

## Organic semiconductors for light-mediated neuromodulation

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Organic semiconductors have generated substantial interest in neurotechnology and emerged as a promising approach for wireless neuromodulation in fundamental and applied research. Here, we summarise the range of applications that have been proposed so far, including retinal stimulation, excitation and inhibition of cultured neurons and regulation of biological processes in other non-excitabile cells from animal and plant origins. We also discuss the key chemical and physical phenomena at the basis of the interaction between materials and cells. Finally, we provide an overview of future perspectives, exciting research opportunities and the remaining challenges hampering the translation of this blooming technology into the clinic and industry.

Neural stimulation is a pivotal technique for investigating the nervous system and alleviating neurological and mental disorders. For decades, it has been routinely performed using intracellular or extracellular electrodes wired to electric pulse generators delivering brief electric pulses to excitable neurons. Only recently, the research effort converged into investigating new methodologies for the wireless modulation of neural functions. Among various approaches, photovoltaic technology emerged to provide artificial vision in blind patients with retinal implants, and it recently reached clinical assessment<sup>1</sup> by exploiting silicon-based technology. Photovoltaic technology is convenient for retinal prostheses since the retina is made to absorb light that enters the pupil. Electrical stimulation is achieved using pulsed illumination projected into the pupil, absorbed by a semiconductor layer embedded in the prosthesis, and converted into electric pulses.

At the same time, organic bioelectronics showed the superior performance of mixed electronic and ionic conductivity in organic materials (e.g. poly(3,4-ethylenedioxythiophene) polystyrene sulfonate; PEDOT:PSS) operating in electrolyte solution<sup>2</sup> as required in bioelectronic and neural interfaces<sup>3</sup>. Biocompatibility, flexibility and stretchability (upon specific manufacturing), high absorption coefficient in thin films, and consequently lightweight are among the main advantages of using organic technology in bioelectronic interfaces. These features motivated researchers in neuromodulation to exploit materials and concepts developed for organic electronics and photovoltaics. Therefore, it is not surprising that many organic materials found applications in such a dynamic and interdisciplinary research field.

The first set of reports<sup>4,5</sup> documenting the structural, morphological and optoelectronic stability of organic semiconductors immersed in aqueous environments encouraged their exploitation for sensing and stimulation applications in living cells. Over the past decade, organic semiconductors have been used for various biomedical applications: primarily for retinal stimulation<sup>6</sup>, but also for the excitation<sup>7</sup> and inhibition<sup>8</sup> of cultured neurons and nerves in-vivo<sup>9</sup>. Additionally, these materials were used towards regenerative medicine<sup>10,11</sup> and to investigate and regulate biological processes in neurons<sup>12</sup>, astrocytes<sup>13</sup>, other non-excitabile mammalian cells<sup>14</sup>, animals<sup>15</sup> and plants<sup>16</sup>. Further studies contributed to disentangle the complex phenomena occurring at the material-electrolyte interface that subsequently generate biological responses<sup>17</sup>.

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Today, there is growing interest in exploring novel photovoltaic materials and technologies for neural stimulation and, more generally, bioelectronic medicine and biotechnology. This article presents an overview of the recent developments in the field and an insight into the fundamental chemical and physical phenomena behind organic bioelectronic interfaces for neuromodulation. Last, we explore new opportunities for the research area and provide a critical discussion on the next challenges towards the clinical and industrial translation of this rising technology.

### Organic photovoltaic materials in organic bioelectronics

The core component of an organic photovoltaic interface is the organic semiconducting material, or a heterostructure, acting as a light absorber and transducer. Organic semiconductors typically have high optical absorbance coefficients allowing thin and flexible films: a characteristic for which organic technology stands out in bioelectronic interfaces compared to the inorganic counterpart. When immersed in electrolyte solution, they convert absorbed light into electricity via capacitive and reversible Faradaic processes, heat via photothermal conversion, and chemical species via photocatalytic reactions (Fig. 1a). In an ideal scenario, neural stimulation is conventionally achieved via safe capacitive or reversible Faradaic reactions, although photothermal approaches can also be exploited for wireless neuromodulation. However, for organic semiconductors, the three processes (electrical, thermal and chemical) might coexist, and

each contribution might be subject to the illumination parameters (wavelength, duration and intensity), the material properties and the device structure<sup>18</sup> (Fig. 1b).

