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Multimodal Platforms for Light-Mediated Organic Bioelectronics

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The development of bioelectronic devices has significantly advanced the field of clinical diagnosis and therapy. Recent progress in light technology has attracted considerable attention as a promising approach for wireless modulation of biological functions. In addition to classic electrical interaction, the integration of optics in bioelectronics introduces new complementary paths for interfacing cells. In this perspective article, the working principle of optobioelectronics, is discussed highlighting the advantages of using organic materials. Then, an overview of the achievements are provided in terms of electrical and molecular regulation of biological processes, with a special focus on devices based on poly(3-hexylthiophene) (P3HT) and poly(3,4-ethylenedioxythiophene):poly(styrene sulfonate) (PEDOT:PSS). A multimodal platform that combines different classes of light-responsive organic materials to create a highly dynamic interface is finally envisioned. It is suggested that this approach will enable the seamless integration of bioelectronics with biological tissues and the creation of a stable communication pathway.

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1. Introduction

Born in the late 18th century,[1,2] bioelectronics aims to integrate biological systems with electronic devices to monitor and regulate various biological activities, ultimately diagnosing and treating pathological disorders while restoring lost physiological functions.[3–5] The fabrication of the first microelectrode in the 1950s paved the way for bioelectronic devices that interface with electrogenic cells (**Figure 1**).[6–8] The development of electrodes with micron-scale dimensions allowed for the replacement of patch clamp and cellular electroporation techniques, enabling non-invasively stimulation and recording of action potentials in cardiac cells and neurons with single-cell resolution.[9–12] Depending on the desired type of stimulation, different materials have been employed to realize bioelectronic devices in various configurations, ranging from multi-electrode arrays to field effect transistors.[13–17] Additionally, efforts have been made to design micro- and nanopatterned substrates with 2.5D/3D topographies to enhance cell-electrode coupling, thereby improving the efficiency of cell-chip communication.[18–21]

These advancements have been applied in both in vitro fundamental research and in vivo therapeutic applications. Beginning with the first cardiac pacemaker in 1958, numerous cutting-edge implantable bioelectronic devices have been developed for specialized biomedical purposes, and the number of studies and applications in this field is expected to grow significantly in the coming years.[22,23] According to the *Global Bioelectronics Market 2024* report, which analyzes manufacturers, regions, types, and applications with forecasts extending to 2030, the global bioelectronics market was valued at USD 16.39 billion in 2023 and is anticipated to reach USD 23.72 billion by 2030. Despite these advancements, cell interface technologies have primarily made a notable clinical impact due to the various unresolved biological and technological challenges that must be addressed to achieve precise, reliable, and long-term tissue recording and stimulation without causing adverse effects within the biological system.[17,23–25]

Organic semiconductors, discovered in 1977, have shown great potential for these applications due to their biocompatibility, low mechanical stiffness, stability, and mixed conduction properties.[26–28] These characteristics enable a more biomimetic, tissue-like assembly, facilitating long-term integration and minimizing the immune response to foreign devices.[4,29,30] For

