torsi (University of Bari, Italy) reported that the transistor throughput current was altered upon exposure to different gases (O_2 and H_2O vapor as targets). OFETs were produced that included 1,4,5,8-naphthalene tetracarboxylic dianhydride (NTCDA) as the active materials (Fig. 5a).[48] The interaction between different analytes and the organic solid was believed to induce charge-trapping sites. This explains that both the transistor threshold voltage as well as the field-effect mobility varies upon exposure to the gases.

To enable OFET sensors to operate in biological environments the "ambient" is rarely air; it is rather an aqueous cell-culturing medium containing compounds vital for cell proliferation. OFET transistors must accordingly function in aqueous media. In OFETs high electric fields are generated at the very close vicinity of the drain and source electrodes. Considering the high electric fields, and accompanying potential differences, electrochemistry with water is expected to occur. Takao Someya and Ananth Dodabalapur (then both at Bell Laboratories, USA) addressed this challenge by developing an OFET with drain and source contacts capped by a fluorinated polymer.[49] Due to its low energy surface as compared to the less hydrophobic organic semiconductor, the fluorinated material defines guidance of water. The authors produced a series of experiments in which different organic semi-

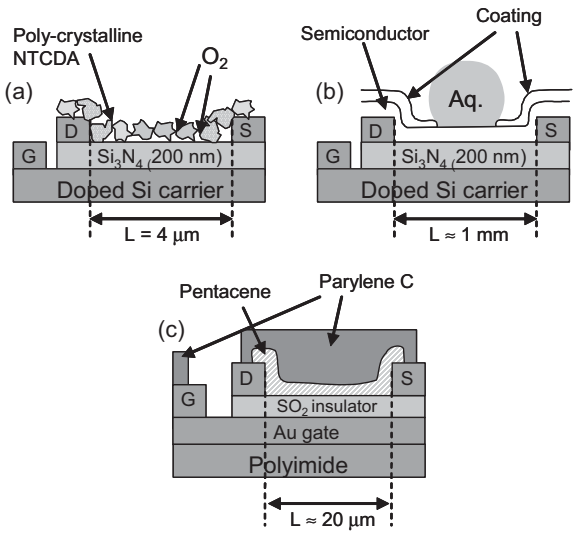

Figure 5. a) OFET sensor for gas sensing [48]. b) OFET sensor including pentacene and α-sexithiophene as the semiconductor to detect detect glucose and lactic acid in aqueous solutions [49]. c) Parylene C coated OFETs realized on polyimide to enhance the biostability characteristics of organic bioelectronics [51].

conductors, such as pentacene and α-sexithiophene, were tested initially in pure water. Then the organic semiconductors were used as sensors to detect glucose and lactic acid in aqueous solutions (Fig. 5b). The prime result of this study was that water has an obvious effect on the drain-source current but this does not override the sensing signal of the target (glucose and lactic acid). The sensitivity threshold was found to be approximately 10 μM. In addition, the authors included the OFET sensors along the floor of a microfluidic channel, in order to estimate the associated sensor response and recovery time. Small volumes of 1 M lactic acid were injected into the water flow up-stream with respect to the OFET sensor, and the associated response and recovery times were found to be in the order of 10 s. Because the sensory function originates from induced traps at grain boundaries, crystallinity and the overall morphology of the organic semiconductor is expected to predict the performance of the sensor to a large extent.[50]

