Advanced Electrical and Optical Microsystems for Biointerfacing

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1. Introduction

The desire to better understand biological science and investigate enormous biosystems has driven the rapid development of novel biointerfaces for diagnostics and therapies.[1–3] Biointerfaces, also known as the interfaces between synthetic materials and biological systems,[4–5] is a highly interdisciplinary area that requires synergistic efforts from materials scientists, chemists, electrical engineers, mechanical engineers, biologists, etc., to progress. In the past few decades, biointerfaces based on microelectromechanical systems (MEMS), microsystems, and optoelectronics have enabled recording and/or modulating signals from single-unit to large populations of cells and whole body levels, which not only provide the scientific research community technologies to thoroughly understand lives but also offer novel platforms for clinical medicine. For example, silicon nanostructures can now be used to record or control intracellular processes.[6,7] Electrical stimulation technologies, such as deep brain stimulation (DBS),[8] vagus nerve stimulation,[9,10] and spinal cord stimulation,[11] are now widely clinically used to treat Parkinson’s disease, tremor, epilepsy, depression, and chronic pain. It is clear that innovative functional biointerfaces will continue to be important platforms for biological and biomedical research.

Electrical and optical biointerfaces are among the most commonly used methods to study biological systems, such as neurons, cardiomyocytes, and skeletal muscle cells. Biosystems are in general curvilinear and soft while conventional electronics are much more rigid. The mechanical mismatch between conventional electrical and optical devices and biosystems imposes significant challenges for reliable biointegration and often lead to severe tissue damage and performance degradation from encapsulation and inflammation.[12,13] As such, extensive research efforts have emerged to improve the material design, device fabrication, and circuit assembly to achieve high-performance flexible and/or stretchable systems in biocompatible formats for more comfortable biointerfacing with improved accuracy.[2,14–16]

In this Review, we highlight recent progress in electrical and optical Microsystems for biointerfacing, with particular attention in materials science, device design, and integration strategies for minimally invasive in vivo neuroscience applications and the exception of pulse oximeters for healthcare monitoring. The discussed material and device design strategies are also helpful to develop advanced in vitro tools for interfacing with cultured cells or tissue slices. Meanwhile, devices for in vitro experiments are generally less invasive and consist of a larger number of sensing and/or modulation sites for high-throughput cell analysis with less stringent requirements for power, connectivization, safety, and reliability.[17–19] For example, in vitro systems are normally directly connected to data acquisition systems and do not require wireless energy harvesting and data communication. It is worth noting that there are significant advances in wearable and implantable devices for skin and cardiovascular applications, which are beyond the scope of this article. Examples of excellent reviews can be found in recent literature.[20–22] We first introduce advances in materials, structures, and devices for electrical recording and stimulation, such as organic and inorganic conductors and nonpenetrating and penetrating electrodes. Then, we highlight optical modulation and recording microsystems and their design strategies, including miniaturized implantable systems for optogenetics, photometry, and wearable...
and implantable oximeters. Following that, recently developed multimodal electrical and optical biointerfaces are discussed with different emphasis. Finally, we conclude with an overview of unsolved difficulties and future research directions for continued fundamental and translational research.

2. Materials and Devices for Electrical Biointerfacing

Electrical recording and stimulation have been the gold standard to study biological systems in research and clinical medicine for more than a century. Intracellular electrodes are still the most widely used tools for investigating single-unit physiology. Extracellular electrodes, on the other hand, allow detection of low-frequency local field potentials (LFPs) with high temporal resolution. In this section, we provide examples of electrode materials and structure design strategies and their applications in developing both nonpenetrating and penetrating biointerfaces.

2.1. Electrode Materials and Design Strategies

A tremendous amount of research effort has been devoted to improving the performance and longevity of biointegrated electrodes. The substrates, electrode materials, geometries, and sizes are engineered to control the electrochemical properties, mechanical properties, and biocompatibility (a major failure factor of recording electrodes) of the interfaces.

2.1.1. Substrates

Multiple substrate materials have been explored, such as silicon, glass, and polymers. Microwire electrodes based on nontoxic metals (e.g., gold, platinum, stainless steel, and tungsten) are one of the earliest electrodes for biological research from 1950s. The diameter of the microwire tip is in general less than a few hundred micrometers. The tip records the electrical signals while the rest of the microwire is normally encapsulated with an insulating material. Based on the number of the wires used, the microwire electrodes can be subclassified as single and multiple wire electrodes for intracellular (single wire) or extracellular (multiple wire) recording. Microwire electrodes have been used to record the action potentials in various animals including rats, monkeys, pigs, etc. Wise and coworkers recorded 247 individual cortical neurons simultaneously from implanted microwire arrays in awake macaque monkey’s brain up to 18 months after implantation. However, microwire electrodes have a list of disadvantages such as surgical complications from the transcutaneous wire connection and microwire bending during implantation into brain. Glass micropipette-based patch-clamp techniques were used to elucidate electrophysiology in the 1970s. Later, with the development of MEMS, microfabricated silicon microelectrode arrays (MEAs) with high spatiotemporal resolution were introduced in the 1980s. Single-shank Michigan-type MEAs can address the limitations in microwire electrodes by significantly increasing the density of electrode sites on the surface of each shank (Figure 1a). Another MEMS-based silicon electrode is the Utah-type MEAs, originally developed at the University of Utah (Figure 1b). Utah-type MEAs generally consist of 10 × 10 shanks of needle-like silicon electrodes (diameters are a few to several hundred micrometers) fabricated from silicon wafers. Although for implantable electrodes a moderate rigidity is desired to support accurate penetration with minimal tissue damage, silicon has a Young’s modulus around 130–170 GPa, which is significantly larger than soft tissue (0.1–100 kPa). This mechanical mismatch results in significant long-term tissue damage and inflammatory responses (e.g., formation of glial scars and neuronal death) around the probes and loss of signals. To reduce the mechanical mismatch between rigid, planar silicon substrates and the soft tissues, polymers such as polyimide, parylene, SU-8, and polydimethylsiloxane (PDMS) are used as flexible and/or stretchable substrates. Those polymer materials have Young’s modulus closer to those of biological tissue. For example, Kim et al. reported a device with electrodes embedded in an ultrathin (<10 μm) polyimide mesh, supported by a biodegradable film of silk fibroin (Figure 1c). The silk is dissolved after implantation to create

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conformal contacts between the device and brain surface driven by capillary forces. No immune reactions are observed after 4 weeks of device implantation. The effective modulus of the substrates is further reduced by ultrasoft hydrogel-based materials (Figure 1d). Here, conductive polymer poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS)-based hydrogel serves as the electrode and an elastic photoresist as the encapsulation layer. The electrode arrays exhibit an overall modulus of \( \approx 30 \text{kPa} \) for low-voltage (50 mV) electrical stimulation of peripheral nerves in mice for 6 weeks.

2.1.2. Electrode Materials

Noble metals are chemically inert and exhibit good electrical conductivity with no toxicity. They are used as the electrodes since the inception of recording and stimulation microelectrodes.

**Figure 1.** a) Images showing four different types of layouts for Michigan-type MEAs (NeuroNexus Technologies). Reproduced with permission.\(^{[40]}\) Copyright 2008, Society for Neuroscience. b) A top/side view of the 100 microelectrodes Utah-type MEA. Reproduced with permission.\(^{[41]}\) Copyright 1999, Elsevier. c) Photograph of an ultrathin MEA on a feline brain. Reproduced with permission.\(^{[53]}\) Copyright 2010, Springer Nature. d) Schematic of the synthesis process of PEDOT:PSS conductive hydrogel. Reproduced with permission.\(^{[56]}\) Copyright 2019, Springer Nature. e) Scanning electron microscopy (SEM) image showing a nanopillar electrode tightly engulfed by the cell. Reproduced with permission.\(^{[64]}\) Copyright 2012, Springer Nature. f) SEM images of the electrode after recording from the monkey visual cortex. Reproduced with permission.\(^{[59]}\) Copyright 2008, Springer Nature. g) SEM image of a CNT-modified electrode. Reproduced with permission.\(^{[67]}\) Copyright 2014, Wiley-VCH. h) Electrochemical impedance spectra of Au, PEDOT:PSS/Au, Pt, and PEDOT:PSS/Pt with electrode diameters from 20 to 2000 \(\mu\text{m} \). Reproduced with permission.\(^{[76]}\) Copyright 2017, Wiley-VCH.
Gold and platinum have been extensively studied and used. Electrochemical impedance and charge injection capacity (CIC) of the electrodes are crucial parameters that determine the recording and stimulation performance at the abiotic and biotic interface. A small impedance will ensure a high-quality electrophysiological recording of small amplitude signals (e.g., extracellular signals can be as small as several tens of μV). Likewise, a high CIC is desired for stimulation. To record action potentials from or stimulate individual neurons, the electrodes need to have small dimensions. However, reduction in electrode sizes will lead to undesired increase in impedance and decrease in CIC. As such, there is a trade-off between selectivity and sensitivity of the electrodes. Therefore, metal electrodes often suffer from a poor electrochemical performance at this small geometry.

