MRS Communications (2022) 12:565–577

https://doi.org/10.1557/s43579-022-00269-3

MRS Communications
Early Career Materials Researcher Prospective

Towards organic electronics that learn at the body-machine interface: A materials journey

Heejung Roh, Camille Cunin, Sanket Samal, and Aristide Gumyusenge, Department of Materials Science & Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave, Cambridge, MA 02139, USA

Address all correspondence to Aristide Gumyusenge at **aristide@mit.edu**

(Received 4 May 2022; accepted 6 September 2022; published online: 16 September 2022)

Abstract

It has been over four decades since organic semiconducting materials were said to revolutionize the way we interact with electronics. As many had started to argue that organic semiconductors are a dying field of research, we have recently seen a rebirth and a major push towards adaptive on-body computing using organic materials. Whether assisted by the publicity of neuroprosthetics through technological giants (e.g., Elon Musk) or sparked by software capabilities to handle larger datasets than before, we are witnessing a surge in the design and fabrication of organic electronics that can learn and adapt at the physiological interface. Organic materials, especially conjugated polymers, are envisioned to play a key role in the next generation of healthcare devices and smart prosthetics. This prospective is a forward-looking journey for materials makers aiming to (i) uncover generational shortcomings of conjugated polymers, (ii) highlight how fundamental chemistry remains a vital tool for designing novel materials, and (iii) outline key material considerations for realizing electronics that can adapt to physiological environments. The goal is to provide an application-guided overview of design principles that must be considered towards next generation organic semiconductors for adaptive electronics.

Introduction

Computational capabilities continue to impact our daily lives and will undoubtedly play a vital role in modern society. The way we interact with computers has evolved to become more intimate over the past decade and is expected to become even more seamless in the form of wearables and implanted electronic devices.[1] These electronics are particularly attractive in healthcare where continuous monitoring of vitals, timely interventions, and reliable data collection are needed for decreasing mortality rates. Such abilities are highly anticipated in this sector, which in 2020 alone accounted for a 9.7% increase in the national GDP spending in the US.[2,3] Consumer products that are in physiological contact have also been proposed.[4,5] With the current capabilities in terms of software and data handling, hardware designs for electronics able to collect relevant information, accurately process signals, and relay them onto either biological organs or prosthetics are the obvious next step towards the realization of smart body–machine interfaces. Such electronics, often termed *Bioelectronics,*[6] date back to Galvani's "Twitching Frog Leg" experiment in the 1780s and have since then seen substantial developments in terms of materials and devices. The integration of electronics onto and/or into our bodies, however, has proved to be no easy task. Several challenges, most of which are rooted in materials including biocompatibility, mechanical mismatch, signal reliability, and long-term operation, to name a few, remain to be addressed before on- and in-body sensing and computing can become a reality.[1,2,7]

A few decades ago, organic semiconductors emerged as promising candidates to address the above-listed challenges. From their discovery by Heeger and coworkers,[8] organic semiconductors remain an attractive class of materials owing to their soft nature, and their tunability at the molecular, nano-, and micro-scales; they have been studied for the realization of electronic devices that can operate at the body–machine interface.[9] In fact, several successful demonstrations of materials and devices have been reported using organics.[9,10] Analogous to CMOS technology, the field of *Bioelectronics* has leaned towards the use of high-density transistor-based computing. It has thus been envisioned that the design of high-performing (silicon-like) organic semiconductors would drive this field forward.[11] To merge electronics with biology, such devices ought to respond to biological signals. In that regard, organic electrochemical transistors (OECTs) have been studied as building blocks able to respond to ionic signals and transduce them into amplified and detectable electrical outputs.[7,12] Such signal recording and transduction using organic materials have recently sparked a new era of electronics with the highly anticipated commercialization by Neuralink, Brainco, BrainGate, and others.[7] From the Galvani era to Musk's potential commercialization, the ultimate bottleneck towards seamless integration of electronics remains around materials design. Additionally, there is a generational disconnect between engineers and materials chemists regarding the design of adaptive electronics at the biological interface calling for a cross-disciplinary discussion on the future of bioelectronics.

Heejung Roh and Camille Cunin have contributed equally to this article.

In this prospective, we aim to provide an overview of application-guided material design approaches toward next-generation organic electronics able to interface with biology (Fig. 1). Our goal is to highlight successful examples and underpin design principles that might guide materials makers to synthesize novel systems to complement engineering efforts in meeting current and future needs. Our discussion will focus on organic semiconductors as these device components are subject to more stringent requirements and face more challenges compared to other components (e.g., substrates, dielectrics, electrolytes). Using literature examples, we will highlight the evolution of organic semiconductors, especially conjugated polymers in electrochemical transistor devices. Our discussion will also underline electrochemical considerations when designing bioelectronics and relevant characterization methods to relate structure to performance at the biological interface. Such cross-disciplinary discussions are becoming more crucial toward bridging materials design and device engineering with the ultimate applications in mind. Lastly, we will provide an outlook on next-generation semiconductors with an emphasis on cross-disciplinary and application-driven approaches to address the remaining challenges.

Interfacing with the biological circuit

The human nervous system

Before addressing interfaces between machines and the biological (human) neural system, it is appropriate to have a better understanding of the rather complex functionality of the latter. The human nervous system is divided into the central nervous system (CNS), which includes the brain and the spinal cord, and the peripheral system (PNS), which accounts for the rest of the nerves at the periphery. To control the multitude of functions across the body, the nervous system is made up of a large variety of cells, such as neurons and support cells (e.g., glia cells), which communicate via electrical or chemical mechanisms. One key role of neurons is to maintain a concentration gradient of ions—mainly sodium, potassium, chloride, and calcium—which flow across the neuron's membrane via specific ion channels. The movement of these ions results in a local difference of electrochemical potential, as dictated by the Nernst equation, and can trigger an electrical response in the form of a brief spike called action potential.[13] These localized shifts from negative to positive potentials in the membrane cause adjacent locations to similarly depolarize, propagating the electrical signals through a particularly long projection (the axon) until it reaches the synaptic cleft. In electrical synapses, the signal can travel directly between neurons through channel proteins that connect adjacent neurons.[14] In chemical synapses, the predominant type of synapses in the body, the action potential causes the pre-synaptic neuron to release chemical neurotransmitters that diffuse across the synaptic cleft which then bind to the receptors of the post-synaptic cell.[15]

A particularly interesting property of synaptic connections is their ability to strengthen or weaken over time, in response to potentiation or depression of their activity. These phenomena, known as synaptic plasticity, are involved in learning and memory, brain development and homeostasis, sensorial training, and recovery from brain lesions. Plasticity changes have been demonstrated to depend on the number of neurotransmitter receptors located in the post-synapse and can either act on a timescale of tens of milliseconds to a few minutes (short-term plasticity), or of minutes to hours (long-term plasticity).[15] Although short-term plasticity can occur both at excitatory and inhibitory

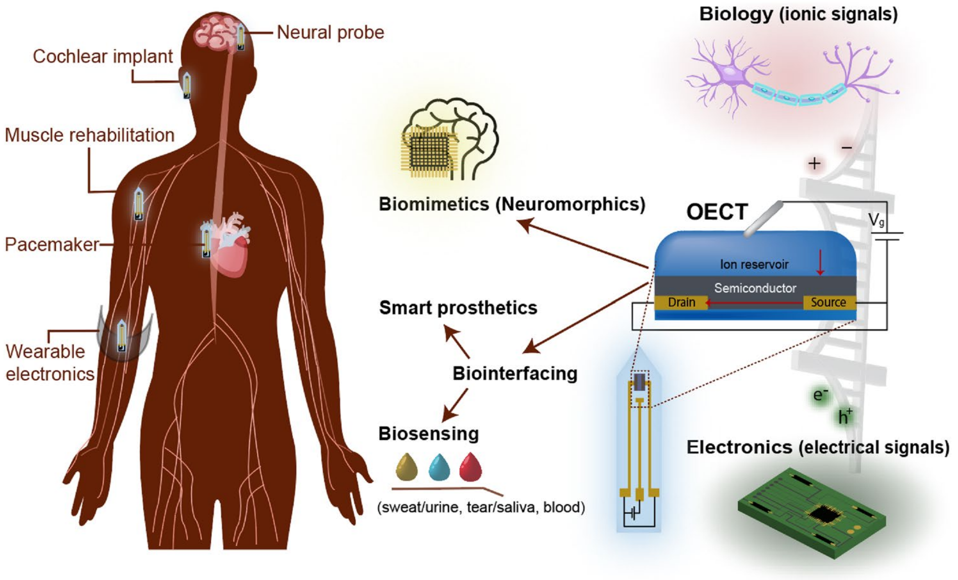

Figure 1. Illustration of electronics that learn at the body–machine interface. Organic electrochemical transistors (OECTs) are overviewed in this prospective as the bridge between biology and electronics towards smart prosthetics and biomimetics.

synapses resulting in synaptic enhancement or depression, long-term plasticity only occurs at excitatory synapses. The intrinsic tunable and nonvolatile nature of synapses makes them inspiring models for the field of neuromorphic computing. Intensive efforts are currently being made to develop, and/or exploit materials that exhibit any type of neural behavior, including switching abilities, short- and long-term potentiation, or time-dependent plasticity. In neuromorphic computing, for instance, the feed-forward nature of neural signals has inspired artificial neural networks in which the weight of the connection between two neurons mimics the strength of a synapse.[16] The evolution of materials and device architectures capable of simulating the human neural system has led to dramatic advances toward highly compliant body–machine interfaces.