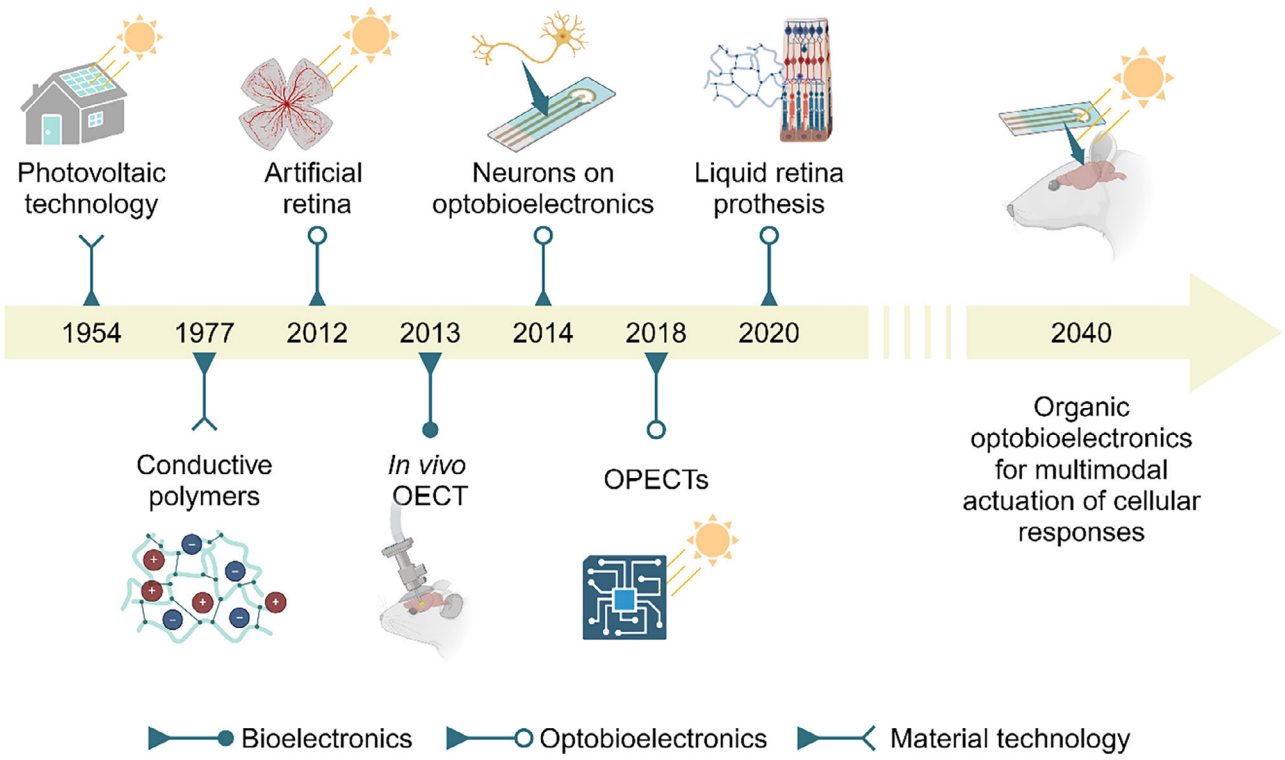

Figure 1. Key steps in the development of light-mediated organic bioelectronics. A series of strategies were developed over the years to improve the recording and stimulation of cellular electrical signals. Material science gave a boost to the development of bioelectronic devices with the discovery of photovoltaic materials in 1954[42] and conductive polymers in 1977.[43] The combination of these concepts led to the first interfacing of electrogenic cells with optoelectronic devices in 2012 for vision restoration[44] and in 2014 for light-mediated neuronal stimulation.[45] A new type of organic device, Organic Photo-ElectroChemical Transistor (OPECT), was introduced in 2018 as a high-performance platform for numerous biological detections, other than neuromorphic devices.[46] The first optobioelectronic prosthesis was implanted in 2020 and involved the use of light-sensitive conductive polymers to rescue visual functions.[47] Taking together these advances with the knowledge on cellular mechano-transduction and wearable electronics will soon provide us with the next-generation of organic optobioelectronic devices with multimodal actuation of cellular behavior. Milestones in the world of bioelectronics are indicated by the filled circle, while major advances in optobioelectronics are shown with an open circle, and discoveries in material technology by an inverted arrow.

example, organic electrochemical transistors (OECTs) have recently emerged as powerful bioelectronic devices with their capability to transduce biological signals.[31] However, it was nearly three decades after their initial development before OECTs were used in an in vivo application.[30]

Advancements in optics and materials technology have introduced a new paradigm in the field of bioelectronics.[32,33] Starting with the fabrication of the laser in 1960, several highly complex optical elements have been introduced to control the spatial profile of light beams and allow the generation of both static and dynamic light patterns, finding applications in high-resolution microscopy,[34] endoscopy,[35] phototherapy,[36] and optogenetics.[11] On the materials side, research in optobioelectronics was boosted by the ability of photovoltaic technology to stimulate electrogenic cells and the retina, demonstrating the potential of organic semiconductors in organic optobioelectronics.[37–39] By leveraging light, it is now possible to remotely modify the properties of specific photosensitive conductive electrodes, enabling electrical, mechanical, or biochemical actuation of cells with high spatial and temporal resolution, without the need for potentially damaging voltages or genetic modifications. Furthermore, the dynamic tuning of these optobioelectronic devices more effectively mimics the native biological environment.[38,40,41]

This perspective provides an insight into the multiple applications enabled by light-sensing bioelectronics and an overview of organic materials and devices developed in the field, which have found application in the biomedical field for both electrogenic and non-excitable cells. Last, we provide a critical discussion on the upcoming challenges in the research area, with an outlook on new opportunities toward the clinical and industrial translation of this emerging technology.

