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Brain-Inspired Organic Electronics: Merging Neuromorphic Computing and Bioelectronics Using Conductive Polymers

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Neuromorphic computing offers the opportunity to curtail the huge energy demands of modern artificial intelligence (AI) applications by implementing computations into new, brain-inspired computing architectures. However, the lack of fabrication processes able to integrate several computing units into monolithic systems and the need for new, hardware-tailored training algorithms still limit the scope of application and performance of neuromorphic hardware. Recent advancements in the field of organic transistors present new opportunities for neuromorphic systems and smart sensing applications, thanks to their unique properties such as neuromorphic behavior, low-voltage operation, and mixed ionic-electronic conductivity. Organic neuromorphic transistors push the boundaries of energy efficient brain-inspired hardware AI, facilitating decentralized on-chip learning and serving as a foundation for the advancement of closed-loop intelligent systems in the next generation. The biocompatibility and dual ionic-electronic conductivity of organic materials introduce new prospects for biointegration and bioelectronics. Their ability to sense and regulate biosystems, as well as their neuro-inspired functions can be combined with neuromorphic computing to create the next-generation of bioelectronics. These systems will be able to seamlessly interact with biological systems and locally compute biosignals in a relevant matter.

1. Introduction

Artificial intelligence (AI) applications have recently made an impact in several fields of science and technology, ranging from image processing and health care, to autonomous driving and text generation, and the demand for such applications is expected to increase in the coming years. However, this AI revolution also presents some "hidden costs" in terms of computational resources and energy requirements.[1]

Most of the modern AI applications are implemented as software artificial neural networks,[2] running on digital computers where memory and computing units are separated. The need for shuttling information between these two units to perform computations (also known as the "Von Neumann bottleneck") is one of the main causes for the high energy demands of software artificial neural networks, especially when these consists of millions (or even billions) of trainable parameters.[3]

Neuromorphic computing aims to address these challenges by implementing AI applications and artificial neural networks in hardware systems. Drawing inspiration from the architecture and functioning of biological neural networks, neuromorphic devices perform computations *in memory*, bypassing the Von Neumann bottleneck and therefore reducing time and energy demands. Despite several promising proof-of-concept and small-scale implementations exist, fabrication, and training of complex neuromorphic hardware still poses many challenges, such as the integration and scale-up of several computing units into monolithic systems and the need to co-design training algorithms and hardware.

With recent advancements in the field of organic transistors new opportunities for neuromorphic systems and smart sensing applications arise.[4] The emerging organic devices and materials provide unique properties such as neuromorphic behavior, mixed ionic-electronic conduction, low voltage operation, and a flexible, stretchable, soft nature mimicking highly efficient biological computing systems.[5–7] Fabrication techniques based on solution processing enable large-scale implementations and offer cost-effective alternatives to conventional complementary metal-oxide semiconductor (CMOS) manufacturing processes.[8] Chemical synthesis facilitates the development of novel or customized organic materials with improved, tailor-made characteristics.[9,10]

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Moving further toward neuro-emulating hardware AI, organic transistors enable decentralized on-chip learning and provide a platform for the next generation of closed-loop intelligent systems.[11,12] Because of their soft mechanics, they also provide the mechanical ability to interact with and be shaped by their environment that allows for wearable patch devices, compliant implants and embodied mechanical intelligence.

Organic materials also present novel prospects in terms of biointegration and bioelectronics. Indeed, thanks to their biocompatibility and dual ionic-electronic conductivity, significant breakthroughs have been made both in terms of sensing and regulation of biosystems.[13–16] Additionally, organic devices have shown neuro-inspired functions closely mimicking their biological counterparts,[5,17–19] such as short-/long-term plasticity of synapses or spiking behavior of neurons, which enables local preprocessing of biological signal and a seamless communication with biology.

When combined with neuromorphic computing, organic devices could represent the next-generation of bioelectronics. Ranging from point-of-care systems to implants and prosthesis, they could be capable of sensing, computing, and regulating in situ in a biologically relevant way. However, challenges such as monolithic integration, fabrication scaling, and long-term stability must be addressed before the development of these closed-loop and self-adapting systems.

In this review, we highlight these challenges and emphasize potential avenues for achieving greater device integration and resolving complex computing tasks. Initially, we offer an overview of organic transistors and the methodologies employed in their fabrication. Differently from previously published reviews, we provide a non-exhaustive overview of published works focused on real-life implementations of neuromorphic systems rather than computational studies or simulated scenarios. We also suggest new research directions to advance the field of organic neuromorphic computing, favoring a multi-disciplinary approach that takes into account material properties, device and system architecture, and learning algorithms. In Section 4, we explore the interactions between bioelectronic materials and living organisms, examining their applications in neuro-inspired systems and, following up in Section 5 with the adoption of these systems to accomplish adaptive sensing and processing. In Section 6 we investigate how recent advancements in the field of AI can be beneficial to the training and the architecture of brain-inspired systems. Ultimately, we propose strategies for the development of a new generation of organic neuromorphic systems, and offer insights into the future prospects of co-designing such systems with learning algorithms.

2. Organic Transistors

The organic transistor architectures discussed in this review are based on three-terminal devices with source, drain, and gate metal electrodes (**Figure 1**a–c). Source and drain electrodes are connected through an organic (semi-)conductor thin film operating as channel material. The gate electrode is used to modulate the electronic current flow inside the channel material by doping or dedoping it with ions through a gate potential. Commonly, we consider three main transistor types: organic field effect transistor (OFET), electrolyte-gated organic field effect transistor (EGOFET) and organic electrochemical transistor (OECT).

2.1. OFET

In an OFET (Figure 1a), the gate is separated from the channel material by an insulator. This prevents the exchange of charges between layers and leads to a formation of charge barriers at the insulator interface if a voltage is applied at the gate. Charges of opposite polarity collect on the gate and channel side of the insulator, which creates a parallel plate capacitor of insulator thickness. Thus, doping and dedoping of the channel material is controlled through the field effect of the internally created capacitor.[20]

A special type of OFET is the electrolyte-gated FET. The channel material is in direct contact with an electrolyte. Via a gate voltage, ions inside the electrolyte form a charge layer at the interface of the channel material. Inside the channel, electronic charges of opposite polarity accumulate. This leads to a high capacitance as the distance between both charge barriers is determined by the ionic radius.[21]

2.2. OECT

Similar to the EGOFET, the channel material is in direct contact with an electrolyte. Through application of a gate voltage the ions in the electrolyte are able to penetrate into the channel material with (de-)doping occurring over the full volume of the channel (Figure 1b). Thus, the device is characterized by a volumetric capacitance, which leads to significant higher amplification and transconductance compared to OFET structures.[22] Materials used for this device type are organic mixed ionic-electronic conductors.[23]

2.3. EC-RAM

Since OECT have mixed conduction they display two different time responses, ionic, and electronic, over different orders of magnitude with hysteresis. This slow kinetics effect was first exploited in a system to display device adaptivity similar to that of a biological synapse (**Figure 2**a,b). Since then, many neuromorphic functions have been demonstrated for organic transistors.[5,17,18] Neuromorphic functions refer to brain-inspired behaviors such as synaptic plasticity and spike-based information transfer (Figure 2c–g). Short-term plasticity in organic neuromorphic devices is often shown through paired pulse facilitation. A train of pulses is applied at the gate, the conductance is changed by the first pulse and this change is increased even more by the following pulses if they follow closely after. The strength of the conductance change also depends on the nature of the spike and is influenced by spike duration, spike voltage/height and the spike timing (Figure 2c–f). Long-term plasticity has also been shown and refers to a more permanent change of conductance that lasts for many seconds, minutes or even hours (Figure 2g). This creates a non-volatile memory effect leading to the electrochemical random access memory (EC-RAM).

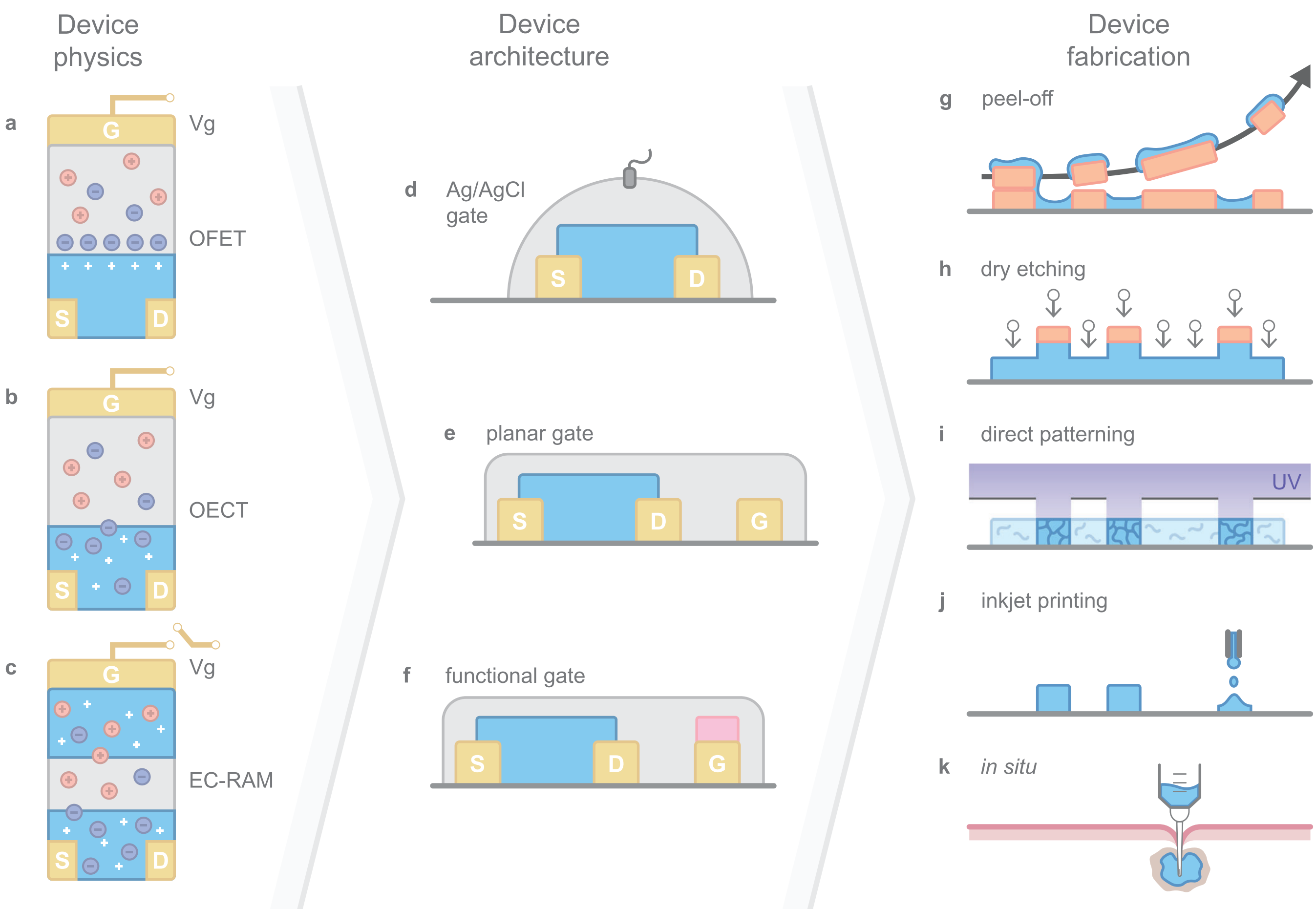

Figure 1. Overview on organic-based transistors. Device physics (first column) behind different types of organic transistors, exemplary shown for gate voltage $V_g < 0$ V: a) The organic field-effect transistor (OFET) forms a double layer of charges at the (semi-)conductor/insulator interface. b) The organic electrochemical transistor (OECT) is defined by a volumetric capacitance meaning that ionic charges from the electrolyte/insulator can penetrate into the channel material, a mixed ionic-electronic conductor. c) The electrochemical random access memory (EC-RAM) is able to trap charges inside the channel material for longer times (i.e., by using a high resistance or switch at the gate) achieving long term plasticity that can be harnessed for in-memory computing. Depending on the use case, different architectures of organic transistors (second column) are needed: d) A non-polarizable gate electrode such as Ag/AgCl can easily be submerged in liquid electrolytes. e) Planar devices with the gate placed on the same plane as the source and drain contact enable the use of a solid-state electrolyte, a necessity for fully-integrated circuits. f) The gate electrode can be functionalized by an additional layer on top of the electrode. This layer can be of the same material as the channel or is chemically tuned to have unique properties for analyte detection. Different patterning techniques can be used for the organic material (third column). g) The most common way is the manual peel-off of a sacrificial layer, leaving however undesired material on the sidewalls. h) A sacrificial layer can deposited on top of the organic material and used as an etch mask during a dry etching process. i) Direct UV patterning is also possible by either trapping the organic material in an interpenetrating network, or by directly cross-linking the polymer chains together. j) Printing techniques, such as inkjet printing, are also suitable for organic material, allowing a low-cost and large-scale fabrication. k) Semiconductor polymers can be polymerized in situ, by either applying an external voltage, or using metabolites for in vivo fabrication.

Based on the general OECT structure, organic neuromorphic devices mainly differ by their probing conditions (Figure 1c). In order to achieve stable, long-term retention of charges the gate current is limited by a high resistance at the gate.[6] Additionally, after applying a gate potential (write) the gate is disconnected from the channel with a switch to prevent leakage of charges and the drain current can be measured decoupled (read). By changing the layer thickness of the channel material a similar effect can be achieved.[24] Innovative material concepts such as evolvable OECTs present new ways of separating between short-term and long-term plasticity by providing different material mechanisms for changing the conductance.[25]

2.4. Architectures

The electrodes and channel material can be stacked in different configurations that are dependent on the fabrication methods and the type of application. For top/bottom configuration, the gate is placed above/below the channel material that connects the planar source and drain contacts(top contact in Figure 1d). In a fully planar layout, the gate contact is in-plane with the source and drain contacts (Figure 1e,f). This is especially helpful for wearable design or more intricate circuits and often simplifies fabrication.[22] A recently adopted layout is a vertical configuration where source and drain are stacked on top of each other.