Increasing the effective electrochemical surface area (ESA) without changing the geometrical surface area (GSA) is a powerful strategy to improve the electrochemical performance. Both organic and inorganic materials are used to modify the electrode surfaces. For inorganic materials, metal oxides and metal nanostructures are coated on the surface of the electrodes to maximize ESA. The metal nanostructures can be subclassified into nanorod, nanopillar, nanograin, and nanoflake shapes. For example, Xie et al. demonstrated one of the first nanopillar-based electrodes using platinum nanopillars to record intracellular potentials (Figure 1e). The additive ion-beam process used to deposit platinum nanopillars allows a high level of process control. Carbon-based materials, such as carbon nanotubes (CNTs) and graphene, have been explored as viable coating options to boost the electrochemical performance of the electrodes. The maximum charge density for CNT-coated electrodes can be greater than twice the value from iridium oxide-based electrode. Keefer et al. demonstrated that CNTs could be electrochemically deposited on the tips of tungsten and stainless steel microwire electrodes to reduce the electrochemical impedance (Figure 1f). The electrochemical impedance of CNT-coated electrodes at the biologically relevant frequency of 1 kHz is 38 kΩ whereas the impedance of the reference electrode is 940 kΩ. In addition, an ~40-fold increase in charge transfer is observed after CNT coating. Shin et al. showed that CNT bundles can be coated on a tungsten electrode tip to record action potentials from mice brains (Figure 1g). In addition to being used as coating materials, CNTs and graphene are used as transparent electrodes for stimulation and recording applications, which are discussed in detail in Section 4.3. Conductive polymer coatings have long been used to significantly reduce the electrochemical impedance and CIC without increasing GSA through spin coating or electrodeposition. The improved electrochemical performance is from the increased ESA for ionic-to-electronic charge transfer at the biotic–abiotic interface. It is important to note that the capacitance of conductive polymers is proportional to volume instead of GSA like in the metal electrodes. PEDOT:PSS-coated gold and platinum microelectrodes exhibit impedance values ~100 kΩ at 1 kHz, which is one order of magnitude smaller than pristine platinum and gold microelectrodes, respectively (Figure 1h). In addition, conductive polymers can act as a mediator at the interface to mitigate the mechanical mismatch and reduce the foreign-body responses.

2.1.3. Structure Designs to Achieve Stretchable Microelectrodes

Advanced structure design strategies have been recently investigated to fabricate stretchable microelectrodes, which originate from the methods to design stretchable electronic devices. An “island-bridge” structure with rigid functional components (island) connected by stretchable interconnections (bridge, such as serpentine traces) is a widely used approach. In this structure, the interconnections possess low effective stiffness and greatly reduce the strains on the functional components during stretching. To achieve a good durability, the interconnections need to undergo only elastic deformation to withstand the repeated strains. Otherwise plastic deformation will accumulate damage and cause cracks and device failure. Meacham et al. reported MEAs using gold electrodes and serpentine interconnection traces on the PDMS substrate. The MEAs could stretch up to 8% without degradation in electrochemical performance (Figure 2a). Ji et al. demonstrated serpentine-shaped gold (thickness 300 nm) microelectrodes based on Ecoflex substrate (50 μm) (Figure 2b,c). The impedances values at 1 kHz remain almost unchanged after 5000 repetitive stretching cycles with 50% strain (61.7 ± 14.8 kΩ vs. 65.5 ± 18.7 kΩ).

Prestrain strategy that transfers nonstretchable electrodes on a pretrained elastomer substrate and then releases the prestrain is another effective method to realize stretchable electrodes for electrophysiology. The resulting “wavy” structure withstands larger compressive and tensile strains by increasing the buckling wavelength and decreasing the buckling amplitude while the strain inside the electrodes is much lower. Qi et al. fabricated stretchable gold nanobelt electrodes based on the pretrained PDMS substrate with a unique out-of-plane tripod structure (Figure 2d–h). During repeated stretching and releasing cycles, sinusoidal textures are formed without delamination of the gold nanobelts, the devices can sustain a strain up to 130% with good durability (no serious performance decay after 10,000 cycles). The same group later demonstrated stretchable polymeric polypyrrole (PPy) MEAs using the prestrain method (Figure 2i–k). The MEAs are based on PPy nanowires (NWs)/PPy film, which show a high stretchability (~100%) and interfacial adhesion (~1.9 MPa).

2.2. Nonpenetrating Electrodes

Brain activity can be recorded through various methods. Electroencephalography (EEG) and electrocorticography (ECoG) are two commonly used technologies, respectively. They rely on electrodes that do not penetrate the cortex to monitor physiological health, diagnose disease, and for brain–computer interfaces (BCIs). EEG records the average electrical activity in the brain with millisecond resolution from ionic current flow within the neurons through the skull. Large surface electrodes are placed on the scalp during EEG recording in the least invasive way without the need for a surgical implantation. EEG was first used to record human brain electrical activity in 1924, by Hans Berger, a German physiologist and psychiatrist. Nowadays, EEG is widely used to evaluate different clinical conditions such as epilepsy, coma, sleep disorders, and other neurological disorders. However, EEG is often not sufficient
to achieve a high spatial resolution and precision to analyze a specific brain region. ECoG is an invasive alternative of EEG that records from the cerebral cortex using subdural MEAs. Compared to EEG, ECoG measures the averaged brain signals from the superficial layers of the brain and has been clinically used to localize seizure focus and study cognition in human.  

In this section, we will discuss some recent progress of flexible nonpenetrating electrodes for EEG and ECoG applications.

2.2.1. EEG Interfaces

Minimizing the electrochemical impedance between the skin and electrode surface is a major challenge for EEG. Traditional wired bulk metal electrodes operate with conductive gels to decrease the interface impedance, which is not only time-consuming but also undesired for long-term measurement as the aqueous gels normally dry after several hours. Recent advances in materials and structure designs discussed in Section 2.1...
together with device integration schemes and data acquisition systems provide opportunities to address these limitations. For example, Alba et al. demonstrated that crosslinked poly(sodium acrylate) hydrogels swelled with electrolyte solution can be used as electrodes to enable a conformal contact with the skin even in hairy scalp. The electrochemical performance is improved compared with commercial EEG electrodes. The hydrogel can hold 91% electrolyte solution (by weight) for over 1 day under normal air exposure. Leleux et al. reported a PEDOT:PSS flexible electrode for EEG (Figure 3a). The 250 μm polyimide substrate endowed flexibility and conformability to the curved surface of brain. The PEDOT:PSS electrode exhibits a better resolution than gold electrode in the band of interest (8–13 Hz). The recording results of somatosensory-evoked potentials suggest PEDOT:PSS electrode to be a good candidate for chronic noninvasive recording of pathologic electrical activity in the brain. The electrochemical performance and long-term stability of the PEDOT:PSS electrode can be improved by ionic liquid gels coating, such as 1-ethyl-3-methylimidazolium ethyl sulfate.

An alternative strategy is to design micro/nanoscale structures using photolithography that shapes inorganic electronic materials into different layouts (e.g., serpentine, fractal) in soft elastomeric matrices, also known as epidermal electronics. The resulting devices can laminate softly on the surface of the skin to measure various physiological parameters (e.g., EEG, temperature, strain) with no irritation due to the good alignment of their physical characteristics with epidermis. Figure 3b shows a representative EEG electrode of this type mounted conformally on the auricle and mastoid. The device shows a low effective modulus (<130 kPa) that ensures robust soft adhesion to the skin with Van der Waals interactions and a high signal-to-noise ratio (SNR). The serpentine design enhances a stretchability of ≈50% to accommodate average skin deformations (10–20%). The capacitive electrodes and tripolar concentric ring design provide sufficient spatial resolution and robustness that allow multiple cycles of cleaning with soap, water, and isopropyl alcohol antiseptic. The electrode is capable of serving as a persistent BCI to enable word spelling by the monitoring of EEGs and steady-state visually evoked potentials. Recently, Tian et al. reported ultra-large full-scalp EEG interfaces for cognitive monitoring (Figure 3c–e). The devices have total areas over 200 cm² and are compatible with magnetic resonance imaging (MRI). The systems are easy to mount and allow stable chronic recordings (over 5 days) without interfering with daily activities and enable high-density mapping without the risk of short circuit among nearby channels. Rogers group further developed wirelessly powered epidermal devices using radio frequency (RF) communication to enable tether-free EEG (Figure 3f). Figure 3g shows that the wirelessly collected signals are consistent with reference signals collected using wired data acquisition systems.