Body–machine interfacing

The field of bioelectronics has opened unprecedented opportunities toward the development of a variety of platforms capable of interfacing with the human body. From wearable biosensors to implantable neural probes, body–machine interfaces offer great promises for next-generation point-of-care devices. Successfully interfacing with the body, however, involves developing interfaces with sufficient biocompatibility, stability, and electrical performances.[17–19] One major challenge associated with body–machine interfaces stems from putting a hard, dry, hydrophobic electronic interface in contact with a soft, ion-rich, and hydrophilic tissue (Fig. 1). The mechanical mismatch at the interface between microelectronic devices (Young's modulus ~ 100 GPa) and human tissues (Young's modulus ~ 1 kPa) not only triggers immune response and elicits scar tissue formation,[20] but it also leads to increased impedance and poor signal collection. Because incompatible signal conduction mechanism and huge gaps in physical and mechanical properties lead to inferior communication efficiency and failures in bioelectronic applications, the device interface needs to "fit" the natural curve of the tissue while mimicking its natural properties to maximize the signal and limit adverse effects. Compared to their inorganic counterparts, organic electronic materials have demonstrated enormous potential for integration into body–machine interfaces due to their better compliance with mechanical properties of tissues, ability to operate in harsh biological environments, ease of integration into miniaturized architectures, low-cost production, low-power consumption, and tunability. Interfacing with the body can either be performed internally (e.g., implanted devices), or externally (e.g., wearable electronics) (Fig. 1) through a broad range of transducing strategies.

Transducing biological signals

In biological systems, information is carried by ions, while in electronic systems, signals are conveyed by electrons (Fig. 1). Hence, to interact with biological tissues, bioelectronic devices must act as transducers to convert biological signals (in the form of ionic currents induced by neural activity) into readable signals either electronic, optical, or mechanical. This transduction can be achieved using conventional metal electrodes as passive conductors or using transistors in which the active semiconductor channel is used to amplify or switch electrical signals. Recently, combinations of the two approaches have also been investigated where functionalized electrodes are used for signal detection and adjacent transistor channels are used for amplification.[7] As a result, over the past few years, bio-interfaces based on miniaturized transistors has enabled the direct acquisition and amplification of signals while improving signal-to-noise ratio.[21,22] Among them, electrolyte-gated transistors (EGTs) have emerged as powerful tools in bioelectronics due to their stability in aqueous environments, low-voltage operation, and ability to both transduce and amplify biological signals into electronic signals by directly interfacing with the biological environment under study (e.g., blood, saliva, tears, cells, skin) as illustrated in Fig. 1. The use of an electrolyte brings an extra analogy with biological synapses through which signals are transmitted via the ionic flux of neurotransmitters in the synaptic cleft. Organic EGTs can be subdivided into two categories: organic electrolyte-gated field effect transistors (OEGFETs) and OECTs. OEGFETs are made of ion-impermeable semiconductors and rely on the charge accumulation at the 2D-interface between the electrolyte and the semiconductor. On the other hand, in OECTs, the channel is permeable to ions, and ionic–electronic interactions involve the entire three-dimensional volume of the semiconducting channel. Organic mixed ionic–electronic conductors (OMIECs), also classified as ion-permeable organic semiconductors (OSCs), have thus emerged in recent years as excellent channel materials for OECTs owing to their compatibility with both ions and electrons, mechanical matching (compared to inorganic counterparts), biocompatibility, and structural tenability.[23] This multifunctionality enables unprecedented set of properties such as energy-efficient sensing and learning/computing.[23,24] These conductors, which will be discussed in more details in later sections, are mostly conjugated polymers with polar sidechains that can interface with electrolytic environments and translate ionic signals into electrical signals in terms of their conductance change upon ionic insertion. Considering recent advances in the fields of neuromorphics and bioelectronics, OMIEC-based transducing devices are envisioned to complement the body in the form of smart prosthetics (e.g., monitoring, sensing, nerve regeneration).[25] The integration of OMIEC materials into smart electronics is also envisioned to yield full replacement of malfunctional body parts by mimicking biological mechanisms (e.g., neuromorphic computing for biological applications).

Characterizing materials for body–machine interfaces

The above discussed OECT, as first demonstrated by Wrighton et al. in the mid-1980s, consists of a semiconducting layer put in direct contact with two metal electrodes (source and drain) and under indirect control of a gate electrode through an electrolyte (Fig. 1).[26] Unlike the organic field-effect transistor

(OFET) where only interfacial charge accumulation is targeted, the operation of an OECT depends on ionic–electronic interaction throughout the bulk of the channel. In this aspect, traditional OSCs have been adjusted to incorporate ionic conduction which has led to the evolution of OMIECs as effective channel materials.[27] These design strategies are detailed in later sections. OECT operation is controlled by potential applied to the gate (V_G) and to the drain (V_D), both of which are referenced with regards to the source electrode. Ions are then injected from the electrolyte into the OSC channel in a controlled manner via V_G, thus changing its doping state by compensating electron/hole charge (accumulation mode) or by replacing doped counterion (depletion mode). The conductivity of the channel, and hence the current flowing between the source and drain, is modulated as a function of the gate polarity.[21] The drain voltage induces a current through the channel (I_D), which is proportional to both the mobility of carriers and the concentration of mobile charge carriers in the channel. Since the latter is controlled via V_G and requires a threshold potential (V_T), it serves as an indicator of the doping state of the OSC. In other words, OECTs make effective use of ion injection from an electrolyte to modulate the bulk conductivity of an organic semiconducting channel thereby transducing (amplifying or on/off switching) a small voltage signal at the gate into significant changes in drain current. At the physiological interface, such response is highly desirable for sensing minute changes in biological media. This key transducing characteristic is typically quantified as transconductance (g_m). In the saturation regime of a depletion mode device, the transconductance is expressed as[28]:

$$g_m = \frac{W}{L}.d.\mu.C^*.(V_T - V_G).$$

Thus, g_m can largely be controlled either by adjusting the channel dimensions (W: width, L: length, and d: semiconductor thickness), or most importantly, by changing the channel material (μ and C^*). Commonly, μC^* is used as a reduced performance metric to benchmark materials. g_m is also related to application-specific metrics including, but not limited to, on/off ratio, signal to noise ratio (SNR), sensitivity, and available number of states. Among these, on/off ratio and SNR might also be affected by the type of operation mode; accumulation mode is oftentimes favored over the depletion mode in which device is turned on at zero gate voltage, involving side effects such as leakage current.[21] One of the key hard-to-crack trade-offs in OECTs is that high g_m comes at the cost of a higher time constant (e.g., slower operation). Mostly, ionic current is the limiting current rather than the electronic current in terms of device speed, however, depending on the target application, organic semiconductors have shown to successfully match the speed of biological signals.[21,22] Another crucial metric for OECTs at the bio-interface is the device stability which can be quantified as: (1) operational stability (which is the ratio of initial and final value of the performance of interest, normally measured after 10^4 cycles for OECTs) and (2) environmental stability (which is linked to possible side redox reactions). A low threshold voltage (V_T) is favored as it enables energy efficiency and minimizes the possibility of undesirable side redox reactions. Similarly, the electrochemical window of the electrolyte utilized should also be considered to ensure that the operation voltage does not exceed either of extremes.[12] It is thus noteworthy to point out that, when benchmarking novel materials, OECTs metrics should be carefully extracted and that depending on the application, relevant requirements must be considered for designing semiconductors accordingly. To relate structure to performance, a set of morphological, spectroscopic, crystallographic, and charge dynamics measurements must be carried out and complemented by simulations. Operando characterization techniques and relevant methods at various length scales have been extensively reviewed in other reports.[29] When thoroughly investigated, an OECT becomes a facile platform for testing a material's performance ex-vivo and with enough tunability at the electrolyte interface to emulate the target working environment of the final device application.

Among several characterization techniques for in silico and *operando* methods relevant for OECTs, electrochemical impedance spectroscopy (EIS) is a notable versatile tool to elucidate several parameters (e.g., exchange-current densities, diffusion coefficient, charge-transfer resistances and double-layer capacitance) as well as the device working mechanisms, which are essential for rational guidance of materials design for body–machine interfaces. While many other electrochemical measurements drive systems far from equilibrium with potential or step sweeps, EIS has a competitive advantage as it utilizes small perturbations from equilibrium enabling linear approximations. This approach not only simplifies the analysis, but also minimizes morphology change as well as undesirable redox side reactions, both of which might significantly affect OECT properties otherwise. In the simplest layout, the electrode–electrolyte interface can be modeled with a Randles' equivalent circuit, consisting of a resistor (R_S) in series with a parallel resistor (R_P) and a capacitor (C), which facilitates the analysis at each interface. Particularly, EIS has been serving as a robust tool for studying various biological phenomena including bio-recognition of target molecules (e.g., antigen–antibody binding) since 1925.[30] It has been shown to be effective for bio-interfaces characterizations where lower impedance is pursued (i.e., high C and low R) and are desirable for bioelectronic communication such as recording and stimulation. In biosensing applications, for detecting subtle changes in a highly dynamic environment, the above-discussed OECT layout has been complemented by EIS measurements which account for capacitive changes at each interface of the device.[2,31] For instance, a gate electrode functionalized with bio-recognition elements that can selectively interact with biomarkers of interest, can be modelled as a polarizable electrode with a known resistance and capacitance. The entire device, hence, completes a typical Randles' circuit with the gate and the channel in-series via the electrolyte. Thus, any interaction with the select biomarker will affect not only the gate electrode but also the ion flux from the gate to the channel. Such changes are then accurately detected using EIS, are manifested in the device's V_T as a function of the analyte concentration, and are amplified through the changes in the source-drain current.[2,31–33] The sensitivity can be tuned by adjusting the ratio of capacitive contributions of different components of the model circuit.