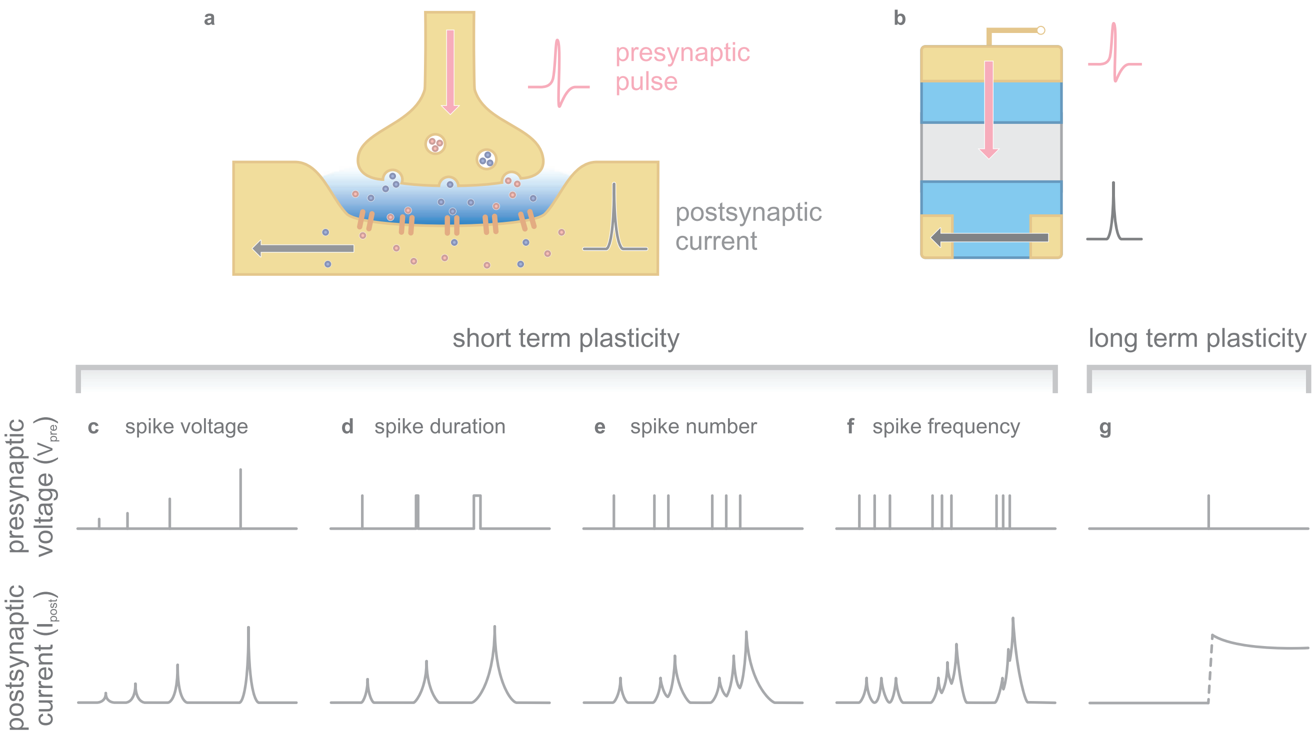

Figure 2. Synaptic behavior showing short-term and long-term plasticity. a) The biological synapse transfers a presynaptic voltage spike V_{pre} (action potential) via the distribution of neurotransmitter. The neurotransmitter travel from the presynaptic neuron through the synaptic cleft into the postsynaptic neuron leading to the creation of a postsynaptic current I_{post}. The synaptic strength is determined by the amount of ejected neurotransmitter and postsynaptic receptors. b) The neuromorphic organic transistor behaves in a similar manner: When applying a gate voltage V_{pre}, ions are moved from the presynaptic gate terminal into/out of the the channel changing the overall conductivity of the channel material. The resulting source-drain current I_{post} is therefore adapted through a change in conductivity representing the synaptic weight. The changes in the postsynaptic current I_{post} depend on c) the spike voltage, d) the spike duration, e) the spike number, f) the spike frequency also often referred to as spike timing dependent plasticity (STPD) of the presynaptic voltage V_{pre}. If the change in the postsynaptic current I_{post} is of a more permanent nature, this is called g) long-term plasticity.

They are only separated by a thin insulation layer that allows for very short channel length.[26,27]

The gate electrode is ideally made from a non-polarizable material such as Ag/AgCl (Figure 1d) to prevent a large voltage drop at the gate/electrolyte interface. If this is not possible polarizable metal electrodes (Pt, Au) are an alternative. It was also recently shown that coating the metal electrodes with the organic polymer poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) helps to reduce the effect of polarization and allows a similar OECT performance as Ag/AgCl electrodes.[28] The gate electrode can also be covered with use-specific materials to let it functions as a sensor or receptor for certain materials (Figure 1f).

The electrolyte contains the ions that induce (de-)doping of the channel material. It can be a simple salt/water mixture or a more complex fluid such as sweat or cell culture medium. An alternative to aqueous electrolyte are hydrogels or ionic liquids/gels.[6] These also enable the fabrication of solid-state devices, which is important for scalability and moving toward fully-integrated systems.

An architecture of multiple devices that is particularly relevant for neuromorphic application is the crossbar array.[29,30] Here, multiple inputs lines cross over with multiple output lines. They are connected at the cross-points by (organic) transistors (Figure 5n). Crossbar arrays allow an easy translation of artificial neural networks architecture into larger-scale circuits: each weight of the networks is represented by one neuromorphic (organic) transistors.[4] More details and concrete implementations are explained in Section 5.2.1.

3. Patterning of Organic Semiconductor

Patterning conductive polymers (CPs) has been one of the main challenge toward miniaturization and scalability of organic devices. As these materials are sensitive to conventional photoresists, traditional photolithography processes had to be adapted, leading to poorer reproducibility, scalability, and resolution. In the recent years however, the development of new material and techniques, such as orthogonal photoresists and photopatterning, have lead the way toward highly integrated organic circuits. Moreover, additive manufacturing is one of the great strength when using CPs, which can be printed using different techniques, or even polymerized in situ.

3.1. Lift-Off

Lift-off process is a conventional microstructuring technique, traditionally used for patterning metallic interconnects. It relies on depositing a sacrificial photoresist layer with an inverse pattern onto the substrate. The target material is then deposited and the remaining sacrificial layer is stripped away. Lift-off has been used for patterning organic materials, but remains extremely challenging due to poor chemical compatibility between the photoresists and the conductive polymers. Nevertheless, different workarounds have been developed.

Conventional sacrificial photoresists have been used to pattern conductive polymers, such as poly(3-hexylthiophene-2,5-diyl) (P3HT).[31] Instead of dissolving the CP into chloroform, a solvent incompatible with most of commercially available photoresists, the authors used xylene and successfully patterned P3HT. Unfortunately, this technique cannot be adapted for every organic material. PEDOT:PSS is for example not suited for the majority of photoresists due to its acidity. To overcome this issue, it is possible to pattern an interlayer of SU-8 below the PEDOT:PSS, before dissolving the unexposed SU-8.[32] This remaining SU-8 interlayer may however cause issues for more complex circuitry.

One of the main techniques to pattern organic materials has been the physical lift-off of a sacrificial layer.[33] It relies on the deposition of two parylene layers separated by an anti-adhesion layer. After patterning the double stack through dry etching, the CP is spincoated and the top layer of parylene is physically peeled off (Figure 1g). However, due to its manual nature, this technique is not fully scalable, and device reproducibility is poor compared to other techniques such as dry plasma etching.[34,35] Finally, an issue common to any lift-off process of organic materials is the lack of well-defined geometry after the stripping process. The undercut profile of the edges of the photoresist should ensure a discontinuous film, which is however not the case for spincoated CPs where "ears" are typically visible at the edges of the patterns.

3.2. Dry Plasma Etching

Dry plasma etching process relies on the patterning of a photoresist on top of the CP layer and acts as a protective mask during the plasma etching step (Figure 1h). The residual photoresist is then stripped away at the end of the process. Protective interlayers have been used on top of the organic layer to protect it from incompatible photoresists. Silver or copper has been used on top of PEDOT:PSS and acts as an etch mask during the plasma etching of the organic material.[36,37] Commercially available photoresists have also been directly patterned on top of PEDOT:PSS.[35,38] The critical step for this fabrication is the overnight soaking in deionized water of the CP to remove the top PSS layer that would normally interferes with the photoacid chemistry of the resist. Finally, orthogonal photoresists based on fluorinated monomers have been developed to fabricate sub-micrometer patterns and represent one of the main leap for the miniaturization of organic devices.[39]

3.3. Photopatterning

Direct patterning of organic materials using UV light is a fast and chemically friendly technique where substantial breakthroughs have been achieved in recent years. Direct photopatterning relies either on the entrapment of the organic material in an interpenetrating polymer network, or on the direct cross-linking of adjacent polymer chains through azide chemistry (Figure 1i).

The main principle behind the entrapping of CP using UV light is the mixing of the organic material with a photocrosslinkable monomer and a photoinitiator. Upon exposure, the monomer cross-links and traps the CP, acting as a negative photoresist. Radical polymerization[40–42] or cycloaddition[27] have been used to create these interpenetrating networks and showed excellent CP characteristics, sometimes surpassing their pristine counterparts. Moreover, these networks can enhance the chemical resistance of the organic materials[40] as well as improve the stretchability of the polymer film.[41,42]

Polymer chains of the organic material can also be directly cross-linked using well-suited photoinitators based on azide.[43] The decomposition of azides upon UV exposure generates singlet nitrenes, which can react with C-H and N-H bonds, yielding a cross-linked matrix of the CP. This technique is universal for materials comprising the reaction groups and has been used for semiconductors[41,43,44] as well as dielectrics.[44,45]

3.4. Printing

Another advantage of organic semiconductors is the possibility of printing using large-scale fabrication techniques such as screen or inkjet printing[46,47] (Figure 1j). It gives the opportunity to manufacture low-cost devices using roll-to-roll methods with high flexibility in terms of substrate choice, and without the need of expensive photomasks or lithography equipment.[48] The main challenges rely in the composition of the inks to achieve good film homogeneity without compromising the printing process.[46]

3.5. In Situ Polymerization

A specific trait of organic polymers is their ability to be polymerized in situ.[49] Indeed, electrochemical oxidation of monomers can be triggered by applying a voltage across electrodes and allows a fast and localized patterning of CPs.[50] Evolvable and dynamic organic circuitry can therefore be fabricated thanks to the high spatial and temporal control of this technique.[25,51] External DC voltage can create a complete coverage between electrode, whereas an AC signal generates dendritic growth,[52,53] opening the possibility for complex architecture and computing.[54] Moreover, the polymerization can be triggered by metabolites and electrode formation has been shown in zebra fish and leech,[55] paving the way to in vivo electronic fabrication (Figure 1k).

For a long time, the difficulties in patterning organic materials yielded poor scalability and reproducibility in polymer devices. In recent years however, the development of orthogonal photoresists and direct photopatterning have partially answered these challenges and should be the main focus for future research on high-resolution organic circuitry (**Table 1**). On the other hand, though the printing processes sacrifice resolution (which is not a necessity for certain applications), it allows for the large-scale fabrication of low-cost devices.

4. Bioelectronics

Biological systems typically rely on ions and molecules to communicate and process information. Action potentials, one of the

Table 1. Comparison of different fabrication techniques for organic materials.

		Process complexity	Resolution	Scalability	Cost
	Conventional lift-off	High	High	High	High
Lift-off	Peel-off	High	High	Low	High
Dry etching		Low	High	High	High
	Interpenetrating network	Moderate	High	High	High
Photopatterning	Azide assisted	Low	High	High	High
in situ polymerization		High	High	High	Moderate
Printing		Moderate	Low	High	Low

most basic form of communication between neurons, are generated through the opening and closing of ion channels. The action potentials propagate along the axon before reaching the synapse, where an influx of calcium ions triggers the release of neurotransmitter, carrying information to the next cell. Conversely, the vast majority of human-made technologies employ electronic charges as carriers. Thus, interfacing biological systems requires a translating agent capable of conducting both electrons and ions/molecules. For this specific reason, organic mixed (semi)conductor polymers have been recognized as a highly viable option thanks to their dual conductivity. Furthermore, they offer ease of synthesis, flexibility in processing, functionalization, biocompatibility, and softness.[13]

Sensing using biosensors or neural probes has allowed to increase our understanding of biological processes, whereas neuromodulation has been achieved by electrical, chemical, mechanical, and optical stimulation. Sensing and regulating biosystems have been, in that sense, the cornerstones of bioelectronics platforms. However, the expansion of the capabilities of these platforms has sparked an interest in neuro-inspired processing functions, such as synaptic plasticity and artificial spiking neuron. It would allow the creation of seamless and adaptive biohybrid systems capable of sensing, processing, and regulating in a biologically relevant manner.

4.1. Bioelectronics and Sensing

4.1.1. Biosensors

Biological processes, such as proliferation, differentiation, or wound healing, are intimately linked to the presence or absence of specific metabolites. Prime examples are found in studies on cancer, where perturbation of the metabolism has been linked to malignant transformation growth, and maintenance of tumors.[56] Detecting and measuring these metabolites is therefore crucial to understand these biochemical processes and monitor health status. By relying on a recognition and a transducer unit, biosensors offer a way of detecting these metabolites. The recognition unit interacts with the analyte of interest, ideally with a high selectivity and specificity, and produces a signal, usually chemical, that can be transmitted to the transducer unit. There, the input signal is transformed into a readout signal, that can be optical, mass-related or electrical. Biosensors have been widely used for detecting metabolites in vitro[15] as well as in vivo[16] and are anticipated to be a major player in the market of closed-loop continuous and wearable technologies that aim at personalized and local control.[57]

The main part that interacts with the analytes is the recognition unit, which can be separated in five categories: enzymes, antibodies, aptamers, riboswitches, and molecularly imprinted polymers.[16] Enzymes are proteins that can catalyze a reaction and convert the analyte (also called substrate or ligand) into a product. The most common ones are oxidoreductases that use a redox reaction to regenerate themselves after interacting with the the substrate. This reaction generates electroactive species that can be used by the transducer unit. Enzymes offer good selectivity, but are sensitive to environmental conditions, such as temperature or pH, and are generally expensive. Antibodies are proteins used by our body in response to foreign agent and can recognize antigens. The antigen-binding domain of the Y-shaped molecule is typically located on the arms and the binding event can be transduced through changes in electrochemical, piezoelectric, or amperometric signal.[58] Antibodies are nonetheless very sensitive, expensive, and suffer from batch-to-batch variability. Aptamers are artificial sequences of RNA or single-stranded DNA that have the ability to bind to a target and are quite similar to antibodies in that sense. The readout can be fluorescence, electrical, or mass-sensitive[59] and thanks to their synthetic nature, aptamers offer a much stabler, and cheaper solution compared to antibodies. Riboswitches are segments of messenger RNA and are made out of two components: an aptamer that can selectivitely detect the target and an expression platform that translates the binding of the target into a gene expression. The readout sensor therefore needs to detect the level of expression of this gene, which makes it challenging to use in a complex system, as this level can be influenced by environmental conditions. Finally, molecularly imprinted polymers are synthetic functional monomoners that are polymerized with a template molecule. This template molecule represents the analyte of interest and is removed after polymerization, yielding a matrix with recognition cavities. This recognition unit works in a similar manner to antibodies and antigens, while being more affordable. However, the complexity lies in finding the right monomer for the templating step.