2.2.2. ECoG Interfaces

Compared with EEG, ECoG utilizes implantable subdural MEAs that can avoid noises between dura and scalp with improved SNRs. Flexible, conformal, and compliant ECoG devices with low bending stiffness can be achieved using ultrathin active materials and polymer substrates (e.g., polyimide, polyethylene terephthalate [PET, parylene] with total device thicknesses ranging from a few to several tens of micrometers. Viventi et al. reported a breakthrough example using thin silicon nanomembranes (thickness 260 nm) to support, amplify, and multiplex an active array with 360 electrodes (dimensions at 300 × 300 μm², spacing at 500 μm) on the polyimide (Figure 4a,b). The single-crystal silicon flexible transistors enable high-speed multiplexing (<5 μs) and sampling rates >10 ks s⁻¹ per recording channel with very low crosstalk (<−65 dB). The thin geometries of the active materials endow good mechanical flexibility to mount on gyral surfaces. Very recently, Chiang et al. further developed a flexible, multiplexed electrode array (Neural Matrix) with >1000 channels over a centimeter-scale area and effective encapsulation strategies that can support stable long-term in vivo recording over 1 year in rodents and nonhuman primates (Figure 4c–e).

Khodagholy et al. demonstrated both active and passive ECoG arrays with organic polymer PEDOT:PSS-coated electrodes on 2 μm parylene substrates (Figure 4f,g). The active arrays using the organic electrochemical transistor (OECT) structure allow direct amplification of the measured current at the recording sites to achieve a higher SNR (52.7 dB) than passive PEDOT:PSS surface electrodes (30.2 dB) or iridium-penetrating electrodes (32.0 dB). The conformal OECT arrays can effectively measure epilepsy in a rat model and detect low-level activity that is barely detectable by surface electrodes (Figure 4h). The transistor performance can be further optimized to increase signal quality by optimizing OECT geometries. However, OECTs require additional wiring compared with passive electrodes. As a result, the spatial resolution for OECT-based active arrays is lower than passive arrays that give the same interconnect line width. Meanwhile, the passive Neurogrid MEAs in Figure 4i include 256 spin-coated PEDOT:PSS electrodes with dimensions of 10 × 10 μm². The cellular-scale electrode sizes and small interelectrode spacing (30 μm) allow scientists to track individual neurons from the cortical surface in both rodents and humans for days for the first time.

Biodegradable ECoG devices that eliminate secondary surgeries for device removal after short-term operations represent another important research area. Yu et al. demonstrated high-performance multiplexed biodegradable ECoG arrays based on silicon nanomembrane transistors (Figure 4j,k). In this design, poly(lactic-co-glycolic acid) serves as the substrate, silicon dioxide (SiO₂) works as the gate insulator, and molybdenum is used as interconnect for the source, drain, and gate. All the materials are biocompatible and biodegradable. This particular device can laminate on the cortical surface of a rat brain, measure ECoG for a programmed time period, and then dissolve in rat body afterward.

2.3. Penetrating Electrodes

Surface recording or stimulation electrodes are not sufficient to investigate neuronal activity in deep-brain regions. As such, implantable penetrating devices with capabilities complementing those of surface electrodes are required. The silicon-based Michigan-type (Figure 1a) and Utah-type (Figure 1b) MEAs are important neural recording or stimulation...
platforms due to their compatibility with monolithic integration methods developed in the semiconductor industry. Recent developments in complementary metal–oxide–semiconductor (CMOS) technology to construct integrated circuits have now allowed direct integration of multiplexing circuits on these silicon-based MEAs to maximize the electrode site count and minimize the width of a single probe.\textsuperscript{[108}–\textsuperscript{111]} For example, Harris and colleagues developed Neuropixels probes with \textsuperscript{109} electrodes on a 1 cm-long and 70 \(\times\) 20 \(\mu\)m\(^2\) shank using a Michigan-type design (Figure 5a).\textsuperscript{[109]} The probes were fabricated with a custom 130 nm CMOS process with each pixel at 12 \(\times\) 12 \(\mu\)m\(^2\) and a pitch at 25 \(\mu\)m. The average impedance of the electrodes is at a low value of 149 \(\pm\) 6 k\(\Omega\) at 1 kHz. The Neuropixels probes allow simultaneous independent monitoring of neuronal activity from hundreds of neurons in tissues next to the probes (e.g., multiple deep-brain regions). Similar design strategies are adopted to fabricate NeuroSeeker probes, which can achieve an even higher number of recording electrode sites at 1344 (Figure 5b).\textsuperscript{[110]} The 20 \(\times\) 20 \(\mu\)m\(^2\) titanium nitride recording electrodes with an average impedance of 48.1 \(\pm\) 2.5 k\(\Omega\) at 1 kHz are densely packed on a 50 \(\mu\)m-thick, 100 \(\mu\)m-wide, and 8 mm-long shank. The electrodes consist of in situ circuits located under each electrode for direct signal amplification. The NeuroSeeker probes can simultaneously record LFPs and multi- and single-unit activity from neocortical, hippocampal, and thalamic brain regions. Those CMOS-based devices hold the potential to be cheaply made for wide distribution in the community due to the highly integrated scalable fabrication
techniques. Combining multiple Michigan-type probes into 3D array structures will permit mapping of neuronal activity in both vertical and lateral dimensions. Figure 5c shows a representative example of 3D MEA probes for 3D dense electrophysiology. Here, 2D passive arrays of miniaturized shanks are individually fabricated and then stacked into a precise 3D array geometry with 1024 electrodes.

Despite the advantages in the high-spatial-resolution recording, these rigid silicon penetrating probes have limitations in invasiveness, reliability, and biocompatibility. Flexible penetrating electrical neural interfaces have been explored to improve the interface biocompatibility and long-term device performance. Fiber-like designs represent an effective approach to address this challenge. Kozai et al. reported ultra-small carbon fiber-based organic electrodes with poly(p-xylylene) (800 nm) dielectric barriers and PEDOT:PSS-doped recording tips for the chronic recording of single-unit activity in rats (Figure 5d). The electrodes exhibit subcellular cross-sectional dimensions (diameter \( \approx 7 \) µm) that are an order of magnitude smaller than traditional recording electrodes, resulting in a significantly reduced stiffness of 4540 N m\(^{-1}\) compared with other silicon probes (\( \approx 150 \) kN m\(^{-1}\) with cross-section dimensions of 15 \( \times \) 120 µm\(^2\)) and commercial electrodes for DBS (\( \approx 1 \) MN m\(^{-1}\) with diameters of \( \approx 100 \) µm). As a result, they elicit much
reduced chronic tissue responses after implantation. In addition, Guitchounts et al. demonstrated 16-channel arrays built from ultrathin (diameter ≈ 4.5 μm) carbon fiber to record LFPs across multiple cortical regions in birds with negligible immune response.[115] Implantable CNT fibers with superior electrochemical properties, good softness, and biocompatibility are used for chronic in vivo neural interfacing.[116] The CNT fibers have a low average impedance at 11.2 ± 7.6 kΩ and a high CIC at 372 ± 56 mC cm² and can either stimulate or detect single neurons over several weeks with comparable recording performance to metal microwire electrodes, while introducing a much reduced inflammatory response.

Another alternative approach is to develop thin, flexible polymer-based penetrating probes to reduce tissue damage and glial responses during long-term operation. Luan et al. reported a neural electrode that consists of arrays of nanoscale platinum or gold electrodes (thickness 500 nm) on a 10 μm-wide and 1.5 μm-thick SU-8 photoresist substrate, which is one of the smallest neural probes ever reported.[117] A temporary 20 μm tungsten microwire or 7 μm carbon fiber shuttle facilitates the insertion of electrodes into mouse brains. The effective bending stiffness of the probe is only 10⁻¹⁵ N m², significantly smaller than stainless steel microwires or silicon probes. The ultra-small and flexible probes greatly reduce the surgical damage from tissue displacement and are suitable for chronic recording, as demonstrated by stable impedance, noise level, and single-unit yield in the somatosensory cortex and visual cortex of mice for up to 4 months. The “Neuralink” array in Figure 5e represents an additional example,

![Figure 5](image-url)
which includes 96 ultrafine polymer probes with 32 iridium oxide or PEDOT:PSS-coated electrodes to yield a total of 3072 electrodes for monitoring or stimulating individual neurons across different locations in the brain.\textsuperscript{[118]} As the probes are ultrathin, a temporary tungsten–rhenium wire shuttle guides the insertion into tissue, facilitated by a neurosurgical robot. Iridium oxide or PEDOT:PSS coatings realize low electrochemical impedance ($56 \pm 7 \text{k}\Omega$ for iridium oxide and $37 \pm 5 \text{k}\Omega$ for PEDOT:PSS) at the interface. The overall system package, including the implantable devices, custom chips for on-board amplification, and digitization, only occupies less than $23 \times 18.5 \times 2 \text{mm}^3$ to enable simultaneous recording from all channels.

