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PERSPECTIVE

From neuromorphic to neurohybrid: transition from the emulation to the integration of neuronal networks

Ugo Bruno[1,2,5], **Anna Mariano**[1,5], **Daniela Rana**[3,4,5], **Tobias Gemmeke**[3], **Simon Musall**[4] **and Francesca Santoro**[1,3,4,*]

1 Tissue Electronics, Istituto Italiano di Tecnologia, 80125 Naples, Italy
2 Dipartimento di Chimica, Materiali e Produzione Industriale, Università di Napoli Federico II, 80125 Naples, Italy
3 Faculty of Electrical Engineering and IT, RWTH, Aachen 52074, Germany
4 Institute of Biological Information Processing—Bioelectronics, IBI-3, Forschungszentrum, Juelich 52428, Germany
5 These authors have equal contribution.
* Author to whom any correspondence should be addressed.

E-mail: f.santoro@fz-juelich.de

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Abstract

The computation of the brain relies on the highly efficient communication among billions of neurons. Such efficiency derives from the brain's plastic and reconfigurable nature, enabling complex computations and maintenance of vital functions with a remarkably low power consumption of only ∼20 W. First efforts to leverage brain-inspired computational principles have led to the introduction of artificial neural networks that revolutionized information processing and daily life. The relentless pursuit of the definitive computing platform is now pushing researchers towards investigation of novel solutions to emulate specific brain features (*such as* synaptic plasticity) to allow local and energy efficient computations. The development of such devices may also be pivotal in addressing major challenges of a continuously aging world, including the treatment of neurodegenerative diseases. To date, the neuroelectronics field has been instrumental in deepening the understanding of how neurons communicate, owing to the rapid development of silicon-based platforms for neural recordings and stimulation. However, this approach still does not allow for *in loco* processing of biological signals. In fact, despite the success of silicon-based devices in electronic applications, they are ill-suited for directly interfacing with biological tissue. A cornucopia of solutions has therefore been proposed in the last years to obtain neuromorphic materials to create effective biointerfaces and enable reliable bidirectional communication with neurons. Organic conductive materials in particular are not only highly biocompatible and able to electrochemically transduce biological signals, but also promise to include neuromorphic features, such as neuro-transmitter mediated plasticity and learning capabilities. Furthermore, organic electronics, relying on mixed electronic/ionic conduction mechanism, can be efficiently coupled with biological neural networks, while still successfully communicating with silicon-based electronics. Here, we envision neurohybrid systems that integrate silicon-based and organic electronics-based neuromorphic technologies to create active artificial interfaces with biological tissues. We believe that this approach may pave the way towards the development of a functional bidirectional communication between biological and artificial 'brains', offering new potential therapeutic applications and allowing for novel approaches in prosthetics.

1. Introduction

The brain is one of the most complex and efficient systems found in nature. It is able to sense, process and propagate stimuli while ensuring all the vital functions of the human body, on an energy budget of ∼20 W [1]. Such efficiency derives from the brain's dynamical and reconfigurable structure with billions of neurons, passing information to each other via trillions of synapses [2]. The brain is also highly plastic and possesses the remarkable ability to continuously reshape its numerous synaptic connections to allow an efficient representation of new information and signal propagation as we experience novel inputs and acquire new skills. The efficiency of the brain is therefore not dependent on the activity of single neurons, but rather the complex functional connections across large neural networks [3], making the brain remarkably robust [4] as it can flexibly reconfigure neural interactions to optimize its function [4]. By imitating features typical of biological neural networks (BNNs), artificial neural networks (ANNs) have been developed, in which billions of simulated neurons are connected in different topologies to perform complex tasks, such as object recognition and task learning beyond human performance levels [5]. ANNs have deeply revolutionized the information technology field, leading to the development of more optimized and autonomous artificial intelligence systems [6]. However, since ANNs run on classic Von Neumann machines, they require a very large amount of power even when running on optimized hardware, such as on graphical processing units (GPUs) [7]. To resolve this problem and better approximate energy efficient BNNs, spiking neural networks (SNNs) were developed in which computations are asynchronous and not synchronized by an external clock. SNNs can run on neuromorphic processors that allow analog-like asynchronous communication [8] and several commercial solutions are now available (Intel Loihi, IMB's TrueNorth, SpiNNaker) [9]. Furthermore, significant effort has been devoted towards the development of novel biomimetic devices to effectively mirror the biological mechanisms which make neuronal communication so efficient in the human brain. To this aim, novel inorganic materials have been explored, leading to hardware-based neuromorphic devices able to act like biological neurons, emulate synaptic plasticity, and show learning capabilities [10]. While the neuromorphic engineering field has largely focused on the development of computational devices that imitate brain function, the recent development of neuro-inspired biomimetic platforms to directly interface with neurons has contributed enormously to our understanding of inter-neural communication. This is particularly relevant to develop new treatments for age-related neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's Disease (PD), which are increasingly common in aging societies [11, 12], placing a devastating burden on individuals and their relatives [13]. Despite great efforts devoted to reveal the mechanisms underlying neuronal communication and their disruption by neurodegenerative diseases, effective therapeutic strategies are still lacking. To this end, a platform to locally monitor the status of a diseased brain and directly intervene when needed would be highly desirable.

Here, we will discuss how future neurohybrid systems might establish such a platform in which the efficiency of the human brain and the computational power of well-established silicon platforms may be combined through a bridge system. A bridge to mediate information propagation between silicon and biological circuits overcoming the drawbacks of current neuromorphic and neuroelectronic technologies, such as energy efficiency, heat dissipation and data size, should be able to mediate information propagation in both directions [14, 15]. A prominent candidate to achieve this goal are organic conductive polymers (CPs), due to their great biocompatibility, low impedance, and high electrochemical transconductance [16]. In particular, organic electrochemical transistors (OECTs) are able to both interface and communicate with biological tissue, while fulfilling all the fabrication and integration requirements needed in the fabrication of an electronic circuit. Relevantly, both 2- and 3-terminal OECTs have been used to mimic some of the brain's properties (i.e. synaptic plasticity) [17]. Moreover, CPs will guarantee efficient and bidirectional real-time communication between the biological and the digital realms. In addition, relevant information will be processed locally, using similar spiking signals as biological neurons to establish an adaptive, functional and highly efficient biohybrid interface. Biomimetic devices will also modify their own structure in response to external stimuli, establishing energy-efficient adaptation, to dynamically adjust their function to match the constant plastic changes of brain circuitry. Such neurohybrid system might therefore not only be able to record and stimulate neuronal activity but also repair or eventually replace a damaged neural circuit, paving the way for novel therapeutic approaches for the treatment of neurodegenerative disease and neuroprosthetics.

