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Organic Bioelectronics: Bridging the Signaling Gap between Biology and Technology

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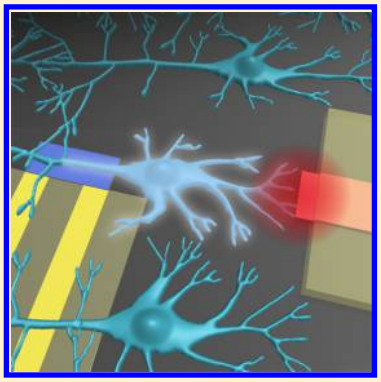
ABSTRACT: The electronics surrounding us in our daily lives rely almost exclusively on electrons as the dominant charge carrier. In stark contrast, biological systems rarely use electrons but rather use ions and molecules of varying size. Due to the unique combination of both electronic and ionic/molecular conductivity in conducting and semiconducting organic polymers and small molecules, these materials have emerged in recent decades as excellent tools for translating signals between these two realms and, therefore, providing a means to effectively interface biology with conventional electronics—thus, the field of organic bioelectronics. Today, organic bioelectronics defines a generic platform with unprecedented biological recording and regulation tools and is maturing toward applications ranging from life sciences to the clinic. In this Review, we introduce the field, from its early breakthroughs to its current results and future challenges.



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1. INTRODUCTION

Organic bioelectronics comprises the development and studies of organic electronic devices that operate as translators between the signals and functions of biology and those of human-made electronic processing systems. Utilized in one translation direction, organic bioelectronics can be used to regulate the physiology and processes of cells, tissues, and organs in a chemically specific manner and at high spatiotemporal resolution. Conversely, organic bioelectronics can also be applied to biological systems to selectively sense, record, and monitor different signals and physiological states, as well as convert relevant parameters into electronic readout for further

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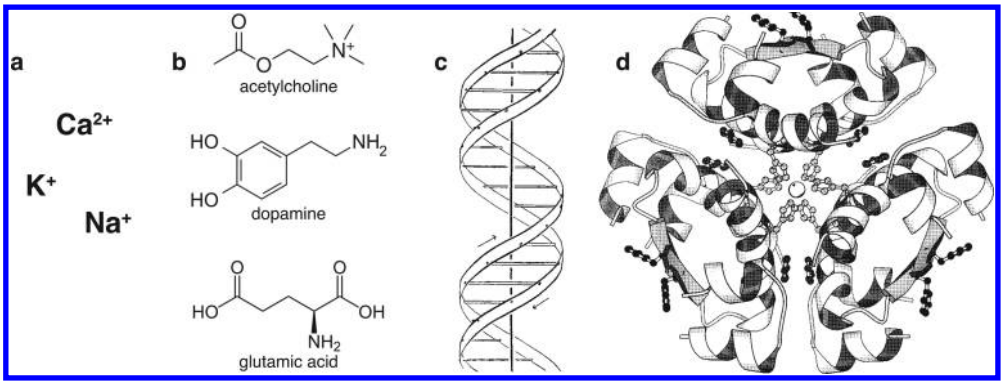

Figure 1. Examples of signals in living biological systems: cations (a), neurotransmitters (b), exemplified by acetylcholine, dopamine, and glutamic acid, (c) the structure of DNA, and (d) the nonsymmetric R6 hexamer of human insulin. Part c reproduced with permission from ref 3. Copyright 1953 Macmillan Publishers Ltd., Nature. Part d reproduced with permission from ref 7. Copyright 1997 American Chemical Society.

processing and decision making. Organic electronic materials can conduct and process both electronic and ionic (bio)signals, tightly coupled via electron−ion charge compensation. Moreover, organic electronic molecules and polymers can be designed via synthesis to possess several desired physical and chemical properties, thus enabling the manufacture of bioelectronics devices and systems that exhibit desired flexibility, elasticity, and morphology, and with a surface chemistry that promotes biocompatibility and stability over extended periods of time. Together, these properties make organic bioelectronics truly unique as a communication bridge across the biology−technology gap. In this Review, a survey of organic bioelectronics is included that covers the earliest experiments to the most recent achievements, targeting various applications in biology and medicine. At the end of the Review, we present our understanding and view of the remaining challenges and objectives for organic bioelectronics before successful implementation and commercialization is achieved in true therapy, diagnostics, and biotechnology applications.

1.1. Signal Carriers in Biology and Organic Electronics

1.1.1. Signaling in Biology. Signals in biological systems, such as those regulating the physiology and defense mechanisms in animals, are typically represented by various molecular entities ranging in size from small cations[1] and neurotransmitters[2] to giant-sized macromolecules such as DNA[3] and proteins.[4] The physical and chemical characteristics of the included molecular groups, their position within the molecule, together with the overall orientation and (primary to quaternary) structure define the specificity and function of the signaling entity; see Figure 1. Biological signals are produced and/or concentrated by various advanced biological machineries. For instance, across the walls of cells, different transmembrane proteins are immobilized that selectively pump or gate the passage of alkali ions, such as Ca^{2+}. Proteins are macromolecular structures that perform many of the active functions within living organisms and are also the key building block of a vast array of biological structures. A protein is manufactured via a complex, fast, and very precise production process within the cells based on the genetic information encoded in the DNA. First, the gene's double-strand DNA is made into single-strand copies. These copies, called mRNA, are introduced into the cell cytoplasm. The RNA strand is built up of a linear code, including the A, C, G, and U bases—a quaternary code compared to the binary 1s and 0s of digital technology. The mRNA is then decoded by the ribosomes, molecular machines found inside the cell, which translate the genetic code into 20 different amino acids which are polymerized into specific proteins. This process is fast; a protein, such as insulin, is manufactured from scratch in just a second or two.

Neurotransmitters are manufactured in the presynaptic nerve terminal and then packaged inside vesicles by the Golgi apparatus,[5] an organelle that is a part of the endomembrane system.[6] The vesicles remain inside the cells until a proper trigger signal (i.e., action potential) is received, forcing the vesicles to migrate toward the membrane boundary where they fuse with the outer membrane at a synapse and "burst", releasing their contents (neurotransmitters) through the process known as exocytosis. This is the prime signaling mechanism of the "presynaptic" nerve terminal; see Figure 2.

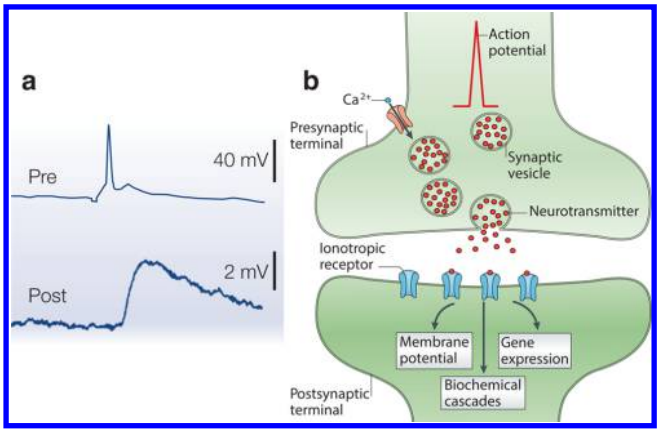

Figure 2. Action potential at the presynaptic terminal causes vesicles to migrate toward the synaptic cleft and release their contents. (a) Presynaptic and evoked postsynaptic potentials. (b) Illustration of the biochemical process. Part a adapted with permission from ref 8. Copyright 2004 Macmillan Publishers Ltd., Nature Reviews Neuroscience. Part b reused with permission from ref 9. Copyright 2014 Macmillan Publishers Ltd., Nature Reviews Neuroscience.

After the neurotransmitters have traveled across the narrow (30−50 nm) synaptic cleft, the "postsynaptic" terminal receives them. Here, the neurotransmitter molecules bind to receptors on the postsynaptic cell membrane, which then regulate the transport of cations, such as Ca^{2+} and Na^{+}, across the membrane, thus depolarizing the cell; see Figure 2.

This depolarization triggers yet another signal that rapidly may either travel through a new set of nerve cell protrusions,

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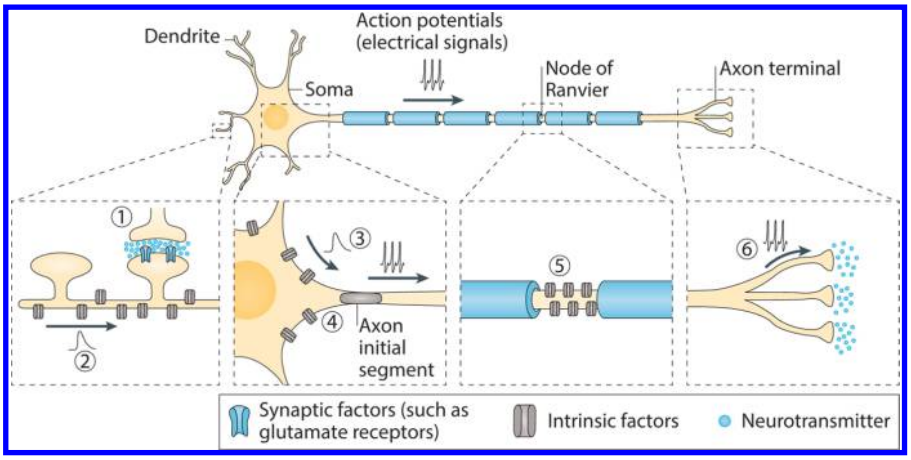

Figure 3. Signal received by a neuron through presynaptic neurotransmitter release (1) travels through successive subcellular compartments before it can transmit the information to the next neuron. At the synaptic level (1), glutamate generates an excitatory postsynaptic potential (EPSP) that is influenced by intrinsic factors (such as voltage-gated ion channels: K^+, Na^+, and Ca^{2+}) as it travels along the dendrite (2), soma (3), axon hillock, and axon initial segment (4). If an EPSP is strong enough to depolarize the membrane to action potential threshold, then action potentials are generated and will be further influenced by intrinsic factors, for example, those located at the nodes of Ranvier (5), as they travel along the axon, until they reach the axon terminal (6), where they will trigger neurotransmitter release. The myelin sheathes are depicted as the blue cladding. Reused with permission from ref 10 . Copyright 2013 Oxford University Press.

the axodendritic system, or trigger a specific function within a receiving organ. The rapid transport through the neuronal protrusions, i.e., the axons, is called the action potential (Figure 2 and Figure 3).

The action potential is a short-lasting and rapid transport of a distortion of the rest-potential of the membrane. As spikes, these signals travel along the axons, which include voltage-gated ion channels that are built up from protein structures. At the resting potential, these voltage-gated ion channels, which gate Na^+, K^+, and Cl^-, are closed. Because the membrane of the axon is most permeable to K^+, the Nernst potential for K^+ dictates the overall potential across the axon membrane. The resting potential is below—but close to—the threshold that opens the voltage-gated ion channels. As the membrane potential increases above the threshold, ion channels in the vicinity of this local potential swiftly open. This results in a net influx of Na^+ ions, which then forces the ion channels to reclose. The resulting depolarization travels along the axon at a speed up to ∼100 m/s. The capacitance is large across the cell membrane of the axons, and the depolarization is associated with voltage changes on the order of 100 mV. In part, the axon is coated with a fatty electrical insulator, the myelin coating, which promotes fast transport of the neuronal signal; see Figure 3. In myelinated nerves, the action potential is regenerated at the so-called Nodes of Ranvier, located in between the myelin sheets.

The interplay of ions, neurotransmitters, proteins, and DNA in neuronal signaling along with the action potential and synaptic signal transfer is just one example of a signaling cascade in biology. In parallel, there are many other biochemical signaling entities and pathways exemplified by the transport of hormones within the vascular system. Motivated by a further understanding of biology, diagnostics, and therapy, various tools have been developed to map and selectively record and trigger some of these pathways. With tools such as molecular probes, recording electrodes, or inorganic-based semiconductor devices, one can translate the status and concentration of a biomolecule into optical or electronic singles, and vice versa. Thus, this enables us to translate information across the biology−technology gap. One of the greatest challenges with present "translation" technology is that it is typically neither compatible nor stable when interfaced with biological systems. Further, present technology often also falls short to a great extent regarding biochemical selectivity and sensitivity. Organic electronic and optoelectronic materials can be synthesized to include various receptors or anchoring sites, as well as to express desired chemical characteristics, all of which can facilitate highly selective "translation". These materials can also be produced with geometries, morphologies, and mechanical properties that provide minimal invasiveness and biostability over long periods of time.

1.1.2. Organic Electronics, Materials, Structures, and Characteristics. *1.1.2.1. Classes of Organic Electronic Materials, Conduction, and Mobility.* The conduction of electrical charge in organic polymer and molecular solids has attracted great attention by scientists and engineers for many decades, in fact for more than a century. In the form of an ion, electrical charges may migrate through an organic solid material if enough cross section (i.e., pore size) and molecular dynamics (e.g., flexibility) are provided by the conducting solid. Polymers represent a unique class of materials for the conduction of ions, and several "plastic electrolytes" have been explored in vastly different electrochemical applications. In gel polymer electrolytes,[11] a relatively large amount of liquid, e.g., water, is stored within a cross-linked polymer scaffold along with the dissociated electrolyte. Ion conduction actually occurs throughout the solid bulk, and water typically has a major impact on the conductivity as its presence increases the dissociation of the electrolyte components. Polyelectrolytes[12] are yet another class of conducting plastics where the polymer itself is ionizable. The polymer then serves both as the scaffold medium and as the compensating ion for counterions, which can migrate under an electric field. Polyelectrolytes can be divided into polyanions and polycations, each being selective for transporting cations and anions, respectively. Polymer electrolytes, polyanions, and polycations can be included in various electrochemical, monopolar, and bipolar membrane device structures to form signal-processing devices for charged biomolecules, such as in the electrochemical cell, the organic electronic ion pump

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(OEIP),[13,14] the ion bipolar membrane diode,[15] and the ion bipolar transistor;[16] see Figure 4 and section 2.3. The

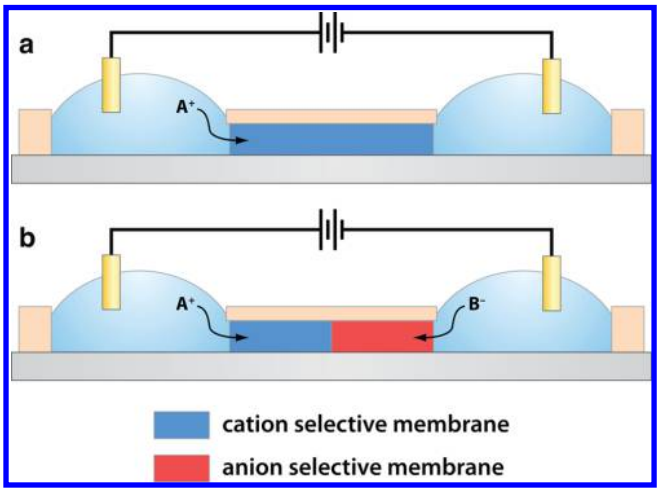

Figure 4. Device architectures of (a) an ion-selective resistor (e.g., an organic electronic ion pump (OEIP)) and (b) an ion bipolar membrane diode.

counterions of polymer electrolyte-based devices can be represented by various signals relevant—or even identical to—the ones included in signaling cascades of biological systems, e.g., biological cations and neurotransmitters. Further, by applying an addressing signal to the electrodes of such devices, which make use of particular-signal processing properties such as amplification or rectification, one can provide a technology platform to sense and deliver relevant substances to biological systems in a highly specific and complex manner.

In aromatic and conjugated organic molecules[17] and polymers,[18] the π-orbitals are delocalized along the molecule, giving rise to electronic mobility both along the chain and between adjacent chains via interaction between their π-orbitals. Adding or removing electrons to such material systems may result in a high electronic conductivity. In the form of positively charged polarons and/or bipolarons, electronic charges can thus migrate within and in between different molecules. Depending on electronic structure, density of charge carriers, and morphology, organic electronic materials can exhibit semiconducting,[19] semimetallic,[20] and even metallic[21,22] conductivity, all of which have been extensively explored in various solid-state electronic devices. Historically, most organic electronic materials are synthetic, but there has always been a parallel interest in naturally occurring organic conducting materials.[23−26] More recently, there has been growing interest in biologically derived "green" organic electronics to derive ion conductors,[27] organic semiconductors,[28] and dielectrics.[29] We foresee that these materials will soon become standard components for future organic bioelectronics.

Perhaps the simplest device structure is a thin organic film contacted by two electrodes, which provide charge injection and collection (Figure 5a). This structure is suitable for the study of charge conduction along the film but is also the fundamental configuration used in chemical resistors, or "chemiresistors". In these devices, the charge conduction varies depending on chemical reactions or material ad/absorption occurring on the surface or within the organic film.[30] If the two electrodes are instead sandwiching the organic film, the typical structure of a diode is achieved; see Figure 5b. In the diode

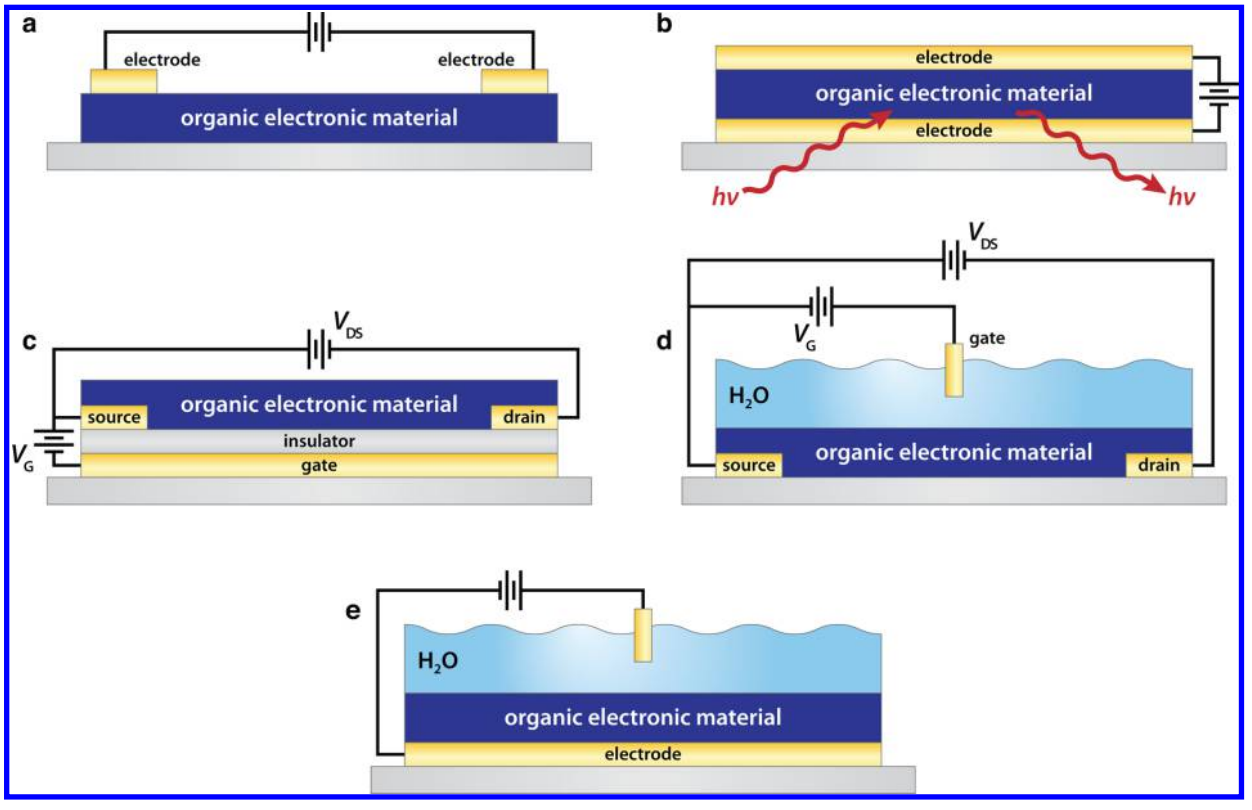

Figure 5. Device structures of (a) an organic chemiresistor, (b) a diode (e.g., light-emitting or photovoltaic), (c) a field-effect transistor, (d) a water-gated transistor, and (e) an electrode operated in aqueous medium.

