

Organic Synaptic Transistors for Bio-Hybrid Neuromorphic Electronics

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Neuromorphic electronics that emulate biological synapses and nerves can provide a solution to overcome the limitation in energy efficiency of von Neumann computing systems. With increasing demands on bio-medical applications such as healthcare monitoring and neuroprosthetic devices, bio-hybrid neuromorphic electronics are evaluated as ways to process biological information and replace biological systems. Successful realization of bio-hybrid neuromorphic systems requires replication of various synaptic properties in a single device, along with other characteristics such as biomimetic neural functionality, biocompatibility, soft mechanical properties, and low energy consumption. To satisfy these requirements, organic synaptic transistors (OSTs) are widely investigated as essential components of these applications. If the requirements can be met, bio-hybrid neuromorphic systems that use OSTs can be compatible with biological systems, and can operate stably at bio-electronic interfaces. Here, fundamentals of the OSTs emulating biological synapses and nerves are presented followed by a discussion of the requirements of the neuromorphic device/systems for bio-hybrid application. Finally, recent research on implementations of bio-hybrid neuromorphic devices and systems with future research directions, are reviewed.

big data computing. By emulating biological nervous systems, this “von Neumann bottleneck” can be solved by using artificial synapses that combine memory and processing functions in one cell, as in biological nervous systems.^[1,2] Emulation of biological synapses and nerves also provides the sensing and responding functions with human-like abilities such as event-driven processing and high-accuracy perception, which are limited in conventional human-interactive systems such as e-skins, human-machine interfaces, and neuro-prostheses.^[3–6]

In biological nervous systems, sensory signals are evoked by external stimuli (e.g., pressure, light, temperature) and transmitted through sensory nerves in the peripheral nervous system (PNS) to the central nervous system (CNS), that performs perceptual processing of information. Afterward, the processed signal is transmitted along nerves to generate appropriate responses to the stimulus.

1. Introduction

Conventional von Neumann computing architecture separates memory from processing, so calculations require swapping of data between the units. This physical connection constrains further increase in achievable speed and energy efficiency of


Neuromorphic systems that emulate biological PNS and CNS may enable energy-efficient operation to process sophisticated real-world problems by detecting and responding to environmental information. The artificial sensory nerves consist of sensors, artificial neurons, and artificial synapses to emulate this perceptual processing. The sensory signals are converted to voltage spikes (i.e., action potentials) by artificial neurons, then processed by artificial synapses. These artificial sensory nerves emulate the event-driven operation of biological nerves and thus consume energy only while responding to inputs. Therefore, artificial nerves consume much less energy than conventional artificial sensory systems, which require periodic scanning of sensing/processing units, and that use standby energy when input is absent. Furthermore, the artificial nerves can be promising for prosthetic applications because they can generate biocompatible spike signals without bulky and rigid external encoding units.^[7] After perceptual processing, biological responses can be achieved by stimulating target organs and tissues. Integration of these neuromorphic systems with biological systems to form so-called “bio-hybrid neuromorphic systems”, will realize biomimetic signal transmission and information processing at bio-electronic interfaces. Thus, these systems successfully emulate efficient biological perception processing, that has sensing and responding abilities, and therefore, show promise for use in next-generation healthcare monitoring and neuroprosthetic devices that need to detect bio-signals in a

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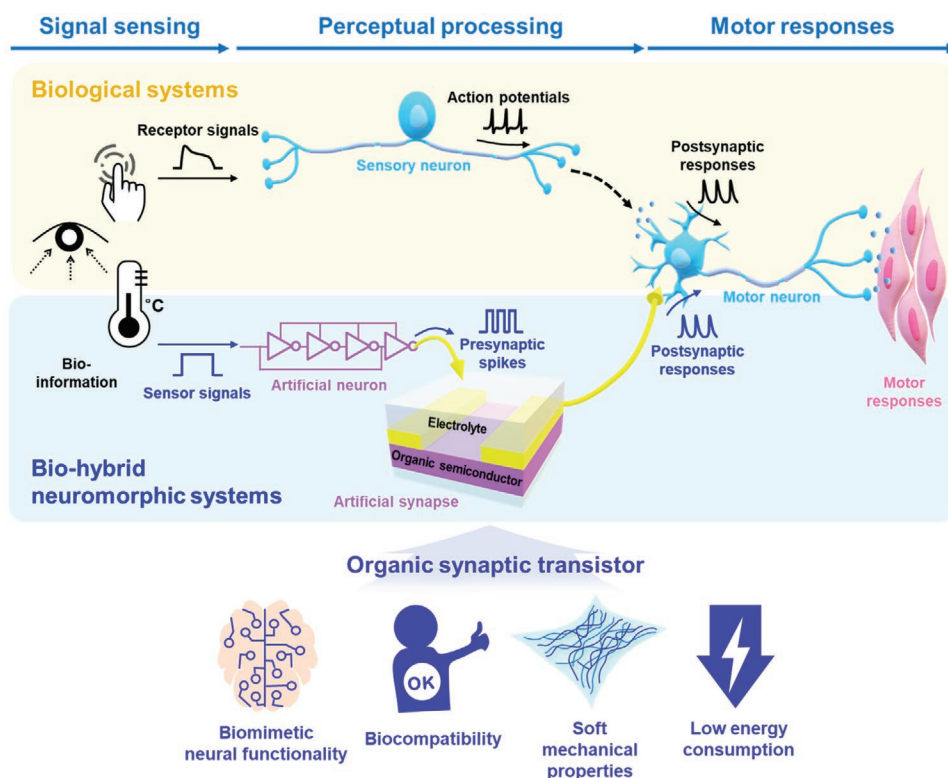


Figure 1. Schematics of OSTs for bio-hybrid neuromorphic systems.

human body, and to stimulate biological organs for appropriate responses. For the realization of these applications, bio-hybrid neuromorphic electronics that integrate the artificial synapses/nerves with biological systems, have been developed.

Organic synaptic transistors (OSTs) have been regarded as promising components of bio-hybrid neuromorphic systems, due to advantages such as electrical properties that can be tuned by molecular design, simple fabrication processes, soft mechanical properties, low-power consumption, and biocompatibility.^[8–11] This type of artificial synapse is being developed to emulate biological synapses, in which the strength of synaptic connection between pre- and postsynaptic neurons can be modulated. This ability is known as synaptic plasticity; it is the basis of learning and memory in nervous systems, so it is an essential property of neuromorphic devices and systems. Therefore, the OSTs can be used as biorealistic artificial neural components for neuromorphic computing, smart sensors of the internet of things, and neural prostheses (**Figure 1**). Especially, OSTs that use electrolytes as gate insulators can process biological information such as electrophysiological signals, biophysical signals, and bio-chemical signals because electrolytes (e.g., liquid, ion gel) enable interfacing of the devices with biological bodies and organs; in healthcare monitoring and biomedical applications, these abilities enable the OST to assess the bearer's health. In addition, the devices have been integrated with sensing and actuating components to mimic biological sensory and motor nerves, so highly accurate preceptive and adaptive electronic systems are possible.^[12,13] As implantable neuroprostheses for neural diseases, OSTs may eventually replace biological nerves partially or wholly.^[14,15] For these

bio-medical applications, bio-signals should be closely monitored and biological nerves can be replaced potentially while minimizing possible detrimental effects on the body. To achieve this objective, many researchers have developed approaches to demonstrate biocompatible and stably-operating bio-hybrid neuromorphic devices and systems that use OSTs.^[16–18]

Here, we provide fundamental requirements of OSTs for bio-hybrid applications, and associated research trends and direction in neuromorphic bioelectronics. First, we present the basic background about biological synapses and their properties. Second, we introduce the advantages of OSTs and recent progress in development of artificial synapses and nerves. Third, we provide the requirements to ensure that artificial synapses and nerves can be adopted in biological systems; examples include biomimetic neural functionality, biocompatibility, soft mechanical properties, and low energy consumption. Next, we cover recent progress toward achieving stable bio-hybrid neuromorphic devices and systems. Finally, we suggest future research directions toward successful implementation of bio-hybrid neuromorphic systems.