Along with EIS where inputs are fixed potentials with a small oscillation superimposed while measuring impedance, cyclic voltammetry (CV) is another commonly used technique relevant for bio-interfaces. Here, the input is a linear potential sweep while measuring current. To complement the OECT layout, the channel material is designated as the working electrode with the source and drain contacts at the extremities and is indirectly connected to the gate electrode (assigned as the counter or reference electrode) through the electrolyte. Within a given voltage range, CV helps determine the potential ranges of stable injection of holes and electrons into the active materials (oxidation and reduction, respectively). Two main working mechanisms at electrolyte/semiconductor interface are envisioned: the formation of an electrical double layer (EDL) and/or a faradaic reaction, inducing a total current which can be ascribed as $I_{\text{total}} = I_{\text{faradaic}} + I_{\text{capacitive}}$. When the overall process is reaction-limited, I_{faradaic} dominates and the Randles–Sevcik relation can be used to extract relevant properties such as diffusivity (D). In the case of a diffusion-limited process, $I_{\text{capacitive}}$ dominates and thus, the current depends on the scan rate, v, according to the relationship: $I_{\text{capacitive}} = \frac{dQ}{dt} = Cv$, where Q denotes total amount of charge transferred for a given duration (t). In this scenario, any detected redox peaks can provide insights on the capacitive charging behaviors of the semiconductor and hence its C^*. Both cases involve changes in the concentration of the species of interest in solution near the electrodes. Using the Nernst equation, the electrochemical cell potential (E) (relative to a standard potential (E_0)) is used to extrapolate the activities (i.e., concentrations) of the oxidized and reduced analytes.[29] Energy levels information can also be extracted from a CV via measured onset potentials.[34] The HOMO level of the semiconductor can be estimated by $E_{\text{HOMO}} = -[4.8 + (E_{\text{OX}} - E_{1/2(\text{ferrocene})})]$ eV, where E_{HOMO} and E_{OX} are the HOMO energy level and the onset oxidation potential of the conjugated polymer, respectively, and $E_{1/2}$ is the average potential between the reduction peak ($E_{\text{p,r}}$) and the oxidation peak ($E_{\text{p,o}}$) obtained from the voltammogram. CV thus becomes a versatile method to quantify: (i) stability and reversibility of a semiconductor in a given electrolyte (e.g., performance degradation and side redox reaction/stability window), (ii) physical parameters such as response rate and diffusivity, (iii) relevant energy levels, and (iv) allows to pre-select gating probes according to redox potentials. These parameters are crucial when developing new materials, especially organic semiconductors for smart body–machine interfaces.

Developing organic semiconducting materials for electrochemical bioelectronics

OSCs have enabled a variety of different organic electronics (e.g., photovoltaics, OFETs, OLEDs, and wearable/stretchable electronics), owing to their low-cost/large-scale fabrication, variable synthetic modularity, doping-dependent conductivity, low Young's modulus, and flexibility/stretchability. Amongst the first employed OSCs were polypyrrole (PPy) and polyaniline (PANI).[13] Since then, there have been few more reports of PPy being utilized in OECTs (e.g., penicillin sensor), but this material has become scarcer due to its oxidative instability as its doped state can easily crosslink, rendering devices inoperable.[35] PANI demonstrated similar level of conductivity with higher stability (compared to PPy), but it requires low operation pH (~ 1) as the chemical de-doping of its highly conductive emeraldine salt form into the poorly conducting base occurs at higher pH (~5.5).[36,37] Thus far, poly(3, 4-ethylenedioxythiophene) doped with poly(styrene sulfonate) (PEDOT:PSS) is the most commonly utilized material for a variety of applications in bioelectronics, owing to its commercial availability and solution processability. Especially, its high electronic conductivity (as high as 1000 S cm^{-1} upon processing optimization)[38] has made PEDOT:PSS an appealing candidate for many organic electronics such as OFETs and interlayer for photovoltaics. In OECTs, PEDOT:PSS as a channel material has demonstrated reasonable performances (e.g., g_m in the range of mS and a response time in the range of $100 \mu s$).[39]

Despite its attractive properties as an OECT channel material in terms of switching speeds, g_m, and operation potential, PEDOT:PSS still presents critical drawbacks: (i) high structural complexity which limits its use as a model system for structure–property relationships and further modifications, (ii) the acidic and bulky nature of PSS that limits application (e.g., incompatibility with biosystem and corrosiveness) and negatively affects volumetric capacitance by lowering the portion of active material, respectively, (iii) operating via depletion mode due to inability to be reduced to its charge neutral form, resulting in lowering on/off ratio and large operation power consumption, (iv) electrical performance that heavily relies on processing conditions, and (v) high intrinsic Young's modulus requiring mechanical engineering for bio-interfacing.[40] To address some of these limitations, molecular modifications such as (i) the replacement of PSS with a tosylate analogue for higher C^*,[41] (ii) amine-based molecular de-dopants for enhancement-mode OECTs,[42] (iii) chemical cross-linking and blending utilizing additives [e.g., 3-glycidoxypropyltrimethoxysilane (GOPS)] for aqueous stability enhancement,[43] (iv) introducing co-dopants such as ionic liquid and dodecylbenzenesulfonate (DBSA) to yield higher g_m.[44] These chemical approaches have also been complemented by engineering strategies where mechanical, electrical, and electrochemical properties can be extrinsically tuned.[45] Despite various synthetic efforts and the engineering knowhow in different research groups, PEDOT:PSS has yet to meet all the requirements for the demonstration of fully integrated bioelectronics. Particularly, for electronics in contact with physiological media, long-term stability seems to be the major challenge. In such conditions, the electronic materials must endure swelling and de-swelling processes while discerning various ionic signals. Besides operational stability, PEDOT:PSS has also not showed enough stability to endure the foundry conditions for its implementation in hardware manufacturing.[46] The goal of this section is to overview successful approaches towards next generation semiconductors for bioelectronics applications. For the sake of completeness of discussion, materials requirements for high-performance OECT will first be discussed before delving into several generations of materials.

The fundamental advantage of OECTs in bioelectronics is that the channel material should be ion-permeable and thus respond to ionic flux. Mixed ionic–electronic conduction has thus become the center piece for developing novel semiconductors.[24] As such, electronic transport becomes equally crucial as ionic transport (or diffusion) especially in electrolyte-swollen state rather than dry pristine state, calling for new high-performing channel materials. The bottleneck here becomes the concomitant optimization of ionic transport and electronic conductivity, two counteracting processes, especially in a single material (Fig. 2). While facile insertion of hydrated species into the semiconducting bulk favors ion transport, it tends to disrupt the pristine morphology and to induce coulombic pinning/charge traps compromising the electronic mobility. Other fundamental challenges include high operating voltage (or high V_T) that leads to low energy-efficiency and performance instability (e.g., redox-irreversibility), synthetic challenges (e.g., harsh synthetic conditions and low yield), as well as the lack of n-type semiconductors, which has limited complementary circuits, are among other hurdles facing this research area. Therefore, to achieve subtle balancing of trade-offs as well as the delicate multifunctionality needed for real world applications, advances in novel channel materials in a systematic manner is essential so that structure–property–performance relationship can be obtained. In this section, several effective molecular design principles for high-performance OECTs are discussed with the hope to incite further optimization and potential deployment.

A material-focused re-interpretation of the OECT's figures of merits is essential here to serve as an effective guide for novel molecular designs. (i) The threshold voltage, V_T, is related to the ease to inject electrons/holes into the channel material and thus changing its conductivity. V_T can thus be adjusted, molecularly, by tuning the energy levels (e.g., HOMO/LUMO) hence the redox potentials (Fig. 2). (ii) Stability in electrolytic environments is also tightly connected to energy levels since when the input voltage goes beyond a certain threshold value (electrochemical stability window), undesirable side reactions occur. For instance, the reduction potential should be lower than that of oxygen and water (materials with deeper LUMOs should be targeted), given an aqueous electrolyte is used. (iii) Charge carrier mobility, depends on both intra-molecular (band-conduction) and inter-molecular (hopping) transport. The former depends on molecular ordering (i.e., π-conjugation and chain length) and the latter depends on bulk percolation and crystallinity (i.e., π–π stacking distance and lamellar distance). (iv) The volumetric capacitance depends heavily on the material's ability to uptake and retain ions. In OECTs, it is particularly important to ensure balanced volumetric capacitance, ion conductivity, and fast transit time, while retaining efficient electronic transport. Molecular polarity is thus critical for such balance without further deterring the dissolvability in organic solvent required for synthesis. In addition to these parameters, mechanical properties and biocompatibility must also be considered to avoid adverse effects and maintain reliable performance at bio-electronics interfaces. PEDOT:PSS has shown to fulfil some of these requirements, individually, but a more concerted approach is needed for practical use.