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structure, the work functions of the two electrodes are chosen so that electrons can easily be injected from one electrode while holes can be injected from the other. This unbalance in work functions gives the classical current rectification versus voltage characteristics.[31] If the injected electrons and holes form excitons, and if the material is highly luminescent, this device can produce electroluminescence very efficiently. Organic light-emitting diodes[32] have thus been extensively studied and developed into a technology that is widespread in various commercial applications today. If the lifetime of the excitons is long enough, and if the organic semiconductor does not quench these excitations by itself, this diode structure can also serve as a photovoltaic device[33] for solar cell and photodiode applications. As light is absorbed in the material, the resulting excitons can dissociate into holes and electrons, in particular with the help of donor and acceptor phases defined in the organic semiconductor bulk.[34] These can then be collected at the two electrodes. By combining a vertical electrode configuration with a lateral one and also including a gate insulator, the classical field-effect transistor structure[35] is achieved (Figure 5c). The gate-insulator-semiconductor-source stack forms a capacitor configuration. By applying a voltage difference between the gate and the source, the number of charge carriers inside the semiconductor layer closest to the gate insulator is increased. The electronic current running from source to drain is field-effect modulated by the gate terminal and is highly sensitive to any modifications of the morphology, density of charge traps, dipoles, etc. in the channel. Such modifications can be due to reactions caused by chemicals or biomolecules. The transistor structures can be dismantled into two configurations, with one part including the source, drain, and transistor channel, while the gate electrode represents the second one. In such a device, a highly polarizable liquid medium, such as water, can serve as the "gating" medium; see Figure 5d. When a potential difference is applied between the gate and the source, Helmholtz layers are formed along the gate electrode and the organic transistor channel. If the electrolyte components do not penetrate the organic channel, field-effect gating is achieved, while if the ions pass across the liquid−semiconductor interface, ion exchange and charge compensation occur.[36] The latter is sometimes referred to as electrochemical gating.[37] "Water-gating"[38] of organic transistors has proven to be successful in sensing various biological and biochemical processes because this configuration provides an intimate coupling between biological receptors and reactions with the charge accumulation and transport in the transistor channel. Conducting organic films have also been extensively evaluated as electrochemical electrodes in bioelectronics applications. As the electrode is addressed versus a counter electrode, ions and biomolecules may flow in and out, and the affinity and adsorption characteristics can be modulated (see section 2.1).

2. ORGANIC BIOELECTRONICS: ELECTRODES, DEVICES, AND CIRCUITS

2.1. Electrodes

2.1.1. Low-Impedance, High Charge-Capacity Interfaces. The electrode interface acts as a transducer between the electrons, processed in electronic circuits, and the ions of biological tissue, allowing for currents and potentials to cross the biology−technology interface. The transduction can occur either by charging of the electric double layer (EDL) along the electrode surface or by faradic electrochemical reactions of components of the electrolyte. In most bioelectronic applications, faradic currents are undesirable as they alter the chemical composition of the electrolyte and may therefore create toxic byproducts.[39] The challenge is therefore to create an electrode interface that effectively can transduce signals by charging and discharging of EDLs. The measure of how easily the conversion between electronic and ionic currents is performed is the impedance of the electrode. To achieve low impedance characteristics per electrode area, a high amount of charge needs to be stored at the interface and the interface needs then to be easily accessed by the ions from the electrolyte. The key to increase the amount of charge that can be stored at a surface is to increase the effective surface area by the incorporation of porous structures or equivalent conducting 3D structures. Suitable pore geometries also facilitate ion conduction, thus resulting in a low-impedance electrode.

Certain conductive polymers are attractive for electrode applications, as they can create porous coatings with high charge storage capacity and fast ion conduction.[40] Further, the chemical composition can be tailored to optimize impedance, stability, and biocompatibility. Early work on conducting polymer electrodes was pioneered by the Martin group,[41,42] who used electropolymerization to deposit conducting polymer layers on neural electrodes. Ever since then, electrochemical polymerization has been the most common method for electrode coatings, as it can yield low-impedance cladding layers with good adhesion to the substrate. Also, the films are only formed at the electrode openings,[41] thus eliminating any further need of patterning, which is required if chemical polymerization is used.[43] In the vast majority of reports on conducting polymer electrodes, polypyrrole (PPy) or poly(3,4-ethylenedioxythiophene) (PEDOT) have been used.[41,42,44−46] Both polymers can be electropolymerized from monomer solutions together with a wide array of complementing counterions.[47,48] The Py monomer is readily soluble in water, in contrast to EDOT, which exhibits poor water solubility. Most of the early work was focused on PPy, although in more recent work a shift toward PEDOT has occurred. The main reason for this is the superior stability of PEDOT,[40] which is critical in biological applications. Derivatives of PEDOT have also been explored as electrodes.[49,50] Electropolymerization allows for precise control of film thickness, as the amount of deposited material can be controlled through the total charge applied to the electrode (Figure 6a−d).[42] The morphology of the film depends on a wide array of parameters such as the kind of electrodeposition method used, the solvent, and the counterions.[51] The impedance often exhibits a minimum for a certain film thickness.[42] The ionic conduction is often the prime limiting factor, and it can be heavily influenced by the film morphology and the choice of counterions.[48,52,53] The porosity of coatings can be improved by the use of dissolvable templates, e.g., by growing the conducting polymer around polystyrene beads or electrospun nanofibers (Figure 6e−g).[54,55]

A general problem for conducting polymer electrodes is that they lose electroactivity over time, especially when cycled over extended periods of time. In 2008 it was demonstrated that the incorporation of carbon nanotubes (CNTs) in the conducting polymer could improve the electroactive stability of the electrode.[56] The composite approach is now a popular approach as the CNTs provide mechanical strength, good electrical transport, and a porous and open structure that allows for growth of the conducting polymer material (Figure 6h, i).[57−64] CP-CNT composite electrodes have some of the

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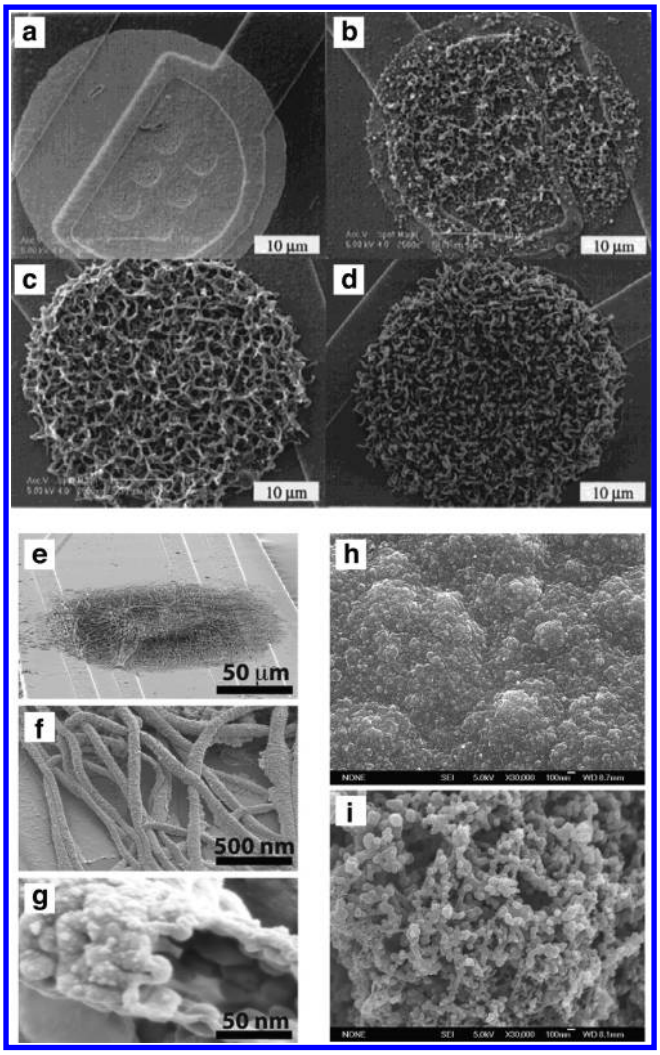

Figure 6. Scanning electron microscopy (SEM) images of conducting polymer electrodes. (a–d) PPy deposited with 0, 1, 4, and 10 μC of charge. (e, f) PEDOT nanotubes grown around a sacrificial poly(L-lactic acid) (PLA) nanofiber mesh. (h) Pure PPy:PSS (PSS = poly(styrene sulfonic acid)) and (i) PPy:PSS deposited on single-wall carbon nanotubes (CNTs). Parts a–d reproduced with permission from ref 42. Copyright 2001 John Wiley and Sons. Parts e and f reproduced with permission from ref 55. Copyright 2009 John Wiley and Sons. Parts h and i reproduced with permission from ref 63. Copyright 2010 Elsevier.

highest measured surface capacitances of any electrode to date.[65]

2.1.2. Bioactive Surfaces. Most uses of organic electronics, biological or not, are in thin-film form. This presents an opportunity to leverage the surface or bulk film properties to influence cells or tissues. In recent years, it has been well-established that cells and tissue respond to the mechanical and physicochemical properties of the surfaces or matrices to which they are exposed.[66,67] Because conducting polymer films—that is, surfaces or electrodes—are able to undergo mechanical or physicochemical changes when electronically addressed, these surfaces present a useful tool for cell interfacing. Furthermore, as conducting polymer surfaces can be inherently softer and/or more three-dimensionally structured than planar metal or other inorganic interfaces, they possess an innate "biocompatibility" (albeit, a contentious term).[68] Finally, because these devices are essentially bare electrodes, they can be fabricated in any or all ways imaginable for conducting polymers.

In the mid-to-late 1990s, Langer and co-workers demonstrated pioneering work using electropolymerized PPy in cell biology applications.[69,70] For example, they demonstrated that embryonic cells were able to develop neuron-like features (neurite projections) more efficiently on the PPy surface than on traditional cell culture surfaces such as poly(L-lactic acid) (PLA). This seminal work on conducting polymer surfaces for cell interaction illustrates the basic principle: influencing the growth and spreading of cells or tissue on a polymer electrode immersed in some physiological medium. Indeed, this basic experiment has been repeated and expanded upon since the early demonstration (see section 3.2).

Already during the early work performed by the Langer team, it was realized that the relative hydrophobicity or hydrophilicity of the surface dominated the specific interactions with cells. Surface energy is known to influence cell adhesion and proliferation,[71] and it has been demonstrated that the redox state of a conducting polymer electrode has a strong effect on wettability.[72] While the original work by Langer presents some interesting speculation on the then-unknown mechanisms,[69] it is now generally agreed that wettability switching is related to the doping level, i.e., the level of charge accumulation inside the polymer and associated ion exchange. When charges is introduced into the polymer film (e.g., oxidation), usually in the form of polarons or bipolarons, counterions rearrange to compensate this charge. This rearrangement introduces dipoles, which can effectively change the surface energy along the film/electrolyte interface.[73,74] Likewise, rearrangement of the counterion can cause a reorientation of molecules, for example, amphiphilic molecules can be forced to reorient at the surface depending on the charge state of the polymer film, presenting either a charged (hydrophilic) end or a nonpolar (hydrophobic) end.[75] In the extreme case, the biological interaction at the surface is modulated by actual release of counterion molecules. For example, this was demonstrated by Wallace's group when they explored heparin-loaded polypyrrole films[76] as the electroactive surface to promote adhesion and growth of human endothelial cells. However, this form of "surface" is more appropriately considered as a controlled-delivery electrode.

Cells adhere to surfaces using receptors in their cell membranes that couple to extracellular "adhesion" proteins such as fibronectin.[77] The rearrangement of charge and subsequent change in wettability can also be used to modulate the effective adhesion of cells via induced reorientation of adhesion proteins. Work performed by our group[78,79] and the team of Malliaras[80,81] have demonstrated this effect using various PEDOT derivatives. Both groups have proposed that electrochemical changes in the PEDOT films result in reorganization of proteins responsible for adhesion and proliferation. While there has been some uncertainty in the specific mechanisms and responsible protein confirmation, the most exhaustive study by the Malliaras team indicates that, in the case of fibronectin-mediated adhesion, reduced (i.e., more neutral) PEDOT causes the adhesion proteins to unpack in a manner that is not favorable to cell binding.[81]

While triggering of specific biochemical and morphological changes in cells and tissues is of great value in biomedical research, conducting polymer surfaces can also be of use for electronically modulated cell/tissue release. Today, the predominantly used method for cell or tissue detachment

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relies on enzymatic cleavage (i.e., using trypsin) of the adhesion proteins. These adhesion proteins are generated by cells and serve as binding promoters to surfaces, extracellular structures, and each other.[82] While highly useful and easy to apply to generic cell and tissue culture hardware in any lab, enzymatic cleavage indiscriminately effects cell membrane proteins, including growth factor receptors, anchoring proteins, and signaling sites.[83] In a manner somewhat similar to the actuation pioneered by Pei and Inganäs[84] and Wallace and co-workers,[85] self-doped PEDOT materials—specifically, PEDOT-S[86] —can be made to dissociate when electrochemically switched.[87,88] PEDOT-S possesses covalently attached negatively charged sulfonate groups that can dope/compensate the positively charged (oxidized) backbone of adjacent chains. When changing the oxidation state of the polymer, additional counterions will be incorporated into the film, causing swelling and eventually film breakup and disintegration. When cells or tissue are cultured on this film, they will be released along with the dissociated PEDOT-S.[88] This release mechanism results in detached cells with fully intact binding receptors, unlike enzymatic release techniques. However, as the PEDOT-S film is fully dissociated, devices are not reusable. Still, as the technology is again essentially a bare conducting polymer electrode, it opens up the possibility of patterning selective regions for release.[89]

2.1.3. Scaffolds. In living organisms, cells and tissue develop and function in a complex 3D environment—not much like the essentially planar surface of a Petri dish or conducting polymer electrode.[90] This 3D extracellular environment can take many forms: bone scaffolding, other cells or tissue, or fibrous biological support networks. This last category refers generally to the extracellular matrix (ECM), a scaffolding of cell-excreted protein-based fibers that cells attach to via the same adhesion mechanisms referred to in section 2.1.2.[91] Indeed in recent years, various studies have demonstrated that the 3D porous structure of the ECM and ECM-analogues can have a dramatic effect on cells' and tissues' ability to develop, adhere, and behave.[92−94] Likewise, in the case of bone formation, the 3D physicochemical structure of the cells' surrounding environment can have significant effects on the resulting tissue.[95] The advantages for cell culture and tissue engineering in moving from passive 2D surfaces (Petri dish) to 3D-structured systems are parallel to the advantages in moving from conducting polymer surfaces to conducting polymer scaffolds. That is, the benefits of biocompatible and electronically modulated polymer−biological interfaces discussed in section 2.1.2 can be utilized in more biologically relevant 3D structures.

In principle, 3D scaffolds based on conducting polymers can be considered as an extension of 2D surfaces, but with significantly higher surface area, larger effective volume, and varying degrees of porosity. Two basic methods have been used to develop 3D conducting polymer scaffolding. First, conducting polymers can be deposited onto nonconducting 3D-structured materials, such as electrospun fibers[96−98] or 3D-printed tissue-regeneration scaffolds.[99,100] A second general method of fabrication involves creating the scaffold directly with the conducting polymer material, for example, as demonstrated by the groups of Wallace[101] or Malliaras.[102]

The resulting conducting scaffolds can then be addressed and utilized in a similar fashion to 2D surface electrodes. However, the 3D structure can provide a synergy between porosity—which can greatly enhance in-growth and tissue (re)-generation—and electrical addressability—which can have significant effects on cell behavior, proliferation, etc.

2.2. Organic Field-Effect Transistors

Conducting and semiconducting polymers and molecules have been explored as the active material in electronic sensors since the 1980s. In some of these early experiments, the conductivity of the organic electronic material, either defined as a thin film or composited with a scaffold, e.g., filter paper,[103] was examined under the exposure to electron-donor or -acceptor gases, such as NO_2, H_2S, NH_3,[104] ammonia, and more. Because the field-effect transistor, along with its associated device parameters, represents a powerful probe for the investigation of the fundamental electronic charge transport properties of organic solid-state semiconductors, a natural next step was to explore organic semiconducting thin films as the active sensing element for gases and vapor in organic field-effect transistor (OFET) structures. Already in 1990, Inganäs and co-workers, at Linköping University in Sweden, reported changes in the device parameters of OFETs based on poly(3-hexylthiophene) upon exposure to NH_3 gas.[105] A decade later, the Bell Laboratories team guided by Dodabalapur used 1,4,5,8-naphthalene tetracarboxylic dianhydride (NTCDA) films as the active channel in OFETs for sensor application, targeting detection of different molecular species, H_2O, O_2, and N_2. The authors found that the mobility, threshold voltage, and drain current on/off value were affected by the exposure to these gases.[106] In a follow-up study,[107] this team reported an extensive study of 11 sensor materials and their response effects upon exposure to 16 different vapors or odors, e.g., vanillin, eugenol, etc. A year later, the group of Someya and Dodabalapur demonstrated successful operation of OFETs in aqueous media.[108] Stable operation was achieved by applying a protective coating along the drain and source electrodes. Interestingly, these OFETs were able to sense dilute organic solutes at the *ppm* level. There was also some degree of semiconductor−solute specificity identified in this sensor device setup. This demonstration of stable OFET sensor operation in aqueous media encouraged several OFET researchers to evaluate the OFETs also for biological and medical applications. During the first years after 2000, several groups utilized organic molecular and polymeric semiconductors in OFET structures to detect, sense, and monitor the presence, level, and concentration of humidity,[109−111] pH,[112] ions,[113] and chemical compounds.[114] At that time the underlying sensor mechanism observed in the OFET sensors was tentatively explained by modulation of charge transport, upon exposure to the analyte, caused by effects introduced at the grain boundaries[115] residing at connections between semiconductor domains and overall changes of morphology or volume.