2. Organic Synaptic Transistors for Synaptic Properties

2.1. Biological Synaptic Properties

Neurons communicate with each other by exchanging signals through synapses. These synapses are categorized as electrical or chemical, depending on signaling mechanisms.

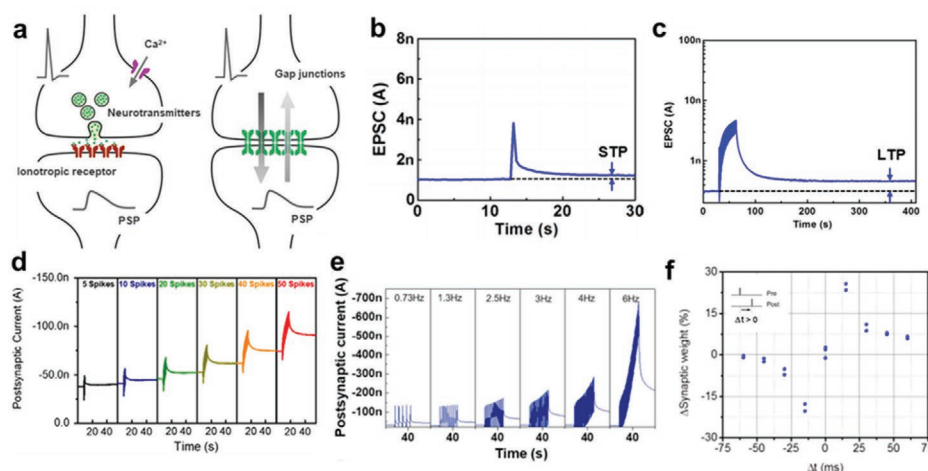


Figure 2. Types of biological synapses and their synaptic properties emulated by OSTs. a) Chemical synapses (left) and electrical synapses (right). Reproduced with permission.^[19] Copyright 2018, Frontiers Media S.A. b) STP, c) LTP, d) SNDP, e) SFDP, and f) STDP characteristics of artificial synapses. (b,c) Reproduced with permission.^[43] Copyright 2016, American Association for the Advancement of Science. (d) Reproduced with permission.^[28] Copyright 2020, Wiley-VCH. (e) Reproduced with permission.^[30] Copyright 2019, Elsevier B. V. (f) Reproduced with permission.^[43] Copyright 2016, American Association for the Advancement of Science.

Electrical synapses rapidly convey signals through electrically-coupled gap junctions. Chemical synapses transmit signals from presynaptic neurons to postsynaptic neurons by releasing neurotransmitters into the synaptic cleft, through which neurotransmitters diffuse and bind to receptors in the postsynaptic cells (Figure 2a).^[19,20] In response to activation of the receptors by various neurotransmitters, chemical synapses can amplify and transform presynaptic signals, to impart complex effects on the postsynaptic neurons; that is, presynaptic signals induce either excitatory post-synaptic potential (EPSP) or inhibitory post-synaptic potential (IPSP).

Synaptic plasticity is an important property of synapses. It refers to an activity-dependent change in the strength of (“weight”) of the connection between presynaptic neurons and postsynaptic neurons. The synaptic plasticity makes important contributions to modification of subsequent thoughts, feelings, behavior, and memory.^[20–23] The synaptic plasticity is largely divided into short-term plasticity (STP) and long-term plasticity (LTP) depending on the decay time of the altered synaptic weight (Figure 2b,c).^[24–26] STP is a rapid decay of synaptic weight to the initial state. LTP is a slow decay of this weight; the slow decay of synaptic plasticity is evoked by frequent or repetitive activation of excitatory or inhibitory synapses that lead to strengthening or weakening of the synaptic weight.

Many kinds of synaptic characteristics are shown in biological synapses. For example, a post-synaptic potential that is induced by two consecutive pre-synaptic action potentials can be amplified, which is paired-pulse facilitation (PPF), or decreased, which is paired-pulse depression (PPD).^[27] In addition, the synaptic weight can be modulated as the number of pre-synaptic action potentials is changed; this is spike number-dependent plasticity (SNDP) (Figure 2d).^[28] The frequency of pre-synaptic action potentials can also affect the synaptic weight; this response is spike-frequency-dependent plasticity (SFDP). Moreover, the temporal correlations between pre-synaptic action potential and post-synaptic action potential

induce the synaptic plasticity; this is spike-timing-dependent plasticity (STDP) (Figure 2e,f).^[29–31]

2.2. Organic Synaptic Transistors for Artificial Synapses and Nerves

To emulate the properties of biological synapses, OSTs have been investigated in neuromorphic electronics and related applications, due to advantages of simple fabrication,^[32,33] mechanical flexibility or stretchability,^[10,34] low energy consumption,^[35–38] and biocompatibility.^[39,40] In OSTs, ionically-conducting but electronically-insulating electrolytes in contact with organic channel layers are frequently used as gate insulators (Figure 3a). Electrolytes in OSTs can be liquid, solid, ion-gel, and even aqueous cell culture medium such as phosphate buffered saline (PBS) solution.

The mechanism of the OSTs that use electrolytes mainly rely on the migration of ions in them. The operating modes of these OSTs are categorized into an accumulation mode and a depletion mode. Typically, the accumulation mode is exhibited by OSTs that use intrinsic organic semiconductors (OSCs.) Due to relatively low conductivity of the OSCs, the devices show low current level at the initial state (normally OFF). When a negative pre-synaptic spike is applied at the gate electrode, mobile anions from the electrolyte move toward an electrolyte-semiconductor interface, where they cause formation of electric double layers (EDLs), and can even become trapped in the case of ion-permeable OSCs (Figure 3b). These processes accumulate holes at the semiconducting channel, and thereby increase the current level (ON state). After the voltage spike is removed, anions diffuse back to their initial distribution, so the current decreases to its initial level.^[9,40]

The decay time can be controlled by the interaction between ions in the electrolyte and OSC. In the case of ion-impermeable OSC, the ions rapidly diffuse back to their initial distribution in the electrolyte; this response takes ≈ 1 ms because EDL is