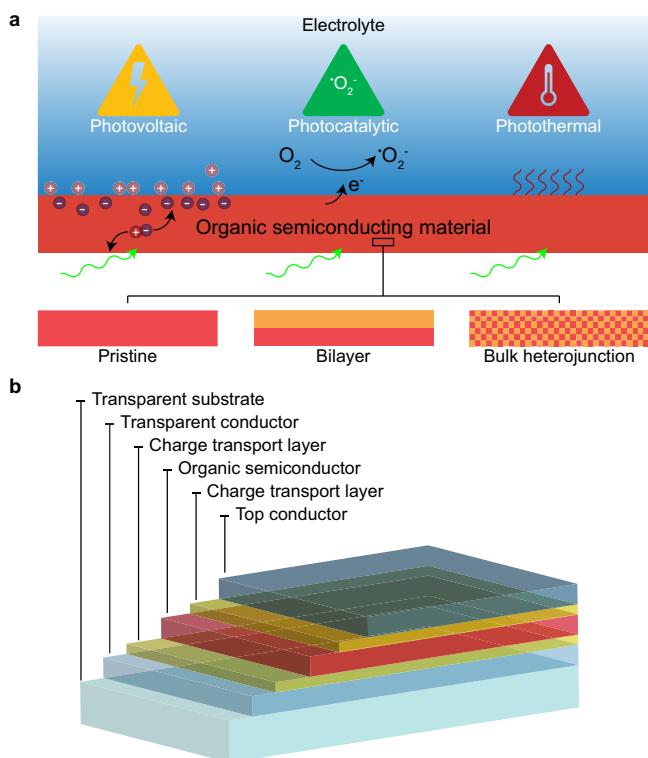
Photocatalytic reactions with organic semiconductors in electrolyte solution have been previously reported<sup>19</sup> upon high-intensity and prolonged exposure to light (in the order of seconds or more) which are substantially longer than durations conventionally used in neurostimulation. In particular, oxygen reduction reactions to superoxide or hydrogen peroxide might be favoured, and the use of these reactive oxygen species (ROS) to modulate cellular processes is now under investigation<sup>14</sup>.

Heat generation is unavoidable upon light absorption. Photothermal neuromodulation requires substantial changes in temperature of at least a few degrees, therefore it is likely to occur with both short (milliseconds) and long (milliseconds and seconds) pulse durations within a moderate-high range of intensity levels (10 mW mm<sup>-2</sup> or more). Heat transfer could play a relevant role in neurotechnology for neuromodulation. Photothermal neuromodulation already provided evidence of safe and reproducible excitation and inhibition of neuronal firing both in-vitro and in-vivo via temperature-dependent activation of transient receptor potential vanilloid (TRPV) channels<sup>20</sup> or transient change of the membrane capacitance<sup>21</sup>. Initially, it has been explored via direct infrared exposure of excitable tissue<sup>22</sup> but, more recently, photothermal neuromodulation mediated by light absorbers became predominant with either inorganic<sup>23</sup> and organic absorbers<sup>24</sup> and, if necessary, paired with the genetic expression of temperature-sensitive ion channels<sup>25</sup>.