Dipentoxy-substituted polyterthiophene (Poly-DPOT) was examined as a sensor layer for biologically relevant compounds in 2004 by Torsi and co-workers.[116] Thin films of Poly-DPOT exposed to 1-hexanol and ethanol showed an extrapolated sensitivity approaching 0.7 ng/ppm, as measured from quartz crystal microbalance (QCM) and from field-effect transistor studies. For OFET sensors gated at $V_G = -40$ and -60 V, drain current modulations of around 0.2% and 3% were reported upon exposure to 700 ppm of ethanol and 1-hexanol, respectively, in nitrogen atmosphere; see Figure 7. Later the same year, the group of Dodabalapur and Torsi reported the further development of alcohol sensors using instead thermally

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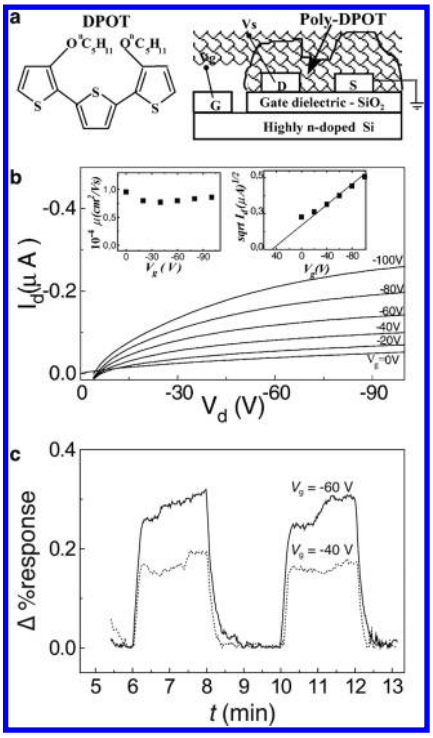

Figure 7. Poly-DPOT (a) included as the sensor layer in an OFET geometry and (b) its transistor performance. (c) Relative percentage responses evaluated from the source-drain transient current variation upon exposure to 700 ppm of ethanol. Reproduced with permission from ref 116. Copyright 2004 Elsevier.

evaporated pentacene as the semiconductor layer. In this study, presented at a SPIE meeting in 2004, the authors found that optimization of the gate biasing conditions is crucial in boosting the overall sensitivity.[117] A step toward tailor-making conjugated polymers as a selective sensor layer for a target biological compounds with high selectivity was taken by Tanese et al. in 2004. With poly(phenylene ethynylene) (PPE) conjugated polymer bearing glucose units, detection of different carvone enantiomers was achieved. This study then suggested that an organic semiconductor is promising as a highly selective sensor in electronic transducer devices. When including this in QCM and chemiresistor setups, Tanese and co-workers were able to discriminate between two different carvone enantiomers.[118]

2.3. Electrochemical Devices

2.3.1. Organic Electrochemical Transistors. Electrolyte-gated transistors in which the doping level modulation occurs in the bulk of the polymer are typically labeled organic electrochemical transistors (OECTs). The first OECTs were developed by the Wrighton group in the mid-1980s and were based on electrochemically polymerized polyaniline and poly(3-methylthiophene).[119,120] Although the performance and stability were improved in the following years,[121] the widespread use was hampered due to complicated electrochemical deposition methods used at that time to manufacture transistor channels. The introduction of chemically polymerized poly(3,4-ethylenedioxythiophene)/poly(styrene sulfonic acid) (PEDOT:PSS) into OECTs was reported by our group in 2002, and this device constituted a step forward in terms of processability and performance.[122] Since then, PEDOT:PSS has been chosen as the prime material of choice for OECTs, although several other aspects of the transistors have been greatly improved, most notably by the Malliaras group.[123,124] OECTs can provide high currents as the whole film is contributing to the charge transport in the channel, in contrast to FETs where only a thin layer adjacent to the dielectric or aqueous system is contributing. As each polaron is compensated by an ion, a change in the doping level requires the transport of ions in and out of the polymer film (Figure 8).

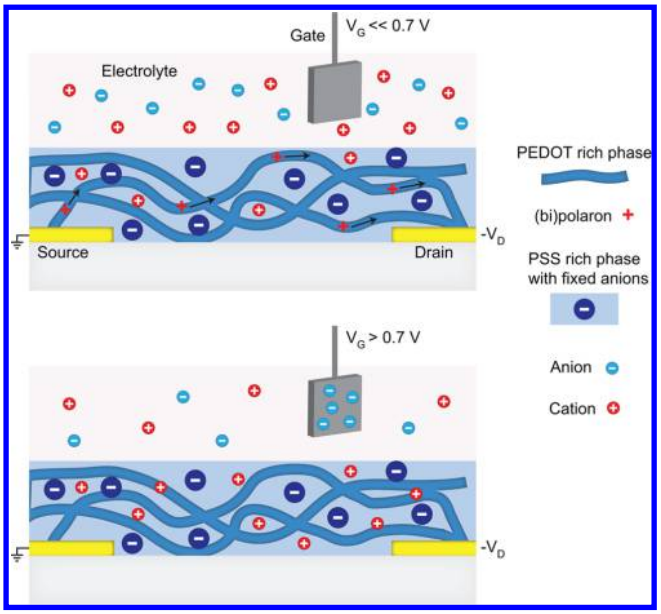

Figure 8. PEDOT:PSS-based OECTs. A conductive channel is formed for gate voltages that cause the PEDOT to be in the doped state (top). By reversing the gate potential, the PEDOT can be undoped by replacing the polarons with ions from the electrolyte, rendering the channel nonconductive (bottom). The ionic transport in and out of the film is facilitated by the gate electrode, either by charging and discharging of the EDL of the electrode (shown) or by electrochemical reactions.

PEDOT:PSS-based OECTs are depletion-mode transistors as PEDOT is in the doped state when in equilibrium with air. The measured characteristics of an OECT depend on the configuration of the gate, as the applied source-gate voltage is divided between the gate and the channel.[125] Thus, the maximum modulation is achieved when a relatively much larger gate or a nonpolarizable gate (e.g., Ag/AgCl) is used. The state of the art model for OECTs is based on the regular OFET equations where the dielectric capacitance has been replaced by a "volume capacitance" to account for the bulk doping of the channel.[126] The model fits experimental data fairly well, especially when mobility dependence on the doping level is included.[127] The characteristics of an OECT can be tailored by changing the channel geometry.[128] The drain current, and thus the transconductance, increases with channel width and thickness and decreases with channel length. The cutoff frequency of an OECT is limited by the channel length, the charge carrier mobility, and the ionic transport in and out of the film. For thicker polymer films the ionic transport limits the speed of the transistor switching but a relatively higher transconductance can be obtained. The PEDOT-based OECT[129] is today widely used in the organic bioelectronics community. Groups have used this device in combination with different receptor or selective membranes to detect and monitor, e.g., ascorbic acid,[130] marine diatoms in the seawater

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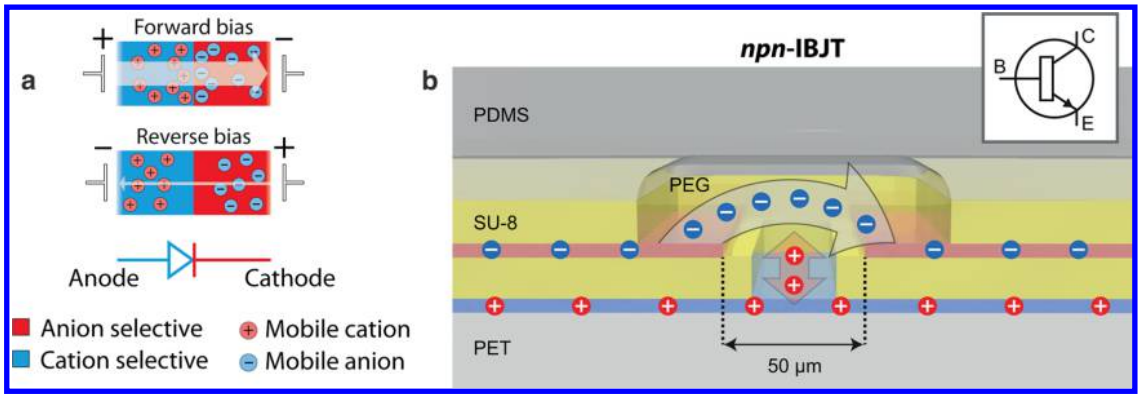

Figure 9. Ion motion in bipolar membrane based ionic devices. (a) The ion distribution at the bipolar membrane junction is dependent on the bias direction, resulting in ion current rectification. (b) In the npn-ion bipolar junction transistor, the anion current between emitter (left red layer) and collector (right red layer) is modulated by injection/extraction of cations from the base (bottom blue layer). Part a reproduced with permission ref 153. Copyright 2014 John Wiley and Sons. Part b adapted with permission from ref 154. Copyright 2012 Macmillan Publishers Ltd., Nature Communications.

medium,[131] dopamine,[132] acetylcholine, and glutamate.[133] Further, recently PEDOT-OECTs were successfully utilized in combination with optical techniques to monitor the integrity and status of the tight junctions of formed tissues.[134]

2.3.2. Organic Electronic Ion Pumps. In contrast to electrons, ions, or charged biomolecules, can possess and induce very specific biological action. Therefore, there has been an interest to develop devices that use ions as charge carriers, in order to facilitate controlled transport and release of ions. The organic electronic ion pump (OEIP) is one path that has been explored for controlling ion flows, where a ion conductive channel is used to connect two electrolyte reservoirs; see Figure 4a.[135] One reservoir (the source) is filled with an electrolyte containing the ion to be transported. The other reservoir serves as a target for the delivery, where, for example, a cell culture or tissue can be placed. The channel, connecting the two electrolytes, is composed of polyanion, where the negative and fixated charges on the polymer are electrostatically compensated by mobile cations while mobile anions are repelled. The high ratio of mobile cations to anions renders the channel primarily cation-conductive. Migration of mobile ions can be induced by the application of an electric field between electrodes immersed in the electrolytes at each side of the channel. Cations will then migrate from the positively biased electrolyte (the source), through the channel, into the negatively biased electrolyte (the target). The hydrated ions also carry with them small amounts of water.[136] High spatial resolution is achieved by forming the negative biased side of the channel into a narrow, down to 10 μm (ref 137), strip, thus forming a well-defined release point for the cations into the target electrolyte. Further, the ion delivery rate is controlled by the applied electrochemical current between the electrodes, enabling precise dosing of the ion/biomolecule.

The ion-conductive PSS phase in PEDOT:PSS-coated plastic films was initially used as channel material,[135] but PSS can also be spin-coated from solution.[138] In the former case, the PEDOT is electronically deactivated by chemical overoxidation. The ion conductor is patterned into micrometer channels by standard photolithography and dry etching. An encapsulation layer is also patterned on top, to protect the channel and to define the electrolyte reservoirs.

The dense polymer structure of the channel material renders the OEIP best suitable for delivery of low-molecular-weight ions that can penetrate the polyanion. Transport of protons,[139] metallic ions such as potassium[13] and sodium,[140] and small-sized charged biomolecules such as acetylcholine,[137] glutamate,[141] and GABA[142] have been reported. The ion mobility in PEDOT:PSS films has been reported to be close to that of bulk water.[143] Delivery of similar anions, such as chloride and glutamic acid, is also possible by changing from a polyanion to a polycation.[144] Larger molecules, such as hormones and peptides, have not yet been successfully transported, possibly due to the polyelectrolyte acting as a size-exclusion membrane preventing the molecules to enter.

2.3.3. Ionic Diodes and Transistors. Ion-conducting diodes and transistors offer even more electronic control over ionic currents as compared to OEIPs. Nanofluidic channels have extensively been used for realizing ion diodes and transistors, but their function depends on surface charges and are thus sensitive to high electrolyte concentration.[145] They are also based on hard, nonflexible materials. However, the ability of polyelectrolytes to selectively conduct either cations or anions makes them ionic analogues to electron- and hole-conducting (semi)conductors, and can thus be used for polymer-based, bulk-conductive ion diodes and transistors. A structure containing a junction between a polyanion and a polycation is called a bipolar membrane and was first described by Frilette[146] and has since then primarily been used for industrial electrolysis applications. The electrical characteristics of bipolar membranes are well studied and explored.[147] Similar to semiconductor pn-junctions, bipolar membranes act as current rectifiers, i.e., the conductivity across the junction is direction-dependent. As they use negative and positive ions as charge carriers instead of electrons and holes, diodes,[148] transistors,[16] circuits,[149] and logic functions[148,150] using polyelectrolytes have attracted attention for soft ion-based bioelectronic communication.

Ion bipolar membrane diodes and transistors can be fabricated in numerous different ways. Most simple is to form a stack of two oppositely charged polyelectrolytes between two electrodes.[151] More advanced and smaller geometries, and also integrated circuits, have been achieved by microfabrication methods. Bipolar membranes can, for example, be formed inside microchannels[148] or through photolithographic patterning and etching of spin-coated thin films.[16]

2.3.3.1. Diodes Based on Bipolar Membranes. The rectification behavior of bipolar membranes is typically explained by the changing polarity at the junction. The

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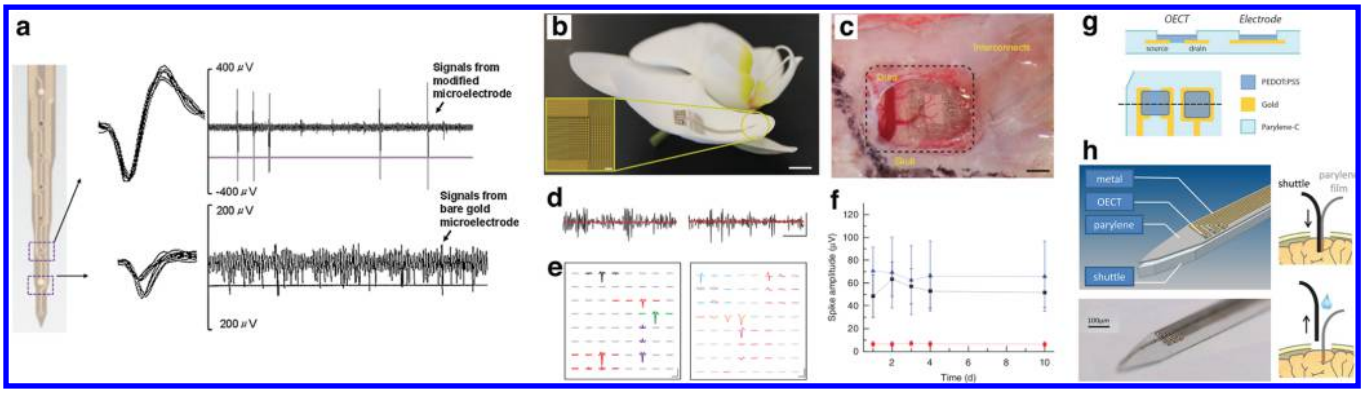

Figure 10. Conducting polymer neural interfaces. (a) The MWCNT-PEDOT coating drastically improves the recording quality of the microelectrode probe. (b–f) The NeuroGrid is a high-density flexible multielectrode array with PEDOT-coated microelectrodes. The high density and low impedance of the electrodes allow for spike recordings from individual neurons from the surface of the brain for days. (g, h) The probe comprises PEDOT-based electrodes and OECTs fabricated on a thin and flexible parylene substrate. The probe is placed in the rat neocortex with the aid of a stiff shuttle from which the flexible probe is delaminated after insertion. Part a reproduced with permission from ref 60. Copyright 2013 Elsevier. Parts b–f reproduced with permission from ref 179. Copyright 2015 Macmillan Publishers Ltd., Nature Neuroscience. Parts g and h reproduced with permission from ref 180. Copyright 2015 John Wiley and Sons.

majority of the mobile ions on one side of the bipolar membrane are represented by cations and on the other side are represented by anions; see Figure 4b. Upon the application of an electric bias, the migration of these mobile ions causes accumulation/depletion of ions at the junction depending on the direction of the applied bias[148] (Figure 9a). The bipolar membrane is in forward bias when the polyanion side is positively biased, and mobile ions on both sides of the junction then migrate toward the junction, where they accumulate due to the change in membrane polarity. At sufficiently high ion concentration, the selectivity of the bipolar membrane fails and ions can start to pass the junction.[152] The elevated ion concentration inside the bipolar membrane leads to high conductivity in the forward bias. For the reverse voltage bias, the mobile ions instead migrate away from the junction, rendering the junction low of mobile ions and thus poorly conductive.

For most bipolar membranes, an increase in conductivity is observed at elevated reverse bias potentials.[147] Here, the applied electric field across the depleted junction is high enough to accelerate the protolysis of water (water splitting), thus forming ions in the junction.[155] Such bipolar membranes only offer rectification in a small voltage range (±1 V)[156] but can also be used as pH-gradient generators.[157] Methods for avoiding water splitting include incorporating a neutral middle layer into the junction,[16] thus reducing the electric field, and using polyelectrolyte materials that do not catalyze the reaction.[158]

2.3.3.2. Ion Bipolar Junction Transistors. Construction of transistors that modulate ion currents have also been realized using bipolar membranes, so-called ion bipolar junction transistors.[16] These resemble semiconductor bipolar transistors and contain three terminals, emitter, collector, and base, in either pnp or npn configuration. For an npn-ion bipolar junction transistor, the emitter and collector are polycations and the base is a polyanion,[144] and vice versa for the complementary pnp version.[16] Experiments[16] and simulations[159] have shown that, like the semiconductor version, the (ionic) current between emitter and collector in the ion bipolar junction transistor can be modulated by the injection and extraction of charges (ions) into the junction through the base terminal. For an npn-ion bipolar junction transistor in common-emitter configuration and with a positive collector voltage, a positive base voltage injects cations from the base into the junction (Figure 9b). Introduced positive charges are countered by an injection of anions from the emitter, leading to a high junction ion concentration and high conductivity. This is the on state, or the active mode, where anions are transported from the emitter to the collector. If the base voltage is negative, cations and anions are instead extracted from the junction through the base and collector, respectively. The low ion concentration leads to a low conductivity and the off state, or the cutoff mode, of the transistor. For a pnp-ion bipolar junction transistor, the transport mechanism is similar but with reversed polarities.