Injectable mesh electrodes represent an effective approach to interface soft tissue with a minimized immune response. Tian et al. reported the first mesh electronics platform with microporous flexible NW nanoelectronic scaffolds for 3D interpenetration with biomaterials (Figure 6a).\textsuperscript{[119]} The scaffolds can be used for culture and extracellular recordings of neurons, cardiomyocytes, and muscle cells. Later Liu et al. developed a syringe-injection process to inject ultrathin mesh electronics into internal cavities within deep tissues (Figure 6b).\textsuperscript{[120]} The electronic mesh with 16 recording electrodes is fabricated in a 2D geometry on SU-8 using standard photolithography. The bending stiffness of the mesh electronics ($0.087 \text{nN m}$) is several orders of magnitude smaller than those for silicon probes ($4.6 \times 10^{-5} \text{nN m}$).\textsuperscript{[121]} This small bending stiffness allows the devices to spontaneously fold when transferring through hollow needles and unfold into 3D interfaces in vivo to allow high spatiotemporal mapping of LFPs with minimized chronic immune responses. In addition to injection with a needle, the mesh electrodes can be frozen in liquid nitrogen for efficient stereotaxic insertion into the cortex.\textsuperscript{[122]} More recently, stable chronic recordings over 8 months were demonstrated using the injectable mesh electronics.\textsuperscript{[123]} The astrocytes and microglia around the devices decrease to a normal distribution 6 weeks post-implantation. Time-dependent immunohistology studies reveal that the mesh electronics–tissue interfaces exhibit no long-term immune response.\textsuperscript{[124]} In another report, a 4 × 4 mesh MEA was injected into mice retinal ganglion cell (RGCs) to study the dynamic interaction between the retina and related central nervous system.\textsuperscript{[125]} When coated on the highly curved retina, it enables 16-channel recordings of several types of RGCs with robust responses to visual stimuli for over 2 weeks without influencing normal eye functions. Lieber and coworkers recently developed the “neuron-like electronics” (NeuE) probe with an interconnect cross-section of $1 \times 0.9 \mu\text{m}^2$ (Figure 6c)\textsuperscript{[126]} and a bending stiffness comparable with those of the axon.\textsuperscript{[127]} NeuE is the first neural probe with flexibility matching a subcellular component and eliminating typical inflammatory responses.

3. Microsystems for Optical Biointerfacing

Optical stimulation and recording devices are complementary to electrical recording and stimulation tools. In this section, we provide an overview on implantable and wearable optical Microsystems with a focus on optogenetics, oximetry, and photometry.

3.1. Optical Modulation Devices

The advent of optogenetics has revolutionized our ability to interrogate specific neural circuitry through the genetic introduction of light-sensitive ion channels (opsins) into neurons or other cells.\textsuperscript{[118,129]} Opsins are transmembrane proteins that undergo conformational changes upon light illumination and drive changes of membrane potential in opsin-expressing cells. Excitatory opsins, such as channelrhodopsin-2 (ChR2),\textsuperscript{[128,130]} are cation channels that depolarize neurons in response to light. Inhibitory opsins, such as halorhodopsin\textsuperscript{[131,132]} and archaerhodopsin,\textsuperscript{[133,134]} are proton or chloride pumps that hyperpolarize neurons under illumination. In the past decade, a variety of opsins with different absorption spectra and kinetics have been developed.\textsuperscript{[115–138]} Despite the rapid advances in opsins, the supporting technologies to precisely deliver optical stimuli into targeted tissues to activate opsins improve more slowly. An ideal optogenetic implant needs to meet the following requirements: 1) site-specific light delivery and/or uniform illumination of a certain brain volume; 2) lightweight and wireless operation to minimize impact on animal behaviors; 3) minimally invasive and biocompatible to reduce tissue damage and immune response; and 4) tunable wavelengths with high switching speeds.

Thermally drawn silica optical fibers, traditionally used in telecommunications, represent one of the most widely used optoge netic waveguides for light delivery into the brain.\textsuperscript{[135,148]} Optical fibers typically consist of a core and cladding material. The core has a higher refractive index than cladding to achieve total internal reflection and confine light in the core. Tapered optical fibers are introduced to modulate the illumination depths and volumes

Figure 6. a) SEM image of side view of a mesh NW nanoelectronic scaffold. Scale bar, 100 µm. Reproduced with permission.\textsuperscript{[119]} Copyright 2012, Springer Nature. b) Schematic illustration of injectable mesh electronics. Red–orange lines highlight the mesh structure. Reproduced with permission.\textsuperscript{[120]} Copyright 2015, Springer Nature. c) Schematic demonstration of structural similarities between NeuE probes and neurons at both subcellular and network levels (inset). Reproduced with permission.\textsuperscript{[126]} Copyright 2019, Springer Nature.
and enable simultaneous illumination of multiple-wavelength photons to multiple regions (Figure 7a). Optical fibers produced from soft polymers with a lower modulus than silica reduce the mechanical mismatch between fibers and neural tissue. Lu et al. developed multimaterial reduced from soft polymers with a lower modulus than silica, silicon nitride, silicon oxynitride, and SiO2. These flexible fibers can optically invoke neuronal activity in the spinal cord of anaesthetized ChR2-expressing mice at a blue light irradiance of 32 mW mm\(^{-2}\) without inducing significant inflammatory reactions. Sheng and co-workers developed biodegradable optical fibers with poly (L-lactic acid) (PLLA) as the core material for light delivery and detection (Figure 7b). The PLLA fibers are prepared by thermal drawing with similar dimensions (diameter 220 μm) to standard silica fibers. When coupled to a 473 nm laser light source, the PLLA fibers can deliver optogenetic stimulation to induce seizure that activates mice and increases travel distance.

Integrating waveguides on shafts is an alternative approach for delivering photons to the brain. Waveguides normally use thin layers of two materials with distinctive refractive indices as core and cladding. Since silicon-based devices have the longest tradition in implantable neural probes, silicon is extensively used as the substrate for integration of waveguides. A variety of materials including SiON, silicon nitride, silicon oxynitride (SiON), zinc oxide, SU-8, and parylene are deposited as waveguides. Either a single-shank design with a single or multiple waveguides or multiple shanks split up from a single base are adopted to achieve light delivery into one or more regions in the brain. Zorzos et al. proposed multiple-ridge multimodal waveguides on a single silicon shank. Each waveguide consists of a SiON core and SiO2 cladding and a corner mirror at 90° to reflect light away from the shank in 2D or 3D array structures. Flexible polymers have been used as alternative substrates to integrate waveguides as well, which reduce the mechanical mismatch with the soft tissue.

Although optical fibers and other waveguides are effective in many contexts, they are connected to external light sources, and the associated physical tethers can alter naturalistic behaviors. Sheng and co-workers developed alternative battery-free energy harvesting techniques that generated highly miniaturized wireless platforms suitable for use in freely moving small animals and complex 3D environments. Figure 8a shows the first wireless multimodal optogenetics probe that can induce place preference in freely moving mice through optically modulating anxiety-like behaviors. Energy-harvesting circuits with small form factors can be used for unfunctional optogenetic implants as they require less power than multimodal platforms. Figure 8b shows such a device containing blue μ-ILEDs integrated with far-field RF power-harvesting systems using copper serpentine traces as the stretchable antenna. The devices are built on elastomer substrates that support tensile strains up to 30%. The devices can be applied to interface with the brain, spinal cord, and peripheral nerves. Far-field power transfer allows the transmitting and receiving antennas to be meters apart while the power-harvesting efficiency is sensitive to orientations and positions of the antennas. Figure 8c shows an alternative example consisting of a small flexible printed circuit board (FPCB) and an injectable probe. Wireless power harvesting relies on the near-field magnetic resonant coupling between a primary antenna that encircles the experimental arena and a secondary receiving antenna in the FPCB. The magnetic resonant coupling greatly reduces the overall device size and specific absorption rate and minimizes the dependence of power-harvesting efficiency on antenna orientations and obstacles in the environment. The small dimension (diameter \(\approx 9.8\) mm, thickness \(<1.3\) mm), mechanical flexibility, and lightweight (\(\approx 30\) mg) features allow fully subdermal implantation in small animals. A bilayer encapsulation with parylene and PDMS enables superior long-term stability and biocompatibility for chronic applications. The μ-ILEDs cover a broad spectrum, including ultraviolet (UV), blue, green, yellow, and red regions for activating a variety of opsins.

Recently, organic light-emitting diodes (OLEDs) have emerged as the new type of light sources for optogenetics research. OLEDs offer several attractive features including spectral tunability, mechanical flexibility, high brightness, low heating, and potentials to achieve an extremely high spatial resolution. Figure 8d shows an OLED array consisting of individual blue OLEDs with a single pixel dimension at \(6 \times 9\) μm\(^2\), which matches the sizes of individual cells such as neurons. The blue OLEDs can activate ChR2 and control Drosophila locomotor behavior.
3.2. Optical Recording Systems

In addition to optogenetics, optical recording technologies represent crucial tools that are broadly adopted for monitoring of physiological information and improving diagnosis and treatment of diseases. Recent advances in flexible and stretchable optoelectronic devices enable comfortable and conformal attachment on the human skin[94,178] or minimally invasive implantable applications in the brain of animals[157,179] to achieve continuous and accurate optical measurements. Compared with electrical recording platforms, optical recording has unique features such as deeper penetration depths in tissues, higher spatial and spectral resolutions, etc.