Last, organic semiconductors drive neural excitation by electrical stimulation via a capacitive coupling or reversible Faradaic process occurring at the surface or within the bulk material. Charges generated upon light absorption either accumulate at the surface exposed to the electrolyte solution and charge/discharge the surface-electrolyte double layer or are transferred into solution via faradaic reactions. Efficient electrical stimulation occurs when an energetic asymmetry is present in the semiconductor and coupling/transfer mechanism occurs for the charges at the interface with the electrolyte solution. Spatial asymmetry provides efficient carrier generation, and it is conventionally achieved via bulk<sup>26</sup> or bilayer<sup>27</sup> heterojunctions between electron donor and acceptor materials (or p-type and n-type semiconductors), although possible also in pristine materials<sup>7</sup>. Then, carrier separation induces a potential difference influencing the surrounding electrolyte. Higher efficiency is reached using a device structure with the organic semiconductor paired to one (conductor/semiconductor interface) or two (conductor/semiconductor/conductor interface) conductors working as anode and/or cathode. The stimulation mechanism mostly depends on the materials interfaced to the electrolyte which favour capacitive<sup>6,27</sup> coupling or reversible Faradaic processes<sup>28,29</sup>. Organic semiconductors enable photovoltaic neurostimulation with pulse durations from few ms to few tens of ms, within the range of conventional neurostimulation, from low intensity levels largely below 1 mW mm<sup>-2</sup>. Differently from thermal or photocatalytic effects, in photovoltaic stimulation light must be pulsed to allow charging and discharging of the interface for safe neurostimulation. This requirement makes daylight or ambient light not suitable for photovoltaic stimulation. In addition, the irradiance level of daylight or ambient light is typically too dim to drive organic photovoltaic devices.

### Application of organic semiconductors for neuromodulation

Organic photovoltaic materials were pioneered for stimulation of cultured neurons in 2011 using a bulk heterojunction, composed of poly(3-hexylthiophene-2,5-diyl) (P3HT) and [6,6]-Phenyl-



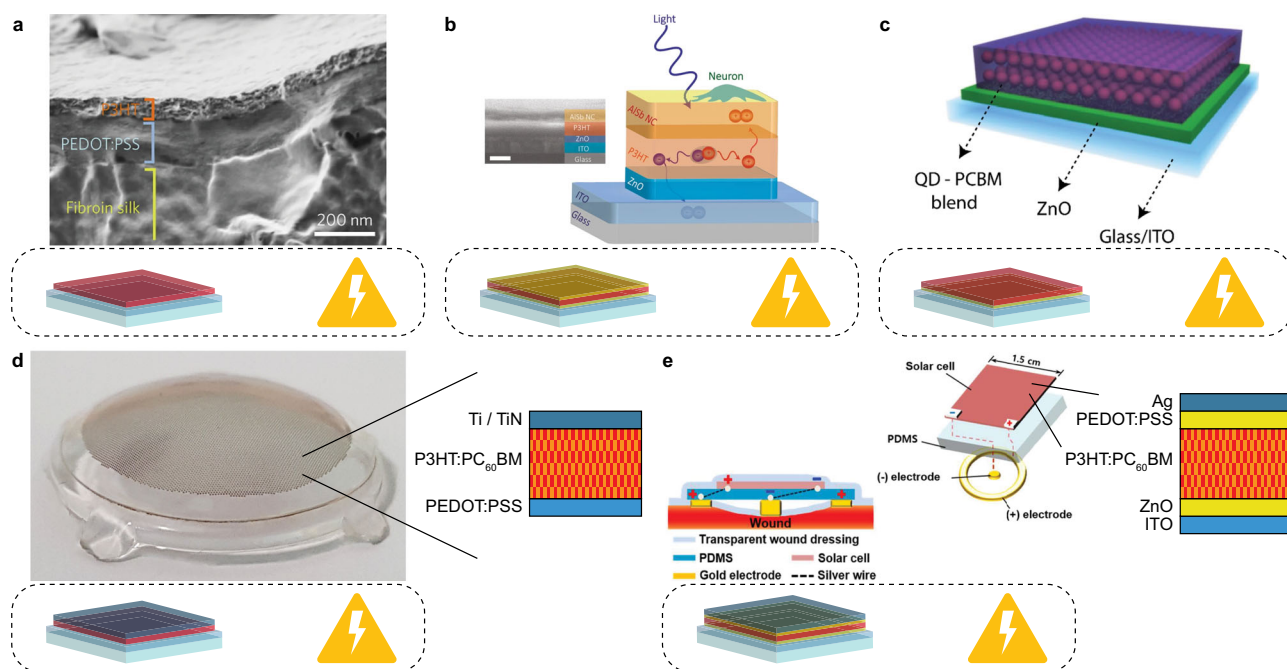
**Fig. 1** Structure and function of organic interfaces. **a** Main processes occurring upon light absorption in organic semiconducting films when immersed in electrolyte: photovoltaic, photocatalytic and photothermal conversions. The organic semiconducting layer can be a single pristine material or multiple materials in a bilayer or a bulk heterojunction. **b** Full layer-by-layer structure of a photovoltaic device for neuromodulation. The organic semiconducting layer can be interfaced directly to the electrolyte (as in **a**) or paired to one (conductor/semiconductor interface) or two (conductor/semiconductor/conductor interface) conductors working as the anode and cathode. Charge (hole and/or electron) transport layers can be used to enhance the stimulation efficiency.