2. Neuromorphic computing

When in 1950 Alan Turing was looking for an answer to the question 'Can machines think?', he started a decades-long effort to understand if and how a machine can imitate thought and which aspects of the brain could be mirrored in such a system [18]. Through his 'Imitation Game', Turing showed that a machine can indeed 'think', but with a completely different mechanism from that used by the human brain [18]. These early efforts laid the foundation of modern neural computing and artificial intelligence and current ANNs can perform intelligent tasks such as object recognition, data mining and learning with human-like performance [5]. However, despite the evolution of powerful algorithms that enable these features, their application requires great computational power, making brain-like calculations still hard to achieve on modern computers [19]. The main reason for this gap is that much of the information processing on computer hardware is performed serially, which is fundamentally at odds with the highly parallelized information flow that is embedded in living neural networks. To resolve this use, new neuromorphic devices, inspired by their biological counterparts, have drastically reduce the gap between brain and computers, thereby paving the way towards the next generation of intelligent machines [20].

2.1. How does the brain think?

The quest for a computer system to perform brain-like calculations has led scientists to closely look at the brain and mirror some of its computationally efficient features. The brain is one of the most complex and efficient systems found in nature and can perceive, interpret, and store an incredible amount of information on an incredibly low energy budget of only ∼20 W [1]. The brain consists of a highly interconnected network of neurons, which communicate by sending electric pulses (i.e. action potentials) through an intricate and elaborate neural circuitry consisting of axons, dendrites and synapses [2]. On average, the human brain contains about 100 billion neurons. Each neuron may be connected to up to 10 000 other neurons, passing signals to each other via as many as 1000 trillion synapses [2]. Here, action potentials from a presynaptic neuron are relayed through different types of neurotransmitters to modulate the activity of a postsynaptic neuron [2]. Synapses are a key feature of neural information transfer and the geometry and architectural organization of individual synapses is crucial for the energy-efficient information transfer between neurons [21–24]. Moreover, the frequency of synaptic activation determines the probability of neurotransmitter release and is essential in determining the efficacy of synaptic connections [25]. The brain is highly plastic and constantly reshapes its connections, adjusting its architecture to respond promptly and adapt to the environment when humans make new experiences [26]. This neural plasticity has been found to be crucial in learning and memory and it may involve the strengthening or weakening of existing brain circuits and synaptic connections as well as the formation of new synapses [27–29]. Experience-dependent plasticity enables the coordinated activation of specific groups of neurons at various frequencies which is a major factor of the brain's computational capabilities [30]. Newborn neurons may also continue to develop during adulthood, contributing to coping with the dynamic and plastic aspects of learning and memory [26, 31] or preventing interference of newly formed and already consolidated memories [32]. Because the brain is shaped by experience, inactive synaptic connections are also regularly pruned, effectively increasing the efficiency of signal propagation [33]. Lastly, brain computations are remarkably robust because they do not rely on single neurons or individual synaptic connections, but rather on the redundancy of the whole-brain functional networks [3]. Information propagates through highly parallelized and redundant neural pathways that can be flexibly reconfigured to enable new interactions between spatially distributed networks [34, 35].

2.2. How do machines 'think'?

First attempts at grasping the complexity and the efficiency of the brain date back to 1943, when McCulloch and Pitts proposed the first mathematical model of a neuron. Here, each neuron was represented as a simple element of summation, emulating the integration of the input stimuli at the cell body, and a non-linear function to account for the all-or-none principle of action potential generation [36].

Even though this model could not explain the mechanisms underlying neuronal electrical communication, it successfully mirrored the computational paradigm of a neuron, laying the foundations for much more complex models and applications. For instance, a similar approach was exploited by Rosenblatt in 1958 who formulated the first supervised linear classifier, the perceptron. In this case, a weighted sum of inputs enables the separation of several linearly separable classes [37]. Some decades later, thanks to Dreyfus, the introduction of backpropagation algorithms and the introduction of non-linearities that allow to handle non-linearly separable problems [38], along with the abrupt evolution of GPUs, it became possible to optimally train ANNs, leading to the rapid development of machine learning and then deep learning that would revolutionize both information technology and everyday life.

State-of-the-art ANNs are usually structured in several layers of artificial neurons organized in complex topologies [6]. If on the one hand the emulation of the brain connection and organization is what allows such software structures to mimic high-end parallel computation typical of the brain, on the other hand ANNs are designed to run on a hardware very different from the brain, such as Von Neumann machines, that normally rely on GPUs, abruptly increasing power consumption [7]. The huge gap in the power consumption between artificial and BNNs are due to fundamental differences in the functional principles of the two systems [39].

ANNs run on Von Neumann architectures, which require huge amount of energy to access large datasets to perform billions of operations per second. In addition, all the operations are synchronized by an external signal (clock) and the information is encoded in the digital domain. In contrast, neuronal information in BNNs is transmitted digitally, by single cells that fire asynchronously, as well as in an analogue mode fashion [40, 41] making it much slower than modern electronics. The straightforward emulation of the computation paradigm of BNNs is still challenging to achieve because of a clear mismatch between the digital synchronized approach of Von Neumann architectures and the energy-efficient, analogue, and asynchronous communication of the brain [42]. In order to fill this gap new approaches have been developed, including SNNs [43]. In SNNs the communication between neurons takes place in continuous time through electrical signals (i.e. action potentials or spikes) [43]. Such networks can take advantage of recently developed neuromorphic hardware (such as Intel's Loihi or IBM's TrueNorth systems) which exploit dedicated neuron-like cores [9, 44]. However, training SNNs remains a major challenge. In fact, the event-driven, non-differentiable signaling of SNNs prohibits the computation of gradient descent and backpropagation algorithms, which are required to train neural networks [45]. In order to overcome these issues, brain-inspired approaches, in which stochastic signaling increases the robustness of information propagation are exploited to allow training of SNNs [45]. For instance, an event-driven random backpropagation was implemented on neuromorphic hardware to achieve task accuracy comparable to those obtained in ANNs running on GPUs [45]. SNNs and neuromorphic chips implementing them can now be trained used the same gradient-based techniques that power deep learning [46, 47] and provide top–down principles for designing local gradient-based synaptic plasticity rules [48]. Recent advances in neuromorphic engineering enable solutions to optimize the trade-off between computational efficiency and power consumption that is still lacking for both ANNs and SNNs [49]. For example, devices featuring crossbar arrays, exploiting non-volatile memory elements are suitable for hardware implementation of ANNs with reduced energy, while accelerating the training process [50]. For instance, a ferroelectric semiconductor junction crossbar array was shown to perform online training achieving an accuracy of 92%, requiring an energy amount of 1.53 mJ [51]. Furthermore, hafnium diselenide based memristor crossbar arrays were used in convolutional image processing, as it happens in convolutional neuronal networks. Here, hardware kernels were designed, performing hardware edge detection with an energy efficiency of eight-trillion operations per Watt [52]. Moreover, grey-scale face classification was demonstrated performing online learning on a neuromorphic hardware, achieving an accuracy close to the result of a central processing unit, but with an energy consumption 20 times lower than state-of-the-art commercial hardware [53]. At the same time, novel biomimetic devices are being developed to implement the biological mechanisms that make neuronal communication so efficient. This has been achieved by either exploiting different physical properties of novel materials that mirror complex electrochemical dynamics, such as the ionic conductivity of neurons, or hardware architectures (i.e. silicon neurons) in which many computing units are integrated to overcome the von Neumann bottleneck [1].