3.2.1. Pulse Oximetry

Pulse oximetry measures blood oxygen saturation by optically determining the concentrations of deoxyhemoglobin (without binding oxygen) and oxyhemoglobin (binding and transporting oxygen) in the pulsating arterial blood.[180,181] A typical pulse oximeter consists of a photodetector and two LEDs of different emission wavelengths (e.g., red [660 nm] and infrared [IR] [940 nm]).[182] In general, deoxyhemoglobin and oxyhemoglobin have significantly different molar absorption coefficients at the two wavelengths. The optoelectronic components can be placed horizontally next to one another to operate in a reflection mode or vertically with the photodetector and two LEDs on different sides of the finger to operate in a transmission mode to satisfy different application requirements.[21,183–185] Photons from two LEDs must penetrate the skin, travel through venous blood, pulsating and nonpulsating arterial blood, and other tissues, and the responses are measured by the photodetector (Figure 9a).[186] The maximum light absorption is from the systole (heart contraction) whereas minimum light absorption occurs during diastole (heart relaxation) in the artery. Those alternating current (AC) signals correlate with human pulse. The rest of the direct current (DC) signals are from nonpulsating arterial blood, venous blood, and tissue. As such, pulse oximetry provides an efficient way for health monitoring.

OLEDs and organic photodetectors (OPDs) are attractive candidates for pulse oximeters due to their excellent mechanical properties.[187,188] Lochner et al. reported all-organic pulse oximeters based on red and green OLEDs and an OPD blade coated on a polyethylene naphthalate substrate (Figure 9b).[186] The OLEDs have peak emissions at 532 and 626 nm and the OPD has external quantum efficiencies of 38% and 48% at these two wavelengths, respectively. The optoelectronic components are organized in the transmission mode and allow measurements of oxygenation and pulse rate with only 2% and 1% errors, respectively. The same group later demonstrated a printed reflective pulse oximeter array consisting of red and near-IR (NIR) OLEDs and OPDs.[189] The array design enables 2D oxygenation mapping at various positions (Figure 9c), which is impossible with commercial oximeters. Someya and coworkers developed an extremely flexible photonic skin with multicolor
OLEDs and OPDs on a 2 μm polymer substrate (Figure 9d).[178] A multilayer stacked encapsulation using parylene and SiON (Figure 9e) ensures stable operation for 4 days. The device easily adheres to the human skin to track and display pulse rate and blood oxygen level (Figure 9f). In addition to all-organic active components-based oximeters, OLEDs have been integrated with silicon photodetectors to generate a hybrid reflection mode pulse oximeter (Figure 9g).[185] In another report, Xu et al. developed an epidermal photoplethysmogram (PPG) sensor integrating an organic phototransistor (OPT) and an inorganic LED that encompases a finger (Figure 9h).[190] The OPT has an NIR responsivity that outperforms commercially available silicon photodetectors.

The PPG sensor continuously monitors the heart rate: when combined with electrocardiogram results measured from commercial devices, the sensor can track blood pressure changes at various body positions. Rogers and coworkers recently demonstrated two near-field communication (NFC)-enabled battery-free wearable oximeters.[188,190] NFC protocols are favorable for data transmission in wearable devices due to the low power consumption. The reflection mode oximeter in Figure 9f[185] uses an IR LED (peak emission 950 nm) and a red LED (peak emission 625 nm) and a photodetector positioned in between the LEDs to capture backscattered light from the blood. The device is extremely thin (≈0.9 mm) and lightweight (≈0.15 g) and can form a conformal contact with the earlobe and fingernail (Figure 9j,k). Those features together with the battery-free wireless operation mode enable continuous and motion artifact-free PPG measurements using a smartphone or tablet computer for readout, which is highly desired for remote healthcare monitoring. In addition to wearable oximeters, Rogers and coworkers recently developed a wireless subdermally implantable reflection mode oximeter for local tissue oximetry measurement in the brain, which facilitates investigations of the local oxygen-mediated physiological process (Figure 9l).[192]

### 3.2.2. Photometry

Optical methods that use genetically encoded calcium or voltage indicators (GECIs or GEVIs) to monitor neuronal activity are increasingly important in neuroscience research.[193] GECIs and GEVIs are fluorescent proteins that offer complementary advantages over electrophysiological approaches by enabling recording from specific subtypes of cells.[194–196] Fiber photometry uses an implanted optical fiber to both excite and measure fluorescence signals from GECIs or GEVIs, which directly correlate with changes in the neuronal activity of genetically defined subpopulations of neurons. Figure 10a shows a typical fiber photometry setup.[197] Although fiber photometry does not allow monitoring of individual neurons compared with wide-field and two-photon imaging,[140,198] it is compatible with moving animals and is scalable to simultaneously monitor multiple...
distinct brain regions in the same animal through frame-projected independent-fiber photometry.\(^{199}\) We reported a wireless, miniaturized, battery-powered photometer for measuring calcium transients from GECIs at the point of implantation in a tether-free manner (Figure 10b).\(^{157}\) The injectable probe integrates a \(\mu\)-ILED and a microscale inorganic photodetector (\(\mu\)-IPD) coated with a narrow-band dye absorber on a thin biocompatible polyimide filament. The device has a weight of <0.5 g with a small rechargeable battery as the power supply for operation and an IR communication module for wireless data transfer (Figure 10c). The photometer achieves stable collection of neuronal activity in the basolateral amygdala in freely moving mice during a foot shock test with SNRs comparable with commercially available fiber photometry systems (Figure 10d). More recently, we further developed a wireless, battery-free fully implantable photometry system (Figure 10e).\(^{179}\) The system avoids the use of head-mounted batteries and is instead powered wirelessly by magnetic resonant coupling between a primary antenna in the environment and a secondary receiving antenna in the device. This feature reduces the overall device weight to 45 mg and allows chronic stable operations without concerns from the limited operational lifetimes associated with batteries. The system is fully compatible with MRI and microcomputed tomography and allows recording in experimental paradigms that are challenging with current technologies, such as during forced swim tests.

4. Multimodal Microsystems

An important future direction in bioelectronics is to design multimodal systems that combine electrical recording with electrical, optical, and/or pharmacological stimulations for improved levels of biointegration. When applied to neuroscience, those multimodal recording and stimulation devices will enable studying the casualties of neural networks with real-time loss- or gain-of-function manipulations to unravel neural dynamics and brain functions. In this section, we discuss and highlight the recent progress in multimodal devices with at least one electrical or optical modality.

4.1. Electrical Recording and Stimulation

Electrical stimulation works by charge injection to cells to induce membrane depolarization or hyperpolarization.\(^{200}\) Such methods have been widely used clinically to treat neurological disorders such as depression and Parkinson’s disease through DBS.\(^{201–204}\) Moreover, electrical stimulation has been used to

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Figure 10. a) A typical fiber photometry experimental setup. Reproduced with permission.\(^{197}\) Copyright 2014, Elsevier. b) Left, optical image of an injectable wireless battery-powered photometer probe. Scale bar, 2 mm. Right, SEM image of the probe tip. Scale bar, 200 \(\mu\)m. c) Schematic of the electrical operating principles of the wireless photometer in (b). d) Recorded neuronal activity during a foot shock test using a commercial fiber photometry system (upper) and the battery-powered wireless photometer (lower). b–d) Reproduced with permission.\(^{157}\) Copyright 2018, PNAS. e) Optical image of a fully wireless, battery-free, subdermally implantable photometer for chronic recording of neural dynamics in freely moving animal subjects. Reproduced with permission.\(^{179}\) Copyright 2020, PNAS.
treat neuropathic pain and achieve nerve regeneration and weight control through electrodes that interface with the spinal cord and peripheral nervous system. Yang and coworkers reported a multimodal four-layer stacked graphene ECoG array for treating epilepsy (Figure 11a). The ECoG array consists of 10 recording and 20 stimulation channels, respectively. The single electrode site has a dimension of 60 μm × 60 μm. The array is ultrathin with a thickness of 6 μm and can laminate on the somatosensory and/or motor cortical area in anaesthetized animals to detect epilepsy and conduct electrical stimulation to terminate abnormal activities using parameters adapted from DBS systems (e.g., amplitude 1 V, frequency 100 Hz, duration 30s). Figure 11b shows a syringe-injectable mesh electronic device with low-impedance platinum recording and stimulation electrodes. The small thickness (<800 nm) and width (20 μm) of the mesh electronics yield a low bending stiffness of ≈0.1 nN m. The system allows for simultaneous chronic stimulation and recording of neurons for 4–14 weeks postinjection in moving mice.