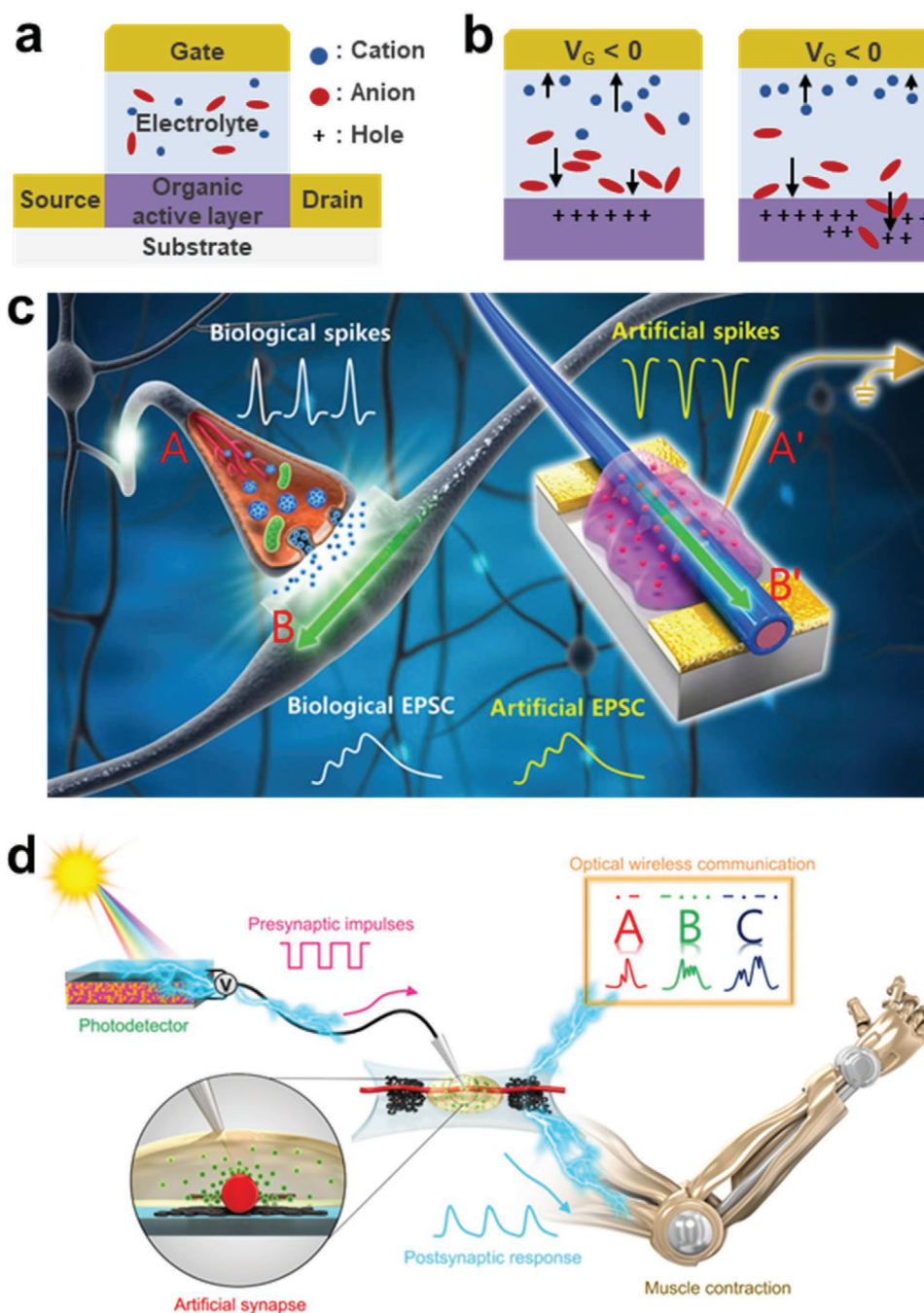


Figure 3. OSTs and their applications for artificial synapses/nerves. a) Schematic of device structure of OSTs using electrolytes. b) Working mechanism of IGOSTs. When no bias is applied, cations and anions are distributed in equilibrium as in (a); when bias is applied, cations migrate to the gate and anions migrate to the OSC. They can either accumulate at an impermeable OSC (left), or penetrate a permeable OSC (right). c) Schematic of device structure of a core-sheath OSNW-based synaptic transistor. Reproduced with permission.^[43] Copyright 2016, American Association for the Advancement of Science. d) Schematic of organic optoelectronic sensorimotor nerve consisting of photodetector, synaptic transistor, and artificial muscle actuator (polymer actuator). Reproduced with permission.^[44] Copyright 2018, American Association for the Advancement of Science.

very thin (a few nanometers). If the OSC is permeable to ions, relatively long retention time over a few s is acquired as ions penetrate the electrolyte–OSC film interface under the additional gate voltage. In contrast, depletion mode had been demonstrated by OSTs that use poly(3,4-ethylenedioxythiophene): polystyrene sulfonate (PEDOT:PSS) as the channel material.^[36]

PEDOT:PSS intrinsically exhibits high conductivity, so the OST using PEDOT:PSS shows high current levels at the initial state (normally ON). As a positive gate voltage is increased, cations from the electrolyte are moved and injected into the PEDOT:PSS film, so the amount of holes in the PEDOT polymer is decreased, resulting in OFF state of the device

entering the OFF state. Due to the intrinsically high conductivity, the PEDOT:PSS-based OSTs are reported to show high energy consumption and limited dynamic range, whereas normally-OFF devices that use intrinsic OSCs have shown the low energy consumption and wide dynamic ranges, which are important for low-power and high accuracy operation of neuromorphic computing devices.^[7,41,42]

For applications of neuromorphic computing and artificial sensory systems, much efforts have been directed toward emulating both STP and LTP by using OSTs. Especially, ion-gel gated organic synaptic transistors (IGOSTs) can have good tunability between STP and LTP, like biological synapses. For instance, engineering microstructures of the OSC film in IGOSTs affects doping and de-doping dynamics of ions, so it can control the decay time; the microstructures can be modified by various fabrication conditions including annealing temperature, and use of a self-assembled monolayer on substrates.^[28,30] In addition, IGOSTs that use core-sheath organic semiconducting nanowires (OSNWs) can efficiently demonstrate both STP and LTP characteristics according to the number of electrical spikes. The core-sheath OSNWs consist of a polymer semiconductor (poly(3-hexylthiophene-2,5-diyl), P3HT) core wrapped with a polymer semiconductor (polyethylene oxide, PEO) sheath, so the different interactions (trapping and detrapping) of ions with PEO and P3HT facilitate both demonstration of STP and of LTP, depending on the presynaptic spikes (Figure 3c).^[43]

Furthermore, biological sensory and motor nerves have been developed using IGOSTs. In artificial nerves, IGOSTs process information received from sensory organs, and produce motor responses that depend on the processed information. An artificial sensorimotor nerve has been demonstrated;^[44] it consists of a photodetector, an IGOST, and polymer actuator; these components correspond to a photosensitive neuron, a neuromuscular junction, and a muscle fiber, respectively (Figure 3d). The photodetector generates excitatory pre-synaptic spikes when it receives optical signals. When the pre-synaptic spikes are applied to the electrolyte through the gate electrode of the IGOST, excitatory post-synaptic currents (EPSCs) are generated. They are converted to voltage signals by a trans-impedance circuit, then induce contraction of the polymer actuator to emulate the behavior of a muscle fiber. As the number of post-synaptic spikes is increased, the contraction of the polymer actuator is strengthened. The mimicry of a biological synapses and sensorimotor nerves using IGOSTs may enable demonstration of increasingly biorealistic sensing and responding operations, which are highly desired in bio-inspired electronics and neuro-robotics.

3. Requirements for Bio-Hybrid Neuromorphic Systems

Artificial synapses and artificial nerves have potential uses in wearable smart sensors and neural prostheses, and therefore, must be able to interact with a living body. Thus, bio-hybrid neuromorphic systems should be constructed by considering the interface between electronic devices and biological systems such as skin, heart, brain, and even a single neuron. Biological systems are composed of organic materials, protect themselves

from foreign bodies, have complex neural networks and behaviors, and process physiological signals that encode important information about the body. Therefore, to successfully realize bio-hybrid neuromorphic systems at bio-electronic interfaces, several features of neuromorphic devices should be well-matched to those of biological bodies. In this section, we survey recent research on neuromorphic devices and bio-electronics, then introduce strategies to meet the requirements that enable use of the OSTs to construct bio-hybrid neuromorphic systems and stably operate. Bio-hybrid neuromorphic systems that meet these requirements can be applied to healthcare devices, biomedical therapeutics, and prostheses.

3.1. Biomimetic Neural Functionality

Much recent research on neuromorphic electronics has focused on the emulation of various types of synaptic plasticity in a single artificial synapse, that is, considering only one synaptic connection between two neurons. Although replicating these characteristics is a basic but significant step for developing neuromorphic electronics, further investigation should consider the integrated, macroscopic level.

A real neural network performs much more sophisticated and complex operations and signaling than current neuromorphic electronics can achieve. Hence, as one approach to emulating the sophisticated information transmission and processing of the biological neural system, neuromorphic devices have been designed to have neural architecture and functionality that resemble those of biological neural systems. For example, in the body, neurons are immersed in a uniform environment, and global parameters including temperature and hormone concentration regulate the overall behaviors of complex neural networks that consist of intricately-interconnected neurons and synapses. This process is called homeostatic plasticity;^[45,46] it is the process of regulating synaptic weights throughout the network, and is therefore highly important for the stability of the neural network.^[46,47]

The homeostatic plasticity in a neuromorphic device was first demonstrated using OSTs that exploit liquid-electrolyte; the process of global gating was introduced by using a common electrolyte with a 4×4 array of the OSTs (Figure 4a).^[48] All conducting polymer channels (PEDOT:PSS) were in contact with the common electrolyte membrane, and Au electrodes were used as source, drain, and the global gate electrodes. Application of voltage spikes to the global gate electrode induces EPSCs in all OSTs by migration of anions in the common electrolyte. This simple concept of global gating with the shared electrolyte can demonstrate various modulations that originate from the homeostatic plasticity; that is., the output O_i of local synaptic weights can be effectively suppressed by increasing the amplitude of global gate voltage V_G from 0 to 700 mV (Figure 4b,c).^[46–48] Hence, the global gating structure offers biomimetic behavior that resembles the coupling between local activity and global oscillations in biological neural networks.

