Minireview

Bio-hybrid electronic and photonic devices

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Impact statement

This review brings together information from a wide range of sources and disciplines, putting the emerging field of bio-hybrid devices into context and describing current and potential applications of these emerging technologies.

Abstract

Bio-hybrid devices, combining electronic and photonic components with cells, tissues, and organs, hold potential for advancing our understanding of biology, physiology, and pathologies and for treating a wide range of conditions and diseases. In this review, I describe the devices, materials, and technologies that enable bio-hybrid devices and provide examples of their utilization at multiple biological scales ranging from the subcellular to whole organs. Finally, I describe the outcomes of a National Science Foundation (NSF)–funded workshop envisioning potential applications of these technologies to improve health outcomes and quality of life.

Keywords: Semiconductors, conducting polymers, nanomaterials, optogenetics, 3D printing

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Introduction

The role of genetic and biochemical cues for directing cell fate and behavior has long been apparent, even if the specific genetic and biochemical cues had not yet been elucidated. A myriad of tools and techniques for manipulating cell, tissue, organ, and organismal physiology have resulted from our increased understanding, beginning with Mendelian genetics and leading to CRISPR gene editing today. Moving beyond genetics and biochemistry, research from the last few decades has begun to elucidate and benefit from the role of electrical[1] and mechanical[2] stimuli to affect biological behavior. In the medical regime, this has resulted in several bioelectronic devices, with the potential for many others. Bioelectronic devices have been employed in several arenas, most notably cardiac pacemakers, which celebrated their 50th anniversary in 2010,[3] cochlear implants, approved by the Food and Drug Administration (FDA) in 1985, which have enabled tens of thousands of profoundly deaf people to communicate in a hearing world,[4] and deep brain stimulation, which became widely used in the 1990s to treat the Parkinson disease and essential tremor.[5] Despite the success of these devices, we have only begun to scratch the surface of the potential for bioelectrical and biophotonic devices, limited in part by challenges in the tissue–device interface and the potential tissue damage due to device insertion.

Efforts to create novel bio-hybrid devices must confront two critical challenges: (1) developing devices that match the size scales and mechanical properties of the cells, tissues, or organs to avoid damage to the biological system and (2) developing devices that can withstand the wet, salty, proteinaceous chemical environment of biological systems while maintaining contact with the biological system to permit information transfer either electronically or using integrated photonics. The ultimate goal of these approaches will be to create devices in which cells, scaffolds (either biological, synthetic, or a combination), and electronic and/or photonic devices are assembled and used *in vitro* for fundamental studies or *in vivo* for regenerative, sensing, or gain of function applications as shown in Figure 1.

Inorganic devices

Approaches to create bio-hybrid devices can be broadly grouped into organic and inorganic devices, particularly inorganic semiconductors, but these two groups are not mutually exclusive as a variety of polymer coatings can be applied to protect devices from aqueous environments or to create a softer substrate with greater mechanical biocompatibility and flexibility. Both the Tian group at the University of Chicago and the Lieber group at Harvard University have investigated the use of nanoscale-structured semiconductors, particularly silicon, for fabrication of devices capable of interfacing with cells and tissues and integration into biological systems.[6–11] Using a combination of top-down and bottom-up fabrication strategies, they have been able to create structures with similar length scales as the biological systems of interest and apply them to a variety of sensing and actuating applications as shown in Figure 2. These structures include nanoscale kinked silicon wire field-effect

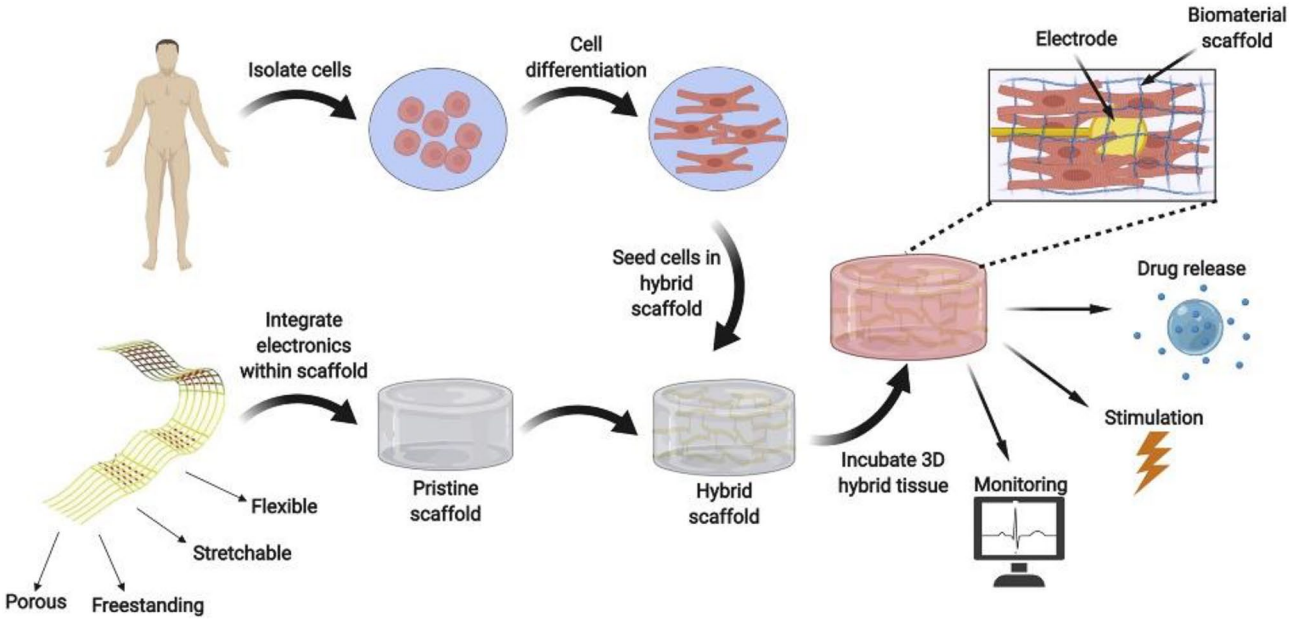

Figure 1. Approaches and applications for integrating electronics with engineered tissues. The electronics are integrated within 3D biomaterial scaffolds and then seeded with cells to form the 3D hybrid tissue. The electronics include sensing, stimulating, and controlled drug release elements for regulating tissue function. (A color version of this figure is available in the online journal.)
Reprinted from Feiner and Dvir.[23]