2. Light-Mediated Actuation of Cellular Activity

The core element of a light-responsive bioelectronic device is the semiconductive material, which acts as both a light absorber and a transducer. When a photo-responsive material immersed in an electrolyte solution is exposed to light, three key mechanisms can be activated (**Figure 2**): photo-thermal, photo-electrical, and photo-chemical.[48–50] These processes play different roles in modulating cellular activity.

In the photo-thermal process (Figure 2a), photon energy is converted into heat, leading to an increase in the temperature

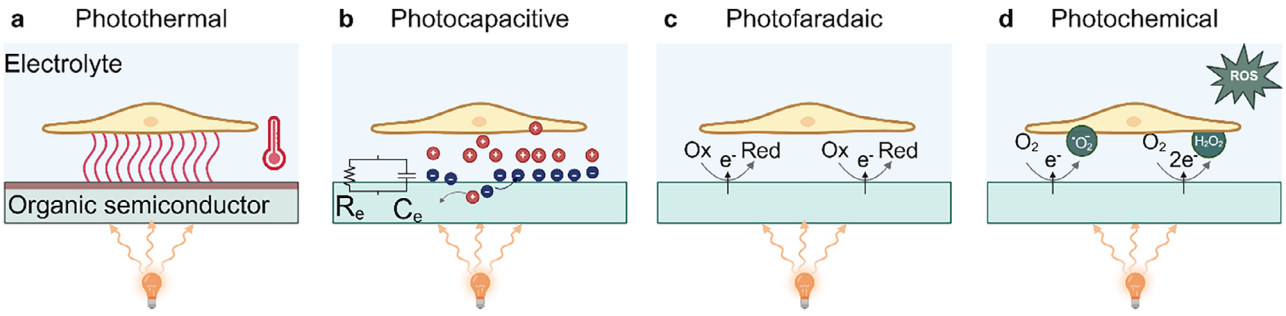

Figure 2. Schematics of light-mediated cell stimulation in bioelectronic devices. When organic films immersed in a cellular environment are exposed to light, four main processes occur at the cell-electrode interface: a) photothermal, b) photocapacitive, c) photofaradaic, and d) photochemical.

of the surrounding environment. If cell membranes are in close proximity to the material, this temperature rise can influence cell proliferation and metabolic pathways. Additionally, the electrostatic properties of electrogenic cell membranes are temperature dependent. Specifically, an increase in temperature induces a depolarizing current—an inward flow of positive ions—that enhances double-layer capacitance and reduces impedance. This membrane depolarization, in turn, triggers intracellular signaling pathways primarily mediated by calcium ions.[51–53]

The working principles of electrical actuation are based on the injection of current from an electrode into a physiological medium to alter the membrane potential of nearby excitable cells. In photoactive bioelectronic devices, light absorption is translated into the generation of current at the electrode interface via capacitive or faradaic processes.[50] This current can create a voltage gradient in the extracellular space that polarizes the cell, thereby actuating voltage-gated channels and leading to action potentials. In photo-capacitive mechanisms (Figure 2b), light induces the reversible formation of electrochemical double layers [54] while in photo-faradaic mechanisms (Figure 2c), light triggers redox reactions that may or may not be reversible.[55]

In the photo-chemical mechanism (Figure 2d), light generates excited states, mainly charged states, which give rise to specific chemical reactions at the surface. For instance, oxygen rapidly forms reactive oxygen species (ROS), which play a crucial role in regulating many cellular processes like cell differentiation and signaling.[56–58]

3. Organic Opto-Bioelectronic Devices

The development of electronic devices has traditionally relied on inorganic materials such as silicon and metals due to their high conductivity, ease of handling, abundance in nature, long-term stability, manufacturing reliability, and energy efficiency. However, when transitioning to biological applications, these materials face a significant challenge: integration with living tissues. Their mechanical properties differ greatly from those of biological tissues: silicon semiconductors have a Young's modulus of ≈130 GPa, whereas biological tissues range from 1 kPa to 20 GPa.[59,60] This mismatch results in poor cell-chip coupling and an increased risk of immune response.[61,62]

A promising alternative for bio-interfacing is soft organic materials, though they are typically insulators. This has driven recent research toward developing new classes of organic materials for bioelectronics, such as conjugated polymers (CPs) and hydrogels, which combine conductivity with favorable mechanical properties.[4,27,63,64] Moreover, in optoelectronics, organic materials have a distinct advantage over inorganic counterparts, as they exhibit high optical absorption coefficients, making them ideal for thin, flexible films.[65]

While several conductive and semiconductive polymers have been identified for bioelectronic applications (summarized in **Table 1**), current opto-bioelectronics research is focused on polythiophene derivatives.