Closed-loop neuromodulation systems are highly desired to treat various neurological conditions by adjusting delivered therapeutics in response to real-time recorded information. Zhou et al. recently reported a battery-powered wireless artifact-free neuromodulation device (WAND) that enables simultaneous electrical recording and stimulation with low-latency biosignal processing and high-throughput data streaming (Figure 11c). Tungsten electrodes with an impedance between 500 and 800 kΩ are used as recording electrodes, while platinum–iridium electrodes with impedance between 200 and 350 kΩ are used as stimulation electrodes, respectively. The miniaturized device is capable of recording and stimulation on 128 channels and fully cancelling stimulation artifacts by on-board processing. Demonstrations with freely moving macaque monkeys reveal that the device allows long-term recordings of LFPs with minimal stimulation artifacts and closed-loop stimulation to obstruct movement preparatory activity in a delayed-reach task. Meanwhile, several key challenges limit the utility of multimodal electrical recording and stimulation devices in fundamental biological studies. For example, both electrical recording and stimulation are unable to investigate the activity of specific subtypes of cells.

4.2. Electrical Recording and Optical Stimulation

Devices that integrate high-spatial-resolution optogenetic modulation with high-temporal-resolution electrical recording, sometimes known as optrodes, combine the advantages of electrical and optical techniques, which are desired to study the causal connectivity of neural circuits with cell-type specificity.

Early-stage approaches to design optrodes involve the manual attachment of microwires and silicon probes to optical fibers or integrating a single electrical recording site to optical fibers via a thin-film metal deposition process. Optical fibers with metal electrodes coated at the tip can be further incorporated into existing Utah-type MEAs to generate a single optical input in multiple electrical output systems. Alternatively, Zhao et al. reported a “nanoelectronic coating” strategy in which an ultrathin (<1 μm) MEA is adhered conformally to the curved surface of micropipettes or optical fibers by Van der Waals interactions (Figure 12a). To stimulate and record from multiple sites, systems with multiple optical inputs and electrical readout channels have been developed, including...
multishank silicon electrical recording probes with integrated fiber guides,[224] optical fiber bundles with multiple metal electrodes,[225] and tapered optical fibers with multiple light windows combined with single-shank silicon probes containing linear arrays of recording electrodes.[226] More recently, Lu et al. reported stretchable multimodal optical fibers incorporating silver NW recording electrodes for probing spinal cord circuits of mice (Figure 12b).[227] The fibers are thermally drawn with PC core and COC cladding, which are then dip coated with a mesh of conductive transparent silver NWs (diameter 70 nm, length 40 mm) and encapsulated by PDMS. The silver NW electrodes exhibit an impedance around 50 kΩ at 1 kHz, which can be programmed via tuning the concentrations of NW solutions. The diameters of the multimodal fibers range from 105 to 135 μm, determined by the dimensions of the fiber cores (100–130 μm). The hybrid fibers can be stretched up to 100% strain while maintaining electrical conductivity. In vivo demonstrations show that the stretchable fibers are able to optically evoke neuronal activity in the spinal cord of moving mice and simultaneously record the stimulated signals with the NW electrodes.

As discussed in Section 3.2, various microscale waveguides fabricated by standard microfabrication techniques (e.g., photolithography, chemical vapor deposition [CVD], etc.) are used to deliver photons to different regions in the brain for optogenetics after being coupled to external light sources. As a result, waveguides can be multiplexed into recording probe configurations to enable simultaneous optical stimulation along the recording probes. Integrating a single waveguide in one probe is a popular design and multiple probes can then be integrated into array structures to increase the number of optical stimulation sites without increasing fabrication complexity.[155,228] Compared with optical fiber-based optrodes, waveguide approaches allow flexibility in probe designs because the geometrical parameters (e.g., thickness, spacing between waveguides and electrodes, width, etc.) can be precisely defined by lithography, which guarantees a high reproducibility for manufacturing. Yoon and coworkers reported an optrode consisting of a SiON dielectric waveguide and eight iridium recording electrodes in a silicon shank for simultaneous excitation of specific neurons and acute recording of single-unit activity in rat neocortex and hippocampus.[229] SU-8 epoxy is another commonly used waveguide core material.[151,152,228] Figure 12c shows a silicon optrode with multiple electrodes surrounding a microscale SU-8 waveguide core.[228] The 2D optrode array design allows delivering of light into multiple brain sites. In addition to planar waveguide-based optrodes, Lee et al. developed an out-of-plane optrode with 4/C2 tapered indium tin oxide (ITO)-coated zinc oxide-based waveguide array.[150] The transparent zinc oxide functions as both an optical waveguide and a recording electrode. Integrating μ-ILEDs in the vicinity of recording electrodes is another promising technique to design optrodes. This strategy removes the requirement of external light sources, allows the integration of μ-ILEDs with different emission wavelengths on the same optrode for simultaneous modulation of multiple opsins, and enables high-spatial-resolution light delivery. μ-ILEDs can be integrated into optrodes in two ways: 1) direct monolithic fabrication of μ-ILEDs on the optrode substrate or 2) transfer printing μ-ILEDs from a source wafer to the optrode substrate. Yoon and coworkers reported the first silicon optrodes with multiple monolithic integrated μ-ILEDs and recording electrodes.[230] The devices include a four-shank probe with 12 indium gallium nitride μ-ILEDs and 32 titanium/platinum/iridium recording electrodes. The μ-ILEDs have cellular-scale...
dimensions around $10 \times 15 \times 0.5 \, \mu m^3$. The small form factor allows the µ-ILEDs to output 1 mW mm$^{-2}$ irradiance under a small forward current value less than 8 μA. The optrodes enable optical stimulation and recording of CA1 neurons with single unit resolution in the pyramidal layer of moving mice. However, for monolithic integration, choices of substrates are always limited due to the requirement of lattice match for epitaxial growth of the emitting layers. Kim et al. reported one of the first µ-ILED-based multimodal devices for brain research.[160] The multilayered, miniaturized injectable probe includes four gallium nitride µ-ILEDs ($50 \times 50 \times 6.45 \, \mu m^3$), a µ-IPD ($200 \times 200 \times 1.25 \, \mu m^3$), a 20 µm-wide serpentine platinum temperature sensor, and a 20 µm-diameter platinum recording electrode. Transfer printing and patterned deposition of passivation and interconnect layers place and electrically connect the µ-ILEDs on the polymer substrates. Bonding the ultrathin probe to a releasable microneedle with silk fibroin provides the required rigidity for surgical implantation. Importantly, the multimodal device relies on wireless power harvesting and control modules for remote, untethered operation in freely moving animals. More recently, Jia et al. developed a battery-powered flexible and implantable ECoG recording and optical stimulation device using commercially available µ-ILEDs ($220 \times 270 \times 50 \, \mu m^3$).[231] A reflow soldering process mechanically holds µ-ILEDs at desired locations and electrically connects the µ-ILEDs to prepatterned interconnects. In vivo experiment demonstrates that the device can achieve the bidirectional neuro-modulation of primary visual cortex neurons in freely moving rats using Bluetooth data communication for up to 21 days after implantation. In addition to applications in neuroscience research, multimodal wireless optoelectronic devices combining µ-ILEDs and stimulation electrodes have been applied to cardiac research to realize multisite optical and electrical pacing for studying the pathogenesis of cardiovascular diseases.[232] Nonetheless, thermal management during the operation of the implantable µ-ILEDs is crucial to avoid thermal damage and complications to behaviors from overheating. The operation mode and power input have to be carefully optimized to minimize temperature increases.

4.3. Transparent Microelectrodes

The multimodal optoelectronic probes in Section 4.2 use non-transparent metal MEAs to record neuronal activity. Those opaque metal microelectrodes not only generate optical shadows that prevent direct optical interrogation of cells under the microelectrodes but also produce severe light-induced electrical artifacts that can be difficult to distinguish from real neuronal activity.[233,234] One approach to overcome those limitations is to design optically transparent microelectrodes, which will allow crosstalk-free integration of electrophysiological recording/stimulation with optogenetics and/or optical imaging.

Current transparent microelectrodes for electrophysiology include ITO,[235] graphene,[126,236,237] CNTs,[238] metallic NWs,[239] metal grids,[240] and their hybrid composites.[241,242] ITO exhibits excellent transparency across the visible spectrum (85–95%) and low sheet resistance (4–40 Ω sq$^{-1}$).[243,244] It is the most widely used transparent conductive electrodes in optoelectronic devices, such as liquid crystal displays,[245,246] OLEDs,[247,248] and solar cells.[249,250] Early-stage transparent MEAs use thin ITO layers patterned on glass substrates for multisite recording of extracellular processes in cultured cells.[251] Recently, Ledochowitsch et al. demonstrated micro-ECoG (µ-ECoG) arrays that consisted of 96 ITO (thickness 110 nm) microelectrodes on a 3 µm transparent polyethylene substrate for electrical readout of cortical circuits under external optogenetic stimulation.[235] The ITO microelectrodes (diameter 40 µm) exhibit an average transmittance > 90% across the visible spectrum and an electrochemical impedance < 1 MΩ at 1 kHz. The ITO MEAs successfully recorded optogenetically evoked auditory responses at the stimulation sites in transgenic mice. Kunori et al. combined ITO MEAs with an epifluorescence microscope to perform epidural cortical electrical stimulation and simultaneous optical imaging of signals from cortex neurons underneath the stimulating microelectrodes.[252] The ITO MEAs (thickness 100 nm, diameter 250 µm) are fabricated from a commercially available ITO-coated PET film and a photolithography process. Although ITO/PET films are commercially available for optoelectronic applications, the cyclic flexibility and bending tolerance of those devices are inadequate for chronic applications in curvilinear biosurfaces because of the brittle nature of ITO.