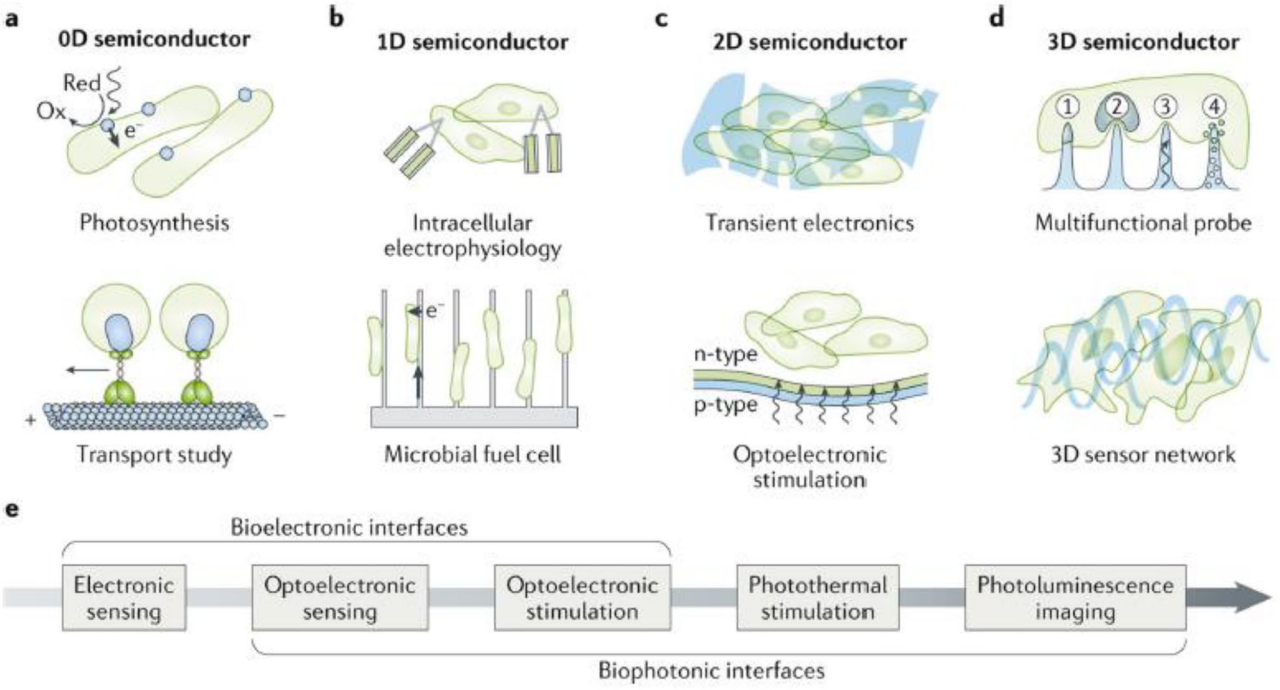

Figure 2. Semiconductor geometries and example applications for biointerfaces. (a) 0D semiconductors can be used to mimic photosynthesis, for example, using CdS nanoparticles that are precipitated on the cell wall of a bacterium to sensitize non-photosynthetic bacteria through photo-induced electron transfer pathways. Photoluminescent quantum dots can be coupled to motor proteins to enable the tracking of intracellular transport mechanisms. (b) 1D semiconductors – for example, nanoscale-kinked Si nanowire field-effect transistors – allow intracellular recordings of single cell action potentials. Nanowire-bacteria hybrids can photoelectrochemically fix carbon dioxide and produce value-added chemicals. (c) 2D semiconductors – for example, biodegradable Si – provide a physically transient form of electronic devices. The photovoltaic effect of thin-film Si diode junctions can be used for the optical control of biological activities. (d) 3D semiconductors – for example, semiconductor micropillar or nanopillar arrays – can detect cellular electrophysiological signals, potentially probe nucleus mechanics, deliver optical stimuli for photostimulation, and release drugs. Strain-engineered 3D mesostructures of Si can serve as electronic scaffolds for neural networks. (e) Typical signal transduction mechanisms of semiconductor devices involve electrical or optical inputs and outputs. (A color version of this figure is available in the online journal.)
Source: Reprinted by permission from Jiang and Tian.[7]
Ox, oxidation; Red, reduction.

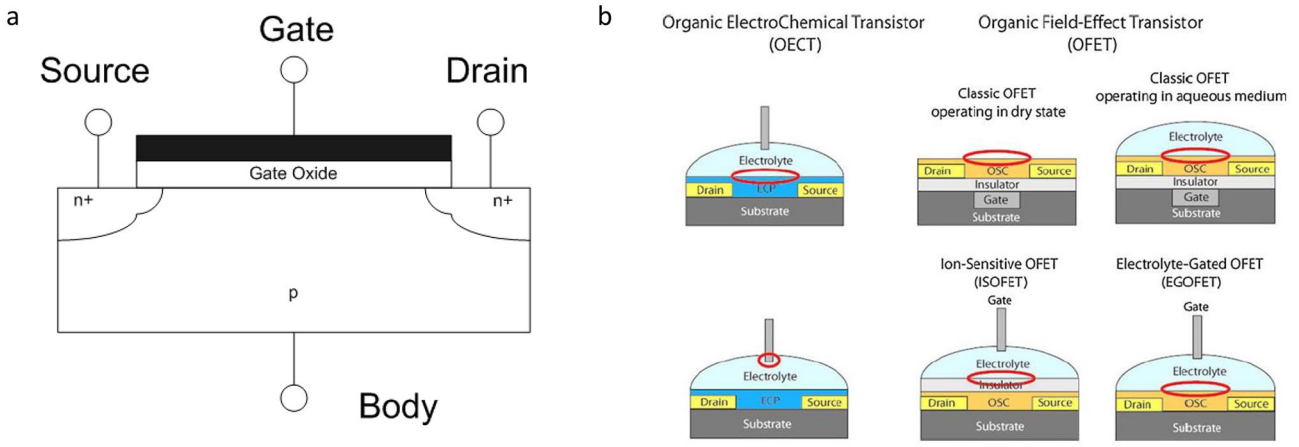

Figure 3. Transistor structures used in bio-hybrid electronic devices. (a) Field-effect transistor (FET). Charged particle movement (electrons or holes) from source to drain are modulated by the potential applied to the gate. Both N- and P-type silicon can be used in FETs. https://commons.wikimedia.org/wiki/File:FET_cross_section.png used under CC BY-SA 3.0. (b) Variations on FETs containing organic compounds that can be used as possible biosensors. Organic electrochemical transistors (OECT) contain electrically conducting polymers (ECPs), while organic field-effect transistors (OFETs) contain organic semiconductors (OSCs). The red circle indicates the different interfaces involved in the detection of biomolecules. (A color version of this figure is available in the online journal.)
Source: Reprinted by permission from Loïg Kergoat *et al.*[30]

transistors (FETs; Figure 2(b), upper panel; Figure 3(a)), thin-film silicon diode junctions (Figure 2(c), lower panel), semiconductor micropillars (Figure 2(d), upper panel), and strain-engineered three-dimensional (3D) mesostructures of silicon (Figure 2(d), lower panel). A critical aspect of the synthesis of these structures is the use of a vapor–liquid–solid (VLS) growth process and modulation of synthesis parameters such as pressure and temperature.[8,9] The Lieber group, in particular, has focused on the creation of mesh electronics, semiconductors at length scales that can seamlessly bridge brain tissues and electronics with feature sizes similar to neuron somata and mechanical properties akin to brain tissue.[11] They first developed nanowire FETs as general biological nanosensors, which they applied to detecting propagating action potentials from neurons. They later expanded this activity to 3D nanoscale FET cellular probes that could be seamlessly integrated into several types of synthetic tissues permitting detection of chemical signals, mechanical strain, and extracellular potentials, as well as simultaneous electrical stimulation and recording allowing for bidirectional flow of information.

An important aspect of silicon-based devices is the potential for biodegradability.[12,13] Hwang and co-workers observed that nanomembranes (NMs) of device-grade, monocrystalline silicon (Si) can dissolve in water to biocompatible end products, thus setting the stage for the field of transient electronics in biological systems.[12] They further created devices that included transistors, diodes, inductors, capacitors, and resistors, with interconnects and interlayer dielectrics, on a thin silk substrate using magnesium for the conductors, magnesium oxide for the dielectrics, and monocrystalline Si NMs for the semiconductors. Conversely, the potential for unwanted degradation is an issue that can potentially be addressed by passivation, for example, by growing strontium titanate, a material used in bone tissue engineering, on the silicon surface.[7] In addition to the biodegradability of silicon, the biocompatibility has been extensively characterized, including for a wide range of nanoscale structures.[14–20]

Beyond silicon, a variety of other inorganic materials can play a role in generating bio-hybrid devices. These materials include CdSe nanoparticles and ZnO microwires, which can be used as fluorescent tags for a variety of biological systems.[7] Single-wall carbon nanotubes (which are considered by some to be organic compounds) can be easily functionalized to permit endocytosis, creating intracellular interfaces, while molybdenum sulfide-graphene heterostructures can form tight interfaces with retinal tissue, delivering programmed electrical stimuli to the retina.[7,9]

Organic devices

A wide range of organic materials are also increasingly used for a variety of electronic and photonic applications, including conducting polymers, carbon nanotubes, graphene, organic light-emitting diodes, and diamond films fabricated via chemical vapor deposition.[21] The use of polymeric materials, particularly conducting polymers, for manufacture of bio-hybrid devices is an area that has received increased interest.[21–24] Polymers are naturally flexible and have Young's moduli similar to biological tissues. In particular, polypyrrole (PPy), polyaniline (PANI), and poly (3,4-ethyle nedioxythiophene):poly(styrene sulfonic acid) (PEDOT:PSS) are attractive as they are naturally conductive, soft, and biocompatible.[23] The swelling characteristics of organic materials are also beneficial, as they can lead to soft interfaces and good compatibility with biological tissues.[25] The resistivities of conducting polymers are significantly higher than metals (10^{-1} to $10^{-3}\,\Omega$cm for conducting polymers vs $10^{-6}\,\Omega$cm for metals); however, they are frequently deposited on metal electrodes to improve functionality in biological settings, presumably by improving the cell contacts due to the conformable nature of the polymers.[23] In addition, the conductivities of carbon nanotubes begin to approach those of metals.[21]

Baek and co-workers have explored conjugating a wide range of polymeric side chains to a polymer backbone

Table 1. Different technologies for fabricating flexible electronics.