Furthermore, neurons compose neural networks including an immense number of synapses, and neuromodulators, such as astrocytes that regulate the synaptic weight to adapt to various complicated situations within pre-neurons and

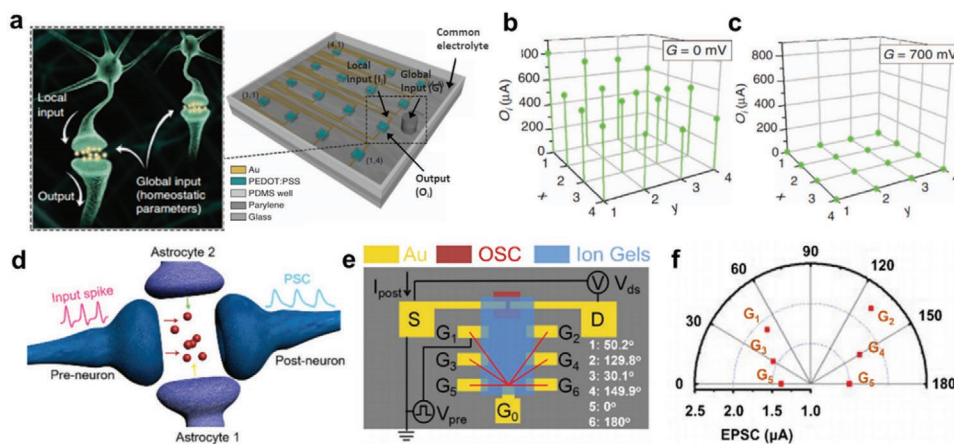


Figure 4. Biomimetic neural functionality of homeostatic plasticity and multi-input processing emulated by OSTs. a) Schematic of homeostatic plasticity emulated by the global-gating structure. All channels are in contact with a common electrolyte in which a global gate electrode serves as homeostatic parameters. b,c) Resultant outputs O_i depending on the amplitude of global inputs G . Reproduced with permission.^[48] Copyright 2017, Springer Nature. d) Schematic of multi-connections composed of two astrocytes, pre- and post-synaptic neurons. Reproduced with permission.^[47] Copyright 2020, The Royal Society of Chemistry. e) Schematic illustration of an IGOST with a multi-gate structure. f) Determination of spatial orientations of the input pulses; this was deduced by the different amplitude of EPSCs from the input pulses. Reproduced with permission.^[54] Copyright 2017, American Institute of Physics publishing.

post-neurons (Figure 4).^[49–52] These complicated connections between neurons and neuromodulators endow human neural networks with an ability to recognize hundreds of types of information about changes in cellular activity over space and time, even in the presence of noise.^[53]

To mimic the sophisticated multi-connections of biological neural networks, multi-gate synaptic transistors have been developed. IGOSTs with the multi-gate structure are composed of several in-plane gate electrodes and a common ion-gel polymer electrolyte (Figure 4e). The in-plane gate electrodes G_1 to G_6 are presynaptic neurons that receive external information; OSC channels are in contact with the common ion gel electrolyte and the Au source and drain electrodes are considered as the postsynaptic neurons that extract output signals. Each output has a distinct amplitude due to the different distance between G_0 and G_1 to G_6 . Thus, when the gate electrodes are stimulated by input spikes, their spatial orientations can be determined by comparing the amplitude of each output (Figure 4f).^[54]

3.2. Biocompatibility

Bio-signal sensing and prosthetic applications require neuromorphic devices that interface with biological systems without causing immune responses or damage to the body. Normal operation of bio-hybrid neuromorphic electronics requires that biological cells and bodies should be alive while they interface with electronic devices. To avoid ethical restrictions and minimize costs, initial stages of research use in vitro tests in which the devices usually interface with cells outside of living bodies; this approach provides an efficient way to evaluate operation at bio-electronic interfaces.^[39] The viability of cells can be reduced by the cytotoxicity of component materials of the device, and non-adhesive surface of the materials to the cells, so the biocompatibility of the devices can be unsatisfactory without

solving the issues of the cytotoxicity and surface adhesion of the materials.^[55,56]

Development of non-toxic synaptic devices and its cell-level integration has been focused for initial evaluation of biocompatibility. OSTs composed of fully non-toxic materials including natural biomaterials have been demonstrated as a solution to these problems.^[57,58] The OSTs were fabricated by using dinaphtho[2,3-b:2'',3''-f]thieno[3,2-b]thiophen (DNTT) as a semiconductor, Au as source/drain/gate electrodes, and dextran as a gate insulator. Dextran is a natural polysaccharide; this was its first reported use as a biocompatible gate insulator in an OST. All material components are non-toxic to living cells, so after complete immersion of the device in the cell culture medium, the cells survived for 5 days, and the number of cells had increased after 10 days, because they metabolized the dextran. In contrast, when OSTs composed of conventional gate insulating material (polystyrene) were used, the cells died just after 15 s (Figure 5a); these results reveal that OSTs composed of natural biomaterials are not cytotoxic, and can even be beneficial as nutrients.

Cell adhesion related to surface characteristics (e.g., topology, wettability, surface chemistry) of biocompatible synaptic devices can also improve cell viability.^[56] Furthermore, sensing and stimulating functions of electronic devices require close contact between the devices and biological tissues to transport charges and ions, so adhesion is an important property required for bioelectronics.^[59] OSCs that have hydrophilic surfaces promote cell adhesion better than hydrophobic surfaces because air bubble trapping on hydrophobic surfaces hinders protein adsorption (Figure 5b).^[60] In addition, implants composed of materials that have biologically non-adhesive surfaces are encapsulated and isolated by foreign body reactions, even if the materials do not induce toxic reactions and mechanical damage. Therefore, research on the surface properties of OSTs to improve surface adhesion will be a next direction in development of biocompatible artificial synapses.

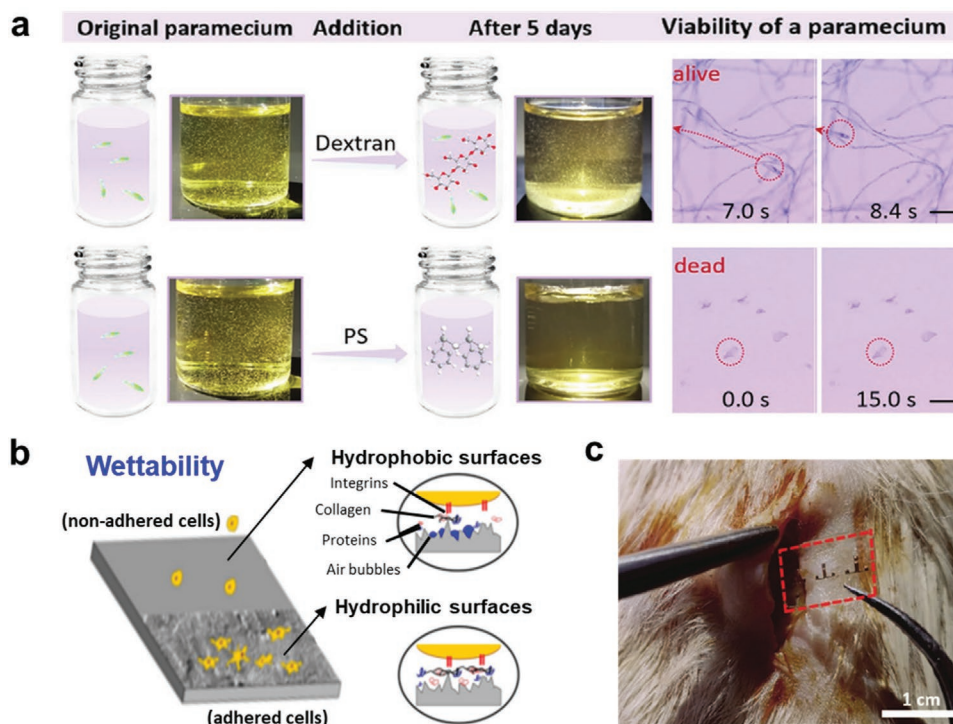


Figure 5. Biocompatibility for bio-hybrid neuromorphic systems: cytotoxicity, cell adhesion, and immune response. a) Evaluation of cytotoxicity of the OSTs composed of biomaterial (top) and conventional organic material (bottom). Reproduced with permission.^[58] Copyright 2020, Wiley-VCH. b) Effect of wettability on cell adhesion and viability. Reproduced with permission.^[60] Copyright 2018, Frontiers Media S.A. c) Photograph of implanting electrolyte-gated organic transistor into rat subcutis. Reproduced with permission.^[61] Copyright 2020, Wiley-VCH.