2.3.3.3. Performance. Bipolar membrane-based diodes and transistors are generally slow in comparison to their semiconductor counterparts, as the typical diffusion coefficients for different ions are magnitudes lower than those for electrons and holes. Further, their switching is primarily dependent on the amount of ions that needs to be injected/extracted to modulate the current from the off state to the on state, and vice versa. It is thus advantageous to be small and well-defined. Using a 10 μm long junction, rise/fall times of 4 s have been achieved in ion bipolar membrane diodes, while a 2 μm long junction in ion bipolar junction transistors has shown on/off speeds of 2 s.[153] The rectification ratio between forward and reverse bias can reach 800.[158] As with other devices based on ion-conductive membranes (e.g., the OEIP), the dense structure of the polyelectrolytes is limiting for transport of large ions. In addition to metallic salt ions, transport of fluorescein,[148] rhodamine B hydrazide,[152] acetylcholine,[16] and glutamic acid[144] has been shown.

2.3.3.4. Protonic Wire Devices. Proton wire devices are a polymer-based alternative to bipolar membrane based diodes and transistors for modulation of protonic currents.[160] The active material in these devices is acid-doped polysaccharide, which forms hydrogen bonds with the surrounding water and thereby supports proton ion movement by a hopping mechanism. Moreover, the proton ion concentration, and thus the conductivity, can be modulated by the potential at a gate electrode, resulting in electric field-effect-operated proton transistors.[160] Changing to a base-doped polysaccharide gives a complementary, hydroxide ion conducting transistor and also

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enables fabrication of proton/hydroxide ion conducting diode junctions.[161]

3. ORGANIC BIOELECTRONICS APPLICATIONS

3.1. Electrodes and OECTs for Neural Interfaces

The immense complexity of the nervous system makes it a challenging task to electrically interface with it. The benefits of such an interface are, however, huge, as electrical stimulation is already in clinical use for treating diseases and disorders like Parkinson's, epilepsy, deafness, chronic pain, and blindness.[162−164] Moreover, recording of neural signaling is an invaluable tool to understand and map the function of the brain, as well as for controlling artificial limbs. Conducting polymers have been widely used to improve the electrode−tissue interface, in terms of both electrical properties and biocompatibility.[40,165] Much of the early work was focused on electrode coatings of neural depth probes that penetrate into the brain. The conducting polymer coatings improved the impedance of the electrodes, which resulted in better recordings with a higher signal-to-noise ratio (Figure 10a).[55,62,166] Another problem that has been addressed is the degradation of the electrode−tissue interface over time.[167−170] Significant effort has been put into studying and modifying the biocompatibility of the conducting polymer coatings with various biomolecules.[42,48,171−173] Conducting polymer nanotubes, which can be loaded with anti-inflammatory drugs, have also been reported for enhancing neural recording.[55,174] In an attempt to establish a good electrode−tissue interface, PEDOT has even been electropolymerized in vitro and in vivo.[175−177] Recently, thin and flexible high-density multielectrode arrays for neural recording have been developed.[178] In these devices chemically polymerized PEDOT:PSS was spin-coated and sequentially patterned, an approach that deviates from most earlier work. These multielectrode arrays have allowed scientists, for the first time, to record from and track individual neurons from the surface of the brain for extended periods of time (Figure 10b−f).[179]

Although most studies of conducting polymer coatings have been focused on recording, there have been several attempts to improve stimulation electrodes as well. For electrical stimulation, the benefit of conducting polymer coatings lies in lowering of the electrode impedance. This decreases the stimulation voltages, which reduces the amount of potentially harmful electrochemical side reactions. A major problem for conducting polymers in stimulation applications is the limited potential range in which they are stable, which often results in fast degradation of the electrode performance during stimulation. Fortunately, it seems like the stability can be improved with CNT-PEDOT composites, which have shown cycling stability for up to three months in PBS buffer.[64] It remains to be seen how well this performance enhancement translates to in vivo applications.

Recently, the Malliaras group introduced OECTs in electrocorticography.[181] The advantage of OECTs over regular electrodes is that the measured current is amplified on site, which improves the signal-to-noise ratio and allows for low measuring impedance despite a small recording area. The main disadvantage of the approach is the additional wiring, as each OECT requires two wires compared to only one for a regular electrode. The achievable spatial recording resolution for a fixed line width is thus lower for OECTs than for electrodes. By optimizing the OECT geometry, the transistor characteristics can be optimized to improve the signal quality in EEG recordings.[182] OECTs have also been inserted into a rat brain by the use of a delamination depth probe to achieve high-quality recording and stimulation (Figure 10g, h).[180]

3.2. Controlling Biology with Electronic Surfaces and Scaffolds

One of the most crucial aspects of all bioelectronics research and technology is the interface between, on the biotic side, cells, tissue, or organs, and on the abiotic side, electrodes, devices, and components. In standard cell and tissue culture, the abiotic side of this interface is generally a Petri dish, often composed of polystyrene—that is, an inert plastic slab. In the case of organic bioelectronics, the abiotic component can comprise tunable electronic *and* ionic properties, offering a much wider range of possibilities for controlling the adhesion, proliferation, and fate of cells or tissue. Such control leads directly to applications in both basic research as well as tissue regeneration.

Using conducting polymers at this biotic−abiotic interface began in the mid-1990s with work by Langer and co-workers. Having been inspired by its switchable wettability and surface energy, they utilized polypyrrole (PPy), then one of the most promising and versatile organic electronic materials,[165] as a cell-growth substrate. In some of their first experiments, they grew bovine aortic endothelial cells on electropolymerized PPy (on indium tin oxide (ITO)), functionalized with the adhesion-promoting protein fibronectin.[69] Comparing reduced (i.e., more neutral) and oxidized fibronectin-PPy to fibronectin-coated ITO electrodes and standard Petri dishes, they found that reducing the fibronectin-PPy to the neutral state caused a significant change in the cells' ability to anchor to the substrate. Together with Schmidt et al., they continued with a similar experiment using PC-12 cells, a common model cell line for neuronal differentiation. They observed that, compared to tissue culture polystyrene or PLA or poly(lactic-*co*-glycolic acid) (PLGA) substrates, the cells electrically stimulated by the PPy substrate exhibited significantly more and longer neurite projections.[70]

Taking this principle a step further, in 1999 Wallace and co-workers investigated the role of biologically relevant counterions in switchable conducting polymer surfaces.[76,183] Specifically, they used heparin, a biopolymer with both anticoagulant properties and a role in the extracellular matrix, as the counterion in electropolymerized PPy surfaces. Rather than relying on simple surface-energy changes, they were able to reorient the heparin-PPy composite in such a way that up to three times higher heparin concentration would be exposed to cells when reducing the PPy. When compared to PPy at different oxidation states, or with other counterions, they found significantly better cell attachment and morphology with the heparin-exposed reduced PPy. In 2000, Schmidt and co-workers used a similar principle with hyaluronic acid, another primary component of the extracellular matrix, as the counterion for PPy.[184] They not only found similar results with PC-12 cells in vitro, but also demonstrated that the films, when placed in vivo, promoted vascularization and did not cause significant inflammation.

Such counterion-modulated conducting polymer surfaces for cell culture have been a mainstay of organic bioelectronics ever since. For example, in 2011, Teixeira and co-workers used the same principle of heparin "doping" to guide stem cell differentiation.[185] In their work, they bound fibroblast growth

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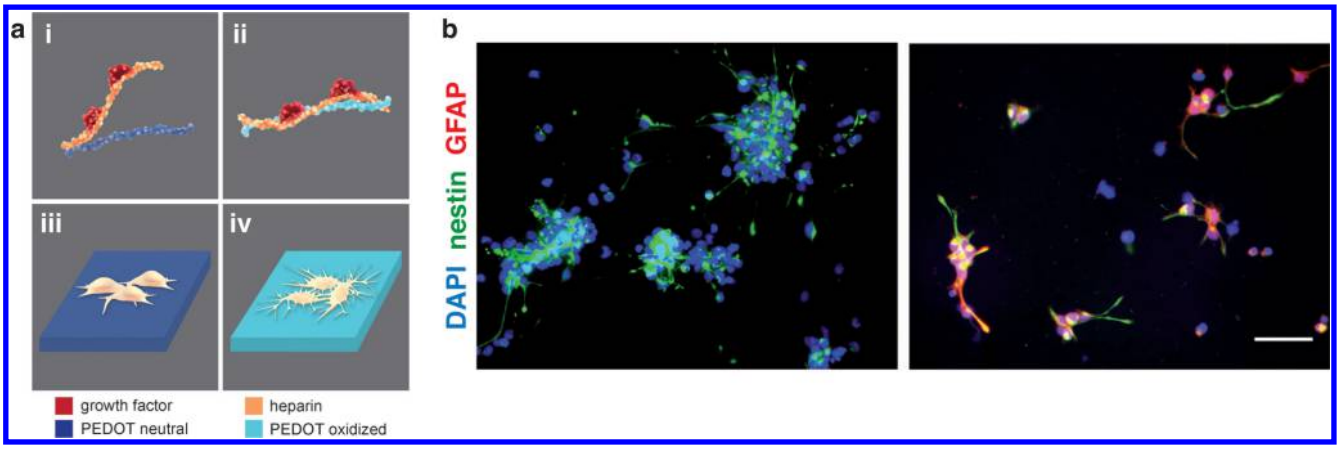

Figure 11. Electrochemical control of growth factor bioavailability to steer neural stem cell differentiation. (a) Neutral (reduced) PEDOT causes heparin-growth factor compounds to be exposed/available to stem cells (i), keeping them undifferentiated (iii). Oxidized PEDOT binds heparin-growth factor compounds (ii), leading to less availability, and stem cell differentiation (iv). (b) Neural stem cells cultured for 4 days on PEDOT:heparin surfaces were kept at open circuit (left) or oxidized with live cells (right). GFAP staining (red) indicates differentiated cells. DAPI (blue) indicates cell nuclei, and nestin (green) indicates neural stem cells. Scale bar: 75 μm. Reproduced with permission from ref 185. Copyright 2011 John Wiley and Sons.

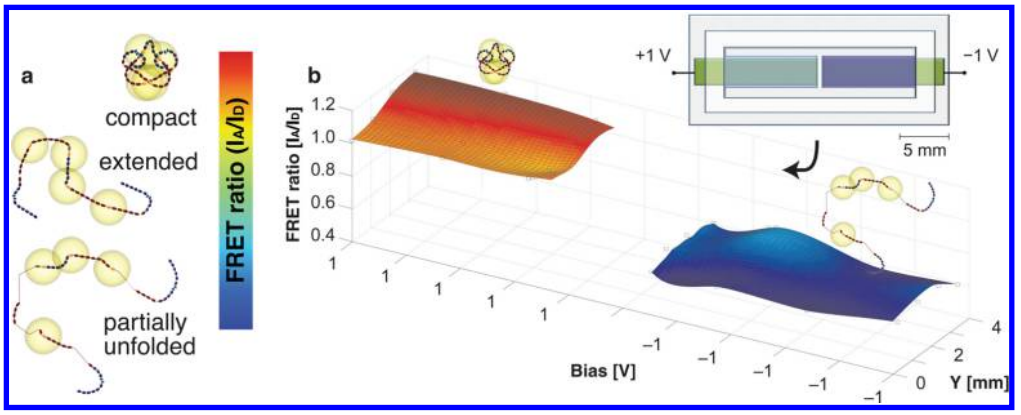

Figure 12. PEDOT surfaces control binding protein confirmation. (a) Color map of FRET ratio to fibronectin conformation. (b) FRET ratios on a two-electrode device as a function of applied bias and position. Color of the surface indicates local fibronectin conformation as described in part (a), and the corresponding schematics of conformation are shown above the surface. The inset shows the device configuration. Reproduced with permission from ref 81. Copyright 2012 John Wiley and Sons.

factor-2 (FGF2) to the heparin polymers and used this composite as the counterion in electropolymerized PEDOT. FGF2 causes the stem cells to remain in their predifferentiated state. Reducing the PEDOT to the (near) neutral state caused the heparin-FGF2 to become more exposed (Figure 11) at the surface, thus exposing more active FGF2, resulting in undifferentiated cells. Oxidizing the PEDOT caused a "retraction" of the heparin-FGF2 and allowed the cells to begin differentiating. In another more recent example, Jager and co-workers returned to electropolymerized PPy to investigate bacterial differentiation.[186] They examined the effects of four different counterions—dodecylbenzenesulfonate (DBS), polystyrenesulfonate, tosylate, and chloride—on five common bacterial cultures. They found that varying surface roughness and surface energy elicited different effects depending on the particular bacterial strain. Ultimately, they demonstrated that, by tuning the counterion and redox state of the PPy film, they could reliably discriminate the various bacteria.

Continuing with the focus on exposure or presentation of adhesion- or differentiation-promoting compounds, other groups have investigated the specific effects of redox-switching on cell-adhesion proteins. In 2008, our own group demonstrated that different oxidation states of PEDOT:tosylate caused changes in adhesion of extracellular matrix proteins, leading to changes in neural stem cell adhesion.[78] The results indicated a stronger and denser protein binding to the reduced (i.e., more neutral) PEDOT:tosylate but, interestingly, better cell adhesion and proliferation on the oxidized side. At the time, it was postulated that the denser protein layer on the reduced side could have interfered with optimal orientation for cell binding, thus reducing overall cell counts. Similar experiments a year later using kidney epithelial cells (MDCK) on planar PEDOT:tosylate electrodes yielded complementary results.[79] That is, cells appeared to adhere and thrive better on the reduced PEDOT side. In this case, the argument was put forward that redox of the electrode caused conformational changes in the fibronectic adhesion proteins, leading to favorable conformations only on the reduced PEDOT. The same year, both Malliaras and co-workers[80] and our own group[187] were investigating cell adhesion along redox gradients of PEDOT. In both cases, peak cell adhesion was found to be at neither the fully oxidized nor the fully reduced extreme, but rather somewhere closer to the midpoint. It was not until 2012 when Malliaras and co-workers were able to explain these

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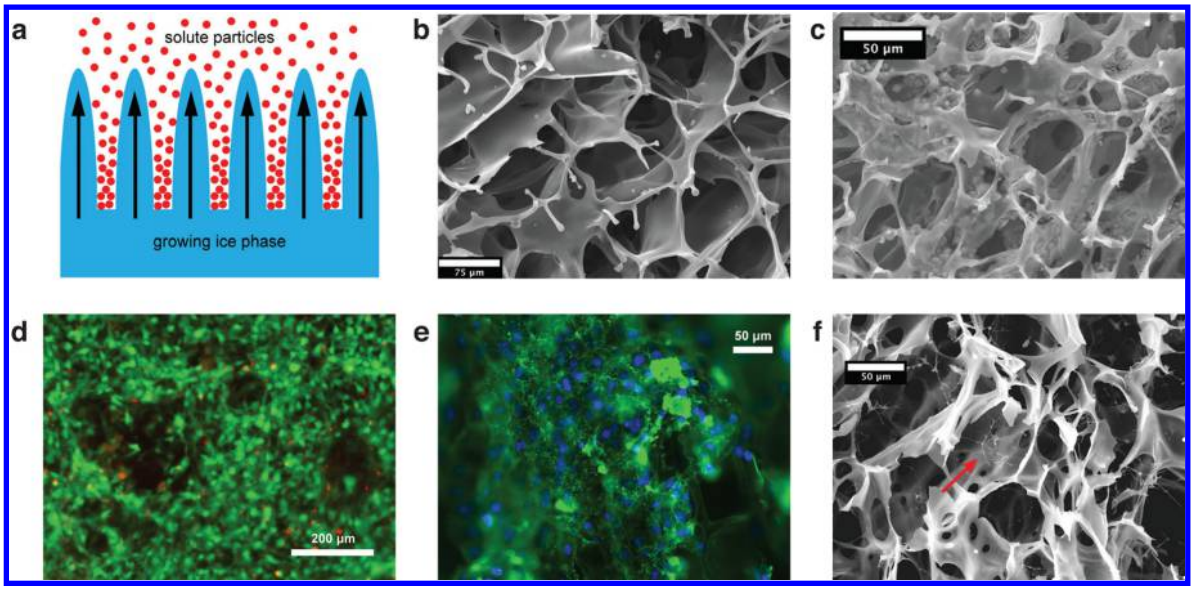

Figure 13. Ice-templated PEDOT scaffolds. (a) Schematic of the templating process. SEM micrographs of the scaffold (b) after fabrication and (c) after 24 h of cell culture, showing invasion of the scaffold by fibroblast cells ("clumps" inside the voids). (d) Fluorescence micrograph of a scaffold after 7 days of fibroblast cell culture, showing very high cell viability. Live cells are stained with calcein (green), and dead cells are stained with propidium iodide (red). The pores of the scaffold are visible as large circular dark regions. (e) Fluorescence micrograph of a scaffold with cell-deposited fibronectin fibers (green) after 24 h culture. Cell nuclei are stained with DAPI (blue). (f) SEM image of a decellularized scaffold, showing protein fibers produced by fibroblast cells. Reproduced with permission from ref 102. Copyright 2015 The Royal Society of Chemistry.

effects conclusively. They used Förster resonance energy transfer (FRET) imaging to directly ascertain the adhesion protein confirmation (Figure 12).[81] They found that oxidized PEDOT caused compact folding of the fibronectin, whereas the reduced side caused partial unfolding. When assessing cell binding using mouse fibroblasts, they found significantly higher adhesion on the compactly folded fibronection (oxidized PEDOT). However, taken together, the above results indicate that the specific combination of conducting substrate, binding protein, and cell type can significantly influence the effect of relative redox state on cell binding and proliferation.

On the basis of the same arguments as described in section 2.1.2, many groups have attempted to convert 2D organic electronic cell and tissue surfaces into functional 3D structures. This is of course motivated by the highly complex 3D environment in which cells and tissue thrive in their native biological settings, for example, cells in the extracellular matrix or bone tissue in a mineral scaffold.[91,95] One path to 3D scaffolding has been to use 3D-structured nonconducting scaffolds as the "substrate" for the conducting polymer. In 2009, Xia and co-workers used electrospun poly(caprolactone) (PCL) and poly(L-lactic acid) (PLA) fibers as the template for chemical polymerization of PPy.[98] Using explanted dorsal root ganglion cells, they observed good adhesion and neurite outgrowth on the functionalized scaffolds. Furthermore, by aligning the fibers of the scaffold, they could get the neurites to grow along a specified direction and modulate the length of the neurites using electrical stimulation through the PPy. That same year, our own group demonstrated Ca^{2+} signaling in neuroblastoma cells modulated by a similar scaffold system—vapor-phase deposited PEDOT on electrospun poly(ethyleneterephthalate) (PET) fibers.[97] In the study, the cells, which were plated on top of the fiber scaffold, were observed to actually adhere *into* the fibers and resulted in a markedly different Ca^{2+}-signaling profile. This was explained by the increased likelihood of the 3D electrode material being in proximity to voltage-operated Ca^{2+} channels (VOCCs).