Technology	Fabrication	Components	Young's modulus	Resistivity/conductivity
Stretchable conductive polymers	Electropolymerization	Various polymers such as polypyrrole, polyaniline, and poly(3,4-ethylenedioxythiophene)	GPa; thin layers allow for flexibility	~10^{-1}–10^{-3} Ω cm
Doping elastomers	Mixture of conducting or semiconducting elements within an elastomer (e.g. PDMS or SEBS) followed by photolithography	Elastomer and conductive or semiconductive elements	Depends on elastomer thickness, dopant	Depends on the choice of dopant and concentration
Conductive hydrogel-based electrodes by photolithography	Mixture of an ionic liquid with a conductive polymer and subsequent photolithography	A hydrogel of the conductive polymer poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate)	~30 kPa	~0.02 Ω cm
Buckled metal conductors	Deposition on a prestretched elastomer and release of the strain	Metal conductor and elastomer substrate	Depends on thickness of elastomer substrate	–10^{-6} Ω cm depending on choice of metal
Localized bonding to prestretched elastomer	Microfabrication using photolithography and thin-film metal deposition with release and transfer to a prestretched elastomer with predefined bonding sites	Primarily polyimide or SU-8 and a metal conductor on top of an elastomer	Varies depending on device thickness kPa – GPa	–10^{-6} Ω cm depending on choice of conductor
Stretchable architecture or ultrathin electronics	Microfabrication using photolithography and thin-film metal deposition	Substrate such as polyimide or SU-8 and a metal conductor	Varies depending on device thickness kPa – GPa	–10^{-6} Ω cm depending on choice of conductor

Source: Adapted from Feiner and Dvir.[23]
PDMS: polydimethylsiloxane; SEBS: polystyrene-block-poly(ethylene-ran-butylene)-block-polystyrene.

with side chains including acrylates, ethers and styrene and polymer backbones such as poly(phenylene vinylene) (PPV), poly(phenylene ethynylene) (PPE), PPy, and PEDOT. They explored both grafting, with the conjugated polymers attached to an electrode surface and conjugation in solution, resulting in functionality such as pH responsiveness, biomolecule capture, dry adhesion, and stretchability.[26] Šafaříková *et al*.[27] investigated the biocompatibility of organic semiconductors using two representative low-molecular weight organic semiconductors, triisopropylsilyethynyl pentacene (TIPS-pentacene) and diketopyrrolopyrrole (DPP(TBFu)$_2$) along with two semiconducting organic polymers, poly(3-hexylthiophene-2,5-diyl) (P3HT) and PEDOT:PSS, examining their stability and wettability as well as their suitability as substrates for culture of NIH 3T3 fibroblasts and murine cardiomyocytes. Some leachates were observed from the PEDOT:PSS, but these were addressed by extensive washing with ethanol and phosphate-buffered saline (PBS). Interestingly, the wettability of the PEDOT:PSS was superior to the other polymers examined, with a contact angle of 60 degrees. To assess biocompatibility, NIH 3T3 fibroblasts were grown for 48 h on TIPS-Pentacene, DPP(TBFu)$_2$, P3HT, and PEDOT:PSS deposited on glass slides. Both cell adhesion and viability were assessed. TIPS-Pentacene, DPP(TBFu)$_2$, and P3HT showed somewhat reduced cell adhesion compared with tissue culture plastic and glass, while the attachment of cells to the PEDOT:PSS was very poor with little coverage and misshapen cells. Similarly, the viability, as measured by ATP and MTT assays, was significantly lower for cells grown on the PEDOT:PSS, while the other materials showed a moderate decrease, which was likely due to their hydrophobicity. To improve the biocompatibility, a number of biological coatings were evaluated (collagens, fibronectin, and Matrigel), and collagen IV was found to improve viability, bringing the results for some of the organic coatings close to those of tissue culture plastic as well as protecting the PEDOT:PSS coating from delaminating.

In addition, conducting polymers can be doped, allowing them to act as semiconductors, creating organic transistors and similar devices.[24] Alternatively, conducting materials such as metals can be deposited onto or incorporated into elastomers such as the commonly used biocompatible polymers polydimethylsiloxane (PDMS) or polystyrene-block-poly(ethylene-ran-butylene)-block-poly-styrene (SEBS).[23] The range of techniques for creating flexible electronics is summarized in Table 1. Generation of polymer nanocomposites in which inorganic nanomaterials such nanoparticles, nanotubes, nanosheets, nanowires, or nanoclay are dispersed in an organic polymer matrix presents an additional option. These materials can be assembled using a layer-by-layer assembly method or by grafting polymers to the surface of various nanoparticles.[28] Layer-by-layer assembly is performed by sequential deposition of oppositely charged species, where the polymers can be chemically synthesized species or biopolymers. Grafting techniques often employ surface-initiated atom transfer radical polymerization (ATRP), which produces polymer nanocomposites with good control of polymer molecular weight, polydispersity, and composition, and can be applied to a wide range of monomers.

Cellulose, a biopolymer consisting of long, crosslinked polymeric chains of glucose, has been of increasing interest for development of flexible electronic materials.[29] Possible applications include electronic–ionic conductors, electrolytes, and electrochemical electrode materials in flexible circuits, sensors, conductive transistors, organic light-emitting diodes (OLEDs), organic thin-film transistors (OTFTs), supercapacitors, batteries, triboelectric nanogenerators (TENGs), and tissue bioelectronics. Features of cellulose that provide utility in these systems include degradability and biocompatibility, unique dielectric and piezoelectric properties, and intra- and inter-molecular hydrogen bonds, which provide good mechanical properties, a high aspect ratio, ease of modification, and integration into a variety of systems.

In addition to cellulose, a number of organic materials can be used in the fabrication of OTFTs. These devices are potentiometric transducers with low working voltages (<1 V) and high sensitivity and come in two primary configurations, organic electrochemical transistors (OECTs, Figure 3(b)) and electrolyte-gated organic field-effect transistors (EGOFET, Figure 3(b)).[25,30] A typical OECT or EGOFET consists of three components, a channel, an electrolyte, and a gate. OCETs are based on electrochemical doping and dedoping processes that occur upon bulk injection of ionic species into active channel materials, while EGOFETs have the channel current modulated by a gate voltage via a capacitive field-effect mechanism at the channel–electrolyte interface.

Finally, moving one step beyond organic polymers, there is increasing interest in using hydrogels in organic bioelectronic devices. Hydrogels consist of hydrated hydrophilic polymers such as poly(ethylene glycol) or poly(vinyl alcohol) with high water content (up to 90%) and Young's moduli in the kPa to 100's of kPa range, similar to some of the stiffer biological tissues. Their high water content and porous architecture permit dissolution of ionic species, increasing the conductivity and allowing them to serve as a bridge between biological tissues and more rigid electronic devices.[31] Encapsulation or coating of bioelectronic devices in hydrogels is a common approach and the electrical properties of the hydrogels can be increased by creating nanocomposites with electronically conductive nanomaterials including metallic nanoparticles and nanowires, carbon nanotubes, and graphene to augment the conductivity provided by the ionic species. In addition, conducting polymers can be intercalated with polymer hydrogels by forming molecular-level composites or interpenetrating networks (IPNs) between conducting polymers and non-conducting hydrogel templates. More recently, hydrogels have been prepared from conducting polymers without the non-conducting hydrogel components.