Graphene and CNTs have been recently reported as alternative flexible transparent microelectrode materials.[253–256] They exhibit good electrochemical properties, high transparency, and improved flexibility compared with ITO.[256,257,257] CVD is widely used to grow high-quality and large-area graphene and CNTs. Different transfer methods can then prepare them onto an arbitrary substrate. Kuzum et al. reported transparent doped graphene MEAs on a 25 µm polyimide substrate (Figure 13a).[257] Doping graphene with nitric acid decreases the electrochemical impedance up to 50% at 541 kΩ. In vitro experiment with rat hippocampal slices reveals that graphene MEAs enable high-temporal-resolution electrical recording of high-frequency neuronal population spikes whereas calcium imaging captures activity from individual neurons under the MEAs with a high spatial resolution. In addition to chemical doping using nitric acid, Lu et al. reported that the impedance of graphene microelectrodes could be reduced by 100 times by electrodepositing platinum nanoparticles on CVD graphene.[258] However, the improved electrochemical performance comes at a cost of reduced transparency as platinum nanoparticles are opaque. In addition to calcium imaging, optogenetic modulation is integrated with graphene MEAs.[259] Four layers of CVD graphene are transfer printed and patterned onto a 15 µm polyethylene substrate as electrodes. The MEAs show a transparency > 90% from UV to IR region and an average impedance of 243.5 ± 5.9 kΩ at 1 kHz, which is slightly higher than that of the platinum reference (188.8 ± 92.9 kΩ). In vivo electrical recording of optogenetically evoked cortical neuronal activity demonstrates the capabilities of graphene MEAs. A more recent study shows that optical imaging, optogenetic stimulation, and cortical recording with graphene MEAs can be realized in the same in vivo experimental setup in a crosstalk-free manner.[251] In addition to flexible graphene MEAs, CNT networks are integrated in elastomer substrates such as PDMS to achieve stretchable CNT-based transparent MEAs. Figure 13b shows an example of transparent and stretchable CNT MEAs developed by Zhang et al. for in vivo
electrical and optical interrogation of cortical activity in GCaMP-
or ChR2-expressing mice. The stretchable MEAs consist of PDMS elastomer substrate, CVD-produced CNT electrodes and interconnects, and SU-8 encapsulation. The 100 × 100 μm² CNT microelectrodes exhibit a transparency > 85% in the entire visible and IR range and an average electrochemical impedance of 200 ± 30 kΩ. Meanwhile, they exhibit ≈55% increase in electrochemical impedance upon a tensile strain of 50% whereas the impedance of graphene microelectrodes increases by 10 times under a smaller strain of ≈3%. Due to the excellent optical, electrical, and mechanical properties, CNTs can be used to continuously monitor cortical activity under simultaneous optical stimulation/imaging in mechanically active environments with negligible light-induced electrical artifacts. Meanwhile, for graphene and CNTs, their properties are sensitive to the fabrication technologies and they suffer from controversial results associated with their cytotoxicity for chronic applications.

Similar to CNTs, metallic NWs have been recently shown as promising candidates for transparent MEAs. The silver/gold core-shell NW microelectrodes maintain low resistance during cyclic tests with strain values of 60%, exhibit high optical transmittance values between 69% and 83%, and a low normalized impedance between 1.1 and 3.2 Ω cm².

As previously mentioned in Section 2.1, it is challenging to decrease the microelectrode sizes due to the undesired scaling of electrochemical impedance and increased noise with reduced electrode dimensions. Qiang et al. reported transparent 32-channel MEAs consisting of a gold (thickness 25 nm)/PEDOT:PSS (thickness 85 nm) bilayer nanomesh on a 10 μm parylene substrate (Figure 13c). The bilayer MEAs exhibit a transmittance of >70% at 550 nm and impedance of 130 kΩ at 1 kHz with the single microelectrode diameter at 20 μm, comparable with the dimensions of single neurons. The electrochemical performance of the bilayer nanomesh MEAs is significantly improved compared with graphene and ITO alternatives. In vivo experiment demonstrates that the MEAs can record activity from multiple neurons with a high spatial resolution and are compatible with simultaneous two-photon calcium and epifluorescence imaging on the visual cortex of awake mice. In addition to gold nanomesh, PEDOT:PSS coating can effectively improve the electrochemical performance of other transparent MEAs such as graphene. Recently we demonstrated that covering the open spaces between interconnected metal grid transparent microelectrodes with ITO could significantly increase the effective ESA without changing GSA. The resulting microelectrodes exhibit improved electrochemical impedance (5.4–18.4 Ω cm²) than both metal grid and ITO references, high optical transparency (59–81%), and superior mechanical flexibility with no changes in electrical performance after 5000 bendings against a small radius at 5 mm.

State-of-the-art transparent microelectrode technologies rely on physically separated bulk optical components such as microscopes and optical fibers to conduct simultaneous multimodal investigations, which limits their future implantable applications. Kwon et al. reported a multichannel Opto-μECoG array that integrates a transparent ITO MEA and a blue μ-ILED array for epidural electrical recording and optical stimulation of cortical activity. The ITO MEA and the μ-ILED array are separately prepared on parylene substrates and then aligned and bonded together using adhesives. More recently, we reported a monolithic integrated flexible multimodal biointerface containing transparent gold nanogrid microelectrodes on top of μ-ILEDs for colocalized electrophysiology and optophysiology (Figure 13d). Integrating gold nanogrids above the μ-ILEDs greatly minimizes the light-induced electrical artifacts during multimodal operations. The gold nanogrid microelectrode is
ultrathin (40 nm) and shows a high transmittance >70% with a superior normalized impedance of 5.9 \( \Omega \text{ cm}^2 \). As a result, the thickness of the multimodal devices is comparable with unfunctional optogenetic stimulation devices. Ex vivo demonstrations reveal that the multimodal biointerfaces enable simultaneous detection of abnormal heart rhythm in transgenic mouse hearts using the microelectrodes and restoring the sinus rhythm via optogenetic pacing of ChR2-expressing cardiomyocytes using the \( \mu \)-ILEDs.

4.4. Multimodal Chemical Modulation Systems

Pharmacological techniques are a well-established approach to control cell-specific neuronal activity without using genetic modifications. Localized delivery of various biological and chemical agents to the brain to treat brain tumors and neurodegenerative disorders such as Parkinson’s and Alzheimer’s has been an important clinical practice for many years.[265–268] Metal cannulas have been the standard method to support pharmacological infusions to different brain regions.[269] Advances in lithographic fabrication techniques have allowed integrating microfluidic drug delivery channels into miniaturized electrical and optical neural probes to conduct multimodal pharmacological modulation with concurrent electrical recording/stimulation and/or optical modulation and study the complex neural circuit dynamics more effectively.

Early-stage multimodal chemical modulation and electrical recording devices rely on silicon-based MEMS fabrication techniques.[270–274] Figure 14a shows a single neural probe that allows chemical modulation of neurons through multiple microchannel drug delivery and simultaneous recording of neuronal activity via an MEA located near the fluidic outlet.[274] The microfluidic channels are based on silicon and contain two or five \( 5 \times 10 \mu \text{m}^2 \) channels in parallel, fabricated by deep reactive-ion etching. The iridium recording electrodes are small \((19 \times 19 \mu \text{m}^2)\) and show an average impedance of 800 k\( \Omega \) at 1 kHz. This multimodal probe successfully triggered seizure by delivering baclofen to the thalamus of head-fixed mice and recorded the resulting changes in neuronal activity with the MEA. In addition to single-shank silicon probes, 3D multishank multimodal microfluidic probes integrating gold recording electrodes have been developed based on a silicon island structure and a folding procedure.[275] The 3D probes allow modulation across a large area of the brain. Various biocompatible polymer substrates such as polyimide,[151,276,277] parylene,[278] SU-8,[52] and PDMS[279] have been used to create soft multimodal microfluidic implants. Metz et al. demonstrated one of the earliest flexible multimodal microfluidic neural probes with gold recording electrodes \((200 \times 200 \mu \text{m}^2)\).[276] The polyimide microchannels can be fabricated in various shapes and dimensions via a layer transfer and lamination technique. PDMS represents one of the most attractive material options to construct microfluidic channels due to its high optical transparency in the visible region, good biocompatibility, and low modulus \((\leq 0.1–10 \text{ MPa})\).[15] Soft lithography is widely used to prepare PDMS patterns. Ultrathin PDMS-based microfluidic channels can be fabricated by bonding two oxygen plasma-treated PDMS layers together.[280] Minev et al. reported soft multimodal microfluidic neural implants with stimulation electrodes to enable