More recently, some groups have been investigating building the 3D scaffolding using the conducting polymer itself. In 2012, Wallace and co-workers demonstrated a single-component conducting polymer hydrogel for tissue-engineering applications.[101] They used a cross-linked polythiophene derivative, poly(3-thiophene acetic acid). The carboxyl groups on the acetic acid moieties provided significant hygroscopic properties, and the resulting hydrogel was characterized for cell culture and stimulation purposes. They were able to culture primary myoblasts (premuscle cells) on the hydrogels, indicating applications in muscle regeneration, especially given the ability to electrically address the resulting tissue. Finally, in 2015, Malliaras and co-workers demonstrated an ice-templating method for porous PEDOT:PSS scaffolds (Figure 13).[102] Their elegant technique involved controlled growth of ice crystals into a solution of PEDOT:PSS particles, resulting in tunable porosity and structure. They returned to their analysis of fibronectin confirmation on the (3D structured) surfaces using FRET imaging and found comparable results to their 2012 results with 2D surfaces.[81] Furthermore, they observed, and were able to modulate, cellular excretion of angiogenic compounds, indicating the exciting potential for enhanced vascularization in tissue regeneration implants based on such 3D technologies.

3.3. Optical Stimulation and Sensing

3.3.1. Organic Optoelectronic Biosensors. Optical-based assays are widely used in life science, for example, for concentration analyses of biomolecules and detection of biomarkers. In the pursuit for miniaturization of such assays into low-cost lab-on-a-chip devices, organic optoelectronic components are of interest for biosensor applications for a variety of reasons: low-voltage operation and the possibility to optimize spectral properties by chemical tuning; opportunities to miniaturize components; and ability to manufacture using

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solution-processing techniques, or even embedding components directly into "standard" assay consumables.

Organic light-emitting diodes (OLEDs) and/or organic photodiodes (OPDs) have been extensively used as integrated light sources[188,189] and detectors,[190] respectively, in various photoluminescence sensors for chemical or biological components. One approach, used by Shinar and co-workers, has been to coembed a suitable oxidase enzyme (e.g., glucose oxidase, an enzyme that consumes glucose and oxygen, for glucose sensing) with an oxygen-sensitive fluorescent probe into a film and use an integrated blue-layered OLED to excite the fluorescent probe (Figure 14a).[189] Multianalyte sensing is then possible using an array of pixels with different oxidase enzymes, but the method is limited by the availability of such enzymes. A more general approach is thus to use fluorescent probes that bind directly to the analyte.[191]

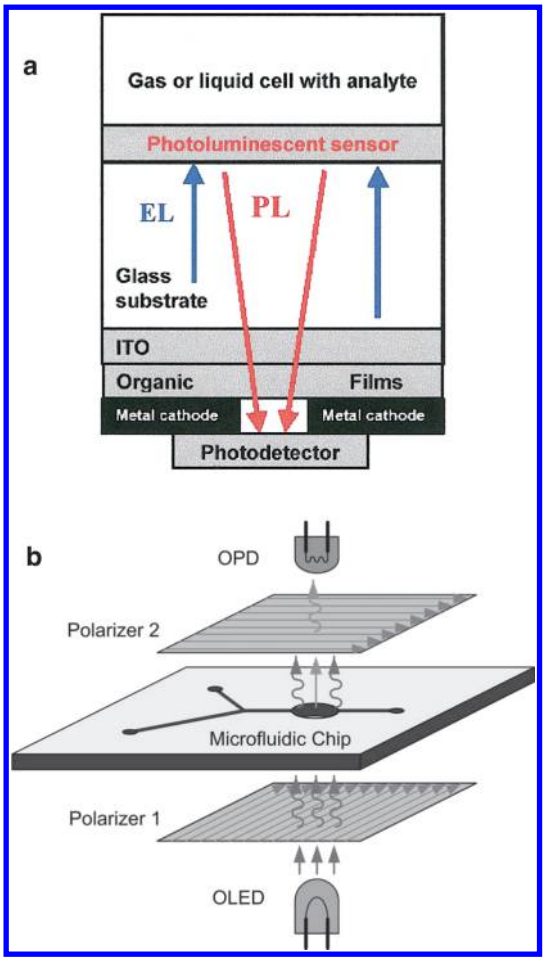

Figure 14. OLED- and OPD-based biosensors. (a) An OLED excites a photoluminescent film, containing glucose oxidase, in contact with the analyte solution, and the fluorescence is measured using a photodetector. (b) Separation of OLED-excitation and OPD-photoluminescence sensing using two cross-polarized filters. Part a reproduced with permission ref 189. Copyright 2004 AIP Publishing LLC. Part b reproduced with permission from ref 192. Copyright 2008 The Royal Society of Chemistry.

Separation of excitation light from the detected emission signal is a general problem for photoluminescence sensors, as the signal-to-noise ratio is otherwise reduced. This is also highly relevant when using OLEDs and OPDs, as their spectral emission and response, respectively, are quite broad. To ensure that the light reaching the detector primarily originates from photoluminescence in the analyte and not from the excitation source, various filters, such as dye filters[193] or cross-polarization filters[192,194] (Figure 14b), have been integrated into the sensor. A dye filter can act as a long-pass filter to block the lower-wavelength excitation light from entering the sensing element, while in a cross-polarization filter the excitation light is polarized prior to reaching the analyte and subsequently blocked by a second orthogonal polarization filter located before the detector. A filterless alternative is to measure photoluminescence decay time (instead of intensity), as this is done after an excitation pulse.[195]

Label-free optical detection techniques are often advantageous to photoluminescence-based sensing, as there is no need for specific fluorescent labels or enzymes. Distributed feedback (DFB) lasers have been used for such label-free sensors. In a DFB laser sensor, the analyte solution is in contact with the laser gain medium surface (Figure 15). Changes in refractive index of the analyte solution at the laser surface alter the effective refractive index of the laser mode, and thus a detectable shift in the laser emission wavelength. Specificity toward the analyte is achieved by functionalizing the gain material surface with biomolecule-recognition elements that selectively bind to the analyte, e.g., specific proteins, antibodies, or complementary DNA strands. The first organic DFB laser sensors used dye-doped polymers as a gain medium and optical pumping, and could detect protein monolayers[196] and binding of antibodies.[197] Laser-based sensors with dye-doped polymer gain medium have also been shown for detection of cytokine tumor necrosis factor,[198] human epidermal growth factor receptor 2 (ref 199), and cells.[200]

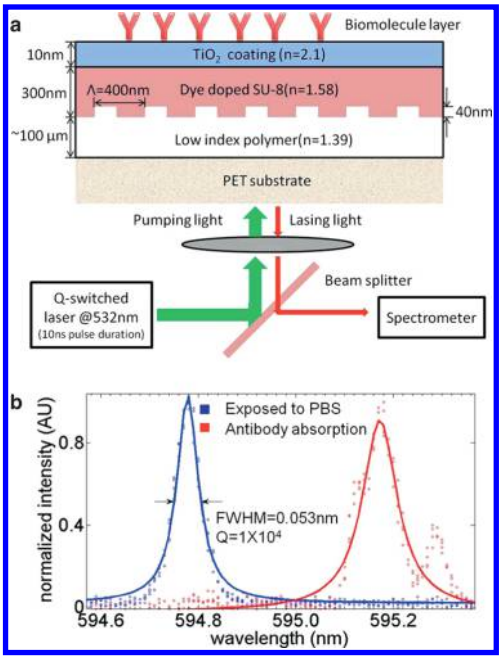

Figure 15. DFB laser biosensor. (a) Binding of analyte to the recognition layer (here antibodies) on top of the laser structure changes the effective refractive index of the laser. (b) Laser wavelength shift upon biomolecule (antibodies) deposition to the laser surface. Reproduced with permission from ref 198. Copyright 2012 IEEE.

More recently, semiconducting polymers have been introduced as gain medium instead of dye-doped polymers. This has yielded increased resistance to photoemission quenching and

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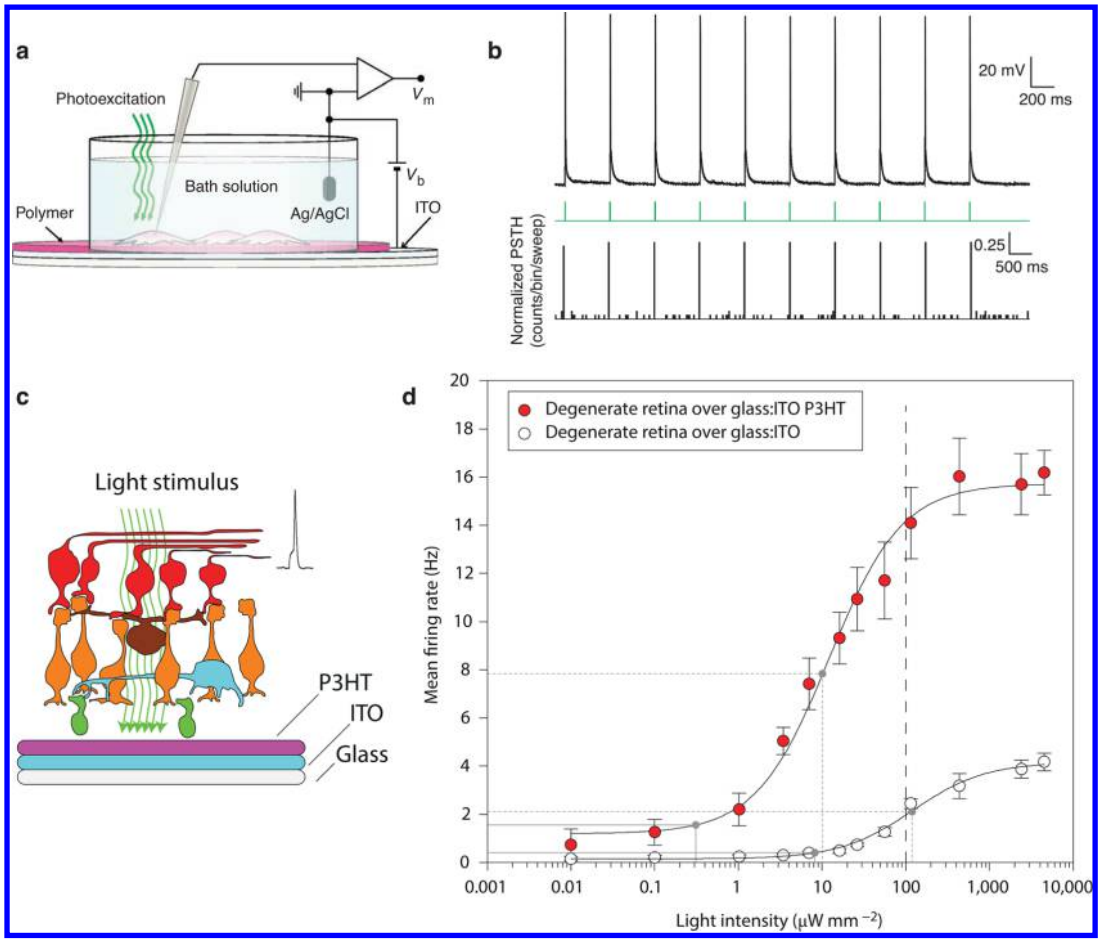

Figure 16. Photostimulation of neurons using bulk heterojunction structures. (a) A neuron, grown on top of the bulk heterojunction polymer layer, is patch-clamped and exposed to light pulses. (b) Action potential responses after light pulse stimulations (green). (c) Restoration of light sensitivity to a degenerated rat retina oriented with photoreceptors face down to the polymer layer. (d) Light intensity-dependent action potential firing rate. Parts a and b reproduced with permission from ref 208. Copyright 2011 Macmillan Publishers Ltd., Nature Communications. Parts c and d reproduced with permission from ref 211. Copyright 2013 Macmillan Publishers Ltd., Nature Photonics.

higher refractive index of the gain layer, and thus more efficient interaction between the analyte and the laser mode,[201,202] yielding an increased sensitivity.[203] DFB laser sensors with semiconducting polymer gain layer have also been combined with a hydrogel-based 3D recognition layer, to increase the number of analyte-binding sites, reduce nonspecific binding, and increase biomolecule stability.[204]

Label-free sensing has also been realized using OLEDs as the light source, by coupling the excitation light into a waveguide in contact with the analyte solution. Ratcliff et al. constructed a dual-beam, waveguide-based refractometer,[205] and Ramuz et al. demonstrated surface plasmon resonance sensing,[206] both with OLED excitation and OPD detection.

3.3.2. Organic Optoelectronics For Stimulation. Optical methods are an attractive alternative to electronic stimulation for interfacing with cells, primarily due to the high spatiotemporal resolution that can be archived by pulsed, focused light. Organic optoelectronic devices that have been explored for biostimulation applications are primarily polymer−fullerene bulk heterojunction photodiodes operated in photovoltaic mode. Lanzani and co-workers have, for example, used the canonical poly(3-hexylthiophene)/phenyl-C61-butyric acid methyl ester (P3HT:PCBM) bulk heterojunction solar cell structure,[207] operated in photovoltaic mode with electrolytic cathode, for stimulating action potential firing in neurons cultured onto the active organic layer (Figure 16a, b)[208] and for modulation of whole-cell conductance of astrocytes[209] via photo stimulation. The function of the heterojunction is to absorb the light pulse and produce capacitive charging at the polymer/electrolyte and the electrolyte/cell interface, leading to ion movement around the cell and membrane depolarization. However, a possible side-effect of photostimulation mediated by heterojunction structures is the potential heating of the cells and their immediate environment, which can also lead to cell activation, an effect known to stimulate cells in pulsed infrared laser experiments.[210] Recently, Martino et al. also found a slower response component, due to thermal heating, after photostimulation in addition to the fast response attributed to capacitive charging in the bulk heterojunction.

The spectral response, zero-bias operation, flexibility, and biocompatibility also render these photodiode structures suitable for retinal implants. Ghezzi et al. placed acutely dissected rat retinas with light-induced degeneration of the photoreceptor layer on P3HT/ITO substrates, with the external layer (which normally contain the photoreceptor cells) facing the P3HT (Figure 16c), in an effort to restore light sensitivity to the tissue.[211] After photostimulation at 532 nm around a target, patch-clamped neuron, neuronal activity was seen, with a firing rate dependent on light intensity and a dynamic range between 1 and 100 μW/mm^2 (Figure 16d). The

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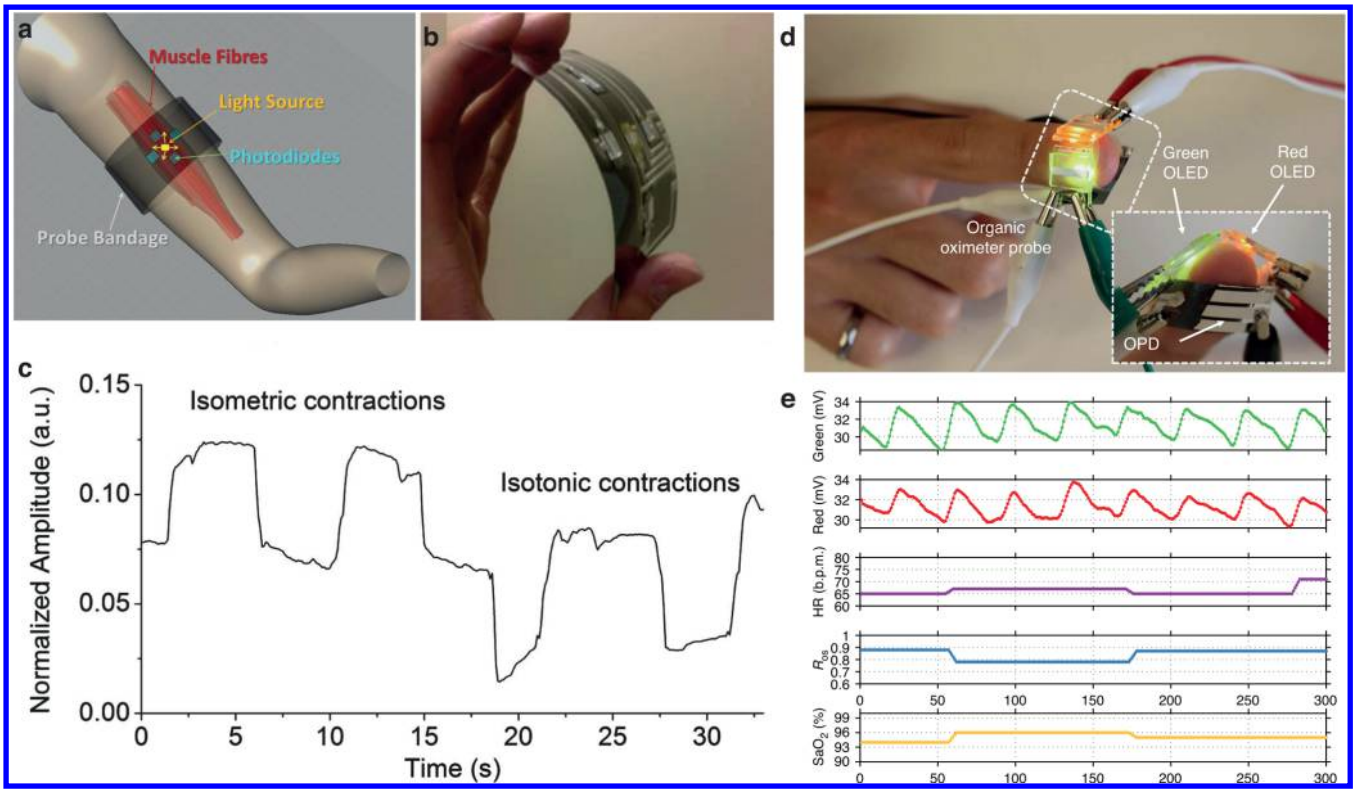

Figure 17. Wearable OLED/OPD sensors. (a–c) Flexible muscle-contraction sensor utilizing one OLED surrounded by four OPDs. (d, e) Oximeter probe for measuring heart rate and blood oxygenation using green and red OLEDs. Parts a–c reproduced with permission from ref 215. Copyright 2014 John Wiley and Sons. Parts d and e reproduced with permission from ref 216. Copyright 2014 Macmillan Publishers Ltd., Nature Communications.

authors noted that the range does not completely overlap the typical daylight intensity of 0.1–10 $\mu W/mm^2$, and that increased sensitivity in the polymer layer and/or increased stimulation efficiency between the polymer and the neuron would be needed.