After recognition of the target, the signal needs to be transduced, and the interface between the two units is crucial in order to achieve good sensitivity. The transduction can be optical, mass-

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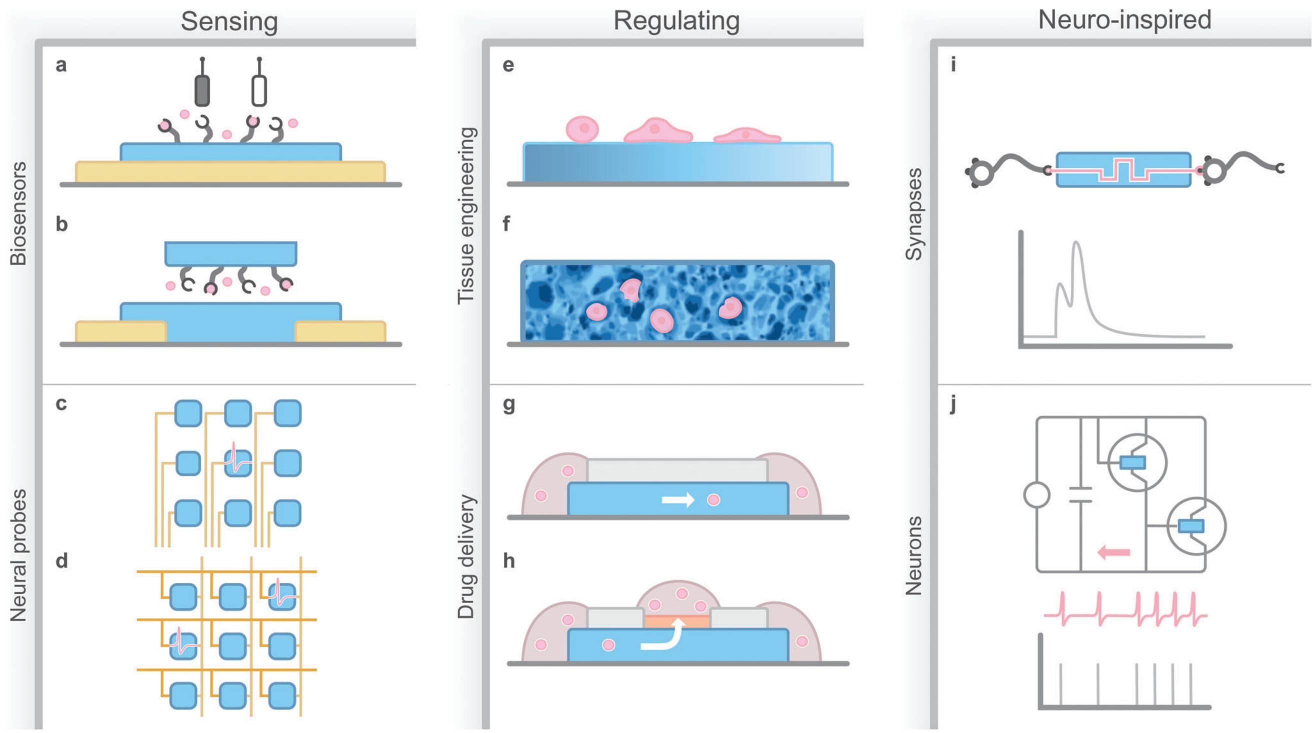

Figure 3. Overview of the different aspects of bioelectronics using organic (semi-)conductors. Sensing (first column) can be used to detect metabolites in vitro or in vivo. a) Electrodes can be functionalized with recognition units and coupled with reference and counter electrodes. b) More complex architectures such as the EGOFET or OECT can be used to increase the sensitivity and signal-to-noise ratio. Either the gate or the channel of the transistor can be functionalized. The electrical activity of neuronal cells can also be recorded using either c) polymer-coated electrodes or d) transistor array to increase density, signal-to-noise ratio, and allow multiplexing. Another aspect of bioelectronics is the regulation of the biosystem (second column). e) The doping state of the organic material can control attachment, metabolism, and function of cells. f) 3D scaffolds can also be fabricated using conductive polymers, paving the way for biorealistic tissue structure capable of electrical stimulation. g) Thanks to their inherent dual conductivity, ions pumps have been realized with conductive polymers allowing for precise drug or metabolite delivery. h) Advanced circuitry, such as ion diodes, have been fabricated as well and allow fast and addressable release sites. In the prospect of creating a seamless connection with biology, neuro-inspired bioelectronics play an important role (third column). i) Synapses are the first element to process biosignals and their artificial counterparts needs to possess the same synaptic plasticity, such as short/long-term potentiation and depression. j) Artificial neurons, on the other hand, allow to encode information in a spike-based matter for a better coupling with the nervous system.

related, or electrical. Organic materials such as graphene,[60] carbon nanotubes,[61] or conductive polymers[62] have been extensively studied as transducers thanks to their high level of functionalization through covalent or non-covalent techniques, their large surface area, and their good electrical properties.[16,62] This section will mainly focus on transducers using CPs with an electrical readout as they present additional benefits, such as softness, ion/electron (or mixed) conductivity, ease of fabrication, and relatively low cost.[16]

The electrical signal created by the transducer unit upon recognition of the analyte can be drastically different from one sensor to the others. The sensing can be based on a change of current (amperometric), change of potential (potentiometric), or change of conductivity (conductometric). This distinction is sometimes not obvious depending on the type of sensors and measurement conditions. Three different architectures of sensors are therefore presented below with their sensing mechanism.

The most simple type of architecture is a CP-coated electrode. This electrode can work in a potentiometric mode where changes in ionic concentration lead to a potential shift between the reference and the working electrodes (**Figure 3**a). The working electrode can be functionalized with molecularly imprinted polymers and either capture bi-product ions, or create a charged species when capturing the analyte, but the response of the sensor is slow and diffusion limited.[16] The electrode architecture also works in an amperometric mode where an electroactive species undergo oxidation or reduction. A voltage between the reference and working electrodes is applied to trigger the reaction, and the redox current is measured. The working electrode can be occasionally functionalized with recognition units coupled with redox mediators to generate electroactive species that are more easily oxidizable. High selectivity using amperometric measurement is difficult as redox reactions involving other electroactive analytes can be activated, and toxic byproducts may also be produced. Finally, this sensor architecture can work in an impedimetric detection, where the impedance of the whole system is measured using an AC signal at different frequencies. The change in impedance, due to the presence of the analyte, is then fitted to an adequate equivalent circuit, which is one of the main challenges when using this technique.

The second type of architecture is the EGOFET. This type of device works in a potentiometric mode in biosensors and the recognition unit can either be placed at the gate level, or at the channel level (Figure 3b). During the detection of an analyte, the effective gate voltage applied on the channel is affected, inducing a modulation of the channel current. This detection must be made under equilibrium conditions, meaning a null gate current. It has been shown that EGOFETs work solely via capacitive-coupling and that the gate current is negligible at all times.[63] EGOFETs also show a much higher sensitivity compared to traditional potentiometric sensors,[63] illustrating the potential of amplification through the transistor architecture.

The last type of architecture is the OECT¨ˆˆ. These transistors are similar to the EGOFETs and can be used in potentiometric measurement, as long as they follow the zero gate current condition. However, this architecture has mainly been used in an amperometric mode, usually relying on oxidoreductases.[64] But the amplification of this mechanism has been challenged by recent papers.[63,65–67] Indeed, experimental results show that the relative current change upon sensing is of the same magnitude for the gate current as for the drain current,[63] meaning that the faradaic current created at the gate is not amplified. Using an OECT architecture, however, shows an improvement in terms of signal-to-noise ratio.[68] To overcome the amplification issue, a new architecture called reaction cell OECT has been developed.[65] In this architecture, a potentiometric measurement is performed in a reaction cell. The potential change between the reference and working electrodes is then applied at the gate voltage of a physically separated OECT, which amplifies the signal. Another conceptual architecture has been suggested where a current amplifying transistor, such as a bipolar junction transistor, could amplify a faradaic current.[63]

All of these architectures can be used for detection of biomarkers in different settings. Point-of-care devices rely on taking and analyzing samples on-site, while wearables bypass the sampling step and directly interface the body surface. Finally, in vivo biosensors are implanted inside the biological environment for the detection of metabolites. The examples below are focused on sensor based on conductive polymers with an emphasis on applications that directly interface real biological samples. A more complete overview of carbon-based biosensors can be found in the following reviews.[15,16]

Conventional analysis of metabolites relies on collecting a sample from a patient, such as blood, saliva, or urine, and analyzing it in a laboratory. Point-of-care devices aim at creating a miniaturized laboratory to perform the analysis on-site. Glucose and lactate sensors are for instance implemented in a dual channel microfluidic chip.[69] Oxidases are immobilized at the gate of the OECT and upon addition of the metabolites, oxidation of the byproduct hydrogen peroxide (H_2O_2) results in a decrease of the drain current of the PEDOT:PSS channel. The glucose sensor is also integrated into a portable readout system for saliva analysis, showcasing the ease-of-use, portability, and small amount of reagent needed of the whole system. Similarly, a microfluidic channel containing glucose, lactate, and cholesterol sensors is presented for multianalyte saliva testing.[70] As the array of enzymatic OECTs operated in a common electrolyte, the chemical cross-talk linked to the diffusion of H_2O_2 has to be managed. By creating a microenvironment containing the enzyme and an electron mediator (ferrocene), the redox reaction is spatially constrained to the gate electrode of each PEDOT:PSS channel. This technique shows good results in terms of selectivity, even when working in a common electrolyte and relying on three different types of enzymatic reaction. Showcasing the low-cost and eco-friendly aspects of conductive polymers, a fully inkjet-printed and disposable sensor is fabricated on paper for daily monitoring of glucose in saliva.[71] Functionalization of the working electrode is performed by the printing of an aqueous solution containing glucose oxidase and a ferrocene complex. Additionally, a biosensor based on PEDOT modified carbon fiber is used for glucose detection by immobilizing glucose oxidase on the working electrode.[72] The electrode shows long-term stability and could be a viable option for blood glucose test strip. The n-type copolymer P-90 has also been used and relies on the interaction with the enzyme itself for the detection of analytes and not the H_2O_2 byproduct.[68] An OECT integrated in a microfluidic channel for detection of glucose shows an increase in the signal-to-noise ratio thanks to the transistor architecture. Although the majority of OECT biosensors are based on an enzymatic detection of the analyte, other recognition unit, such as aptamers, can be used to increase the selectivity. A novel gate electrode based on aptamers, gold nanoparticles, and graphene is used for detection of thrombin and could contribute to the development of cheap and easy-to-handle point-of-care diagnostics.[73] In [74], the authors develop an aptamer-based OECT for detection of tobramycin and present a "pulsed gate potential" to increase the drain current modulation. Moreover, OECTs can be fabricated on more unconventional substrate, such as fibers.[75] The sensor is integrated in a diaper and used for detection of glucose in artificial urine. An increasing amount of research has also focused on more complex circuitry for metabolite sensing.[76] For example, a complementary OECT circuit is developed for ion detection.[77] The circuitry relies on a push-pull amplifier configuration using PEDOT:PSS and BBL OECTs in series. Through the change of ion concentration of the electrolyte, a shift in the threshold voltage of the transistor is observed. A multiscale approach is taken in order to measure small variations of the base level over a large range of concentration without losing performances. Despite OECTs being predominant in the field of biosensors, EGOFETs have also been intensely investigated for metabolites detection. A label-free immunosensor based on P3HT has been used for detection of procalcitonin, an important sepsis marker, by immobilizing antibodies on the surface of the conductive polymer.[78] A similar EGOFET sensor is developed for detection of C-reactive protein in saliva and shows the prospect of using such technology for point-of-care devices.[79] The authors in ref. [80] perfectly demonstrate this aspect by developing a self-powered platform using glucose fuel cell for the detection of HIV-1. A P3HT EGOFET is used with a fixed drain and gate voltage to allow an output readout measurable with a handheld voltmeter.

However, point-of-care technologies have limitations when it comes to continuously measuring analytes as they require active sampling from the patient, and recent research has focused on devices that interface directly with the body to allow an uninterrupted flow of information. Integration of organic materials in wearables are of great interest for such sensors thanks to their softness and lightweight. For example, a PEDOT:PSS OECT fabricated on a cotton fiber can monitor adrenaline in sweat.[81] The use of a platinum gate enables the independent detection of adrenaline oxidation, regardless of the saline content, which is measured by another OECT featuring a silver gate. Similarly, a PEDOT:PSS OECT for sweat sensing is fabricated using screenprinting on textile.[82] Electroactive metabolites such as adrenaline, dopamine, and ascorbic acid are detected and the sensors show robustness even after multiple handwashing. In ref. [83], the authors implement another type of sweat sensors to measure cortisol, a metabolite linked to stress level. A molecularly selective membrane is fabricated to create an ion-permeable layer, and is placed between the PEDOT:PSS channel and Ag/AgCl gate. In the absence of cortisol, doping, and dedoping of the channel can occur through the movement of the ions. However, the presence of the metabolite seals and blocks the molecularly selective membrane, reducing drain current. The device is integrated into a wearable patch and used for human sweat measurements. Additionally, a molecularly imprinted polymer based OECT monitors the cortisol level in sweat by using a Prussian blue redox probe embedded in a polypyrrole polymer.[84] Similarly, the presence of cortisol blocks the electron transfer pathway needed for Prussian blue oxidation, leading to a decrease in the recorded current. The platform allows detection of the analyte by a simple press of the fingertip, and without any external stress-inducing activity. Likewise, Prussian blue is embedded in a PEDOT:PSS film with oxidase for glucose sensing and uses reverse iontophoresis to extract metabolite from the interstitial fluid from the skin.[85]

A more intrinsic approach for precise detection of metabolite is to integrate sensors in vivo. Neurotransmitters, the metabolites responsible for the communication between neuronal cells, are of particular interest to reveal interconnected regions of the brain. For instance, an OECT array consists of a PEDOT:PSS channel and platinum gate for in vivo oxidation and detection of dopamine in rat brain.[86] The miniaturization of the devices allows the simultaneous recording of dopamine release inside and outside the nucleus accumbens structure while stimulating from the ventral tegmental area (**Figure 4**a). Lower working voltage and higher signal-to-noise ratio compared to other measurement techniques are possible thanks to the OECT architecture. Pushing the miniaturization even further, organic transistors have been fabricated at the nano-scale. A nanopore extended field-effect transistor, created at the top of a nanopipette and gated by a PPy gate, monitors DNA and protein with various artificial receptors similarly to an ionic channel.[87] Similarly, a PEDOT:PSS OECT is fabricated on nanopipette tips by using a double barrel capillary for the channel and a single barrel for the gate.[88] With such spatial resolution, the transistor can be a potential candidate for single-cell measurement of dopamine release. in vivo applications are however not limited to neuronal-related analytes.[89] For instance, researchers use an OECT based on enzymatic sensing for detection of glucose and sucrose in the xylem vascular tissue of hybrid aspen trees.[90] In-line monitoring in cell culture environment has also seen many benefits of using OECTs. Among others, a PEDOT:PSS OECT is used for measuring H_2O_2 in a Transwell support.[91] Upon stimulation by injection of a peptide, the hydrogen peroxide produced by the adherent cells is oxidized by the gate, allowing a live and continuous monitoring of the metabolite during cell culture. Moreover, glycan quantitation on cell surface is performed by covalently bonding cells to the gate electrode of an OECT and by measuring the catalysis of H_2O_2 produced by horseradish peroxidase.[92] Continuous in-line sensing and monitoring of cells are essential for in vitro drug testing, and organic electronics have become increasingly popular in this research.[93] Recently, OECT are utilized not only to measure metabolite, but also to monitor cellular barriers using a current-driven[94] or dynamic-mode current-driven[95] approach to enhance sensitivity. Tight junction opening can be monitored through the addition of a drug and demonstrate the potential of such sensors for real-time measurement.

Biosensors based on conductive polymers have a great potential for metabolite detection thanks to their biocompatbility, functionalization capacity, ease of fabrication, and low working voltage. Ranging from point-of-care to in vivo sensors, organic electrochemical transistors have been the main player in the field, and more complex and advanced circuitry has been recently explored to further enhance CPs capabilities. Although the research is still in its early phase of development, these devices are the building blocks for the next generation of closed-loop bioelectronic system that will allow sensing, computing, and interfacing in situ. However, there are critical challenges that must be addressed. Long-term stability of devices and device-to-device variability are a well-known Achilles' heel of conductive polymers, but have often been overlooked and need to be addressed by the community. Finally, to achieve systematic improvement and possible industrial applications, standardization in terms of material, fabrication, circuitry, and characterization is required. Despite the call for standardization made years ago,[13] additional efforts are required to provide organic biosensors a genuine opportunity.

4.1.2. Neural Probes

Through an immensely intricate network of neuronal cells, the central nervous system (CNS) receives sensory information, processes it and decides of the course of action in a matter of milliseconds. Capturing the communication between these cells has therefore been crucial to understand and map functions of the brain, and is a necessity to treat neurodegenerative and psychiatric conditions.[13] Neuronal signaling can be recorded by electrodes that detect the disruption of the extracellular electric field caused by ion flux during the generation and propagation of action potentials. State of the art probes, such as the Michigan or Utah array, are made out of micromachined silicon and paved the way to groundbreaking discoveries.[100] However, they suffer from major intrinsic drawbacks, such as their rigidity. The high mechanical mismatch between the soft tissue and stiff implant triggers a neuroinflammatory response of the body, leading to neuronal loss and scar formation around the foreign body.[101] The next generation of neural probe aims at reducing this mechanical mismatch by using softer materials like polymers, elastomers, and hydrogels, or more compliant geometries like serpentine, mesh, and ultrathin devices.[102] They also attempt to lower the impedance of the recording sites by using porous or nanostructured material[103] in order to increase spatial resolution without compromising signal-to-noise ratio, and to reduce the required voltage during electrical stimulation.