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**Figure 14.** a) A single-shank silicon probe with eight iridium recording electrodes and embedded microfluidic channels. Reproduced with permission.[274] Copyright 2015, The Royal Society of Chemistry. b) A thin, soft, and stretchable multimodal electronic dura meter with platinum–silicone composite electrodes and microfluidic channels. Reproduced with permission.[279] Copyright 2015, American Association for the Advancement of Science. c) A trimodal single-shank silicon probe-integrating microfluidic channels, SU-8 waveguide, and eight iridium recording electrodes. Reproduced with permission.[281] Copyright 2019, Springer Nature. d) Cross-sectional microscope image of a multimodal multimaterial optical fiber that integrates fluidic channels and electrodes. Reproduced with permission.[282] Copyright 2015, Springer Nature. e) A flexible battery-powered optofluidic probe that includes \( \mu \)-ILEDs with microfluidic channels. Reproduced with permission.[283] Copyright 2015, Elsevier. f) Schematic illustration of a fully wireless and implantable optofluidic peripheral nerve cuff for multimodal optogenetics and pharmacology. Reproduced under the terms and conditions of the CC-BY license 4.0.[284] Copyright 2019, The Authors. Published by American Association for the Advancement of Science.
electrochemical and electrical stimulation of the spinal cord for neuroprosthesis (Figure 14b).\(^{279}\) The recording electrodes exhibit stable performance up to 45% tensile strain.

Combining microfluidic channels, electrophysiological recording modality with optogenetics, allows for dissecting neural circuitry with high specificity. Figure 14c shows a monolithic integrated multishank silicon probe containing silicon microfluidic channels for pharmacology, SU-8 waveguides for optogenetics, and eight iridium electrodes for recording neural signals on each shank.\(^{281}\) The individual shank has a width and thickness at 128 and 40 µm, respectively. The small form factor and thin geometry reduce mechanical stiffness of the probes and tissue damage during implantation. The trimodal devices could modulate the hippocampal excitatory pathway between CA1 and CA3 neurons with receptor antagonists and optogenetically stimulate CA3 neurons. The MEAs efficiently record the neural spikes in CA3 and CA1 regions. Polymer-based microfluidic channels could be integrated with optical waveguides and low-temperature electrodes into multimaterial fibers via a thermal drawing process.\(^{282}\) Figure 14d shows a multimaterial fiber with transparent PC core, COC cladding, and carbon-loaded conductive polyethylene electrodes. Experiments in transgenic mice show that the microfluidic channels can deliver a glutamate receptor blocker and suppress the optogenetically evoked action potentials reversibly.

Integrating optofluidic microsystems with wireless modules can minimize physical tethers and tissue damage due to the tethered tubing. Following the development of wireless optogenetics technologies,\(^{190}\) Jeong et al. reported the first wireless optofluidic probes (Figure 14e)\(^{283}\) which rely on a head-mounted small-scale battery (0.66 g) as the power supply. Four soft lithography-fabricated PDMS fluidic channels (10 × 10 µm\(^2\)) with an array of four µ-ILEDs (100 × 100 × 6.54 µm\(^3\)) allow combined in vivo pharmacological and optogenetic manipulation of neuronal circuits in the deep brain. An IR communication module provides independent control of optical and pharmacological components. A thermally expanded pump design enables programmed dispensing of pharmacological agents. Experimental demonstrations include optogenetically controlled place aversion and preference with concurrent pharmacological suppressing of optically stimulated behavior in freely moving mice. More recently, Qazi and coworkers developed battery-powered, smartphone-controlled optofluidic devices integrating refillable and disposable cartridges and Bluetooth wireless module that allows long-range operations.\(^{284}\) To further minimize the device dimensions and overcome limited operational lifetime associated with battery-based operation, Noh et al. reported a miniaturized battery-free wireless soft optofluidic system that uses RF wireless energy-harvesting techniques to support device operation.\(^{285}\) The number of traces in the RF antenna can be increased to realize independent wireless control of fluid and light delivery. In addition to applications in the brain, Zhang et al. reported a fully implantable wireless optofluidic cuff system integrating PDMS-based microfluidic channels and blue µ-ILEDs for modulation of the peripheral nervous system (Figure 14f).\(^{286}\) An electrochemical pumping mechanism is adopted to minimize power consumption and heat generation from the previously discussed thermally expanded pumping mechanism. The lightweight optofluidic cuff system allows for chronic modulation of targeted peripheral nerve activity in freely moving mice via localized drug delivery and optogenetic stimulation without damaging the associated peripheral nerve. Although current flexible wireless multimodal microfluidic chemical modulation microsystems have shown promise, additional efforts are required to address challenges associated with limited spatiotemporal resolution, unsatisfactory storage volumes for chronic pharmacological treatment, simultaneous wireless operation in multiple animal subjects, seamless integration with various organs (e.g., brain, heart, spinal cord, and peripheral nerves), etc.

It is important to note that besides the electrical, optical, and chemical modulation methods, several other neuromodulation techniques such as ultrasound, magnetic, and thermal based methods also provide important new capabilities to modulate specific brain regions or neuronal populations. Ultrasound is an acoustic wave that produces thermal or mechanical effects to cells in deep tissues, depending on the pulse regime.\(^{287}\) It is a noninvasive neural modulation tool with deep penetration depth. The acoustic wave can be focused into particular brain regions without influencing cells along the propagation path. The spatial resolution is proportional to the wavelength of the driving ultrasound frequency (≈3 mm at 0.5 MHz). For example, high-intensity focused ultrasound can be transmitted through the skull to achieve thermal ablation in the deep human brain with millimeter-scale spatial resolution.\(^{288,289}\) Despite the advantages, the precise mechanistic understandings of ultrasound-based neuromodulation remain to be clarified. Transcranial magnetic stimulation (TMS) is another noninvasive neuromodulation method that applies a strong magnetic field (>0.5 T) using magnetic coils to induce electric fields in the underlying tissue that depolarize cells and trigger neuronal activity.\(^{290,291}\) The stimulation effects are controlled by magnetic field strength, duration, pattern, number of pulses, etc. TMS offers advantages in biocompatibility and consistency compared with electrical stimulation\(^{292}\) whereas it suffers from limited spatial resolution and high-peak power consumption. Thermal neuromodulation relies on temperature-induced changes in cell membrane capacitance and/or the conductance dynamics of thermosensitive transient receptor potential ion channels.\(^{292,293}\) A number of methods are used to deliver thermal energy, such as direct optical absorption of IR\(^{293}\) or visible\(^{294}\) light by tissues or nanomaterial stimulation that relies on nanoparticles to absorb RF radiation or photons\(^{296}\) and heat the surrounding tissue. Thermal neuromodulation provides control of deep-brain neuronal activity with submillimeter spatial precision and a temporal resolution ranging from millisecond to second. However, it lacks cell specificity compared with optogenetics.

5. Summary and Outlook

Electrical and optical devices for biointegration have now been well established and are in widespread use as effective treatment tools for an expanding set of health conditions. In this Review, we have discussed and detailed the latest development of materials, design strategies, electrical engineering, soft mechanics, and systems for biointerfacing, mainly focusing on neural interfaces. In particular, different electrical and optical sensors and stimulators (both wearable and implantable) are discussed and the multimodal tools that provide simultaneous recording and modulation
capabilities are presented, some with wireless schemes for power harvesting, control, and data communication. Many of these bio-interfaces are in different stages of animal tests and the develop-ment for particular envisioned applications in clinical medicine is ongoing. The recently developed wireless optogenetics tools by Rogers and coworkers\cite{37} are already commercially available for the neuroscience research community to conduct fundamental studies with freely moving animal models.

A number of critical challenges still remain in translating the state-of-the-art electrical and optical biointerfaces into clinical applications. For example, the dimensions, geometries, and encapsulations of implantable probes have to be further improved to minimize foreign-body response and realize long-term biocompatibility for specific applications. This requires innovations in fabrication techniques (e.g., CMOS techniques), materials (e.g., low-dimension materials and organic–inorganic hybrid composites), and mechanics. So far, Lieber and coworkers have achieved stable chronic in vivo brain mapping using flexible mesh electronics for 8 months.\cite{123} In addition, further scaling up the number of recording or modulation sites (over several thousand channels) is undoubtedly highly preferred to achieve operation with a high spatiotemporal resolution. Moreover, the combination of effective recording and actuating modalities at both small (cellular) and large (populations of cells) scales will enable the multimodal closed-loop investigation of the basic operating principles of physiology at multiple levels. Last but not least, fully wireless operations of those devices represent an important engineering goal for animal studies and clinical translation. The results summarized in this Review present great opportunities to use advanced optical and electrical biointerfaces in future basic and translational research.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

biointegrated electronics, biointerfaces, electrophysiology, flexible electronics, optoelectronics

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