Besides acting as sensors, OFETs may serve nature in other ways. In the human body, the sensory organs generate an information flow of about 10^{10} bit s^{-1} during active moments. The retina alone contains ca. 10^8 receptors located in 10^5–10^6 pixels scattered over the inner surface of the half sphere of the eye. Globally, millions of people suffer from different incurable and progressive eye diseases, for example, retinitis pigmentosa and macular degeneration, which frequently cause blindness. Biomedical implants, in the form of neural prostheses can restore some functions of the eye. This generates great promises for a future technology that will aid people to regain their vision, at least partially. The technology of such prostheses comprises densely packed detector elements, for example, in the form of an $m \times n$ matrix, that record the optical wavelengths captured by the eye, and electrodes that stimulate the nerve cells. Unique direct addressing of each pixel requires exclusive wires to each individual pixel device, that is, at least $m \times n$ wires. However, bundles of wires can not be used, as the available anatomical space of the eye is limited. Instead, transistors can be used as addressing switches in combination with the detector device, accordingly, only the order of $m + n$ wires will be required for a full matrix readout or stimulation. Field-effect transistors are known to suffer from malfunction or at least fast degradation upon exposure to harsh environments, such as inside the human body. Thomas Stieglitz and his co-workers at the Frauenhofer Institute for Biomedical Engineering in St. Ingbert, Germany, have developed pentacene-based transistors on flexible polyimide foils devoted to processing and addressing functional electrical stimulation in neural prostheses applications. 10 μm of Parylene C were coated, at room temperature, onto the evaporated pentacene thin film, leaving only the gold gate, drain, and source electrode pads uncoated.[51] The flexible polyimide carrier, combined with the parylene coating on top, showed very promising results in terms of biocompatibility and biostability. The Parylene C formed pinhole-free films, thereby preventing any kind of direct physical contact between the sensitive transistor channel and the body fluids. Recent work from the same group addresses the use of these encapsulated OFETs in true physiological environments.[52]

2.3.2. Electrochemical Transistors

EC-OTFTs[15,53,54] have been studied during the past few decades and have been explored in various sensor applications.[38,55] The EC-OTFTs operate at relatively low voltages (limited risk for hydrolysis), and they transduce ions to electrons very efficiently. Together, these features make EC-OTFTs suitable for an array of different biological sensor applications. As the EC-OTFT gate is addressed, electrochemical half-reactions occur at the gate electrode and in the polymer channel. Ions cross the gate/electrolyte and the channel/electrolyte interfaces, and the latter controls the overall doping level and therefore the impedance inside the channel that links the drain and source contacts. This defines the principle of operation for the EC-OTFTs and is recorded as a change in drain-source current level.

PEDOT:PSS has been utilized in many different electrochemical devices as well as in bioelectronics in the form of the electrode or transistor channel in electrochemical sensors. By switching the oxidation state of PEDOT:PSS, its bulk conductivity can be controlled over five orders of magnitude which, in part, make this material an excellent candidate as an ion-to-electron transducer. George Malliaras and his team at Cornell University, USA, recently demonstrated a cascade of PEDOT:PSS-based sensor transistors for different bioelectronic applications. Due to their simple and robust device architecture, PEDOT:PSS-based EC-OTFT sensors are promising candidates for single-use printed sensor and analysis systems. One medically relevant problem that stresses the need for a

single-use sensor system relates to glucose sensing. The Cornell team utilized a PEDOT:PSS-based transistor that included a PBS solution as the electrolyte (Fig. 6a). As the gate was biased (0.6 V applied to a Pt wire) the current between the drain and source decreased moderately as a consequence of faint reduction of PEDOT in the transistor channel. Addition of GOx[40] to the PBS solution caused a similar, moderate reduction of the conduction inside the channel. In the third step, when glucose was added to the PBS-GOx solution, a dramatic change of the current through the channel was observed (Fig. 7).[56] When addressing the gate, it was observed that the current modulation along the channel versus the concentration of glucose is close to linear, in the range of 0.1–1 mM. The authors attributed the sensor response mechanism to one or several electrochemical effects. GOx catalyses glucose, thereby producing gluconic acid and hydrogen peroxide (H_2O_2). The production of H_2O_2 in the PBS solution may affect the activities at the electrodes of the Pt/PBS/PEDOT:PSS two-electrode cell and may shift any of the associated potentials. Interestingly, this PEDOT:PSS EC-OTFT sensor operates with stable response characteristics from pH 5 to pH 9, indicating that the nature of the sensor function is entirely electrochemical.

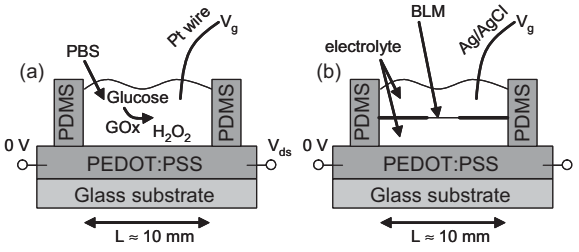

Figure 6. a) An EC-OTFT sensor, based on PEDOT:PSS as the ion-to-electron transducer transistor, used to sense glucose in PBS solution. b) The same PEDOT:PSS-based transistor, now combined with a BLM.