In particular, P3HT and PEDOT:PSS are extensively studied due to their high conductivity, thermal stability, biocompatibility, and the possibility to tune their optical and electrical properties through doping and structural modifications.[71] These characteristics make them highly suitable for bioelectronic and optoelectronic applications, including devices such as biosensors, cell interfaces, and phototransducers.[37,72,73] On one hand, PEDOT:PSS stands out due to its exceptional electrical conductivity, mechanical flexibility, long-term stability, also in humid environments, and ability to be processed in water. Moreover, PEDOT can be synthesized in various forms such as nanofilms, nanorod arrays, and nanofiber mats, offering flexibility in device design and integration.[74] On the other hand, P3HT is the most widely used p-type semiconducting polymer in optoelectronics and electronics due to its wide availability, low cost, and easy processability. Beyond its electrical applications, P3HT is increasingly being explored in bioelectronics, particularly in the phototransduction of ROS.[75] This study will specifically explore the latest advancements in using these two materials for opto-bioelectronic applications.

4. Light-Actuated Bioelectronics with CPs: The P3HT Case

P3HT is a polymer belonging to the thiophene-based materials family. Its unique optoelectronic properties stem from the weakness of π bonds, allowing electrons in these bonds to be excited by photons in the visible range. Initially, this excitability made it valuable for photovoltaic applications, but after confirming its biocompatibility, researchers began exploring its potential for interfacing with biological systems at different levels: in vitro, in vivo and ex vivo.[76–78] This interface offers the advantage of opto-electrical stimulation, enabling precise modulation of biological activity.[37] Several studies have demonstrated how this material

Table 1. Properties of conductive polymers commonly used in bioelectronics.

Polymer	Key Properties	Applications	Advantage	Disadvantage	Refs.
PEDOT:PSS	High conductivity, processable in water, (PEDOT:PSS)	OECTs, biosensors, and drug delivery	High stability, excellent biocompatibility, and electrochemical responsiveness	Limited photoactivity	[66]
P3HT	Semiconductive, photoactive, soluble in organic solvents	Optically driven neurostimulation, biosensors, antibacterial/anticancer surfaces, organic photovoltaics	Photoresponsive, good film-forming properties, model system for organic semiconductors	Lower conductivity, less stable in ambient conditions, moderate biocompatibility	[67]
Polypyrrole	Conductive, biocompatible, and mechanically flexible	Muscle/neural stimulation, tissue engineering scaffolds, biosensor	Easy synthesis, flexible, and known biointegration	Can degrade under prolonged stimulation	[68]
Polyaniline	Tunable conductivity, low flexibility	Biosensors, electrochemical devices, and environmental sensors	Tunable electronic properties, inexpensive, and chemically robust	Poor solubility, lower biocompatibility, rigid	[69]
Phenyl-C61-butyric acid methyl ester	Electron acceptor, often paired with P3HT	Organic photovoltaics, photodetectors, and electron transport in blends	High electron mobility, used in blends for charge separation	Poor biocompatibility, typically used only in composites	[70]

can influence cellular behavior. Furthermore, P3HT can be used to either stimulate or inhibit cell proliferation and differentiation, directing cellular activity in a controlled manner.[76,79,80]

The use of P3HT has already been shown to be suitable for theragnostic applications, which consist of the ability to localize and treat specific cells. In the work of Han et al., core–glycoshell theragnostic nanomaterials based on fluorescent glycoprobes and P3HT were developed for the treatment of cancer cells.[81] Core–glycoshell theranostic dots can be endocytosed by cells, and upon stimulation with a broadband light, they produce a concentration of ROS that destroys these cells. Ciocca et al. achieved similar results with neuroblastoma cells (SH-SY5Y) using a spin-coated film made of P3HT as the biohybrid interface.[82] The application of a specific and repeated light stimulation protocol, consisting of the alternation of 1 s of white light and 1 s of dark for 30 min twice a day, inhibited the cells proliferation, making P3HT even more suitable for the treatment of cancerogenic cells (**Figure 3**a,b).