Similar results were reported by Gautam et al., but with embryonic chick retinas, where the photoreceptors are not yet functional, placed on a P3HT:N2200 bulk heterojunction layer.[212] As opposed to the study by Ghezzi et al.,[211] the retinas were placed with the ganglion cell layer facing the polymer layer, and a multielectrode array was used for recording the neuronal activity. Neuronal activity was observed throughout the 400–600 nm range of the bulk heterojunction absorption, and the latency and number of action potential spikes could be modulated by the stimulation intensity. However, the device was not able to improve the dynamic range reported by Ghezzi et al.[211]

Addressable OLED microarrays have also been used for cell stimulation.[213] Here, the close proximity between the OLEDs and the cells (>2 μm) and the small pixel size (6 × 9 μm) enable spatial and temporal cell stimulation by illumination without the use of optical lenses. As a demonstration, the device was used to influence light-controlled locomotion (phototaxic) of a single-cell species of green alga across the OLED microarray.

3.3.3. Wearable Organic Optoelectronic Sensors/Emitters. Flexible, lightweight, and low-cost organic optoelectronic devices, primarily the OLEDs and OPDs, also have great potential use in continuous, noninvasive on-skin medical applications. Lightweight, wearable, and low-power OLEDs have been used to replace inorganic LEDs for treatment of nonmelanoma skin cancer, thus reducing the exhibited pain and enabling therapy at home.[214] Organic optoelectronics have also been used for on-skin sensing. Bansal et al. combined flexible OLEDs and OPDs into a muscle-contraction sensor, capable of measuring isometric and isotonic muscle contractions (Figure 17a–c).[215] The input from the sensor was further used to move a robotic arm, showing the possibility to use the device for controlling artificial limbs. A similar setup was used by Lochner et al. to replace the typically rigid oximetry sensor, used for measuring pulse rate and blood oxygenation levels in patients, with an all-organic flexible device (Figure 17d, e).[216] In both these cases, the flexibility of the sensor is a key asset, as it allows it to be placed almost anywhere on the body.

3.4. OFET-Based Biosensors

After 2005, many of the active scientists in the OFET sensor area steered their attention toward including selective and dedicated receptor systems in proximity, on, or within the transistor channel. The aim was to establish platforms of OFET sensors targeting sensing and monitoring of specific biological signals, for diagnostics and therapy within future health care systems, such as low-cost, single-use labels for home diagnostics applications. In a report from 2007, Torsi and co-workers outlined strategies and reported initial results from OFET sensors including phenylene thiophene (PTO)-based semiconductors functionalized with biomolecules. In this demonstration,[217] she and her co-workers showed sensitivity to chiral citronellol, a compound found in nature and commonly used in perfumes and insect repellents. Later on, this approach was further exploited in OFETs including a channel based on a bilayer film composed of PTO coated with other thiophene oligomers decorated with different side-group structures;[218] see

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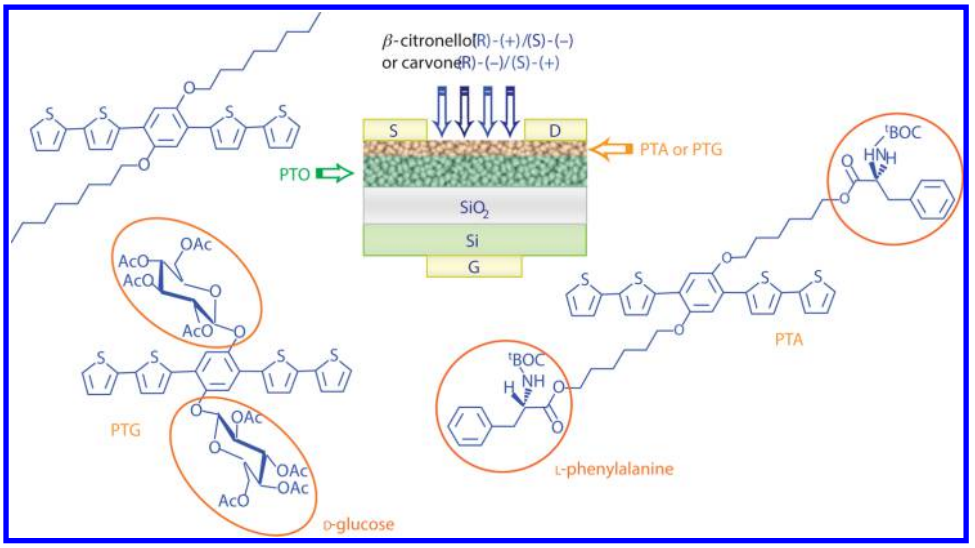

Figure 18. PTO oligomer semiconductor coated with either PTG or PTA, then included as the channel in OFET geometries for the chiral recognition of citronellol and carvone enantiomers. Reproduced with permission from ref 218. Copyright 2008 Macmillan Publishers Ltd., Nature Materials.

Figure 18. With L-phenylalanine amino acid (PTA) and beta-D-glucose (PTG) as substituents, successful chiral recognition of citronellol and carvone enantiomers was achieved. In addition to demonstrating chiral discrimination, the sensitivity was also shown to be far beyond previous achievements, such as when using amperometric approaches. From atomic force microscopy and from morphology studies, the authors found that the channel included grains but also voids. The authors hypothesized that, by choosing appropriate side groups, the degree of analyte/organic semiconductor chemical affinity could be controlled, which then could modulate the drain current as the OFET sensor is operated. This strategy appears to apply to the chiral analytes whose discrimination requires chiral receptors. The Torsi team then moved on toward new concepts including biological macromolecules along the semiconductor, thus potentially providing a technology to electronically read out any reactions occurring in the macromolecule. A lipid bilayer including a photosynthetic membrane protein system, extracted from *Rhodobacter sphaeroides*, was deposited onto the organic semiconductor film (α,ω-dihexylsexithiophene) prior to the deposition of drain and source contacts.[219] Only a slight reduction in OFET device parameters was recorded. This finding may open up for the possibility of coupling protein receptor reactions into the OFET channel,[220] making OFET sensors (even more) promising in drug screening or neuronal recording applications.

Stability in aqueous media is crucial for medical and biological sensing; further work was needed to improve the stability of OFET sensors operated in water. First, stable operation in water typically requires operation within the safe potential window, avoiding electrolysis. Second, it is also important to include materials that exhibit stable morphological properties when exposed to water. Bao and co-workers reported OFET sensors including the p-channel semiconductor 5,5′-bis(7-dodecyl-9*H*-fluoren-2-yl)-2,2′-bithiophene (DDFTTF) and a cross-linked polymer gate dielectric.[221] Stability over 10^4 electrical cycles and sensitivity down to parts per billion for cysteine and glucose was found. Later on, the authors also found that molecular structure, alkyl-chain length, and the overall thin-film morphology strongly influence the electrical characteristics while operated in water.[222]

Various OFET sensor structures and addressing concepts have been explored as yet another strategy to make the OFETs more suitable and tailor-made as the sensor-signal translator in biological applications. With the so-called double-gate[223] OFET, the Bonfiglio team demonstrated that one could separate the sensing surface from the transistor device configuration and also circumvent the need for a ounter electrode;[224,225] see Figure 19. In a recent report,[226] the Bonfiglio group reported further development of this double-gate OFET concept, now called organic charge-modulated field-effect transistor (OCMFET), by including biochemical probes on the floating-gate capacitor surface. Single-stranded DNA probes were anchored onto the gate surface, and

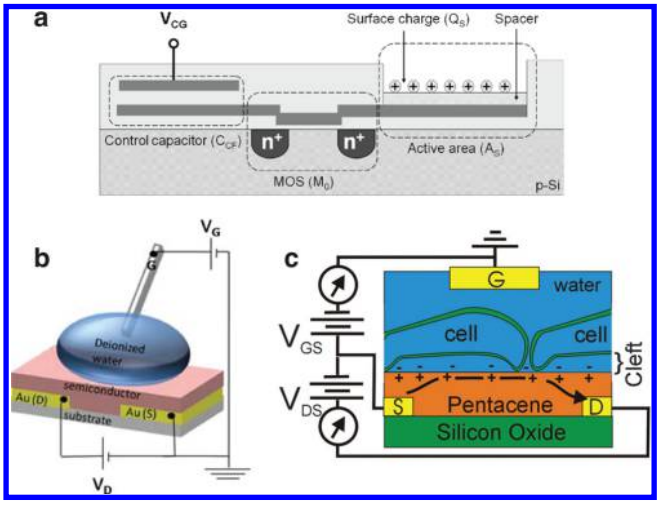

Figure 19. Fundamental device architecture of the double-gate OFET sensor (a), the concept of water-gating in OFET sensing (b), and the recording and stimulation of electrical activity of neurons (c). Part a reproduced with permission from ref 224. Copyright 2006 IEEE. Part b reproduced with permission from ref 38. Copyright 2010 John Wiley and Sons. Part c reproduced with permission from ref 229. Copyright 2013 The Royal Society of Chemistry.

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hybridization of complementary sequences at 1 pM concentration was possible to achieve even at high salt concentrations (<50 mM). This achievement represents an important step toward in vivo applications using OFETs. In yet another recent demonstration, the OCMFET sensor was utilized as a reference-less transducer of the electrical activity of electrogenic cells.[227] Double-gating has also been explored in an effort to understand the potentiometric sensing effect as analytes react within the Debye screening length at the gate. A strong correlation between changes of the electrochemical potential occurring at the second gate and a shift of the threshold voltage have been found.[228]

Another approach to transfer the sensing surface away from the critical dielectric−semiconductor interface is to utilize the aqueous solution as the charge-polarizing medium. With such a "water-gate" approach, stable OFET operation at voltages below 1 V in aqueous solutions is achieved; see Figure 19. In these electrolyte-gated OFETs (EGOFETs), the gate is separated from the transistor channel by the aqueous electrolyte,[38] i.e., the actual medium including the analyte or biological system. This architecture thus provides a unique opportunity to anchor receptors along the aqueous−semiconductor interface.

To make the various OFET sensor configurations selective to specific signaling entities, a receptor is needed to interact specifically with the target analyte. Various strategies have been explored during the past decade to include receptors, enzymes, antibodies, etc. inside the semiconductor, along the dielectric−semiconductor interface, adhered onto the aqueous−semiconductor interface, at the gate electrode, etc., to establish OFETs as a technology platform in applications related to distributed diagnostics (electronic labels), in vitro/in vivo probes, tools for investigating biological functions, and ultimately toward microarray chips and health status monitoring. Examples of receptor systems included in OFET sensor structures (Figure 20) include DNA hybridization,[230] selective detection of DNA via surface-bound peptide nucleic acid,[231] lactate oxidase[232] or diamine oxidase[233] combined with horseradish peroxidase, enzyme-linked immunosorbent assay to create a preeclampsia prognostic,[234] inclusion of a streptavidin protein capturing interlayer aiming for label-free electronic bioanalytical detection,[235] ion-selective membranes on top of the semiconductor for the selective detection of alkali ions,[236] addition of a monolayer of the synthetic cucurbit[6]uril onto the semiconductor surface for the detection of the neurotransmitter ACh down to 10^{-12} M concentrations,[237] and phenolic receptors to detect the nerve agent simulant dimethyl methylphosphonate.[238] EGOFETs operated in the gating-through-water configuration[239] including various anchored receptors along the organic−semiconductor surface facing the aqueous medium have been explored, such as to detect and monitor pH,[240] DNA,[241] penicillin,[242] dopamine,[243] and ions.[244] Moreover, phospholipid layers have been utilized along the aqueous−semiconductor surface,[245,246] potentially enabling monitoring of reactions in transmembrane proteins. In a recent publication by the Biscarini and De Leeuw teams, EGOFET transistors were utilized to achieve the combined recording and stimulation, at a 350 μV peak level, of murine neural stem cells differentiated into neuronal networks.[247]

3.5. Electronic Skin

The skin is the largest organ of our body and it serves us as an effective barrier between the environment and our internal

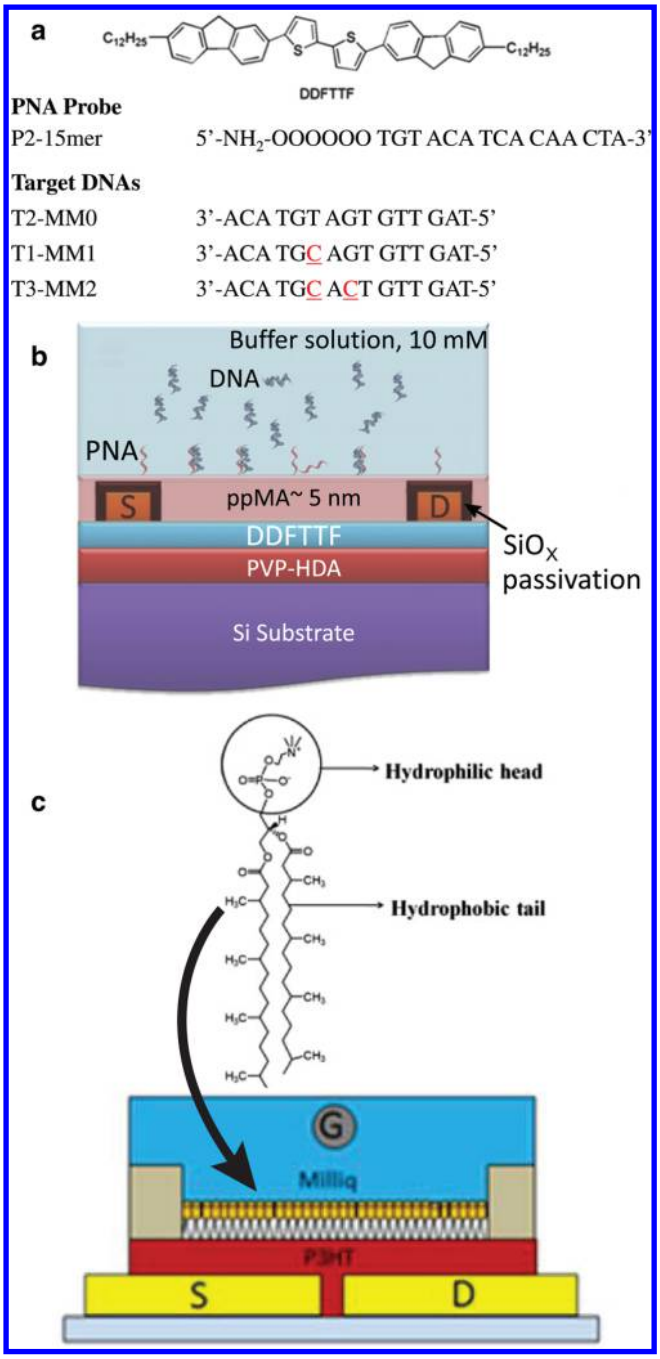

Figure 20. (a, b) Probe, targets, and device structure to characterize the effect of DNA hybridization on the electronic response of PNA-modified OFETs for sensor applications. (c) Device structure of a water-gated OFET including P3HT as the organic semiconductor coated with a phospholipid layer. Parts a and b reproduced with permission from ref 231. Copyright 2012 Elsevier. Part c reproduced with permission from ref 246. Copyright 2013 IEEE.

machinery; it is our first line of defense and it protects us against pathogens, fending off chemical and physical assaults, and suppresses unregulated loss of water and solutes.[248] Further, the skin also plays an important role in temperature regulation and sensation, as well as in the production of vitamin D. Skin is thus of great interest—and poses many interesting challenges—for large-area, flexible, and/or distributed organic bioelectronics. Early demonstrations of large-area and flexible organic electronic displays[249] and printed electronic cir-

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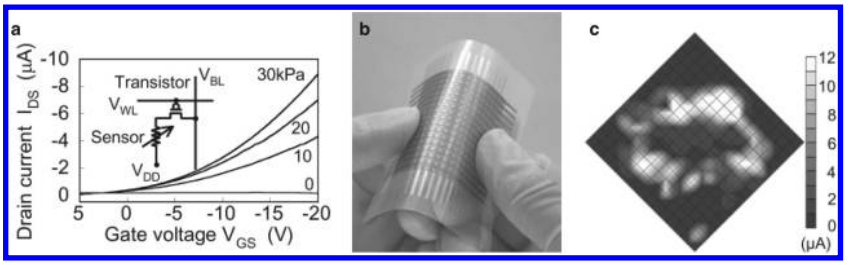

Figure 21. OFET combined with a pressure-sensitive rubber resistor to form the sensory smart pixel (left). The fully integrated and flexible 32 × 32 sensor matrix manufactured on poly(ethylene terephthalate) (PET) foils. A pressure "image" recorded from a kiss applied to the sensor matrix (right). Reproduced with permission from ref 258. Copyright 2004 National Academy of Sciences.

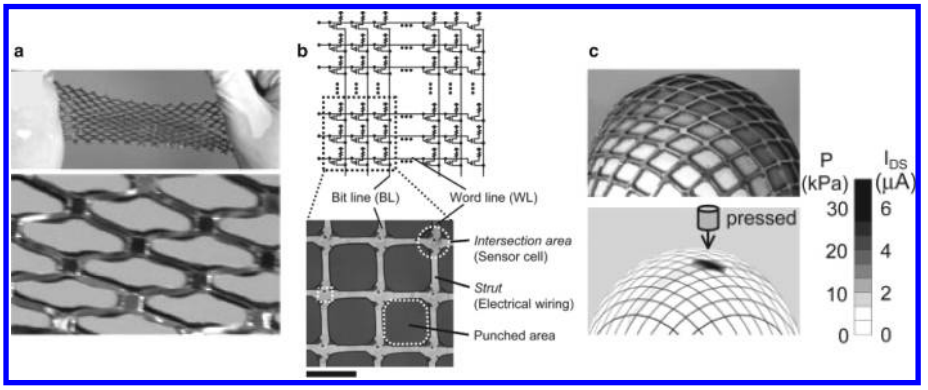

Figure 22. Pressure and temperature sensors have been manufactured on plastic foils, shaped into net structures (a). Each crossing of the net includes a transistor together with sensors (b). The sensor matrix net was then applied to an egg to record sensor patterns applied (c). Reproduced with permission from ref 262. Copyright 2005 National Academy of Sciences.

cuits[250−252] opened up the route toward artificial electronic skin and electronic band-aids based on organic bioelectronics. Our skin includes exteroceptors that sense temperature and touch, the thermoreceptors[253] and mechanoreceptors,[254] respectively. Several research groups have successfully mimicked these 2D-distributed sensory functions by combining matrix-addressed flexible and conformable backplanes with sensor pixels to record pressure and temperature patterns. In 2003, Someya and co-workers presented a large-area pressure sensor matrix fabricated on a plastic sheet by using OFETs combined with rubbery pressure sensor cells.[255] This pressure sensor matrix was the first demonstration of flexible organic bioelectronic area sensors for e-skin applications. These sensor matrices have been possible to assemble using a simple cut-and-paste manufacturing approach.[256] In one setting, the sensor matrices were built up from OFETs, based on pentacene, combined with a pressure-sensitive rubber sheet, comprising polydimethylsiloxane (PDMS) composited with conducting graphite particles.[257] The resistance of the rubber sheet changes as pressure is applied. The associated change in current in individual pixels was then read out via the addressing transistors and collected along the periphery of the matrix. In this way, a spatially resolved pressure "image" could be recorded; see Figure 21. This early work was primarily motivated by robotics applications.