In this regard, ion-sensitive field effect transistors have been used to mimic the generation of an action potential, taking into account for the first time the different ionic contributions due to the presence of voltage-gated ion channels typically found in neuronal membranes [55]. New devices can also mimic the plasticity and learning capabilities of BNNs. For example, in phase-change memory devices the electrical resistivity can be switched between amorphous and crystalline phases, resulting in a binary storage capability [56]. Similarly, the permanent polarization of ferroelectric and ferromagnetic materials can be leveraged to develop neuromorphic devices with short- and long-term memory [57]. For instance, a ferroelectric tunnel junctions (FTJ) based on hafnium zirconium oxide has been used to replicate the usage-dependent weakening or strengthening of synaptic signaling [54] (figure 1(a)).

In spintronics-based technologies, a continuous injected current can be non-linearly transformed into an oscillating voltage, mimicking another important characteristic of the brain, namely the non-linear dynamics at the basis of unsupervised learning [58].

In addition, the quest for innovative materials may be pivotal in reducing the energy consumption of current computing technologies. Memristive artificial synapses, based on different physical mechanisms as valence change, ferroelectric materials or redox reactions, have been shown to outperform conventional technologies, requiring less than a nJ per synaptic event [59]. Furthermore, energy consumption of crossbar arrays and synaptic transistors benefit from innovative materials too [60]. Notably, biocompatible graphene artificial synaptic transistors were shown to operate on a biological-relevant energy budget, with a switching energy efficiency of 50 aJ μm^{-2} [61]. Lastly, optical and optoelectronic neuromorphic technologies were shown to perform handwritten digit recognition with an accuracy of 90.6%, while consuming only 0.35 fJ per synaptic event [62].

However, more accurate biomimetic hardware is required in order to develop novel platforms that perform brain-like computations. Neuronal spiking communication can be replicated on biomimetic hardware architectures, referred to as silicon neurons [20]. Here, the neural activity is approximated as spike trains with a given timing: a single capacitor with a threshold counter could be then employed to mimic the integrate-and-fire behavior of a neuron [63]. A typical example is the Axon-Hillock circuit, shown in figure 1(b), in which the silicon neuron produces a spike event whenever the equivalent membrane voltage crosses a potential threshold [64]. Furthermore, major efforts are geared towards the development of neuromorphic hardware at the nanometer scale to enhance the emulation of synaptic information

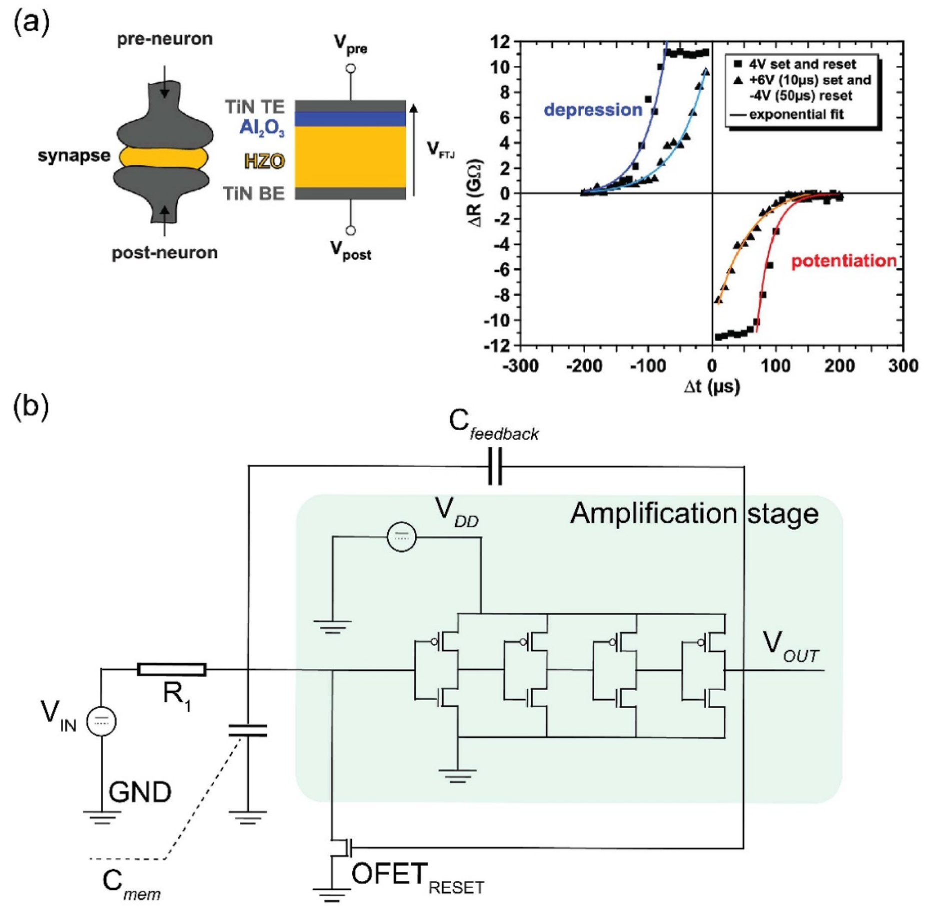

Figure 1. Biomimetic inorganic neuromorphic computing. (a) On the left, a schematic representation of a biological synapse and an FTJ. On the right, two curves showing synaptic strengthening (in red) and weakening (in blue). Reprinted with permission from [54]. Copyright (2020) American Chemical Society. (b) A circuit diagram of an Axon-Hillock spiking neuron.

transmission in large-scale networks [9, 65]. Lastly, silicon neurons can exhibit synaptic plasticity, resembling the conductance variation of the biological membrane during an action potential, making such devices a more accurate hardware representation than simpler numerical models [20]. These features are enabled by the mixed analog/digital nature of a silicon neuron, exploiting a biomimetic approach to process information [66].