Cell proliferation can be inhibited not only in human cells but also in bacteria. CPs have emerged as important materials for the photothermal treatment of bacteria, providing a valuable tool when antibiotics alone are insufficient for pathogen control (Figure 3c,d).[83]

In biomedicine, CPs also play a role in drug delivery systems, offering the potential for targeted and controlled drug release in response to light stimulation. This is particularly relevant in the field of dermal drug delivery, where drug confinement minimizes the risks of side effects.[84] One example is the development of dermal patches made of polycaprolactone and P3HT fibers, which, when stimulated by light, promote skin regeneration (Figure 3e,h).[85]

Tissue regeneration can be achieved through drug treatments at specific sites or by using induced pluripotent stem cells. Abdel Aziz et al. demonstrated that the timing and the effectiveness of human adipose derived stem cells differentiation can be influenced by using a thin P3HT film. Upon green light stimulation, P3HT is excited and, in turn, modulates cell membrane potential and Ca^{2+} concentration.[79]

The employment of P3HT for tissue regeneration is further confirmed by the work of Campione et al., which highlights not only its optoelectrical properties but also its surface characteristics–such as topography, stiffness, surface free energy, and roughness–as key factors in promoting the osteogenesis of human adipose-derived mesenchymal stem cells.[86] Additionally, P3HT serves as a bioactive stimulus, as demonstrated by Moccia et al. where the neovascularization is induced through the activation of the transient Receptor Potential Valloidin 1 by the optical excitation of the organic semiconductor (P3HT).[87] These are just a few examples in the literature of the applicability of P3HT polymer in different fields.

5. Other Opportunities for Light-Actuation with Conductive Polymers: The PEDOT Case

PEDOT:PSS is a p-doped composite material in which PEDOT (the conductive backbone) provides electrical conductivity, and PSS acts as a counter-ion to balance the charge and improve the water solubility and processability of PEDOT. As a result, the blend forms a soft conductive polymer with tunable mechanical properties, mixed ionic and electronic conductivity, and excellent processability.[72,88] The advantages of PEDOT:PSS include high conductivity, transparency, mechanical flexibility, and biocompatibility.[72,89] Moreover, due to its excellent processability, it can be easily deposited in thin layers by using techniques such as electrodeposition and spin coating, as well as patterned through lithographic methods.[89,90–92] PEDOT:PSS is a versatile material that combines numerous advantageous features, making it highly suitable for a wide range of organic electronics and bioelectronics applications.

In the electrodeposited version, for example, the PEDOT:PSS film is highly effective in maintaining stemness and promoting neurogenic differentiation, making it a promising material for neural tissue engineering.[93] The high conductivity of PEDOT:PSS has already enabled efficient electrical communication with biological tissue, and as an interface, it supports the development of neuronal networks.[94] Its potential