Conducting polymers have emerged as a prime candidate for electrode coating, thanks to their intrinsic ionic conductivity, yielding a high surface area and low impedance[13] (Figure 3c).

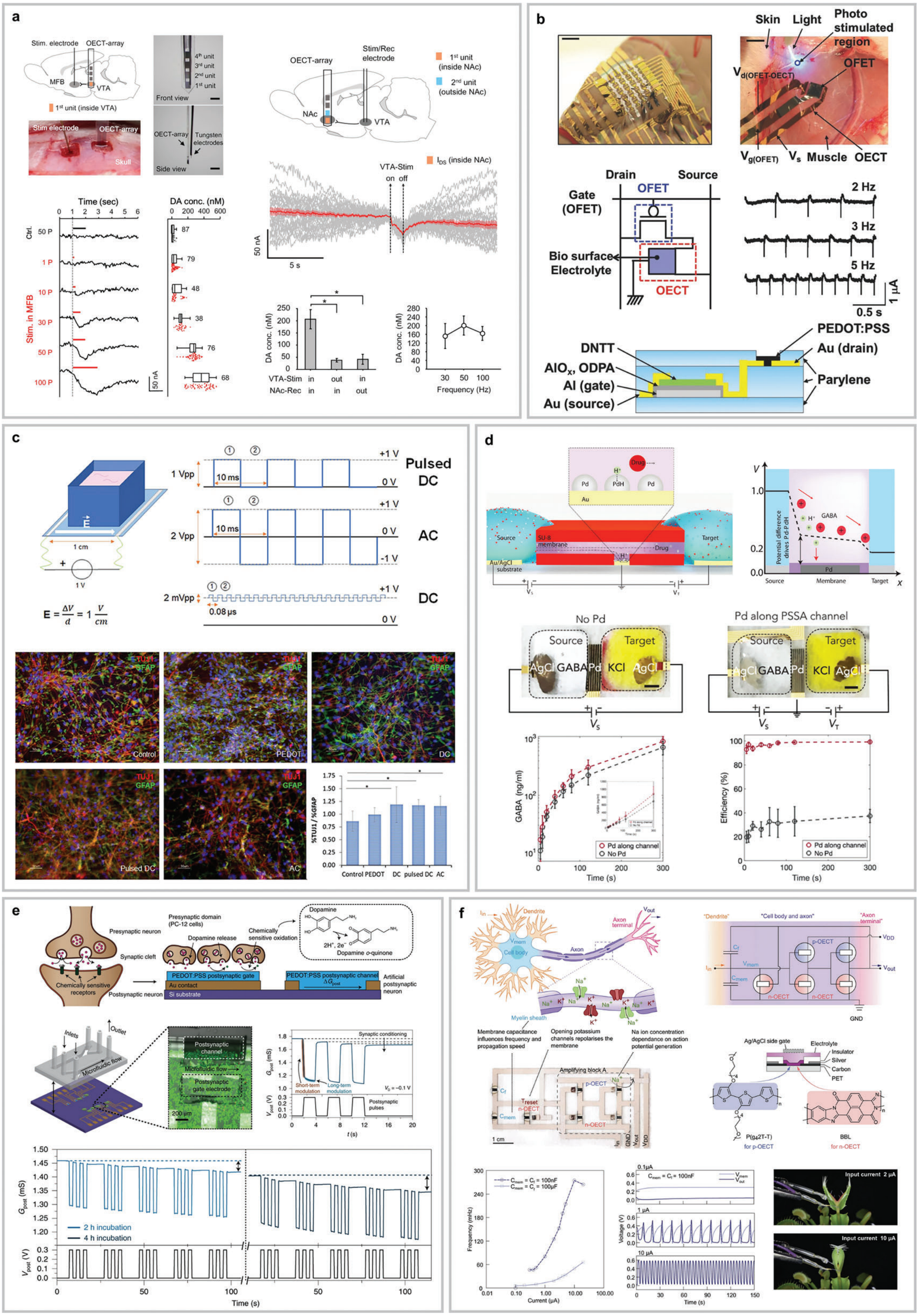

Figure 4. Examples of bioelectronics using conductive polymers. a) An OECT array is used to highlight different dopaminergic pathways in vivo. Reproduced under the terms of a CC BY 4.0 license.[86] Copyright 2020, The Authors, published by eLife. b) A flexible multi-electrode array combining OFETs as an active matrix and OECTs for electrophysiological recordings is developed using a low temperature fabrication process. Reproduced with permission.[96] Copyright 2016, WILEY-VCH. c) Different electrical stimulation protocols are compared for neuronal differentiation of neural stem cells using various cross-linkers for the conductive polymer. Reproduced under the terms of the CC BY 4.0 license.[97] Copyright 2021, The Authors, published

Moreover, their biocompatiblity and softness is hypothesized to help reducing the inflammatory response from the body. Furthermore, CPs can be functionalized with biomolecules, protein, or drugs to enhance tissue integration around the implant and lower the foreign body reaction,[104,105] Although concerns have been raised regarding the stability of CPs for long term recordings,[106] the incorporation of cross-linkers in PEDOT:PSS coating shows improved stability in cell culture environment.[107] NeuroGrid is one of the first flexible probes based on PEDOT:PSS to record local field potentials and action potentials from the surface of the cortex thanks to its high conformability, enhanced signal transduction, and high density, highlighting the benefits of using conductive polymers.[108] To further showcase the capabilities of CPs, a fully stretchable array based on PEDOT:PSS is used for electrophysiological recordings, showing superior performances compared to rigid and flexible counterparts.[42]

As a means to further increase signal-to-noise ratio and density of recording sites, pre-amplification in situ and multiplexing are necessary.[109] These two aspects are for example used to create high-density silicon probes, where 384 recording channels out of 960 can be addressed at the same time.[110] For organic arrays, pre-amplification is predominately done using OECTs, as OFETs usually require high(er) voltage to operate. By using OECTs as voltage-controlled current-source amplifier, the signal of PEDOT:PSS devices can be amplified directly at the recording site and shows higher signal-to-noise ratio compared to PEDOT:PSS coated electrodes.[111] Additionally, multiplexing using OECTs is achieved by wiring the drain terminals together, and using them as scan lines[112,113] (Figure 3d). As this architecture can potentially increase crosstalk and energy consumption, having an access transistor for each recording site is preferable.[114] The authors in ref. [96] therefore use a fully organic circuit consisting of OFETs as access devices and OECTs as the pre-amplification circuit for high temporal electrophysiological recordings (Figure 4b). However, one of the drawback of OECTs is the well-known trade-off between high amplification and high speed, parameters that are both crucial for neuronal recording. To address this issue, new OECT architectures are proposed, namely the vertical OECT[115] or the internal ion-gated OECT,[116,117] which show an increase in cut-off frequency without sacrificing amplification.

The recording of neuronal signals has undoubtedly been the cornerstone for unraveling the first secrets of the nervous system. However, many challenges still remain especially concerning the inflammatory response and probe failure, which hinder long-term recordings.[101] The reasons behind these issues are extremely complex and different approaches have been explored to solve them, such as material or geometrical optimization. However, a more multidisciplinary approach with optimization across multiple parameters is necessary to understand the underlying causes.[118] Conductive polymers are hypothesized to be a good candidate owing to their ionic-electronic conductivity, softness, and functionalizable nature. Their potential to be implemented in transistors and multiplexed arrays makes them even more valuable. Nonetheless, long term studies to evaluate stability and inflammatory response are still lacking. Moreover, more efforts in terms of standardization are needed to increase the scalability and reproducibility of implants. Nevertheless, the perspective of recording and stimulating the nervous system, allowing to potentially bypass dysfunctional tissues or treat neurodegenerative diseases,[100] provides an additional motivation for research in the field of organic neural probes.

4.2. Bioelectronics and Regulation

4.2.1. Tissue Engineering

Although the regulation of growth and function of cultured cells is typically controlled through the addition of supplements in the culture media, the mechanochemical pathways related to the interaction between cells and their substrate are similarly crucial.[119] Charge density, wettability, and morphology of the substrate have been shown, for example, to control attachment, metabolism and function of cells.[120] Another important tool for the modulation of growth and function is electrical stimulation, which can inflect proliferation, migration, or differentiation of cells.[121] Mechanobiology and electrical stimulation are thus pivotal aspects to study in tissue engineering and regenerative medicine applications.

Conducting polymers are in these aspects a unique class of material as their intrinsic properties can be changed by applying an external potential. As the CP undergoes doping or dedoping, ions diffuse in and out of the bulk material, changing its properties, and therefore offering a noninvasive way to alter the synergy between cells and substrate. Polypyrrole (PPy) precoated with fibronection for example is used as substrate to control growth of aortic endothelial cells.[120] In its oxidized state, the substrate promotes normal cell spreading and DNA synthesis, whereas in its neutral state, cell rounding and inhibition of DNA synthesis is observed (Figure 3e). Similarly, a PEDOT:heparin film functionalized with fibroblast growth factor-2 controls the cell function of embryonic neural stem cell.[122] The neutral state of PEDOT:PSS exhibits weaker ionic binding and increases the bioavailability of the growth factor, promoting proliferation, while the oxidized state leads to greater cell differentiation. These noninvasive bioswitches are made possible thanks to conductive polymers and are therefore valuable tools for stem cell therapy. CPs are also used to promote vascularization through the degradation of hyaluronic acid embedded in PPy films,[123] or to create micropatterns as guidance cues for neurons.[124,125]

Additionally, conductive polymers offer a straightforward platform for electrical stimulation. For example, the stimulation of

by MDPI. d) An organic electronic ion pump for delivery of neurotransmitters showcases high selectivity and efficiency by introducing proton traps inside the cation exchange membrane. Reproduced under the terms of the CC BY-NC 4.0 license.[98] Copyright 2021, The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. e) A biohybrid synapse exhibiting short-term and long-term modulation upon exposure to dopamine is coupled with PC-12 cells to create a neurotransmitter-mediated neuromorphic device. Reproduced with permission.[99] Copyright 2022, Springer Nature Limited f) An organic electrochemical spiking neuron based on complementary OECTs is used to directly interface with a Venus Flytrap to induce lobe closure. Reproduced under the terms of a CC BY license.[18] Copyright 2022, The Authors, published by Springer Nature.

neurons using different cross-linked PEDOT:PSS films shows an increase of differentiation[97] (Figure 4c). Furthermore, electrical stimuli on a PPy film increase neurite outgrowth of PC-12,[126] which is traced back to a higher adsorption of protein during stimulation.[127] Such enhancement is also realized by combining functionalization of a PPy film with nerve growth factor and electrical stimulation,[128] truly showcasing the advantages of using CPs.

More recently, 3D scaffolding, a significant advancement toward biorealistic tissue engineering, have been created using conductive polymers (Figure 3f). Hydrogels are for instance used for skin grafting and wound healing.[129] Other fabrication methods, such as freeze drying or electrospinning, are also adapted for CPs to create highly porous scaffolds[130] and fiber networks that enhance neuronal differentiation upon electrical stimulation.[121]

By means of doping and dedoping, conductive polymers have the ability to noninvasively modify their properties and interact with the mechanobiology of cells. In addition to their electrical characteristics for stimulation and functionability, these qualities make CPs a promising option for tissue engineering and regenerative medicine.[15,62,131,132]

4.2.2. Drug Delivery

Thanks to their inherent ionic and electronic conductivity, CPs have been explored as drug delivery from an early stage. Relying either on the release of trapped molecules[133] or migration through ion exchange membranes,[13,134] CPs enable a highly controlled delivery of drugs at a precise location without any liquid transport[135] or substance degradation, and could theoretically reach the speed of synaptic signaling.[136] Moreover, it opens up possibilities for implantable and closed-loop systems in which the biosensing properties of CPs could be integrated with drug delivery mechanisms.

Originally, conductive polymers emerged as a promising candidate for drug delivery due to their two distinct redox states. It is hypothesised that one of these states could be used for binding the ionic substance to the charged polymer and the other one to release it. Glutamate is for example incorporated inside a PPy film by oxidizing the CP, and the neurotransmitter is released afterwards by applying a negative voltage.[137] Conversely, positively charged drugs, such as dopamine, are delivered using a co-polymer poly(N-methylpyrrole)/poly(styrene sulfonate) electrode.[138] Similarly, a p-toluene sulfonate doped PPy film is used for the delivery of cationic risperidone, an antipsychotic drug.[139] This system demonstrates the advantage of having implantable devices, as adherence rates to orally prescribed antipsychotic drugs are generally low. Additionally, in vivo and localized drug delivery can lower the systemic exposure of the drug, which for certain drugs, like the anticoagulant heparin, can lead to degradation when ingested orally. An example of this is a PVA-heparin hydrogel on PPy for the controlled release of the drug.[140]

Despite the potential of confining ions within a CP film, several limitations exist, namely low on/off release upon stimulation, low storing concentration of drugs and poor correlation between stimulation and ions delivery.[141] The development of the organic electronic ion pump tries to address these limitations by relying on the migration of ions from a source to a target reservoir through an electronic-insulating, ionic exchange membrane. The CP electrodes in organic electronic ion pumps convert an electronic current into an ionic current between the two reservoirs. Applying a positive voltage on the source oxidizes the CP and drives cations inside the ionic exchange membrane, while a negative voltage on the target electrode reduces the CP and draws the cations inside the reservoir (Figure 3g). Cation exchange membranes have been fabricated using overoxidized PEDOT:PSS, a process known to break conjugation and thus, reduce electronic conductivity.[142] Coupled with PEDOT:PSS electrodes, organic electronic ion pumps delivers K^+ and Ca^{2+} to control signalling in neuronal cells.[143] They are also used to create pH gradient and proton oscillations, a highly interesting tool for lab-on-a-chip applications.[141] This technology is then adapted for implantable devices to directly deliver neurotransmitters to the auditory system of guinea pigs.[144] In recent years, research in the field has led to faster organic electronic ion pumps with smaller lag times between activation and delivery,[145] better selective delivery[98] (Figure 4d) as well as more versatile ionic exchange membranes.[146,147] More complex ionotronic circuit are also developed, such as diodes to improve speed of delivery and provide addressability of individual release sites[148] (Figure 3h). Additionally, conversion of an AC to DC flux of ions is realized by building a four-diode bridge rectifier circuit.[149]

The use of conductive polymers allows for the creation of fast and highly controlled drug delivery systems. As the technology relies solely on ions movement, issues linked to liquid microinjection such as increased pressure, chemical gradient disruption, or convection are entirely circumvented. Furthermore, implantable devices with addressable release sites are available thanks to advanced circuit architectures and standard microfabrication processes. This places organic electronic ion pump and its derivatives at the forefront of next-generation implants capable of influencing their bioenvironment through chemical release.

4.3. Neuro-Inspired Bioelectronics

Creating adaptive closed-loop systems such as brain-machine interfaces, implants, or prostheses requires the implementation of hardware-based devices capable of sensing biological activity, process these events, and control the biosystem. The processing capabilities are critical for enabling a seamless feedback on the organism and should be inspired by their biological counterparts. In that sense, neuro-inspired devices, such as artificial synapses, neurons, or nerves, emulate neuronal processing in an attempt to create more coherent biohybrid interfaces. Owing to their direct interaction with aqueous electrolytes, organic semiconductors have been implemented as devices capable of bioinspired computation[17,150] (Figure 3i). This section will focus on applications where neuro-inspired organic electronics are directly interfacing biological entities to create biohybrid systems.