3. Can we do more?

The world is aging. The number of people over 60 years is expected to rise from ~850 million in 2013 to more than 2 billion in 2050 [67]. As populations get older, age-related neurodegenerative diseases such as AD and PD have become increasingly common [11, 12], placing a devastating burden on individuals, their families and society at large [13]. Despite the exciting recent discoveries and their potential to serve as therapeutic tools for age-related neurodegenerative diseases [67–69], effective treatments are still lacking, raising the question 'can we do more?'. Neuromorphic engineering has already been pivotal in the development of new technologies that are changing our daily lives and may be the key to answer this question. While silicon-based and inorganic electronics in general aim to build efficient computational platforms, neuro-inspired devices to directly interface with the brain and introduce adaptive between neural and electronic circuits are not yet available. The development of brain-inspired technologies which can effectively record, decode and interpret neuronal activity as well as intervene directly to repair or replace a damaged neural circuit, is a powerful new way to treat neurodegenerative disease and enable new types of neuroprosthetics.

The central role played by neural electrical communication in higher brain functions and the lack of therapeutic strategies able to efficiently restore damaged brain circuits have led to the use of electrical stimulation as an alternative approach to alleviate neurological illnesses. Transcranial alternating current stimulation has already been used to modulate dysfunctional brain networks [70]. However, in order to target a particular neural circuit, implantable brain computer interfaces are necessary and are showing promising results in animals [71].

In this scenario, more efforts are needed to achieve brain-inspired systems that can efficiently record and decode the electrophysiological activity of neurons and interact dynamically with the biological environment. The first use of microelectrodes in neural investigations dates back to the 1950s, when metal wire electrodes and glass pipettes were used to monitor the extracellular electrical activity of neurons [72] or to characterize individual ion channels from single neurons with unprecedented resolution [73]. Since then, more sophisticated silicon-based passive electrodes have been introduced, which are still the dominant tools for neural recording and stimulation today [74]. It was only in the 1990s that the first silicon electrode with active electronic components was developed by Peter Fromherz, consisting of a direct junction between a single neuron and a silicon-based insulated-gate field effect transistor [75]. Since this pioneering work, various types of FETs have been developed [76], enabling the recording and mapping of electrical signals at a subcellular resolution thanks to their nanoscale dimensions and increased signal strength [77–80]. Such high-quality recordings of neural signals are not only essential for neuroscience research, but also for the development of a new generation of brain–machine interfaces.

Recording high-fidelity and high-quality electrophysiological signals from neurons is essential not only in fundamental electrophysiology research, but also in neuroscience-related disciplines, including the neuron–machine interface and brain-circuitry mapping. In this scenario, the modeling of the electrical characteristics of the neuron-electrode interface at a single neuron level becomes critical to support the design of more effective microelectrode array [75, 81–84]. Taking inspiration from the biological world, several engineering strategies have been developed over the last few years in order to maximize the interactions between neurons and electrodes and drastically increase the quality of the recorded signals [85].

While silicon-based substrates have been instrumental in deepening our understanding of neuronal electrical communication, the mechanical mismatch between these hard electronics and the much softer neural tissue hinders the long-term application of such devices *in vivo* [86–90]. Current neural interfaces (e.g. intracortical probes or electrode arrays on the brain surface) are usually highly invasive and do not ensure efficient and long-lasting communication at the neuro-implant interface [86–90]. This is mainly due to a foreign body response of the brain, causing the encapsulation of the electrodes by insulating scar tissue and the reduction of the number of neurons in the close proximity of the probe [86–90]. As a result, the amplitude of the recorded signals can degrade over time and render the devices ineffective a few months after implantation [91–94]. Another important shortcoming of silicon-based neuroelectronic platforms is that, to the best of our knowledge, they are not yet able of adaptive sensing and *in loco* computation of biological signals. This is primarily due to the fact that inorganic electrodes are impermeable to ions and their operation in aqueous environments is hindered by the creation of oxide layers that make these materials unstable [95]. It is therefore clear that new solutions are required to make the development of new therapeutic tools for neurodegenerative diseases and novel approaches in prosthetics applications a concrete reality.

4. Neurohybrid

Despite the advancements in the neuromorphic and neuroelectronic fields, currently available devices do not possess all the requirements to effectively address neurodegenerative diseases and achieve their potential to offer novel prosthetics solutions. Moreover, silicon-based technology is still required in the processing of biological signals due to its unmatched computational power.

The development of the next generation of devices that are not only able to effectively interface with neurons but also possess enough computational power to decode and interpret neuronal activity *in loco* and repair or replace damaged neural circuits therefore requires a trade-off to combine the best of both worlds. Here, the development of a neurohybrid system may be conceived, where a bridge system is able to conjugate the efficiency of human brain and the computational power of well-established silicon platforms (figure 2). To overcome the current limitations of neuromorphic and neuroelectronic hardware, such a bridge should be able to mediate information propagation in both directions. The bridge should monitor the status of the neural tissue by recording raw biological signals and process them *in loco* before routing them to the digital component. The output of the digital processing should then be converted in an analogue signal that could be then delivered to the biological system, in an energy efficient manner.

The bridge system needs to fulfill some fundamental requirements:

1. Seamless integration: the bridge should integrate with living tissue without causing damage or an inflammatory response, while ensuring a tight interface between neurons and the electronic apparatus, stable both electrically and mechanically.
2. Bidirectional communication: the bridge should exhibit both ionic and electronic conduction mechanisms to guarantee a bidirectional and real-time communication.

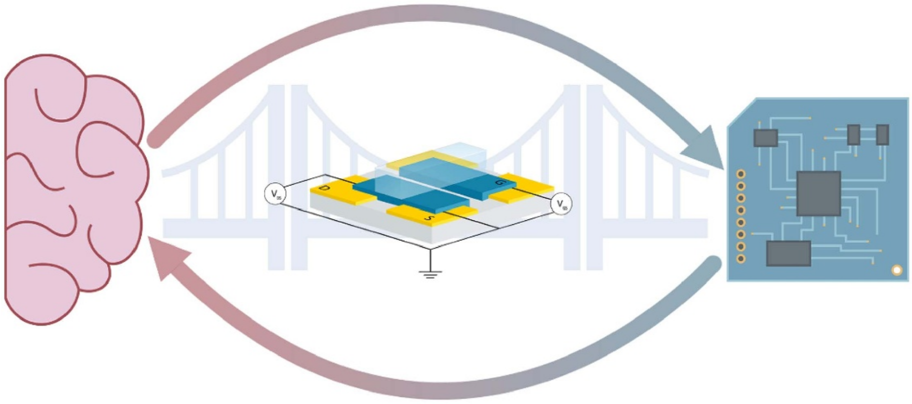

Figure 2. A schematic of a neurohybrid system. Biological and digital realms are seamlessly integrated through an organic platform that effectively acts as a bridge.