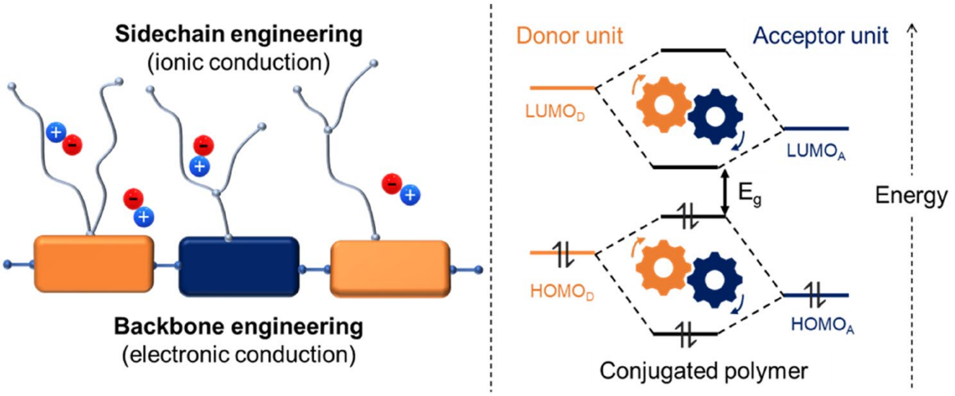

Figure 2. A generalized design strategy for OMIEC materials. Sidechain and backbone engineering have been proposed to attain balanced ionic and electronic conduction. Structural fine tuning in polymers has also been proposed for controlling energy levels. Adapted from Ref. 23 with permission.

With these parameters in mind as a starting point for strategic exploration of structure–property relationship departing from PEDOT:PSS, materials chemists have developed a new library of channel materials for OECTs. The initial approach has been to directly borrow conjugated polymers developed for more mature organic device architectures such as OFETs and OPVs.[47] However, most of the stellar performers within these fields mostly target electronic transport, thus not ideal for OECTs. Typically, these conjugated polymers are hydrophobic in nature and are impermeable to hydrated species, they are not suitable to bio-interfaces. The emerging approach is to design polymers based on either glycolated semiconducting polymers (GSPs) or conjugated polyelectrolytes (CPEs).[24] At the simplest level, both types possess two main structural features: (i) a π-conjugated backbone enabling electronic charge carrier transport and (ii) pendant polar sidechains serving ionic transport, which can either be ionic (CPEs) or hydrophilic but non-ionic (GSPs).[24,48] With the molecular tunability of conjugated polymers, structural fine tuning (as illustrated in Fig. 2) has been studied generating a wide library of semiconductors.[27] Backbone building blocks, the ratio between different repeat units and their distribution, electron deficiency (n/p type polymers), molecular weight (length), the use of heteroatoms, are among common strategies for designing novel polymers.[27] In terms of polar pendant groups, sidechain types, their length and branching, their density/ratio and distribution have been varied to develop new polymers with mixed ionic–electronic conduction.[24,49]

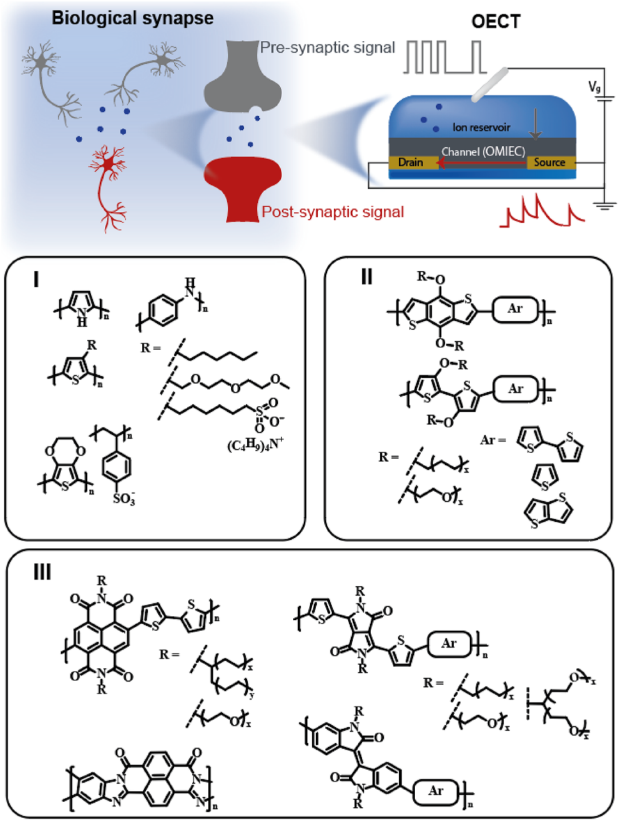

Figure 3. Development of mixed ionic–electronic conducting polymers for bioelectronic applications. Driven by the ability of OECTs to mimic adaptive behavior of biological synapses, conjugated polymers have continued to evolve in structure and performance. The first generation (I) consists of homopolymers with anchored polar sidechains, and later generations (II and III) majorly utilize copolymerization approaches of diverse donor and acceptor units.

First generation OMIECs

Starting with a model conjugated, poly(3-hexylthiophene) (P3HT), a first generation of OMIEC polymers, which can be described as CPE homopolymers consisting of single repeat units, mostly thiophene or thiophene-derivatives [e.g., thiophene, 3, 4-ethylenedioxythiophene (EDOT)] flanked with polar sidechains, has been studied (Fig. 3). As such, polar sidechains in place of the alkyl groups have been used to impart ionic conductivity onto conjugated polymers. For instance, polythiophene derivative with ethylene glycol (EG)-based sidechains, with ether groups placed at varying positions from the backbone have been reported and showed tunable electrolyte uptake and electrochemical transistor performance.[50,51] Particularly, the insertion of alkyl spacers with varying length has been highlighted in modulating the placement of polar sidechain with respect to backbone because of its effect on maintaining the overall crystallinity and thus achieving balanced ionic/electronic mixed-conduction properties. Alternatively, ionic sidechains have been shown to be effective towards balanced ionic–electronic conduction in polythiophenes. The earliest report by Inal et al. utilized a sulfonate group linked to a polythiophene to form a CPE, poly(6[thiophene-3-yl]hexane-1-sulfonate) tetrabutylammonium (PTHS), with excellent ionic and electronic transport and increased OECT transconductance.[52] More intriguingly, PTHS could yield devices operational in the accumulation mode owing to its lowered HOMO level and more controllable doping, as opposed to PEDOT:PSS which exists in the doped state in pristine form. However, modest OECT performance (g_m of 2.0 mS at $V_G = 0.8$V) and slow operation speed, possibly due to low ionic conductivity, were reported using PTHS. A similar strategy was subsequently used to flank EDOT with a sulfonate-functionalized alkyl chain to make poly(4-(2, 3-dihydrothieno-(3, 4-b)-(1,4)dioxin-2-yl-methoxy)-1-butanesulfonic acid, sodium salt) (PEDOT-S). PEDOT-S-based devices showed enhanced device performance (g_m of 16.2 mS at $V_G = 0.2$V), improved redox stability, and electrical conductivity, but lead to slow switching speed, as well as and depletion mode operation. To address some of these shortcomings, a blending approach has also been investigated where, for instance, sodium poly(2-(3-thienyl)ethoxy-4-butylsulfonate) (PTEB-S) operating in accumulation mode was mixed with PEDOT-S with high electrical stability.[53] Though this approach aims to combine the best of each component, only modest OECT performance could be achieved. Besides, this approach intrinsically disables systematic investigations. The most critical shortcoming of CPEs is their solubility in water necessitating either further crosslinking chains or employing ionic liquid as the electrolyte limiting applicability toward bio-interfacing. To adjust the hydrophilicity of CPEs, counterion exchange approach has been taken utilizing different length of alkyl functionalized with ammonium chloride such as (Nonyl)NH_3Cl and $(Oct)_2$ NH_2Cl to yield charge-neutral PEDOT-S.[53] Though this first generation of OMIECs still falls short in terms of yielding high performance devices for next generation body–machine interfaces, it offers an excellent model system for balancing ionic and electronic conduction in conjugated polymers.

Second generation OMIECs

Further backbone designs have recently generated a second generation of OMIEC polymers which can be classified as poly-thiophene-derived copolymers, oftentimes donor–acceptor (D–A) types, with balanced densities of polar and alkyl sidechains (Fig. 3). These D–A polymers have been extensively studied owing to their huge energy level adjustability, better and tunable rigidity/planarity of the backbone, high charge carrier mobility, and hence high OECT performance.[24,27] In this category, the conjugated backbones are mostly based on derivatives of EDOT and thiophene with varying density of sidechain functionalization via co-polymerization. The stellar performers in this class combine electron-rich and coplanar backbones, tunable and efficient molecular packing, with sidechain distribution to achieve high performance OECTs.[24,27] A notable candidate in this category was first reported by Giovannitti et al. by copolymerizing a fused-thiopene unit and a thiophene with strategically placed glycolated sidechains.[54] The resulting polymer, poly(2-(3,3′-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-[2, 2′-bithiophen]-5-yl)thieno[3,2-b]thiophene), [p(g2T-TT)] in fact remains one of the stellar materials studied in OECT devices. It exhibits several record-setting OECT metrics, including fast switching speed on the microsecond scale and high μC^* (261 F $cm^{-1}V^{-1}s^{-1}$). Owing to its performance and structural simplicity, p(g2T-TT) has been utilized in synaptic transistor devices with unprecedented neuromorphic characteristics.[55,56] Despite the recent success in these polymers, several challenges such as facile oxidation, poor environmental stability, and unstable morphologies especially in aqueous environment remain. Intuitively, strategic balancing of the polar sidechains has been investigated to design modified derivatives of p(g2T-TT) with where the ratio of TEG and alkyl sidechains was varied from 100 to 0%.[57] The redistribution of sidechains showed to lead to tunable electronic performance, improved device cycling stability, and electrolyte compatibility.[57] Such structural versatility enabled by the copolymerization strategy has inspired further backbone designs towards next generation semiconductors.