To introduce selectivity, electrochemical sensor transistors have been combined with various membranes and electrodes. These additional materials link sensing selectivity to a desired control of the impedance characteristics of the transistor. Bilayer lipid membranes (BLM), a cornerstone in biology, have been extensively studied by biologists and physicists for a long time. The BLMs organize spontaneously and form dense layers known to block and control ion permeability at voltage differences even exceeding 100 mV across the membrane. The BLMs can be made permeable to specific ions on the inclusion of ion channels that allow passage of specific ions. In a next generation of the PEDOT:PSS-based EC-OTFTs the Malliaras team explored the possibility of using a BLM to separate the gate from the transistor channel (Fig. 6b).[57] At low gate voltages, BLM suppressed the migration of cations in the (electrolyte) solution, thus inhibiting reduction to occur inside the PEDOT:PSS channel. By incorporation of gramicidin ion channels[58] in the BLM, monovalent ions, in this case

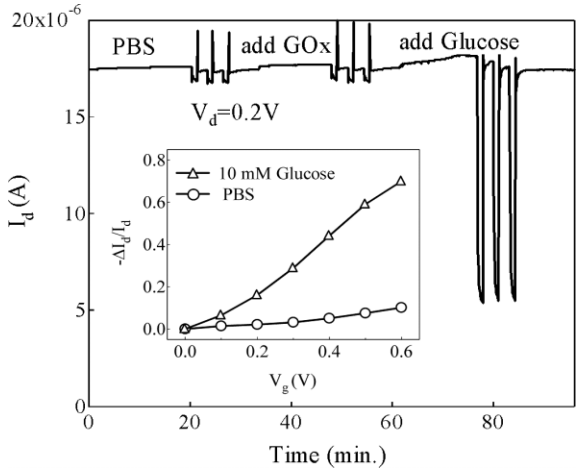

Figure 7. The sensor response characteristics of the PEDOT:PSS-based glucose sensor developed by Malliaras and co-workers. Large modulation of the current is observed only when GOx and Glucose both are present in the analyte solution. Reproduced with permission from [56]. Copyright 2006 The Royal Society of Chemistry.

K^+, could easily pass through the membrane, which enabled modulation of the drain-source current. In the third experiment, a $CaCl_2$-electrolyte was tested and, again, a very low gate-induced modulation of the channel current was observed. Collectively, this suggests, and is in agreement with prior experiments,[58,59] that gramicidin makes BLMs permeable to monovalent rather than divalent ions.

2.4. Actuators

Organic polymer-based electrochemical devices are typically composed of at least one polymer thin-film electrode, a counter electrode, and in some cases, a reference electrode. All of them are in galvanic contact with a common electrolyte. By altering the doping concentration of the polymer thin film, the bulk conductivity and surface tension characteristics can be controlled, as well as its volume changes. Switching the polymer oxidation state is accompanied by mass transport in the form of doping ions and solvent molecules, which move in and out of the polymer bulk. This explains the resulting volume change, which has been extensively explored in various actuator devices during the last 15 years.[60–63] In these actuators, the polymer film is often placed on top of a thin, inorganic, metallic (often gold) flexible sheet, which serves both as the electrode and as the electrochemically inert supporting carrier. Upon biasing the bi-layer electrode structure versus the counter (and reference) electrode, the volume changes of the polymer causes a bending like motion (Fig. 8). Such bending-type actuation can be operated in air by replacing the electrolyte with its solidified equivalent.[64] Polymer actuators have been explored in several medical and biological applications, for example, to mimic muscular functions and as micromanipulators in surgery.

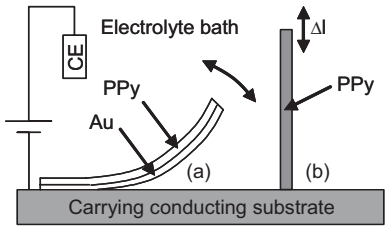

Figure 8. Bending-type (a) and elongation-type (b) actuations from electrochemical polymer micromuscles.

Typically ten sutures are required in the time-consuming and technically challenging procedure of reconnecting the two ends of a damaged blood vessel. At Micromuscle AB, a smart blood-vessel connector has been developed based on a unimorph polymer actuator performing the "rocking-chair" bending type of motion. This smart connector is composed of a Au/PPy bilayer and is shaped into a cylinder just by rolling the bilayer foil. Initially, the connector cylinder is in its contracted state, that is, in the small-diameter state, when it is inserted into the outlet and inlet openings of the damaged vessel. By applying 1 V to the connector, the cylinder slightly unrolls, thereby increasing its diameter. This forces the two vessel ends to form a tight connection (Fig. 9).