For applications in living bodies (in vivo), evaluation of biocompatibility including immune responses induced by implanted devices should also be conducted in vivo, even if they are non-toxic and provide good cell adhesion in vitro. The immune response to an electrolyte-gated transistor composed of biocompatible and biodegradable materials was tested (Figure 5c).^[61] After implantation of this biocompatible and biodegradable electrolyte-gated transistor into the subcutis, which is a layer of skin below the dermis of rat, the only initial immune responses were to the surgical incision and to foreign materials that had contaminated the lesion. The device dissolved in the body, and 7 days later, the tissues had fully regenerated. This electrolyte-gated transistor provided bio-signal recordings from the heart of the rat, without inducing any foreign-body response. This in vivo operation of the implanted OST verified its biocompatibility for implantable prosthetic applications.

3.3. Soft Mechanical Properties

Mechanically-flexible and even stretchable bioelectronic devices have been demonstrated. Flexible devices can be bent, compressed, and twisted, and stretchable devices can function even in response to physical deformations caused by natural motions of the body such as skin deformation, finger touch, and heart-beat (Figure 6a).^[62–65] Therefore, to be compatible with bio-hybrid applications, neuromorphic electronic devices should be flexible and stretchable. Furthermore, for bio-applications,

electronic devices must have a low Young's modulus Y that matches well with those of organs and tissues such as brain, heart, skin, blood vessels, and nerves; a low Y indicates softness.^[66–69] When a rigid device is attached to soft tissues, it can be easily detached by tissue movements; this process can lead to functional failures or even injure adjacent tissues.^[70–74] Especially for implanted devices, the mechanical matching of implants with tissues can avoid inflammation such as foreign-body reaction, and can induce favorable cell adhesion and differentiation of neural cells.^[75–78] Hence, to achieve desirable mechanical properties (softness), bioelectronic devices have been produced using materials (e.g., polymers) that have low Y and high stretchability comparable to those of target tissues. Especially, many bioelectronic devices have been composed of elastomers, because they have Y of only a few megapascals, which minimizes the mechanical mismatch between devices and tissues, so the devices adapt well to physical deformations of tissues (Figure 6b).^[79,80] Mechanically-biocompatible electronic devices can also be developed by exploiting geometrical structural modulations such as wavy patterns,^[81,82] origami,^[70,83] and kirigami,^[71,72] which can impart stretchability to the devices.^[73] These soft mechanical properties are important both to increase devices' lifetime and prevent health impairment.

A fully-stretchable synaptic transistor was first demonstrated using poly(dimethylsiloxane) (PDMS) as the elastomer (Figure 6c).^[74] PDMS has a low $Y \approx 1$ MPa, so it is widely used as the substrate and matrix of stretchable devices. For stretchable source and drain electrodes, Ag nanowires coated with Au nanoparticles (AgNWs–AuNPs) were embedded in PDMS. This

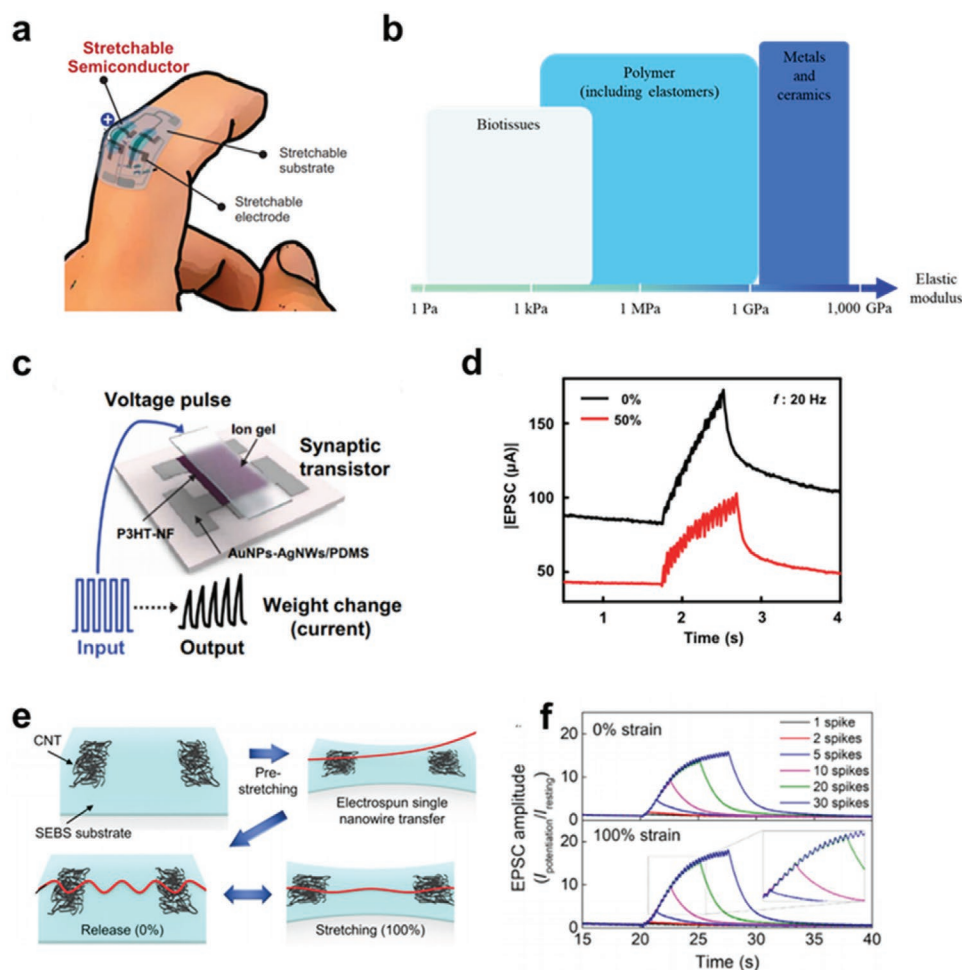


Figure 6. Soft mechanical properties required for OSTs. a) Schematic of fully stretchable and wearable devices on a finger. The stretchable electronic device must endure various physical deformations that originate from skin deformation. Reproduced with permission.^[62] Copyright 2017, American Association for the Advancement of Science. b) Elastic modulus of materials compared to bio-tissues. Reproduced with permission.^[80] Copyright 2019, The Royal Society of Chemistry. c) Schematic device structure. d) EPSC graphs measured after 20 successive pre-synaptic spikes of a stretchable IGOST. Black lines: non-stretched devices; red lines: 50% stretched devices. Reproduced with permission.^[74] Copyright 2019, American Association for the Advancement of Science. e) Fabrication procedure of the stretchable IGOST with wavy patterned semiconducting OSNW. f) SNPD characteristics with 1 to 30 spikes under 0% and 100% strains. Reproduced with permission.^[44] Copyright 2018, American Association for the Advancement of Science.