3. Adaptive and efficient computation: all the bridge computing operations should be adaptive, neuro-inspired and executed *in loco* in an energy efficient way.

The ideal candidates to achieve all these requirements and bridge the biological and electronic realms in a neurohybrid system are organic neuromorphic devices.

4.1. Seamless integration

Although current neural interfaces are able to acquire high-quality, multiplexed electrophysiological recordings, the materials commonly used for electrodes' fabrication (silicon, metals, and metal-oxide) [96] are very rigid and far from the flexibility of living neural tissues [97]. Minimizing this mechanical mismatch at the neuroimplant interface is therefore crucial for the development of mechanically compliant soft neural interfaces. Here, elastomers and organic polymers have drawn a lot of attention as encapsulation layers for implantable electrodes owing to their reduced elastic Young's modulus, a measure of their mechanical behavior, which make them more bendable and stretchable [16, 98–101]. For instance, several recent neural prostheses rely on highly compatible and conformable polymeric substrates, such as polyimide and parylene-C [16, 98–101], or silicones, such as poly(dimethylsiloxane), to match and adhere to the highly convoluted brain surface or to curvature of the eye [99]. However, although these flexible materials have an elastic modulus two orders of magnitude lower compared to silicon [102], they are still much stiffer than the brain [92, 103]. To further decrease the mismatch, stiff polymers can also be micropatterned into thin meshes that allow injection in the brain and mechanical compliance with the nervous tissue [104, 105]. Only recently, the development of softer hydrogels has enabled to more accurately match the brain Young's modulus [106]. Such hydrogels have already been used to improve biocompatibility of neural implants by reducing the interfacial stiffness of otherwise rigid substrates [106]. Shape-memory soft polymers have also become increasingly popular for neural interfaces. Such polymers can be purposely engineered to soften and actuate once they are implanted [107–109] or to change shape for highly adaptive interfaces [110, 111]. Despite the great potential of soft and flexible materials for neural interfaces, they still require the presence of rigid, inorganic electrodes. To resolve this issue, organic CPs have emerged as ideal candidates for neural interfaces as they meet the mechanical criteria for a soft and biocompatible interface and are also conductive, allowing them to be used as functional elements of soft neural interfaces (figure 3(a)). Among the most frequently used CPs, polyacetylene, polythiophene, poly [3,4-(ethylenedioxy)thiophene] polystyrene sulfonate (PEDOT:PSS), polypyrrole, polyphenylene, and polyaniline have found application in the development of 3D scaffolds for tissue electronics [112, 113] or for the development of printed [114] or injectable conductive hydrogels [115], due to the possibility of conjugating biocompatibility, softness and conductivity [116]. For example, 3D scaffolds with nanoelectrodes have been developed for action potential recordings [117–120] and stimulation [121]. Furthermore, CPs can be easily combined with biodegradable organic polymers when a permanent implant is not necessary [16] or with viscoplastic polymers for morphing and mechanically compliant adaptive interfaces [122]. Such devices can be engineered to change their shape and adapt to growing nerves causing minimal damage (figure 3(b)), enabling chronic electrical stimulation and monitoring for up to 8 weeks [122] (figure 3(c)).