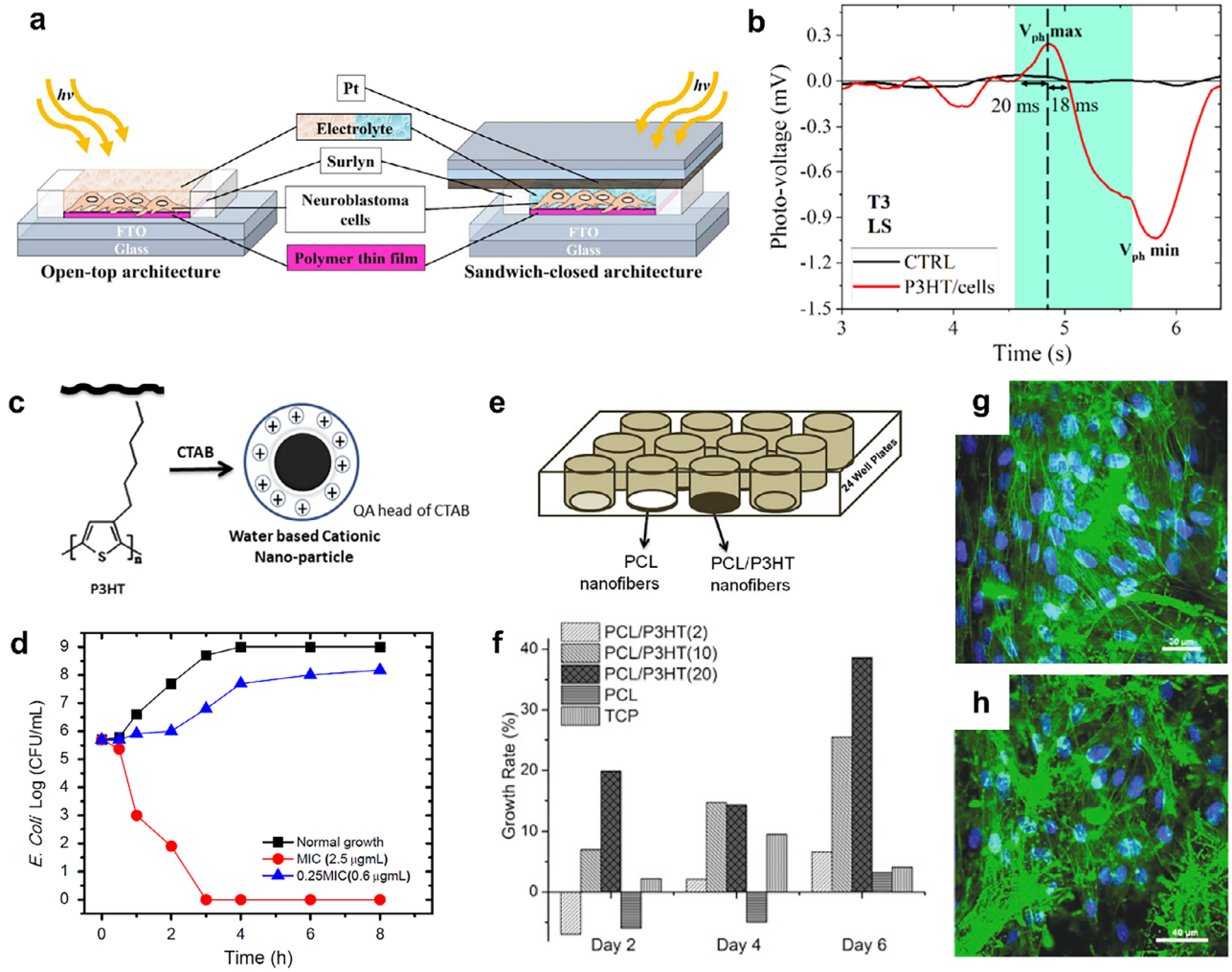

Figure 3. P3HT applications. a) Schematic of two different architectures of the bio–photoelectrolytic platform. b) Current clamp measurements for cells cultured on P3HT and on a control device exposed to light illumination (shaded green area). c) Structure of nanoparticles. d) Time-killing curves for P3HT nanoparticles against *E. coli*. e,h) Schematic of the working principle of the cell scaffold constructs (e), growth rate of cells on them with and without light stimulation (f), and confocal microscopic micrographs of cells grown on the scaffold with (g) and without light stimulation (h). a,b) are reproduced under the terms of the CC-BY license.[82] Copyright 2023, The Authors. Published by Wiley-VCH GmbH. c,d) are reproduced under the terms of the CC-BY license.[83] Copyright 2021, the Authors. Published by MDPI. e–h) are reproduced with permission from.[85] Copyright 2012, The Royal Society of Chemistry and Owner Societies.

application results are even more reliable when considering its long-term implantation properties and its use with bioelectronic devices.[10,89] Although PEDOT:PSS itself is not light-responsive, several strategies have been adopted to combine it with light-actuable materials, leveraging the unique properties of the respective polymers.[95] For example, Corrado et al. demonstrated the chemical functionalization of PEDOT:PSS with azobenzene moieties. Their use as a gate electrode in OPECT can emulate the visual pathways of the vertebrate retina.[96] These materials modulate current flow in response to light irradiation, enabling dynamic control of electrical signaling in biological tissues. Similarly, Kalachyova et al. exploited this chemical functionalization to modulate the conductivity of PEDOT:PSS through light-induced changes in the azopolymer component. Light exposure triggers the isomerization and redistribution of azopolymer chains, influencing the island-like distribution of PEDOT and thereby modulating its conductivity (**Figure 4a,b**).[97] These advances represent a significant step toward the realization of dynamic and responsive bioelectronic devices for a variety of biomedical applications.