system of AgNWs–AuNPs in PDMS allows the electrodes to have high stretchability during repeated stretching cycles.^[65,84] The stretchy semiconductor was formed by blending a semiconductor (poly(3-hexylthiophene) nanofibrils, P3HT-NFs) with the elastomeric matrix (PDMS). This blended system of semiconductor in PDMS can increase the stretchability of the P3HT, while retaining the electrical properties of the semiconducting polymer even in a stretched state.^[85] The P3HT-NFs were evenly embedded in PDMS throughout the blends, so the uniformity of the IGOST and mechanical stability of device responses under strain were improved. The device showed various synaptic properties such as EPSC, PPF, STP, and LTP up to 50% stretching deformation. In the synaptic transistor, the current level and linearity of potentiation decreased in the stretched state, because stretching degraded the P3HT crystallinity and the geometric parameters of channel length and width (Figure 6d).^[86] Maintaining synaptic characteristics of fully-stretchable synaptic transistors under mechanical deformation remains a challenge.^[44]

Another fully stretchable synaptic transistor was developed by introducing a geometrically stretchable layout of wavy patterns as the semiconducting layer (Figure 6e).^[44] Organic semiconducting nanowire (OSNWs) was fabricated on a pre-stained (100%) elastic substrate of styrene ethylene butylene styrene (SEBS).^[44] As the strain was released, the shrinkage of the substrate transformed the ONWs to a “wave-like” structure. The device retained various synaptic properties even under 100% strain, without any detrimental effects on the semiconductor (Figure 6f).

Further, free-standing nanomesh-structured devices that have no substrates have been developed in the field of stretchable electronics, and can be applied to bio-hybrid neuromorphic electronics.^[87] Because of their thinness, freestanding types exhibit conformal contact to arbitrary surfaces.^[88,89] In addition, the nanomesh-structured conductors and semiconductors are composed of randomly-deposited fibers in a plane, and various porous structures can be adopted in these

electronics. Therefore, nanomesh-structured devices are highly stretchable due to randomly distributed nanowires and porous structures.^[90] Moreover, nanomeshes are porous and therefore permeable to air and extracellular medium, which are vital to the survival of biological tissues.^[87,91] Durable, gas-permeable, highly stretchable, and lightweight nanomeshes have been demonstrated.^[92] Recently, a fully nanomesh-structured electrolyte-gated transistor using PEDOT:PSS as an active layer, which has the same structure with OSTs, were implemented. This device on free-standing nanomesh was attached to a human's fingertip and acquired ECG signals.^[93] Thus, these technologies are applicable to artificial nerves and increase the mechanical stretchability of devices.

3.4. . Low Energy Consumption

Applications of bio-hybrid neuromorphic electronics to health-care monitoring, biomedical systems, and smart sensors for IoT, require portability and the ability to process bio-signals on skin or even inside the body. To realize this ability, neuromorphic systems should operate without the need for abiotic devices and bulky integration.^[94–98] As a solution, neuromorphic devices must have low energy consumption, to enable minimization of the size of power supplies such as batteries and self-powered nanogenerators.^[99] Energy consumption E [J] of OST is a product of spike voltage V [V], the peak of output current I [A], and duration of output current t [s] as $E = V \times I \times t$. To reduce each value, two approaches to modification of OSCs have mainly been studied;^[100] (1) facilitation of ion penetration in the OSC and (2) miniaturization of the devices.

Molecular design of conjugated polymers by use of side-chain engineering increases the ion injection and transport

of electrolyte-gated transistors.^[100] A polymer with alkoxy side chains (poly(2-(3,3"-bis(tetradecyloxy)-[2,2"-bithiophen]-5-yl)thieno[3,2-b]thiophene), that is, p(a2T-TT)) showed mixed interfacial/bulk doping of ions in the electrolyte, whereas a polymer with ethylene glycol side chains (poly(2-(3,3"-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)[2,2"-bithiophen]-5-yl)thieno[3,2-b]thiophene), that is, p(g2T-TT)) dominantly exhibited bulk doping of ions due to increased ion conduction in the channel (Figure 7a). Specifically, glycol side chains promote interaction with the ions, so even at a low voltage of 0.5 V, the ions were easily doped into the p(g2T-TT). Thus, p(g2T-TT) devices showed higher volumetric capacitance at lower operating voltage than p(a2T-TT) devices.

Organic nanowires (ONWs) are advantageous for minimizing device size, which effectively reduces energy dissipation. OSTs that used electrospun PEDOT:PSS/polyacrylamide(PAAm) ONW channels and PBS solution containing Na^+ , K^+ , and Ca^{2+} cations achieved low switching energy ≈ 113 fJ (Figure 7b).^[41] Hydrophilic PSS provides ion-conducting sites, and the large surface-to-volume ratio of ONWs endows easy ion injection from all directions. Moreover, decreasing the number of ONWs in the device decreased channel width and therefore reduced energy consumption.

The lowest energy consumption of ≈ 1.23 fJ, which rivals the energy consumption of biological synapses, was reported by using a single P3HT/PEO core/shell ONW (Figure 7c,d).^[43] With the aid of nanowire lithography, IGOSTs that have ≈ 300 -nm channel length and width were achieved. This deep downsizing enables highly reduced energy dissipation of the IGOSTs.

As further directions for energy-efficient bio-hybrid applications, low energy consumption of artificial sensory systems should be also demonstrated. Recently, two approaches have

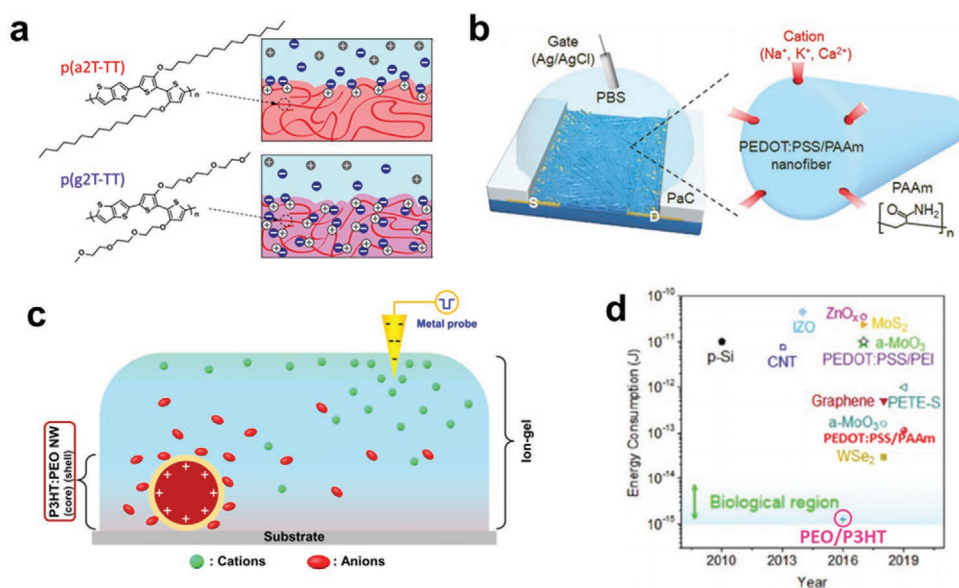


Figure 7. Strategies to achieve low energy consumption by OSTs. a) Ion doping on the polymer with the alkoxy (red) and glycol (blue) side chains attached to polythiophene backbone. Reproduced with permission.^[100] Copyright 2016, National Academy of Sciences. b) Ions can be injected to PEDOT:PSS/PAAm ONW channels from all directions. Reproduced with permission.^[41] Copyright 2021, Wiley-VCH. c) IGOSTs using P3HT/PEO core/shell ONWs. Reproduced with permission.^[43] Copyright 2016, American Association for the Advancement of Science. d) Comparison of energy consumption for STP operation of synaptic transistors depending on the active layer. Reproduced with permission.^[41] Copyright 2021, Wiley-VCH.

been studied: (1) artificial sensory synapses and (2) self-powered artificial nerves.