C61-butyric acid methyl ester (PC<sub>60</sub>BM), paired to an indium tin oxide (ITO) conductor (ITO/P3HT:PC<sub>60</sub>BM)<sup>26</sup>. A few years later, two studies showed the potential of organic semiconductors in retinal stimulation for artificial vision<sup>30,31</sup>. The effort culminated in the demonstration of recovery of visual functions in a rat animal model of blindness with an organic device composed of a silk substrate, a PEDOT:PSS conductor and a P3HT semiconductor layer<sup>32</sup> (Fig. 2a). Since then, a large number of studies have demonstrated the potential of organic bioelectronics for the photovoltaic stimulation of the retina or neuromodulation in general.

Several conductor/semiconductor interfaces have been explored for neuronal stimulation in-vitro. Rand et al.<sup>27</sup> proposed a p-n bilayer structure composed of two organic pigments, phthalocyanine (H<sub>2</sub>Pc, p-type) and N,N'-dimethyl perylene-3,4:9,10-tetracarboxylic diimide (PTCDI, n-type), layered on top of a chromium/gold anode. Results showed the direct activation of cultured primary neurons and retinal ganglion cells in an embryonic chick retina with short pulses in the deep red via a capacitive coupling. Concurrently, Nizamoglu et al.<sup>7,33–35</sup> are investigating other device structures with nanomaterials to maximise the stimulation efficiency of the conductor/semiconductor interface. Han et al.<sup>7</sup> introduced a hybrid organic/inorganic structure exploiting a thin film of aluminium antimonide (AlSb) nanocrystals coated on top of a pristine P3HT film as the hole transport layer and interface layer to cultured neurons (Fig. 2b). The device structure had four layers: ITO as bottom conductor, zinc oxide (ZnO) as electron transport layer, P3HT and AlSb. Photocurrent measurements upon 20-ms blue light illumination showed strong capacitive currents at low irradiance leading to action potential generation in cultured neurons up to

20 Hz of repetition rate. Karatum et al.<sup>33</sup> showed that interfaces based on InP/ZnS core/shell quantum dots (QDs) generated Faradaic currents leading to either membrane depolarisation and action potential generation or membrane hyperpolarisation depending on the device structure (ITO/titanium oxide/QD for depolarisation and ITO/QD/ZnO for hyperpolarisation). In a second report<sup>34</sup>, authors further explore QDs for capacitive current generation at the material/electrolyte interface by exploiting a heterojunction composed of InP/ZnO/ZnS core/shell/shell QDs as the electron donor and PC<sub>60</sub>BM as the electron acceptor layered over a ITO/ZnO conductor (Fig. 2c). Last, Srivastava et al.<sup>35</sup> proposed a high open-circuit voltage bulk heterojunction composed of poly[4,8-bis(5-(2-ethylhexyl)thiophen-2-yl)benzo[1,2-b;4,5-b']dithiophene-2,6-diyl-alt-(4-(2-ethylhexyl)-3-fluorothiopheno[3,4-b]thiophene)-2-carboxylate-2,6-diyl] (PTB7-Th) blended with [6,6]-Phenyl-C71-butyric acid methyl ester (PC<sub>71</sub>BM) coated over a ITO/ZnO conductor to elicit spikes in cultured primary neurons.