Another approach is implemented in the work of Terenzi et al., who fabricated organic light-deformable conductive bilayered materials by spin-coating a first layer of azobenzene-based polymer, followed by a second layer of PEDOT:PSS. The light-responsive conductive interfaces can be reshaped by light into pillar-like structures, which are a well-known cell-instructive interface. The azopolymer/PEDOT:PSS substrate also facilitates the successful formation of supported lipid bilayers (SLBs), which are essential element for mimicking cell membranes and enabling biorecognition. Most importantly, these SLBs remain intact during substrate deformation, ensuring continuous functionality.[98] These methods allow for the preparation of

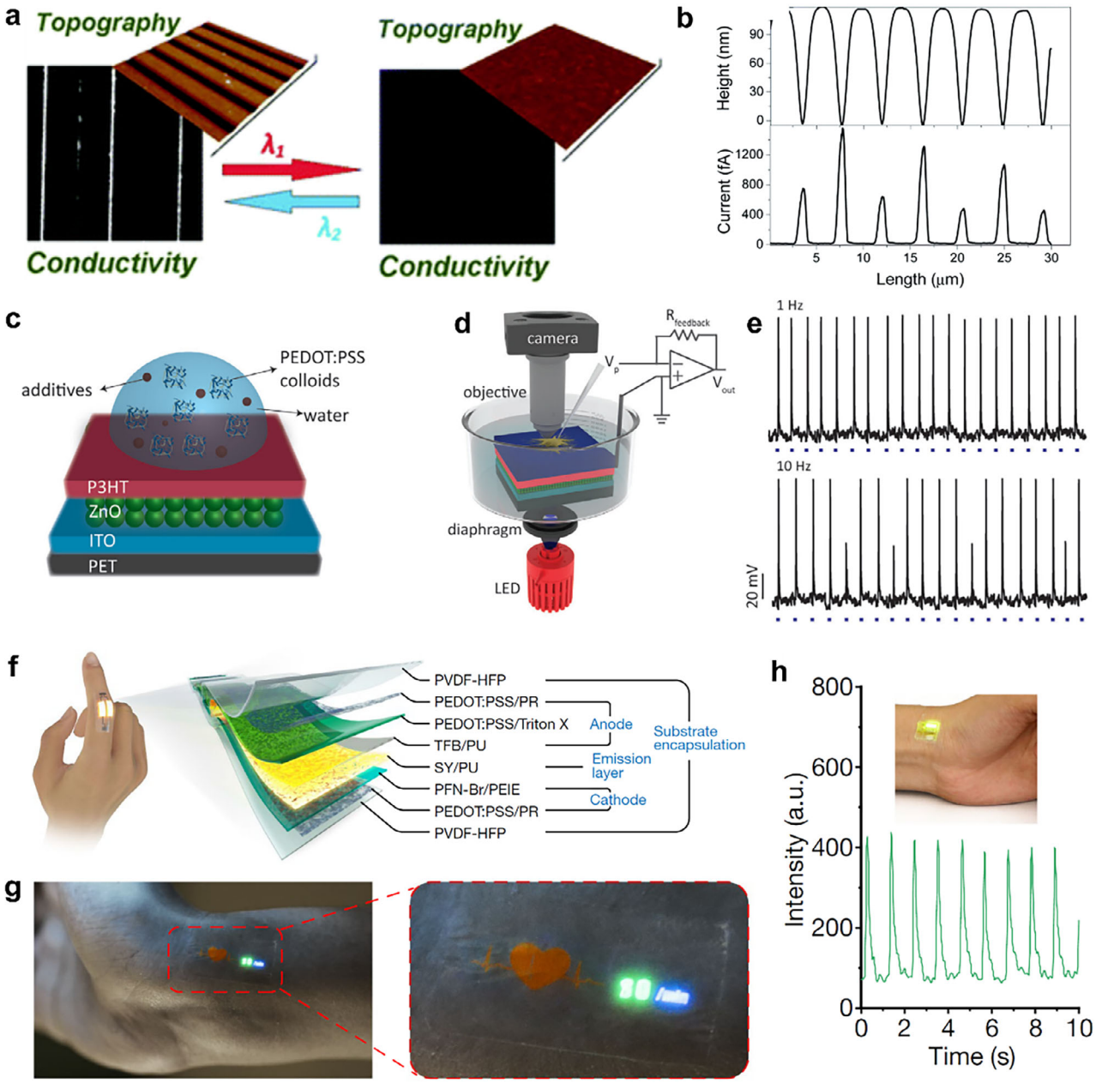

Figure 4. PEDOT:PSS for light-mediated bioelectronics. a) Surface morphology of the patterned PEDOT:PSS thin film with and without laser inscribed pattern. b) Comparison of the surface morphology profile and the corresponding conductivity map. c–e) Schematic of the hydrogel-integrated optoelectronic biointerface (c) and of electrophysiology patch-clamp measurement system (d) used to record the activity of primary hippocampal neurons (e). f) Structure of the wearable APLED. g,h) Photograph of the three-color light-emitting film attached to the arm (g) and real-time pulse measurement (h). a,b) are reproduced under the terms of the CC-BY license[97] Copyright 2018, The Authors. Published by the Royal Society of Chemistry. c-e are reproduced with permission.[100] Copyright 2022, Wiley-VCH GmbH. f–h) are reproduced under the terms of the CC-BY license.[101] Copyright 2024, the Authors. Published by Wiley-VCH GmbH.

composites that couple the electrical conductivity of PEDOT:PSS with the light-sensitive properties of azopolymers, opening new avenues for advanced materials in bioelectronic applications.