In the neuronal system, synaptic connections serve as the primary means of communication between neurons. Thanks to their dynamic nature and continuous evolution in response to neural activity such as neurotransmitter releases, synapses are

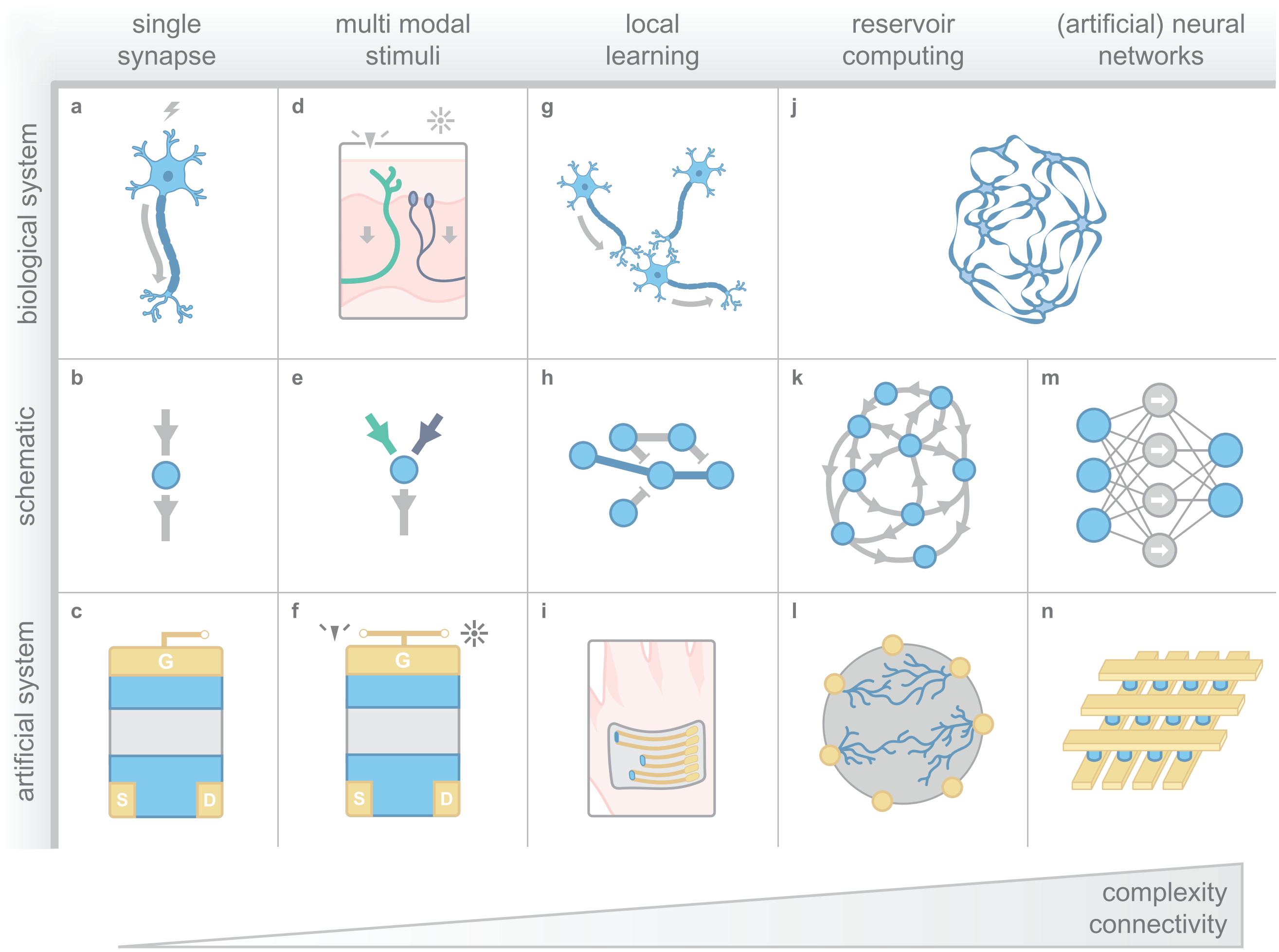

Figure 5. Analogies between biological systems and artificial systems including schematic representations. a) A biological neuron receives a stimuli and forwards it to the synapse. b) A schematic representation shows a neuron as a node and synapses as arrows. c) The organic EC-RAM functions as artificial synapse. d) Receptors for example in the human skin transfer different stimuli (touch and heat) via the neurons and synapses. e) One neuron is able to handle multiple inputs. f) The gate of one EC-RAM can also be connected to different sensor types. g) Biological neurons form connections with each other via synapses to transfer information from one place to another. These connections are adaptable and perform learning on a local level. h) Synaptic connections can strengthen or weaken over time which means they can locally amplify (excitation connection) or dampen (inhibitory connection) the initial signal. i) The EC-RAM is also able to adapt with incoming signals performing local learning in hardware. j) Big cluster of neurons form biological neural networks capable of performing complex tasks, the most impressive one being the human brain. Artificial counterparts can be distinguished between two type of networks: k) A network of nodes connected by random connections is called reservoir. l) Trough electropolymerization, branch-like organic polymer structures can be grown to create a random network. m) The second type is an artificial neural network that has structured, directed connections of different strengths between nodes connecting an input and output layer. n) Similarly, crossbar arrays can be used to handle vector-like inputs and process them via EC-RAM structures to an output line.

the first element to process biosignals.[151] This synaptic plasticity can be artificially reproduced by using a PEDOT:PSS OECT as a postsynaptic element.[99] Gate pulses induce short-term modulation by injection of ions in the channel, while long-term modulation is achieved thanks to the oxidation of dopamine present in the electrolyte. Neuron-like PC-12 cells are seeded with the artificial synapses, and exocytosis and endocytosis of dopamine are emulated by the addition of a microfluidic system (Figure 4e). Similarly, unidirectional synaptic coupling between live neurons is created by linking them with an organic memristive devices.[152] Action potentials are then evoked in one of the cells via patch-clamp stimulation, and gradually reduce the resistance of the memristive device, until eventually evoking a spiking activity in the second cell. Although the artificial synaptic connection shows more an off-to-on behavior rather than plasticity, this study provides evidence of unidirectional event-based coupling of live neurons.

Another essential element for neuro-inspired devices is the ability to encode information in a spike-based manner, to closely mimic biological processing and communication. Recently, organic oscillatory electronics have been used to create artificial spiking neurons (Figure 3j). An organic artificial neuron based on a S-shaped negative differential resistance shows spiking behavior modulated by ionic concentration.[19] Similarly to biological neurons, the organic artificial neuron displays spike latency and integration behavior. The firing frequency of the device exhibits sensitivity to ionic concentration and is therefore used to process the integrity of a biomembrane, showcasing the biohybrid nature of the artificial neuron. Another organic spiking neuron mediated by ionic species and based on a Axon-Hillock circuit is used to modulate the opening and closing of a Venus flytrap by changing the frequency of the electrical stimulus[18] (Figure 4f). In an effort to bring modulation to the stimulation, an artificial synapse based on electropolymerization of ETE-PC is introduced and shows paired pulse facilitation and depression as well as long-term potentiation and depression. Combining the artificial neuron and synapse allows to show spike-timing-dependent plasticity, where the synaptic strength significantly increases when the pre- and post-synaptic inputs arrive in sync, consequently increasing the firing frequency. However, firing of the postsynpatic input before the presynaptic one also induces increase of the synpatic weight.[151] Nonetheless, these examples demonstrate the necessity of establishing systems based on spiking to ensure seamless interaction with biology.

In our body, the somatosensory system allows the transmission of sensory information, such as touch, proprioception, temperature, or pain, between the peripheral receptors and the central nervous system.[151] Afferent nerve fibers are responsible for relaying signal from the sensory systems to the CNS and the creation of an artificial counterpart has naturally been explored. A fully organic artificial afferent nerve consists of a pressure sensor, a ring oscillator and a synaptic transistor.[7] The pressure is encoded in the frequency of the ring oscillator, which in turn modulates the postsynaptic current of the transistor. The combination of a cluster of pressure sensors to one ring oscillator allows the identification of braille characters thanks to the integrative nature of the synaptic device. The artificial afferent nerve is also connected to efferent nerves of a cockroach and emulates a reflex arc through pressure on the sensors. In an attempt to close the signal loop, an artificial efferent nerve, which conveys information from the CNS to the peripheral nervous system, is presented.[153] The input of an artificial synaptic transistor is modulated by a strain sensor mimicking proprioception, a natural feedback loop in the body that allows the sense of self-movement. In the absence of proprioception, degradation of the locomotion, and damage on the muscle are observed, and is therefore crucial to implement this aspect in artificial nerves. The neuromorphic efferent nerve enables bipedal walking locomotion in a paralyzed mouse, and its neurorehabilitation ability is demonstrated by using electropyhsiological signals to stimulate the flexor and extensor of a leg.

Organic neuro-inspired architectures will likely be a requirement for in situ closed-loop system and will help reducing the circuit's complexity while providing a more biologically relevant output. Artificial synapses will bring the adaptivity and learning thanks to their plasticity, whereas artificial neurons will introduce the spiking-behavior characteristic of the nervous system. While proof of concepts have already shown the full integration of artificial nerves capable of bypassing an injured tissue and producing natural locomotion movement, creating artificial biorealistic circuitry requires the involvement of biologists and neuroscientists in the early stages of conception. Moreover, more intense processing features will require fabrication upscaling. These points should be the main focus of future research on neuro-inspired bioelectronics.

5. Bio-Inspired Adaptive Sensing and Processing

Since the dawn of computing researchers have been trying to understand and replicate the immense skillset and power of the human brain and body. The breakthroughs in AI of the past decade have led to massive strides in handling complex tasks such as image classification and language processing and underline the huge potential of artificial bio-inspired systems.[2] Nevertheless, the efficiency and capability of biological systems remains unmatched by far.[1]

Conventional processing and control systems operate fundamentally differently from biological control systems. They are based on binary computations in a top-down architecture, while in nature information is conveyed via frequency-regulated ion transfer in locally connected structures. With recent advances in organic electronics, neuro-mimetic behaviors such as synaptic plasticity and spike-dependent behaviors have successfully been implemented in organic mixed ionic-electronic conductors[5,6,17] (Figure 6a).

Bio-inspired organic devices could potentially be the missing link between the ion-based, soft systems of nature and highly controllable and programmable computing systems.

Here, we analyze the recent efforts to move from biosensing and biohybrid organic devices to fully artificial organo-electronic nerve systems and brain-inspired computing.

To get a better understanding on how to replicate the powerful performance of the brain, we first look into the properties that makes it so unique.

The human nervous system is divided into two parts: the CNS that includes the brain and spinal cord and the peripheral nervous system (PNS). The peripheral nervous system connects all parts of the body to the central nervous systems and vice versa. Voluntary actions and body movement (such as muscle contractions) are controlled by the somatic or sensory nervous system of the PNS. Efferent nerves (coming from the CNS) transmit commands to the motor nerves that lead to muscle contractions and movement. Afferent nerves (leading to the CNS) relay information from the sensory neurons and their receptors.[154]

The CNS is the main computing hub of the body responsible for more complex assessments and predictions. It also defines abstract notions like intelligence, emotion, thought, memory, and personality and controls higher functions such as creativity, reasoning, and problem-solving. The CNS is highly adaptable and constantly adjusts to the current circumstances.[155] Both CNS and PNS consist of a densely connected, tunable network of neurons and synapses (**Figure 5**a,b,j).

5.1. Artificial Sensory Systems

Our environment provides a very rich and complex stream of information that cannot be grasped with a single type of sensor or sensory neuron. Already Aristotle divided the human perceptive system into the five senses: hearing, vision, taste, smell, and touch. Nowadays, balance and proprioception, which is the understanding of body position and self-movement, are considered a sixth sense. Yet we also experience different sensations within one sense, a meal can taste sweet, sour, salty, bitter, or umami.

This concept of sensory modalities subdivides our senses depending on the received stimuli, thus a distinct sensory receptor is required to handle the respective stimuli[156] (Figure 5d,e). The receptors can be classified in the following categories according to the received stimuli: mechanoreceptors (hearing, touch, balance, pressure), electromagnetic receptor (light/vision, temperature), chemoreceptors (smell, taste) and nociceptor (pain). Once a receptor is activated, it translates the characteristics of the initial stimuli, such as strength and duration into electrical impulse patterns that are transduced via the sensory neuron and further processed in the nervous system. Many of these receptors only process one type of stimuli while for example nociceptive neurons often integrate different stimuli into a multimodal pain/no-pain signal.[157]

To handle the abundant data of our environment, our peripheral sensory system declutters and restructures the received information in order to prevent an overload of computations in the central nervous system, primarily the brain. The sensory neurons conduct the electrical spikes generated at the receptor via synapses to the next neurons. The synapse plays a crucial role in conveying the information as it adapts the forwarded signal in regards to features of the incoming signal (strength, frequency) and prior experience (Figure 2a). It accounts for momentary variations (short-term plasticity) as well as changes over hours, days or months (long-term plasticity) (Figure 2c–g). That way, instead of forwarding every stimuli to the brain as a singular piece of information to process, the synapses already filter the data according to relevancy.[158]

In general, the synaptic activity is based on the stochastic process of releasing neurotransmitter into the synaptic cleft that causes a current between pre- and postsynaptic neuron. A higher number of incoming spikes increases the probability of releasing (more) neurotransmitter.[159] Additionally, each neuron is connected to thousands of other neurons forming a dense and redundant network.[155] This creates a system of high accuracy and incredible fault tolerance that is flexible to new inputs and robust against stochastic disturbances such as noise.

The sensory complex therefore operates as local sensing unit while simultaneously providing efficient information (pre-) processing in the periphery.

Because of this, the human body is almost effortlessly able to manage the vastness of its environment and to adapt to unexpected events, while most machines are still struggling with handling big data inputs[160] or adjusting to new situations.[161] With the recent advancements in AI, an ever growing data feed and an increasing demand for intelligent and autonomous applications, conventional computing systems are now more and more confronted with their limits. This is especially true for sensitive, highly complex tasks that require elaborate (data) handling while having limited energy and computing resources at disposal.

In taking inspiration from biological systems, artificial sensory systems can potentially offer more adaptivity, flexibility, robustness, accuracy, and energy efficiency for sensing, processing, and computing units. In the following, we explore the latest advancements regarding bio-inspired adaptive sensing and processing, focusing on state-of-the-art devices, and systems. An overview is provided in **Table 2**.

5.1.1. Single-Synapse Systems

The sensory receptor serves as a primary gateway for environmental stimuli and, along with the sensory neuron, constitutes the initial stage in a series of data processing procedures reaching up to the brain (Figure 5a,b,d,e). These receptors are crucial to gain an understanding of the surrounding environment, body position, and even personal well-being. They are essential for perception, movement control and understanding risk assessment.[176] Receptors specialized on the detection of neurotransmitter are generally found inside the synapse, but synaptic adaptation is an attribute that translates to receptors for other types of stimuli as well.[177] Embedding synaptic features such as spike-timing dependent plasticity (STDP), paired pulse facilitation (PPF), or long-term plasticity into artificial sensing systems can aid in filtering out repetitive or disorganized data. Recent literature[176,178,179] offers comprehensive reviews on (organic) synaptic sensing technologies. Here, we highlight specific examples to emphasize critical features of organic artificial synapses (Figure 5c,f).