These successful early demonstrations encouraged further activities in the Someya and Sekitani team; an impressive cascade of e-skin demonstrators and developments has been reported since 2003. A crucial and required feature in e-skin applications is that the electronic circuits can withstand continuous and repeated stretching and bending. The Someya and Sekitani team studied and developed various approaches to make transistors operate on ultraflexible substrates and carriers in a stable manner. These studies have included understanding the origin and impact from strain and bending on the electrical transistor characteristics.[259] In pentacence-based transistors made on polyethylene naphthalate (PEN) substrates, a 900 nm thick cross-linked polyimide gate insulator was included. The excellent adhesion and flexibility properties of this 2D cross-linked polyimide insulator enabled reversibility in device characteristics even after exposing the transistors to a bending radius of 4.6 mm. Further, placing a pentacene-based transistor at a neutral position reduced the effects from strain even further. Transistors were manufactured on 13 μm polyimide "thick" films and then covered with an equally thick polychloro-*para*-xylylene layer. At this neutral strain position, steady transistor performance, with a mobility reaching 0.5 $cm^2/(V\ s)$, was achieved even when the transistors were experiencing repeated (60 000 times) bending at a radius of 1 mm.[260] In 2005, the team also reported conformable, flexible, large-area OFET networks including both thermal sensor cells and pressure sensor cells, thus demonstrating an even more complex e-skin system combining two kinds of exteroceptor technologies with matrix addressing.[261] The transistor matrix along with the sensors was manufactured on a plastic film that was later processed to form a net-shaped structure. The resulting sensor net could then be applied onto double-curved surfaces (such as an egg) and subsequently used to measure and record pressure patterns; see Figure 22.

The early achievements toward organic bioelectronic e-skins, reported from 2004 through 2006 by the Someya−Sekitani team, sparked enthusiasm worldwide. In an e-skin[263] effort performed by Bao and co-workers to achieve prosthetic skins and healthcare monitoring technology,[264] pressure-sensitive OFETs were produced on poly(ethylene terephthalate) (PET) foils including a PDMS gate insulator. As a pressure is applied

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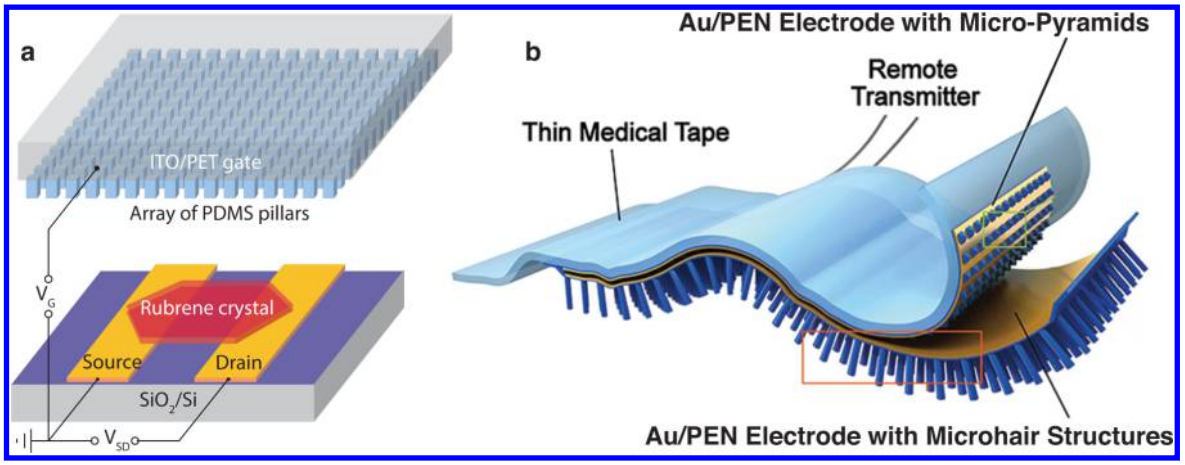

Figure 23. OFETs for pressure sensors including a microstructured PDMS gate insulator. A capacitor and temperature sensors have been manufactured on plastic foils, shaped into net structures. Each crossing of the net includes a transistor together with sensors. Part a reproduced with permission from ref 265. Copyright 2010 Macmillan Publishers Ltd., Nature Materials. Part b reproduced with permission from ref 266. Copyright 2015 John Wiley and Sons.

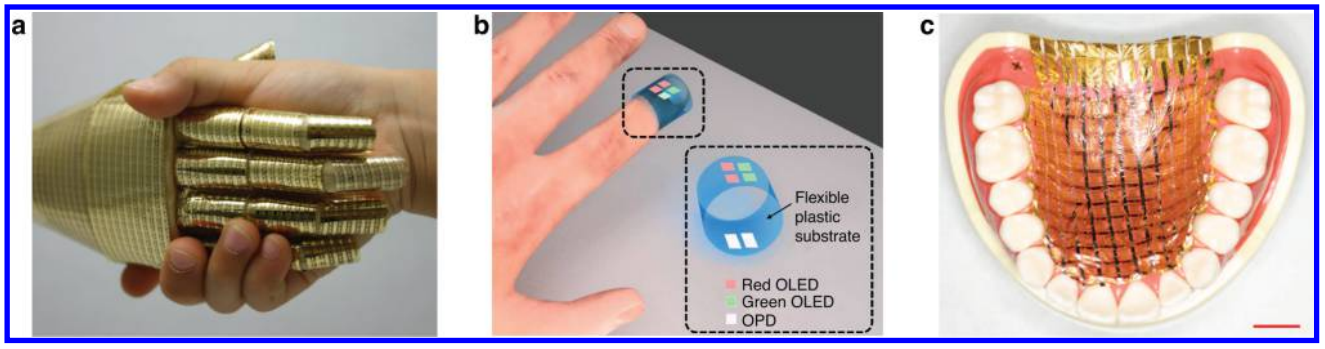

Figure 24. E-skins explored as the artificial skin for robotic applications (a) and applied as sensor circuits for pulse oximeter (b) and a tactile sensor sheet tightly conforming to a model of the human upper jaw (c). Part a copyright Someya Group. All rights reserved. Part b reproduced with permission from ref 216. Copyright 2014 Macmillan Publishers Ltd., Nature Communications. Part c reproduced with permission from ref 270. Copyright 2013 Macmillan Publishers Ltd., Nature.

to the transistor, the physical dimension of the PDMS layer is controlled, which modulates the drain current in a way that provides the desired sensor functionality;[265] see Figure 23a. In a more recent effort, the Bao team has developed a capacitance sensor integrated with a microhair-structured PDMS contact layer;[266] see Figure 23b. With this microhair-based sensor, a 12-times increase in the signal-to-noise ratio in the generated capacitive signals was achieved. The resulting ultraconformal microhair pressure sensor was capable of measuring weak pulsations of internal jugular venous pulses from the human neck.

From a fundamental point of view, the charge transport characteristics in OFETs, and the corresponding device parameters, are sensitive to both temperature and pressure. Various approaches have thus been considered to leverage these fundamental dependencies for e-skin technologies. In 2005, Klauk, Dehm, and co-workers reported pressure sensitivity in pentacene-based OFETs. At that time, this effect was attributed to a change in mobility, threshold voltage, and/or contact resistances.[267] The Bonfiglio group reported similar devices in 2006 about such inherent pressure sensitivity in OFETs on flexible carriers, also based on pentacene.[268] Later on, this sensor effect was explained by a reversible change in conductivity of the semiconductor, and successful prototypes of inkjet-printed OFET sensors were achieved on plastic films.[269] Besides mimicking the thermo- and mechanorecepters of the skin, there is also an interest in deriving e-skins for other parameters as well, such as for medical diagnostics and monitoring.[263,270] The Bonfiglio group has developed pressure sensor matrices based on piezoelectric polymer films, based on polyvinylidene fluoride (PVDF) integrated onto flexible printed circuit boards.[271,272]

Over the years, e-skin technology has been explored as an artificial skin technology for robotic applications and as monitoring and diagnostics technology for health care. Thanks to the flexibility, conformability, and elasticity, e-skins have been possible to apply or explore for applications related to monitoring external or internal parameters expressed on the fingers,[273] hands, arms, and even in the mouth;[270] see Figure 24. Flexible, conformable, and large-area organic electronic e-skins have been evaluated and explored in many different settings. The early efforts were primarily targeting robotics applications, whereas most of the latest efforts relate rather to healthcare and medical diagnostics and monitoring, e.g., electrocardiography.[274]

3.6. Drug Delivery and Chemical Stimulation

Chemical delivery using conducting polymers has been a mainstay of the field all the way back to Zinger and Miller's work in 1984.[275] Even in this early work, they were attempting electrically controlled delivery of the excitatory neurotransmitter glutamate, although with little success (they switched to

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ferrocyanide release). The reasoning behind their work and all the work that followed is simple: conducting polymer films undergo (counter)ion exchange during accumulation or depletion of electronic charges, so can they be used for targeted drug delivery? The motivation is also straightforward: many situations requiring chemical or drug delivery would benefit greatly from local delivery, only at the required position and time, rather than systemic administration. For example, chemotherapeutics for cancer treatment are known to wreak havoc on the body when taken intravenously via injection or orally but could be potentially side-effect-free if delivered in controlled dosage directly into the tumor or at least in close proximity.

Since Zinger and Miller's work, the majority of drug delivery technologies based on conducting polymers have followed their basic model. Conducting polymer films, usually PPy, PEDOT, or derivatives thereof, are prepared with the compounds to be delivered acting as counterions (usually anionic, balancing the charge-accumulated/-depleted conducting polymer) or co-ions (usually cationic, balancing the charge of the embedded counterions in the neutral state of the polymer) (Figure 25).[276] A comprehensive discussion of the history, mechanism,

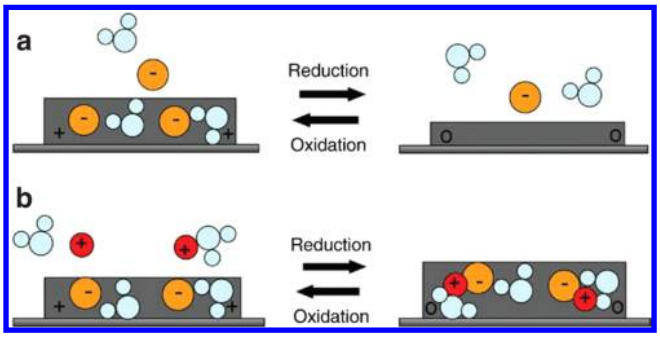

Figure 25. Controlled release from a conducting polymer electrode. (a) PPy prepared with mobile anions will release anions on reduction accompanied by polymer contraction. (b) PPy prepared with immobilized anions will incorporate cations on reduction accompanied by swelling; cations can later be released on oxidation. Reproduced with permission ref 277. Copyright 2010 Elsevier.

and state-of-the-art of this type of "controlled delivery electrode" can be found in the review by Svirskis et al.[277] Here, we will highlight just a few of the many developments and applications over the years.

In 2000, Pernaut and Reynolds demonstrated release of adenosine triphosphate (ATP) from PPy films.[278] ATP is fundamental to all biological systems as a storage unit of chemical energy, and the ability to control its local concentration opens a range of opportunities to modulate biochemical processes. Pernaut and Reynolds used a chemical redox approach, rather than an electrochemical: the PPy was reduced using hydrazine or alkaline medium rather than cathodic potential. The intention was to show that chemical triggers (i.e., biosensing events) could initiate controlled release from a conducting polymer. In 2002, Massoumi and Entezami demonstrated dexamethasone release from PPy and polyaniline (PANI) bilayer structures.[279] Dexamethasone is a steroid pharmaceutical commonly used as an anti-inflammatory medication. Systemic exposure and long-term use has side-effects, so localized delivery would be a useful method of administration. The use of the bilayer structure, comprising what was essentially a conducting ion-exchange membrane, allowed for better control of delivery dynamics. In 2006, Martin and co-workers demonstrated a somewhat parallel technology using dexamethasone-loaded electrospun fibers coated with PEDOT (Figure 26).[174] They loaded the anti-inflammatory

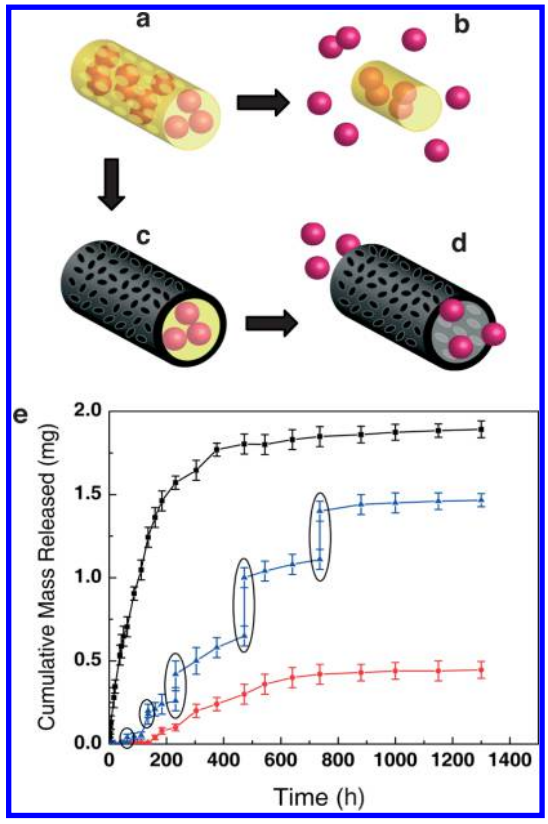

Figure 26. Dexamethasone release from core–shell fibers. Schematic illustration of release: (a) dexamethasone-loaded electrospun PLGA, (b) hydrolytic degradation of PLGA fibers leading to release of the drug, and (c) electrochemical deposition of PEDOT around the dexamethasone-loaded electrospun PLGA fiber slows down the release of dexamethasone (d). (e) Cumulative mass release of dexamethasone from PLGA nanoscale fibers (black squares), PEDOT-coated PLGA nanoscale fibers (red circles) without electrical stimulation, and PEDOT-coated PLGA nanoscale fibers with electrical stimulation of 1 V applied at the five specific times indicated by the circled data points (blue triangles). Reproduced with permission from ref 174. Copyright 2006 John Wiley and Sons.

compound into PLGA fibers and demonstrated passive release. When the fibers were conformally coated with the electroactive PEDOT layer, they were able to turn the passive release into active delivery: by addressing the PEDOT, they could trigger controlled delivery. They argued that the volume actuation of the PEDOT coating caused the dexamethasone to be expelled by hydrodynamic force, but they also alluded to the possibility of cracking or degradation of the PEDOT encapsulation as another possible mechanism for release. More recently, Wallace and co-workers demonstrated antibiotic delivery from core–shell fibers based on PEDOT:PSS and PPy.[280] They were able to release the drug ciprofloxacin from the outer PPy cladding, using the PEDOT:PSS core as support and electrical conductor. When testing their system against *Streptococcus* and *E. coli* bacteria strains, they found that the ciprofloxacin maintained its antibiotic efficacy and could inhibit bacterial growth.

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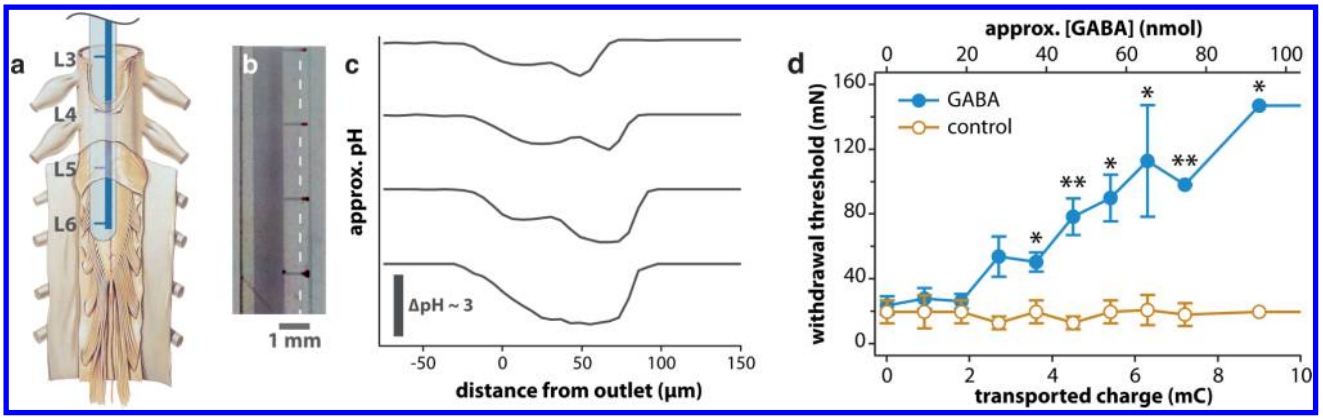

Figure 27. Organic electronic ion pump (OEIP)-based therapy for neuropathic pain. (a) Depiction of the four outlets of the OEIP aligned with the sites where the nerve bundles associated with the pain model enter the spinal cord. (b) Microscope images during delivery of H^+ into indicator (red = low pH). (c) Approximate pH profiles at the four delivery tips. (d) Pain response as paw withdrawal threshold (higher threshold corresponds to less pain) as a function of delivered therapeutic. Reproduced with permission from ref 287. Copyright 2015 AAAS.