PEDOT:PSS can be also directly coupled with P3HT to build optoelectronic biointerfaces.[99,100] In particular, Han et al. coated a P3HT layer with conductive PEDOT:PSS hydrogels. The resulting devices enabled the stimulation of individual hippocampal neurons under low light intensities and facilitated light-triggered control of the beating frequency of cardiac myocytes (Figure 4c–e).[100]

Another way of utilizing light while taking advantage of the softness and transparency of PEDOT:PSS is through All Polymers Light-Emitting Diodes (APLEDs), which are now considered an ideal platform for wearable bioelectronic devices.[72] An example is the work of Zangh et al. that reported the fabrication of a stretchable APLED based on PEDOT:PSS electrodes and

light-emitting polymers. This flexible bioelectronic device can be applied to the skin and is capable of measuring human heartbeats (Figure 4f–h).[101]

6. Outlook

The studies presented highlight the transformative potential of light-responsive conductive polymers for different ranges of applications. These materials can simultaneously influence electrophysiological and proliferative cellular activities while modulating mechanical responses. This multi-functionality becomes particularly significant when different surface topographies are applied, offering the possibility to design complex shapes across multiple scales, from nano to macroscale.

We envision a future where bioelectronic systems are constructed from modular building blocks that can be selectively activated to elicit specific cellular behaviors. These behaviors may arise from a single stimulus—mechanical, electrical, or biochemical—or from synergistic combinations of these inputs. Light plays a pivotal role in this vision, serving as the cornerstone of technology. Its unique capacity for spatiotemporal control enables precise, on-demand stimulation, making it ideal for seamless integration into biological environments.

The materials studied thus far address critical challenges, including stiffness mismatches, biorecognition, and 3D structuring. However, the complexity of biological systems presents a major hurdle: the biological environment is inherently dynamic, characterized by continuous structural and functional reconfiguration. Consequently, there is a pressing need for bioelectronic devices that are not only functional but also adaptive—capable of maintaining their performance while responding to the evolving properties of the tissue they interface with. Light-responsive materials offer a compelling solution to this challenge. For instance, azobenzene-based polymers exemplify the potential of such materials. These polymers have been successfully integrated with organic semiconductors in bioelectronic devices, demonstrating biocompatibility and structural modifications that promote cell-instructive behavior.[102,103] Moreover, there are several ways of patterning them, including 3D printing, making them highly versatile.[104,105]

Looking forward, we propose that future research should prioritize the development of materials that integrate electrical conductivity with reshaping capabilities, particularly using additive manufacturing techniques. Coupling organic electronics with advanced 3D printing could provide new opportunities for precise spatial control over bioelectronic device components and circuits. Engineering light-responsive, conductive, and reshapable polymers compatible with such manufacturing methods would enable the rapid and cost-effective fabrication of flexible bioelectronic devices. These innovations would reduce intrinsic interfaces, enhancing seamless integration with biological tissues. Such devices would interact with cells in a multimodal fashion, adapting their behavior based on the specific triggers provided. Moreover, bioprinting, combined with the deposition of (bio)electronic inks, could improve biorecognition at the fabrication stage. Tissue engineering efforts should also consider employing human-induced pluripotent stem cell-derived cells, as these are likely to be found for clinical application in the near future.

This next generation of bioelectronic devices will initially provide profound insights into the mechanisms governing cellular and tissue behaviors, elucidating the intricate interplay between stimuli and biological responses. Ultimately, they will evolve to actively control these processes, unlocking new possibilities in regenerative medicine, therapeutic implementations, and advanced tissue engineering.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

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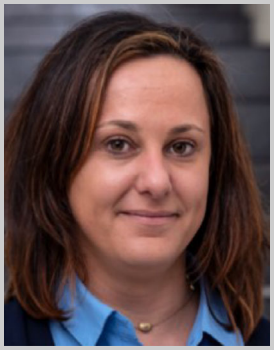

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