An artificial neuron containing a tactile sensor (receptor), an ionic cable (axon) and a synaptic device (synapse) is able to distinguish between different spatiotemporal patterns.[162] The tactile sensor is made from carbon nanotubes in polydimethylsiloxane (PDMS) forming a resistive pressure pad. It is connected to polyvinyl alcohol based ionic cable that also operates as the gate dielectric of the synaptic OFET. The indium tungsten oxide OFET showcases spike voltage and spike duration dependent plasticity and paired pulse facilitation. Two pressure pads that connect to the gate dielectric are activated in different patterns. The conductance states of the synaptic transistor are clearly distinguishable based on the applied pattern. The artificial neuron is able to integrate and modulate spatiotemporal patterns of tactile stimuli with two pressure sensors coupled to one synaptic device (Figure 1e).

A different approach is taken by Qian et al.[163] Their synaptic OFET consists of a layer of copper-phthalocyanine deposited onto pentacene on SiO_2/Si substrate. The organic semiconductor is known for its sensitivity toward the air pollutant NO_2. Spike voltage dependent and STPD of the device is proven. Long-term changes of the synaptic behavior occur in the presence of NO_2. Low and high concentrations of NO_2 raise the postsynaptic current correspondingly. This process is also reversible by either applying the inverse/inhibitory gate voltage or by purging the air chamber to remove the pollutant. Furthermore, the device is integrated into a feedback control loop with two neuron units (non-inverting Schmitt-Triggers). The chamber can now be opened or purged depending on the activation of the neurons. This successfully simulates risk-response and avoidance systems of biological nervous systems.

While this system offers a unique realization of risk control, the sole presence of the chemical stimulant NO_2 is not enough to evoke a response. A continuous chain of voltage pulses with an amplitude of $\geqslant$20V at the gate is needed to maintain functionality. The event-driven computation and low voltage operation (mV) are essential traits of biological systems,[178] which this synaptic system falls short to replicate. Nonetheless, integrating a more conventional control loop (like Schmitt-Triggers) with an organic synaptic transistor counterbalances the stability

Table 2. Overview on organic devices used for adaptive sensing and processing tasks. Synaptic properties are noted as follows: excitatory/inhibitory postsynaptic potential (EPSC/IPSC) to showcase both synaptic potentiation and depression, spike voltage dependent plasticity (SV), spike duration dependent plasticity (SD), spike rate/frequency dependent plasticity (SR/SF), and paired pulse facilitation (PPF) as a two pulse example of SR/SF, short term memory (STM), long term memory (LTM).

Refs.	Type	(Semi-)Conductor	Gate insulator	Synaptic properties	Application/Sensor
[162]	OFET	indium tungsten oxide (IWO)	polyvinyl alcohol (PVA)	EPSC/IPSC, SV, SD, PPF	pressure
[163]	OFET	CuPc, pentacene	SiO_2	PPF, SV, LTM	NO_2/air pollutant
[164]	OFET	PBDTTT-C-T	P(VDF-TrFE)	PPF, SV, SD, SN, LTM	light and dopamine
[165]	OFET	ITO	PVA	SV, SD	pressure and light
[166]	solar cell	P3HT, perovskite	–	EPSC/IPSC, PPF, SD, SN, SF, SV	light
[167]	OFET	FT4-DPP:PEO	ion gel EMIM:TFSI with PS-PMMA-PS	EPSC, PPF, SV, SN, SF	light, polymer actuator
[168]	OFET	P3HT, PDMS	ion gel	PPF, STM, LTM	pressure, soft actuator
[169]	FET	ZnO		EPSC/IPSC, SV, SN, SR, LTM	pressure, electronic skin
[11]	OECT, EC-RAM	p(g2T-TT)	ion gel EMIM:TFSI, PVDF-HFP	STM, LTM	light/reflection, touch, actuator
[170]	ferroelectric OFET	PEDOT:PSS, P3HT	P(VDF-TrFE)	SN, SV, LTM	pressure/tactile, electronic skin
[10]	OECT, EC-RAM	P-3O	ion gel (EMIM:TFSI, PVDF-HFP), NaCl solution	LTM	in-sensor computing (simulation)
[171]	OECT, EC-RAM	p(g2T)	organo-hydrogel with NaCl	LTM	in-sensor computing (prototype and simulation)
[54]	OECT	PEDOT: PF_6	$TBAPF_6$	SF, fading LTM	reservoir computing
[172]	OECT	SPAN	water/humidity	SF, fading STM	reservoir computing
[173]	OFET	p-NDI	ionic gel	PPF, SR	reservoir and in-sensor computing
[30]	EC-RAM	PEDOT:PSS	Nafion	LTM	hardware neural network (prototype and simulation)
[174]	memristor	parylene	–	LTM	hardware neural network (prototype and simulation)
[175]	EC-RAM	P3HT	EMIM:TFSI	LTM	hardware neural network (prototype and simulation)

uncertainty that organic electronics still struggle with and delivers reliable and stable control systems.[180] The synaptic device is also ideally equipped for monitoring the air pollutant as the channel material itself functions as the receptor. The variety of nowadays available organic (semi-)conductors provides many options for choosing a suitable channel material respective to the application and in some cases there might be an opportunity to custom-make a functionalized material.[181]

Lee et al. take their artificial synaptic system a step further and combine chemical sensing and photodetection in a single device[164] (Figure 1e,f). Their artificial synapse is based on a dual-gated OFET architecture stacking the photoconductive polymer semiconductor PBDTTT-C-T between two insulators, SiO_2 on the bottom and P(VDF-TrFE) at the top. The photoconductive polymer shows ferroelectric (memory) characteristics in top gate configuration and hysteresis-free p-type transfer for bottom gate. Through capacitive coupling of both dielectrics in the dual-gate approach, the changes of the surface potential are amplified without the need of external amplification circuits. The top gate electrode is extended and functionalized to detect the neurotransmitter dopamine. A PDMS well on top of the extended top gate contains the liquid analyte. The synaptic device exhibits short-term plasticity, paired pulse facilitation, as well as long term plasticity. Upon exposure to light or dopamine, an increase in postsynaptic current is detected. Simultaneous exposure with both stimuli leads to an associative signal modulation mimicking the biological effect of improved cognitive performance due to light exposure.

Parallel processing of multiple sensory signals as demonstrated here is required for multimodal perception and facilitates the handling of more complex sensations (Figure 1d,f). The synaptic systems also performs rudimentary preprocessing in form of signal amplification. Using liquid analyte solutions as an electrolyte creates novel avenues for signal processing, such as global sensing and wetware/in-liquido computing.[182] This topic is discussed in greater depth in Section 5.2.3.

The development of single device systems represents the first step toward creating more complex synaptic systems. The incorporation of diverse types of sensory receptors (tactile, chemical, photo, etc.) demonstrates the flexibility and adaptability of organic electronics for this purpose.[162–164] They enable multimodal sensory fusion at the single device level with low-level processing comparable to biological sensory neurons. However, there is currently no clear roadmap for scaling up these single-synapse systems into larger network-like structures. This issue will be revisited in section 5.1.4.

5.1.2. Sensorimotor Systems

The interaction between sensing and movement is crucial in our ability to comprehend and learn about our environment and adapt to new settings. The environment is a complex source of information that must be explored before determining the best course of action[183]

The simplest form of sensorimotor interaction, known as sensorimotor integration, is achieved through the reflex arc. This direct link between sensory neurons, motor neurons, and the spinal cord bypasses the brain as a processing unit, resulting in faster response times and reduced computational load on the brain. The reflex arc serves as a basic mechanism for self-protection and risk management within our nervous system.[184] More voluntary muscle movements regulated by the somatosensory nervous system are influenced by multimodal sensory inputs, simultaneously these movements can alter our perception of the surroundings (active exploration).[185] Sensorimotor adaptation is inherently challenging because it requires coordinating multiple sensory inputs and memory of past experiences in real-time to achieve a particular goal.

Despite the increasing emphasis on active exploration in robotics, sensorimotor integration has yet to reach technological maturity. One of the most significant issues is the meaningful handling of sensory data.[186] The (multi-)sensory inputs need to contain information on the stimuli strength and localization. Ideally, this happens in real-time and allows for dynamic adaptions leading to local learning effects (Figure 1g–i). By moving from software to hardware-based systems, these characteristics can all potentially be embodied in the organic artificial synapse and initial implementations show promising results.

A light-triggered pupil reflex is replicated in an artificial organic sensorimotor system by Gong et al.[166] An optoelectronic synapse based on perosvkite and the organic polymer P3HT is constructed. The synapse regulates its postsynaptic current based on the light intensity and pulse duration. The dilation of the pupil is simulated with Ni–Ti alloy artificial muscle fibers. Through applying exitatory or inhibitory synaptic signals, the artificial muscle fibers either contract or dilate the pupil.

A different architecture of an optoelectronic synapse with sensorimotor integration is shown in ref. [167]. Visible light excites an organic photodetector, the electric signal is conveyed to a synaptic transistor based on FT4-DPP:PEO nanowires that activates a polymer actuator. The researchers also demonstrate temporal encoding of the input stimuli through short term memory. Each letter of the English alphabet in Morse codes shows a characteristic output amplitude. Handling multiple consecutive stimuli in a single device showcases the high accuracy and temporal robustness of the system. A similar setup with a tactile and a light stimuli is used for spatiotemporal integration.[165] Flexible organic synapses easily integrate into a soft and moving object without significant performance loss due to their inherent compliance. Inspired by the movement of the earthworm, Shim et al. developed a biomimetic soft robot that moves into defined directions upon tactile stimuli on the actuator.[168]

In addition to linking sensory input and motor output, the sensorimotor loop is also capable of long-term adaptation through changes in synaptic connections based on past experiences. In an experiment involving a robot navigating a maze, the sensorimotor loop was able to adapt through a reward-based system after a few unsuccessful attempts, showcasing real-time associative learning and long-term memory function[11] (**Figure 6**b).

Although these are only first implementations of sensorimotor learning in artificial organic synapses, they exhibit many of the missing features in current robotic research. Most robotic systems nowadays consist of rigid structures controlled by either complex computation-heavy learning schemes or fixed control algorithms. The combination of low power devices, local learning and soft-natured materials allow the development of autonomous biomimetic systems on mechanical and electrical level. Upscaling of these systems will show the true potential of organic electronics for active exploration.

5.1.3. Artificial Skin

Sensory and motor activities influence each other mutually through sensorimotor integration. In broader terms this means, the physical structure of a system shapes how it can react and behave in a certain environment. The material properties (i.e., a rigid robotic finger versus soft human finger) of a system define the dynamics of each interaction with the surroundings. This phenomenon is called embodiment.[187] The skin is our biggest external sensory organ and an ideal example of embodiment. It continuously provides haptic information about the environment. Human skin contains different type of sensory receptors that are distributed all over our bodies providing the most obvious form of embodiment[156] (Figure 5d). The different sensory modalities in the skin are helpful to get a deep understanding of the surroundings, but they also have a second function: self-protection. Through pain, the skin signals potentially dangerous situation, so damage can be prevented and precautions can be taken.[188] At the same time, the mechanical properties of the skin such as softness and texture enhance the sensory inputs. Grasping an object is much more difficult with a stiff gripper, and slip is easily detected through the friction ridges on the fingertips.[189]

These integrated safety features and the simplification of complex sensor inputs through mechanical design are highly desired qualities for robotics, artificial skin replacements and electronic skin as well. For now, robotic and prosthetic designs for interaction rely heavily on structured, well-defined tasks in constrained environments that are then analyzed in software.[190]

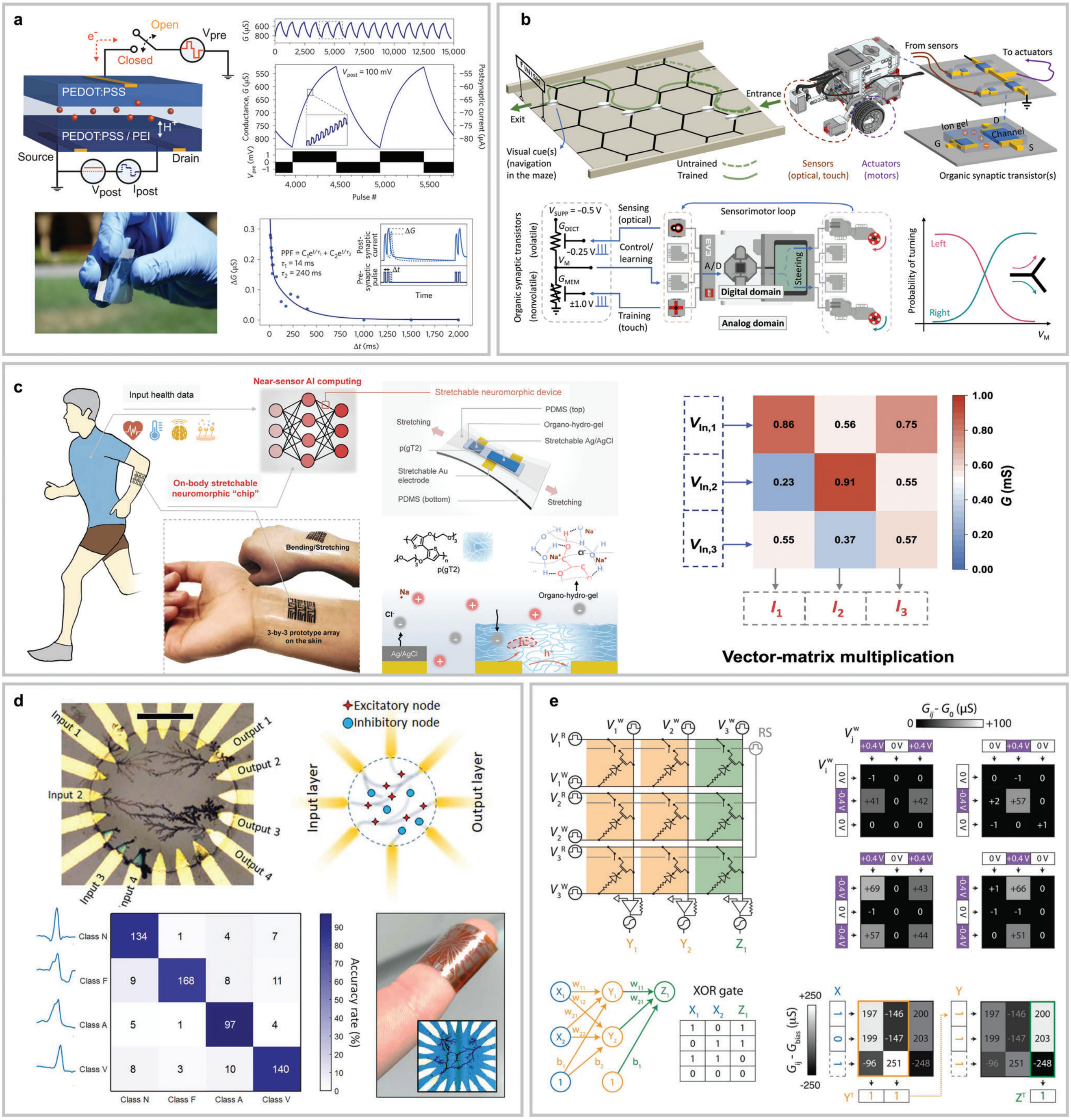

Figure 6. Examples of brain-inspired artificial systems. a) An artificial synapse based on PEDOT:PSS showcases synaptic plasticity. Reproduced with permission.[5] Copyright 2017, Springer Nature. b) Multimodal sensory inputs are used for intelligent actuation of a robot in a maze via an adaptive organic neuromorphic circuit. Reproduced under the terms of Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC).[11] Copyright 2021, The Authors, published by AAAS. c) A stretchable neuromorphic 'chip' shows highly stable computing performance and demonstrates on-chip vector-matrix multiplication. This type of wearable devices enables local learning and in-sensor computing. Reproduced with permission.[171] Copyright 2022, Elsevier Inc. d) PEDOT:PF6 fibers construct a dendritic network that possesses short-term memory with the ability to carry out non-linear transformations. Exploiting these characteristics, reservoir computing is implemented to classify biosignals such as ECG data. Reproduced under the terms of the Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC).[54] Copyright 2021, The Authors, published by AAAS. e) A 3x3 array of organic synaptic devices is arranged in a crossbar architecture to allow for parallel programming of multiple devices. This technology is potentially scalable to accomodate large artificial neural networks. Reproduced with permission.[30] Copyright 2019, AAAS.