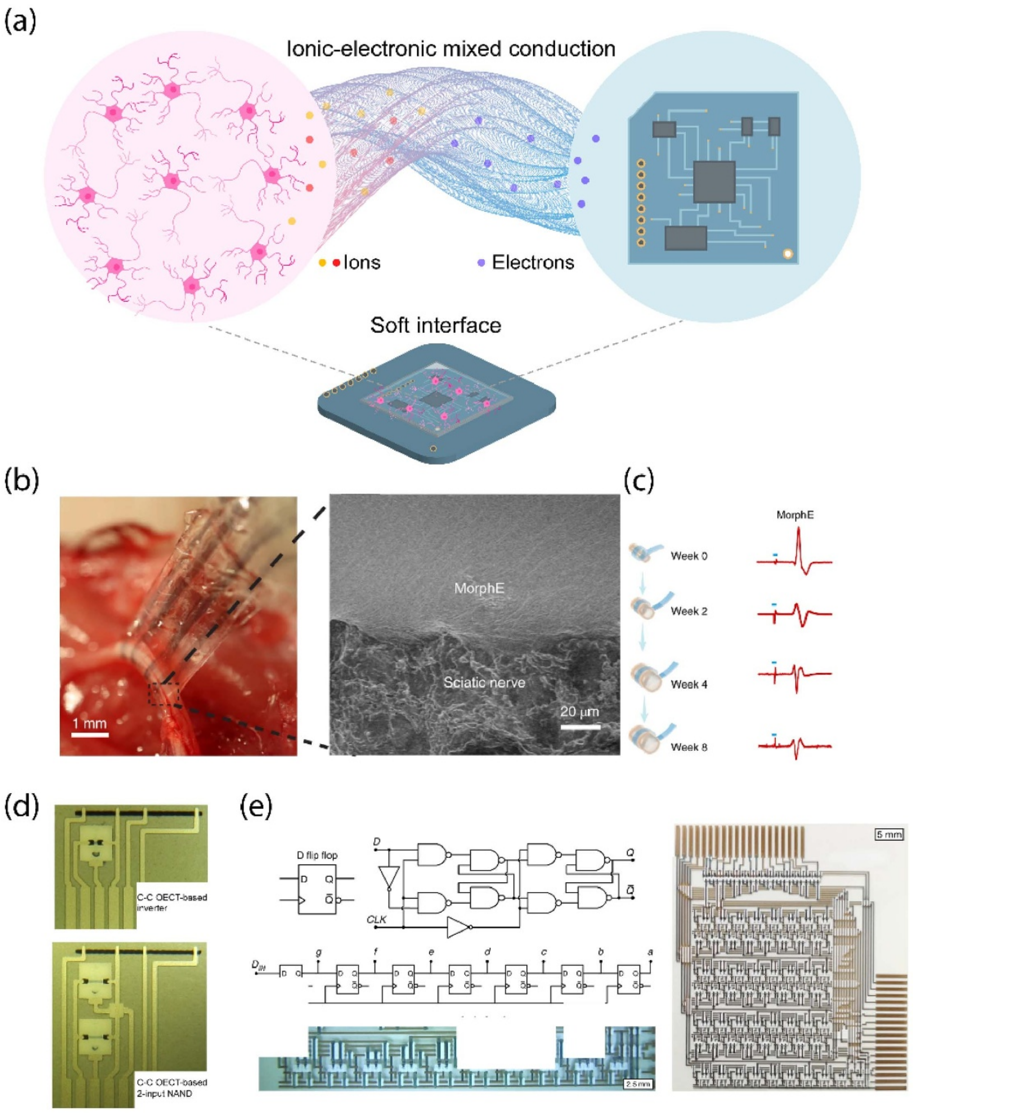

Figure 3. Organic neuromorphic for seamless integration and bidirectional communication. (a) A schematic representation of an organic neural interface. CPs, owing to their mechanical properties and ionic-electronic mixed conduction, can be employed to efficiently interface electronics with the nervous system. (b) An image and a SEM micrograph of a morphing device wrapped around a sciatic nerve showing a robust and intimate neural interface. Reproduced from [122], with permission from Springer Nature. (c) A schematic representation of the morphing device enabling the recording of action potential for up to 8 weeks. Reproduced from [122], with permission from Springer Nature. (d) Above, a screen printed OECT-based circuit of an inverter. Below, an OECT-based two-input NAND gate. Reproduced from [123]. © IOP Publishing Ltd. CC BY 3.0. (e) On the left, a schematic of a Master-Slave D flip-flop with inverters, two-input NAND gates, and a seven-bit shift register cascading seven stages of D flip-flop. Below, an exemplary photograph of the all-printed flip-flop. On the left, an exemplary photograph of the all-printed seven-bit register [127]. Reproduced from [127]. CC BY 4.0.

4.2. Bidirectional communication

Fluxes of ions are at the base of the electrical communication of the brain [124], while electronic charge transfer is what powers digital computers. The bridge, being at the interface between such diverse worlds, should exhibit a mixed conduction mechanism. Therefore, owing both ionic and electronic conduction is essential to ensure an adequate and harmonized communication between all the parts involved [125] (figure 3(a)).

Organic materials have been identified as the best candidates to replace silicon technologies at the interface with living systems [126]. CPs are characterized by an excess of positive or negative charges on their backbone. When ions are injected inside the bulk of CPs, an electrical current is induced by the motion of the charges from one chain to another, resulting in an ionic-electronic coupling [16]. If holes exceed, the polymeric structure is p-type doped, otherwise it is n-type doped. In this regard, one of the major advantages of using these materials is their operability in aqueous environments, while being stable in contact with air [95].

CPs therefore allow a bidirectional information propagation between the biological and electronic realms (figure 3(a)). For instance, PEDOT:PSS has been used to improve the performance of state-of-the-art devices for neural recordings [128–131] or to develop PEDOT:PSS-based electrodes for electrophysiological measurements [132, 133]. CPs have also been instrumental in the development of OECTs, three terminal devices in which a source and a drain electrode are connected by an organic semiconductor channel. Their electrical operation depends on the injection of ions from an electrolyte into the organic channel which modulates its conductivity through electrochemical doping. The efficiency of the ionic-to-electronic signal transduction is hereby described by the transconductance, defined as the derivative of the channel current (output signal) with respect to the gate voltage (input signal) [17].

The variation in ionic flux due to the activity from nearby neurons modulates the current flow through a semiconducting channel of an OECT [134–138], which amplifies the electrical signals and provides significantly improved recording quality compared to passive recording techniques [134, 137, 138]. The electric field generated by OECTs may also be used to stimulate neurons to trigger an action potential, further highlighting their potential in stimulation applications [134].

However, the application of OECTs at the interface with the biological world go beyond the measuring and stimulation of electric signals. They can be used to monitor the formation and disruption of tight junctions in cell-barrier tissues [139–141] or electrochemically detect various biomolecules [142, 143]. In particular, electroactive neurotransmitters can be detected by secondary processes such as enzymatic sensing, immune-sensing, and aptamer sensing [144] or they can be directly oxidized or reduced at the gate electrode [145]. In this case, the ions released by the redox reaction will change the doping state of the CP, making the biosensing mechanism possible [145].

Given the analogue nature of biological signals, it is essential to be able to process such recordings in an analogic fashion. OECTs, owing to their high transconductance, can also be used for energy efficient and *in loco* signal transduction [146]. For example, using organic materials and specific geometrical parameters of OECTs, such as channel thickness and width-to-length ratio, allows to tune the gate voltage needed to achieve the maximum transconductance. This allows organic operational amplifiers (OPAs) to amplify biological signal when biased with 0 V applied at the gate terminal, paving the way to a facile biointegration [147]. Furthermore, organic OPAs can perform sensing and amplification of signals as low as 100 uV with a gain of more than 30 dB [148] and can operate with a power consumption of as low as 50 nW [149]. By leveraging OPAs, one can create different analogic circuits widely employed in signal processing, such as integrators, differentiators, oscillators and trans-impedance amplifiers, which are essential current–voltage converters for the transduction of low current signals from biological ion flows into electronics compatible voltage signals [149].

The versatility of conducting polymer has also led to the development of organic electronic-based digital circuits, matching the operative voltage of standard PCB-based electronics [146], such as logic gates, fundamental for the integration with digital microprocessors, allowing to propagate and compute binary 0/1 information. The elementary building block of such structures is the inverter, and the simplest organic inverter architecture is based on the resistor-ladder logic (RLL) [150, 151]. Here, a resistor ladder is coupled with a p-type OECT that is used to switch the circuit between an ON and OFF state. By simply connecting several of these structures, it is possible to create more complex logic gates computing NAND or NOR logic functions [150] or ring oscillators [151]. For instance, a screen printed RLL inverter and a two-input NAND gate are shown in figure 3(d) [123]. RLL was then exploited to build basic memory units, like flip-flops or 2-bit shift registers [152]. Furthermore, more complex function may be achieved by integrating NOT and NAND gates on the same substrate: four 2-input NANDs and six inverters may combine into a 2-to-4 decoder, while four 3-input NANDs, one 4-input NAND and two inverters can be connected into a 4-to-1 multiplexer. In addition, by cascading seven master-slave D flip-flop a 7-bit shift register was successfully printed, as shown in figure 3(e) [127]. Lastly, a binary-coded decimal 4-to-7 encoder, made by all-printed PEDOT:PSS-based OECTs was employed to drive an organic electrochromic display with only four data bits [127]. Besides RLL, unipolar inverters exploiting two identical p-type OECTs have been successfully developed [153]. Lastly, recent advancements in material design, and fine tuning of the OECTs geometry, allowed for the implementation of CMOS-like logic gates, based on both p- and n-type OECTs integrated on the same structure. For instance, poly(benzimidazobenzophenanthroline) was used to fabricate a complementary NOT gate exhibiting high gain at low voltage supply (0.6 V) [154].