Artificial sensory synapses combine sensory and synaptic functions in a single device, so they are advantageous to reduce the size of the neuromorphic systems by eliminating the need for additional sensing and wiring elements. For example, free-standing pyramid-structured ion-gel was used as a dielectric layer for pressure sensing in IGOSTs.^[101] When pressure was applied, the capacitance of the ion gel increased due to the increase of contact area between the top electrode and ion-gel, so the synapse produced EPSCs because of the increase of the effective gating to the OSC channel.

Self-powered sensors generate the sensory signals by converting bio-signals without a power supply and they can even store the energy to feed the whole system for long-term and continuous operation in the human body. Therefore, self-powered neuromorphic systems can process the bio-signal without consuming energy or needing a power supply that must be replaced surgically. For example, an energy-efficient optoelectronic neuromuscular system was demonstrated by integrating self-powered photodetectors with IGOSTs and artificial muscle (polymer actuator).^[18] The system perceived and propagated optical sensory inputs and generated informative synaptic responses and subsequent motor outputs. In the human body, thermal and chemical energies can also be used as the energy source for self-powered systems.^[102] Therefore, self-powered neuromorphic systems that use IGOSTs will realize energy-efficient monitoring of various bio-signals such as body temperature, respiration rate, and blood glucose level.

4. Implementation of Bio-Hybrid Neuromorphic Devices and Systems

Bio-hybrid neuromorphic systems will realize biomimetic signal transmission at bio-electronic interfaces for bio-medical applications such as neuroprostheses and healthcare monitoring. To achieve these applications, bio-hybrid neuromorphic devices and systems have been constructed by integrating the artificial synapses/nerves with biological systems. This section reviews recent research on implementation of bio-hybrid neuromorphic devices and systems that use electrolyte-gated synaptic transistors as artificial synapses.

4.1. Bio-Hybrid Neuromorphic Devices

In biological neural networks, the synapse is the basic unit of signal transmission. Therefore, emulation of synaptic characteristics by artificial synapses and their co-implementation with living neurons, are important to construction of bio-hybrid neuromorphic systems. For this purpose, an OST interfaced with neuronal cells in liquid electrolyte had been reported.^[103] In the OST, Au nanoparticles were embedded in the interface between OSC (pentacene) and a substrate; the device demonstrated STP characteristics with various spike frequencies at bio-voltage of 50 mV (Figure 8a,b). In addition, human neural stem cells adhered to and differentiated on the OSC of the OST, and in the presence of the cells, the OSTs maintained STP response. After

6–7 days of differentiation of the stem cells to form neurons on the devices, the amplitude of the STP response changed.

A liquid-electrolyte-gated OST was coupled with dopaminergic cells to constitute a bio-hybrid synapse that showed neurotransmitter-mediated synaptic plasticity. A bio-hybrid synapse exhibited synaptic plasticity with neurotransmitters (dopamine) released from the cells.^[17] In these bio-hybrid synapses, the presynaptic domain of pheochromocytoma cells (PC-12) that release dopamine was seeded on a postsynaptic PEDOT:PSS gate to form a bio-hybrid synaptic cleft, and the cell culture medium of PC-12 was used as the electrolyte (Figure 8c,d). Dopamine released from the PC-12 cells was oxidized at the PEDOT:PSS postsynaptic gate; this process changed the charge state of the gate electrode and induced ion flow in the electrolyte. The result was a change in conductance of the PEDOT:PSS postsynaptic channel. During the process, the induced ion flow caused short-term change of synaptic weight (independent of dopamine concentration), whereas dopamine oxidation caused long-term change of the neuromorphic channel (Figure 8e). This cell-level interactive biochemical signaling in bio-hybrid synapses may demonstrate a way to combine artificial neuromorphic systems with biological neural networks for actual applications of complex bio-hybrid systems.

4.2. Bio-Hybrid Neuromorphic Systems

Further attempts to integrate neuromorphic devices with biological components at the system level have connected artificial sensory nerves to biological cells or nerves. Artificial sensory nerves that had sensing and information-processing functions were developed and used in these bio-hybrid neuromorphic systems.^[16]

A bimodal artificial sensory nerve was interfaced with skeletal myotubes to demonstrate a bio-hybrid neuromuscular junction (Figure 9a).^[16] When one interacts with one's surroundings, one receives sensory information from various types of receptors, then processes it to achieve accurate and reliable recognition of the environment. To emulate this sophisticated perceptual behavior, the systems consisted of a pressure sensor and a photosensor that converted external haptic and visual information to electrical signals. For signal integration and processing, these signals were transmitted through an ionic cable to an OST by using an indium–tin-oxide channel layer and polyvinyl alcohol (PVA) ion-gel. This sensory nerve with haptic-visual fusion exhibited multiple current levels, depending on the extent of synchronization between two sensory inputs, and this synchronization determined the output voltage that stimulated the myotubes. As synchronization improved, the contraction of myoblasts was strengthened (Figure 9b). Thus, this bio-hybrid system successfully mimicked biological multimodal perceptual capabilities and body-motion control.

Although artificial sensory nerves with cell-level integration have been used to emulate biological functions and achieve biological responses, bio-medical applications require body-level integration. To achieve these purposes, artificial sensory nerves have been integrated with biological motor nerves of an insect leg to demonstrate a bio-hybrid reflex arc (Figure 9c).^[18] An artificial sensory nerve emulated both the perceptual processing

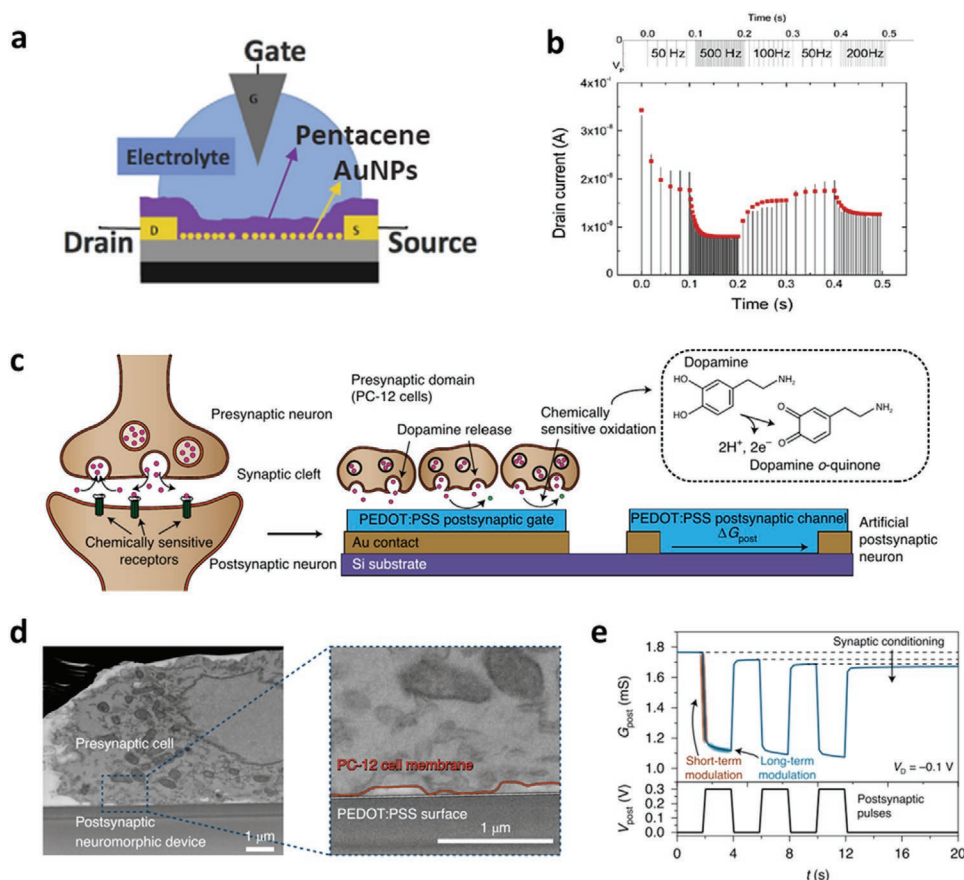


Figure 8. Bio-hybrid neuromorphic devices; interfacing an OST with biological neurons. a) Schematic representation of OST based on AuNPs and pentacene. b) Frequency-dependent STP responses of OST using -50 mV. Reproduced with permission.^[103] Copyright 2016, Elsevier B.V. c) Schematic of the structure of bio-hybrid synapses consisting of PC-12 cells and the PEDOT:PSS-based OST. d) Cross-sectional scanning electron microscope image of a PC-12 cell plated on PEDOT:PSS. Inset: cell membrane (red)/electrode (white) interface. e) Synaptic modulation of conductance of PEDOT:PSS postsynaptic channel by postsynaptic spikes. Reproduced with permission.^[17] Copyright 2020, Springer Nature.