One- and two-dimensional materials

Over the last few decades, nanotechnology has provided a variety of nanomaterials, including zero-dimensional (0D) nanoparticles such as quantum dots, one-dimensional (1D) nanotubes and nanowires, and two-dimensional (2D) nanosheets including graphene and carbon nanotubes, all of which can potentially interface with biological structures. In particular, silicon nanowires (SiNWs), carbon nanotubes (CNTs), graphene and graphene-related materials (e.g. graphene oxide), and transition-metal dichalcogenides (TMDs) have attracted significant attention for a variety of properties that provide utility in developing bioelectronic devices, particularly the ability to match the scaling of biological structures and their ability to conform to the shapes of cells, tissues, and organs.[10,32]

Silicon nanowires have a uniform composition and 1D structure with diameters ranging between 3 and 500 nm and lengths ranging from hundreds of nanometers to millimeters. The crystalline structure and smooth surface of chemically synthesized NWs reduce scattering and result in enhanced electrical properties.[10] Five classes of Si nanowire structures are available today, a basic homogeneous structure, an axially modulated structure, core/shell nanowires, branched nanowires, and kinked nanowires.[10] SiNWs are most commonly synthesized by a nanoparticle-catalyzed VLS mechanism, specifically using chemical vapor deposition with a volatile gaseous precursor such as SiH_4 or $SiCl_4$, as the silicon source. As described above, they are frequently used for FETs, which can be used for applications such as protein, nucleic acid, and virus detection. Examples include the detection of the Ebola glycoprotein in PBS, human serum and plasma using a graphene FET, detection of *Escherichia coli* and prostate-specific antigen using antibodies immobilized on gold nanoparticles on top of the FET, and measurement of a nucleic acid marker for Down syndrome using an immobilized complementary DNA sequence.[33]

Graphene is a single layer of sp^2-hybridized carbon atoms arranged in a honeycomb array. It is commonly generated by mechanical cleavage of highly oriented, pyrolytic graphite and exhibits excellent electronic characteristics including high carrier mobility, high carrier density, and low absorption of visible light.[32] However, graphene obtained by mechanical exfoliation is limited to lateral dimensions of tens to hundreds of micrometers. Other top-down production methods yield similar or smaller pieces of graphene.[34] If larger sheets are desired, they can be synthesized by chemical vapor deposition onto metal substrates such as copper, nickel, palladium, iridium, and ruthenium. Unfortunately, this approach introduces impurities into the graphene, degrading its properties. Graphene is particularly notable for its exceptional mechanical strength, up to 25% tensile strain, making it a good candidate for use in flexible devices. Carbon nanotubes are effectively rolled up tubes of graphene, with either a single layer (single-walled carbon nanotube, swCNT) or multiple layers (multiwalled carbon nanotube, mwCNT). The diameter of an swCNT is typically 1–2 nm, while the diameter of an mwCNT ranges from 2 nm to over 100 nm.[35] The length of the nanotubes can reach up to ~0.5 m, although typically shorter (mm to cm) length tubes are produced. CNTs are commonly synthesized on a solid support using surface-programmed assembly methods and can have either metallic or semiconductor properties with various band gaps, depending on the bonding structure. CNTs have particularly high tensile strength and elastic moduli; hence, they do not have the conformability of biological tissues, although as described above, they can be functionalized for endocytosis. As both graphene and CNTs are composed exclusively of carbon, they exhibit high biocompatibility and easy functionalization and consequently are used for a wide range of devices, particularly, biosensors.[35,36]

TMD monolayers are atomically thin semiconductors of the type MX_2, with M a transition-metal atom (e.g. Mo and W) and X a chalcogen atom (S, Se, or Te). One layer of M atoms is sandwiched between two layers of X atoms. In contrast to the semimetal graphene, TMD monolayers MoS_2, WS_2, $MoSe_2$, WSe_2, and $MoTe_2$ have a direct band gap, and can be used in electronics as transistors and in optics as emitters and detectors. MoS_2, in particular, has been identified as a potential 2D material for soft bioelectronics due to its band gap (1.8 eV for monolayers and 1.2 eV for bulk material), which provides unique properties not found in graphene.[37] Many of these materials are integrated into multilayer arrays

Table 2. Characteristics of 2D materials that provide utility for bio-hybrid devices.

2D materials	Characteristics	Soft bioelectronic devices utilizing characteristics
Graphene	Flexibility	Wearable glucose patch, electrocorticography (ECoG) sensor for optogenetics, wearable touch sensor
	Transparency	Glucose monitoring lens, smart endoscope for tumor theragnosis, ECoG sensor for optogenetics
	Ease of functionalization, large surface/volume ratio, giving high sensitivity	Wearable glucose patch, glucose monitoring lens, wireless bacteria sensor
	Biocompatibility	Smart endoscope for tumor theragnosis, cell-sheet–graphene hybrid, ECoG sensor for optogenetics
MoS_2	Superior photoabsorption	Curved image sensor array
	Softness	Soft retinal prosthesis
	Piezoresistivity	Ultrathin tactile sensor, MoS_2 bilayer strain gauge
	Large surface area/volume ratio	Highly sensitive humidity sensor, pH sensor, streptavidin biosensor
	Intrinsic defects	Non-volatile memory
Black phosphorus	Hydrophilicity, large surface/volume ratio	Selective humidity sensor
MXenes (transition-metal carbides, nitrides or carbonitrides)	Layered structure	Smart endoscope for tumor theragnosis

Source: Adapted with permission from Choi *et al.*[37]
ECoG: electrocorticography.

with graphene, graphene oxide, and/or hexagonal boron nitride for a wide range of applications. Table 2 highlights some features of 2D materials for bio-hybrid devices and a variety of applications that exploit these physical properties.

3D printing and other additive processes

Fabrication of inorganic semiconductor devices is most commonly performed using a top-down approach in which layers of substrate are grown or deposited and subsequently patterned using photolithography. Using state-of-the-art technology, features with nanometer sizes can be obtained. In contrast, organic bioelectronic materials are typically synthesized in a bottom-up approach by deposition or self-assembly, which does not permit the exquisite structural control of conventional photolithography. Applying biomolecules or cells in a patterned approach is also generally not possible with conventional photolithography as these molecules or cells are often unable to withstand the harsh processing conditions used in conventional semiconductor processing. An alternative approach is to use 3D printing or other additive manufacturing processes to obtain the desired structures of organic compounds and biological materials.

A variety of printing techniques – including screen printing, gravure printing, and inkjet printing – can be used to manufacture printed electronics and bioactive products.[38] In addition, dip-pen nanolithography, a nanofabrication technique that uses the nanoscale tip of an atomic force microscope to direct-write functional inks, has been used to deposit both biomolecules and electrode materials.[39] Extrusion-based 3D printing, in which the materials are extruded through a nozzle, is another option, permitting incorporation of a wide range of materials with viscosities up to 10^6 mPa s and with disparate properties including nanomaterials, fibers, cells, tissues, organs, ceramics, metals, and polymers such as elastomers, gels, and biomaterials.[40] 3D printing processes, particularly those involving co-printing of soft materials and functional nanoscale inks, minimize mechanical discrepancies between the biological tissues and the fabricated devices. In addition, while the materials may be synthesized and/or processed under harsh, high temperature conditions to create high quality functional nanomaterials, the printing process is typically performed under ambient conditions via a bottom-up assembly process. Finally, the 3D printing process naturally allows for the hierarchical assembly of functional materials in three dimensions, commensurate with biology and permits a multiscale manufacturing approach.[40]