Ghezzi et al.<sup>6,36,37</sup> developed a photovoltaic wide-field spherical array for retinal stimulation, embedding several thousands of photovoltaic pixels composed of a P3HT:PC<sub>60</sub>BM layered between a polymeric anode (PEDOT:PSS) and an inorganic cathode (titanium/titanium nitride, Ti/TiN) for efficient capacitive stimulation (conductor/semiconductor/conductor interface) (Fig. 2d). Results demonstrated efficient network-mediated stimulation of retinal ganglion cells with very high spatial resolution equivalent to the pitch of the photovoltaic pixels embedded in the array<sup>37</sup>. The same device was proposed exploiting a different electron donor material, the poly[2,6-(4,4-bis(2-ethylhexyl)-4H-cyclopenta[2,1-b;3,4-b']dithiophene)-alt-4,7(2,1,3-benzothiadiazole)] (PCPDTBT) blended with the PC<sub>60</sub>BM electron acceptor



**Fig. 2 Conductor/semiconductor and conductor/semiconductor/conductor bioelectronic interfaces.** **a–c** Representative examples of conductor/semiconductor devices for neuromodulation. **a** Scanning electron microscopy image of a fully organic retinal prosthesis for artificial vision. Implantation in the subretinal space restored visual functions in blind rats. Image reprinted by permission from Springer Nature<sup>32</sup>. **b** Photovoltaic interface based on aluminium antimonide nanocrystals for the capacitive stimulation of primary neurons. The scale bar in the insert is 200 nm. Image adapted under the Creative Commons Attribution (CC-BY) license<sup>7</sup>. **c** Sketch of a quantum dot nano-heterojunction allowing strong photocapacitive current generation. Image adapted under the Creative Commons Attribution (CC-BY) license<sup>34</sup>. **d, e** Representative examples of conductor/semiconductor/conductor devices for neuromodulation. **d** The image shows the POLYRETINA device for artificial vision. Image adapted under the Creative Commons Attribution (CC-BY) license<sup>37</sup>. **e** Sketch of a photovoltaic patch exploited for wound healing. Image adapted under the Creative Commons Attribution (CC-BY) license<sup>11</sup>. In each panel, the dashed box shows a layer-by-layer sketch of the device and the putative main neuromodulation mechanisms.

(PCPDTBT:PC<sub>60</sub>BM) to provide sensitivity in the near infrared spectrum<sup>38</sup>, crucial for applications in retinal stimulation.

Besides capacitive and Faradaic neuronal stimulation, heat generation can be exploited for neuromodulation. Martino et al.<sup>39</sup> showed that a thin P3HT film, or its bulk heterojunction with PC<sub>60</sub>BM, layered on an insulating glass substrate led to membrane depolarisation on Human Embryonic Kidney (HEK-293) cells, grown on top, mediated by heat transfer for sufficient long and intense exposure. Membrane depolarisation was associated with a temperature-dependent change in the membrane capacitance. Feyen et al.<sup>8</sup> extended this approach reporting that prolonged illumination (e.g. ~150 ms or longer) of the P3HT film led to membrane hyperpolarization and silencing of neuronal firing in cultured primary neurons, epileptic hippocampal slices and explanted blind retinas. The ability to silence neuronal firing might find applications in several conditions, such as inhibition of nerve activity for pain relief<sup>24</sup> or silencing epileptiform activity. While in these reports, the photothermal modulation of the cell membrane was independent of TRPV channels, Lodola et al.<sup>40</sup> showed that the same interface could activate TRPV1 channels, when they were stably transfected in HEK-293 cells (Fig. 3a). This possibility is also a key tool in neurotechnology due to the importance of TRPV1 channels as a receptor involved in body temperature regulation, heat and pain detection in sensory nociceptive fibres and functions in the central nervous system including response to neurogenic inflammation, cytoskeletal remodelling, synaptic remodelling and plasticity, neuronal excitability and cell survival<sup>41</sup>.

Apart from neurons, photostimulation of astrocytes, critical for supporting neuronal function, was also attempted<sup>13</sup>. Photoexcitation of the ITO/P3HT:PC<sub>60</sub>BM conductor/semiconductor interface caused membrane depolarisation mediated by the ClC-2 chloride channel, highlighting the possibility to use organic semiconducting materials to probe ion channels in non-excitable cells.