Third generation OMIECs

A third generation of OMIEC polymers can be classified as D–A polymers based on more extended units beyond thiophene and EDOT with different degrees of functionalization with polar sidechains. Here, the expansion of building blocks is utilized to further balance ionic and electronic conduction. D–A polymers including diketopyrrolopyrrole (DPP) and isoindigo (IID), which are extensively studied for other applications, have been targeted.[27] By introducing polar sidechains onto the DPP core and/or the aromatic donor, copolymers with tunable ionic conductivity, concomitant with efficient electronic transport, have been synthesized.[58–60] Besides OECT performance optimization, DPP-based OMIECs have also afforded better operation stability through molecular design. For instance, a pyridine–DPP copolymer with optimized density of polar sidechains has shown to achieve energy levels, and hence a device operation window, much more compatible with biological environments, compared to PEDOT:PSS and the above-discussed p(g2T-TT).[61] The structural versatility of DPP copolymers is thus envisioned to continue yielding new semiconductors, especially once target metrics are utilized to guide the molecular designs. Similarly, isoindigo-based polymers have been shown to marry effective electronic transport with ionic uptake when the highly planar acceptor is copolymerized with optimal donor units.[62] Thus far, our discussion focused on p-type polymers as n-type polymers remain underexplored despite their high demand for completing organic circuits. Recently, naphthalene-diimidebithiophene (NDI)-based polymers have demonstrated remarkable success in OECTs as well as neuromorphic devices, but further investigation on this class is warranted.[63,64] Similar to p-type counterparts, the design of n-type OECTs materials targets the placement and balancing of polar sidechains onto known good electron conductors. An exception can be made here for a highly rigid n-type conductor, poly(benzimidazobe nzophenanthroline) (BBL), which has recently demonstrated ground-breaking and unique performance in OECT devices.[65] Historically speaking, the library of n-type organic semiconductors has been less rich likely due to poor performances and environmental stability found in these materials. In OMIECs, since electronic conduction is not the sole targeted metric, more materials will be repurposed if a modest electronic performance can be balanced with ionic transport.

As discussed above, among the metrics of interest in OECTs, although priority might vary depending on specific applications, electronic mobility balanced with capacitance and ionic transport are the main targets. However, hard-to-crack trade-off relationships (i.e., μ vs. C^*) have existed which has hampered further performance improvement. In that regard, clear structure–property relationship is essential but has not been well established as (i) no general optimization principles exist as best-performing sidechain configurations (i.e., length, type and distribution) may vary with different backbone units; (ii) measured parameters and thus performance depend not only on the semiconducting polymer itself but also device architecture, dimension, and electrolyte, which are equally important elements to be investigated in order to push the record forward; and (iii) lack of unified measurement settings for each performance metric that has complicated materials comparisons.

Thus, novel materials for channel along with innovations in device architecture, processing and measurement skills will usher unprecedented opportunities towards the integration of biology and electronics, potentially blurring the boundary between humans and machines.

Recent success of organic semiconductors in bioelectronics

Organic electronic materials, like OMIECs, serve a broad range of biological applications, not only for metabolite sensing and electrophysiology, but also for synaptic and neuromorphic simulation.[9,46] The field of organic neuromorphics is of particular interest as it offers a large variety of opportunities from prosthetics and robotic devices, aiming at complementing the body and restoring its dysfunction, to the next generation devices that would be capable of replicating physiological functions, towards complete or local takeover of bodily functions. As exemplified by the recent demonstration by Neuralink, highly adaptive electronics can be the future of how we interface with our surroundings. Accurate data collection and timely motor responsiveness enabled by intimate body–machine interfaces are the holy grail of this field of research. Mechanical flexibility, biocompatibility, ability to withstand the constantly changing biological environments, long lifetimes, wearability, chemical tunability, low-cost production, low-power consumption; these are some of the key parameters that define organic electronic materials as unique candidates for a broad range of the biomedical applications and a central theme of their recent successes in bioelectronics. In this section, we aim to highlight recent successful demonstrations in bioelectronics with an emphasis on how novel materials, especially organic semiconductors, are utilized to enable device functions and how their tunability might enable future advancements.

Recording biological signals

When interfacing with biology, biocompatibility and mechanical flexibility are of paramount importance for guarantying both proper signal transduction and high conformability with biological tissues. Integration of transparent, thin, and/or stretchable organic electronic materials into electrodes has improved the quality of signal recording by reducing the mechanical mismatch at the body–machine interface. For instance, processing PEDOT:PSS into microneedle, array-based electrodes have been demonstrated to reduce skin impedance, leading to enhanced electrochemical performance compared to wet electrodes.[66] Similarly, PEDOT:PSS and poly lactic-*co*-glycolic acid (PLGA), both biocompatible conductive polymers, have been used as flexible substrates for electrocardiographic recording.[67] With the purpose of improving electrophysiological recordings, novel polymers have been investigated in different device architectures to achieve lower-power operation and enhance biosensing abilities. For example, electrophysiological sensing was demonstrated using the subthreshold regime of p(g2T-TT) in OECT devices.[68] Operation in the subthreshold regime, at lower current, is expected to improve transduction and biosensing performance by minimizing Faradaic parasitic reactions and overall degradation of the device. Among the wide range of transistors available for biomedical applications, EGTs are appealing transducing devices, due to their potential for miniaturization and ability to locally transduce and amplify biological signals. Both features make them suitable interfaces for implantable and wearable devices and promising candidates for the future of health and point-of-care monitoring. The first employment of EGTs in in vivo electrophysiology was performed with PEDOT:PSS-based OECTs to record epileptic seizure in rats, leading to a signal-to-noise ratio significantly higher compared to regular electrodes.[69] PEDOT:PSS-based OECTs also found applications in electrocardiography, electrooculography, and electroencephalography.[70]

Cell monitoring and metabolite biosensing

The ability of organic electronic materials to adapt to the complexity of the biological environment makes them suitable for integration into electrodes to monitor cells and tissues. Common applications include monitoring cell adhesion, growth, and differentiation with planar electrodes, studying tissue resistance with opposing electrodes, or recording extracellular potential from electrogenic (e.g., neurons or cardiac) cells using multielectrode or transistor arrays.[21] For instance, Yao et al. were able to record transepithelial ion transport in human airway epithelial cells using an OECT array.[32] Similarly, multi-transistors arrays were developed by Gu et al. for in vitro monitoring and mapping of cardiac action potential.[71]

Owing to their highly selective catalytic activity and the rapid detection scheme at the electrode interface, enzyme-based electrochemical biosensors are sometimes considered as the most promising devices for the detection of a broad range of metabolites and stimuli (Fig. 4). Thus far, successful demonstrations rely mostly on coupling a redox reaction catalyzed by an enzyme with an electrochemical transducer. The conducting nature of organic electronic materials, in addition to their ability to polymerize in the presence of active molecules, makes them particularly appealing transducing units. Due to their ease of integration and biocompatibility, PPy, PANI, and PEDOT:PSS are some of the most common conducting polymers used for biological application.[70] Higher sensitivity can also be achieved by tuning organic electronic materials structure for increasing their surface-to-volume ratio. A strategy used by Yang et al. to develop a conducting polymer/enzyme-based, nanometer scale glucose sensor.[72] Furthermore, recent progress towards efficient integration of electrochemical transducers into textile and flexible medium has yielded minimally invasive, implantable sensors. Chu et al., for instance, integrated a flexible, PDMS-based electrode into a soft, contact-lens type glucose sensor to monitor tear glucose in situ.[73] Conducting polymers are, thus, not only efficient electron relays, but they also provide improved selectivity by

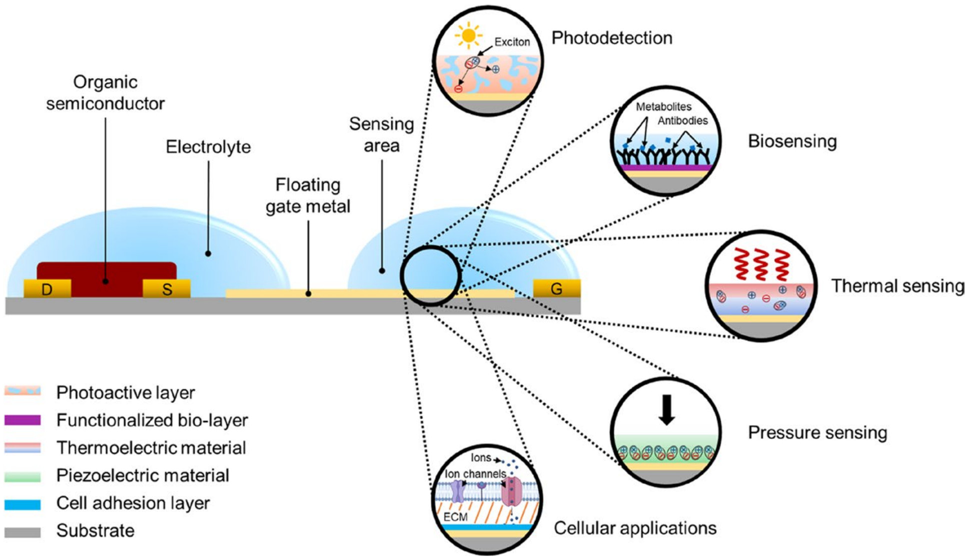

Figure 4. Illustration of recent approaches in bio-sensing using organic electrochemical transistors. Functionalized electrodes are used to detect physiological changes and adjacent transistor channels are used for signal detection and amplification.

acting as permselective membranes—ion exchange materials allowing passage of ions of a specific polarity only. These demonstrations of metabolite monitoring, among others, show that, with proper device designs, organic materials can detect and transduce minute changes due to cellular activities. Further advancements in more accurate and reliable monitoring are envisioned especially given the versatility on in device design as illustrated in Fig. 4.