and component functions of biological counterparts. For this purpose, the artificial sensory nerve consisted of a pressure sensor, an organic ring oscillator, and an IGOST which respectively correspond to a mechanoreceptor, a nerve fiber, and a synapse. Pressure information received by the pressure sensor was converted to spike-form signals by the ring oscillator, then the signals were fed to the IGOST for information processing. This artificial sensory nerve was interfaced with biological motor nerves of a detached insect leg to form a bio-hybrid reflex arc. In this system, the movement speed of the insect leg increased as pressure was increased. Among the bio-hybrid neuromorphic devices and systems, this work demonstrated the same frequency range of action potentials as biological systems (Table 1). Thus, this successful demonstration of biological processes, structures, and parameters suggests the applicability of artificial sensory nerves for use in neuroprostheses.

5. Conclusion and Outlook

We have reviewed recent progress in bio-hybrid neuromorphic systems that use OSTs. OSTs have emulated various synaptic properties of biological synapses. Integration of OSTs with

sensors and actuators has yielded biomimetic sensory and motor nerves. Implementation of these neuromorphic electronics in bio-hybrid applications requires OSTs that mimic the functionality of biological nerves, and must be biocompatible, mechanically flexible/stretchable, and consume low energy. Recent research on bio-hybrid neuromorphic electronics is in an early stage, so it has mainly focused on emulation of simple functions and structures of biological nerves. Among the OSTs, IGOSTs have demonstrated synaptic plasticity and sensori-motor functions due to good tunability between STP and LTP, like biological synapses. As state-of-the-art systems, bio-hybrid nerves that connect artificial sensory nerves using IGOSTs to biological motor nerves, demonstrated the bio-hybrid reflex arc.

For further studies, the OST-based bio-hybrid neuromorphic systems can adopt closed-loop operation, so feedback can be conveyed to the biological systems by electrical, optical, or chemical stimuli, depending on the processed outputs of bio-signals; this feedback operation can then help to determine the next step in bio-signal processing. Thus, these systems are capable of bi-directional signaling with biological systems, and of in situ adaptive and user-dependent operation that is beneficial for bio-medical applications. Use of artificial synapses and nerves may remediate loss of sensory functions and

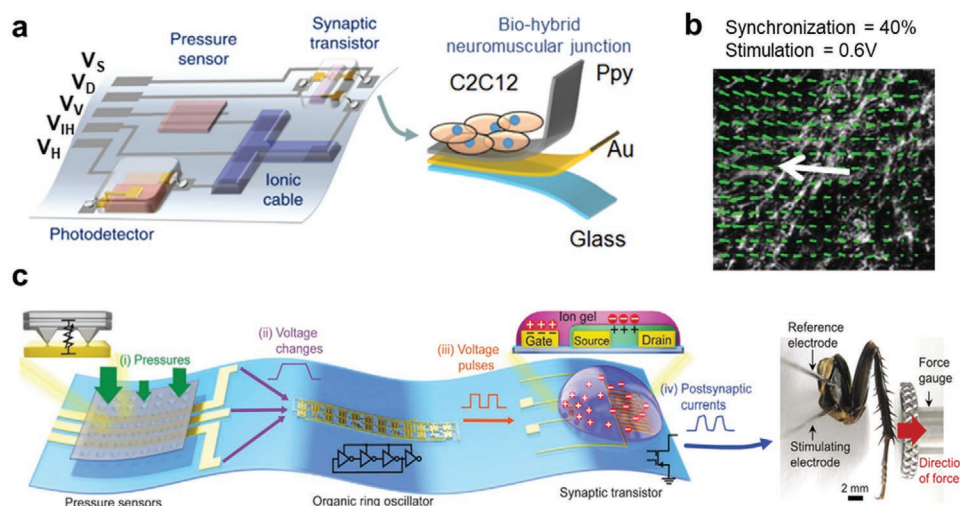


Figure 9. Bio-hybrid neuromorphic systems; artificial sensory nerves used to actuate biological muscle cells and motor nerves, respectively. a) Schematics of bimodal artificial sensory neuron with visual–haptic fusion and bio-hybrid neuromuscular junction by connecting the artificial neuron to the myotubes. b) Velocity mapping of muscle contraction. With increasing synchronization between pressure and light inputs, the contraction of myoblasts was strengthened; arrows: direction of myotube motion. Reproduced with permission.^[16] Copyright 2020, Springer Nature. c) Schematics of bio-hybrid reflex arc composed of artificial sensory nerves and biological motor nerves. Reproduced with permission.^[18] Copyright 2018, American Association for the Advancement of Science.

degenerative neural diseases, such as Alzheimer's and Parkinson's diseases. For this purpose, replacement and connection of biological neurons with artificial ones can be realized owing to similarity of signal transmission. In addition, by replacing the autonomic nervous systems that communicate with internal organs, artificial systems can regulate physiological processes such as blood glucose trends, heart rate, and respiration. Finally, regeneration of biological tissues may be promoted by stimulating damaged cells. These suggestions indicate that bio-hybrid neuromorphic electronics can provide various functions that include diagnosis and therapeutics of diseases, replacement of damaged or degenerative biological nerves, and regeneration of biological tissues.

Researchers have already accomplished tremendous advances in bioelectronics, and they are coming close to

commercialization. We envision that, with these advances, bio-hybrid neuromorphic electronics that exploit OSTs will be used in next-generation healthcare monitoring and neuroprosthetic systems for a wide range of bio-medical applications.

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Table 1. Bio-hybrid neuromorphic devices and systems emulating biological functions and parameters.

Emulated parts	Interfacing biological parts	Emulated property	Parameter comparison between biological and artificial systems			Ref.
			Emulated parameters	Biological systems	Neuromorphic systems	
Synapse	Neurons	Operating voltage of action potential	Operating voltage	$\approx 100 \mu\text{V}^{\text{a}}$	$\approx 50 \text{ mV}$	[103]
Synaptic cleft	Neurons	Neurotransmitter-modulated synaptic plasticity	Detection limit for neurotransmitters	Single vesicle from a single synapse	Numerous vesicles from many synapses of cultured neurons ^{b)}	[17]
Neuromuscular junction	Muscular cells	Bimodal perceptual capability ^{c)}	Time interval for synchronization ^{d)}	$\approx 45 \text{ ms}^{\text{e}}$	$\approx 1000 \text{ ms}$	[16]
Reflex arc	Motor nerves	Tactile perception	Frequency of action potential ^{f)}	0–100 Hz	0–100 Hz ^{g)}	[18]

^{a)} Extracellular action potential; ^{b)} Artificial synapses modulate synaptic weight by detecting plenty of neurotransmitters released by many synapses in cultured neurons, whereas biological synapses can change the weight at a single-vesicle level; ^{c)} Biological systems receive and process various types of sensory information, that is, multimodal perception, to achieve accurate and reliable recognition of the environment; ^{d)} For multimodal perceptual capability, different types of sensory information should be synchronized; time interval between two signals determines whether they are synchronous or not; ^{e)} For visual and haptic signal synchronization of human beings, the maximum time interval between these two signals was $\approx 45 \text{ ms}$ ^[104]; ^{f)} Biological SA-I afferent nerves fire the action potentials in the frequency range of 0–100 Hz^[18]; ^{g)} Operating frequency of the artificial afferent (sensory) nerves.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

artificial nerve, artificial synapse, bio-electronic interface, bio-hybrid system, ion-gel gated organic synaptic transistor

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