Apart from the controlled-delivery electrodes described earlier, there have been other notable uses of conducting polymers for drug delivery applications. The volume actuation of conducting polymers is well-known and has actually been a facet of drug delivery systems since Zinger and Miller's work (see Figure 25). However, the volume change can also be utilized in itself for actuation purposes. For example, consider the PPy-based "electrochemical muscles" developed by Inganäs, Pei, and Jager.[84,281,282] Throughout the 2000s, the group of Madou used just this actuation mechanism to develop microelectromechanical systems (MEMS) for drug delivery applications. In 2000, they proposed using sphincter, plunger, and iris configurations of conducting polymer actuator as liquid flow valves.[283] In that article, they proceeded to evaluate actuator materials based on polyaniline but did not actually show drug release results. In 2006, they presented another delivery MEMS based on hinged flaps covering drug-loaded reservoirs.[284] In this case, they used a colored dye to visualize successful release dynamics. While based on moving parts, and thus subject to mechanical failure, Madou and co-workers' actuator-based systems have one significant advantage over other conducting polymer-based delivery systems: there is no limitation on the size or chemical makeup of the drug. As long as the drug or therapeutic compound can be solubilized, the MEMS system could be used for local delivery.

Another notable use of conducting polymer drug delivery technology is the organic electronic ion pump (OEIP), developed in our research group over the past decade. As described above in section 2.3.2, OEIPs and the similarly operating ion bipolar membrane diodes and ion bipolar junction transistors leverage "long-range" ionic conductivity through the polymer to effect precision electrophoretic transport. OEIPs were originally developed to investigate neural cell signaling in vitro. In 2007, the first of these experiments demonstrated that Ca^{2+} signaling in human cortical neurons (HCN-2) could be triggered by K^+ delivery through the OEIP.[13] The cells were cultured directly on the PEDOT:PSS electrodes of the device but only exhibited a Ca^{2+} response (measured via real-time fluorescence) when high extracellular [K^+] opened Ca^{2+} channels in the cell membranes. In 2009, a similar in vitro experiment was performed, but with a significantly optimized device architecture, for the delivery of the neurotransmitter acetylcholine (ACh).[137] The OEIP was designed in this case to have a preloading channel, enabling on/off dynamics down to ~200 ms temporal resolution. This was also the first time the OEIP was used to deliver a neurotransmitter, which was significant for two reasons: first, the system could address specific neurotransmitter receptors, rather than just changes in metal ion concentration, and second, relatively "larger" molecules could also be transported. This set of experiments also demonstrated the spatial resolution of OEIP delivery. Cells located adjacent to the delivery point (within ~50 μm) could selectively be addressed compared to cells located ~150 μm away. Other groups have also investigated ion-selective membrane-based technologies like the OEIP for biochemical signaling applications. In 2011, Lin, Han, and co-workers demonstrated a device that could modulate physiological ion concentrations (Na^+, Ca^{2+}, etc.) and thereby modulate signaling in sciatic nerve bundle explants.[285] The device was essentially a set of ion-selective "fingers" over metal electrodes. Under bias, ions were drawn into, or expelled from, the ion-selective coatings, causing changes in the environment directly above, where the nerve bundle was fixed. While not a conducting polymer technology, the results indicate a likely path forward for OEIP-like tools.

Most recently, OEIP "iontronics" have been utilized to address specific physiological targets and even disease states. In 2015, we demonstrated a multioutlet device for delivery of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) into a brain-slice model of epilepsy.[138] The brain slices were fixed directly on top of the device, and GABA delivery was able to locally decrease neuronal firing characteristic of an epileptic seizure. Specifically, neurons located on the other side of the explant (away from the OEIP outlets) did not experience reduced epileptiform activity. This result was notable as it highlighted the potential for local drug therapy for this difficult-to-treat disease. In these experiments, the electrophysiological recordings were achieved using standard tungsten electrodes positioned using micromanipulators. In 2016, these experiments were repeated, but using PEDOT-based sensing electrodes[178] integrated into each OEIP delivery point.[286] Specifically, OEIP delivery was achieved *through* the sensing electrodes, allowing both chemical delivery and electrophysiological sensing from each 20 × 20 μm "neural pixel". Again, epileptic activity was recorded and locally stopped by delivery of GABA, but this time the recordings were at the site of delivery.

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During the past few years, OEIPs have also been adapted from an essentially planar structure, suitable for in vitro applications, to encapsulated formats, suitable for implantation in vivo. In 2009, we demonstrated the first of these encapsulated OEIPs in the delivery of the neurotransmitter glutamate to the guinea pig cochlea in vivo.[14] The cochlea is the organ that transduces pressure disturbances into neural signals, which lead up the auditory nerve into the brain. This transduction is achieved using specialized "hair cells". One set of these cells, the "inner" hair cells, utilizes glutamate as its primary signaling compound, while the "outer" hair cells do not have glutamate receptors. Delivering glutamate using the OEIP selectively affected only the inner hair cells (with receptors) even at diffusive distances up to several millimeters. This demonstration was the first example of using flow-free OEIP delivery to chemically target a specific biochemical pathway in vivo, with the experiments showing significant modulation of hearing sensitivity using chemical stimulation, rather than the more typical electrical stimulation (e.g., in a cochlear hearing implant). More recently, the OEIP was used in a longer-term implantation to effect a pain therapy.[287] Neuropathic pain, that is, pain originating from a diseased or malfunctioning neural pathway rather than a stimulus such as heat, muscle fatigue, etc., afflicts a surprising number of people and is very difficult to treat effectively.[288] Studies have shown that malfunctioning GABA pathways in the spinal cord may be a culprit in some forms of neuropathic pain.[289] We thus adapted an implantable OEIP to simultaneously deliver GABA to four points lining up with specific positions along the rat spinal cord (Figure 27). These positions corresponded to the points at which the pain signals entered the spinal cord from the peripheral nervous system—one might say, at the first points at which the pain signals entered into awareness. Using OEIP delivery, pain thresholds in the model system were shown to approach healthy levels, at much lower GABA dosage that would be required using standard syringe (bolus) injection. In addition to the first demonstration of an organic electronic therapy, these experiments also showed the feasibility of OEIPs implanted for several days or weeks in an awake animal.

4. FUTURE OUTLOOK FOR ORGANIC BIOELECTRONICS

4.1. Bioelectronics in a Historical Perspective

Bioelectronics dates back to the early discoveries and experiments of Luigi Galvani, performed in the 1780s, when he applied static electricity provided from an inorganic metal scalpel to the sciatic nerve of detached frogs' legs. Galvani termed this phenomenon *animal electricity*, and he suggested that it involves networks of nerves, including an electrical fluid that transfers and triggers actions in muscles. Later on, Alessandro Volta, a colleague of Galvani, repeated these experiments and also applied more advanced probing and recording techniques, such as the voltaic pile and Johan Carl Wilcke's electrophorus capacitive generator. Volta found that the "animal electricity" was in fact identical to the charge currents generated by electrochemical cells. From these early experiments, several scientific, medical, and technological pathways have branched out during the centuries, such as electrophysiology, neuronal electrodes, the pacemaker, and the field of bioelectronics. The pacemaker is a canonical example of applied bioelectronics. It is essentially a metal electrode device that uses electrical pulses to induce contractions in the heart muscle. Basically, the pacemaker utilizes the same charge-polarization mechanism as the one that was discovered and studied by Galvani and Volta. After several early demonstrations of actuating or regulating ventricular contraction of the heart, conducted in 1889 (MacWilliam), 1926 (Lidwill), and 1932 (Hyman), the first wearable (Bakken) and implanted pacemakers (Elmqvist and Senning) were demonstrated in 1958. Today, millions of patients are carrying an implanted pacemaker, and the success of this device has encouraged generations of electrical engineers, scientists, and medical doctors to further develop the electrode and electronics technology, as well as the materials technology for long-term (even lifelong) implants. Their aim is, of course, even more effective therapies but also new opportunities for wellness monitoring and "e-health". In recent years, this can be seen as a development beyond the fairly basic circuitry of pacemaker electrodes. For example, the Fromherz team have developed a range of solid-state silicon technologies, including signal routing circuits and matrices of metal electrode pads for neuronal communication. In this work, signal transmission between individual field-effect transistors and individual mammalian nerve cells has been demonstrated.[290] During the past decade, this technology has evolved, and flexible inorganic CMOS (complementary metal−oxide−semiconductor) circuits are now available that can be implanted to interface with the heart and brain, providing close proximity of massive electronic signal processing with those of biological and human systems.[291]

During the last 20 years, bioelectronics based on organic materials have evolved and now complement inorganic bioelectronics in a very elegant manner. Today, we can regulate and record biological functions with the help of organic bioelectronics tools—in various systems and in previously unattainable ways. Before suggesting an outline for a successful future for organic electronics in therapy, diagnostics, and health care monitoring settings, it is crucial to position this still-nascent technology in the perspective of maturity and readiness for widespread applications. Similar challenges that the inorganic community experienced when taking a "simple" electrode into the therapeutic technology of the pacemaker will also apply to organic bioelectronics, with the addition that the regulatory thresholds for new techniques in medicine and healthcare are significantly more complicated and stringent compared to the situation in the 1950s.

One of the great benefits of organic electronic materials for biological applications is their versatility: their mechanical, chemical, and physical properties can be precisely controlled and modified. These properties can be tailor-made via synthesis and choice of manufacturing protocols. Thus, we can tune the resulting organic bioelectronics to be highly biocompatible in the broadest sense. However, this versatility is also one of the major drawbacks of organic electronic materials. They are often sensitive to small variations of the ambient conditions, and they are reactive and may degrade under operation or storage. Decades of substantial effort are needed to adapt organic bioelectronics to the techniques and settings widely used in therapy and diagnostics (e.g., autoclaving in hospital equipment, long-term implantation). However, thanks to the unique properties and opportunities of organic electronics in biological applications, we are convinced that this investment in research and development will reap significant rewards, ranging from new insights in materials science to unprecedented personalized therapies. Below, we outline our view on a range of challenges

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and suggestions for how to move forward, along with some future directions within the field of organic bioelectronics.

4.2. Hybrid Organic–Inorganic Bioelectronics: The Best of Both Worlds

So far, organic bioelectronics has evolved more or less as an isolated material science and device technology. However, organic bioelectronics has been applied to a wide range of biological systems in the most successful manner. During the last few decades, and in parallel to the rise of organic bioelectronics, inorganic (CMOS) electronics has also developed in a remarkable way and today can be made all-flexible and biocompatible and can even perform excellently in in vitro and in vivo applications. This inorganic CMOS bioelectronics possesses extreme computing capability, can include circuits for common communication protocols, and offers several different sensor and actuator devices for precise signal translation with biological systems. However, there is a vast array of features and functions, specifically those related to electronic-to-biochemical (and vice versa) translation, which inorganic CMOS cannot do. So, inorganic CMOS technology and organic bioelectronics complement each other perfectly. First, from a technology point of view, high-performing electronic computing and communication performed in CMOS would expand the application targets for the chemical-to-electronic and electronic-to-chemical signal translation provided by organic bioelectronics. Second, shortcomings in organic bioelectronics, related to bias stress and drift of device parameters, can be compensated for by stable signal processing provided by CMOS technology.

4.3. Standardization

Organic bioelectronics is built up from a combination of organic electronic materials, such as permeable/impermeable membranes, semiconductors, conductors, and insulators. Many of the unique capabilities and features of organic bioelectronic devices are made possible thanks to the creation of unique and dedicated organic electronic materials and device architectures. The library of materials and architectures is today enormous and thus presents, in itself, a challenge regarding standardization, protocols, statistics, and benchmarking. Perhaps the field of organic bioelectronics has matured and would thus benefit from selecting or choosing a "standard" setup of materials, protocols, and device architectures to aid development in the field in a more coherent and coordinated manner. This is of utmost importance considering that organic bioelectronics is expected to develop into a medical technology platform with therapy and diagnostics as the major end-user areas.

4.4. Augmenting Existing Medical Technology

Many of the unique features of organic bioelectronics relate to in vivo translation of signaling, for regulation and recording of functions in biology. The pacemaker, deep brain stimulation (DBS) electrodes, or cochlear implants, all in clinical use for decades, may offer the organic bioelectronics community shortcuts into therapeutic applications. Integrating organic bioelectronics components with existing therapeutic technologies promises extended—perhaps even unprecedented—functionality in already-developed therapeutic techniques. If this integration is possible with limited impact on the existing electrode technology, the organic bioelectronics may piggyback on a technology that has already successfully navigated the path from early demonstration to clinical application. In addition to the fact that these technologies have already been approved by regulatory authorities, an additional benefit would be the opportunity to work with clinicians who are already equipped to perform the various medical and bioelectronic procedures.

4.5. Addressable Bioelectronic Circuits in 3D

Organic bioelectronic circuits and systems are today typically manufactured using classical clean-room production (e.g., photolithography) or printing techniques. Those typically produce areal 2D electronic devices or systems. Biology is 3D, and proper technology–biology signal translation *and addressing* must take this dimensionality mismatch into account (see sections 2.1.3 and 3.2). 3D printing is now commonplace and offers the ability to develop and explore 3D electrodes and systems for signal translation throughout a whole organ or tissue. Also, electrospun electrodes and various polymerization and etching techniques have successfully been used to derive spongy or porous electrode systems to optimize signal transfer. In an effort to manufacture 3D electrodes with fully X–Y–Z addressing, and to provide an architecture exactly mimicking that of biology, recent work has demonstrated that one can manufacture bioelectronics, such as electrodes[292] and signal transport pathways across glial scars, inside living tissue.[293] By using in vivo polymerization of PEDOT electrodes within neuronal tissue, excellent impedance characteristics for signal transduction were achieved.

4.6. Looking Beyond the Animal Kingdom

Organic bioelectronics has so far been developed primarily targeting medical applications, such as diagnostics and therapy, and also some niches in cell biology, such as monitoring or controlling the growth of cell cultures. This may be due to a natural anthropocentric bias in all of us, but is certainly due in part to the funding landscape for new tools and techniques for (human) therapies and healthcare. In addition to the animal kingdom, there are many other biological systems to consider where organic bioelectronics has a potential to play a unique and important role, providing novel tools to study, and harvest from, various functions in nature. Indeed, there may be great opportunities to leverage tools and technologies that have been developed and honed in, for example, neuroscience or drug delivery applications, in totally different biological milieus. In addition to providing bioelectronic tools to disciplines that so far have not relied as heavily on electronic interfacing, there is societal and ethical incentive to expand the application areas. For example, researchers working with mammalian cells and tissue, or even live animals, are well-acquainted with the ethical issues (both personal and regulatory) arising in their work. Applying their technology to plant or bacterial systems could be significantly easier, from such an ethical perspective. An example of societal incentive would be the use of organic bioelectronics to augment plant function, which could circumvent the societal hurdles for genetic modification, currently the best tool for such augmentation. We foresee that organic bioelectronics can be applied to—or even *in*—fungi, plant,[294,295] bacteria,[296,297] protista, or archaea systems, thus developing organic bioelectronics into a generic platform for future biocomputing, green technology, and biotechnology.

4.7. Ubiquitous Bioelectronics

With the emerging technology of Internet of things/everything, wearable electronics, active skin patches, and distributed electronics inside the body, the border between the digital world, nature, and humans will become somewhat blurred. In a

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recent essay,[298] we discussed the opportunity of achieving capacitively coupled body-area networks including such distributed electronics and bioelectronics technology, for future health care applications. In analogy to the development of communication, sensor, and actuator technology developed for the automotive industry, we foresee that diagnostics, monitoring, and even therapy will be autonomous and carried out beyond the walls of the hospital. Bioelectronics will have a major impact on society; this development and evolution must go hand-in-hand with a proper societal discussion including ethics, integrity, and safety. For example, capacitively coupled body-area networks can address the issue of broadcasting interdevice communication (e.g., pacemaker-to-drug delivery or biosensor-to-brain electrode) beyond the boundary of our body. Still, great care must be taken at all steps of development to ensure adequate security and adherence to ethical standards. Turning again to developments in the automotive industry, remote and autonomous diagnostics, service, and actuation have revolutionized the reliability and safety of transportation, and security concerns have been an important factor in this development. Will a similar technology be applied to humans to improve the quality, reliability, and safety of healthcare and life?

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Notes

The authors declare no competing financial interest.

Biographies

Daniel Simon received his Bachelor's degree in Physics from the University of Georgia, Athens, in 2000. In 2007, he completed his Ph.D. in Physics at the University of California, Santa Cruz, in the laboratory of Sue Carter. He focused on a range of topics in polymer-based electronics, including biomimetic films on microelectrode arrays, light-emitting electrochemical cells (LECs), and nanoparticle-based nonvolatile memory. Later that year, he joined the Laboratory of Organic Electronics as a postdoctoral researcher, where he focused on converting in vitro organic electronic ion pump technology (see section 2.3.2) for use in a living animal, and later for self-regulating artificial neuron functionality. Since 2011, Daniel has led the Organic Bioelectronics group of the Laboratory of Organic Electronics, becoming Assistant Professor in 2013.

Erik O. Gabrielsson is a postdoctoral researcher at the Laboratory of Organic Electronics at Linköping University. He received his M.Sc. in Engineering Biology in 2009 and his Ph.D. in Organic Electronics in 2014, both from Linköping University. His research is focused on ionic materials, devices, and circuits, as well as hybrid organic−inorganic technologies for applications bioelectronics.

Klas Tybrandt received his M.Sc. in Applied Physics and Electrical Engineering in 2007, and his Ph.D. in Organic Electronics in 2012, both degrees from Linköping University. During his Ph.D. studies he developed the first Ion Bipolar Junction Transistors and iontronic circuits based on these devices. In 2013, he received an International Postdoc Fellowship from the Swedish Research Council and joined the Laboratory of Biosensors and Bioelectronics, ETH Zürich. During the two-year postdoc period he developed stretchable electronics materials and systems, including conductors, bioelectronics and displays. In 2016, he joined the Laboratory of Organic Electronic, Linköping University, as a Research Assistant Professor with focus on stretchable bioelectronics.

Magnus Berggren received his Ph.D. in Applied Physics in 1996 from Linköping University, Sweden. He then joined Bell Laboratories in Murray Hill, New Jersey, for a one-year postdoc period focusing on the development of organic lasers and novel optical resonator structures. In 1997 he teamed up with Opticom ASA, from Norway, and former colleagues of Linköping University to establish the company Thin Film Electronics AB, where he served as managing director and initiated the development of printed electronic memories based on ferroelectric polymers. In 1999, he returned to Linköping University and became a part-time manager at Acreo Swedish ICT. Since 2002, he is professor in Organic Electronics at Linköping University and the director of the Laboratory of Organic Electronics, today including close to 60 researchers. The group focuses on a broad assortment of topics in organic electronics including printed/paper-based electronics, solid-state devices, new materials, thermoelectrics, theory and modeling, photonics, bioelectronics, and, most recently, plant electronics. In 2012 he was elected member of the Royal Swedish Academy of Sciences, and in 2014 he received the Marcus Wallenberg Prize.

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