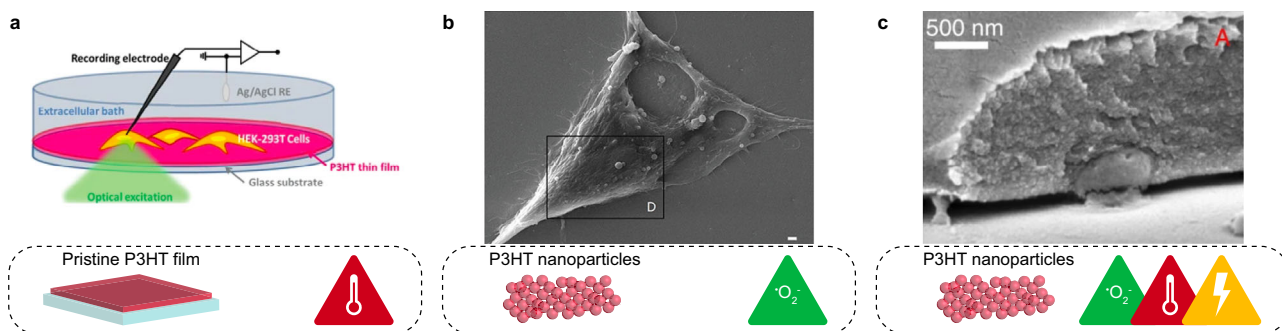
### Organic nanomaterials

A new exciting perspective for organic semiconductors is their exploitation as nanomaterials (e.g. nanoparticles, NPs). In bioelectronic and neural interfaces, nanomaterials have the advantage to decrease the cell-material distance by reaching the plasma membrane and closely interact with the target cells.

Semiconducting polymer nanobioconjugates sensitive to near infrared light (Poly{2,2'-[(2,5-bis(2-hexyldecyl)-3,6-dioxo-2,3,5,6-tetrahydropyrrolo[3,4-c]pyrrole-1,4-diyl)dithiophene]-5,5'-diyl-alt-thiophen-2,5-diyl}, PDPP3T) have been exploited as photothermal nanomodulators<sup>42</sup>. The high photothermal conversion efficiency combined with antibodies selective to TRPV1 receptors allowed for precise spatio-temporal activation of the thermosensitive ion channel in an immortalised neuronal cell line. The binding of NPs with specific biological targets through established techniques, namely antigen-antibody interactions, presents an interesting alternative to optogenetics that is both selective and light-sensitive.

Pristine P3HT NPs (with hydrodynamic diameter between 150 and 300 nm) were first reported to be internalised in cultured HEK-293 cells<sup>14</sup> and simple eyeless polyps<sup>15</sup>. In HEK-293 cells, Bossio et al.<sup>14</sup> demonstrated that P3HT NPs have photocatalytic activity (Fig. 3b). Upon internalisation in cells and light absorption, P3HT NPs form ROS below toxic levels modulating intracellular calcium dynamics<sup>14</sup> without affecting the cell viability or the NP optoelectronic properties<sup>43</sup>. Likewise, the photosensitivity bestowed by P3HT NPs in the freshwater polyp *Hydra vulgaris* has shown increase in the contraction events of the animal body and enhancement of opsin3-like gene expression, part of a superfamily of G protein-coupled receptors that play a key role in vision<sup>15</sup>. Authors ruled out a photothermal effect for P3HT NPs since the total heating due to the contribution of all the internalised NPs resulted to be negligible. In light of the previous report in HEK-293 cells<sup>44</sup>, the increase in cytoplasmic ROS and the subsequent pathways seems to be the cause of the reported physiological changes. In addition, to avoid internalisation and direct the binding of P3HT NPs toward the cell membrane, polythiophenes functionalised with alkyl side chains terminating with N-hydroxysuccinimidyl ester groups have been synthesised (NHS NPs)<sup>44</sup>. These NHS NPs showed higher efficacy in the modulation of the membrane potential.