4.3. Adaptive and efficient computation

The neurohybrid platform must not simply guarantee the mere amphidromous transfer of information between the biological and electronical realms. The amount of data extracted by state-of-the-art devices for neural recordings is huge, hampering the local data processing owing to the memory and power demands.

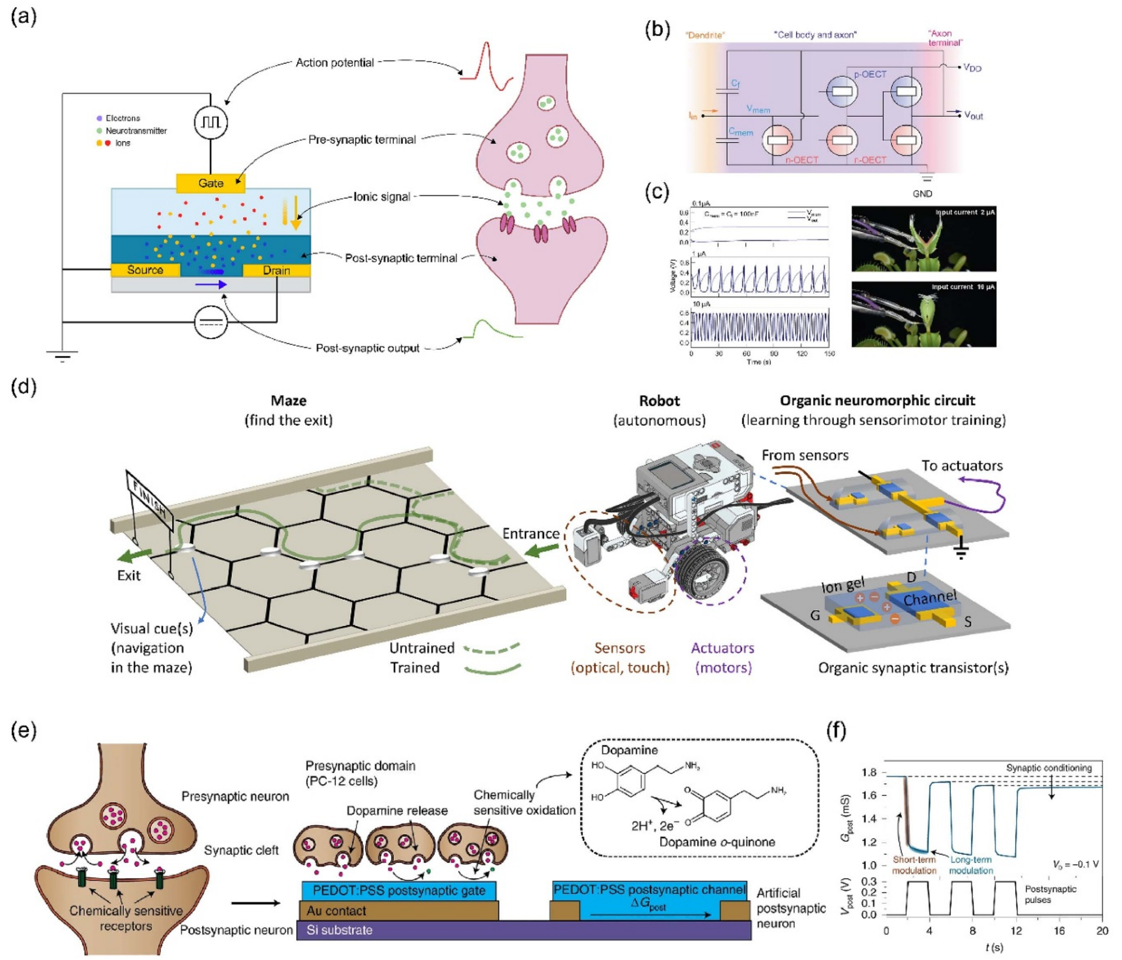

Figure 4. Organic neuromorphic for adaptive and efficient computation. (a) A schematic representation comparing an OECT with a biological synapse. (b) Spiking patterns at three different input currents (0.1, 1, and 10 μA) with $C_{\mathrm{mem}} = Cf = 100$ nF. Reproduced from [155]. CC BY 4.0. (c) Modulation of a Venus flytrap through an artificial neuron: the flytrap does not close its lobes when the input current is 2 μA, but only when the current reaches10 μA. Reproduced from [155]. CC BY 4.0. (d) An autonomous and path-planning robot, able to learn how to navigate towards the exit of a maze through an organic neuromorphic circuit for sensorimotor integration. From [156]. Reprinted with permission from AAAS. (e) A comparison of a biological synapse and a neurotransmitter-mediated neuromorphic device. Reproduced from [157], with permission from Springer Nature. (f) Short-term and long-term modulation of the postsynaptic conductance (G_{post}) in the presence of dopamine, using voltage pulses at the postsynaptic gate ($V_{\mathrm{post}} = +\,0.3$ V, $t_{\mathrm{post}} = 2$ s). G_{post} was measured using a source–drain voltage $VD = -0.1$ V. Reproduced from [157], with permission from Springer Nature.

For this reason, the bridge in an ideal neurohybrid platform should be able to introduce and adaptive and functional biointerface. Such platform, processing relevant information locally, just like a biological neuron, thereby dramatically reducing the amount of data routed from one side to the other and allowing for far more energy efficient operation. Simultaneously, this biomimetic device, by adapting its own structure in response to external stimuli, will promptly provide informative cues to the biological system as well as dynamically adjusting its recording and stimulation patterns to match the plastic changes of brain circuitry.