Emulating biological learning functions

As discussed above, the aim in bioelectronics is to demonstrate devices that can learn and adapt to surroundings like biological systems. Such devices must possess learning abilities emulating the brain.[9] Synaptic and neuromorphic bio-interfaces have demonstrated unprecedented opportunities for advancing our understanding of brain mechanisms and unveiling the complex mechanisms underlying neural dysfunctions.[74] For instance, emulating impaired local field potentials (LFP) in the context or Alzheimer's disease has now become possible with the development of organic memristors capable of interfacing biological environments.[75] More recently, Juzekaeva et al. electrically coupled two live cortical neurons through a memristive PANI-based synapse capable of being trained by a biologically inspired spike-timing-dependent plasticity (STDP) mechanism.[76] This organic memristor made of PANI and lithium salt-doped polyethylene oxide acts as an artificial synapse, mimicking natural excitatory synapses with synaptic strength regulated by neuronal activity. The low switching voltage, large OFF/ON resistance ratio, tunable retention times, and high multilevel resistance switching of this memristive device offer great promises in hardware implementation of spiking artificial neural networks capable of supervised and unsupervised learning.

Hybrid, ionic–electronic artificial sensory neurons with bimodal sensing capability have also been demonstrated by Wan et al.[77] and later by Yoon et al.[78] Using inorganic memristors, these combine both optic and pressure stimuli to generate a summed excitatory postsynaptic current through the synaptic transistor, fusing visual and haptic feedbacks. Although memristors are promising devices for neuromorphic electronics, the need for low-power consumption, high ionic–electronic conductance tunability, and decoupling of write and read operations have placed three-terminal devices, such as EGTs, as emerging candidates for neuromorphic devices compared to their dielectric and two-terminal counterparts. Kim et al. went further by developing a bioinspired afferent nerve.[25] Drawing inspiration from these specific nerves responsible for transducing signals from sensory organs to the CNS, they designed a three-terminal neuromorphic system using a conjugated polymer and an ion gel on a flexible substrate to detect action potential-like spike trains triggered upon application of pressure on a ring oscillator. The hybrid bioelectronic reflex was demonstrated by driving the twitching motion of a cockroach leg connected to the device output.

Further improvements towards highly integrated neuromorphic devices include the use of multi-gate or multi-channel configurations to transduce input signals from different neurons immersed in the same electrochemical environment, mimicking the natural environment of biological neurons. The output would then serve as mutual feedback from multiple inputs. Reversely, a single input can affect multiple outputs, allowing for simulation of functions like selectivity,[79] or homeoplasticity.[80] Eventually, the use of conducting/redox-active polymers

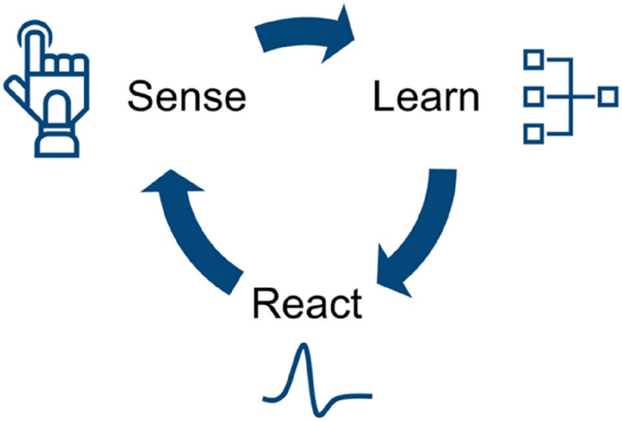

Figure 5. Illustration of the closed-loop concept for smart bioelectronics. Organic materials are envisioned to enable the design and manufacturing of electronics that learn and react, especially at the biological interface.

with artificial synaptic devices would enable the integration of neuromorphic devices with living matter. This would take the form of devices interfacing between human nerves and prosthetic systems, with the ability of being trained by and learn from the dynamic response of biological neurons.

Mimicking biological sensory and motor systems

Current advances in organic materials for neuromorphic devices pave the way for the development of smart electronics capable of not only interfacing with the body, but also of interacting with its biology. The next generation of organic neuromorphic devices will involve the use of materials for sensing, learning, and reacting in response to the surrounding biological environment in an optimized and personalized fashion. Automatic control of the material operation regulated by direct feedback from the biological environment enables the envision of closed-loop, smart drug delivery systems based on hardware and driven by machine learning algorithms (e.g., combination of glucose sensing and insulin delivery, or seizure detection and release of antiepileptic drugs) (Fig. 5). Furthermore, the integration of neuromorphic devices with living tissue for local computation and learning—without involving the CNS—presents exciting opportunities for soft robotics and prosthetics. Hence, smart prosthetic systems such as sensory arms could be developed in the future, for instance, by mimicking the autonomous function of neurons present in large amounts in octopus tentacles.[25,81,82] On this front, Osborn et al. recently developed a neuromorphic prosthesis with an artificial skin capable of transducing touch and pain.[83] Although tactile signals were processed through in silico neurons, organic neuromorphic devices present a legitimate alternative given their increased wearability and low-energy consumption. One can, thus, envision the development of future applications involving several types of sensors—temperature, strain, or light sensors—and mimicking sensory functions of biological systems such as smell, taste, or vision.

Remaining challenges in current materials and scope of development

It is without a doubt that organic materials will continue to bring electronics in closer contact with biology. However, several challenges must be addressed in terms of semiconductor materials before organic adaptive electronics can become ubiquitous. The current major challenges are, but not limited to:

- *Long-term operation stability in physiological environments* the current stellar semiconductors and resulting transistor devices are only stable for a few hundred cycles, while the target applications require long term durability. Careful balancing of molecular energy levels, designing of open structures for reliable uptake and release of ions, and formation of durable microstructures are among some viable material strategies towards durable operation.
- *Synthetic scale-up* the path towards commercialization of plastic-based electronics will require large scale synthesis of functional materials (semiconductors). Currently, most research labs make polymers in amounts of milligrams. Strategies towards sustainable scaling must be investigated as these technologies continue to mature. Approaches such as microwave synthesis (to enable rapid and scalable synthesis), C–H activation polymerization (to reduce catalysts loadings), among others are proposed here.
- *Device manufacturing scalability* the manufacturing of organic circuitries must also target high device density and fabrication yields. Organic semiconductors that are compatible with lithography techniques, able to yield highly uniform films, and with low spatial variability are needed. On this front, OECTs could borrow a few lessons from OFETs manufacturing where, to date, device densities up to 42,000 transistors per square centimeter have been realized.[84] Such densities will require more careful gating schemes, with minimal cross talks and power consumption. With recent demonstrations of *common-gate* architectures in OECTs,[79] one can start to envision high densities bioelectronic circuitries. Additionally, 3D-printing of organic electronics has shown great promise towards the manufacturing of conformable circuits to intimately interface with biology.[85–87] In that regard, further investigations on the incorporation of functional optoelectronic organic materials are warranted towards future bioelectronics.
- *Compatibility with CMOS manufacturing* along with scalability comes another major challenge that has kept organics out of traditional manufacturing routes: poor thermal stability. Though organics are reviewed here as interfacial materials, transistor devices are often part of larger hardware units. Organic materials are thus often required to undergo the back-end-of-line (BEOL) processes. There, temperatures can be as high as 350°C, which remains a challenge for most organic semiconductors, especially the stellar performer PEDOT:PSS. Under such conditions, the polymer films tend to lose their micro- and nanostructures and

degrade in performance. More research on thermally robust semiconductors thus remains essential. Notably, the use of blend composites has been shown as a promising approach towards thermal stability of conjugated polymers,[88] but must be complemented with further molecular modifications. In principle, the use of high energy bonds, design of highly ordered backbones, and crosslinking strategies can boost thermal stability, but their impact on film crystallinity must be balanced with efficient ionic segmentation.

- *Novel computing architectures* adaptive collection of physiological information and its computing will indeed require new data handling approaches. Biology has evolved long enough to recognize even chaotic signals. Reliable multi-responsiveness and detection of multiple inputs (ionic and other biological signals) must continue to be investigated.
- *Learning reliability* to accurately mimic biological functions, artificial adaptive behaviors must be reliable. Neuromorphic devices with linear and symmetrical rehearsing capabilities are sought after. Materials able to realize multiple, stable, and reversible conductance states would be ideal candidates. Particularly, energy level control, effective charge delocalization, and minimal energetic disorder (both in pristine and doped states) are some key target properties (in addition to those mentioned above) when designing such materials.

As overviewed throughout this prospective, organic mixed ionic–electronic conductors are on a promising trajectory towards addressing many of these challenges. To tune operational stability, controlled ionic uptake and release processes, sidechain engineering as well as composites are available to chemists, given they are complemented with effective electronic performance. The structural versatility found in polymer conductors also holds the key to solving other discussed challenges. It however seems necessary that stronger collaborations between chemists, materials scientists, device engineers, surgeons, and software engineers ought to be established to bridge the generational gap across these disciplines towards future body–machine interfaces. From a materials standpoint, the chemical toolkit provided by OMIEC polymers will continue advancing the field of semiconductors that can reliably transduce biological signals. However, an application-guided design approach is necessary for yielding novel high-performance materials.