Critical aspects of any 3D printing process are the physical characteristics of the inks and substrates and the desired objective of the printing process. In screen printing, the patterns are applied using a doctor blade, which controls the quantity of ink that is transferred onto the printing cylinder to press the ink through a screen mask. The finest feature size that can be obtained by screen printing is ~75 to a few hundred micrometers. It can also be adapted to a roll-to-roll process with rotary screen printing. Screen printing requires high viscosity inks and low volatility solvents and is not recommended if good control of film thickness and morphology are required. In the gravure printing technique, the patterns are engraved in the form of crevices or wells on a rotating metallic cylinder. Gravure printing has desirable features for large area production, including high speed, up to 1 m s^{-1} and resolution from 10 mm down to few nanometers. However, it is unsuitable for printing on rigid substrates because a high level of conformity is required between the cylinder and the substrate. Gravure printing is, to date, the fastest technique with a high degree of repeatability. Inkjet printing deposition is also a promising tool for mass production due to its characteristics, that is, relatively high production speed, low cost, selective patterning, and the possibility for contactless printing. An important advantage of inkjet printing is the use of small volumes of ink. The main drawback of this technique is the low resolution compared to lithographic techniques. Engineering of the inks is critical in inkjet printing, with low viscosity inks required. With proper design, low viscosity inks and dilute solutions, there

Table 3. Summary of representative materials and methods to form biocompatible fibers, waveguides, and other biophotonic devices.

Category	Materials	Fabrication process	Pros	Cons
Inorganic materials	Silica, phosphate, silicon oxynitride	Thermal drawing, lithography	Well-established manufacturing technologies, low propagation losses	Mechanical rigidity, fragility, potential toxicity
Natural materials	Silk, cellulose, DNA, chitosan	Thermal drawing, printing, molding	Biocompatibility, biodegradability	Property variability, limited sources, poor designability
	Bacterial cells		Superior biocompatibility	Small size, limited modification methods
Hydrogel	Agarose gel, alginate	Molding	Biocompatibility, biodegradability	Property variability, limited sources, poor designability
	Polyethylene glycol (PEG), polyacrylamide (PAM)		Flexible designability	Non-degradability
Synthetic polymers	Poly (lactic acid) (PLA), poly (lactic-co-glycolic acid) (PLGA)	Thermal drawing, molding	Flexible designability, biodegradability	
Elastomers	Polydimethylsiloxane (PDMS)	Molding	Flexible designability	Non-degradability
	Poly(octamethylene citrate)-poly(octamethylene maleate citrate) (POC-POMC)		Flexible designability, biodegradability	
Multifunctional	Cyclic olefin copolymer (COC), polycarbonate (PC), conductive polyethylene with 5% graphite (gCPE)	Thermal drawing	Formation of multifunctional materials	

Source: Adapted from Shan *et al.*[42] and Nazempour *et al.*[45]

is the potential to create structures that are smaller than the nozzle diameter.[38] A particular challenge in many of these processes, particularly using inks with suspended particles, is the need to obtain a homogeneous distribution of the particles, avoiding the "coffee-ring" effect that occurs during solvent evaporation.

A wide range of devices have been developed using 3D printing and other additive manufacturing approaches including organic photovoltaics, organic FETs, OTFTs, OECTs, microbatteries, and quantum dot LEDs, which have been used for applications such as biosensing, stimulation of PC12 neuronal cell growth, retinal implants, and creation of bionic ears.[38–41]

Photonic devices

The term photonics is broadly used to describe the creation, manipulation, and detection of light, focused on practical applications where the particle or photonic nature of light is important. The term is also used to describe the use of light in applications traditionally employing electronics such as telecommunications and information processing. Photonics includes the use of lasers and LED light sources, the channeling of light through fiber optic cables and waveguides, and the detection of light using charge coupled devices (CCDs) or complementary metal-oxide semiconductor (CMOS) image sensors.

Traditionally, silica-based glass fibers have been used for light propagation due to their high transparency over a broad range of wavelengths, which is characterized by low reflection, absorption, and scattering of light, all of which result in low optical losses. With advances in glass processing, optical losses as low as 0.2 dB/km can be obtained at wavelengths near 1550 nm, well suited for long-distance fiber optic communications.[42] Leveraging the expertise of the microelectronics industry to produce semiconductor devices with high yield, robust processing, and continually decreasing costs, there has been a rising interest in silicon-based photonics.[43] Early efforts focused on the development of wave guides using silicon-on-insulator technology. More recently, there has been a move to other materials including III–V semiconductors and silicon nitride (SiN).[44] SiN is particularly attractive as it is significantly cheaper than III–V semiconductors and covers a broad operation range from visible (~400 nm) to the mid-infrared wavelengths (~4 μm), much larger than the transparency range of silicon (1.1 μm–4 μm).[43]

In addition to inorganic materials such as glass and Si/SiN, there is increasing interest in biocompatible materials that have better mechanical properties for interaction with tissues, such as softness and conformability as well as using natural materials such as silk, chitin, and cellulose or natural material hydrogels such as agarose and alginate, long polysaccharide polymers well known for their biocompatibility.[42,45] Biodegradable materials that can be implanted and then disappear are of particular interest. A summary of organic and inorganic materials used for fibers, waveguides, and other biophotonic devices is shown in Table 3. One challenge for many of these materials is that the loss coefficient is typically ~dB/cm compared with silica fibers that have loss coefficients ~dB/km; however, improvement of materials synthesis and processing methods may lower the light scattering resulting from impurities, rough surfaces, or interfaces.[45] Nature provides examples of many photonic elements, particularly in plants, insects, and sea creatures, that can be emulated in man-made devices. For example, the metallic structural color of Japanese jewel beetles, uses multilayer interferences with alternating layers of chitin and melanin, while the 2D periodic ordering of nanorods of chitin at the surface significantly enhances the optical transparency of the cicada wing.[46] There are a number of reports of top-down patterning and bottom-up assembly of natural materials, including grafting the photoreactive group (2-isocyanatoethylmethacrylate, IEM) onto native silk fibroin proteins, which renders them photosensitive, permitting UV crosslinking. Similar approaches can also be applied to the patterning of cellulose materials. Electron beam lithography has been used on crystallized silk (positive resist) and

Table 4. Performance comparison for silicon photonic biosensors.

Configuration	Technology	LoD (refractive index units)
Interferometric Mach–Zender	Si_3N_4	1×10^{-7}
Interferometric Young	$Si_xO_yN_z$	9×10^{-8}
Interferometric bimodal waveguide	Si_3N_4	2.5×10^{-7}
Ring resonator	Silicon-on-insulator	7.6×10^{-7}
Photonic crystal resonator	Silicon-on-insulator	7×10^{-6}
Integrated plasmonic biosensors based on planar Bragg gratings	Nano-patterned gold on SiO_2	10^{-6}

Source: Adapted with permission from Ciminelli *et al.*[49]
LoD: limit of detection.

amorphous silk (negative resist), creating materials with features ~10 nm in size. Using bottom-up assembly processes, structures with chiral photonic properties have been developed from cellulose nanocrystals, chitin nanocrystals, and amyloid nanofibrils.[46]

Photonic devices and structures have been used in biological and biomedical applications including optogenetic stimulation (discussed in the next section), fluorescence photometry, surgery, phototherapy, biochemical sensing, and imaging. Imaging modalities can include luminescence, photoacoustic, surface-enhanced Raman scattering, and optical coherence tomography, while phototherapies can include photodynamic therapy, photothermal therapy, and light responsive drug delivery.[47] In addition to fibers and waveguides, nanoparticles play a critical role in imaging and phototherapies including acting as photosensitizers, energy absorbers for photothermal therapy, and enhancers for photoacoustic and surface-enhanced Raman scattering-based imaging.[47] Near-infrared (NIR) light (700–1000 nm) and NIR-responsive molecules are of particular interest as NIR light is less hazardous to cells and tissues than UV light and shows much greater penetration into tissues. Examples of NIR-responsive nanocarriers include gold, swCNT, and graphene oxide.[48]