Such local and dynamic adaptation could be achieved by using OECTs, whose operating principles can be considered as a simulacrum of synaptic information transmission, as schematically shown in figure 4(a). Specifically, a square voltage pulse can be applied at the gate terminal mirroring an action potential reaching the pre-synaptic terminal. This voltage causes the injection of cations from the electrolyte to the conductive channel, mimicking the chemical transduction of the information that leads to the neurotransmitters release at the synapse. While in chemical synapses this signaling results in the ionic current at the post-synaptic membrane, a conductance variation and, thus, a modulation of the channel current can be recorded on the conductive channel of the OECT.

Furthermore, novel biomimetic devices can also implement short- and long-term plasticity, using OECTs. For instance, the application of high frequency pulses (>4 Hz) increases the OECTs conductance, resulting in a short-term plasticity similar to the paired-pulse facilitation seen in biological neurons [158]. Different strategies can be used to implement a long-term strengthening of the synaptic communication in OECTs. Such mechanism relies on the retention of charges in the conductive channel to allow for the long-term variation of the doping level. This can be performed through physical barriers (e.g. Nafion membrane [159] or chemical reactions (e.g. redox reactions of the organic film). The neuromorphic behavior of OECTs can also be exploited for the spatial integration of information: by applying a given spatial pattern of voltage pulses at multiple gate terminals of a distributed OECT architecture one can perform various classification tasks [160, 161]. However, organic neuromorphic devices are not confined to single-device level. The integration of OECTs in more complex systems is in fact instrumental in the development of neuromorphic platforms. Organic spiking neurons, for instance, can mirror Hebbian learning through implementation of short- and long-term plasticity (figure 4(b)) [155]. These platforms could operate at low voltages ($<$0.6 V) and adjust their firing frequency in response to an external stimulus, which can be used for adaptive bio-integration, such as stimulating a Venus Flytrap (*Dionaea muscipula)* to close its lobes upon the application of a repeated stimulus (figure 4(c)) [155]. Learning processes can also be replicated using OECTs-based platforms. For instance, reinforcement learning allows a mobile robot stimulated to create appropriate visuomotor associations and successfully navigate through a maze, successfully finding the exit [156] figure 4(d)). Lastly, organic neuromorphic devices have demonstrated the unprecedented ability of communicating directly with neuronal cells through a biohybrid synapse [157] (figure 4(e)). Neurotransmitter secreted by cells was in fact exploited in neuromorphic OECT, *de facto* modulating its conductance level as a response to the cellular activity, proving the feasibility of a hybrid system where synaptic properties of a post-synaptic artificial neuron, such as short- and long-term plasticity, can be mediated by the activity biological neurons [157] (figure 4(f)). This pioneering work has laid the foundations for the neurohybrid system here envisioned, in which an organic platform can locally learn from the interaction with living neuronal cells.

To understand the benefits of a neurohybrid system, it is possible to analyze how it might improve state-of-the-art techniques, such as such as deep brain stimulation (DBS), currently employed in the treatment of brain pathologies. DBS is a neurosurgical procedure relying on the implantation of metal microelectrodes directly into the brain. Such electrodes can be voltage or current-controlled [162] and deliver either continuous or intermittent stimuli to block or modulate the abnormal electrical activity of damaged neuronal circuits. As such, DBS has been widely used to treat neurodegenerative disorders including AD [163] and PD [164], as well as treatment-resistant depression [165]. Despite the success of DBS in the treatment of these disorders, clinical and technical challenges remain. For instance, corrosion of the metal electrodes, erosion of wires, bulky connections and several other hardware-related problems, pose a severe challenge in a conspicuous number of cases [166]. DBS is also a blind treatment and trial-and-error procedures are often needed during the programming session to determine the appropriate stimulation protocol to obtain the desired effect [167]. In addition, current DBS-based treatment solutions lack the ability of sensing the presence of critical biomarkers [162]. These might include neurotoxic proteins, such as amyloid-β, a neuropathological marker of AD [168] or other useful markers that would predict the physiological response to the treatment [162]. Customized and adaptive solutions are therefore needed to face the new challenges posed by a continuously aging world.

If neurohybrid systems would be employed for DBS procedures, the intrinsic properties of organic neuromorphic devices could strongly reduce these shortcomings. First, the soft nature of organic materials would reduce the mechanical mismatch between the implant and the brain, preventing the formation of insulating scar tissue. Second, organic neuromorphic devices are stable in an aqueous ion-rich environment and are therefore immune to electrode corrosion. Third, the adaptive nature of neuromorphic devices could modify the properties of the stimulation electrodes, providing an instantaneous response of the device, coping with local modifications of the biological environment. Lastly, the biosensing capabilities of OECTs, for instance the ability to sense amyloid-β [169], could be used to route biomarker information to the silicon part of the system to monitor overall progress of the treatment and globally adjust the stimulation protocol, when needed, in a closed-loop fashion.

5. Conclusion

The increasing need of therapeutic strategies for neurodegenerative diseases requires the development of novel neurohybrid platforms which conjugate medical necessity to restore fundamental and damaged synaptic connections with the enormous progress made in the neuromorphic computing field.

In the last years, the mechanical mismatch between the hard electronics and the much softer brain has hindered the development of such platforms, despite a plethora of possible solutions has been introduced to improve the cell-chip coupling, exploiting organic materials properties. In addition, with the aim of achieving an efficient and sensitive communication between the biological electro-ionic transduction and the purely electrical signaling of silicon-based technologies, organic neuromorphic devices have been identified as a possible bridge. Here, CPs enable the recording of biological signals and simultaneous generation of a corresponding response, achieving a bidirectional and real-time interaction between the two systems. Efficient interactions also require the inclusion of closed-loop mechanisms with an accurate biomimetic modulation of signals and an adaptive energy-efficient interface. Taken together, the ideas presented here show that organic neuromorphic devices are ideal candidates for the integration of heterogeneous systems, such as the biological and artificial computing realms, with the aim of creating a more complex and more powerful system. However, the neurohybrid technology described here is unlikely to replace silicon-based technologies but rather merge into one system with the ultimate purpose of creating a novel platform that could profit either from the experience and the know-how of the silicon-based world and from the great potential of innovative materials and neuromorphic hardware. To answer Turing question, the idea is that if a machine can be trained to 'think' like a brain, then this machine can train a diseased brain to 'think again'.

Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

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Conflict of interest

The authors declare no conflict of interest.

ORCID iDs

Ugo Bruno https://orcid.org/0000-0003-0419-6541
Anna Mariano https://orcid.org/0000-0002-3630-5055
Daniela Rana https://orcid.org/0000-0002-7929-1191
Tobias Gemmeke https://orcid.org/0000-0003-1583-3411
Simon Musall https://orcid.org/0000-0002-9461-1042
Francesca Santoro https://orcid.org/0000-0001-7323-9504

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