Recently, P3HT NPs were injected subretinally in rats and exploited as a retinal prosthesis<sup>45</sup>. Contrary to the previous reports, P3HT NPs were engulfed but not internalised by neurons remaining extracellular (Fig. 3c). When injected in close proximity to the retina, P3HT NPs endowed remaining retinal neurons with light sensitivity. In this case, ROS are not taken into consideration. Instead, authors proposed a capacitive mechanism relying on the close contact between NPs and the cell membrane as the driver of the evoked retinal responses; although, it remains unclear how a potential difference could affect the electrolyte



**Fig. 3 Pure organic semiconductor bioelectronic interfaces.** **a** The sketch shows a pristine P3HT layer interfaced with HEK-293 cells for the photothermal modulation of the membrane potential and other biological processes via the activation of TRPV1 channels. Image adapted under the Creative Commons Attribution (CC-BY) license<sup>40</sup>. **b** The scanning electron microscopy image shows P3HT NPs being internalised in a HEK-293 cell. Upon absorption of light, the internalised P3HT NPs modulated intracellular calcium dynamics via a photocatalytic process. Image adapted under the Creative Commons Attribution (CC-BY) license<sup>14</sup>. **c** The image shows an ultrastructural analysis of the interaction between a P3HT NP and a cultured primary neuron from a resin-embedded focused ion beam cross-section. NPs were not internalised but established a tight contact with the neuronal membrane. The injection of P3HT NPs in the subretinal space of blind rats endowed remaining retinal neurons with light sensitivity. The mechanism of interaction in-vivo is still unclear. Image reprinted by permission from Springer Nature<sup>45</sup>. In each panel, the dashed box shows a layer-by-layer sketch of the device and the putative main neuromodulation mechanisms.



solution surrounding a spherical P3HT NP without spatial asymmetry in the material or in the device.

### Other opportunities in bioengineering for organic semiconductors

Further from neuromodulation, cardiac cells can also benefit from the photoexcitation of organic semiconductors. Heating cardiac cells can trigger them, allowing the manipulation of their rhythm contraction or reinstating synchronisation should there be a failure. Photothermal coupling obtained by light exposure of a P3HT film increased the contraction rate of human-induced pluripotent stem cell-derived cardiomyocytes in a spatially and temporally precise fashion<sup>46</sup>.

Electrical stimulation can promote tissue regeneration and the ability of organic semiconductors to be wireless, lightweight and flexible makes them good candidates in a solar cell for wearable therapeutic purposes. This has been applied to ischaemic tissue, where it promoted angiogenesis in the mouse hindlimb<sup>47</sup>, and to cutaneous wounds<sup>11</sup>. In both cases, the small solar cell, composed of ITO/ZnO/P3HT:PC<sub>60</sub>BM/PEDOT:PSS with silver (Ag) electrodes, provided sustained low power electrical stimulation throughout the regenerative process (Fig. 2d). By adding an active component to the wound dressing, the organic solar cell was aligned with the wound healing direction and showed marked improvement compared to the passive patch. Along the same vein, the interaction between endothelial colony-forming cells, critical in the reconstruction of vasculature, and a pristine P3HT film enhanced cell proliferation and tubulogenesis via the activation of TRPV1 channels upon light exposure<sup>10</sup>.

The bulk of research into organic semiconductors for bioelectronic interfaces has focused on biomedical impact, being able to utilise the breadth of fundamental biology to elucidate the underlying mechanisms. Recent efforts have been made to introduce organic semiconductors in biotechnology to studies on plants, a critical component of our ecosystem, to modulate them and make them more resilient to environmental risks. Recently, an interface between the plant model *Arabidopsis thaliana* and P3HT NPs was investigated<sup>16</sup>. Authors specifically studied the stoma, which is a pore made of two guard cells that controls fundamental aspects of plant physiology such as the uptake of carbon dioxide and the release of oxygen and water. They found that P3HT NPs were not internalised into these guard cells but were able to reduce the opening of the pore by >20%, which would thus reduce water loss. The exact mechanism of this control was unclear but was not linked to the steric interaction, tested through inert silicon dioxide NPs, and attributed to photocatalytic effects with the production of ROS and modulating the calcium signalling. While still in its infancy, the novel application of these organic semiconductors to plants presents a broad and potentially impactful field of research.