Funding

Open Access funding provided by the MIT Libraries.

Declarations

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Open Access

References

1. T. Someya, Z. Bao, G.G. Malliaras, Nature **540**, 379–385 (2016)
2. A.M. Pappa, O. Parlak, G. Scheiblin, P. Mailley, A. Salleo, R.M. Owens, Trends Biotechnol. **36**, 45–59 (2018)
3. C. Zhao, K.M. Cheung, I.W. Huang, H. Yang, N. Nakatsuka, W. Liu, Y. Cao, T. Man, P.S. Weiss, H.G. Monbouquette, A.M. Andrews, Sci. Adv. **7**, 25–27 (2021)
4. A. Chortos, J. Liu, Z. Bao, Nat. Mater. **15**, 937–950 (2016)
5. W. Bo, Z. Chuanzhen, W. Zhaoqing, Y. Kyung-Ae, C. Xuanbing, L. Wenfei, Y. Wenzhuo, L. Shuyu, Z. Yichao, K.M. Cheung, L. Haisong, H. Hannaneh, P.S. Weiss, M.N. Stojanovic, A.J. Tomiyama, A.M. Andrews, E. Sam, Sci. Adv. **8**, eabk0967 (2022)
6. D.T. Simon, E.O. Gabrielsson, K. Tybrandt, M. Berggren, Chem. Rev. **116**, 13009–13041 (2016)
7. I.B. Dimov, M. Moser, G.G. Malliaras, I. McCulloch, Chem. Rev. **122**, 4356–4396 (2022)
8. C.K. Chiang, C.R. Fincher, Y.W. Park, A.J. Heeger, H. Shirakawa, E.J. Louis, S.C. Gau, A.G. MacDiarmid, Phys. Rev. Lett. **39**, 1098–1101 (1977)
9. Y. Lee, T.-W. Lee, Acc. Chem. Res. **52**, 964–974 (2019)
10. D. Ohayon, S. Inal, Adv. Mater. **32**, 2001439 (2020)
11. E.J. Fuller, S.T. Keene, A. Melianas, Z. Wang, S. Agarwal, Y. Li, Y. Tuchman, C.D. James, M.J. Marinella, J.J. Yang, A. Salleo, A.A. Talin, Science **364**, 570–574 (2019)
12. J. Rivnay, S. Inal, A. Salleo, R.M. Owens, M. Berggren, G.G. Malliaras, Nat. Rev. Mater. **3**, 17086 (2018)
13. A.J. Bard, in *Electrochemical Methods: Fundamentals and Applications*. ed. by A.J. Bard, L.R. Faulkner (Wiley, New York, 1980)
14. E.A. Martin, A.M. Lasseigne, A.C. Miller, Front. Neuroanat. **14**, 12 (2020)
15. A.E. Pereda, Nat. Rev. Neurosci. **15**, 250–263 (2014)
16. C. Mead, *Analog VLSI and Neural Systems* (Addison-Wesley Longman Publishing Co., Inc., Boston, 1989)
17. A. Canales, X. Jia, U.P. Froriep, R.A. Koppes, C.M. Tringides, J. Selvidge, C. Lu, C. Hou, L. Wei, Y. Fink, P. Anikeeva, Nat. Biotechnol. **33**, 277–284 (2015)
18. H. Yuk, B. Lu, X. Zhao, Chem. Soc. Rev. **48**, 1642–1667 (2019)
19. K.-N. Kim, M.-J. Sung, H.-L. Park, T.-W. Lee, Adv. Electron. Mater. **8**, 2100935 (2022)
20. R. Jonathan, W. Huiliang, F. Lief, D. Karl, G.G. Malliaras, Sci. Adv. **3**, e1601649 (2022)
21. F. Torricelli, D.Z. Adrahtas, Z. Bao, M. Berggren, F. Biscarini, A. Bonfiglio, C.A. Bortolotti, C.D. Frisbie, E. Macchia, G.G. Malliaras, I. McCulloch, M. Moser, T.-Q. Nguyen, R.M. Owens, A. Salleo, A. Spanu, L. Torsi, Nat. Rev. Methods Primers **1**, 1–24 (2021)
22. M. Abarkan, A. Pirog, D. Mafilaza, G. Pathak, G. N'Kaoua, E. Puginier, R. O'Connor, M. Raoux, M.J. Donahue, S. Renaud, J. Lang, Adv. Sci. **9**, 2105211 (2022)
23. S.T.M. Tan, A. Gumyusenge, T.J. Quill, G.S. LeCroy, G.E. Bonacchini, I. Denti, A. Salleo, Adv. Mater. **34**, 2110406 (2022)