The monomorph polymer/metal electrode yields the well-known "rocking chair" (bending) type of actuation. However, mimicking muscular action requires an elongation-type of actuation. In comparison to muscles, such pseudo-muscular actuators are likely to perform at least equally well in terms of, for example, displacement forces and response time. In 1996, De Rossi and co-workers reported muscle-like linear actuators based on 90 mm long, 32 μm thick, free-standing films of PPy doped with benzensulphonate ions immersed into an electrolyte bath (Fig. 8b). This very basic polymer actuator was studied with respect to its isotonic displacement and isometric developed force. The authors found that the actuator exhibited a linear strain versus exchanged charge regime in 0.1 $C\,mm^{-3}$ to 0.4 $C\,mm^{-3}$. The overall elongation was in the range of 0.1 % to 0.5 %, with an associated response time of 20 to 30 s. The authors concluded that this form of free-standing conducting polymer actuators truly can mimic the function of muscles, in part due to the linear response and large contraction-elongation swing upon biasing. However, the muscular response time must be considerably faster. This can be achieved by reducing the ion migration path inside the PPy thick film, either by reducing the polymer film thickness or by manufacturing a PPy wire bundle instead of a bulky polymer thick film.

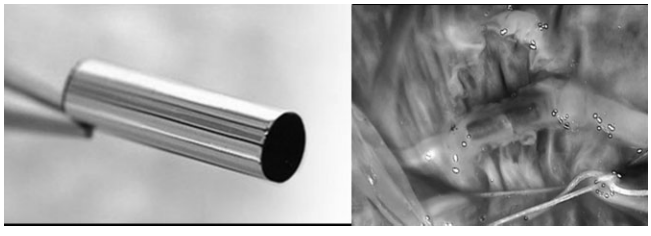

Figure 9. Left, the blood-vessel connector based on a "bending-type" actuator. Right, the same connector inserted (and electrically addressed) into the openings of the damaged vessel. Reproduced by permission of Micromuscle AB.

2.5. Drug Delivery Devices

Pharmaceutical compounds range from small ions to large and complex proteins and molecules. To achieve a proper response to the treatment, the pharmaceuticals must be delivered inside the body at an optimum rate, and in some cases, at a defined site. Drug delivery devices and materials[65] have flourished during the last few decades and are extensively used in various kinds of treatments. In this context, an investigation into conducting polymer-based devices has been conducted to examine how they can serve as electrically controlled drug delivery devices inside the body. One major challenge is to develop a conducting polymer drug delivery device that allows strict control of the ON/OFF state. In addition, such a device must be able to deliver the drug of interest at doses that are required to obtain the therapeutic effect.

In the early 1980s, Larry Miller and his group at the University of Minnesota, USA, developed a range of different electrochemically driven drug delivery devices. Initially, films of cobalt(III) complexes were loaded with neurotransmitters.[66] By reducing this electrode, the neurotransmitters were efficiently released into the solution. In another effort,[67] functionalized polystyrene derivatives that carried cationic isonicotinamide groups were synthesized. The amine portions of these polymers correspond to the neurotransmitters α-aminobutyric acid and glutamic acid. Thin films of these material systems were coated onto glassy carbon electrodes and studied in electrolytic media. At the cathodically addressed electrode (–0.9 V versus the SCE) release of neurotransmitters were observed, though at a very slow rate. The poor rate was explained by a slow propagation of the reduction front throughout the polymer bulk. In 1986, the Miller group reported[68] the use of polythiophenes (PT) and PPy in electrochemically gated drug delivery films (Fig. 10a). By coupling anions, for example, acetylsalicylate, or cations, for example, dopamine, to the conducting polymer matrix, it was found that the reduction and oxidation fronts propagated at a much faster rate in the conducting polymers, as compared to the situation when polystyrene was used as the electrode coating material. In addition, the associated drug delivery rate was found to increase considerably. To explain the observed electrically controlled drug release, it was proposed that depending on the oxidation state of the PT and PPy molecules the anionic and cationic neurotransmitters are imprisoned inside the polymer matrix to a different extent. As the conducting polymer film is electrochemically switched to a different oxidation level, the drug decouples from the associated ionic bonds and can freely diffuse away from the film.