Photonic-based biosensing is another promising avenue for integrating biological systems with photonic devices. In a biosensor, a chemical or biological system is detected (and generally quantitated) through one or more biochemical reactions mediated by enzymes, antibodies, nucleic acids, cells, and so on. This interaction is then transduced, electrochemically, mechanically, piezoelectrically, or optically/photonically.[49] Several different photonic approaches can be employed to transduce the biological signal. Ciminelli *et al.*[49] have reviewed the different detection technologies, comparing their limits of detection (LoDs) as seen in Table 4. While interferometers tend to have the best LoDs, they generally have rather large footprints (>1000 mm^2). Ring resonators have similar levels of performance, but much smaller footprints (<1 mm^2), while the integrated plasmonic sensors and photonic crystal resonators have a somewhat inferior LoD (~10^{-6}) but a much smaller footprint (1–100 μm^2). Cognetti and colleagues have recently developed a creative application of ring resonator technology with a "disposable photonic" sensor platform in which very small (1 × 4 mm) SiN ring resonator sensor chips were paired with plastic micropillar fluidic cards for sample handling and optical detection. They demonstrated the utility of this disposable platform for analyzing antibodies to SARS-CoV-2 in vaccinated and convalescent subjects.[50]

Optogenetics

The techniques described above can be employed for devices inserted directly into tissues in living organisms or for the manufacture of devices using cells from a variety of sources (established cell lines, primary cells, stem cells, or stem cell-derived differentiated cells). Of particular interest is the use of cells specifically engineered to be responsive to optical or electronic stimuli, that is, the fields of optogenetics and electrogenetics. Optogenetic tools were initially developed to perform high-temporal resolution, non-invasive studies of neural activity to elucidate the temporal activity patterns in specific neurons that drive circuit dynamics, plasticity, and behavior.[51] This technique exploited the discovery of two rhodopsins (light sensitive proteins) in the unicellular green alga *Chlamydomonas reinhardtii*: one of them, Channelrhodopsin-1 (ChR1) is a light-gated proton channel, whereas the other, ChR2, is a light-gated cation channel.[52–55] By stably expressing ChR2 in rat neuronal cells using a lentiviral construct, Boyden and co-workers were able to rapidly induce membrane depolarization and return to baseline on millisecond timescales by application of a series of light pulses.[51] Evolution of optogenetic techniques expanded the protein repertoire to including molecules responding to different wavelengths of light and critically, fusion of the light responsive proteins to the signaling machinery of G protein-coupled receptors, extending the functionality beyond ion channel activation to a wide range of light-activated biochemical cellular signaling pathways.[56] As the technique has evolved, optogenetics has been applied to control protein expression using a light-activated modification of the yeast two-hybrid system, to alter expression of certain protein splice variants using a light-regulated split-intein system, and to control subcellular protein localization. Moreover, studies have been performed in a host of organisms including yeast, Chinese hamster ovary cells, zebrafish, and chicken embryos.[57] In addition, using photomasks to expose selected cells in culture dishes, optogenetics has been employed to achieve spatial control of gene expression.

The introduction of optogenetics into bio-hybrid devices is a logical extension, and laboratory-scale devices have been designed for the treatment of diabetes. Shao and coworkers designed and implanted hydrogel capsules carrying both engineered cells and wirelessly powered far-red

light-emitting diodes into diabetic mice. Using either a smartphone or Bluetooth-active glucometer, they were able to control production of murine insulin in a glucose-dependent manner.[58] In an elegant extension to these studies, an electrogenetic device was recently reported, in which an electrical pulse was used to stimulate membrane depolarization using an L-type voltage-gated calcium channel in conjunction with an inwardly rectifying potassium channel to decrease the resting membrane potential. The device, shown in Figure 4, was implanted subcutaneously in a diabetic mouse model and was capable of controlling glycemia in response to electrical stimulation.[59]

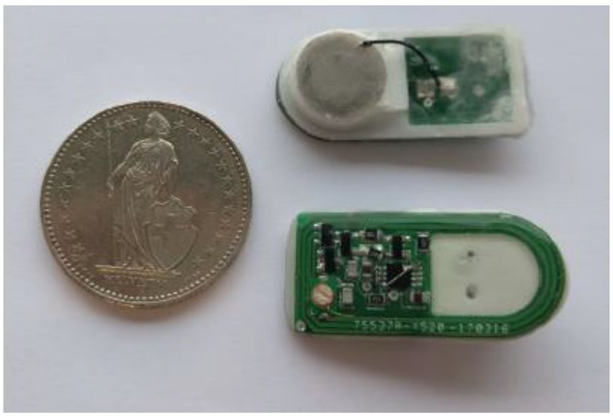

Figure 4. Bioelectronic implant. Coin diameter = 27.4 mm. (A color version of this figure is available in the online journal.)
Source: Reprinted from Krawczyk *et al.*[59] and reprinted with permission from AAAS.

Applications

Biological systems are characterized by a wide range of multiscale systems and interactions both spatially and temporally. Length scales range from the molecular (subnanometer) to the organismal (up to km scale), while time scales range from individual molecular events (microseconds) to organismal and population dynamics (years or even millennia). Thus, bio-hybrid devices have the potential to interrogate and influence biological activity at a wide range of scales ranging from the subcellular to whole organs and even organisms. In this section, a range of applications (and potential applications) will be discussed throughout the varying length scales.

Subcellular

A unique opportunity for semiconductor devices is the ability to measure intracellular signaling, due to the ease of fabricating nanometer-sized devices. Examples include the use of kinked Si nanowires in endothelial cells for intracellular force dynamics recording[60,61] and nanowire FETs for intracellular electrophysiology, recording the natural beating of cardiomyocytes.[62] Bridging the intracellular measurement with tissue-scale recording, Abbott and colleagues developed a CMOS array of vertical nanoscale electrodes with 1024 electrodes, permitting parallel electrical recording of a network of cells. They used this system to interrogate a cardiomyocyte sheet, mapping action potential propagation across the sheet in response to electroporation as well as responses to drug treatment.[63]

Cellular

Metallic microelectrode arrays (MEAs) have been used since the 1970s to record electrical activity in cultured cells, particularly neural cells,[64,65] as well as to stimulate the cells.[66] A limitation in these electrodes is the relatively large size (10–30 μm in diameter), similar in size to the neuronal cell bodies. Reduction of electrode size can improve spatial resolution, but at a cost of increased thermal noise.[10] A critical issue is the size of the cleft at the interface between the cell and the sensor, where decreasing the distance increases the seal resistance, improving the coupling between the cell and the electrode.[67] A variety of different electrode geometries, including 3D electrodes that promote cell membrane wrapping around the electrode, have been used to increase the seal resistance, improving coupling between the electrode and the cell. In another approach to improve the cell–electrode interaction, Cohen-Karni *et al.*[68] cultured cardiomyocytes on thin, flexible sheets of PDMS and then placed the cell-PDMS construct into a well in a cell culture plate containing a nanowire field-effect transistor (NWFET), allowing them to measure the electrical activity with high signal-to-noise ratios and good spatial resolution. Other opportunities for extracellular interactions with electronic and photonic devices include optical modulation of bioelectric activity through either photothermal or photoelectrochemical mechanisms. For example, Parameswaran *et al.*[69] used coaxial p-type/intrinsic/n-type (PIN) Si nanowires consisting of a p-doped core, and intrinsic and n-doped shells, to wirelessly and photoelectrochemically modulate primary rat dorsal root ganglion neuron excitability.