The 'intelligent' mechanical properties (i.e., softness or structured surfaces) are difficult to achieve in artificial system based on brittle silicon. Conducting polymers on the other hand are easily fabricated in a flexible manner.[191,192]

A 4×4 array of dome-shaped soft structures based on two conducting polymers is proposed as electronic skin prototype.[170] The underlying OFET devices exhibit synaptic behavior that allows processing of incoming pressure stimuli. A simulation of an artificial neural network based on the synaptic devices is able to classify different pen-drawn input patterns and shows a high tolerance to input noise.

A larger array of 12x14 array of ZnO nanowire transistors demonstrates high stability even under bending conditions. Through associative learning via spiking pulses in a synaptic device, a robot arm acquires a pain reflex.[169] Larger arrays are needed to ensure good distribution of sensors and coverage of bigger areas.

An electronic skin made from commercially available components on a robotic hand is used to distinguish between round and sharp objects encoded in a software spiking system.[188] The spiking system is then connected with electrodes placed on the an amputees arm at carefully mapped regions of finger sensations. The amputee is able to feel the different types of objects similar to the feel with their own skin. The robotic hand is programmed to show an automated pain reflex in case of the sharp object as a measure of self-preservation. The spiking architecture is not only a biomimetic encoding of information, it is capable of accurately mimicking and replacing the response of human skin.

Embodiment and as such artificial skin supports and promotes intelligent information processing through large-area distribution of organic synaptic sensors. The mechanical design (softness, flexibility) additionally supports the processing of sensory information. Organic transistors provide the right interface for spike-based processing,[18,19] local learning with multimodal sensor inputs and allow fabrication on flexible, soft substrates. One remaining limiting factors, here is the poor scalability and device-to-device variability of the current fabrication processes (i.e., mechanical peel-off). For that, new reproducible fabrication techniques that allow for large-scale integration are needed. If it succeeds to bring all of these characteristics into a unified system, the realization of artificial electronic skin is one step closer to reality.

5.1.4. In Sensor Computing

The physical separation of sensors and processors in conventional electronics leads to an inherent bottleneck when moving data. The bandwidth and latency of the system are internal limiting factors. Most data also has a high level of redundancy that is only eliminated after being passed to the processor. This causes unnecessary energy consumption and strain on the transmission line. Additionally, a conversion from analog to digital domain is generally needed, which entails energy consumption and loss of precision. To reduce this huge data flux from sensors to computing unit, a shift from conventional computing architecture toward local processing has been proposed. In-sensor computing or on-site computing aims to perform low-level tasks (filtering, noise reduction, amplification, pre-assortment of data) and even more advanced computations like classification within or close to the sensory device.[193] Local computation can lower the data load toward the main processor and thus increases the energy efficiency of the system. Besides data transfer is not without risks, especially when working with sensitive biometric data (i.e., heartbeat). With in-sensor computing, many safety and cybersecurity concerns can be bypassed since the goal is to process most data before it leaves the sensor. At the same time, a direct processing of data also eliminates sources of noise that can occur in the system. Sensor-rich systems (autonomous vehicles, intelligent robots, wearable electronics) show a high potential for a profitable implementation of in-memory computation (Figure 5g,h). The unique combination of biocompatibility, flexibility, and low voltage (neuromorphic) operation makes conductive polymers particularly interesting for the realization of autonomous and wearable smart sensing systems (Figure 5i).

Initial implementations of a wearable sensor based on conductive polymer PEDOT:PSS are used to monitor cortisol and ion concentrations in human sweat,[83,194] this concept can be extended to other fluids and gases.[195] The patches adhere directly to the human skin without causing irritation due to the biocompatible nature and flexible design (Figure 5i).

An organic (P-30) inverter with a neuromorphic component amplifies the electrocomyography signal of different hand gestures while preserving the defining envelope.[10] The different gestures require distinct amplification that is adapted through the tunable response of a neuromorphic element. A simulation of 125 organic neuromorphic elements organized in an artificial neural network classifies five different electrocardiography signals with close-to-software accuracy. A similar concept is introduced by ref. [171]. They also provide a proof-of-principle 3x3 array of organic transistors that showcases vector matrix multiplication need for artificial neural networks and withstands strong stretching without forfeiting performance (Figure 6c).

This illustrates the strength of fusing in-sensor computing and wearable organic technologies toward smart autonomous sensors enabling personalized high precision health monitoring and chronic implants.

However, the proposed fabrication methods for these wearables rely on techniques (blade coating, isolation by razor cut, dropcasting) and components (paste, liquid electrolyte) that are not suited for larger-scale integration of these devices. This makes it difficult to move beyond proof-of-principle demonstrations.

A similar issue emerges when looking at long term stability and safety in performance. While many implementations speak of high performance metrics (on-off ratio, state retention, linearity, number of conductance states) for organic transistors, measurement conditions often present idealized (i.e., under inert gas) or custom-tailored (i.e., varying length for long-term state retention, preconditioning of devices). There is no agreed protocol for standard measurement that not only makes it difficult to compare devices but also limits the meaningfulness of the measurements. Additionally, many (semi-)conducting polymers are not commercially available (yet) that obstructs research efforts and limits benchmarking attempts.[196] For now, it remains very difficult to make predictions about the long-term performance and safety, a key requirement when moving toward in-sensor on-/in-body computation.

5.2. Neuromorphic/ Brain-Inspired Computing Systems

After the (artificial) sensory system takes in the relevant data and forward it to the central nervous system, huge networks of cells or devices are needed to perform further processing (Figure 5j,m). Artificial neural networks kick-started the revolution of software AI, but now the research focus is also shifting to hardware-based network architectures.[197] While a lot of simulative research is being conducted in this field, this review focuses on physical implementations of such computing systems with real-life applications.

5.2.1. Neuromorphic Crossbar Arrays

Artificial neural networks and machine learning have become a very important tool for data analysis over the last decade (Figure 5m). With an ever-growing data feed, the reliance on AI is expected to thrive even more. However, with the continuous use, the drawbacks also become more obvious: large memory storage and high energy demand. One solution looks at applying computing principles similar to the ones the brain uses. Performing computing within a single device that also stores information is referred to as 'in-memory' computing. This solves two problems: first, the data transfer between computing and memory unit is eliminated and analogue data is processed directly. Second, computations can run in parallel using physical laws (Kirchhoff, Ohm).[198] Crossbar arrays offer the ideal architecture for this, enabling vector-matrix multiplication between input and output lines (Figure 5n).

Via read and write pulses, the state of the devices changes per column and row allowing massive parallelization of the update. Access devices (switch, transistor etc.) are often required to enable or block the connection to the memory elements. Other requirements for operation are: linear switching behavior for predictable states, low read, and write currents for low energy consumption, prevention of sneak paths, high number of low-noise conductance states for stable operation.[198]

Three terminal devices such as the organic transistor decouple read and write pulse by design that allows for write currents below 10nA that overcome conventional computing efficiency. The conductive polymers are easily adapted to their purpose, by adding chemical additives the overall resistance and threshold voltage are adjusted to the system's demands.[30] In a 3x3 array, the nonlinear XOR function is realized via parallel programming (Figure 6e). The device performance is highly linear. A simulation of 1024x1024 devices for MNIST classification shows software-like accuracy. Similar small-scale implementations of physical crossbar arrays have been shown, but never exceeding an array size of 3×3.[171,174,175]

Most of the research for large-scale integration is still conducted in simulation,[10,30,171] as the fabrication technology is still advancing. Many parameters regarding channel material and electrolyte are not yet perfected and need to be investigated further. This leads to a high device-to-device variability that makes it almost impossible to control neuromorphic devices in a collective update, as each device reacts differently.

At the same time, many neuromorphic crossbar arrays are designed to follow existing computing algorithms, but this dismisses and excludes the use of unique device characteristics. Inherent stochasticity and slower dynamics (μs to ms) are for example attributes present in the brain that are typically discarded as undesired. Collaborative research efforts across multiple disciplines (engineering, computer science, neuroscience, biology, mathematics) are required to develop new computing algorithms.

5.2.2. Spiking Neural Networks

Biological neurons encode and transfer information through discrete action potentials known as "spikes". This makes neuron effectively "active" only when they receive or fire spike trains, making them event-driven and time-dependent functional units. Sparse and efficient information encoding through spikes is thought to be one of the main reasons for the high energy efficiency and robustness to noise displayed by biological neural networks.

Most software and hardware neural networks employed today adopt a non-spiking information transfer.[199] However, inspired by the efficiency of biological neurons, in the last decades several efforts have been made to implement neuromorphic hardware as artificial spiking neural networks, encoding information through discrete spike events rather than real-valued numbers (as in classical artificial neural networks).[200,201] Given the fact that spikes are discrete and non-differentiable, conventional learning algorithms based on gradient back-propagation cannot be applied on this type of networks (see Section 6). However, spiking neural networks allow to leverage STDP, a local learning rule that modifies the synaptic strength based on the relative timing of the spiking activities of the two connected neurons. In particular, if the pre-synaptic neuron fires just before the post-synaptic neuron, the connection is strengthened, while if the pre-synaptic neuron fires just after the post-synaptic neuron, the connection is weakened.

Spiking neural networks have already been implemented in hardware with conventional CMOS processes, such as, to name but a few, the Loihi,[202] and SpiNNaker[203] manycore processors. More recently, implementation of spiking neurons leveraging organic electronics have also emerged.[19,204] However, the step toward an organic spiking network still has to be made. Thanks to their event-driven functioning, spiking neural networks will prove useful in embedded systems, and enable edge computation and ubiquitous intelligence.[200]

5.2.3. Reservoir Computing

Even though brain-inspired computing systems have already succeeded in integrating biomimetic computing paradigms such as synaptic plasticity and spiking encoded information processing, a few crucial factors are still missing: mainly global connection and stochasticity. In the brain, there is a very high connectivity between cells including many unordered and redundant connections between them. The high redundancy allows the brain to perform multiple tasks at once, hence it processes a variety of information in parallel.[205] Additionally, brain cells all operate in the same wet' environment, which additionally couples them via a global electrolyte. This allows cross-talk between the cells and

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introduces noise and stochastic components into the system. The synapse itself also operates by stochastic release of neurotransmitter vesicles.[159]

With reservoir computing a new concept based on recurrence and randomness was born.[206] A (fixed) network of randomly linked nodes (the reservoir) maps an input signal into a higher dimensional space via non-linear transformation in the reservoir (Figure 5k). The dynamics of the reservoir network are fixed, random, and incorporate transient behaviors such as fading memory/echo states (short-term memory). The output signal of the reservoir provides now-separable states that are forwarded to a simple trainable read-out mechanism for classification.[207] Physical reservoirs for computing take advantage of natural phenomena with non-linear behavior (i.e., water ripples).

Conductive polymers have recently proven themselves as great candidates for physical reservoirs. Through electropolymerization of monomer TEDOT, electrodes are covered with TEDOT-polymer films of varying morphology forming OECTs. The difference in structure also results in a stochastic influence regarding electrical performance. For the same input signal of two distinct wave shapes (triangle and square), each of the twelve OECT devices has a unique output characteristic. The output signals of the OECTs are fed into a simple network to classify the wave types with very high accuracy.[208] Further analysis shows that the high variability of devices is indeed needed to perform well at the classification tasks. This bottom-up assembly of highly variable devices through electropolymerization forms a stark contrast to the normally desired precise top-down fabrication of uniform devices, but in this case the non-uniformity plays in favor of the system.

A physical reservoir with redundant and recurrent connections is introduced by Cucchi et al.[54] They grow a non-linear, dendritic network of OECTs through electropolymerization of PEDOT:PF6 (Figures 5l and 6d). The PEDOT:PF6 fibers connect through a global electrolyte allowing cross-talk and form excitatory (bridges) and inhibitory (dead-ends) branch architectures. The dendritic reservoir performs non-linear transformations of time-series data as proven with sine wave frequency transformations. It is then used to perform several computations tasks in combination with a linear regression model in software: (flower) classification and (stock market) time series prediction. As final test, biosignals such as arrhythmic heartbeats are classified with an accuracy of 88%. The reservoir system proves itself as very energy efficient, biocompatible computing system that needs only minimal training.

A similar application employing a nanoscale reservoir network of sulfonated polyaniline is shown in ref. [172]. They demonstrate an accuracy of 70% for the classification of cochleagrams by using the non-linear transformation of the reservoir in combination with ridge regression.

An all-organic-based system demonstrates a larger-scale implementation for classification tasks.[173] The light-reactive semiconducting polymer p-NDI shows fading memory characteristics as OFET that allow the implementation for reservoir computing. The reservoir is organized as a crossbar array. The analysis of the reservoir output signal is handled by memristive organic diodes. The fully-organic system achieves an overall accuracy of 88% for classifying the MNIST and FMNIST data sets. It is however unclear, how the recurrency and high variability of devices are achieved in the reservoir.

Reservoir computing is a great example of material-algorithm co-design. The strength that comes from adapting algorithms into or for specific computing systems becomes apparent in the high energy efficiency and simple (re-)trainability of reservoir systems. It is important to give more thought to the meaningful interaction and fusion of device operation and learning algorithm.

6. Learning Algorithms for Neuromorphic Applications

In the fast growing field of organic neuromorphic computing, much emphasis has been put on the development of new, synapse-like materials, trying to reproduce some of the biophysical features of biological neurons.[1,4,209] This led to a large variety of neuro-inspired materials and devices, each with unique characteristics, such as operation speed, energy consumption, and resemblance to their biological counterpart. However, this has not yet been followed by device standardization, characterization, and their systemic integration into larger ensembles of connected devices. To implement complex behaviors and functions with organic neuromorphic devices such integration and scaling are essential, and they must be accompanied by the development of novel learning algorithms.[210]

Currently, research into neuromorphic learning algorithms is still lagging behind compared to the effort put into developing new (organic) neuromorphic systems for two reasons.[4,211] First, much of the neuroscience research in the past years has focused on dissecting the structures responsible for cognitive tasks in the brain, but to date, we still have a poor understanding of how complex cognitive functions emergence from a network of local synaptic interactions.[212,213] Second, contrary to neural networks implemented in software, the variety of neuromorphic devices and their characteristics entails that there is no one-size-fits-all algorithm that can be applied to train these devices.

What made the use of software neural network possible and ubiquitous for AI applications was the combination of the backpropagation algorithm and optimizers based on gradient descent.[214] Although several variations exist, most of the software neural networks that are employed today are trained with these two algorithms. However, reproducing these two methods in hardware neural networks without involving some form of digital computation is not trivial.[210,215–217] Backpropagation requires complete knowledge of all computations in the forward pass and memory to store their results, while gradient descent requires to compute the derivatives of a differentiable mathematical model. Moreover, software neural networks are all based on digital representations of their weights, while hardware neural networks store them exploiting different physical phenomena.[218,219]

Given the variety of architectures and materials used in neuromorphic computing, new learning algorithms need to be co-designed together with their hardware counterpart.[215] In this way, the learning algorithm can be tailored to the characteristics of the operating devices, such as number of states, (non)linearity, noise, switching mechanism, and energy required per state switch.