The majority of the approaches presented above have been inspired from research in organic photovoltaics. This community continues to excel with materials and methods aiming for thinner, cheaper and more efficient devices for wearable applications<sup>48</sup>. Wearable devices capitalise on the flexible and light-weight nature of organic photovoltaic materials to be incorporated in clothing<sup>49</sup> or to be worn on skin<sup>50,51</sup>, harvesting solar energy for powering organic sensors. Further advancement has allowed organic photovoltaics to power wearable ion pumps<sup>52</sup>. These encouraging results bodes well for organic photovoltaics to eventually power subcutaneous implantable devices.

### Outlook

Current efforts in organic semiconductors have certainly shown promise as a tool to investigate and modulate biological processes

or as part of a medical device for neuromodulation. A broad base has been established but several key challenges exist for applying organic semiconductors to further neurostimulation purposes.

For organic photovoltaic devices to be considered as an alternative to electrical neurostimulation, a key factor is the efficiency of the system. The predominant mechanism of organic semiconductors altering neurons is in the form of a solar cell through electrical currents. The power output of a solar cell is dependent on its area. A smaller device can offer better spatial resolution; however, the output power is reduced and further subject to resistive losses. An increase in efficiency would allow the existing applications to enhance in their capabilities, for instance through further miniaturisation of photovoltaic pixels in an array for retinal stimulation or cultured neurons. Further expansion of organic solar cells for neurostimulation where the threshold for activation is higher, such as nerve or epicortical stimulation, device size or efficiency must be increased. Larger devices are inherently more invasive and less spatially selective so improving efficiency is preferred either by careful consideration of the design of the device or proper choice and optimisation of materials, more likely a combination of both. The choice of the light absorbing material is doubly important when we consider that biological tissue absorbs a great deal of visible light but is more transparent in the near infrared spectrum. This aspect is crucial when light is delivered externally and a bulk of the irradiance is lost before hitting the organic semiconductor. As such, many materials lose their functionality due to the physical barrier and would benefit from a shift towards materials sensitive to near infrared light.

The combination of light and neuromodulation is also offered by optogenetics in fundamental research, which naturally have high resolution with cellular and subcellular targeting capability. The process to express optogenetic tools involves the insertion of genes into the cell for it to produce. Organic semiconductors offer a natural in-between from light to material to neuron in a non-genetic mechanism, thereby innately not immunogenic or subject to viral vector delivery. In NP form, organic semiconductors are a powerful tool to interface with cells with specific surface functionalisation, such as harnessing antigen-antibody interactions, supporting tremendous advancement in their biological application. Additionally, investigating the cell response to heat treatment and ROS exposure are additional options not yet achieved with optogenetics.

The photothermal and photocatalytic effects are most apparent when pristine organic semiconductors are the only element exposed to the electrolyte and offer interesting modulatory effects on cells and tissue. Focused heat and ROS generation offer highly novel means to modulate cells however their existence in excess may also hinder the translation to the clinic due to toxicity. Specific quantification and analysis of these semiconductor/cell interactions, particularly when generated from NPs, need to be closely probed as it ventures into the in vivo space. Through appropriate choices in the illumination protocol or the NP structure, independent control of each phototransduction mechanism could be achieved thus facilitating the use of NPs as a biological tool.

As the field progresses, using a combination of innovative nanomaterials and carefully designed devices, organic semiconductors have the potential to occupy a larger space in neuromodulation. Subsequently, it can then push for medical grade devices through defined regulations and convincing applications stemming from rigorous laboratory research. Future work should focus on efficiency, reproducibility, stability and safety to allow organic semiconductors to grow from the capabilities demonstrated thus far and enter the medical industry and clinics.

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## Author contributions

D.I.M. and D.G. wrote the article.

## Competing interests

The authors declare no competing interests.

**Additional information**

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