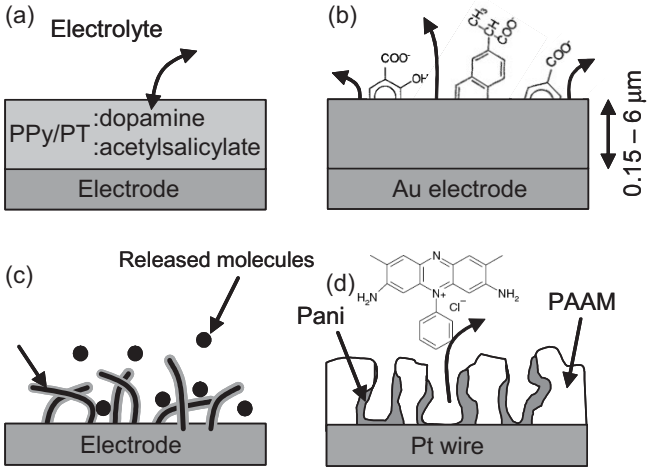

Figure 10. a,b) Electrochemical active polymer films loaded with different biomolecules. c) Inert fibers coated with a drug-releasing conducting polymer providing an increase in the effective area. d) A similar approach where polyacrylamide gels are used as scaffold for Pani.

Major efforts have been devoted to optimizing the conditions of conjugated polymers for ion-gated, or electrochemically triggered, drug release. The processing conditions predict the morphology of the polymer to a great extent, and accordingly, dictate the ion-exchange and electrochemical behavior of the resulting film. Both of these features are of utmost importance for drug delivery. During the late 1990s Sundholm and co-workers at HUT in Finland, optimized the electropolymerization route for PPy-based drug delivery films[69] for a range of different anionic drug molecules that exhibit specific therapeutic activity, for example, salicylate, naproxen, and nicoside (Fig. 10b). The membranes were produced of electropolymerizing films of PPy:sodium tosylate, with thicknesses ranging from 150 nm to 6 µm. By cycling the membranes between different potentials, efficient ion exchange between the sodium tosylate and the desired dissolved anion was promoted. To evaluate the electrochemically triggered drug delivery characteristics, the drug-loaded PPy films were exposed stepwise to increasingly negative voltages versus the reference electrode. The authors found large variations in the triggered release of the drug molecules tested, probably as a result of their great differences in electroactivity.[70] The overall rate of drug release from electropolymerized PPy is rather low, which suggests that drug delivery based on PPy membranes as investigated here, are restricted to compounds that provide the desired therapeutic effects already at very low doses.

To increase the drug release rate in conjugated polymer membranes, different approaches have been explored. These relate primarily to enhancing the drug diffusion rate inside the polymer electrode in order to promote rapid escape of the drug. This can be achieved by producing a sponge-like porous polymer electrode, in which the receiving fluid can intermix with the polymer material. Coating the drug releasing conducting polymer along the surface of inert fibers, a fabric-like fluffy electrode[71] with a large effective surface is achieved (Fig. 10c). An alternative route to increase the release rate, as well as to enable release of more voluminous ionic drug molecules, is to combine the drug-emitting polymer with a hydrogel scaffold. In 2005, Córdoba de Torresi et al reported[72] that a polyaniline-polyacrylamide network electrode could be used for electrochemically controlled release of Safranin, (Fig. 10d). The hydrogel scaffold was synthesized according to a recipe[73] that produces a desired open and porous character. In a next step, Pani was electro-polymerized inside the gelled scaffold, using a Pt wire as the working electrode. Finally, the electrode was decorated with the bulky cationic Safranin molecules. The release was found to be surprisingly fast and the overall release rate could be electrically modulated over almost one order of magnitude. As the Pani-PAAM electrode is switched, Pani changes its chemical character along the inner surface of the pores as well as slightly changes the size of the pore cavities. Both these effects are expected to contribute in controlling the release rate.