Tissues

Moving to the next level of complexity, a variety of devices have been developed to interface with both natural and synthetic tissues. Qing and coworkers created Si nanowire transistor arrays to map neural circuits in brain slices with high spatial resolution and sensitivity and rapid response rates.[70] Using a similar PIN SiNW approach as described above, Parameswaran generated a freestanding polymer–SiNW mesh containing a random SiNW network and employed a moving low-irradiance laser input for optical stimulation of cultured neonatal rat cardiomyocytes and adult rat hearts *ex vivo* driving them to beat at a target frequency.[71] An additional opportunity is the development of 3D electronic interfaces with synthetic tissues.[72,73] In the development of these synthetic tissues, the sensing scaffold is developed first, beginning with an array of Si nanowires, followed by the addition of electronic components such as FETs or electrical stimulators which are connected using lithographic techniques. The device components are organized into a flexible porous scaffold, possibly including biomaterials such as collagen or alginate. Finally, cells are seeded into the scaffold for maturation, and the engineered 3D tissues are integrated with the embedded nanoelectronics used for *in situ* sensing and stimulation.[74] This approach was employed to generate an engineered vascular tissue construct that could sense the pH of solutions running through the tissue lumen.[73]

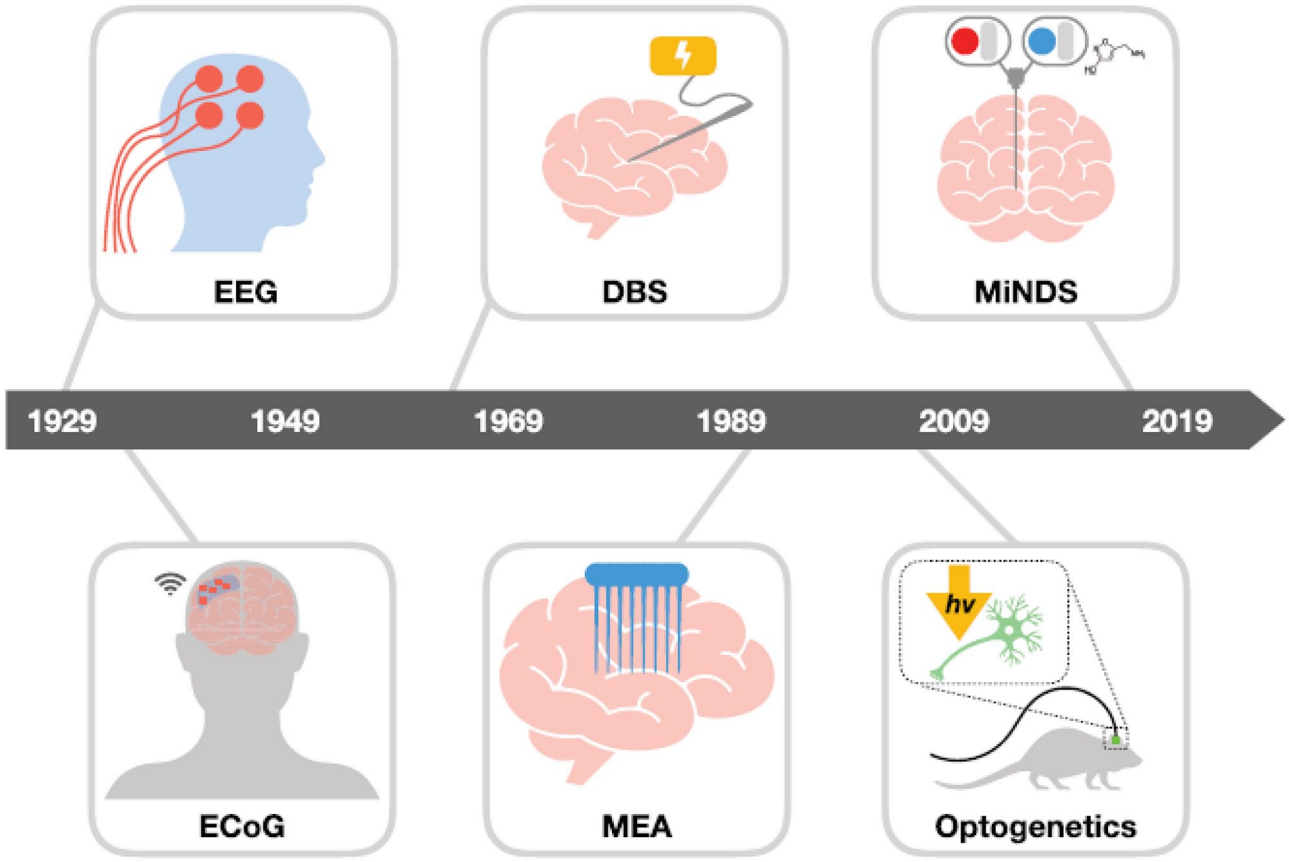

Figure 5. Timeline of developments in brain-interfacing technologies. (1) Non-invasive electroencephalography (EEG) which permits recording with non-penetrating leads. (2) Invasive electrocorticography (ECoG) which allows for transcranial recording with non-penetrating leads placed above or below the dura. (3) Implanted penetrating probes for deep brain stimulation (DBS). (4) Multielectrode arrays (MEAs) consisting of high numbers of penetrating electrodes permitting recording from a larger region of the cortex. (5) Optogenetics for the activation of neural networks using light from penetrating electrodes. (6) Miniaturized neural drug delivery systems (MiNDSs) for precise delivery of therapeutics into deep brain regions. (A color version of this figure is available in the online journal.)
CPSO: Reprinted with permission from Obidin *et al.*[77]

Organs and organ-on-chip models

The complex multicellular nature, hierarchical structures, and multiple cell types found in organs represent an additional challenge to interfacing with electronic and photonic devices. In addition, to move from research or preclinical devices in laboratory animals into patients, a variety of safety issues must be addressed. However, interfacing with electronic and photonic components adds increased functionality to organ-on-chip devices (reviewed by Soucy *et al.*[75]) used for basic biology studies and increasingly, for drug discovery and development. While electrically active tissues such as neural and cardiac have been a prime focus, there is increasing interest in epidermal electronics both from a health-care perspective as well as for consumer electronics.[76] In addition, with our aging population and a need for regenerative medicine therapies, implantable and possibly injectable therapies bridging tissues and electronic and photonic devices are clearly in our future.

Central nervous system

Owing to the electrical activity of the brain, there is a long history of brain-interfacing technologies as shown in Figure 5. These include non-invasive electroencephalography (EEG), which is widely used today to monitor brain activity; invasive electrocorticography (ECoG), which is used in diagnosis and treatment of epilepsy; deep brain stimulation used to treat Parkinson's and other motor disorders; cortical microelectrode arrays, which are under investigation for prosthetic interfacing, and the experimental optogenetic and miniaturized neural drug delivery systems.[77] As these devices advance, they trend to smaller, more conformable devices, moving from metal electrodes to semiconductor devices using microfabrication technology. One novel approach is the use of injectable neural interfaces in which an ultrathin, mesh-like grid of electrodes is injected into deep brain structures via a syringe.[11] This approach has been used successfully in rodent studies with minimal immune response in the brain.[78–80] Another novel approach is the use of bioresorbable silicon sensors composed of a membrane of poly(lactic-co-glycolic acid) (PLGA, with a thickness of 30 μm), sealed against a supporting substrate of nanoporous silicon (60–80 μm thick; 71% porosity). These sensors were employed for continuous monitoring of intracranial pressure and temperature with a potential application to the treatment of traumatic brain injury.[81]

Peripheral nervous system

Unsurprisingly, the Defense Department is a significant driver for advances in peripheral nerve interfaces. Currently,

the Defense Advanced Research Projects Agency (DARPA) funds projects in three application spaces: prosthetics (to restore sensorimotor function), electrical prescriptions (to diagnose, monitor, and treat disease), and neuroplasticity (to improve learning).[82] The Hand Proprioception and Touch Interface (HAPTIX) program was launched in 2014 with an objective to develop a fully implantable, bidirectional neuroprosthetic system for upper-limb amputees. The key aspects of the desired technology are that it must contain motor "decoders" to translate descending neural activity from residual muscles and/or nerves into motor commands, as well as sensory "encoders" to convey sensory feedback, allowing, for example, manipulation of an unseen object. The Electrical Prescriptions (ElectRx) program, launched in 2015, has the goal of using peripheral neuromodulation to provide non-pharmacological treatments for medical conditions such as pain, rheumatoid arthritis, joint inflammation, post-traumatic stress disorder (PTSD), irritable bowel disease (IBD), and metabolic disorders such as diabetes. Finally, the Targeted Neuroplasticity Training (TNT) program initiated in 2017 seeks to improve learning by pairing peripheral nerve stimulation with task training. This approach is based on the hypothesis that peripheral nerve stimulation can induce changes in synaptic plasticity through central neuromodulator release when paired temporally with sensorimotor or cognitive training tasks. The objectives in this project are to develop non-invasive nerve stimulators such as ear buds to improve performance on tasks such as language learning, intelligence analysis, and marksmanship. Devices developed for these programs may include implantable devices, particularly for prosthetic applications, but will likely also include skin-based devices and auditory stimulation.