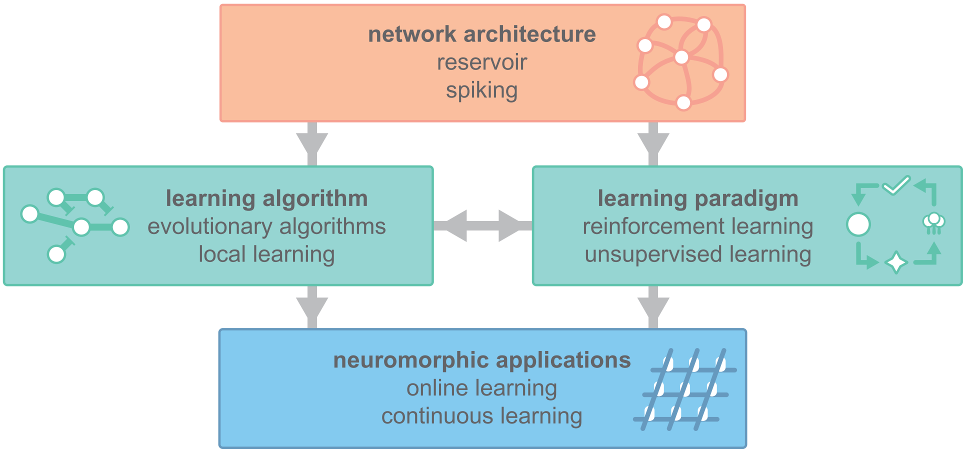

Figure 7. Schematic representation of the elements that constitute a neuromorphic application. The architecture of the network constrains the choice of learning algorithm and paradigm. The latter two in turn interact to train the network and achieve successful neuromorphic applications. In each box, examples of approaches that are alternative to the ones established in the literature for software neural networks are reported.

Neuromorphic computing offers the opportunity to go beyond the dominant paradigm in software neural networks, that is, supervised learning in deep networks trained with backpropagation. We envision that organic neuromorphic applications could benefit from the investigation of novel approaches in three different areas of neuromorphic computing (**Figure 7**):

- different network architectures, such as spiking and event-driven networks and reservoir computing;
- different learning algorithms, such as the ones not involving gradient computation and global information sharing;
- different learning paradigms, such as unsupervised and reinforcement learning, and their application in online and continuous on-chip learning.

While neuromorphic architectures were already discussed in Section 5.2, we discuss opportunities and challenges offered by different learning approaches in the following sections.

6.1. Gradient-Based and Gradient-Free Learning

The backpropagation algorithm allowed to scale up the size of software neural networks, efficiently training large networks of mathematical transformations in the digital domain to achieve complex tasks.[2,220,221] Neuromorphic devices embody these transformations in hardware, by exploiting physical processes that are in principle isomorphic to their digital representations. As a consequence, many neuromorphic devices are trained on conventional computers, by performing digital computations and then mapping the digital network's weights to their physical counterparts.[5,222–224] However, performing the training of the neuromorphic devices on a digital machine poses two main drawbacks: digital operations are slower and less energy efficient than in hardware operations, and the mapping between the "physical" and digital weights is not always straightforward, as the latter do not take into account noise and non-linearities typical of physical systems. Several methods are being developed to address these challenges in non-organic neuromorphics, some of which could also be applied to organic devices.

In ref. [216], the authors present a general-purpose, physics-aware training framework that addresses these challenges by using mismatched forward and backward passes while training with backpropagation. The forward pass is performed directly in the hardware, while the backward pass is executed on a digital machine that employs a differentiable computational model of the neuromorphic device and the outcome of the forward pass to calculate the gradients of the loss function with respect to the trainable parameters. The physics-aware training outperforms fully digital training (even when employing the same computational model) in classification tasks using neuromorphic devices implemented with mechanical, electronic, and optical devices, thanks to the energy-efficient, in hardware execution of the forward pass accounting for noise and non-linearities. However, this method still requires an accurate and differentiable computational model, which might not be readily available, and the calculation of the gradients on a digital machine.

To avoid the use of digital simulations, Zhang et al.[225] introduce a novel on-chip learning algorithm for multilayer neural networks implemented on resistive random access memory neuromorphic devices. The algorithm, named sign backpropagation, is based on the idea of backpropagating the sign of the error between the device output and the data label, using this information to perform discrete updates of the resistive memory states. Such backward pass is implemented with auxiliary logic circuits, which allow the neuromorphic devices to converge and achieve state of the art accuracy on the MNIST dataset. Albeit its scalability needs to be proven, the use of limited information during the backward pass could inspire new learning algorithm for devices where complete knowledge on the errors' gradients is not available, such as in organic neuromorphic devices.

As mentioned before, other optimization algorithms can be employed to learn the network weights without the need of gradient information. Such gradient-free strategies generally rely on the use of global optimization algorithms[226,227] or reinforcement learning,[228] which treat the neuromorphic device as a "black box" performing the inference phase of the learning. As a consequence, such algorithms do not need detailed information regarding the physical properties of the devices or the errors' gradients, and they can naturally incorporate sources of physical noise in the inference phase performed on-chip, something that is hard to achieve with offline digital modeling. For example, in ref. [229] the authors develop a physics-agnostic, gradient-free learning framework based on a genetic algorithm[230] to train optical neural networks. Genetic algorithms take inspiration from natural selection to evolve a population of candidate solutions by means of "genetic operators" (namely crossover, and mutation) until an optimum is reached. Thanks to their ease of implementation and lack of complex mathematical operations, the authors implemented a genetic algorithm on an auxiliary digital circuit used to train and control the optical neuromorphic chip. The results show that the learning algorithm exploiting the genetic algorithm outperforms digital training based on gradient descent, in classification tasks across different datasets (iris, MNIST, CIFAR-10), and across several device architectures. Moreover, the genetic algorithm-based method scales better in terms of power consumption and latency time with increasing neural network sizes. Thanks to these characteristics, genetic algorithms and other gradient-free algorithms are a valuable tool to perform on-chip learning, and they could be used to train organic neuromorphic devices in supervised or reinforcement learning schemes.

6.2. Reinforcement and Unsupervised Learning

Most of software neural networks that are being used today are trained with a supervised learning paradigm, that is, they learn from large datasets comprising labeled examples. Albeit very successful in some fields (for example, in image recognition), this paradigm also presents a few drawbacks that hinder its applicability on neuromorphic hardware. Labeled datasets require a larger storing capacity, and for many real-world datasets labels are not readily available or time-consuming to obtain, such as for biomedical applications. Moreover, supervised learning inherently requires to separate the training phase from the performance evaluation phase. Different learning paradigms exist, that can address these limitations and widen the range of applicability of neuromorphic devices, namely unsupervised learning and reinforcement learning.

In reinforcement learning, an intelligent agent learns a series of actions that maximizes cumulative rewards (or minimizes punishments) provided by the environment it interacts with.[228] This paradigm proves to be particularly successful for neuromorphic applications: on the one hand, it allows for gradient-free learning, while on the other hand neuromorphic hardware can interact directly with the real environment to get rewards or punishments. For example, Amaravati et al.[231] present a mobile robot able to learn to avoid obstacles thanks to a CMOS-based spiking neuromorphic chip, coupled with digital circuits and a digital microprocessor implementing a reinforcement learning procedure. Similar approaches have proven successful as well in the field of organic neuromorphic,[11] and they could be further exploited by coupling reinforcement learning and gradient-free learning algorithms to train larger networks and achieve more complex tasks.

In ref. [232], the authors present a learning-to-learn framework for training neuromorphic hardware. Learning-to-learn consists of two nested optimization procedures: an inner optimization loop, where a (hardware) neural network is trained to solve a specific task; and an outer loop that optimizes the learning performance across a range of different tasks. This framework endows artificial learning systems with transfer learning capabilities, making it possible to faster achieve better performances for a wide class of similar tasks. These two loops learn features at different time-scales (the inner loop being the faster one, and the outer loop the slower one), mimicking many learning processes that can be found in nature, such as evolution/adaption dynamics and fast/slow learning in the amygdala and striatum regions of the brain.[228] Specifically, in ref. [232] the inner learning loop involves a reinforcement learning problem, while the outer loop is implemented as an evolutionary strategy, a gradient-free algorithm that emulates evolutionary processes[233,234] similarly to genetic algorithms (previously discussed in Section 6.1). By training a CMOS-based spiking neural network, the authors show how learning-to-learn can improve both speed and performance of reinforcement learning, while, at the same time, producing intelligent agents that can extract abstract knowledge from previous experiences and speed up the learning of new, but related tasks.

Given how organic neuromorphic devices display memory effects at different time-scales, and they can naturally interact with reward/punishment molecules present in biological nervous systems (such as neurotransmitters), we argue that reinforcement learning approaches could be readily leveraged to train such devices.

Unlike supervised and reinforcement learning, in unsupervised learning the learning agent is tasked with forming homogeneous groups out of unlabeled data, a process known as clustering, in order to capture emerging patterns within the dataset. Several attempts have been made in the software domain to train neural networks in an unsupervised fashion, resulting in methods such as self-organizing maps[235] and neural gas.[236] Both of these methods exploit lateral connections between the neurons that enable the synaptic weights to self-organize and map data into a lower feature space, forming clusters.

Specifically, the goal of unsupervised learning is to have neurons that are close in the network to fire together in response to similar groups of input data, while neurons that are further away in the network should fire in response to different types of data. This emerging behavior is achieved by means of two types of lateral connections: excitatory connections, if the highest firing neuron promotes firing of its neighboring neurons; inhibitory connections, if the highest firing neuron decreases activation of the other neurons (winner-takes-all). Such connections are inspired by learning phenomena observed in biological neurons, such as STDP.

Lateral inhibition/excitation was exploited to implement unsupervised learning on neuromorphic hardware implemented on conventional CMOS processes. Diamond et al.[237] develop an unsupervised neuromorphic clustering algorithm that operates on CMOS-based spiking neuromorphic hardware. The neuromorphic network consists of three layers of spiking neurons, connected with synapses endowed with STDP. In the last two layers, each neuron is also connected to its neighboring neurons in the same layer by means of inhibitory lateral connections, ensuring a "winner-takes-all" effect once the neuron is fired. After training, this system achieves clustering performance comparable to state-of-the-art digital algorithms, such as self-organizing maps, neural

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gas and k-means, when tested on the MNIST dataset. A similar approached is followed in ref. [238], where a resistive random access memory crossbar array displaying lateral inhibitory connections is trained using STDP and reached high test accuracy on the same dataset. Existing examples of unsupervised learning in organic neuromorphic hardware are mainly based on STDP, and have been demonstrated only at single-device level.[239–241] Learning with STDP in organic spiking networks has been demonstrated only by means of computational analyses.[242]

We argue that incorporating lateral connections and implementing unsupervised learning paradigms to enable self-organization of network weights may have significant advantages for organic neuromorphic devices. Inhibitory connections and winner-takes-all behaviors could effectively limit the cross-talk between synapses that frequently affects large networks, by "silencing" non-firing neurons. Weight self-organization could reduce the effects arising from device-to-device variability, by having synapses adjust their state on the basis of the other networks units surrounding them.

6.3. Online and Continuous Learning

Learning in the brain is inherently time-dependent, and our brains continuously receive sensory stimuli and, at the same time, learn from them, without a clear separation between training and inference phases. Many modern AI applications deal with continuous data streams as well, such as autonomous vehicle control and smart health monitoring devices.[217] Thanks to their physical implementation, inherent parallelization, and the fact that they can be physically connected to sensory systems, neuromorphic devices represent a promising tool to continuously learn from data streams.

Significant efforts in this direction have already been made with CMOS-based neuromorphic hardware. Imam and Cleland[243] show the implementation of an online learning algorithm on a neuromorphic olfactory circuit implemented on Intel Loihi neuromorphic hardware. Specifically, the algorithm exploits STDP to train the chip to recognize different odourants from the activity of chemosensor arrays mounted in a wind tunnel. The authors show that the algorithm can efficiently train the hardware in distinguishing up to ten different chemical species, with performances comparable to digital processing and digital deep neural networks. The neuromorphic approach outperforms digital neural networks when tasked with one-shot or few-shots learning, and in online and continuous learning settings, it displayed the ability to generalize beyond experience. Remarkably, contrary to digital networks, the neuromorphic chip maintains the memory of previously learned patterns after training on new ones. Learning on neuromorphic hardware could prove useful in embedded systems deployed in unpredictable environments, where rapid, robust, and energy efficient learning matters.

Continuous learning algorithms can also be used to mitigate some of the limitations affecting organic neuromorphic hardware. In ref. [244], the authors design a computational model of a crossbar array consisting of PEDOT:PSS synapses to demonstrate how algorithm-hardware co-design can efficiently counteract state loss and self-discharge due to parasitic reactions in electrochemical synapses. The authors use periodic reminder pulses to restore the programmed state on the synapses, showing how these pulses can be tuned to maintain high classification performance with a limited increase in energy cost. However, long-term forgetfulness could also be exploited as useful feature in continuous learning, for example to erase learned patterns that are not useful anymore, or to achieve learning at different time-scales.[228]

Given their characteristics, neuromorphic hardware and algorithms could open the way to online and continuous learning in a more accurate and energy efficient way when compared to digital software implementations. Organic neuromorphics in particular could be exploited for continuous learning tasks in soft robots, in bio-hybrid applications, and in wet-ware sensing and computing devices.

7. Challenges and Outlook

The field of organic electronics has made significant advancements in the last decade, especially in the design of novel bio-inspired and biomimetic materials that found applications in smart sensors and neuromorphic hardware. However, several challenges still lie ahead and need to be addressed in order to achieve reliable, fully-integrated sensing, and neuromorphic devices displaying complex computing capabilities.

The introduction of novel CPs should be accompanied by thorough characterization of their physicochemical properties. In this regard, computational modeling can further improve our understanding of polymer properties and possibly guide material design. Taken together, modeling, and characterization will facilitate the standardization of device fabrication and measurements, and help in establishing common benchmarks to test their performances. Although a call for standardization was previously made,[13,22] additional efforts are required in order to truly achieve it.

Characterization of CPs and standardization of fabrication will allow to scale up the integration of several computing/sensing units into single devices. Moreover, they might prove useful in tackling the limitations that still affect the integration of many devices into a monolithic system, such as parasitic currents and device-to-device variability. Having multiple, integrated computing units will be fundamental to increase the computational power of the organic devices and making them able to implement more complex behaviors for smart sensing and neuromorphic applications.

The design of learning algorithms for organic neuromorphic applications poses some new challenges as well. Differently from software neural networks, learning algorithms based on gradient calculation and backpropagation are difficult to implement on neuromorphic hardware, due to limited memory capacity and the requirement for global information sharing to communicate neural activities across the entire network. In contrast, biological neural networks exhibit local synaptic plasticity, where synapses have access only to the activity of upstream and downstream neurons they are connected to. To overcome these limitations, research efforts need to go beyond the paradigm established by software neural networks based on supervised learning and backpropagation. Several approaches based on gradient-free optimization and local information processing already exist in software, but their application in hardware has yet to be fully investigated.[229,245,246] More in general, learning algorithms need to be co-designed with novel organic hardware, so that the former can exploit the peculiar features of the latter.

Organic electronics offers the unique opportunity to implement smart sensors and neuromorphic devices that interact with or mimic living matter, thanks to its soft-nature, the ability to be chemically functionalized, and act as an ionic transducer. We envision that such devices will prove useful in hybrid biomachine interfaces, to implement smart wetware able to compute in liquid environments and inside or in contact with living organisms. The scale-up of device integration and better learning algorithms will pave the way to smart point-of-care devices, implants and prostheses,[247,248] bio-mimetic robots,[168] and computing systems able to perform classification and neuro-optimization.[10,249,250]

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Conflict of Interest

The authors declare no conflict of interest.

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