In the previous experiments, the drug molecules were ionically coupled to the bulk of the conducting polymer, which restricts the applications of the device to small cationic or anionic drug molecules. Recently, Langer and his team at MIT, USA, presented a drug release device based on surface switching effects in PPy doped with biotin.[74] A monolayer of streptavidin was immobilized at the biotin sites along the PPy surface. Finally, biotinylated neural growth factors were allowed to adhere along the PPy surface. While switching the PPy electrode, the growth factors were launched away from the PPy surface. This enabled electric control of rather large molecules, since diffusion through the polymer bulk was avoided.

A completely different approach to deliver drugs upon electric stimulations has recently been explored. Marc Madou at The Ohio State University, USA, proposed various kinds of electronic cap actuators that function as micro-valves for small drug containers (Fig. 11). In the first initiatives he ex-

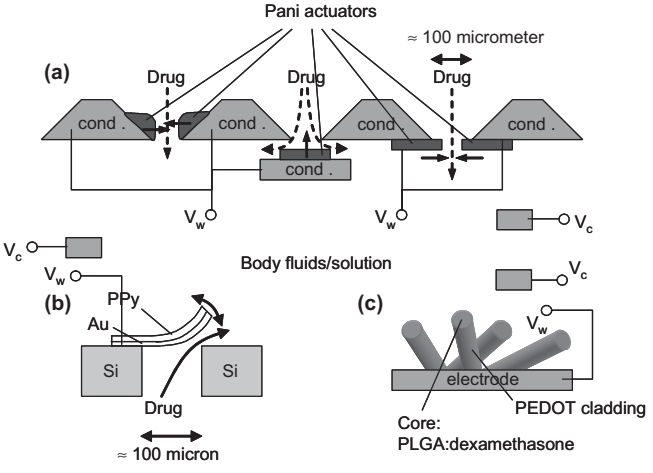

Figure 11. a) Pani actuator valves, which regulate the release rate of biomolecules from the container reservoir to the receiving fluid [76]. b) Use of a bending-type of actuator as a roller-cap for a drug container. c) PEDOT-coated poly(lactide-*co*-glycolide) fibers enabling fast release of dexamethasone [78].

plored the elongation-type as well as volume-type of actuations of Pani films to act as the electronic valve controlling the outlet of millimeter-sized drug containers.[75] In a recent publication[76] a PPy/metal electrode bilayer structure[77] was presented that serve as the roller-cap for smaller (micrometer) sized drug reservoirs. These complex micromechanical devices have great potential, in part because they offer huge contrasts in the drug delivery rate. In comparison to polymer membranes, these devices promise for a much higher overall delivery rates and they are not restricted to delivery of small charged (bio-)molecules.

Recently, the group led by David C. Martin reported a drug releasing system based on PEDOT-coated fibers. Using this approach, poly(lactide-*co*-glycolide):dexamethasone fibers were formed and grown using electrospinning onto a supporting electrode,[78] and PEDOT was thereafter electrochemically grown along the surface of the fibers. The release characteristics of dexamethasone were studied while the carrying electrode was biased at different voltages. The cumulative mass release of dexamethasone was found to increase dramatically as short voltage pulses were addressed to the electrode hosting the PEDOT/poly(lactide-*co*-glycolide):dexamethasone fibers. The electrically controlled release in this case is tentatively attributed to two parallel effects. First, as the oxidation state of PEDOT cladding layer is switched, a contraction force on the poly(lactide-*co*-glycolide):dexamethasone fiber core is induced. This force squeezes the core of the fiber, affecting the transport as well as the kinetics of the drug molecule. More important, it is expected that the PEDOT-cladding may crackle during a switch cycle. This will give rise to additional pathways for the dexamethasone drug to escape the poly(lactide-*co*-glycolide) core host via nano-cracks through the PEDOT cladding.

2.6. Organic Bioelectronics in Microfluidics

In addition to using microfluidic systems as multiplexer for analytes and reagents, they are also utilized in models representing the capillary system within biological species. Because organic electronic devices perform well on a broad range of carrying substrates, they are also expected to become easily integrated into muicrofluidics.