Cardiac

Beyond the traditional pacemaker, a variety of alternative approaches to cardiac regulation are currently under investigation. Jenkins and coworkers demonstrated that pulsed 1.875 µm laser light can be used to regulate the pacing of an intact heart *in vivo*.[83] While previous investigators had shown similar results with visible or ultraviolet light, UV light is damaging to tissues and the visible light studies employed high power lasers that generated reactive oxygen species, which were also damaging. Variations on this approach were employed by Gentemann and colleagues who used gold nanoparticles irradiated by a 532-nm pulsed laser[84] and Savchenko *et al.*[85] who placed cardiomyocytes on graphene-based biointerfaces that were subsequently irradiated with green laser light.

Skin

As the largest organ in the body, the skin serves as both a barrier to protect the rest of the body and as a window providing insight into overall physiological status. Three types of information – physical, electrical, and chemical – can be measured by wearable or on-skin sensors.[76] To be successful, wearable electronics should be highly flexible, conformally attached to the human body, and operational under various mechanical strain conditions, such as bending, twisting, and stretching deformations. In addition, these sensors must be very sensitive to the appropriate stimuli. Skin-based electrophysiological measurements targeting electrical signals (e.g. EEG), and sensors targeting motion, body temperature, skin properties or vascular dynamics combine ultrathin conformal electrode interfaces with capabilities in wireless communication and low power electronics, suitable for monitoring over long periods of time. The sensing mechanisms included potential, resistive, capacitive, and piezoelectric sensors.[86] Many of these sensors build on the conducting polymers and/or composite materials discussed previously, particularly PEDOT:PSS and a variety of polymers doped with CNTs. Biochemical signals generally focus on compounds in sweat, although similar measurements can be made from tears and saliva. A variety of metabolites can be evaluated, employing commonly used biological detection methods (enzymes, antibodies, DNA, or whole cells) combined with electrochemical, optical, or piezoelectric sensing methods.[86] These approaches frequently replace blood sampling with its attendant discomfort and allow for real-time monitoring of metabolites such as glucose, lactic acid, chloride, and other electrolytes and hormones such as cortisol. Recent measuring devices include mouthguards and tattoos.

Organ-on-chip

Organ-on-chip or microphysiological systems (MPS) aim to recapitulate *in vivo* physiology for various organs for both basic biological understanding of the complex physiological systems in organs and as models for drug testing that provide greatly improved data compared with 2D culture systems and greater relevance than animal models. These systems build on developments in microfluidics and tissue engineering to create 3D tissue structures, resembling *in vivo* organs. Historically, interrogation of these systems had been limited to measurements of metabolites and microscopy investigations of either living systems or fixed, stained cultures. However, the incorporation of electronics into these systems provides new avenues for exploration of physical and chemical properties. As shown in Figure 6, electrical measurements that can be made for tissues in MPS devices include extracellular potential measurements of nerves and muscle tissue, impedance measurements of cardiomyocytes and other adherent cells, capacitive measurements of cell monolayers, identification and quantitation of surface ligands using amperometric sensing, measurement of transepithelial resistance, electrochemical measurements of metabolites, and real-time cardiac tissue force quantification via resistance change caused by the deformation of piezoelectric MTF chips.[75] As described in the review by Soucy *et al.*, MPS have been developed to model the central and peripheral nervous system, heart, liver, lung, adrenal glands, kidneys, vascular and gut as well as cancerous tissues.

Future directions

As part of a National Science Foundation-funded grant on Future Manufacturing of Bio-hybrid Electronic and Photonic Devices, a brainstorming workshop was held to envision future applications of these technologies to various biological systems, which could improve health outcomes, provide biological information, and/or perform health screenings

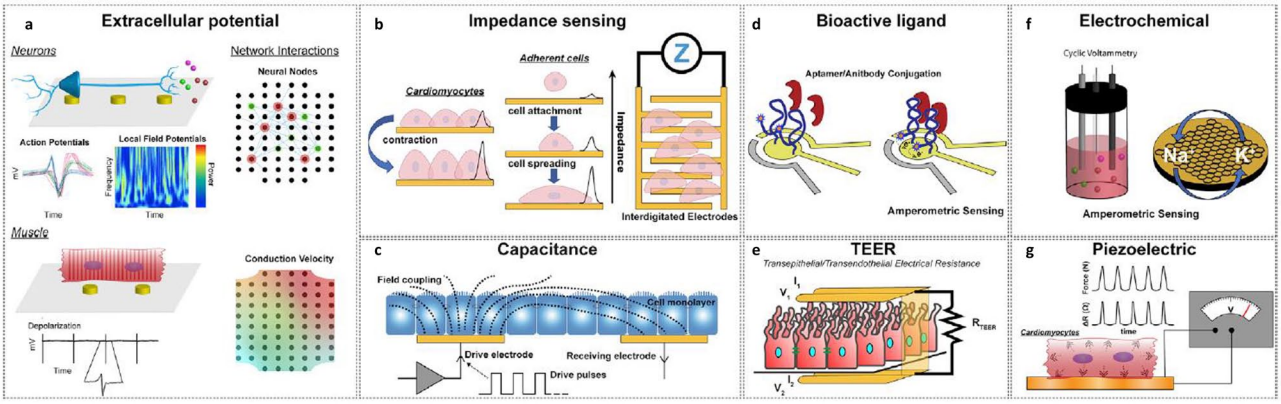

Figure 6. Overview of passive and active electric-based sensing integrated into microphysiological systems. (a) Measurement of neuronal and muscle cell function by interrogation of bioelectronic properties. (b) Measurement of cardiac activity on microelectrode arrays. Electrical impedance measurements between interdigitated electrodes can provide real-time indications of cell adhesion or cytotoxicity. (c) Cell capacitance directly correlates to the surface area of the cell monolayer. (d) Functionalization of conductive materials with ligand-binding aptamers or antibodies permits the utilization of traditional electronic materials for bioelectronic sensing. (e) Transepithelial electrical resistance (TEER) measurements are a direct measure of bioimpedance, typically utilized on a tightly formed monolayer resistant to the passive flow of ions in cell media. (f) Cyclic voltammetry can be used for real-time measurement of a variety of analytes including ions and small molecules such as epinephrine and norepinephrine. (g) Piezoelectric measurements used for real-time cardiac tissue force quantification via the change in resistance caused by the deformation of piezoelectric muscle thin-film chips. (A color version of this figure is available in the online journal.)
Source: Reprinted from Soucy *et al.*[75]

for the auditory, endocrine, musculoskeletal, blood, gastrointestinal, nervous, cardiovascular, respiratory, and visual systems. Proposed devices include sensors to detect infection and mechanical wear in joint replacement, a real-time measurement device that would be used for monitoring acoustic neuromas using an implantable sensor that detects auditory loss, an external abdominal distention monitor that would target ultrasound treatment to relieve discomfort, an anaphylactic shock sensor that would sense histamines, recognize anaphylactic shock potential, and prevent the airway from constricting, and an implantable oral device to monitor saliva production and stimulate nerve function. While many of these applications are not yet realizable, advances in technologies and manufacturing capabilities will certainly drive this field to the point where only imagination will limit the potential.

AUTHOR CONTRIBUTIONS

STS conceived, wrote, and edited the manuscript.

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