24. B.D. Paulsen, K. Tybrandt, E. Stavrinidou, J. Rivnay, Nat. Mater. **19**, 13–26 (2020)
25. Y. Kim, A. Chortos, W. Xu, Y. Liu, J.Y. Oh, D. Son, J. Kang, A.M. Foudeh, C. Zhu, Y. Lee, S. Niu, J. Liu, R. Pfattner, Z. Bao, T.W. Lee, Science **360**, 998–1003 (2018)
26. G.P. Kittlesen, H.S. White, M.S. Wrighton, J. Am. Chem. Soc. **106**, 7389–7396 (1984)
27. P. Li, T. Lei, J. Polym. Sci. **60**, 377–392 (2022)
28. J. Rivnay, P. Leleux, M. Ferro, M. Sessolo, A. Williamson, D.A. Koutsouras, D. Khodagholy, M. Ramuz, X. Strakosas, R.M. Owens, C. Benar, J.-M. Badier, C. Bernard, G.G. Malliaras, Sci. Adv. **1**, 1–6 (2015)
29. R. Wu, M. Matta, B.D. Paulsen, J. Rivnay, Chem. Rev. **122**, 4493–4551 (2022)
30. E.P. Randviir, C.E. Banks, Anal. Methods **5**, 1098 (2013)
31. T. Tang, A. Savva, W.C. Traberg, C. Xu, Q. Thiburce, H.-Y. Liu, A.-M. Pappa, E. Martinelli, A. Withers, M. Cornelius, A. Salleo, R.M. Owens, S. Daniel, ACS Nano **15**, 18142–18152 (2021)
32. C. Yao, C. Xie, P. Lin, F. Yan, P. Huang, I.-M. Hsing, Adv. Mater. **25**, 6575–6580 (2013)
33. G. Méhes, A. Roy, X. Strakosas, M. Berggren, E. Stavrinidou, D.T. Simon, Adv. Sci. **7**, 2000641 (2020)
34. J. He, L. You, J. Mei, ACS Appl. Mater. Interfaces **9**, 34122–34130 (2017)
35. H.S. White, G.P. Kittlesen, M.S. Wrighton, J. Am. Chem. Soc. **106**, 5375–5377 (1984)
36. G. Williams, A. Gabriel, A. Cook, H.N. McMurray, J. Electrochem. Soc. **153**, B425 (2006)
37. G. Williams, H.N. McMurray, Electrochem. Solid State Lett. **8**, B42 (2005)
38. Y. Hirokazu, K. Kazuki, M. Kazumasa, O. Hidenori, Sci. Adv. **5**, eaav9492 (2022)
39. M. Moser, J.F. Ponder Jr., A. Wadsworth, A. Giovannitti, I. McCulloch, Adv. Funct. Mater. **29**, 1807033 (2019)
40. M. ElMahmoudy, S. Inal, A. Charrier, I. Uguz, G.G. Malliaras, S. Sanaur, Macromol. Mater. Eng. **302**, 1600497 (2017)
41. S. Inal, G.G. Malliaras, J. Rivnay, Nat. Commun. **8**, 1–7 (2017)
42. S.T. Keene, T.P.A. van der Pol, D. Zakhidov, C.H.L. Weijtens, R.A.J. Janssen, A. Salleo, Y. van de Burgt, Adv. Mater. **32**, 2000270 (2020)
43. J. Rivnay, S. Inal, B.A. Collins, M. Sessolo, E. Stavrinidou, X. Strakosas, C. Tassone, D.M. Delongchamp, G.G. Malliaras, Nat. Commun. **7**, 11287 (2016)
44. L. Wang, Q. Sun, L. Zhang, J. Wang, G. Ren, L. Yu, K. Wang, Y. Zhu, G. Lu, H. Yu, Macromol. Rapid Commun. **4**, 2200212 (2022)
45. B. Lu, H. Yuk, S. Lin, N. Jian, K. Qu, J. Xu, X. Zhao, Nat. Commun. **10**, 1043 (2019)
46. A. Gumyusenge, A. Melianas, S.T. Keene, A. Salleo, Annu. Rev. Mater. Res. **51**, 47–71 (2021)
47. H. Lee, Y. Won, J.H. Oh, J. Polym. Sci. **60**, 348–376 (2022)
48. X. Chen, A. Marks, B.D. Paulsen, R. Wu, R.B. Rashid, H. Chen, M. Alsufyani, J. Rivnay, I. McCulloch, Angew. Chem. Int. Ed. **60**, 9368–9373 (2021)
49. I.P. Maria, B.D. Paulsen, A. Savva, D. Ohayon, R. Wu, R. Hallani, A. Basu, W. Du, T.D. Anthopoulos, S. Inal, J. Rivnay, I. McCulloch, A. Giovannitti, Adv. Funct. Mater. **31**, 2008718 (2021)
50. L.Q. Flagg, C.G. Bischak, J.W. Onorato, R.B. Rashid, C.K. Luscombe, D.S. Ginger, J. Am. Chem. Soc. **141**, 4345–4354 (2019)
51. P. Schmode, A. Savva, R. Kahl, D. Ohayon, F. Meichsner, O. Dolynchuk, T. Thurn-Albrecht, S. Inal, M. Thelakkat, ACS Appl. Mater. Interfaces **12**, 13029–13039 (2020)
52. S. Inal, J. Rivnay, P. Leleux, M. Ferro, M. Ramuz, J.C. Brendel, M.M. Schmidt, M. Thelakkat, G.G. Malliaras, Adv. Mater. **26**, 7450–7455 (2014)
53. E. Zeglio, M. Vagin, C. Musumeci, F.N. Ajjan, R. Gabrielsson, X.T. Trinh, N.T. Son, A. Maziz, N. Solin, O. Inganäs, Chem. Mater. **27**, 6385–6393 (2015)
54. A. Giovannitti, D.-T. Sbircea, S. Inal, C.B. Nielsen, E. Bandiello, D.A. Hanifi, M. Sessolo, G.G. Malliaras, I. McCulloch, J. Rivnay, Proc. Natl Acad. Sci. USA **113**, 12017–12022 (2016)
55. A. Melianas, T.J. Quill, G. LeCroy, Y. Tuchman, H.V. Loo, S.T. Keene, A. Giovannitti, H.R. Lee, I.P. Maria, I. McCulloch, A. Salleo, Sci. Adv. **6**, eabb2958 (2021)
56. I. Krauhausen, D.A. Koutsouras, A. Melianas, S.T. Keene, K. Lieberth, H. Ledanseur, R. Sheelamanthula, A. Giovannitti, F. Torricelli, I. Mcculloch, P.W.M. Blom, A. Salleo, Y. van de Burgt, P. Gkoupidenis, Sci. Adv. **7**, eabl5068 (2022)
57. M. Moser, T.C. Hidalgo, J. Surgailis, J. Gladisch, S. Ghosh, R. Sheelamanthula, Q. Thiburce, A. Giovannitti, A. Salleo, N. Gasparini, A. Wadsworth, I. Zozoulenko, M. Berggren, E. Stavrinidou, S. Inal, I. McCulloch, Adv. Mater. **32**, 2002748 (2020)
58. M. Moser, A. Savva, K. Thorley, B.D. Paulsen, T.C. Hidalgo, D. Ohayon, H. Chen, A. Giovannitti, A. Marks, N. Gasparini, A. Wadsworth, J. Rivnay, S. Inal, I. McCulloch, Angew. Chem. Int. Ed. **60**, 7777–7785 (2021)
59. G. Krauss, F. Meichsner, A. Hochgesang, J. Mohanraj, S. Salehi, P. Schmode, M. Thelakkat, Adv. Funct. Mater. **31**, 2010048 (2021)
60. X. Luo, H. Shen, K. Perera, D.T. Tran, B.W. Boudouris, J. Mei, ACS Macro Lett. **10**, 1061–1067 (2021)
61. A. Giovannitti, R.B. Rashid, Q. Thiburce, B.D. Paulsen, C. Cendra, K. Thorley, D. Moia, J.T. Mefford, D. Hanifi, D. Weiyuan, M. Moser, A. Salleo, J. Nelson, I. McCulloch, J. Rivnay, Adv. Mater. **32**, 1908047 (2020)
62. Y. Wang, E. Zeglio, H. Liao, J. Xu, F. Liu, Z. Li, I. Petruta Maria, D. Mawad, A. Herland, I. McCulloch, W. Yue, Chem. Mater. **31**, 9797–9806 (2019)
63. A. Giovannitti, C.B. Nielsen, D.-T. Sbircea, S. Inal, M. Donahue, M.R. Niazi, D.A. Hanifi, A. Amassian, G.G. Malliaras, J. Rivnay, I. McCulloch, Nat. Commun. **7**, 13066 (2016)
64. Y. Zhang, G. Ye, T.P.A. van der Pol, J. Dong, E.R.W. van Doremaele, I. Krauhausen, Y. Liu, P. Gkoupidenis, G. Portale, J. Song, R.C. Chiechi, Y. van de Burgt, Adv. Funct. Mater. **32**, 2201593 (2022)
65. H. Sun, M. Vagin, S. Wang, X. Crispin, R. Forchheimer, M. Berggren, S. Fabiano, Adv. Mater. **30**, 1704916 (2018)
66. Y. Chen, W. Pei, S. Chen, X. Wu, S. Zhao, H. Wang, H. Chen, Sens. Actuators B **188**, 747–756 (2013)
67. A. Campana, T. Cramer, D.T. Simon, M. Berggren, F. Biscarini, Adv. Mater. **26**, 3874–3878 (2014)
68. V. Venkatraman, J.T. Friedlein, A. Giovannitti, I.P. Maria, I. McCulloch, R.R. McLeod, J. Rivnay, Adv. Sci. **5**, 1800453 (2018)
69. J.E. Tyrrell, M.G. Boutelle, A.J. Campbell, Adv. Funct. Mater. **31**, 2007086 (2021)
70. P. Leleux, J. Rivnay, T. Lonjaret, J.M. Badier, C. Bénar, T. Hervé, P. Chauvel, G.G. Malliaras, Adv. Healthc. Mater. **4**, 142–147 (2015)
71. X. Gu, C. Yao, Y. Liu, I.-M. Hsing, Adv. Healthc. Mater. **5**, 2345–2351 (2016)
72. G. Yang, K.L. Kampstra, M.R. Abidian, Adv. Mater. **26**, 4954–4960 (2014)
73. M.X. Chu, K. Miyajima, D. Takahashi, T. Arakawa, K. Sano, S.I. Sawada, H. Kudo, Y. Iwasaki, K. Akiyoshi, M. Mochizuki, K. Mitsubayashi, Talanta **83**, 960–965 (2011)
74. D.-G. Seo, G.-T. Go, H.-L. Park, T.-W. Lee, MRS Bull. **46**, 321–329 (2021)
75. S. Battistoni, V. Erokhin, S. Iannotta, Neural Plast. **2017**, 6090312 (2017)
76. E. Juzekaeva, A. Nasretdinov, S. Battistoni, T. Berzina, S. Iannotta, R. Khazipov, V. Erokhin, M. Mukhtarov, Adv. Mater. Technol. **4**, 1800350 (2019)
77. C. Wan, P. Cai, X. Guo, M. Wang, N. Matsuhisa, L. Yang, Z. Lv, Y. Luo, X.J. Loh, X. Chen, Nat. Commun. **11**, 4602 (2020)
78. J.H. Yoon, Z. Wang, K.M. Kim, H. Wu, V. Ravichandran, Q. Xia, C.S. Hwang, J.J. Yang, Nat. Commun. **9**, 417 (2018)
79. P. Gkoupidenis, D.A. Koutsouras, T. Lonjaret, J.A. Fairfield, G.G. Malliaras, Sci. Rep. **6**, 27007 (2016)
80. D.A. Koutsouras, G.G. Malliaras, P. Gkoupidenis, MRS Commun. **8**, 493–497 (2018)
81. S. Schara, R. Blau, D.C. Church, J.K. Pokorski, D.J. Lipomi, Adv. Funct. Mater. **31**, 2008375 (2021)
82. Y. Jiang, Z. Zhang, Y.-X. Wang, D. Li, C.-T. Coen, E. Hwaun, G. Chen, H.-C. Wu, D. Zhong, S. Niu, W. Wang, A. Saberi, J.-C. Lai, Y. Wu, Y. Wang, A.A. Trotsyuk, K.Y. Loh, C.-C. Shih, W. Xu, K. Liang, K. Zhang, Y. Bai, G. Gurusankar, W. Hu, W. Jia, Z. Cheng, R.H. Dauskardt, G.C. Gurtner, J.B.-H. Tok, K. Deisseroth, I. Soltesz, Z. Bao, Science **375**, 1411–1417 (2022)
83. L.E. Osborn, A. Dragomir, J.L. Betthauser, C.L. Hunt, H.H. Nguyen, R.R. Kaliki, N.V. Thakor, Sci. Robot. **3**, eaat3818 (2018)
84. Z. Yu-Qing, L. Yuxin, Z. Donglai, N. Shayla, L. Shuhan, Y. Zhiao, L. Deyu, W. Hung-Chin, Z. Chenxin, L. Jinxing, T. Helen, J.B.-H. Tok, B. Zhenan, Science **373**, 88–94 (2021)
85. X. Liu, H. Yuk, S. Lin, G.A. Parada, T.-C. Tang, E. Tham, C. de la Fuente-Nunez, T.K. Lu, X. Zhao, Adv. Mater. **30**, 1704821 (2018)
86. R.C. Advincula, J.R.C. Dizon, E.B. Caldona, R.A. Viers, F.D.C. Siacor, R.D. Maalihan, A.H. Espera, MRS Commun. **11**, 539–553 (2021)
87. Y. Liu, E. Kim, R. Ghodssi, G.W. Rubloff, J.N. Culver, W.E. Bentley, G.F. Payne, Biofabrication **2**, 22002 (2010)
88. A. Gumyusenge, D.T. Tran, X. Luo, G.M. Pitch, Y. Zhao, K.A. Jenkins, T.J. Dunn, A.L. Ayzner, B.M. Savoie, J. Mei, Science **362**, 1131–1134 (2018)