Traditionally, laser diodes and other solid-state light sources have been used to probe biomolecules inside microfluidics. However, lasers are normally particularly non-compatible with microfluidics, which prevents easy integration of the two techniques. Keyong-Sik Shin and co-workers at the Korea University in Seoul, developed an organic light emitting device fully integrated with a glass microfluidic system (Fig. 12).[79] To achieve a complete fluorescence-detector system, a silicon-based photodetector was integrated into this microfluidic system as well. The OLED-microfluidic system was applied as the excitation source to a competitive assay which included TMR-biocytin, streptavidin, and D-biotin, and was shown to have an associated limit of detection of approximately 1 μM. An all-organic polymer-based fluorescence-detection microfluidic system was recently developed by the group led by Donald D. C. Bradley at the Imperial College in the UK. Here, an all-polymer system was achieved that was suitable for single-use bioluminescence applications.[81] In addition to fluorescence-detection methods, EC-OTFTs and OFETs sensors have been incorporated into microfluidics.[82,83]

Thus, organic electronics have been combined with microfluidics in order to sense and record species of an analyte. Conversely, organic electronics can be used also to regulate the flow of the analyte itself inside the channel, enabling the analytes to intermix with reagents in a desired chronological order. As the electrochemical state of a conjugated polymer is switched, its chemical character inside the bulk as well as at the outermost surface is controlled. This will affect the surface tension, which can be used to control the movement and flow of liquids.[84] In 2005, Gordon Wallace, University of Wollongong, Australia, and his collaborators presented the results of including a surface tension switch based on PPy doped with dodecabenzenesulphonate (DBS) inside the walls of polymethylmethacrylate-based (PMMA) microfluidic channels. As the PPy is switched to the neutral state, the DBS molecules move freely, increasing the hydrophilicity of the PPy surface. In this state, the PPy coating "drags" an aqueous electrolyte inside the PMMA channel. The scientists showed that the electrolyte could be guided up to 10 mm inside the channel, simply because of this effect. In a recent publication, our group reported a microfluidic system in which polyhexylthiophene[85] was included as the surface switch along the floor of a microfluidic system.[80] Here, the polymer surface tension switches could act as the gates to guide an aqueous electrolyte in preceding y-branched intersections (Fig. 12). This suggests that electronic polymer surface tensions switches can be used in "fluidic logics", in which analytes can multiplex with different reactants in a complex manner.

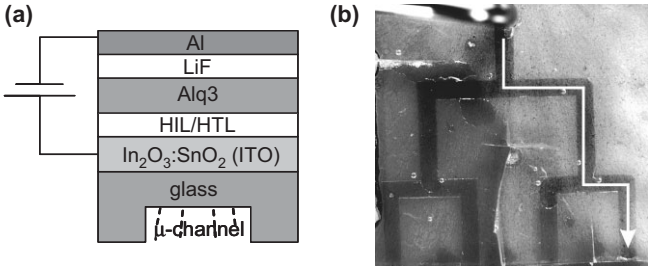

Figure 12. a) A glass-based microfluidic system including an organic light emitting diode serving as the excitation source for fluorescent materials [79]. b) A microfluidic system, including preceding *y*-intersections. Electrochemical surface tension switches, manufactured along the floor of the channel system, guides the aqueous solution Reproduced with permission from [80]. Copyright 2006 The Royal Society of Chemistry.

3. Future of Organic Bioelectronics

Today, organic bioelectronics represents a class of outstanding tools, ready to serve research related to biology and medicine. The outlook for this technology is indeed very promising. Below we take the opportunity to delineate some novel paths towards the future for this technology;

Until now, organic electronics have primarily been explored as recording and regulating devices that interface biological systems in the form of planar surfaces. However, the architecture of tissues is neither planar nor static. In contrast, tissues are soft, very flexible, and contain various degrees of natural movement as part of their physiological functions. Therefore, the softness and flexibility of organic electronic devices must be improved to increase its biocompatibility and biostability. In addition, the novel technology must to a greater extent mimic the overall structure in various biological specimens. Perhaps this is easiest to achieve by using the biological system as template for manufacturing devices.

Other signals, besides molecules and charge polarization, affect biological signaling pathways. This is exemplified by the nature of a surface, or scaffold, which cells adhere to. It is well-documented that proteins such as integrins, used by cells to interact with a surface, may induce signaling pathways leading to cell death in case the surface is inappropriate. In addition, many studies show that cell adhesion and proliferation can be controlled 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 drawback with current drug release (electrochemically active) polymer electrodes is the difficulty of achieving a high enough concentration of the released compound. Efforts must be directed towards developing a truly electronic (not a mechanical) release device with a potential to launch considerably higher numbers of drug molecules per area as compared to what is possible today. It is likely that a combination of device concepts from the electrochemical device technology area can aid in this process.

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